Circulation

ORIGINAL RESEARCH ARTICLE

# Associations Between End-Tidal Carbon Dioxide During Pediatric Cardiopulmonary Resuscitation, Cardiopulmonary Resuscitation Quality, and Survival

Ryan W. Morgan, MD, MTR; Ron W. Reeder, PhD; Dieter Bender, PhD; Kellimarie K. Cooper, BSE; Stuart H. Friess, MD; Kathryn Graham, MLAS; Kathleen L. Meert, MD; Peter M. Mourani, MD; Robert Murray, MD; Vinay M. Nadkarni, MD, MS; Chandrasekhar Nataraj, PhD; Chella A. Palmer, MPH; Neeraj Srivastava, MD; Bradley Tilford, MD; Heather A. Wolfe, MD, MSHP; Andrew R. Yates, MD; Robert A. Berg, MD; Robert M. Sutton, MD, MSCE; for the ICU-RESUS and Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) Investigator Groups*

**BACKGROUND:** Supported by laboratory and clinical investigations of adult cardiopulmonary arrest, resuscitation guidelines recommend monitoring end-tidal carbon dioxide ($ETCO_2$) as an indicator of cardiopulmonary resuscitation (CPR) quality, but they note that "specific values to guide therapy have not been established in children."

**METHODS:** This prospective observational cohort study was a National Heart, Lung, and Blood Institute–funded ancillary study of children in the ICU-RESUS trial (Intensive Care Unit-Resuscitation Project; NCT02837497). Hospitalized children (≤18 years of age and ≥37 weeks postgestational age) who received chest compressions of any duration for cardiopulmonary arrest, had an endotracheal or tracheostomy tube at the start of CPR, and evaluable intra-arrest $ETCO_2$ data were included. The primary exposure was event-level average $ETCO_2$ during the first 10 minutes of CPR (dichotomized as ≥20 mm Hg versus <20 mm Hg on the basis of adult literature). The primary outcome was survival to hospital discharge. Secondary outcomes were sustained return of spontaneous circulation, survival to discharge with favorable neurological outcome, and new morbidity among survivors. Poisson regression measured associations between $ETCO_2$ and outcomes as well as the association between $ETCO_2$ and other CPR characteristics: (1) invasively measured systolic and diastolic blood pressures, and (2) CPR quality and chest compression mechanics metrics (ie, time to CPR start; chest compression rate, depth, and fraction; ventilation rate).

**RESULTS:** Among 234 included patients, 133 (57%) had an event-level average $ETCO_2$ ≥20 mm Hg. After controlling for a priori covariates, average $ETCO_2$ ≥20 mm Hg was associated with a higher incidence of survival to hospital discharge (86/133 [65%] versus 48/101 [48%]; adjusted relative risk, 1.33 [95% CI, 1.04–1.69]; $P$=0.023) and return of spontaneous circulation (95/133 [71%] versus 59/101 [58%]; adjusted relative risk, 1.22 [95% CI,1.00–1.49]; $P$=0.046) compared with lower values. $ETCO_2$ ≥20 mm Hg was not associated with survival with favorable neurological outcome or new morbidity among survivors. Average $_2$ ≥20 mm Hg was associated with higher systolic and diastolic blood pressures during CPR, lower CPR ventilation rates, and briefer pre-CPR arrest durations compared with lower values. Chest compression rate, depth, and fraction did not differ between $ETCO_2$ groups.

**CONCLUSIONS:** In this multicenter study of children with in-hospital cardiopulmonary arrest, $ETCO_2$ ≥20 mm Hg was associated with better outcomes and higher intra-arrest blood pressures, but not with chest compression quality metrics.

**Key Words:** carbon dioxide ■ cardiopulmonary resuscitation ■ heart arrest ■ intensive care units, pediatric

Correspondence to: Ryan W. Morgan, MD, MTR, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Main Hospital – 9NW70, Philadelphia, PA 19104. Email morganr1@chop.edu

*A complete list of the investigators in the ICU-RESUS and Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) is provided in the Supplemental Material.

Presented as an abstract at the Scientific Sessions of the American Heart Association, Philadelphia, PA, November 11–13, 2023.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.066659.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

For Sources of Funding and Disclosures, see page 376.



*Circulation* is available at www.ahajournals.org/journal/circ

ORIGINAL RESEARCH ARTICLE

## Clinical Perspective

### What Is New?

- This prospective, multicenter study of children receiving cardiopulmonary resuscitation in intensive care units is the first clinical study in children to demonstrate an association between end-tidal carbon dioxide during cardiopulmonary resuscitation and survival to hospital discharge.
- An average end-tidal carbon dioxide of at least 20 mm Hg was associated with attaining the return of spontaneous circulation and surviving to discharge.

### What Are the Clinical Implications?

- These data offer support for cardiopulmonary resuscitation guideline recommendations to monitor end-tidal carbon dioxide as a gauge of pediatric cardiopulmonary resuscitation quality and offer a threshold of 20 mm Hg for which clinicians can potentially aim.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CPR** | cardiopulmonary resuscitation |
| **CPR-NOVA** | Validation of Physiologic CPR Quality Using Non-invasive Waveform Analytics study |
| **E-CPR** | extracorporeal cardiopulmonary resuscitation |
| **$ETCO_2$** | end-tidal carbon dioxide |
| **ICU** | intensive care unit |
| **ICU-RESUS** | The ICU-Resuscitation Project clinical trial |
| **PRISM** | Pediatric Risk of Mortality Score |
| **ROSC** | return of spontaneous circulation |
| **SBP** | systolic blood pressure |
| **VIS** | vasoactive-inotrope score |

Cardiopulmonary resuscitation (CPR) quality is a known determinant of survival from cardiopulmonary arrest.[1] Preclinical laboratory studies and clinical investigations of adult cardiopulmonary arrest have highlighted quantitative capnography (ie, end-tidal carbon dioxide [$ETCO_2$]) as a physiological monitor that can be used to assess and titrate CPR technique.[2–6] Supported by these data, a 2013 American Heart Association Consensus Statement on CPR Quality endorsed targeting an $ETCO_2$ ≥20 mm Hg during CPR to improve outcomes.[1] Subsequent iterations of pediatric and adult resuscitation guidelines recommended using $ETCO_2$ as an indicator of CPR quality, but pediatric resuscitation guidelines note that "specific values to guide therapy have not been established in children."[7,8]

As more than 70% of children with in-hospital cardiopulmonary arrests have advanced airways in place that can facilitate use of $ETCO_2$ as a CPR monitor,[9,10] establishing evidence-based $ETCO_2$ targets is a practical means of broadly improving resuscitation quality and outcomes. Although results from a previous single-center pediatric study found that in unadjusted analyses $ETCO_2$ values were higher among patients who achieved return of spontaneous circulation (ROSC), results from another small multicenter study found no association between $ETCO_2$ and outcomes.[11,12] Therefore, in the decade since the 2013 Consensus Statement, minimal scientific progress has been made in this area.

To fill this knowledge gap, the Eunice Kennedy Shriver National Institute of Child Health and Human Development–funded Collaborative Pediatric Critical Care Research Network and the National Heart, Lung, and Blood Institute ICU-RESUS trial (ICU-Resuscitation Project; NCT02837497) investigators prospectively designed an observational cohort study to evaluate the association between $ETCO_2$ during pediatric CPR and: (1) survival outcomes, (2) intra-arrest blood pressures, and (3) CPR mechanics and other CPR quality markers. For our primary analyses, we hypothesized that an event-level average $ETCO_2$ ≥20 mm Hg during pediatric inpatient CPR would be associated with a higher incidence of survival to hospital discharge, higher intra-arrest blood pressures, and superior CPR mechanics and quality characteristics.

# METHODS

## Setting, Design, and Oversight

This prospective observational cohort study was a National Heart, Lung, and Blood Institute–funded ancillary study of the ICU-RESUS trial, entitled CPR-NOVA, (Validation of Physiologic CPR Quality Using Non-invasive Waveform Analytics). The parent study was a hybrid stepped-wedge cluster randomized trial evaluating a CPR quality improvement bundle comprising physiologically focused point-of-care CPR trainings and postarrest debriefings.[13] It was conducted across 10 clinical sites in the United States (18 distinct intensive care units [ICUs]). The institutional review boards of each site and of the University of Utah data coordinating center approved both the parent study and this ancillary investigation with a waiver of informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

## Subject Population

For the ICU-RESUS parent study, pediatric subjects (≤18 years of age and ≥37 weeks postgestational age) with cardiopulmonary arrest requiring chest compressions of any duration in any of the participating ICUs were included. Subjects were excluded if, before the arrest, they: (1) had a terminal illness and were not expected to survive to discharge, (2) had a documented lack of commitment to aggressive ICU therapies, (3) had a determination of brain dead, or (4) had an out-of-hospital cardiopulmonary arrest associated with the current

hospitalization.[13] For this ancillary investigation, subjects were required to have an invasive airway (ie, endotracheal tube or tracheostomy tube) in place at the onset of CPR, regardless of whether they were mechanically ventilated at the time. Subjects were excluded if they did not have at least one evaluable 30-s epoch of $ETCO_2$ data.

Because the ICU-RESUS parent study and intervention focused on intra-arrest invasive arterial blood pressure waveform data, quantitative capnography waveforms were not collected on all patients with endotracheal or tracheostomy tubes initially (October 1, 2016, through May 5, 2019). Prospective collection of quantitative capnography on all patients with endotracheal or tracheostomy tubes commenced with the start of this CPR-NOVA ancillary investigation (May 6, 2019, through March 31, 2021). Before CPR-NOVA, a subsample of subjects had both invasive arterial line waveform data and $ETCO_2$ waveforms collected and submitted (ie, research coordinators transmitted both waveforms despite ICU-RESUS only requiring arterial line data). Both cohorts are included in these analyses.

## Data Collection

The data collection and physiological waveform analysis methods of the parent trial, and subsequent secondary studies, have been previously published.[13–15] In brief, trained research coordinators collected standardized cardiopulmonary arrest data elements,[16] CPR quality mechanics data (eg, compression depth and rate), and physiological bedside monitor data (eg, electrocardiogram, invasive arterial line, and quantitative capnography) for index CPR events (ie, the first event associated with the hospitalization). Baseline Pediatric Cerebral Performance Category [17,18] and Functional Status Scale[19] scores were based on the patient's preadmission baseline and calculated on the basis of documentation review. For patients born during the current hospitalization or who had been hospitalized >90 days at the time of the arrest, baseline Pediatric Cerebral Performance Category and Functional Status Scale scores were determined on the basis of the patient's status before the decompensation associated with the cardiopulmonary arrest. Abstraction of prearrest diagnoses (eg, sepsis or pulmonary hypertension) was largely based on documentation of these diagnoses in the medical record. Explicitly defined diagnoses included respiratory insufficiency (presence of hypoxia or hypercarbia or requirement for invasive or noninvasive mechanical ventilation) and hypotension (systolic blood pressure [SBP] or diastolic blood pressure [DBP] <5th percentile for age or requirement for vasopressor/inotropic support [excluding dopamine ≤3 $\mu g \cdot kg^{-1} \cdot min^{-1}$] after intravascular volume expansion). The cause of arrest (hypotension, respiratory decompensation, arrhythmia, or cyanosis without respiratory decompensation) was based on documentation in the medical record rather than specific criteria with consultation with site principal investigators as needed. The Pediatric Risk of Mortality (PRISM-IV)[20] score was calculated on the basis of data collected between 2 and 6 hours before arrest, and the Vasoactive-Inotrope Score (VIS)[21] was calculated at 2 hours before arrest and 6 hours after arrest.

Physiological waveforms were deidentified locally and then transmitted to the University of Utah data coordinating center for subsequent download and analysis by investigators at the Children's Hospital of Philadelphia. There, investigators reviewed each waveform for critical features such as: (1) the start of CPR, (2) interruptions in CPR, (3) periods of nonanalyzable data, (4) periods of nonsustained ROSC, and (5) the end of the event. Custom MATLAB code (The MathWorks, Inc., Natick, MA) was used to determine SBP and DBP values. To ensure accurate determination of $ETCO_2$ values and ventilation rates, capnographic waveforms were manually reviewed by investigators blinded to outcomes and other patient characteristics (R.W.M., K.G., and R.M.S.). The peak of each capnographic waveform determined $ETCO_2$ values, which were averaged over the course of 30-s data epochs.

Up to the first 10 minutes of hemodynamic and $ETCO_2$ values during CPR were collected for each patient (up to twenty 30-s epochs). Epochs were considered evaluable if they had at least 7.5 s of CPR data, excluding periods of nonanalyzable data or intermittent ROSC. The "event-level" average of each physiological variable was the average of all evaluable epoch-level averages for a given patient.

## Exposures, Outcomes, and Statistical Analyses

The primary exposure was whether the event-level average $ETCO_2$ was ≥20 mm Hg during the first 10 minutes of CPR. A secondary exposure was the percentage of 30-s epochs with average $ETCO_2$ ≥20 mm Hg. The primary outcome was survival to hospital discharge. Using observed parent trial screening and enrollment, we anticipated 280 evaluable events during the planning of this ancillary trial. On the basis of a power analysis using a *t* test (parallel 2-group design) of proportions with a 2-sided alternative and type I error rate of 0.05, we expected >80% power to detect an absolute difference in survival to hospital discharge of 17% (33%–50%) if the $ETCO_2$ was ≥20 mm Hg in 40% to 60% of patients. These estimates were informed by previous network publications.[10,12,22]

Secondary outcomes included ROSC, survival to discharge with favorable neurological outcome (Pediatric Cerebral Performance Category score of 1 to 3 or unchanged from baseline) and new morbidity among survivors (Functional Status Scale score change ≥3 from baseline).[17,19] Patients achieving return of circulation through venoarterial extracorporeal membrane oxygen support (extracorporeal CPR [E-CPR]), were not classified as having ROSC. Intra-arrest physiological variables included: (1) SBP and DBP (mm Hg), (2) achievement of target SBP (≥60 mm Hg for <1 year of age or ≥80 mm Hg for older children),[13] and (3) achievement of target DBP (≥25 mm Hg for <1 year of age or ≥30 mm Hg for older children).[10,13,15] CPR mechanics and quality variables included: (1) chest compression depth (mm), (2) chest compression rate ($min^{-1}$), (3) chest compression fraction (proportion of cardiopulmonary arrest event during which chest compressions are provided), (4) CPR ventilation rate ($min^{-1}$), and (5) pre-CPR arrest duration (a marker of low- or no-flow time before the initiation of CPR, defined as the time in seconds that a patient had an indication for CPR). Among patients surviving at least 6 hours after the return of circulation (ROSC or E-CPR), proximate postarrest outcomes included: (1) lactate (mmol/L),[23] (2) pH, (3) electroencephalogram background,[24] and (4) VIS.[25]

Patient and event characteristics as well as outcomes were summarized by $ETCO_2$ group. In addition, intra-arrest physiological measurements and CPR mechanics and quality measurements, as defined above, were summarized by $ETCO_2$ group. Summaries reported were counts and percentages for categorical variables and median, first, and third quartiles for continuous variables. Associations of summarized variables with

$ETCO_2$ group were assessed with Fisher exact test for nominal variables, the Cochrane-Armitage trend test for ordinal variables (baseline and discharge Pediatric Cerebral Performance Category scores), and the Wilcoxon rank-sum test for continuous variables.

The association of $ETCO_2$ group with outcomes was evaluated with a Poisson regression model using generalized estimating equations to obtain robust error estimates. All models controlled for initial CPR rhythm (pulseless versus nonpulseless [ie, bradycardia with poor perfusion]), respiratory decompensation as an immediate cause of arrest, and arrhythmia as an immediate cause of arrest, covariates selected a priori due to their hypothesized association with $ETCO_2$ group, and survival.

Several exploratory analyses were conducted. First, we sought to evaluate $ETCO_2$ as a continuous rather than dichotomized exposure. We therefore constructed receiver operating characteristic and spline curves to identify an alternative $ETCO_2$ target or range. The optimal cut point from the receiver operating characteristic curve was determined by the Euclidean distance without consideration of covariables. To further visualize the relationship between the exposure and outcome, curves were created with natural cubic splines in logistic regression models, controlling for the same covariates as above. Internal knots for the splines were placed at the 10th, 50th, and 90th percentiles of the data. The number of internal knots was chosen to balance model fit and parsimony and was confirmed by assessment of the Bayesian Information Criterion. Second, scatterplots using epoch-level data were created to investigate the relationship of $ETCO_2$ with: (1) SBP, (2) DBP, and (3) ventilation rate. Tests of association were based on univariable linear regression, with generalized estimating equations used to account for the use of multiple 30-s average values from a given CPR event. Third, to provide a useful bedside marker of probability of resuscitation success (ie, probability of ROSC), the trend in $ETCO_2$ over the first 10 minutes of CPR was depicted in patients with and without ROSC. The mean values were compared between patients with and without ROSC through mixed-effects linear regression modeling with an exponential temporal covariance structure to account for correlated observations. A random-subject effect was also included to give a lower bound on the correlation between 2 different minutes of CPR for the same subject. Mixed-effects linear regression modeling assessed the difference in slope of change in $ETCO_2$ between patients with and without ROSC, again using a temporal covariance structure. Finally, we repeated the primary analyses with event-level $ETCO_2$ <10 mm Hg as an exploratory exposure.

Analyses were performed using SAS 9.4 (SAS Institute; Cary, NC). Reported *P* values were based on a 2-sided alternative and considered significant if <0.05.

## RESULTS

Among the 1129 children experiencing an index cardiopulmonary arrest event in the parent ICU-RESUS trial, 824 (73%) had invasive mechanical ventilation in place at the start of CPR (532 before CPR-NOVA; 292 during CPR-NOVA; Figure 1). Of these events with invasive mechanical ventilation, a total of 234 (28%) events were included in the final analytic cohort (96/532 [18%] before CPR-NOVA; 138/292 [47%] during CPR-NOVA). Table S1 compares patient characteristics across these 2 cohorts. It is notable that pre–CPR-NOVA patients more frequently had preexisting cardiac disease (*P*=0.028) and prearrest hypotension (*P*=0.002) and had higher prearrest PRISM scores (*P*=0.018) and VIS (*P*=0.04). However, absolute differences in survival to hospital discharge across $ETCO_2$ groups (≥20 mm Hg versus <20 mm Hg) did not differ between enrollment periods (pre–CPR-NOVA enrollment period: 36/56 [64.3%] versus 20/40 [50%]; *P*=0.21; during CPR-NOVA enrollment: 50/77 [64.9%] versus 28/61 [45.9%]; *P*=0.038).

Patient characteristics summarized by $ETCO_2$ group are presented in Table 1. In terms of preexisting conditions before CPR, subjects with event-level average $ETCO_2$ ≥20 mm Hg more frequently had respiratory insufficiency (*P*=0.004) and less frequently had hypotension (*P*=0.028). Event characteristics by $ETCO_2$ group are presented in Table 2. Subjects with event-level average $ETCO_2$ ≥20 mm Hg more frequently had arrhythmia as the immediate cause of the cardiopulmonary arrest (*P*=0.034) and less frequently received epinephrine (*P*=0.002), calcium (*P*=0.017), and fluid boluses (*P*=0.046) during CPR. They received E-CPR less frequently than patients with lower $ETCO_2$ (26/133 [19.5%] versus 32/101 [31.7%]; *P*=0.046). Patient and event characteristics by survival to hospital discharge are presented in Tables S2 and S3, respectively.

Intra-arrest physiological and CPR quality metrics are compared across $ETCO_2$ groups in Table 3. In events with event-level average $ETCO_2$ ≥20 mm Hg, intra-arrest SBP and DBP were higher than in events with $ETCO_2$ <20 mm Hg (SBP: 90.6 [75.1, 118.7] mm Hg versus 70.9 [55.5, 86.4] mm Hg, *P*<0.001; DBP: 46.5 [37.9, 57.9] mm Hg versus 33.3 [26.8, 42.9] mm Hg, *P*<0.001). Events with event-level average $ETCO_2$ ≥20 mm Hg were more likely to achieve a priori SBP targets (66/80 [82.5%] versus 48/75 [65.8%]; *P*=0.025) and DBP targets (76/80 [95.0%] versus 61/75 [81.3%]; *P*=0.011) compared with events with lower $ETCO_2$ values.

Chest compression rate, depth, and fraction did not differ significantly between $ETCO_2$ groups (Table 3). In events with event-level average $ETCO_2$ ≥20 mm Hg, pre-CPR arrest durations were shorter (22.8 [0.5, 57.8] s versus 52.9 [15.5, 84.1] s; *P*=0.006), and CPR ventilation rates were lower (26.7 [20.0, 35.2] $min^{-1}$ versus 29.5 [24.1, 40.1] $min^{-1}$; *P*=0.015) compared with events with lower $ETCO_2$ values.

Overall, the average $ETCO_2$ across all events was 23.5±11.94 mm Hg; 133 of 234 (56.8%) patients had an event-level average $ETCO_2$ ≥20 mm Hg. More patients survived to hospital discharge when event-level average $ETCO_2$ was ≥20 mm Hg compared with lower $ETCO_2$ values (86/133 [64.7%] versus 48/101 [47.5%]; *P*=0.011). Multivariable outcome analyses are presented in Table 4. After adjusting for confounders, an

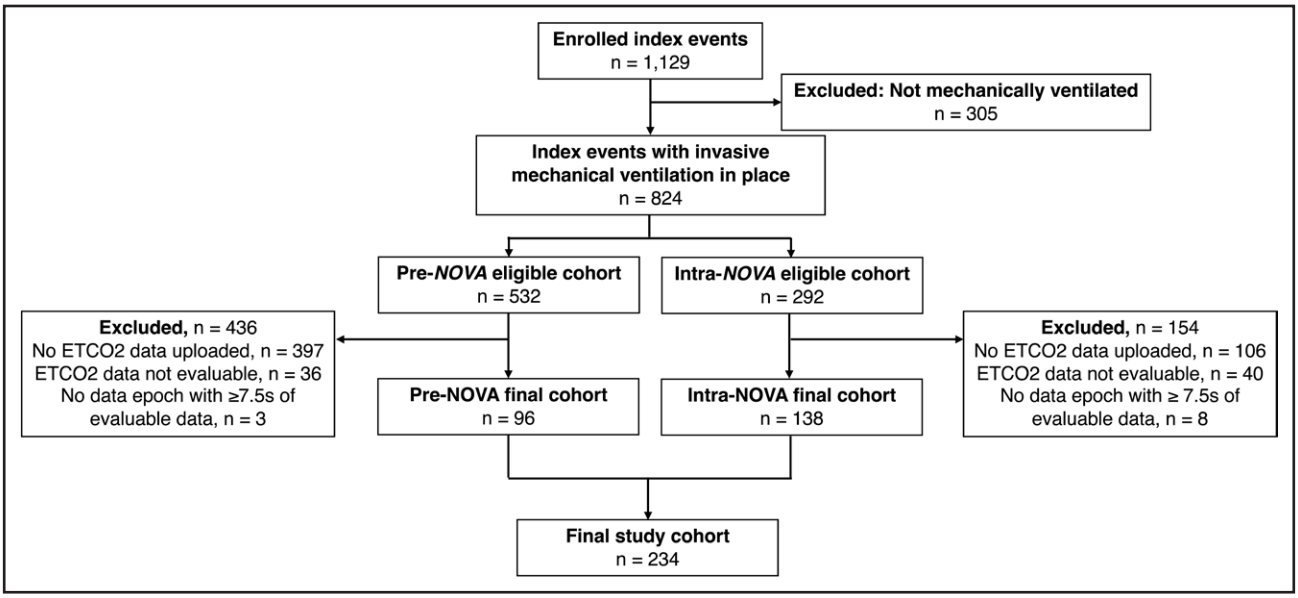


**Figure 1. Patient flow diagram.**
Pre-NOVA refers to patients enrolled in the ICU-RESUS parent study before prospective collection of $ETCO_2$ waveform data for the CPR-NOVA study (October 1, 2016, through May 5, 2019). Intra-NOVA refers to patients enrolled after the start of the CPR-NOVA ancillary investigation (May 6, 2019, through March 31, 2021). $ETCO_2$ indicates end-tidal carbon dioxide.

$ETCO_2$ ≥20 mm Hg remained associated with higher relative risk of survival to hospital discharge (adjusted relative risk, 1.33 [95% CI, 1.04–1.69]; *P*=0.023) and ROSC (95/133 [71.4%] versus 59/101 [58.4%]; adjusted relative risk, 1.22 [95% CI, 1.00–1.49]; *P*=0.046). The percentage of 30-s epochs achieving $ETCO_2$ ≥20 mm Hg was also associated with higher relative risk of survival to hospital discharge (adjusted relative risk, 1.03 per 10% increase in epochs achieving target [95% CI, 1.00–1.06]; *P*=0.034) and ROSC (adjusted relative risk, 1.03 per 10% increase in epochs achieving target [95% CI, 1.01–1.06]; *P*=0.006).

## Exploratory Analyses

Figure 2 depicts the receiver operating characteristic curve and spline analyses of the relationship between $ETCO_2$and survival to hospital discharge. Analogous curves for ROSC are presented in Figure S1. The receiver operating characteristic analyses identified an optimal cut point for survival to hospital discharge of 19.64 mm Hg (sensitivity 0.67, specificity 0.53; area under the receiver operating characteristic curve, 0.57 [95% CI, 0.5–0.65]). The optimal cut point for ROSC was 19.07 mm Hg (sensitivity 0.69, specificity 0.53; area under the receiver operating characteristic curve, 0.62 [95% CI, 0.55–0.7]). On the basis of visual inspection of the spline curves and the close proximity of both cut points to the prespecified $ETCO_2$ threshold of 20 mm Hg, alternative targets were not evaluated further.

The analyses using univariable linear regression to further evaluate the relationships between $ETCO_2$ and SBP, DBP, and CPR ventilation rate are presented in Figure S2A (SBP) and S2B (DBP) and Figure S3, respectively. $ETCO_2$ was positively correlated with SBP (*P*<0.0001) and DBP (*P*<0.001) and inversely correlated with ventilation rate (*P*=0.04).

The trend in $ETCO_2$ during the first 10 minutes of CPR is graphically represented in Figure 3. There was a significant difference in both the mean $ETCO_2$ (*P*<0.001) and the slope of $ETCO_2$ change over time (effect size estimate, 0.74 [95% CI, 0.10–1.38] mm Hg/min; *P*=0.023) among patients achieving ROSC versus those who did not achieve ROSC (*P*=0.011).

Tertiary postarrest outcomes are presented in Table S4. Highest recorded lactate values in the first 6 hours after arrest were significantly lower (5.7 [2.4, 11.6] mmol/L versus 7.5 [4.7, 14.8] mmol/L; *P*=0.01) in the $ETCO_2$ ≥20 mm Hg group compared with the lower $ETCO_2$ group. There were no differences in lowest pH, electroencephalogram background patterns, or VIS.

Finally, an event-level average ETCO2 <10 mm Hg was not associated with survival to hospital discharge or other outcomes (Table 4). It is notable that among 21 of the patients with event-level $ETCO_2$ <10 mm Hg, 20 (95%) achieved return of circulation (ROSC, 7; E-CPR, 13), and 10 (48%) survived to hospital discharge. Of the 21 patients with an event-level ETCO2 <10 mm Hg, 12 (57%) had congenital heart disease, and 6 (29%) had shunt-dependent or passive pulmonary blood flow.

## DISCUSSION

In this multicenter cohort study of pediatric patients with in-hospital cardiopulmonary arrest who had an invasive

**Table 1. Patient Characteristics**

| Characteristics | $ETCO_2$ ≥20 mm Hg (n=133) | $ETCO_2$ <20 mm Hg (n=101) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age, n (%) | | | 0.125 |
| ≤1 y | 75 (56.4) | 67 (66.3) | |
| 1 to <8 y | 34 (25.6) | 15 (14.9) | |
| 8 to <19 y | 24 (18.0) | 19 (18.8) | |
| Male | 69 (51.9) | 48 (47.5) | 0.598 |
| Preexisting conditions, n (%) | | | |
| Respiratory insufficiency | 124 (93.2) | 81 (80.2) | 0.004 |
| Hypotension | 87 (65.4) | 80 (79.2) | 0.028 |
| Heart failure | 19 (14.3) | 15 (14.9) | 1.000 |
| Pneumonia | 17 (12.8) | 6 (5.9) | 0.119 |
| Sepsis | 25 (18.8) | 12 (11.9) | 0.205 |
| Trauma | 4 (3.0) | 1 (1.0) | 0.393 |
| Kidney disease or injury | 22 (16.5) | 16 (15.8) | 1.000 |
| Malignancy | 6 (4.5) | 3 (3.0) | 0.735 |
| Pulmonary hypertension | 26 (19.5) | 18 (17.8) | 0.866 |
| Congenital heart disease | 76 (57.1) | 75 (74.3) | 0.009 |
| Pre-event characteristics | | | |
| Illness category, n (%) | | | 0.083 |
| Medical cardiac | 33 (24.8) | 32 (31.7) | |
| Medical noncardiac | 44 (33.1) | 20 (19.8) | |
| Surgical cardiac | 45 (33.8) | 45 (44.6) | |
| Surgical noncardiac | 7 (5.3) | 3 (3.0) | |
| Trauma | 4 (3.0) | 1 (1.0) | |
| PRISM* | 7 [2, 12] | 7 [3, 12] | 0.679 |
| Vasoactive-inotrope score† | 1.5 [0, 8.0] | 2.5 [0, 10.0] | 0.246 |
| Baseline Pediatric Cerebral Performance Category score,‡ n (%) | | | 0.234 |
| 1 - Normal | 73 (54.9) | 68 (67.3) | |
| 2 - Mild disability | 29 (21.8) | 9 (8.9) | |
| 3 - Moderate disability | 14 (10.5) | 14 (13.9) | |
| 4 - Severe disability | 14 (10.5) | 10 (9.9) | |
| 5 - Coma/vegetative state | 3 (2.3) | 0 (0.0) | |
| Baseline Functional Status Scale‡ | 6.0 [6.0, 10.0] | 6.0 [6.0, 9.0] | 0.092 |

Comparison of patient characteristics between patients with average event-level $ETCO_2$ ≥20 mm Hg vs those with lower $ETCO_2$ values. Analyses performed with Fisher exact test, Wilcoxon rank-sum test, or Cochrane-Armitage trend test. $ETCO_2$ indicates end-tidal carbon dioxide; and PRISM, Pediatric Risk of Mortality score.

*PRISM was evaluated 2 to 6 hours before the event.

†Vasoactive inotrope score was evaluated 2 hours before the event and calculated from the following equation: dopamine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)+dobutamine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)+nitroprusside dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)+ (10×milrinone dose [$\mu g \cdot kg^{-1} \cdot min^{-1}$])+(100×epinephrine dose [$\mu g \cdot kg^{-1} \cdot min^{-1}$])+(100×norepinephrine dose [$\mu g \cdot kg^{-1} \cdot min^{-1}$])+(100 phenylephrine dose [$\mu g \cdot kg^{-1} \cdot min^{-1}$])+vasopressin dose ($munits \cdot kg^{-1} \cdot h^{-1}$).

‡Baseline Pediatric Cerebral Performance Category and Functional Status Scale represent subject status before the event leading to hospitalization.

airway in place at the start of CPR, an average $ETCO_2$ ≥20 mm Hg during the first 10 minutes of CPR was associated with a higher incidence and adjusted relative risk of both survival to hospital discharge and ROSC. To our knowledge, this is the first multicenter pediatric clinical study providing evidence to support monitoring $ETCO_2$ during CPR or provide an $ETCO_2$ target for pediatric CPR. Events with an $ETCO_2$ ≥20 mm Hg during CPR were also more likely to achieve invasive arterial BP targets previously associated with a higher incidence of neurologically favorable survival from pediatric cardiopulmonary arrest,[10,15] providing important physiological mechanistic data to support our primary findings.

There is a substantial body of preclinical laboratory data establishing that $ETCO_2$ is highly correlated with pulmonary blood flow and cardiac output during CPR,[26–29]

**Table 2. Cardiopulmonary Arrest Event Characteristics**

| Characteristics | $ETCO_2$ ≥20 mm Hg (n=133) | $ETCO_2$ <20 mm Hg (n=101) | *P* value |
|---|---|---|---|
| Interventions in place before event,* n (%) | | | |
| Central venous catheter | 103 (77.4) | 76 (75.2) | 0.756 |
| Vasoactive infusion | 80 (60.2) | 71 (70.3) | 0.129 |
| Invasive mechanical ventilation | 123 (92.5) | 89 (88.1) | 0.268 |
| Noninvasive ventilation | 6 (4.5) | 10 (9.9) | 0.122 |
| Immediate cause(s) of event, n (%) | | | |
| Arrhythmia | 24 (18.0) | 8 (7.9) | 0.034 |
| Cyanosis without respiratory decompensation | 6 (4.5) | 3 (3.0) | 0.735 |
| Hypotension | 76 (57.1) | 70 (69.3) | 0.076 |
| Respiratory decompensation | 60 (45.1) | 38 (37.6) | 0.285 |
| Duration of CPR, min | 7.0 [3, 22] | 11.0 [4, 36] | 0.052 |
| CPR timing,† n (%) | | | 0.516 |
| Weekday | 80 (60.2) | 57 (56.4) | |
| Weeknight | 21 (15.8) | 22 (21.8) | |
| Weekend | 32 (24.1) | 22 (21.8) | |
| Medications during CPR | | | |
| Epinephrine, n (%) | 104 (78.2) | 94 (93.1) | 0.002 |
| Number of doses | 3 [1, 5] | 3.0 [1, 6] | 0.549 |
| Average interval between doses‡ | 5.0 [4.0, 7.3] | 5.0 [3.3, 8.0] | 0.575 |
| Time to first dose (minutes) | 1.0 [0, 2.0] | 1.0 [0, 2.0] | 0.423 |
| Atropine, n (%) | 12 (9.0) | 4 (4.0) | 0.191 |
| Calcium, n (%) | 52 (39.1) | 56 (55.4) | 0.017 |
| Sodium bicarbonate, n (%) | 65 (48.9) | 57 (56.4) | 0.291 |
| Vasopressin, n (%) | 6 (4.5) | 4 (4.0) | 1.000 |
| Amiodarone, n (%) | 4 (3.0) | 4 (4.0) | 0.729 |
| Lidocaine, n (%) | 4 (3.0) | 2 (2.0) | 0.701 |
| Fluid bolus, n (%) | 26 (19.5) | 32 (31.7) | 0.046 |
| Extracorporeal CPR,§ n (%) | 26 (19.5) | 32 (31.7) | 0.046 |

Comparison of cardiopulmonary arrest event characteristics between patients with an average event-level $ETCO_2$ ≥20 mm Hg vs those with lower $ETCO_2$ values. Analyses performed with Fisher exact test or Wilcoxon rank-sum test. CPR indicates cardiopulmonary resuscitation; and $ETCO_2$, end-tidal carbon dioxide.

*Documented interventions in the prearrest period. Patients who were intubated in the periarrest period and had an endotracheal tube in place at the onset of CPR could appear in the "noninvasive ventilation" group, and patients with a tracheostomy without ventilator support until the immediate prearrest and periarrest period could be classified as receiving no prearrest ventilatory support.

†Weekday is between 7 AM and 11 PM Monday through Friday; weeknight, after 11 PM Monday through Thursday; weekend, 11 PM on Friday through 7 AM the following Monday.

‡Total duration of CPR in minutes − time to first epinephrine dose in minutes)/(total number of epinephrine doses − 1)

§Successful cannulation onto extracorporeal membrane oxygenation support as the outcome of the CPR event.

and thus is a potentially effective noninvasive monitor of CPR quality. To that end, adult clinical investigations have established that $ETCO_2$ values are generally higher among patients who achieve ROSC versus those who do not,[6,30] that low $ETCO_2$ is associated with mortality,[3,4,6,31,32] and that CPR mechanics quality, namely chest compression depth, is correlated with $ETCO_2$ levels during CPR.[33] Although a single-center pediatric study demonstrated an association between $ETCO_2$ and ROSC,[11] our study provides the first pediatric evidence to identify an association of $ETCO_2$ with survival and demonstrates several significant findings suggesting that $ETCO_2$ is associated with cardiac output during CPR. First, an $ETCO_2$ ≥20 mm Hg was associated with higher intra-arrest blood pressures during CPR, the primary driver of end-organ perfusion. Events with an $ETCO_2$ ≥20 mm Hg were more likely to achieve DBP targets (≥25 mm Hg in infants <1 year of age, ≥30 mm Hg in older children) that have previously been associated with improved neurological survival after pediatric cardiopulmonary arrest.[10,15] Second, lactate levels in the immediate postarrest period were lower when target $ETCO_2$ was achieved, despite similar prearrest PRISM and VIS scores between $ETCO_2$ groups, suggesting that the higher $ETCO_2$ values were associated with improved blood flow

**Table 3. CPR Physiology and Quality**

| Measurement | $ETCO_2$ ≥20 mm Hg | $ETCO_2$ <20 mm Hg | *P* value |
|---|---|---|---|
| Arterial blood pressure data available, n (%) | 80/133 (60.2) | 75/101 (74.3) | |
| CPR mechanics data available, n (%) | 40/133 (30.1) | 24/101 (23.8) | |
| Intra-arrest physiology | | | |
| Average SBP, mm Hg | 90.6 [75.1, 118.7] | 70.9 [55.5, 86.4] | <0.001 |
| Average DBP, mm Hg | 46.5 [37.9, 57.9] | 33.3 [26.8, 42.9] | <0.001 |
| Target SBP,* n (%) | 66/80 (82.5) | 48/73 (65.8) | 0.025 |
| Target DBP,† n (%) | 76/80 (95.0) | 61/75 (81.3) | 0.011 |
| CPR mechanics/quality | | | |
| Average CC rate, $min^{-1}$‡ | 117.7 [108.8, 125.5] n=96 | 117.9 [109.5, 125.1] n=85 | 0.899 |
| Average chest compression fraction‡ | 0.97 [0.93, 1.00] n=96 | 0.96 [0.91, 0.99] n=85 | 0.091 |
| Average depth, mm | 34.26 [24.75, 45.21] n=38 | 32.10 [21.82, 53.70] n=24 | 0.960 |
| Pre-CPR arrest duration, s§ | 22.75 [0.45, 57.80] n=80 | 52.90 [15.50, 84.10] n=75 | 0.006 |
| Average ventilation rate, breaths/min | 26.65 [19.96, 35.22] n=133 | 29.49 [24.11, 40.06] n=101 | 0.015 |

Comparison of intra-arrest CPR physiology and quality measurements between patients with an average event-level $ETCO_2$ ≥20 mm Hg vs those with lower $ETCO_2$ values. Unless otherwise noted, values represent event-level averages during the first 10 minutes of CPR. Analyses performed with Fisher exact test or Wilcoxon rank-sum test. CC indicates chest compression; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; $ETCO_2$, end-tidal carbon dioxide; and SBP, systolic blood pressure.

*Average DBP ≥25 mm Hg for patients <1 year of age or ≥30 mm Hg for patients ≥1 year of age.

†Average SBP ≥60 mm Hg for subjects <1 year of age or ≥80 mm Hg for subjects ≥1 year of age.

‡Calculated on the basis of either arterial blood pressure waveform (prioritized when both available) or CPR quality-monitoring defibrillator.

§Pre-CPR arrest time: Duration (seconds) that a patient has a pulse pressure <10 mm Hg and a low SBP (<40 mm Hg in infants <1 year of age or <50 mm Hg in older children).

during CPR, and not simply a marker of differential prearrest illness. Finally, target $ETCO_2$ values were associated with shorter pre-CPR arrest times, potentially suggesting that faster recognition of cardiopulmonary arrest (ie, briefer periods of "no-flow") allow for superior blood flow during CPR. However, in contrast to adult and preclinical studies,[33–35] chest compression characteristics, including rate, depth, and fraction, did not differ between patients with $ETCO_2$ ≥20 mm Hg and those with lower $ETCO_2$. Thus, the interventions that resuscitation teams should

**Table 4. Patient and Event Outcomes.**

| Outcomes | Event average $ETCO_2$ ≥20 mm Hg | | % CPR epochs $ETCO_2$ ≥20 mm Hg | | Event average $ETCO_2$ <10 mm Hg | |
|---|---|---|---|---|---|---|
| | RR (95% CI)* | *P* value | RR (95% CI)*† | *P* value | RR (95% CI)* | *P* value |
| Primary outcome | | | | | | |
| Survival to hospital discharge | 1.33 (1.04–1.69) | 0.023 | 1.03 (1.00–1.06) | 0.034 | 0.98 (0.59–1.62) | 0.927 |
| Secondary outcomes | | | | | | |
| Sustained return of spontaneous circulation‡ | 1.22 (1.00–1.49) | 0.046 | 1.03 (1.01–1.06) | 0.006 | 0.69 (0.39–1.24) | 0.213 |
| Survival with favorable neurological outcome§ | 1.23 (0.94–1.59) | 0.128 | 1.02 (0.99–1.05) | 0.180 | 0.92 (0.50–1.69) | 0.788 |
| New morbidity‖ | 1.09 (0.62–1.89) | 0.772 | 1.01 (0.95–1.08) | 0.690 | 0.91 (0.27–3.09) | 0.877 |

Association of intra-arrest $ETCO_2$ classification with outcomes. CPR indicates cardiopulmonary resuscitation; $ETCO_2$, end-tidal carbon dioxide; and RR, relative risk.

*Adjusted relative risk is based on Poisson regression with robust error estimates, controlling for initial rhythm (pulseless vs nonpulseless), respiratory decompensation as an immediate cause of arrest, and arrhythmia as an immediate cause of arrest for a priori targets during the first 10 minutes of resuscitation.

†RR is for an increase of 10 in percentage of CPR epochs achieving target $EPTO_2$.

‡Return of spontaneous circulation ≥20 minutes in duration, as defined by Utstein CPR reporting guidelines.

§Survival with favorable neurological outcome is defined as a Pediatric Cerebral Performance Category score of 1 to 3 or no worse than baseline.

‖New morbidity is an increase in Functional Status Scale score ≥3.

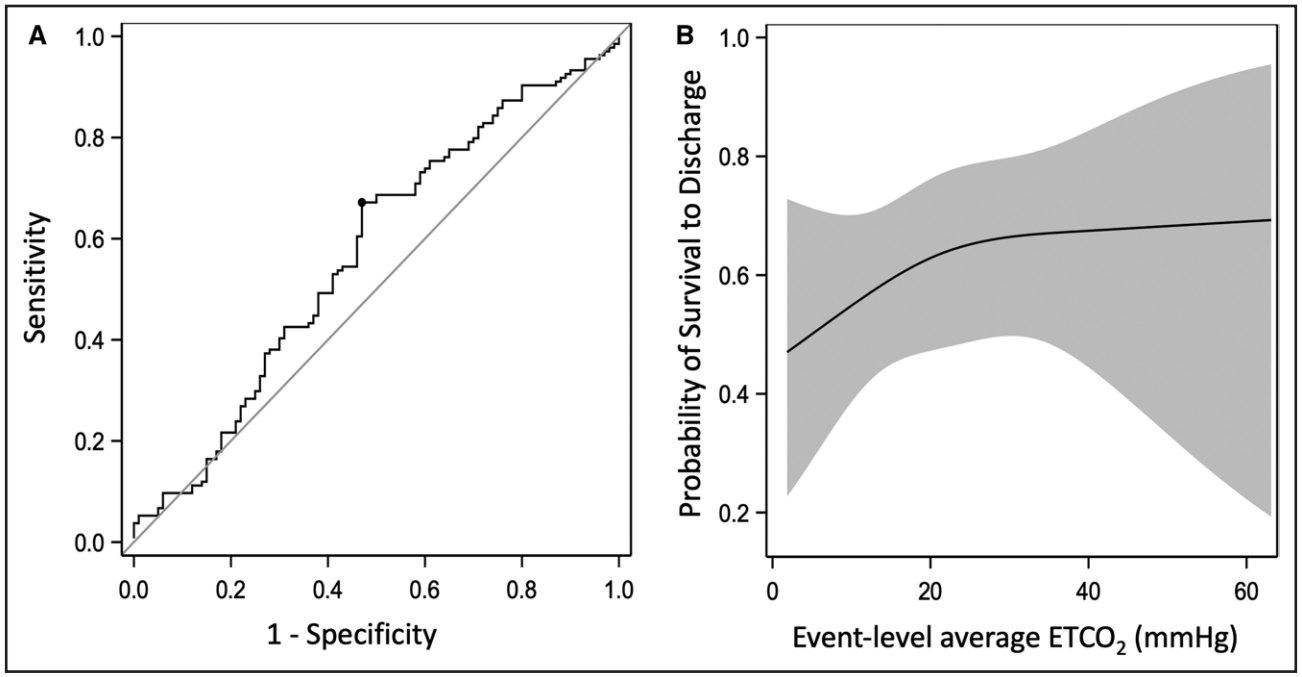


**Figure 2. Relationship between $ETCO_2$ and survival to hospital discharge.**
**A**, Receiver operating characteristic curve. **B**, Probability curves. Receiver operating characteristic curve: optimal cut point: $ETCO_2$ 19.6 mm Hg (sensitivity, 0.67; specificity, 0.53; area under the receiver operating characteristic curve, 0.571 [95% CI, 0.496–0.647]). Probability curves were created with logistic regression and natural cubic splines, controlling for initial rhythm (pulseless vs nonpulseless), and for respiratory decompensation and arrhythmia as the immediate causes of arrest. $ETCO_2$ indicates end-tidal carbon dioxide.

consider in response to a low $ETCO_2$ require independent investigation.

In an attempt to provide an additional clinically useful metric for bedside providers to follow, we investigated whether there was prognostic value in the change in $ETCO_2$ values over time. Clinicians may appreciate temporal changes in $ETCO_2$ more intuitively than the "average $ETCO_2$" during CPR. In this study, we found that the change in $ETCO_2$ during the first minutes of resuscitation is highly associated with the probability of resuscitation success (ie, attaining ROSC). This may support the utility of using $ETCO_2$ to inform treatment decisions. For example, failure of a low $ETCO_2$ to improve in response to resuscitation strategies could potentially trigger rescue strategies such as E-CPR, which was more frequently used in the group with lower $ETCO_2$ values.

Since the 2013 Consensus on Science Statement on CPR Quality, there has been a growing body of literature supporting the idea that rescuers should monitor and titrate the resuscitation effort according to a patient's physiological response, with many of these investigations focused on pediatric cardiopulmonary arrest. In large animal translational pediatric models, altering CPR technique (eg, depth and rate of chest compressions) and vasopressor administration according to either invasive arterial blood pressure[36,37] or $ETCO_2$[34,35] is associated with better cardiopulmonary arrest outcomes. And although prospective clinical observational studies have established arterial DBP targets, similar data establishing the utility of $ETCO_2$ had been lacking until now. As mentioned, previous work was limited by sample size[12] or reliance on CPR quality monitoring defibrillators that are frequently not in place during the first critical minutes of resuscitation.[11] By leveraging the large physiological waveform database of the ICU-RESUS trial, these data have begun to fill an important critical gap in the pediatric resuscitation knowledge base and have the potential to also improve patient-centric resuscitation algorithms.

Finally, the association between CPR ventilation rate and $ETCO_2$ deserves brief comment. Similar to previous adult and pediatric investigations,[12,33] we found that $ETCO_2$ was inversely correlated with CPR ventilation rate (ie, higher ventilation rates presumably led to lower $ETCO_2$). As excessive ventilation can lead to increased intrathoracic pressure, increased right atrial pressure, decreased venous return, and thereby, reduced cardiac output,[38,39] it is possible that either improved ventilation with preserved cardiac output or a reduction in cardiac output due to excessive ventilation is responsible for this inverse relationship. In our study, the median ventilation rate in both $ETCO_2$ groups was within the current recommended range; however, 103 of 234 (44%) events had event-level average ventilation rates exceeding 30 $min^{-1}$, the upper rate of current American Heart Association guideline recommendations.[7] In the end, the complicated relationship between ventilation rate and other ventilation parameters and $ETCO_2$ remains a fertile area for future scientific investigation.

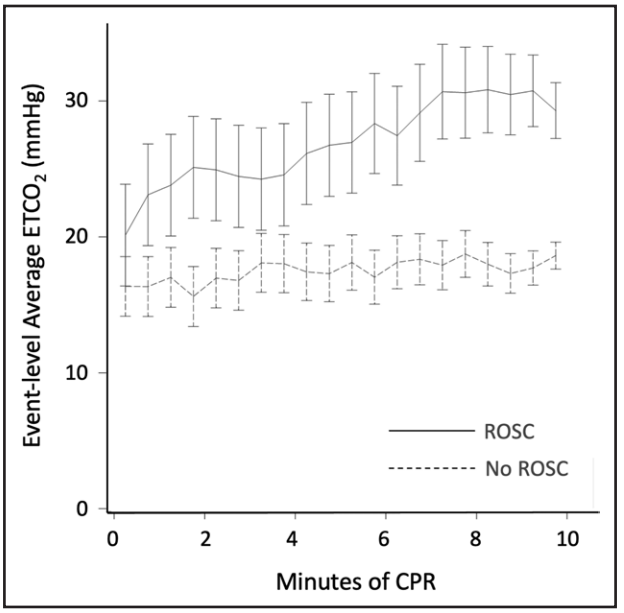


**Figure 3. Temporal relationship between $ETCO_2$ during the first 10 minutes of CPR and return of spontaneous circulation.**

ROSC=solid line; No ROSC=dotted line. Comparisons between patients with and without ROSC performed with mixed-effects linear regression model with an exponential temporal covariance structure to account for correlated observations. Average $ETCO_2$ during the first 10 minutes of CPR was higher in patients with ROSC than in patients without ROSC ($P<0.001$), as determined by the main effect for ROSC in the model. The change in $ETCO_2$ over time was greater in patients with ROSC than in patients without ROSC (effect size estimate, 0.74 [95% CI, 0.10–1.38] mm Hg; $P=0.023$), as determined by the interaction term between time (minutes) and ROSC. Error bars indicate SEM. CPR indicates cardiopulmonary resuscitation; $ETCO_2$, end-tidal carbon dioxide; and ROSC, return of spontaneous circulation.

This study has limitations. First, the observational study design precludes our ability to assign causation between higher $ETCO_2$ levels and improved outcomes. Yet, our findings provide support to suggest a more direct mechanistic relationship between higher $ETCO_2$ values and outcomes (eg, improved intra-arrest blood pressures and lower lactates after arrest). Second, these data were collected as part of the ICU-RESUS trial, which was conducted in a network of tertiary-care hospitals with a documented interest in CPR quality and physiology.[10,13] These characteristics, as well as the previously reported high-quality of CPR performed during the parent trial,[13] must be considered in generalizing our findings across more diverse care environments. Third, all included patients had invasive airways at the start of CPR, and as such, whether our findings can be extrapolated to patients without invasive airways remains an unanswered question. Fourth, we limited our primary evaluation to the first 10 minutes of CPR. We did not investigate the relationship between outcomes and $ETCO_2$ values after longer periods of CPR. However, we contend that by limiting our evaluation to the first 10 minutes, we are providing data that could lead to treatment adjustments that are more likely to affect resuscitation outcomes (eg, early activation of E-CPR rescue). Finally, due to known limitations in the study of continuous capnography during CPR (obstruction from tracheal tube secretions and disconnection for various clinical reasons), we report data from 28% of patients who were eligible for inclusion, raising concerns regarding selection bias. Although most of the patients included in this report are from the CPR-NOVA ancillary study, we did include the convenience sample of patients whose $ETCO_2$ waveforms were transmitted with arterial line waveforms before CPR-NOVA to achieve enrollment goals based on our a priori power calculation. Although there were several important patient characteristics that differed between groups, the absolute difference in survival between $ETCO_2$ groups was similar across enrollment periods.

## Conclusions

In this multicenter study, an $ETCO_2$ ≥20 mm Hg during CPR was associated with improved outcomes from pediatric in-hospital cardiopulmonary arrest, providing support for guideline recommendations that advise monitoring $ETCO_2$ during CPR.

## ARTICLE INFORMATION

Received August 8, 2023; accepted October 27, 2023.

### Affiliations

Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania (R.W.M., K.K.C., K.G., V.M.N., H.A.W., R.A.B., R.M.S.). Department of Pediatrics, University of Utah, Salt Lake City (R.W.R., C.A.P.). Villanova Center for Analytics of Dynamic Systems, Villanova University, PA (D.B., C.N.). Department of Pediatrics, Washington University School of Medicine, St. Louis, MO (S.H.F.). Department of Pediatrics, Children's Hospital of Michigan, Central Michigan University, Detroit (K.L.M., B.T.). Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (P.M.M.). Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus (R.M., A.R.Y.). Department of Pediatrics, Mattel Children's Hospital, University of California Los Angeles (N.S.).

### Sources of Funding

This study was supported by the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01HD049934, UG1HD049981, UG1HD049983, UG1HD050096, UG1HD063108, UG1HD083166, UG1HD083170, and UG1HD083171), the National Heart, Lung, and Blood Institute (R01HL131544, R01HL147616, and K23HL148541), and the Children's Hospital of Philadelphia Research Institute Resuscitation Science Center.

### Disclosures

None.

### Supplemental Material

Tables S1–S4

Figures S1–S3

Appendix: ICU-RESUS Investigators and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigators

## REFERENCES

1. Meaney PA, Bobrow BJ, Mancini ME, Christenson J, de Caen AR, Bhanji F, Abella BS, Kleinman ME, Edelson DP, Berg RA, et al; CPR Quality

Summit Investigators, the American Heart Association Emergency Cardiovascular Care Committee, and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Cardiopulmonary resuscitation quality: [corrected] improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. *Circulation*. 2013;128:417–435. doi: 10.1161/CIR.0b013e31829d8654

2. Trevino RP, Bisera J, Weil MH, Rackow EC, Grundler WG. End-tidal CO2 as a guide to successful cardiopulmonary resuscitation: a preliminary report. *Crit Care Med*. 1985;13:910–911. doi: 10.1097/00003246-198511000-00012
3. Sanders AB, Kern KB, Otto CW, Milander MM, Ewy GA. End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. A prognostic indicator for survival. *JAMA*. 1989;262:1347–1351.
4. Wayne MA, Levine RL, Miller CC. Use of end-tidal carbon dioxide to predict outcome in prehospital cardiac arrest. *Ann Emerg Med*. 1995;25:762–767. doi: 10.1016/s0196-0644(95)70204-0
5. Kern KB, Sanders AB, Voorhees WD, Babbs CF, Tacker WA, Ewy GA. Changes in expired end-tidal carbon dioxide during cardiopulmonary resuscitation in dogs: a prognostic guide for resuscitation efforts. *J Am Coll Cardiol*. 1989;13:1184–1189. doi: 10.1016/0735-1097(89)90282-9
6. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;337:301–306. doi: 10.1056/NEJM199707313370503
7. Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL Jr, Lasa JJ, Lavonas EJ, Levy A, Mahgoub M, et al; Pediatric Basic and Advanced Life Support Collaborators. Part 4: pediatric basic and advanced life support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142:S469–S523. doi: 10.1161/CIR.0000000000000901
8. Panchal AR, Bartos JA, Cabanas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, et al; Adult Basic and Advanced Life Support Writing Group. Part 3: Adult basic and advanced life support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142:S366–S468. doi: 10.1161/CIR.0000000000000916
9. Khera R, Tang Y, Girotra S, Nadkarni VM, Link MS, Raymond TT, Guerguerian AM, Berg RA, Chan PS; American Heart Association's Get With the Guidelines-Resuscitation Investigators. Pulselessness after initiation of cardiopulmonary resuscitation for bradycardia in hospitalized children. *Circulation*. 2019;140:370–378. doi: 10.1161/CIRCULATIONAHA.118.039048
10. Berg RA, Sutton RM, Reeder RW, Berger JT, Newth CJ, Carcillo JA, McQuillen PS, Meert KL, Yates AR, Harrison RE, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) PICqCPR (Pediatric Intensive Care Quality of Cardio-Pulmonary Resuscitation) Investigators. Association between diastolic blood pressure during pediatric in-hospital cardiopulmonary resuscitation and survival. *Circulation*. 2018;137:1784–1795. doi: 10.1161/CIRCULATIONAHA.117.032270
11. Sorcher JL, Hunt EA, Shaffner DH, O'Brien CE, Jeffers JM, Jones SI, Newton H, Duval-Arnould J. Association of end-tidal carbon dioxide levels during cardiopulmonary resuscitation with survival in a large paediatric cohort. *Resuscitation*. 2022;170:316–323. doi: 10.1016/j.resuscitation.2021.10.029
12. Berg RA, Reeder RW, Meert KL, Yates AR, Berger JT, Newth CJ, Carcillo JA, McQuillen PS, Harrison RE, Moler FW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) Pediatric Intensive Care Quality of Cardio-Pulmonary Resuscitation (PICqCPR) investigators. End-tidal carbon dioxide during pediatric in-hospital cardiopulmonary resuscitation. *Resuscitation*. 2018;133:173–179. doi: 10.1016/j.resuscitation.2018.08.013
13. Sutton RM, Wolfe HA, Reeder RW, Ahmed T, Bishop R, Bochkoris M, Burns C, Diddle JW, Federman M, Fernandez R, et al; ICU-RESUS and Eunice Kennedy Shriver National Institute of Child Health. 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. *JAMA*. 2022;327:934–945. doi: 10.1001/jama.2022.1738
14. Morgan RW, Berg RA, Reeder RW, Carpenter TC, Franzon D, Frazier AH, Graham K, Meert KL, Nadkarni VM, Naim MY, et al; ICU-RESUS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigator Groups. The physiologic response to epinephrine and pediatric cardiopulmonary resuscitation outcomes. *Crit Care*. 2023;27:105. doi: 10.1186/s13054-023-04399-5
15. Berg RA, Morgan RW, Reeder RW, Ahmed T, Bell MJ, Bishop R, Bochkoris M, Burns C, Carcillo JA, Carpenter TC, et al. Diastolic blood pressure threshold during pediatric cardiopulmonary resuscitation and survival outcomes: a multicenter validation study. *Crit Care Med*. 2023;51:91–102. doi: 10.1097/CCM.0000000000005715
16. Nolan JP, Berg RA, Andersen LW, Bhanji F, Chan PS, Donnino MW, Lim SH, Ma MH, Nadkarni VM, Starks MA, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A consensus report from a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). *Circulation*. 2019;140:e746–e757. doi: 10.1161/CIR.0000000000000710
17. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr*. 1992;121:68–74. doi: 10.1016/s0022-3476(05)82544-2
18. Topjian AA, Scholefield BR, Pinto NP, Fink EL, Buysse CMP, Haywood K, Maconochie I, Nadkarni VM, de Caen A, Escalante-Kanashiro R, et al. P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) in children: an advisory statement from the International Liaison Committee on Resuscitation. *Resuscitation*. 2021;162:351–364. doi: 10.1016/j.resuscitation.2021.01.023
19. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, Anand KJ, Carcillo J, Newth CJ, Harrison R, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Functional Status Scale: new pediatric outcome measure. *Pediatrics*. 2009;124:e18–e28. doi: 10.1542/peds.2008-1987
20. Pollack MM, Holubkov R, Funai T, Dean JM, Berger JT, Wessel DL, Meert K, Berg RA, Newth CJ, Harrison RE, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. The pediatric risk of mortality score: update 2015. *Pediatr Crit Care Med*. 2016;17:2–9. doi: 10.1097/PCC.0000000000000558
21. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11:234–238. doi: 10.1097/PCC.0b013e3181b806fc
22. Berg RA, Nadkarni VM, Clark AE, Moler F, Meert K, Harrison RE, Newth CJ, Sutton RM, Wessel DL, Berger JT, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808. doi: 10.1097/CCM.0000000000001484
23. Topjian AA, Clark AE, Casper TC, Berger JT, Schleien CL, Dean JM, Moler FW; Pediatric Emergency Care Applied Research Network. Early lactate elevations following resuscitation from pediatric cardiac arrest are associated with increased mortality*. *Pediatr Crit Care Med*. 2013;14:e380–e387. doi: 10.1097/PCC.0b013e3182976402
24. Fung FW, Topjian AA, Xiao R, Abend NS. Early EEG features for outcome prediction after cardiac arrest in children. *J Clin Neurophysiol*. 2019;36:349–357. doi: 10.1097/WNP.0000000000000591
25. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, Walsh AZ, Chang AC, Castaneda AR, Newburger JW, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*. 1995;92:2226–2235. doi: 10.1161/01.cir.92.8.2226
26. Weil MH, Bisera J, Trevino RP, Rackow EC. Cardiac output and end-tidal carbon dioxide. *Crit Care Med*. 1985;13:907–909. doi: 10.1097/00003246-198511000-00011
27. Gudipati CV, Weil MH, Bisera J, Deshmukh HG, Rackow EC. Expired carbon dioxide: a noninvasive monitor of cardiopulmonary resuscitation. *Circulation*. 1988;77:234–239. doi: 10.1161/01.cir.77.1.234
28. Ornato JP, Garnett AR, Glauser FL. Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med*. 1990;19:1104–1106. doi: 10.1016/s0196-0644(05)81512-4
29. Idris AH, Staples ED, O'Brien DJ, Melker RJ, Rush WJ, Del Duca KD, Falk JL. End-tidal carbon dioxide during extremely low cardiac output. *Ann Emerg Med*. 1994;23:568–572. doi: 10.1016/s0196-0644(94)70080-x
30. Callaham M, Barton C. Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. *Crit Care Med*. 1990;18:358–362. doi: 10.1097/00003246-199004000-00002
31. Cantineau JP, Lambert Y, Merckx P, Reynaud P, Porte F, Bertrand C, Duvaldestin P. End-tidal carbon dioxide during cardiopulmonary resuscitation in humans presenting mostly with asystole: a predictor of outcome. *Crit Care Med*. 1996;24:791–796. doi: 10.1097/00003246-199605000-00011

32. Ahrens T, Schallom L, Bettorf K, Ellner S, Hurt G, O'Mara V, Ludwig J, George W, Marino T, Shannon W. End-tidal carbon dioxide measurements as a prognostic indicator of outcome in cardiac arrest. *Am J Crit Care*. 2001;10:391–398.
33. Sheak KR, Wiebe DJ, Leary M, Babaeizadeh S, Yuen TC, Zive D, Owens PC, Edelson DP, Daya MR, Idris AH, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. *Resuscitation*. 2015;89:149–154. doi: 10.1016/j.resuscitation.2015.01.026
34. Hamrick JL, Hamrick JT, Lee JK, Lee BH, Koehler RC, Shaffner DH. Efficacy of chest compressions directed by end-tidal $CO_2$ feedback in a pediatric resuscitation model of basic life support. *J Am Heart Assoc*. 2014;3:e000450. doi: 10.1161/JAHA.113.000450
35. Hamrick JT, Hamrick JL, Bhalala U, Armstrong JS, Lee JH, Kulikowicz E, Lee JK, Kudchadkar SR, Koehler RC, Hunt EA, et al. End-tidal $CO_2$-guided chest compression delivery improves survival in a neonatal asphyxial cardiac arrest model. *Pediatr Crit Care Med*. 2017;18:e575–e584. doi: 10.1097/PCC.0000000000001299
36. Morgan RW, Kilbaugh TJ, Shoap W, Bratinov G, Lin Y, Hsieh TC, Nadkarni VM, Berg RA, Sutton RM; Pediatric Cardiac Arrest Survival Outcomes PiCASO Laboratory Investigators. A hemodynamic-directed approach to pediatric cardiopulmonary resuscitation (HD-CPR) improves survival. *Resuscitation*. 2017;111:41–47. doi: 10.1016/j.resuscitation.2016.11.018
37. Lautz AJ, Morgan RW, Karlsson M, Mavroudis CD, Ko TS, Licht DJ, Nadkarni VM, Berg RA, Sutton RM, Kilbaugh TJ. Hemodynamic-directed cardiopulmonary resuscitation improves neurologic outcomes and mitochondrial function in the heart and brain. *Crit Care Med*. 2019;47:e241–e249. doi: 10.1097/CCM.0000000000003620
38. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med*. 2004;32:S345–S351. doi: 10.1097/01.ccm.0000134335.46859.09
39. Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, Sparks CW, Conrad CJ, Provo TA, Lurie KG. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*. 2004;109:1960–1965. doi: 10.1161/01.CIR.0000126594.79136.61