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End-tidal carbon dioxide during pediatric in-hospital cardiopulmonary resuscitation☆

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ABSTRACT

Background: Based on laboratory cardiopulmonary resuscitation (CPR) investigations and limited adult data, the American Heart Association Consensus Statement on CPR Quality recommends titrating CPR performance to achieve end-tidal carbon dioxide (ETCO2) > 20 mmHg.

Aims: We prospectively evaluated whether ETCO2 > 20 mmHg during CPR was associated with survival to hospital discharge.

Methods: Children ≥37 weeks gestation in Collaborative Pediatric Critical Care Research Network intensive care units with chest compressions for ≥1 min and ETCO2 monitoring prior to and during CPR between July 1, 2013 and June 31, 2016 were included. ETCO2 and Utstein-style cardiac arrest data were collected. Multivariable Poisson regression models with robust error estimates were used to estimate relative risk of outcomes.

Results: Blinded investigators analyzed ETCO2 waveforms from 43 children. During CPR, the median ETCO2 was 23 mmHg [quartiles, 16 and 28 mmHg], median ventilation rate was 29 breaths/min [quartiles, 24 and 35 breaths/min], and median duration of CPR was 5 min [quartiles, 2 and 16 min]. Return of spontaneous circulation occurred after 71% of CPR events and 37% of patients survived to hospital discharge. For children with mean ETCO2 during CPR > 20 mmHg, the adjusted relative risk for survival was 0.92 (0.41, 2.08), p = 0.84.

Abbreviations: CPR, cardiopulmonary resuscitation; CPCCRN, Collaborative Pediatric Critical Care Research Network; PICqCPR study, Pediatric Intensive Care Quality of CPR study; DBP, diastolic blood pressure; ROSC, return of spontaneous circulation; ICU, intensive care unit; PCPC, Pediatric cerebral performance category; DCC, Data Coordinating Center

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The median mean ETCO2 among children who survived to hospital discharge was 20 mmHg [quartiles; 15, 28 mmHg] versus 23 mmHg [16, 28 mmHg] among non-survivors.
Conclusion: Mean ETCO2 > 20 mmHg during pediatric in-hospital CPR was not associated with survival to hospital discharge, and ETCO2 was not different in survivors versus non-survivors.

Introduction

Thousands of children receive cardiopulmonary resuscitation (CPR) for in-hospital cardiac arrests (IHCAs) annually and the primary determinant of survival is quality of CPR [1–3]. Therefore, optimal monitoring of CPR quality is a high priority. Based on animal data and limited adult clinical data, 2015 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation recommend: "it may be reasonable to use physiologic parameters when feasible to monitor and optimize CPR quality [4]." Consistent with this recommendation, observational data have established that survival to hospital discharge was 70% more likely when mean diastolic blood pressure (DBP) was ≥25 mmHg during CPR in infants and ≥30 mmHg in children ≥1 year old [5].

More than 95% of pediatric IHCAs in the US occur in intensive care units (ICU) [6]. Although many do not have invasive arterial blood pressure monitoring during CPR, another potential physiologic approach to assess CPR is quantitative capnometry [3,4,7]. Laboratory CPR studies indicate end-tidal carbon dioxide (ETCO2) during CPR is directly related to pulmonary blood flow and cardiac output, and is therefore associated with survival [3,4,7–12]. Adult investigations demonstrate that ETCO2 < 10 mmHg during CPR is associated with very high mortality rates [10–14], and ETCO2 > 20 mmHg is associated with improved outcomes [10–13,15].

These clinical observations and animal data support the AHA recommendation to titrate CPR performance to achieve ETCO2 > 20 mmHg in adults, and extrapolation to children despite lack of pediatric data [3,4]. To fill this pediatric knowledge gap, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) prospectively evaluated ETCO2 monitoring during pediatric CPR. We hypothesized that: 1) mean ETCO2 > 20 mmHg during CPR is associated with survival to hospital discharge and 2) mean ETCO2 < 10 mmHg during each minute of CPR would preclude ROSC.

Methods

The Pediatric Intensive Care Quality of CPR (PICqCPR) Study is a prospective multicenter cohort study of ICU CPR to assess associations of invasive blood pressure monitoring and quantitative capnography during CPR with outcomes [5]. The blood pressure component of this observational trial is published [5]. All children ≥37 weeks gestation and < 19 years old who received chest compressions for ≥1 min and quantitative capnography monitoring prior to and during CPR in a CPCCRN Pediatric ICU or Pediatric Cardiac ICU were eligible for the ETCO2 component. Patients were enrolled from eleven institutions between July 1, 2013 and June 30, 2016. Cardiac arrests were identified by a 24-h paging system and/or intense daily research coordinator screening. The project was approved with waiver of informed consent by Institutional Review Boards at every site and the University of Utah Data Coordinating Center (DCC).

Data, analytic methods, and study materials will be available to other researchers for purposes of reproducing results or replicating procedures. Study datasets will be publicly available through CPCCRN.org three years after study completion [16].

Inclusion criteria were patients with: 1) quantitative capnography prior to and during CPR with an invasive tracheal tube; 2) first compression of CPR captured on transmitted waveform data; 3) at least one minute of continuous ETCO2 waveforms; and 4) central venous pressure, respiratory plethysmography, arterial blood pressure or ECG artifact available on transmitted waveform data to allow determination of CPR starts and stops. Exclusion criteria were: 1) unable to determine ETCO2 (e.g., lack of capnography waveform because of obstruction from tracheal secretions or disconnection of ETCO2 monitor from tracheal tube) or 2) unable to determine when CPR started and stopped. Patients with hypoplastic left heart syndrome (pre-operative, status post Norwood procedure with modified Blalock-Taussig shunt, status post Norwood procedure with Sano modification, status post bidirectional Glenn [hemi-Fontan]) were also excluded a priori from the primary analyses because of confounding effects on ETCO2.

The primary hypothesis was: mean ETCO2 > 20 mmHg during CPR is associated with survival to hospital discharge. Only index (first) CPR events were evaluated for survival to hospital discharge [17]. Secondary hypotheses were: 1) mean ETCO2 > 20 mmHg during CPR is associated with ROSC; 2) mean ETCO2 < 10 mmHg during each minute of CPR precludes ROSC; and 3) mean ETCO2 during CPR is associated with ROSC and survival to hospital discharge.

We obtained Utstein-style cardiac arrest and CPR data [17], including: 1) patient factors, 2) arrest characteristics, and 3) outcome data. Pediatric Cerebral Performance Categories (PCPC) pre-arrest and at hospital discharge were documented. Survival to hospital discharge with favorable neurologic outcome was defined as PCPC 1–3 or no worse than pre-arrest PCPC [5,17,18]. Paucity of ETCO2 data during CPR in children precluded accurate sample size determination, so CPCCRN investigators chose to gather such data for 3 years.

Waveform analysis

For CPR events that met inclusion criteria, waveform data were printed from ICU central monitoring systems, de-identified, and transmitted and stored at the DCC. De-identified capnography waveforms were manually digitized and analyzed by Children's Hospital of Philadelphia investigators (PlotDigitizer; Version 2.0; University of South Alabama) who were blinded to clinical data and survival outcomes. ETCO2 was defined as the peak of each capnographic waveform (Supplementary Fig. 1). Capnography, arterial pressure, central venous pressure, left atrial pressure, ECG artifact and/or respiratory plethysmography tracings were used to determine start, stop and interruptions of CPR. Mean ETCO2 was determined for each minute epoch of CPR, and mean ETCO2 for each patient was average ETCO2 among one-minute epochs. For patients with < 10 min of CPR, mean ETCO2 was determined for minutes of CPR provided.

Statistical analysis

Patient and event characteristics were summarized using frequencies and percentages or median and quartiles. Differences between patients who did and did not survive to hospital discharge were examined using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for ordinal and continuous variables. All reported P-values are 2-sided and considered statistically significant when < 0.05. A multivariable Poisson regression model with robust error estimates was used to estimate relative risk (RR) of survival to hospital discharge and ROSC for mean ETCO2 > 20 mmHg over the first ten minutes of CPR [19]. Additional models assessed the association between mean ETCO2 as a continuous variable and these outcomes. As further sensitivity analyses, additional models evaluated associations of other potential ETCO2 targets (> 25 mmHg and > 30 mmHg) with outcomes. Because

mean ETCO2 data over 10 min could obscure adverse effects of especially low CPR quality and low ETCO2 throughout the entire 10 min of CPR, we also evaluated associations of mean ETCO2 < 10 mmHg, < 15 mmHg, or < 20 mmHg during each minute of CPR with outcomes. All models were adjusted for mean ventilation rate because of its association with ETCO2 during CPR [15]. Relative risks are presented with 95% confidence intervals (CIs). All analyses were performed using SAS software v9.4 (Cary, NC).

Results

All 55 CPR events in 49 patients with invasive tracheal tube capnometry and ≥1 min of chest compressions met inclusion criteria. After excluding 6 patients with hypoplastic left heart syndrome, we analyzed 48 CPR events among 43 patients. Pre-arrest patient characteristics are described in Table 1. Among 43 children, 60% were < 1 year old, 77% had respiratory insufficiency, 84% had hypotension, 56% had congenital heart disease, 35% were cardiac surgical patients (i.e., postoperative when CPR was performed), 54% had normal baseline PCPC scores and 28% had mildly abnormal baseline PCPC scores. Supplementary Table 1 shows univariable associations of pre-arrest characteristics with ROSC > 20 min for the 48 CPR events. Among pre-arrest characteristics, only illness category was associated with survival to hospital discharge.

Event characteristics are described in Table 2. Seventy two percent had arterial catheters and 53% had DBP data during CPR. Immediate causes of arrests were hypotension in 74%, respiratory decompensation in 28%, and arrhythmia in 14%. During CPR, median ETCO2 was 23 mmHg, median ventilation rate was 29 breaths/min and median chest compression fraction was 0.9. Median duration of CPR was 5 min; 72% received 1–15 min, 16% received 16–35 min, and 12% received > 35 min. Duration of CPR was ≤10 min for 65% of events. Lower survival rates were associated with longer duration of CPR, number of epinephrine doses, and sodium bicarbonate administration. Resuscitation in CICU compared to PICU was associated with survival to discharge (13/23 versus 3/20, P = 0.01). Supplementary Table 2 shows event characteristics for all 48 CPR events among these 43 children with similar findings.

Return of spontaneous circulation was attained in 34/48 (71%) CPR events, and 16/43 (37%) patients survived to hospital discharge. Two patients went on ECMO during CPR without ROSC and one after ROSC < 20 min. All 16 patients who survived to hospital discharge attained ROSC > 20 min and survived with favorable neurologic outcomes.

Table 3 shows associations of mean ETCO2 with survival to hospital discharge and ROSC. Mean ETCO2 > 20 mmHg was not associated with either outcome. Mean ETCO2 was not associated with either survival to discharge or ROSC. Further sensitivity analyses were unable to demonstrate an association between mean ETCO2 > 25 mmHg or > 30 mmHg and either outcome. There was also no association of ETCO2 with these survival outcomes when comparing patients with mean ETCO2 < 10 mmHg, < 15 mmHg, or < 20 mmHg during each minute of CPR versus patients having minutes with the respective higher mean ETCO2.

Among five patients with overall mean ETCO2 < 10 mmHg, three had mean ETCO2 < 10 mmHg during each one-minute epoch of CPR. One of the three was a 5 day old patient who attained ROSC and survived to hospital discharge despite a mean ETCO2 of 4 ± 1 mmHg during the first 10 min of CPR, and 9 mmHg during the last minute of CPR. That patient had a mean DBP during CPR of 39 ± 3 mmHg.

Table 4 and Supplementary Fig. 2 show the association of ETCO2 with DBP for 27 CPR events when both parameters were available. ETCO2 was not associated with DBP targets ≥25 mmHg during CPR in infants and ≥30 mmHg in children ≥1 year. Three events had mean DBP above these targets despite no minutes of ETCO2 > 20 mmHg, three met the DBP targets despite no minute of ETCO2 > 15 mmHg, and two met the targets despite no minute of ETCO2 > 10 mmHg.

Mean ETCO2 and associated outcomes were not demonstrably different among children with: bradycardia/pulses versus pulseless, bicarbonate administration during CPR, and open-chest CPR (Table 5).

Fig. 1 shows the relationship of ETCO2 with ventilation rate during 49 CPR events. Mean ETCO2 during CPR decreased by 3.6 mmHg (95% CI, 1.3–6.0) with each ventilation rate increase of 10 breaths/min.

Six children were excluded because they had unrepaired hypoplastic left heart syndrome (n = 1), Norwood repair with modified Blalock-Taussig shunt (n = 2), Norwood repair with Sano modification (n = 1), or bi-directional Glenn (n = 2). Three of these children survived to hospital discharge. Mean ETCO2 was 9, 24, and 21 mmHg among these three survivors compared with 8, 16, and 24 mmHg among the three hypoplastic left heart syndrome non-survivors.

Discussion

These prospective multi-center PICqCPR data do not support the hypothesis that mean ETCO2 > 20 mmHg during pediatric in-hospital CPR is associated with survival to hospital discharge. There was also no demonstrable association of mean ETCO2 with either survival to hospital discharge or ROSC. Although the power of this study was limited with only 48 CPR events among 43 children, we could not discern any signal suggesting an ETCO2 target during CPR to potentially optimize outcomes despite multiple sensitivity analyses. In addition,

Table 1
Pre-arrest Characteristics by Survival to hospital discharge.

		Survival to hospital discharge		
	Overall (N = 43)	Yes (N = 16)	No (N = 27)	P-value
Age				0.296*
< 1 month	9 (21%)	5 (31%)	4 (15%)	
1 month - < 1 year	17 (40%)	7 (44%)	10 (37%)	
1 year - < 8 years	13 (30%)	4 (25%)	9 (33%)	
8 years - < 19 years	4 (9%)	0 (0%)	4 (15%)	
Male	23 (53%)	9 (56%)	14 (52%)	1.000*
Race				0.261*
White	19 (44%)	8 (50%)	11 (41%)	
Black or African American	10 (23%)	2 (13%)	8 (30%)	
Other	3 (7%)	2 (13%)	1 (4%)	
Not Reported	11 (26%)	4 (25%)	7 (26%)	
Preexisting conditions				
Respiratory insufficiency	33 (77%)	11 (69%)	22 (81%)	0.460*
Hypotension	36 (84%)	13 (81%)	23 (85%)	1.000*
Congestive heart failure	6 (14%)	3 (19%)	3 (11%)	0.655*
Pneumonia	3 (7%)	1 (6%)	2 (7%)	1.000*
Sepsis	6 (14%)	3 (19%)	3 (11%)	0.655*
Renal insufficiency	9 (21%)	3 (19%)	6 (22%)	1.000*
Malignancy	1 (2%)	0 (0%)	1 (4%)	1.000*
Congenital heart disease	24 (56%)	12 (75%)	12 (44%)	0.064*
Illness Category				0.018*
Surgical cardiac	15 (35%)	10 (63%)	5 (19%)	
Medical cardiac	13 (30%)	2 (13%)	11 (41%)	
Surgical non-cardiac	3 (7%)	0 (0%)	3 (11%)	
Medical non-cardiac	12 (28%)	4 (25%)	8 (30%)	
Baseline Pediatric Cerebral Performance Category				0.208†
Normal	23 (53%)	10 (63%)	13 (48%)	
Mild disability	12 (28%)	5 (31%)	7 (26%)	
Moderate disability	6 (14%)	1 (6%)	5 (19%)	
Severe disability	1 (2%)	0 (0%)	1 (4%)	
Coma/vegetative state	1 (2%)	0 (0%)	1 (4%)	
Baseline functional status scale	6.0 [6.0, 9.0]	7.0 [6.0, 9.0]	6.0 [6.0, 10.0]	0.377†

* Fisher's exact test.
† Wilcoxon rank-sum test.

Table 2
Event Characteristics by Survival to hospital discharge.

	Overall (N = 43)	Survival to hospital discharge: Yes (N = 16)	Survival to hospital discharge: No (N = 27)	P-value
Mean ETCO2 (mmHg) over the first ten minutes	22.4 [15.1, 27.6]	20.1 [13.3, 27.6]	23.1 [16.0, 27.6]	0.522*
Mean ETCO2 over the first ten minutes < 10 mmHg	5 (12%)	1 (6%)	4 (15%)	0.635†
All ETCO2 < 10 mmHg	3 (7%)	1 (6%)	2 (7%)	1.000†
Mean Ventilation Rate (breaths/min) over the first ten minutes	29.9 [23.4, 35.6]	32.0 [29.1, 37.8]	26.9 [20.2, 35.6]	0.055*
Chest compression fraction	0.9 [0.9, 1.0]	0.9 [0.9, 0.9]	0.9 [0.9, 1.0]	0.195*
Location of CPR Event				0.010†
PICU	20 (47%)	3 (19%)	17 (63%)	
CICU	23 (53%)	13 (81%)	10 (37%)	
Immediate cause				
Hypotension	32 (74%)	13 (81%)	19 (70%)	0.494†
Respiratory decompensation	12 (28%)	3 (19%)	9 (33%)	0.484†
Arrhythmia	6 (14%)	1 (6%)	5 (19%)	0.386†
First documented rhythm at time CPR initiated				0.041†
Asystole/PEA	7 (16%)	0 (0%)	7 (26%)	
VF/VT	4 (9%)	1 (6%)	3 (11%)	
Bradycardia with pulses	32 (74%)	15 (94%)	17 (63%)	
Duration of CPR (minutes)	5.0 [2.0, 22.0]	2.5 [1.5, 5.0]	11.0 [5.0, 28.0]	0.001*
Duration of CPR (minutes) category				0.015*
1–15	31 (72%)	15 (94%)	16 (59%)	
16–35	7 (16%)	1 (6%)	6 (22%)	
> 35	5 (12%)	0 (0%)	5 (19%)	
Interventions in place				
Vascular access	30 (70%)	9 (56%)	21 (78%)	0.178†
Arterial catheter	31 (72%)	12 (75%)	19 (70%)	1.000†
Central venous catheter	36 (84%)	16 (100%)	20 (74%)	0.035†
Vasoactive infusion	33 (77%)	12 (75%)	21 (78%)	1.000†
Time[a]				0.080†
Weekday	24 (56%)	11 (69%)	13 (48%)	
Weeknight	11 (26%)	1 (6%)	10 (37%)	
Weekend	8 (19%)	4 (25%)	4 (15%)	
Pharmacologic interventions				
Epinephrine	41 (95%)	16 (100%)	25 (93%)	0.522†
# of doses (when used)	2.0 [1.0, 4.0]	1.0 [1.0, 2.0]	3.0 [1.0, 6.0]	0.005*,‡
Calcium	16 (37%)	5 (31%)	11 (41%)	0.745†
Sodium bicarbonate	23 (53%)	4 (25%)	19 (70%)	0.005†

* Wilcoxon rank-sum test.
† Fisher's exact test.
‡ The comparison of # of epinephrine doses is based only on index events for which epinephrine was used.
[a] Weekdays are Mon–Fri, 07:00–22:59; weeknights are Mon–Fri, 23:00–06:59; and weekends are Sat–Sun.

ETCO2 < 10 mmHg during each minute of CPR was not uniformly associated with poor outcomes. These data provide a potential physiologic basis to explain why ETCO2 was not associated with survival outcomes in this cohort, since ETCO2 was also not associated with the primary physiologic determinant of pediatric cardiac arrest survival: DBP during CPR ≥ 25 mmHg in infants and ≥30 mmHg in children ≥1 year old [5].

The overall goal of the PICqCPR study was to evaluate potential physiologic targets during CPR to inform pediatric CPR guidelines. Previously published PICqCPR data established that survival to hospital discharge was 70% more likely when infants attained mean DBP ≥ 25 mmHg and children ≥1 year old attained mean DBP ≥ 30 mmHg [5]. These findings are consistent with animal studies demonstrating that survival following CPR depends on adequate myocardial blood flow during CPR, and the primary determinant of myocardial blood flow is coronary perfusion pressure (DBP minus right atrial diastolic pressure) [20–23].

In this study, there was no demonstrable association of mean ETCO2 > 20 mmHg during the first 10 min of CPR with either survival to hospital discharge or ROSC. Therefore, these findings do not support the recommendation to maintain ETCO2 > 20 mmHg during CPR [3]. To further explore potential ETCO2 targets, we compared outcomes among children with mean ETCO2 > 25 mmHg or > 30 mmHg to those with lower ETCO2. Disappointingly, we were unable to demonstrate differences in survival to hospital discharge or ROSC. Because of concerns that mean ETCO2 data over 10 min could obscure an adverse effect of especially low CPR quality and low ETCO2 throughout the entire 10 min of CPR, we also compared patients with mean ETCO2 < 10 mmHg, < 15 mmHg, or < 20 mmHg during each minute of CPR versus patients having minutes with higher mean ETCO2. Again, none of these ETCO2 groupings were associated with ROSC or survival to hospital discharge.

In contrast to our findings, most adult studies have shown higher ETCO2 among patients who attained ROSC than those who did not [10–12,15]. A recent observational series of 583 adults also showed that chest compression depth was associated with ETCO2 and mean ETCO2 was higher among survivors [15]. Nevertheless, recent meta-analyses of adult ETCO2 CPR studies highlight multiple concerns, including variable times during CPR when ETCO2 was measured, substantial overlap in ETCO2 among survivors and non-survivors, and study designs that did not preclude the possibility that higher ETCO2 in survivors may have in part simply reflected attainment of unrecognized ROSC [11,12,24]. Nearly all of these adult studies have focused on out-of-hospital cardiac arrests and may not be generalizable to IHCAs [10–12].

Characteristics of the PICqCPR ETCO2 study population provide potential physiologic reasons for differences in findings compared with adult data. PICqCPR patients were all critically ill children, and their IHCAs were precipitated by acute hypotension in 75% and acute respiratory decompensation in 25%. Although laboratory studies have established that ETCO2 is associated with pulmonary blood flow and cardiac output during CPR, ETCO2 during CPR is also affected by minute ventilation, sodium bicarbonate administration, and ventilation-perfusion mismatch [4,5,11,24–26]. In this study, ETCO2 was 3.6 mmHg lower on average for every 10 breaths/min increase in ventilation rate, similar to the 3.0 mmHg decrease for every 10 breaths/min during adult CPR [15]. Although this ETCO2 decrease seems to be small, 8% of events had ventilation rates > 50/min. ETCO2 would be 14 mmHg lower with 50 breaths/min instead of 10 breaths/min. In addition, 52% received sodium bicarbonate which can increase CO2 burden and thereby increase ETCO2 without any change in cardiac output or CPR quality [4,25]. Epinephrine was provided to 96%, and is known to decrease ETCO2 during CPR because of increased ventilation-perfusion mismatching [4,25,26]. These issues are common among critically ill children with IHCAs, perhaps undermining the value of ETCO2 as a physiologic monitor during pediatric in-hospital CPR.

Our analytic technique minimized inclusion of ETCO2 measurements post-ROSC through waveform by waveform delineation of ETCO2 and frequent availability of simultaneous invasive BP waveforms. Among children with both invasive DBP and ETCO2 monitoring, there was no association of ETCO2 with DBP targets known to be associated with improved survival rates. This lack of association of ETCO2 with DBP targets provides a potential physiologic explanation for lack of association of ETCO2 with survival.

Numerous adult out-of-hospital cardiac arrest investigations have shown that persistence of ETCO2 < 10 mmHg is associated with very low likelihood of survival [10–14]. Among five children in this study cohort with mean ETCO2 < 10 mmHg and three children with ETCO2 < 10 mmHg during each minute of CPR, one survived to hospital discharge. In addition, another child excluded from the primary

Table 3
Association of ETCO2 with ROSC and Survival to Hospital Discharge.

	ROSC ≥ 20 min		Survival to Hospital Discharge	
	Relative Risk (95% CI)	P-value	Relative Risk (95% CI)	P-value
Mean ETCO2 (mmHg) over the first ten minutes	1.01 (0.99, 1.02)	0.605	0.99 (0.95, 1.04)	0.783
Mean ETCO2 over the first ten minutes > 20 mmHg	1.32 (0.89, 1.95)	0.162	0.92 (0.41, 2.08)	0.839
Mean ETCO2 over the first ten minutes > 25 mmHg	1.02 (0.72, 1.45)	0.899	0.86 (0.36, 2.06)	0.728
Mean ETCO2 over the first ten minutes > 30 mmHg	1.05 (0.64, 1.74)	0.848	0.86 (0.24, 3.06)	0.818
Mean ETCO2 categories		0.237		0.988
< 20 mmHg	Reference		Reference	
20 - < 25 mmHg	1.56 (1.01, 2.42)		1.03 (0.36, 2.93)	
25 - < 30 mmHg	1.17 (0.72, 1.92)		0.88 (0.29, 2.63)	
> 30 mmHg	1.26 (0.73, 2.19)		0.84 (0.22, 3.20)	
All ETCO2 < 10 mmHg	0.71 (0.25, 2.00)	0.520	0.60 (0.11, 3.39)	0.562
All ETCO2 < 15 mmHg	0.88 (0.55, 1.41)	0.593	1.17 (0.45, 3.02)	0.748
All ETCO2 < 20 mmHg	1.03 (0.70, 1.50)	0.886	1.28 (0.55, 3.00)	0.563

Results are based on multivariable Poisson regression models with robust error estimates adjusting for mean ventilation rate (breaths/min) over the first ten minutes.

Table 4
Association of ETCO2 with Diastolic Blood Pressure Target Attainment.

		Average DBP within Target		
	Overall (N = 27)	Yes (N = 16)	No (N = 11)	P-value
Median [IQR][a] ETCO2 (mmHg) over the first ten minutes	22.4 [15.1, 27.6]	23.3 [17.8, 30.7]	20.2 [11.1, 26.9]	0.416*
Median [IQR][a] ETCO2 (mmHg) over the first three minutes	21.1 [13.1, 27.6]	20.8 [14.0, 29.4]	21.4 [11.6, 27.5]	0.941*
Median [IQR][a] ETCO2 (mmHg) over minutes 5–10	22.4 [12.0, 30.6] (N = 13)[b]	27.2 [16.4, 33.2] (N = 9)[b]	13.5 [8.6, 21.9] (N = 4)[b]	0.316*
Median [IQR][a] ETCO2 (mmHg) over the last 5 min	22.4 [14.9, 30.6]	24.8 [18.0, 32.6]	20.2 [11.0, 27.5]	0.312*
All ETCO2 < 10 mmHg	2 (7%)	2 (13%)	0 (0%)	0.499†
All ETCO2 < 15 mmHg	5 (19%)	3 (19%)	2 (18%)	1.000†
All ETCO2 < 20 mmHg	7 (26%)	3 (19%)	4 (36%)	0.391†

* Wilcoxon rank-sum test.
† Fisher's exact test.
[a] Median refers to median of one-minute epochs of ETCO2 and IQR refers to interquartile range. Medians are analyzed because the distributions of data are non-normative and are assessed with non-parametric statistics.
[b] The n is smaller for minutes 5–10 because many of the patients had ROSC before the full 10 min of CPR.

Table 5
Sub-group association of ETCO2 with Survival to hospital discharge.

		Survival to hospital discharge		
Sub-groups	Overall	No	Yes	P-value
First documented rhythm				
Bradycardia with pulses	20.1 [13.2, 27.6] (N = 32)	21.4 [15.0, 26.3] (N = 17)	19.7 [11.5, 27.7] (N = 15)	0.940*
Pulseless (PEA/asystole/VF)[a]	23.4 [18.0, 36.0] (N = 11)	23.7 [18.0, 36.0] (N = 10)	23.4 [23.4, 23.4] (N = 1)	1.000*
Sodium Bicarbonate during CPR				
Yes	23.0 [16.0, 29.3] (N = 23)	23.1 [16.4, 29.9] (N = 19)	15.1 [7.4, 24.5] (N = 4)	0.274*
No	21.4 [15.1, 27.4] N = 20)	20.6 [13.1, 26.8] (N = 8)	21.4 [15.7, 27.6] (N = 12)	0.728*
Open Chest CPR	19.7 [17.9, 21.4] (N = 5)	21.4 [5.0, 40.0] (N = 3)	18.8 [17.9, 19.7] (N = 2)	0.773*

* Wilcoxon rank-sum test.
[a] PEA refers to Pulseless Electrical Activity and VF to Ventricular Fibrillation.

analysis because of hypoplastic left heart syndrome also survived to hospital discharge despite mean ETCO2 during CPR < 10 mmHg. These limited data raise concerns about terminating CPR in children with IHCA based solely on ETCO2 < 10 mmHg. Although the most compelling adult data show that patients with ETCO2 < 10 mmHg after 20 min of CPR very rarely attain ROSC [10–12,14], PICqCPR data only evaluated ETCO2 during the first 10 min of CPR.

Generalizability of findings from this multicenter study should be cautiously interpreted in light of several limitations. Guidelines were not routinely followed: most received sodium bicarbonate during CPR and had ventilation rates higher than recommended. Unlike adult and animal studies, most children received CPR before pulselessness and five had open-chest CPR. Nevertheless, mean ETCO2 and associated outcomes were not demonstrably different among children with: bradycardia/pulses versus pulseless, bicarbonate administration during CPR, and open-chest CPR (Table 5). Data regarding cardiac anatomy and physiology, including potential shunt physiology, are not available for cardiac patients except for the excluded hypoplastic left heart syndrome group. Importantly, power to demonstrate associations between ETCO2 and outcomes was limited with only 43 children. Nevertheless, there was no discernible signal suggesting a potential ETCO2 to target during CPR despite multiple analyses. Survival rates following CPR depend on many other factors besides CPR quality, including underlying causes of the cardiac arrest, co-morbidities and the pre-arrest and post-arrest care. Yet DBP during CPR is associated with survival to discharge despite these issues [5]. CPCCRN sites are all large academic pediatric ICUs, and the quality of care provided before and after cardiac arrests may differ from other institutions. For example, 16 of the 27 CPR events with simultaneous measurement of blood pressure and ETCO2 during CPR had mean DBP ≥ 25 mmHg for infants or ≥ 30 mmHg for children ≥ 1 year old. Perhaps an association between ETCO2 and outcomes could be demonstrable in a cohort with less effective CPR.

Conclusions

This multicenter prospective observational study does not support the hypotheses that children with mean ETCO2 > 20 mmHg during in-hospital CPR are more likely to survive to hospital discharge or attain ROSC. Further studies are necessary to clarify the value of ETCO2 monitoring during pediatric CPR.

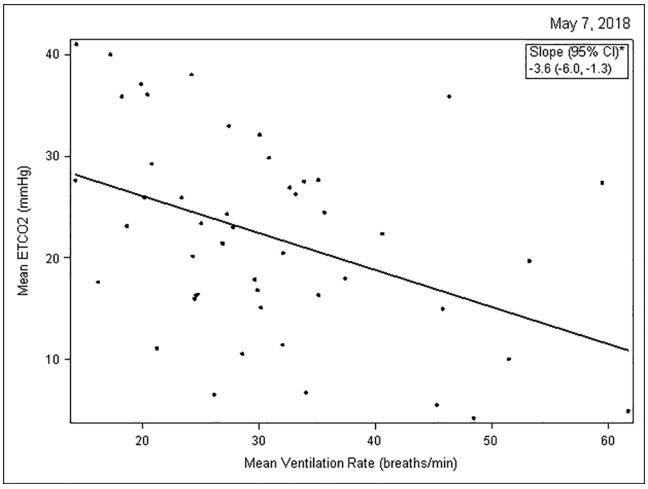

Fig. 1. Mean ETCO2 (mmHg) vs Mean Ventilation Rate (breaths/min). Scatterplot of mean ETCO2 versus mean ventilation rate during CPR. The slope reveals a decrease in ETCO2 by 3.6 mmHg for every 10 breaths in ventilation rate with 95% CI (95% confidence interval) of 1.3 mmHg–6.0 mmHg for every 10 breaths.

Conflicts of interest

None.

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All of the listed authors satisfy the ICMJE authorship criteria and have access to the data. Neither this manuscript nor one with substantially similar content has been published or is being considered for publication elsewhere. We agree to provide access to our data.

Appendix A

CPCCRN PICqCPR Investigators

In addition to the listed collaborators, the following PICqCPR Investigators were involved in study design and/or data acquisition: Athena F. Zuppa M.D. M.S.C.E.,[1] Katherine Graham B.S.,[1] Carolann Twelves R.N,[1] William Landis B.S.E.,[1] Mary Ann DiLiberto R.N.,[1] Elyse Tomanio R.N.,[2] Jeni Kwok J.D.,[3] Michael J. Bell M.D.,[2,4] Alan Abraham M.B.A.,[4] Anil Sapru,[5, 6] Mustafa F. Alkhouli, BA,[5] Sabrina Heidemann M.D.,[7] Ann Pawluszka R.N.,[7] Mark W. Hall M.D.,[8] Lisa Steele R.N.,[8] Thomas P. Shanley M.D.,[9] Monica Weber R.N.,[9] Heidi J. Dalton M.D.,[1◦] Aimee La Bell R.N.,[1◦] Peter M. Mourani M.D.,[11] Kathryn Malone R.N.,[11] Russell Telford MS,[12] Christopher Locandro MS,[12] Whitney Coleman,[12] Alecia Peterson MS,[12] Julie Thelen,[12] Allan Doctor M.D.,[13] Tammara L. Jenkins, M.S.N. R.N.,[14] Robert F. Tamburro, M.D., [14]

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2018.08.013.

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