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Experimental paper

Use of an end-tidal carbon dioxide-guided algorithm during cardiopulmonary resuscitation improves short-term survival in paediatric swine

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Abstract

Aim: To evaluate an algorithm that uses an end-tidal carbon dioxide ($ETCO_2$) target of $\geq$ 30 torr to guide specific changes in chest compression rate and epinephrine administration during cardiopulmonary resuscitation (CPR) in paediatric swine.

Methods: Swine underwent asphyxial cardiac arrest followed by resuscitation with either standard or $ETCO_2$-guided algorithm CPR. The standard group received chest compressions at a rate of 100/min and epinephrine every 4 min during advanced life support consistent with the American Heart Association paediatric resuscitation guidelines. In the $ETCO_2$-guided algorithm group, chest compression rate was increased by 10 compressions/min for every minute that the $ETCO_2$ was < 30 torr, and the epinephrine administration interval was decreased to every 2 min if the $ETCO_2$ remained < 30 torr. Short-term survival and physiologic data during active resuscitation were compared.

Results: Short-term survival was significantly greater in the $ETCO_2$-guided algorithm CPR group than in the standard CPR group (16/28 [57.1%] versus 4/28 [14.3%]; $p = 0.002$). Additionally, the algorithm group had higher predicted mean $ETCO_2$, chest compression rate, diastolic and mean arterial pressure, and myocardial perfusion pressure throughout resuscitation. Swine in the algorithm group also exhibited significantly greater improvement in diastolic and mean arterial pressure and cerebral perfusion pressure after the first dose of epinephrine than did those in the standard group. Incidence of resuscitation-related injuries was similar in the two groups.

Conclusions: Use of a resuscitation algorithm with stepwise guidance for changes in the chest compression rate and epinephrine administration interval based on a goal $ETCO_2$ level improved survival and intra-arrest hemodynamics in this porcine cardiac arrest model.

Keywords: Physiologic feedback, Personalized resuscitation, Paediatric cardiac arrest, End-tidal carbon dioxide, Chest compression rate, Resuscitation algorithms

Introduction

Current paediatric cardiopulmonary resuscitation (CPR) guidelines provide uniform recommendations for resuscitative efforts such as chest compression rate (CCR), chest compression depth, and frequency of vasoactive medication administration, despite variations in the aetiology of cardiac arrest or in patient size.[1] Titration of the CCR or the epinephrine administration interval (EAI) based on a physiologic response to CPR could individualize and optimize resuscitation efforts.[2,3] A consensus statement from the American Heart Association (AHA) recommends that resuscitative efforts be individualized based on target values for coronary perfusion pressure, arte-

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https://doi.org/10.1016/j.resplu.2021.100174
Received 14 June 2021; Received in revised form 28 August 2021; Accepted 28 September 2021
Available online xxxx

rial diastolic blood pressure (DBP), or end-tidal carbon dioxide ($ETCO_2$).[4] Preclinical studies have shown improved survival and haemodynamics with use of a systolic blood pressure target to optimize chest compression depth and a coronary perfusion pressure target to guide the dosing interval of vasoactive medications.[5–9] However, we lack specific algorithms to effectively titrate resuscitative efforts based on a particular physiologic target.

End-tidal carbon dioxide is a good candidate for a physiologic target when performing CPR. When ventilation is constant during CPR, the $ETCO_2$ level represents pulmonary blood flow and is a surrogate for cardiac output.[10,11] Survivors of cardiac arrest have higher intra-arrest $ETCO_2$ levels, and $ETCO_2$ levels < 10 torr are associated with non-survival.[12–14] Quantitative $ETCO_2$ monitors are common at intubating locations and available at arrest locations as portable monitors or incorporated in defibrillator models. $ETCO_2$ can be measured with or without an advanced airway.[15] Our group has previously used $ETCO_2$-guided chest compression delivery in neonatal swine and shown improved survival over standard CPR.[16–18] In those studies, an increased CCR achieved higher $ETCO_2$ values during CPR. The current study evaluates short-term survival with a new CPR algorithm that uses an $ETCO_2$ target value of $\geq$ 30 torr to guide changes in the CCR and the EAI.

Methods

Study design

This was a preclinical, prospective, randomized controlled trial comparing two resuscitation strategies.

Animal preparation

The protocol was approved by the Johns Hopkins University Animal Care and Use Committee and complied with the National Research Council's *Guide for the Care and Use of Laboratory Animals*.[19] Fifty-six, 7 to 14-day-old, 3 to 4 kg male Yorkshire piglets were obtained from a single breeder. Animal preparation has been described previously.[16,18] Piglets were anesthetized with isoflurane, nitrous oxide, and oxygen via nose cone. A cuffed tracheal tube was secured via tracheostomy. A femoral artery catheter was advanced to the mid-thoracic aorta for hemodynamic monitoring and arterial blood gas measurements. A femoral venous catheter was advanced to the mid-thoracic vena cava for hemodynamic monitoring and for administration of sedation during surgery and epinephrine during resuscitation. A sagittal sinus catheter was placed to measure intracranial pressure (ICP) and to sample venous blood. Pressure-controlled mechanical ventilation was adjusted to maintain $PaCO_2$ at 35–45 torr using a rate of 20 breaths/min. The FiO_2 was decreased from 0.30 to 0.21 for 10 min before protocol initiation. After surgery, isoflurane and nitrous oxide were discontinued, and fentanyl and vecuronium were administered. Once the protocol began, no additional anaesthetics were administered.

Experimental protocol

Asphyxial cardiac arrest was induced by clamping the tracheal tube for 11, 14, 17, or 20 min to produce variable durations of cardiac arrest. Most animals lost pulse pressure in the thoracic aorta between minutes 10 and 11 of asphyxia. No-flow intervals therefore approximated 1–10 min depending on the duration of asphyxia. Following asphyxia, we initiated paediatric basic life support (BLS) with chest compressions and mechanical ventilation. Pressure-controlled mechanical ventilation was resumed at the pre-arrest pressures and rate but with an FiO_2 of 1.0. The continuation of ventilation at 20 breaths/min was higher than recommended[20] but prior work showed that during resuscitation the rate is offset by reduced tidal volumes caused by chest compression when using pressure-controlled ventilation.[21] After 6 min of BLS, we initiated advanced life support (ALS) using epinephrine (300 mcg) and defibrillation (30 joules). Physiologic data were recorded before asphyxia and every 30 sec during asphyxia and resuscitation. During asphyxia and resuscitation, we monitored the myocardial perfusion pressure (MPP; diastolic central arterial pressure minus diastolic central venous pressure), the cerebral perfusion pressure (CPP; mean arterial pressure (MAP) minus mean ICP), and the systemic perfusion pressure (SPP; MAP minus mean central venous pressure).

Piglets were randomized to either standard CPR or algorithm CPR targeting an $ETCO_2$ level $\geq$ 30 torr. The $ETCO_2$ goal was based on prior work, which showed that survival after asphyxia was associated with a mean $ETCO_2 \geq 30$ torr during resuscitation[16] and unpublished work showing that using $ETCO_2$ values of $\geq$ 25 torr was less predictive of survival. In both groups, chest compressions were performed with a two-thumb-encircling hands technique, and compressors switched every 2 min. An external depth guide set at 1/3 the anteroposterior diameter was used in both groups (please see description of this device in previous study[18]). Additionally, we used a CPR coach[22] to monitor the quality of CPR and to ensure full release between compressions in real time in both groups. The standard group received a CCR of 100/min and an EAI of 4 min.[1] In the $ETCO_2$-guided algorithm group, the CCR started at 100/min and the CCR was increased by 10/min for every minute that $ETCO_2$ was < 30 torr to a maximum of 150/min (Table 1). Additionally, during ALS, the EAI decreased to every 2 min if the $ETCO_2$ remained <30 torr. Both groups included defibrillation as needed during the compressor changes. An arterial blood gas was drawn at 8 min of CPR. Resuscitation continued in both groups until either return of spontaneous circulation (ROSC) or 20 min of CPR, after which the experiment was terminated. The primary outcome, short-term survival, was defined as ROSC sustained for 20 min with only fluid administration with a MAP >50 mmHg. Autopsies were performed on all animals to evaluate for resuscitation-related injuries.

Statistical analysis

Normality of continuous variables was assessed with the Shapiro-Wilk test. Physiologic data are presented as mean ± standard error of the mean (SEM) for normally distributed data and median with interquartile ranges for non-normally distributed data. Differences in baseline continuous variables were assessed by Student's t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Survival and autopsy findings were compared between the standard and algorithm CPR groups by Fisher's exact test. Sample sizes were estimated from the observed rates of ROSC in our prior study.[16]

To account for repeated measurements over time within the same animal, we compared physiologic parameters between the two resuscitation groups and between survivors and non-survivors using a linear mixed-effects model with a random intercept for each animal. We used the physiologic measurement as the outcome and used the group (CPR group or survival group), time, and interaction between them as predictor variables. Time was treated as a categorical variable by 30-sec intervals because of the nonlinear relationship between time and outcome. Models were fit using restricted

Table 1 – The end-tidal CO_2-guided algorithm for cardiopulmonary resuscitation.*

Resuscitation Duration (min)	Change in Chest Compression Rate (compressions/min)		Epinephrine Administration	
	$ETCO_2$ ≥30	$ETCO_2$ <30	$ETCO_2$ ≥30	$ETCO_2$ <30
0	100	100	Basic Life Support	
1	None	↑ 10		
2	None	↑ 10		
3	None	↑ 10		
4	None	↑ 10		
5	None	↑ 10		
6	None	↑ 10 (max 150)	Yes	Yes
7	None	↑ 10 (max 150)		
8	None	↑ 10 (max 150)	No	Yes
9	None	↑ 10 (max 150)		
10	None	↑ 10 (max 150)	Yes	Yes
11	None	↑ 10 (max 150)		
12	None	↑ 10 (max 150)	No	Yes
13	None	↑ 10 (max 150)		
14	None	↑ 10 (max 150)	Yes	Yes
15	None	↑ 10 (max 150)		
16	None	↑ 10 (max 150)	No	Yes
17	None	↑ 10 (max 150)		
18	None	↑ 10 (max 150)	Yes	Yes
19	None	↑ 10 (max 150)		
20	None	↑ 10 (max 150)	No	Yes

$ETCO_2$, end-tidal carbon dioxide.

* Six minutes of basic life support precede 14 minutes of advanced life support. Modifications were made to the chest compression rate and epinephrine administration interval if the $ETCO_2$ was < 30 torr during the preceding minute. The maximum allowable chest compression rate was 150 compressions/minute and the maximal epinephrine administration interval was every 2 minutes. Interventions were stopped if return of spontaneous circulation was achieved.

maximum-likelihood estimation. When the interaction between time and group was not significant, a model with only main effects for time and group was used. Only physiologic values during active resuscitation were analysed and those obtained after ROSC were excluded. For $ETCO_2$ measurements, we excluded the first minute of resuscitation to account for washout of $ETCO_2$ from asphyxia based on our experience and similar models.[23] Predicted means, predicted differences in means between the two groups, and 95% confidence inter-

Table 2 – Baseline physiologic parameters and asphyxial injury in the standard and $ETCO_2$-guided algorithm cardiopulmonary resuscitation groups.

Parameter	Standard CPR (n = 28)	Algorithm CPR (n = 28)	*p*
Weight, kg	3.80 ± 0.06	3.71 ± 0.07	0.289
HR, beats/min	246 ± 6	233 ± 9	0.216
MAP, mmHg	85 ± 2	88 ± 2	0.424
DBP, mmHg	71 ± 2	74 ± 2	0.465
ICP, mmHg	10 (8, 12)	10 (8, 12)	0.790
SPP, mmHg	78 ± 2	81 ± 3	0.311
MPP, mmHg	66 (54,73)	66 (57, 83)	0.318
CPP, mmHg	75 ± 2	77 ± 3	0.479
$ETCO_2$, torr	48 (47, 52)	50 (48, 53)	0.370
Hb, g/dL	10.0 ± 0.2	10.4 ± 0.3	0.203
Arterial blood gas, baseline			
pH	7.37 ± 0.01	7.38 ± 0.01	0.610
$PaCO_2$, torr	41 ± 1	40 ± 1	0.565
PaO_2, torr	108 ± 8	114 ± 7	0.595
Base deficit, mEq/L	−1.2 ± 0.5	−1.5 ± 0.5	0.662
Arterial blood gas, last min of asphyxia			
pH	6.83 ± 0.02	6.84 ± 0.02	0.715
$PaCO_2$, torr	118 ± 4	119 ± 4	0.879
PaO_2, torr	12 (7, 19)	18 (9, 24)	0.172
Base deficit, mEq/L	−14.1 ± 0.7	−13.7 ± 0.8	0.613

Data were collected prior to asphyxia, unless indicated, and are presented as mean ± standard error of the mean or as median (interquartile range).
CPR, cardiopulmonary resuscitation; CPP, cerebral perfusion pressure; DBP, diastolic blood pressure; $ETCO_2$, end-tidal carbon dioxide; Hb, hemoglobin; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial blood pressure; MPP, myocardial perfusion pressure; $PaCO_2$, arterial carbon dioxide partial pressure; PaO_2, arterial oxygen partial pressure; SPP, systemic perfusion pressure.

vals (CI) were calculated using these mixed-effects models. Two-tail *p* values of < 0.05 were considered statistically significant. Data were analysed in Stata (v15.1, StataCorp, College Station, TX, USA), and graphs were generated in GraphPad Prism (v8.0.0, GraphPad Software, La Jolla, CA, USA).

Results

Baseline characteristics and short-term survival

Baseline variables were normal for swine. Fifty-six pigs underwent asphyxial cardiac arrest. The acidosis, hypercarbia, and hypoxia during asphyxia were similar between the two groups (Table 2). Short-term survival was 35.7% (20/56). Overall, 57% (16/28) survived in the algorithm group versus 14% (4/28) in the standard group (Table 3, $p = 0.002$). At each asphyxial duration, there were more survivors in the algorithm group than in the standard group. One non-survivor in the algorithm group achieved ROSC but for < 20 min. None of the non-survivors in the standard group achieved ROSC of any duration.

Resuscitation variables

Time-to-ROSC, number of epinephrine doses, and time-to-defibrillation were similar in the two groups (Table 4). During ALS, animals in the algorithm group required fewer defibrillation attempts (3 [1, 7]) than the standard group (5 [2, 7]; $p = 0.031$), and more were defibrillated (64% versus 19%; $p = 0.002$; Table 4). In the algorithm group, 50% (8/16) of survivors received > 1 epinephrine dose and 75% (6/8) received a dose earlier than AHA recommendations.[20] Survivors in the algorithm group had an average CCR of 127 (101, 152)/min immediately prior to ROSC. On autopsy, the occurrence of atelectasis, liver laceration, and hemothorax was similar. Epicardial haemorrhage was more frequent in the algorithm group (79%

Table 3 – Return of spontaneous circulation in the standard and $ETCO_2$-guided algorithm cardiopulmonary resuscitation groups.

Asphyxia Duration, min, (n)	Survival		*p*
	Standard CPR, n (%)	Algorithm CPR, n (%)	
Combined, (28/group)	4 (14.3)	16 (57.1)	0.002
11, (7/group)	1 (14.3)	5 (71.4)	0.103
14, (7/group)	2 (28.6)	4 (57.1)	0.592
17, (7/group)	1 (14.3)	4 (57.1)	0.266
20, (7/group)	0 (0)	3 (42.9)	0.192

CPR, cardiopulmonary resuscitation.

Table 4 – Study outcomes in the standard and $ETCO_2$-guided algorithm cardiopulmonary resuscitation groups.

Variable	Standard CPR (n = 28)	Algorithm CPR (n = 28)	*p*
Resuscitation variables			
Time to ROSC (survivors*), min	5.0 (2.0, 17.0)	9.0 (6.0, 15.5)	0.765
Doses of epinephrine (survivors*)	1 (0, 3)	2 (1, 4)	0.298
Doses of epinephrine (all)	4 (4, 4)	4 (1, 7)	0.305
Chest compression rate immediately prior to ROSC (survivors*)	101 (100, 104)	127 (101, 152)	0.079
Successfully defibrillated†, n (%)	5 (19)	16 (64)	0.002
Time to defibrillation‡, min	8 (6, 15)	10 (7, 14)	0.590
Defibrillation attempts	5 (2, 7)	3 (1, 7)	0.031
Arterial blood gas, 8 min of CPR			
pH	7.15 ± 0.03	7.10 ± 0.03	0.219
$PaCO_2$	24 (19, 42)	36 (28, 49)	0.041
PaO_2	104 (77, 164)	122 (89, 180)	0.282
Base excess	−18.2 ± 0.6	−17.2 ± 0.6	0.196
Autopsy results, n (%)			
Atelectasis	27 (96)	25 (89)	0.611
Liver laceration	1 (4)	0 (0)	0.999
Epicardial hemorrhages	8 (29)	22 (79)	<0.001
Hemothorax	2 (7)	1 (4)	0.999

Data are presented as mean ± standard error of the mean or as median (interquartile range), unless otherwise noted. CPR, cardiopulmonary resuscitation; $PaCO_2$, arterial carbon dioxide partial pressure; PaO_2, arterial oxygen partial pressure; ROSC, return of spontaneous circulation.

* Survivors included n = 4 in standard group and n = 16 in $ETCO_2$-guided algorithm group.

† Includes only piglets in which defibrillation was indicated (standard CPR group, n = 26; $ETCO_2$-guided algorithm CPR group, n = 25).

‡ Includes only swine in which defibrillation was successful (standard CPR group n = 5, $ETCO_2$-guided algorithm CPR group n = 16)

versus 29%; $p < 0.001$) but also more common in survivors than non-survivors (95% versus 31%; $p < 0.001$).

Intra-arrest physiology

Using the $ETCO_2$-guided algorithm, resuscitators sustained higher $ETCO_2$ levels during BLS (30.6 ± 2.3 versus 22.0 ± 2.3 torr) and ALS (24.3 ± 2.1 versus 18.7 ± 1.9 torr; Fig. 1A, Supplementary Table 1). An $ETCO_2 \geq 30$ torr was better maintained early in resuscitation, and the difference between groups waned during ALS. In the first 90 sec of BLS, DBP, MAP, MPP, CPP, and SPP peaked transiently in both groups (Fig. 1C, D, F-H). These peaks were higher in the algorithm CPR group. Thereafter, each variable steadily declined until the first dose of epinephrine at 6 min of resuscitation. A small decrease in $ETCO_2$ levels occurred at 6 min with the initiation of ALS in the algorithm group (27.0 ± 2.5 versus 21.2 ± 2.0 torr; $p = 0.094$) but not in the standard group (17.2 ± 1.9 versus 16.7 ± 1 .6 torr; $p = 0.838$). The average CCR increased steadily in the algorithm group to a maximum of 150/min (Fig. 1B). During BLS, the algorithm CPR group had a predicted mean CCR of 117.7 ± 1.4 versus the expected 100.2 ± 1.3/min in the standard group (predicted difference of 17.5 [95% CI, 13.7–21.2] compressions/min; $p < 0.0001$; Supplementary Table 1). Also, during BLS the predicted mean DBP, MAP, and MPP were greater in the algorithm CPR group than the standard CPR group. There were no differences in the predicted mean ICP, CPP, or SPP between the two groups during BLS (Supplementary Table 1).

During ALS, the predicted mean CCR in the $ETCO_2$-guided algorithm CPR group was 145.4 ± 1.7 versus the expected 100.9 ± 1.5 in the standard CPR group (predicted difference of 44.5 [95% CI, 40.1–48.9]/min; $p < 0.001$; Supplementary Table 1). Also, during ALS all six physiologic parameters were greater in the algorithm group (Fig. 1C-H, Supplementary Table 1). Five pigs had ROSC prior to epinephrine, 3/28 (11%) in the algorithm group and 2/28 (7%) in the standard group ($p > 0.999$). Among 46 pigs receiving $\geq$ 1 dose of epinephrine (20/28 in the algorithm group and 26/28 in the standard group), the magnitude of change in the DBP, MAP, and CPP 90 sec after the first epinephrine dose was greater in the algorithm group (DBP: 9.0 [5.0, 20.5] versus 3.0 [1.0, 9.5] mmHg; MAP: 11.5 [6.3, 23.8] versus 4.5 [1.5, 9.0] mmHg; CPP: 10.0 [5.0, 17.0] versus 5.0 [0.8, 10.3]; $p < 0.05$ for all; Supplementary Fig. 1A-C). The magnitude of change in the MPP was not different (6.5 [3.3, 19.8] mmHg versus 3.0 [1.8, 9.0] mmHg; $p = 0.190$; Supplementary Fig. 1D). One pig was excluded from analysis of ROSC before or after epinephrine because it achieved ROSC briefly before epinephrine administration but rearrested and received epinephrine before achieving sustained ROSC.

In a secondary analysis, we divided the cohort into survivors (n = 20) and non-survivors (n = 36) regardless of CPR group. Of particular note, the $ETCO_2$ level was maintained at or above the target of 30 torr during CPR in survivors (36.8 ± 2.3 versus 20.1 ± 1.7 torr during BLS, $p < 0.001$; and 30.0 ± 2.7 versus 18.6 ± 1.5 torr during ALS, $p < 0.001$; Fig. 2A, Supplementary Table 2). A small decrease in $ETCO_2$ levels also occurred at 6 min of CPR in survivors (30.9 ± 3.1 versus 24.4 ± 2.9 torr; $p = 0.153$) but not in non-survivors (18.0 ± 1.7 versus 17.0 ± 1.3 torr; $p = 0.616$). Chest compression rate was not significantly different between survivors and non-survivors during BLS (111.6 ± 2.5 versus 107.3 ± 1.8/min; $p = 0.161$) but was greater in survivors during ALS (137.3 ± 7.0 versus 116.2 ± 3.7/min; $p = 0.008$). Hemodynamic trends resembled the analysis by CPR group with a peak in all parameters during early BLS and a decline until administration of epinephrine (Fig. 2C-H). The peaks for all parameters were greater in survivors than in non-survivors. During both BLS and ALS, survivors had increased $ETCO_2$, DBP, MAP, MPP, CPP, and SPP (Supplementary Table 2).

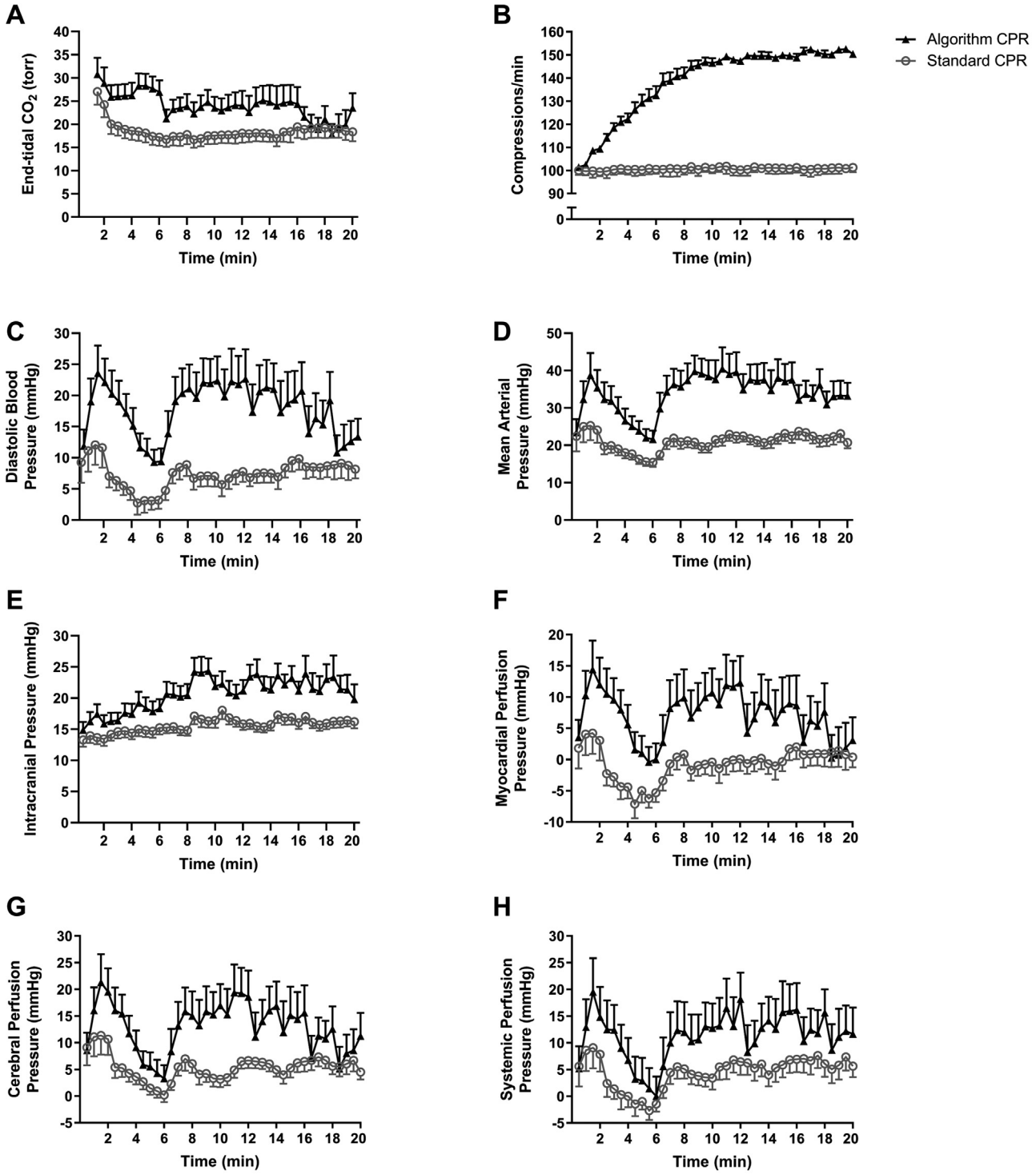

Fig. 1 – End-tidal CO_2 ($ETCO_2$, A), chest compression rate (B), and hemodynamic parameters (C–H) during the 20-min resuscitation period in the standard (n = 28) and algorithm (n = 28) cardiopulmonary resuscitation (CPR) groups. Each data point represents the mean value at 30 sec intervals, and only data during active CPR are presented. The number of animals included in the mean decreases over time as animals that achieved return of spontaneous circulation are excluded. Error bars represent SEM. In the standard CPR group, chest compressions were delivered at a rate of 100/min and epinephrine was administered every 4 min during advanced life support (minutes 6–20). In the $ETCO_2$-guided algorithm CPR group, the rate of chest compression delivery was increased by 10 compressions/min for every minute that the $ETCO_2$ was < 30 torr, and epinephrine was administered as frequently as every 2 min during advanced life support if the $ETCO_2$ was < 30 torr.

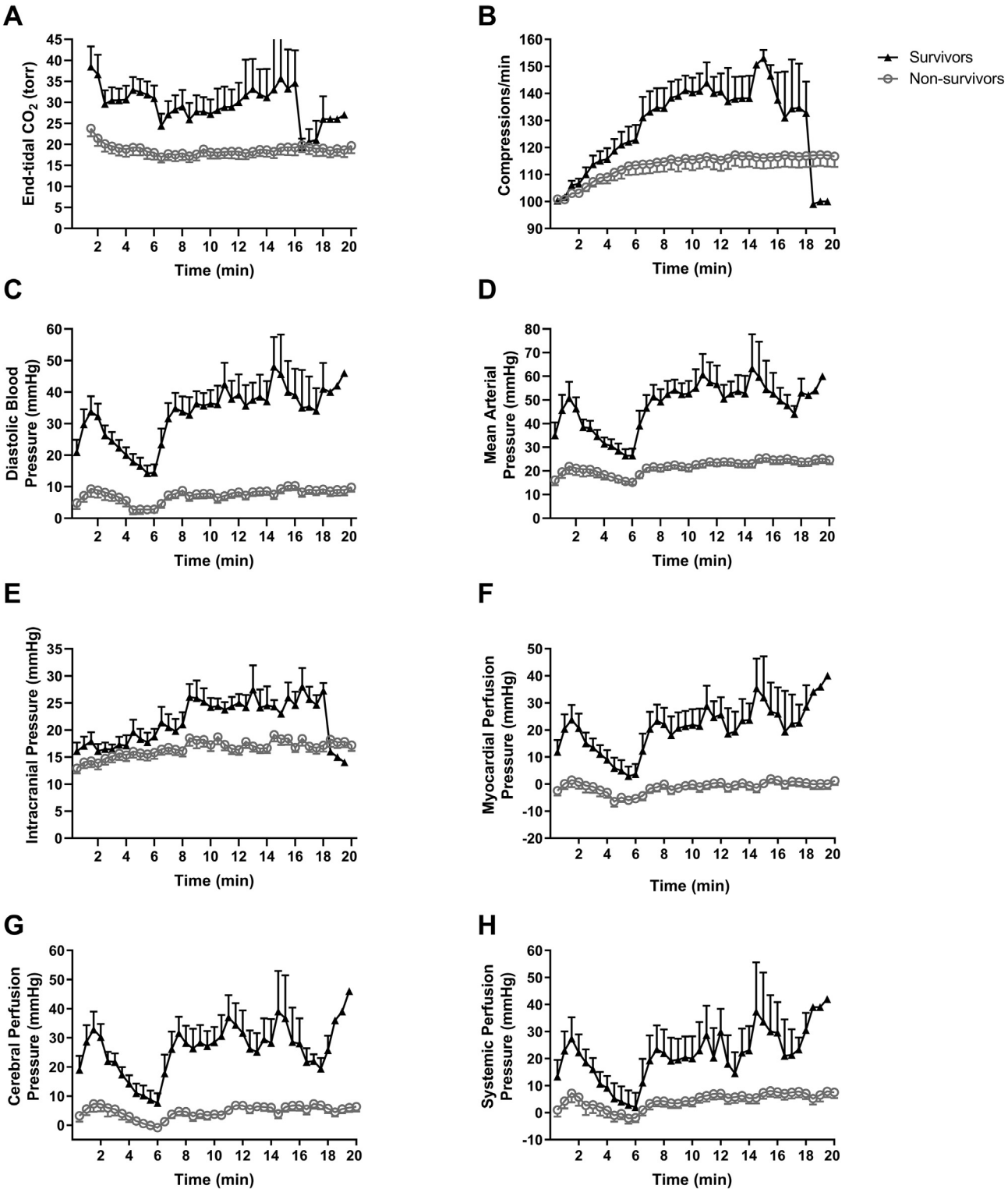

Fig. 2 – End-tidal CO_2 ($ETCO_2$, A), chest compression rate (B), and hemodynamic parameters (C–H) during the 20-min resuscitation in survivors (n = 20) and non-survivors (n = 36). Each data point represents the mean value at 30 sec intervals, and only data during active cardiopulmonary resuscitation (CPR) are presented. The number of animals included in the mean decreases over time as animals that achieved return of spontaneous circulation are excluded. Error bars represent SEM.

Predicted mean ICP was not different during BLS but was increased in survivors during ALS.

Discussion

Use of an $ETCO_2$-guided CPR algorithm improved short-term survival. Improvement in intra-arrest haemodynamics likely contributed to the increased survival. To our knowledge, this is the first description of an $ETCO_2$-guided algorithm that directs stepwise changes in the CCR and EAI during active resuscitation. When looking at our data, the apparent inability to maintain $ETCO_2$ target levels with this algorithm late in resuscitation requires careful examination. When analysed by group, rescuers did not maintain an $ETCO_2 \geq 30$ torr during ALS (mean 24.3 torr) despite adjusting the CCR and EAI in the algorithm group. This result is likely because survivors are not included in the analyses as they achieve ROSC, while non-survivors maintain deteriorating haemodynamics until the end of the 20 min resuscitation and contribute many more data points. When analysed by survival, survivors maintained a mean $ETCO_2$ of 30.0 torr during ALS (Supplementary Table 2). This demonstrates that the target $ETCO_2$ value can be achieved in many survivors using this algorithm.

During the first 6 min of BLS, rescuers maintained an $ETCO_2$ of 30.6 torr in the algorithm group using stepwise increases in the CCR of 10/min (mean of 117.7 versus 100.2/min in the standard group). This small increase in the rate of chest compression during BLS improved DBP, MAP, and MPP. Additionally, 3/28 animals in the algorithm group achieved ROSC during this time without epinephrine administration and an additional 4 achieved ROSC with the first dose of epinephrine and defibrillation. This suggests that $ETCO_2$-guided adjustments to the CCR within the guidelines (100–120/min),[1] may be beneficial early during BLS. It is possible that improved blood flow with the increase in CCR improved the vascular response to the endogenous epinephrine circulation at the start of CPR in the algorithm group. We have previously documented the effect of asphyxia duration on early hemodynamic response to resuscitation that is likely related to the circulation of endogenous epinephrine.[24] Whether the increase in CCR of 10/min is better than smaller or larger incremental changes requires future investigation. An accelerometer did not work in this age group, and we do not have accelerometer data to show that chest compression force was the same in both groups. We did use the same chest compression depth in both groups following an external marker.

During ALS with epinephrine administration, the $ETCO_2$-guided algorithm CPR group had better haemodynamics, greater improvements in haemodynamics after the first dose of epinephrine, required fewer defibrillation attempts, and were more likely to be defibrillated. These findings also suggest that early optimization of cardiac output improves responsiveness to epinephrine administration, myocardial perfusion, and the likelihood of successful defibrillation. Clinically, this could be relevant in cardiac arrests when rescuers experience a delay between initiation of chest compressions and vascular access for epinephrine administration. Many emergency response teams have capnography monitoring in the field.[25] In these situations, optimizing early resuscitation with use of $ETCO_2$ to guide CCR might improve the hemodynamic response to epinephrine and likelihood of ROSC.

Others have reported that epinephrine can increase, decrease, or have no effect on pulmonary blood flow and $ETCO_2$ levels during CPR.[26–28] In the standard group, there was no change in the $ETCO_2$ level with the first dose of epinephrine at 6 min nor at any time during ALS despite standard epinephrine administration at 6, 10, 14, and 18 min of resuscitation. This observation is consistent with our prior work in this swine model of prolonged asphyxial cardiac arrest.[16] In the algorithm group, there was a non-significant decrease in the $ETCO_2$ level after the first dose of epinephrine at 6 min (Fig. 1A). However, 4 pigs in this group achieved ROSC with this first dose of epinephrine and defibrillation. We therefore suspect the small decrease in the $ETCO_2$ level is secondary to these survivors dropping out of the analysis, rather than the administration of epinephrine. A similar pattern is observed in the $ETCO_2$ graph in survivors (Fig. 2A).

The AHA recommends epinephrine administration during ALS every 3–5 min but does not provide recommendations for titration within this range.[1] In our study, survivors in the standard and algorithm CPR groups received a similar total number of epinephrine doses (1–2 doses) and had similar time-to-ROSC. However, 75% of survivors requiring at least 2 doses of epinephrine in the algorithm CPR group received epinephrine more frequently based on an $ETCO_2 < 30$ torr. Improved survival in a paediatric animal model is shown with titration of vasoactive dosing to a coronary perfusion pressure > 20 mmHg during resuscitation.[9] Others have proposed using specific DBP goals to guide both chest compression delivery and vasoactive medication administration in children.[29] However, many children suffering cardiac arrest lack an arterial catheter[30] and early use of $ETCO_2$ may be applicable. Our findings support additional investigation on patient-centric physiologic goals to guide vasoactive administration.

The incremental increase in the CCR to a maximum of 150/min exceeds recommendations and has the potential to limit full recoil and cardiac filling.[31] We have previously published that a faster CCR favoured increased $ETCO_2$ levels while a slower CCR favoured increased DBP levels.[24] In one clinical study, neither DBP nor survival to hospital discharge differed between children who received a CCR >140/min or 100–120/min.[32] The potential for adverse effects of a faster CCR is one of the reasons we chose a stepwise approach. Our average CCR during ALS was 137/min in survivors. Our average CCR of 145/min during ALS in the algorithm group did not result in significant resuscitation-related injuries. We suspect that the small petechial epicardial haemorrhages in survivors are related to reperfusion injury (95% of all survivors had epicardial haemorrhage) which we have also observed in our previous work.[17] However, we do not know the long-term effects of epicardial haemorrhage on survival. Our findings suggest that this CCR range is safe and effective in the short-term in this paediatric model.

The $ETCO_2$-guided algorithm CPR group had higher $PaCO_2$ at 8 min of CPR. This higher PaCO2 level may reflect improved cardiac output and mobilization of tissue CO_2 when using $ETCO_2$ guidance.[21] While this increase in $PaCO_2$ may contribute to an increase in ICP, it was offset by an increase in MAP and therefore the CPP improved in the algorithm group. These observations warrant additional studies to determine whether improved cerebral perfusion during CPR improves neurologic outcomes.

Survivors had $ETCO_2$ levels of 30–35 torr during BLS and ALS, which corroborates prior work[16] and supports the target of 30 torr. There is a lack of paediatric data describing a goal $ETCO_2$ during resuscitation. In critically ill children with in-hospital cardiac arrest, there was no difference in $ETCO_2$ between survivors and non-survivors, nor improvement in ROSC or survival to discharge when

the $ETCO_2$ was > 30 torr.[33] A systematic review of adult arrests found an association between $ETCO_2$ and ROSC. The average $ETCO_2$ in patients with ROSC was 25 torr.[34] Two additional adult studies reported that survivors of cardiac arrest had an average $ETCO_2$ > 30 torr during CPR.[13,35] We do not know if long-term neurologic outcomes are affected by intra-arrest $ETCO_2$ levels and whether even higher $ETCO_2$ targets could be achieved during resuscitation. Determination of paediatric $ETCO_2$ goals and investigation of resuscitation strategies to achieve these goals represent a fertile area for further research.

Survivors in our cohort had an average DBP of 28 mmHg during BLS and 38 mmHg after administration of epinephrine, similar to suggested targets of > 25 mmHg in infants and > 30 mmHg in children with cardiac arrest.[29] Our survivors had an average MPP of 18 mmHg during BLS and 24 mmHg after epinephrine. Adequate myocardial perfusion is associated with survival[36–39] and an MPP > 20 mmHg is necessary for survival in adult cardiac arrest.[39]

Our findings should be interpreted in light of several limitations. First, we did not objectively measure chest compression depth. Chest compression depth can affect $ETCO_2$ levels,[13] and changes to the CCR can affect chest compression depth.[31] It is possible that unintentional differences in the depth of chest compressions, in addition to changes to the CCR and EAI, contributed to improved survival and haemodynamics in the algorithm group. We used CPR coaches in an attempt to maintain similar compression depth, but neither compressors nor coaches could be blinded to group assignment. However, compressors were blinded to other physiologic data during resuscitation apart from $ETCO_2$. Second, the pigs were healthy and without pulmonary disease which may not represent the typical infant who develops cardiac arrest of respiratory aetiology. Ventilation and perfusion mismatching in patients with pulmonary pathology may affect the ability to titrate interventions based on $ETCO_2$ levels. Third, titrated durations of asphyxia (11–20 min) were used to evaluate the effect of injury severity on the ability to resuscitate animals. We have seen the effects of asphyxial duration on rates of ROSC in our prior work.[17] This pilot study was not powered sufficiently to show differences in the rates of ROSC for each asphyxia duration subgroup. Fourth, our primary outcome was short-term survival, and we cannot determine if this CPR algorithm would also improve long-term survival or neurologic outcome. Finally, infant pigs have a compliant chest wall, which favours the response to increased CCR predicted by the cardiac pump mechanism of blood flow during CPR with advantages that may not be relevant in older children.[40]

Conclusions

In conclusion, a novel algorithm that provides rescuers with specific stepwise guidance to modify the CCR and EAI using a target $ETCO_2$-$\geq$ 30 torr improved rates of ROSC and haemodynamics in an asphyxial model. Our results support continued investigation into the use of goal-directed, real-time physiologic feedback as an approach to precision resuscitation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Hunt has served as a consultant for Zoll Medical Corporation, which has provided honoraria and travel expenses for speaking engagements. Dr. Hunt and colleagues have been awarded patents for developing several educational simulation technologies for which Zoll Medical Corporation has a non-exclusive license with the potential for royalties. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

Animal care complied with the National Research Council's Guide for the Care and Use of Laboratory Animals.[19]

Acknowledgements

We are indebted to Leah Jager, PhD, from the Department of Biostatistics at the Johns Hopkins Bloomberg School of Public Health for her support with statistical analyses. We are also grateful for the editorial assistance of Claire Levine, MS, ELS. We would like to acknowledge support for the statistical analysis from the National Center for Research Resources and the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health through grant number 1UL1TR001079. This work was also supported by the Johns Hopkins Department of Anesthesiology and Critical Care Medicine (ACCM) Stimulating and Advancing ACCM Research award (DHS), the Pearl M. Stetler Fund Research Award (CEO), and National Institutes of Health grants R01 NS107417 (JKL), R01 NS113921 (JKL), and R01 NS060703 (RCK).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2021.100174.

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