# End-Tidal Carbon Dioxide–Guided Chest Compression Delivery Improves Survival in a Neonatal Asphyxial Cardiac Arrest Model

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## Abstract

**Objective**—To determine whether end-tidal carbon dioxide ($ETCO_2$)-guided chest compression delivery improves survival over standard cardiopulmonary resuscitation (CPR) after prolonged asphyxial arrest.

**Design**—Preclinical randomized controlled study.

**Setting**—University animal research laboratory.

**Subjects**—1–2-week-old swine.

**Interventions**—After undergoing a 20-minute asphyxial arrest, animals received either standard or $ETCO_2$-guided CPR. In the standard group, chest compression delivery was optimized by video and verbal feedback to maintain the rate, depth, and release within published guidelines. In the $ETCO_2$-guided group, chest compression rate and depth were adjusted to obtain a maximal $ETCO_2$ level without other feedback. CPR included 10 minutes of basic life support followed by advanced life support for 10 minutes or until return of spontaneous circulation (ROSC).

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This work was performed in the research facilities of the Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland.

**Measurements and Main Results**—Mean $ETCO_2$ at 10 minutes of CPR was $34 \pm 8$ torr in the $ETCO_2$ group (n=14) and $19 \pm 9$ torr in the standard group (n=14; $p=0.0001$). The ROSC rate was 7/14 (50%) in the $ETCO_2$ group and 2/14 (14%) in the standard group ($p=0.04$). The chest compression rate averaged $143 \pm 10$/minute in the $ETCO_2$ group and $102 \pm 2$/minute in the standard group ($p<0.0001$). Neither asphyxia-related hypercarbia nor epinephrine administration confounded the use of $ETCO_2$-guided chest compression delivery. The response of the relaxation arterial pressure and cerebral perfusion pressure to the initial epinephrine administration was greater in the $ETCO_2$ group than in the standard group ($p=0.01$ and $p=0.03$, respectively). The prevalence of resuscitation-related injuries was similar between groups.

**Conclusions**—$ETCO_2$-guided chest compression delivery is an effective resuscitation method that improves early survival after prolonged asphyxial arrest in this neonatal piglet model. Optimizing $ETCO_2$ levels during CPR required that chest compression delivery rate exceed current guidelines. The use of physiologic feedback during CPR has the potential to provide optimized and individualized resuscitative efforts.

### Keywords

## INTRODUCTION

Survival to discharge from out-of-hospital cardiac arrest in infants and children remains low (<10%), despite guidelines that emphasize chest compression delivery (1–5). After a prolonged cardiac arrest, resuscitation efforts must be maximally effective to achieve return of spontaneous circulation (ROSC) and minimize neurologic injury (1, 2, 6). Resuscitation methods that incorporate physiologic feedback have the potential to individualize and optimize chest compression delivery, increase the effectiveness of resuscitative efforts, and improve outcome. A previously described resuscitation method that incorporates physiologic feedback is hemodynamic-directed cardiopulmonary resuscitation (CPR), which uses arterial pressure monitoring. Hemodynamic-directed CPR has been used to guide chest compression delivery (increased rate and force) and epinephrine administration frequency in adults (7) and to improve outcome in animal models (8–10).

A novel physiologic parameter for guiding resuscitation efforts utilizes end-tidal carbon dioxide ($ETCO_2$) as an indicator of chest compression efficacy (11). The basis for this method is that the $ETCO_2$ level during CPR represents the movement of blood containing carbon dioxide to the lungs, and thereby becomes a surrogate for resuscitation-generated systemic blood flow (cardiac output). This relationship of the $ETCO_2$ level with systemic blood flow is strong because during CPR, the $ETCO_2$ level becomes less dependent on $CO_2$ production and minute ventilation and more dependent on cardiac output (12–24). An advantage to using $ETCO_2$ level as physiologic feedback during CPR is that it can be measured both easily and continuously. $ETCO_2$ physiologic feedback also has the potential to be used with the currently recommended quality feedback about chest compression rate, depth, and release, and with the promising physiologic feedback method of hemodynamic-directed CPR.

The 2015 American Heart Association (AHA) resuscitation guidelines suggested the use of $ETCO_2$ during adult CPR as a prognostication tool either immediately after intubation or after 20 minutes of resuscitation, but did not provide instruction for using $ETCO_2$ to direct resuscitation efforts (25). The pediatric 2015 AHA guidelines reported a lack of evidence about the use of $ETCO_2$ to direct chest compression delivery and were unable to make a recommendation (26). The 2013 AHA consensus regarding CPR quality and resuscitation outcome improvement suggested the development of "a more reliable, inexpensive, noninvasive physiological monitor that will increase our ability to optimize CPR for individual victims of cardiac arrest" and recommended that future research "determine optimal titration of hemodynamic and $ETCO_2$ monitoring during human CPR" (27).

In our previous study that used a brief (90-second) fibrillatory cardiac arrest, the use of $ETCO_2$ feedback to guide chest compression delivery was equivalent to using quality feedback about compression rate and depth (11). In the current study, we used a more prolonged (20-minute) asphyxial cardiac arrest to determine if $ETCO_2$-guided chest compression delivery can improve survival compared to standard CPR guided by rate and depth feedback. We also investigated concerns that the hypercarbia from asphyxia or the administration of epinephrine during advanced life support (ALS) might confound the use of $ETCO_2$-guided compression delivery. We hypothesized that if extreme hypercarbia and epinephrine administration do not interfere, then the use of $ETCO_2$-guided chest compression delivery after a prolonged cardiac arrest would optimize resuscitative efforts and improve survival over standard CPR.

## MATERIALS AND METHODS

All studies were carried out with approval from the Animal Care and Use Committee of Johns Hopkins University in accordance with institutional guidelines. Twenty-eight male domestic swine (7–14 days old, 3–4 kg) received anesthesia induction and maintenance with 2% isoflurane, 70% nitrous oxide, and 30% oxygen. A 4.0 cuffed tracheal tube was secured via tracheostomy. A femoral artery catheter was advanced to the mid-aorta for hemodynamic and blood gas determinations. A pacing wire placed through one femoral vein was advanced into the right ventricle as indicated by ventricular irritation on electrocardiogram. A catheter advanced through the other femoral vein to a mid-thoracic position was used to measure central venous pressure (CVP) and to administer fluid and epinephrine. A sagittal sinus catheter was placed through a burr hole at the bregma to measure intracranial pressure (ICP) and venous blood gases. Finally, the anteroposterior chest diameter was measured before arrest (and after CPR) to determine compression-induced deformity. After the surgery, isoflurane was decreased and fentanyl (10 mcg/kg) and vecuronium (0.3 mg/kg) administered. A heating pad was adjusted to maintain rectal temperature at 38–39°C. Pressure-controlled ventilation was adjusted to maintain a $PaCO_2$ of 35–45 torr at a rate of 20 breaths per minute, and $FiO_2$ was decreased from 30% to 21%. Vital signs, including $ETCO_2$, mean arterial blood pressure (MAP), mean CVP, arterial relaxation pressure (aka diastolic blood pressure (DBP)), mean ICP, heart rate, and rectal temperature, were recorded before protocol initiation (baseline) and at 30-second intervals during CPR. Hemodynamic values measured during the interval of ALS after ROSC were removed from the values on the graphs displayed as ALS.

## Experimental Protocol

A timeline for the experimental protocol is provided in Figure 1. We produced a 20-minute asphyxial-ventricular fibrillation arrest by clamping the tracheostomy tube for 14 minutes and then inducing 6 minutes of fibrillation by applying 50 mA of alternating current via the pacing wire. This procedure was similar to the model used to study hemodynamic-directed CPR (8). We included the period of fibrillation to prevent ROSC during the 10-minute basic life support (BLS) interval. This guaranteed 10-minute interval without ROSC allowed hemodynamic comparison between study groups during BLS. We chose to induce fibrillation at 14 minutes because this duration allowed the asphyxia to proceed to pulselessness (which usually requires 8–12 minutes) and was not so long that the hypoxemia produced a low amplitude fibrillation that was difficult to detect. After the 20 minutes of arrest, BLS was begun. Ventilation was resumed with an $FiO_2$ of 1.0, the pre-arrest rate of 20 breaths/minute, and the pre-arrest inspiratory pressures. The heating pad was adjusted to maintain rectal temperature at 38–39°C during CPR. In both groups, resuscitators performed chest compressions with a two-thumb, encircling technique at a compression rate that varied by study group (see below). The resuscitators providing chest compression delivery switched every 2 minutes.

**Standard group—**In this group, a marker was placed across the animal at 2/3 the anteroposterior diameter for chest compression depth (see Figure 1 in Hamrick et al. (11)). The targets for chest compression delivery throughout BLS and ALS were a rate of 100/minute, a depth of 1/3 the anteroposterior diameter, and full release between compressions. Real-time video and verbal feedback about the rate, depth, and release were provided. The resuscitators were blinded to the $ETCO_2$ value.

**$ETCO_2$ group—**In this group, resuscitators adjusted the chest compression rate, force, depth, and thumb positions throughout BLS and ALS to maximize the level of $ETCO_2$ produced. $ETCO_2$ level was the only feedback available.

**Both groups—**After the 10-minute interval of BLS, ALS was begun. Resuscitators administered 30 joules of biphasic defibrillation during compressor changes at 0, 2, 4, 6, and 8 minutes of ALS. Additionally, 300 mcg of epinephrine was administered into the mid-thoracic venous catheter at 0, 4, and 8 minutes of ALS. ALS was terminated when ROSC occurred or after 10 minutes (20 minutes of CPR total). Survival was defined as continued ROSC (sustained arterial pulsatility) for 20 minutes without further intervention. Non-survival was no ROSC after 10 minutes of ALS (20 minutes of CPR) or ROSC that was not sustained for 20 minutes. No additional compressions, medications, or defibrillations were provided after ROSC occurred. Arterial and venous blood gases were examined at baseline, 10 minutes of asphyxia, 8 minutes of BLS, and 20 minutes of ALS for non-survivors or 20 minutes of ROSC for survivors. After 20 minutes of ROSC, survivors were euthanized per Animal Care and Use Committee guidelines. We performed autopsies on all animals to determine resuscitation-related injuries (superficial liver injury, hemoperitoneum, hemothorax, hemopericardium, atelectasis, or superficial cardiac injury).

### Statistical Analysis

Descriptive data were used to characterize baseline cardiorespiratory variables. All values are expressed as mean ± SD. Systemic perfusion pressure (SPP) was calculated as MAP – mean CVP. Cerebral perfusion pressure (CPP) was calculated as MAP – mean ICP. Differences between groups in resuscitation and injury statistics were compared with an unpaired, 2-tailed $t$ test for continuous variables, and $X^2$ or Fisher's exact test for categorical variables, as appropriate. $p$-values <0.05 were considered statistically significant. Repeated-measures analysis of variance (ANOVA) was used to investigate the effect of time and group. All data were analyzed in Stata (Version 14; Statacorp LP, College Station, TX).

## RESULTS

Baseline blood gas and hemodynamic results were similar between study groups (Table 1). $PaCO_2$ at 10 minutes of asphyxia averaged 122 and 124 torr in the $ETCO_2$ and standard groups, respectively. $ETCO_2$ at the start of chest compressions exceeded the limit of detection (>99 torr) in both groups. At 30 seconds of chest compressions, $ETCO_2$ averaged 64 and 65 torr, and at 1 minute it was $32 \pm 10$ and $25 \pm 8$ torr ($p$=0.046) in the $ETCO_2$ and standard groups, respectively (Fig. 2A). $ETCO_2$ throughout CPR was >30 torr in the $ETCO_2$ group but fell to 11.5 torr in the standard group. The $PaCO_2$ at 8 minutes of BLS was 54 $\pm$ 20 in the $ETCO_2$ group and $42 \pm 30$ torr ($p$=0.23) in the standard group. The $ETCO_2$ was higher in the $ETCO_2$ group than in the standard group during both BLS and ALS (Table 2). $ETCO_2$ did not change with epinephrine administration at 10, 14, or 18 minutes of CPR in either study group nor when analyzed for survival. $ETCO_2$ level during BLS was higher in survivors (Table 3).

The ROSC rate was greater in the $ETCO_2$ group (50% vs 14%, $p$=0.04; Table 4). Two of the seven non-survivors in the $ETCO_2$ group had ROSC less than the required 20 minutes (8 and 16 minutes), none of the twelve non-survivors in the standard group had ROSC of any duration. There were no differences between groups in defibrillation attempts, time to defibrillation, or epinephrine doses. Figure 3A shows the $ETCO_2$ level during CPR by survival and illustrates that survivors had consistently higher $ETCO_2$ levels after 1 minute of CPR. Figure 3A1 shows the $ETCO_2$ level during CPR by group and survival. In the $ETCO_2$ group, both survivors and non-survivors maintained $ETCO_2$ during CPR in the upper 20s to 30 torr, whereas the $ETCO_2$ in the standard group showed the expected relationship with survival (high 20s in survivors, low 10s in non-survivors).

The chest compression rate over the 20 minutes of CPR was $102 \pm 2$/minute (range, 84–114) in the standard group and $143 \pm 10$/minute (range, 72–182) in the $ETCO_2$ group ($p$<0.0001) (Table 2, Fig. 2B). Compression rate did not differ by survival (Table 3; $p$=0.14).

The DBP (an indicator of coronary perfusion during CPR) did not differ between study groups during BLS, but it was higher in the $ETCO_2$ group during ALS (Table 2, Fig. 2C). The $ETCO_2$ group exhibited a greater increase in DBP than did the standard group 1 minute after the first epinephrine administration (DBP: $20 \pm 16$ vs $7 \pm 7$ mmHg, $p$=0.01). Survivors exhibited higher DBP early in BLS (0–8 minutes; $18.5 \pm 7$ vs $11.6 \pm 7$ mmHg, $p$=0.02), but not during late BLS (8–10 minutes, 10.7 vs 10.7; Fig. 3B). During ALS, DBP was higher in

survivors than in non-survivors (Fig. 3B). Figure 3B1 shows that the DBP during BLS was similar for survival between study groups, unlike the $ETCO_2$ level in Figure 3A1. The first epinephrine administration produced a greater increase in DBP in survivors than in non-survivors ($25 \pm 17$ vs $8 \pm 7$ mmHg, $p$=0.001). ANOVA of DBP by group and survival showed a significant difference during ALS ($p$=0.01), with DBP in $ETCO_2$-guided survivors higher than that in standard group non-survivors ($p$=0.001) and $ETCO_2$ group non-survivors ($p$=0.04; Fig. 3B1).

MAP, CVP, and ICP (but not SPP or CPP) were higher in the $ETCO_2$ group than in the standard group during BLS (Table 2, Fig. 2D–H), but all five variables were higher in the $ETCO_2$ group during ALS. After the first epinephrine administration, we observed greater increases in MAP ($24 \pm 18$ vs $9 \pm 11$ mmHg, $p$=0.02), SPP ($23 \pm 18$ vs $9 \pm 12$ mmHg, $p$=0.01), and CPP ($21 \pm 16$ vs $9 \pm 11$ mmHg, $p$=0.03), but not CVP or ICP, in the $ETCO_2$ group. MAP, CPP, ICP, and SPP were higher in survivors than in non-survivors during ALS (Table 3, Fig. 3C and 3D). After the first epinephrine administration, MAP increased more in survivors than in non-survivors ($33 \pm 18$ vs $9 \pm 8$ mmHg, $p$=0.0001) as did SPP ($30 \pm 21$ vs $9 \pm 9$ mmHg, $p$=0.0005), ICP ($4 \pm 7$ vs $0.3 \pm 3$ mmHg, $p$=0.03), and CPP ($29 \pm 18$ vs $9 \pm 8$ mmHg, $p$=0.0003). ANOVA of SPP by group and survival demonstrated a significant difference during ALS (p=0.02), with SPP in the ETCO2 group survivors and nonsurvivors being greater than that of the standard group non-survivors (p=.006 & p=.031, respectively; Fig. 3C1).

Autopsy results revealed that the chest deformity (change in pre-arrest to post-resuscitation anteroposterior chest diameter) was less in the $ETCO_2$ group than in the standard group ($1.1 \pm 0.7$ vs $1.8 \pm 1.0$ cm, $p$=0.05). This difference may be due to restoration of chest shape by ventilation during the period of ROSC, which occurred more often in the $ETCO_2$ group. Epicardial hemorrhages, which were superficial and along the distribution of the right coronary artery, were greater in the $ETCO_2$ group (77% vs 33%). These superficial hemorrhages were more common in survivors than in non-survivors in both groups (78% vs 37%). If related to resuscitative efforts, their presence did not appear to interfere with the rate of ROSC. We also noted a nonsignificant increase in hemothorax in the $ETCO_2$-guided group. These hemothoraces appeared to be caused by the fibrillation wire perforating the vasculature during BLS and were corrected by withdrawing the wire before CPR in subsequent experiments. Other injuries did not differ between study groups (Table 4).

## DISCUSSION

This proof-of-concept study showed that $ETCO_2$-guided chest compression can improve survival compared to standard CPR for cardiac arrest. By providing real-time, physiologic feedback, $ETCO_2$ monitoring enabled rescuers to adjust chest compression delivery to optimize the patient's response. In this study, resuscitators adjusted chest compression factors such as hand position, rate, depth, force, and release in response to $ETCO_2$ level. The sustained improvement in the $ETCO_2$ level is believed to correspond to improved pulmonary blood flow and systemic cardiac output.

The higher $ETCO_2$ level and ROSC rate in the $ETCO_2$-guided group were due primarily to increases in chest compression rate and force in response to the ongoing feedback. The observers thought that chest compression release was good and that neither group exhibited excessive leaning. In one of the $ETCO_2$-guided experiments, the $ETCO_2$ level improved noticeably when the compressor's thumbs were moved to the left of midline, but no change in $ETCO_2$ was noticed with hand position changes in the other 13 experiments of that group. Because a pediatric accelerometer did not work well on the small chest of the animals, objective data for depth and force are not available. The increases in MAP, mean CVP, and mean ICP seen in the $ETCO_2$-guided group probably represent an increase in force by the resuscitators. The increased force did not cause significant chest compression deformity or injuries detected by autopsy. The chest compression rate was considerably increased by the resuscitators in the $ETCO_2$-guided group to maximize $ETCO_2$ levels (126/minute at 30 seconds to 157/minute at 20 minutes; Fig. 2B). The benefit of the fast compression rate may be specific for our model and relate to the very compliant chest wall and a cardiac-pump type mechanism of blood flow (28). Additional research is needed to determine if the use of compression rates above the guideline recommendations (100–120 per minute) are effective and safe before this method is considered for clinical use.

In our previous study, $ETCO_2$-guided CPR was comparable to standard CPR after a short-duration arrest interval (11). In that study, the group guided by $ETCO_2$ alone saw a 70% rate of ROSC, whereas the standard CPR group, which received verbal and visual feedback about CPR quality saw a 65% rate of ROSC. In the current study, we tested whether $ETCO_2$-guided chest compression delivery would improve the rate of ROSC when survival from standard CPR was likely to be very low. Therefore, we used a prolonged, 20-minute asphyxia-ventricular fibrillation arrest model that produces an ROSC rate of only 15% with standard CPR. The 50% rate of ROSC with $ETCO_2$-guided chest compression indicates that this method has the potential to improve resuscitative efforts after prolonged arrest or during prolonged resuscitation.

An interesting finding is that survivors and non-survivors in the $ETCO_2$ group had similar $ETCO_2$ levels (approximately 30 mmHg) throughout CPR. Low levels of $ETCO_2$ during CPR have been associated with low-quality CPR, a decreased rate of ROSC, and futility while high levels of $ETCO_2$ have been associated with survival (18, 25, 29). Our results indicate that attempting to raise $ETCO_2$ levels during CPR can result in increased $ETCO_2$ levels that do not indicate likelihood of ROSC. Figure 3B1 shows that the relationship between the relaxation arterial pressure (a surrogate for myocardial perfusion (10, 30–32)) and survival is present in both study groups during BLS. In contrast, the $ETCO_2$, SPP, and CPP levels during BLS in the non-survivors of the $ETCO_2$-guided group overlap the survivors of both groups (Fig. 3A1, 3C1, and 3D1). The $ETCO_2$ levels produced by $ETCO_2$-guided chest compression delivery appear to correspond better to systemic perfusion than myocardial perfusion. Despite this apparent disconnect between $ETCO_2$ and DBP, the $ETCO_2$-guided group was more likely to experience ROSC. The increased response in MAP and DBP in the $ETCO_2$ group to early epinephrine administration suggests that improved systemic perfusion better maintains vascular responsiveness during prolonged CPR. A better understanding of the relationship between DBP and $ETCO_2$ during prolonged CPR is needed to determine how to maximize both when ROSC is difficult to achieve.

One concern of using $ETCO_2$-guided chest compression for pediatric arrest has been that significant hypercarbia caused by prolonged asphyxia might cofound implementation of $ETCO_2$ guidance. The $ETCO_2$ in the standard and $ETCO_2$ groups fell to 25 and 32 mmHg, respectively, at 1 minute of CPR, a range that was useful and persisted during the remainder of resuscitation. Others have also reported a similar rapid decrease in $ETCO_2$ after asphyxial arrest (33, 34). Another potential confounder of $ETCO_2$-guided CPR is that epinephrine administration might affect pulmonary blood flow and $ETCO_2$ levels. Others have reported that $ETCO_2$ levels could be temporarily increased or decreased after epinephrine administration (35–42). However, we did not observe fluctuations in $ETCO_2$ in either study group after epinephrine administration at 10, 14, or 18 minutes of CPR (Fig. 2A). The fact that $ETCO_2$ levels did not decrease as the effect of epinephrine on DBP and SPP (Fig. 2C and 2F) wore off at 12 and 16 minutes of CPR may indicate that $ETCO_2$ cannot be used to guide early epinephrine administration and that invasive monitoring would be most useful for this role. We will need additional studies to determine if the lack of $ETCO_2$ responsiveness to epinephrine administration is due to the long arrest interval used in this model. In our previous study that used a short arrest interval, most animals achieved ROSC with the first epinephrine dose, making it difficult to know if the increased $ETCO_2$ level was from epinephrine, ROSC, or both (11).

CPR guided by physiologic feedback has the potential to improve cardiac and neurologic outcomes when resuscitation efforts become prolonged. Extracorporeal CPR (eCPR) technology is improving, but rates of neurologic injury and failure to wean from support after recovery remain high. Hemodynamic-directed CPR has shown great promise for improving survival and neurologic outcome in preclinical models when an arterial line is present to guide epinephrine administration (8–10, 32). Near-infrared spectroscopy measurements and amplitude analysis of ventricular fibrillation are other physiologic responses that have the potential to guide resuscitation efforts. Resuscitation guidelines offer evidence-based recommendations for a common initial resuscitation approach and for CPR quality. The use of physiologic feedback offers the potential to maximize those recommendations, individualize efforts, and, when needed, modify resuscitative efforts beyond current guidelines.

Several limitations of this study deserve attention. First, rate of ROSC is a limited outcome measure for resuscitation studies. Longer-term outcomes and neurologic status are much more useful and will need to be addressed in future studies. With the current prolonged arrest interval, long-term survival will likely require intensive care, and neurologic outcomes may be very poor. Second, we did not have an accelerometer to measure compression depth, force, or release. Chest compression rate was the only objective measure we had of alterations to CPR delivery. It is very likely that force, and possibly depth or release, were different between groups and contributed to our findings. When a neonatal accelerometer becomes commercially available, it would be very useful to add it to our studies. Third, it is unclear whether an asphyxial arrest model in healthy animals is applicable to neonatal, infant, or pediatric arrests. This model might correlate with apnea that leads to arrest in cases of sudden infant death syndrome, choking, suffocation, or drowning. However, the study does not address the usefulness of an $ETCO_2$-guided resuscitation method when lung

disease leads to respiratory and then cardiac arrest. Therefore, we cannot generalize its applicability to all pediatric cardiopulmonary arrests. Fourth, baseline ventilation parameters (a breath rate of 20 per minute) and mechanical ventilation were used during CPR which may limit the clinical applicability of this study. Current recommendations are for reduced breath rates of 10–12 per minute to prevent over-ventilation during CPR. Mechanical ventilation was continued, rather than switching to manual ventilation, to minimize the number of variables under investigator control in this necessarily unblinded study. Pressure controlled ventilation is commonly used in children and its use during experimental CPR can result in reduced tidal volumes and require an increased breath rate. Table 4 shows that the blood gas mean values at eight minutes of BLS are appropriate ($PaCO_2$ 54 and 42 mmHg and $PaO_2$ 132 and 120 mmHg) and that using mechanical ventilation and a breath rate of 20 per minute did not produce over-ventilation. Fifth, the lack of blinding of resuscitators may provide bias in the study. The standard group was observed for performance of the recommended chest compression rate, depth, release, and hand position (see diagrams and description in reference 11) and was blinded to $ETCO_2$ level, whereas the experimental group was instructed to improve $ETCO_2$ levels by adjusting these variables. Thus, improving resuscitator performance in the $ETCO_2$ group was part of the study design. Nevertheless, study outcomes were objectively measured (rate of ROSC, hemodynamic variables, and presence of injuries).

## CONCLUSIONS

$ETCO_2$-guided chest compression delivery has the potential to improve neonatal/infant outcomes from prolonged cardiac arrest over standard CPR. Concerns that interference from hypercarbia or epinephrine administration might interfere with the use of $ETCO_2$-guidance were unsupported. Additional study is needed to determine the benefit on long-term outcomes of $ETCO_2$-guided chest compression delivery and how it can be used to individualize and optimize resuscitation by manipulating parameters within and beyond published guidelines.

## Acknowledgments

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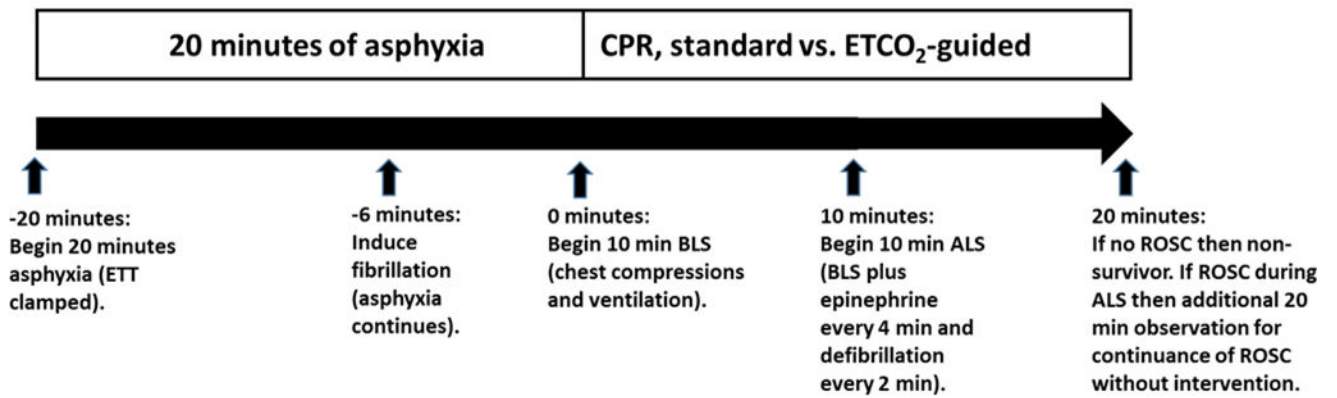
## Experimental Timeline



**Figure 1.**
Experimental timeline indicating events during asphyxia and resuscitation in minutes.
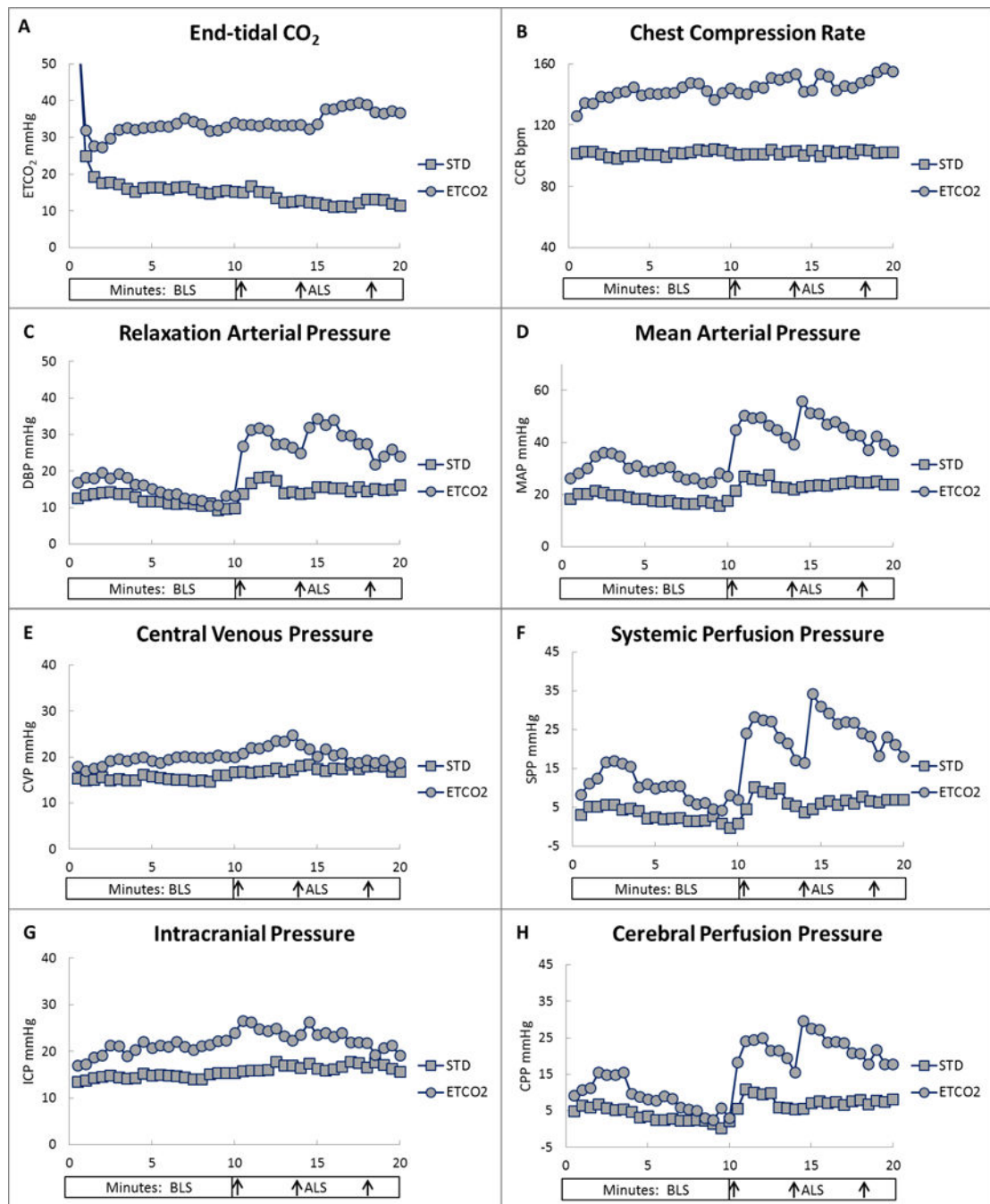
**Figure 2.**
End-tidal CO₂ (ETCO₂), chest compression rate (CCR), and hemodynamic variables by
study group (standard CPR [STD] or ETCO₂-guided CPR [ETCO2]). **A**, ETCO₂. **B**, CCR.
**C**, Relaxation arterial (diastolic blood) pressure (DBP). **D**, Mean arterial pressure (MAP). **E**,
Central venous pressure (CVP). **F**, Systemic perfusion pressure (SPP). **G**, Intracranial
pressure (ICP). **H**, Cerebral perfusion pressure (CPP). Each data point represents the mean
value at 30-second intervals. Y-axis values are in mmHg or beats per minute (bpm). X-axis

values are in minutes of basic life support (BLS) and advanced life support (ALS). X-axis arrows indicate timing of epinephrine administration at 10, 14, and 18 minutes of CPR.
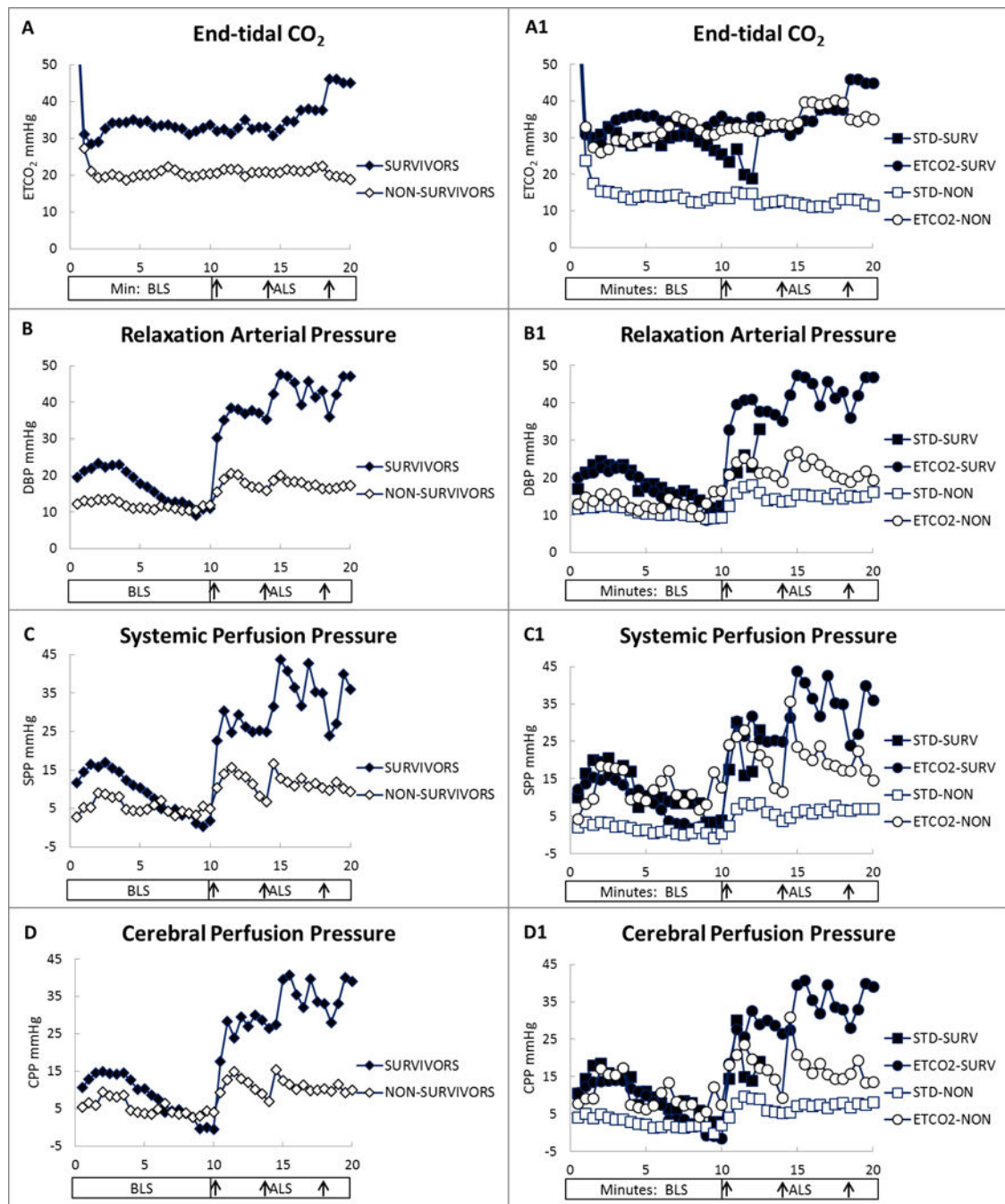
**Figure 3.**
End-tidal $CO_2$ ($ETCO_2$) and hemodynamic variables by survival (STD-SURV = standard group survivors, ETCO2-SURV = $ETCO_2$ group survivors, STD-NON = standard group non-survivors, ETCO2-NON = $ETCO_2$ group non-survivors). **A**, $ETCO_2$. **A1**, $ETCO_2$ by study group and survival. **B**, Relaxation arterial (diastolic blood) pressure (DBP). **B1**, Relaxation arterial pressure by study group and survival. **C**, Systemic perfusion pressure (SPP). **C1**, Systemic perfusion pressure by study group and survival. **D**, Cerebral perfusion pressure (CPP). **D1**, Cerebral perfusion pressure by study group and survival. Each data

point represents the mean value at 30-second intervals. Y-axis values are in mmHg. X-axis values are in minutes of basic life support (BLS) and advanced life support (ALS). X-axis arrows indicate timing of epinephrine administration at 10, 14, and 18 minutes of CPR.

**Table 1**

Baseline Characteristics of Subjects

| Variable | ETCO$_2$ Group | Standard Group | p |
|---|---|---|---|
| Weight (kg) | 3.51 ± 0.6 | 3.57 ± 0.5 | 0.78 |
| ETCO$_2$ (torr) | 45 ± 4.4 | 46 ± 3.1 | 0.56 |
| DBP (mmHg) | 64 ± 11 | 66 ± 13 | 0.59 |
| MAP (mmHg) | 78 ± 12 | 79 ± 15 | 0.87 |
| CVP (mmHg) | 12 ± 2.0 | 11 ± 1.5 | 0.4 |
| SPP (mmHg) | 66 ± 12 | 68 ± 15 | 0.60 |
| ICP (mmHg) | 14 ± 3.0 | 13 ± 1.5 | 0.47 |
| CPP (mmHg) | 64 ± 12 | 66 ± 16 | 0.78 |
| HR (beats/min) | 206 ± 37 | 225 ± 43 | 0.21 |
| pHa | 7.38 ± 0 | 7.37 ± 0 | 0.67 |
| pHv | 7.35 ± 0 | 7.32 ± 0 | 0.07 |
| PaCO$_2$ (torr) | 39 ± 2.9 | 40 ± 4.4 | 0.74 |
| PvCO$_2$ (torr) | 45 ± 2.0 | 45 ± 4.3 | 0.69 |
| PaO$_2$ (torr) | 86 ± 13 | 90 ± 30 | 0.68 |
| PvO$_2$ (torr) | 40 ± 5.7 | 46 ± 16 | 0.22 |
| BEa | −1.6 ± 2.1 | −0.7 ± 4.9 | 0.51 |
| BEv | −0.9 ± 2.7 | −2.3 ± 3.3 | 0.26 |
| SaO$_2$ (%) | 97 ± 2.3 | 95 ± 3.6 | 0.11 |
| SvO$_2$ (%) | 62 ± 15 | 60 ± 16 | 0.73 |
| Hb (g/dL) | 7.6 ± 1.7 | 8.4 ± 1.4 | 0.19 |
| Temperature (°C) | 38.5 ± 0.5 | 38.6 ± 0.7 | 0.65 |

Data are collected prior to asphyxia, separated by study group, and shown as mean ± SD.

BEa = base excess arterial; BEv = base excess venous; CPP = cerebral perfusion pressure; CVP = central venous pressure; DBP = diastolic blood pressure; ETCO$_2$ = end-tidal carbon dioxide; Hb = hemoglobin; HR = heart rate; ICP = intracranial pressure; MAP = mean arterial blood pressure; SPP = systemic perfusion pressure; pHa = arterial pH; pHv = venous pH; SaO$_2$ = arterial oxygen saturation; SvO$_2$ = venous oxygen saturation.

**Table 2**

Hemodynamic Results During Basic and Advanced Life Support by Study Group

| Parameter | BLS (0–10 min) | | | ALS (10–20 min) | | |
|---|---|---|---|---|---|---|
| | ETCO$_2$ (n=14) | Standard (n=14) | p | ETCO$_2$ (n=14) | Standard (n=14) | p |
| ETCO$_2$ (torr) | 34.4 ± 7.5 | 20.7 ± 8.7 | 0.0001 | 34.3 ± 9.5 | 16.2 ± 12 | 0.0001 |
| Comp/min | 140 ± 12 | 102 ± 3 | <0.0001 | 147 ± 19 | 102 ± 2 | <0.0001 |
| DBP (mmHg) | 14.5 ± 9.1 | 11.9 ± 5.5 | 0.37 | 30.7 ± 14 | 18.4 ± 9.9 | 0.01 |
| MAP (mmHg) | 29.5 ± 18 | 18.3 ± 6.5 | 0.04 | 47.4 ± 19 | 28.2 ± 12 | 0.004 |
| CVP (mmHg) | 19.4 ± 6.1 | 15.4 ± 2.1 | 0.02 | 20.5 ± 5.5 | 17.2 ± 2.1 | 0.04 |
| SPP (mmHg) | 10.6 ± 16 | 3.2 ± 1.8 | 0.07 | 27.6 ± 17 | 11.1 ± 13 | 0.004 |
| ICP (mmHg) | 20.7 ± 4.1 | 14.6 ± 1.8 | 0.0000 | 24.1 ± 5.0 | 16.7 ± 2.3 | <0.0001 |
| CPP (mmHg) | 8.8 ± 16 | 3.7 ± 6.9 | 0.29 | 23.6 ± 17 | 11.6 ± 12 | 0.04 |

Data represent the cumulative 30-second values during the 10 minutes of basic life support or the 10 minutes of advanced life support and are shown as mean ± SD.

ALS = advanced life support; BLS = basic life support; Comp/min = compressions per minute; CPP = cerebral perfusion pressure; CVP = central venous pressure; DBP = diastolic blood pressure; ETCO$_2$ = end-tidal carbon dioxide; ICP = intracranial pressure; MAP = mean arterial blood pressure; SPP = systemic perfusion pressure.

**Table 3**

Hemodynamic Results During Basic and Advanced Life Support by Survival Group

| Parameter | BLS (0–10 min) | | | ALS (10–20 min) | | |
|---|---|---|---|---|---|---|
| | Survivors (n=9) | Non-survivors (n=19) | p | Survivors (n=9) | Non-survivors (n=19) | p |
| ETCO$_2$ (torr) | 35.1 ± 7.1 | 24 ± 10 | 0.007 | 32.5 ± 8.5 | 21.8 ± 14 | 0.06 |
| Comp/min | 130 ± 19 | 117 ± 22 | 0.15 | 126 ± 22 | 120 ± 25 | 0.59 |
| DBP (mmHg) | 16.9 ± 6.4 | 11.4 ± 7.4 | 0.06 | 34.6 ± 11 | 19.7 ± 12 | 0.004 |
| MAP (mmHg) | 28.0 ± 7.6 | 22.0 ± 16 | 0.31 | 49.1 ± 12 | 32.5 ± 18 | 0.02 |
| CVP (mmHg) | 19.1 ± 7 | 16.6 ± 3.5 | 0.21 | 20.3 ± 6.1 | 18.2 ± 3.4 | 0.25 |
| SPP (mmHg) | 9.4 ± 3.7 | 5.7 ± 3.1 | 0.24 | 29.3 ± 13 | 14.6 ± 17 | 0.02 |
| ICP (mmHg) | 19.8 ± 3.7 | 16.7 ± 4.4 | 0.09 | 23.5 ± 5 | 18.9 ± 5 | 0.03 |
| CPP (mmHg) | 8.2 ± 9.3 | 5.3 ± 14 | 0.57 | 26.1 ± 12 | 13.6 ± 16 | 0.04 |

Data represent the cumulative 30-second values during the 10 minutes of basic life support or the 10 minutes of advanced life support and are shown as mean ± SD. ALS = advanced life support; BLS = basic life support; Comp/min = compressions per minute; CPP = cerebral perfusion pressure; CVP = central venous pressure; DBP = diastolic blood pressure; ETCO$_2$ = end-tidal carbon dioxide; ICP = intracranial pressure; MAP = mean arterial blood pressure; SPP = systemic perfusion pressure.

**Table 4**

Outcomes, Blood Gas, and Cardiopulmonary Resuscitation-related Injuries by Study Group

| Variable | ETCO$_2$ Group | Standard Group | p |
|---|---|---|---|
| Outcome results | | | |
|   Successful ROSC, n (%) | 7/14 (50) | 2/14 (14) | 0.04 |
|   Time to ROSC (survivors), min | 15.2 ± 3.9 | 15.6 ± 6.2 | 0.9 |
|   Successfully defibrillated, n (%) | 9/14 (64) | 5/14 (36) | 0.26 |
|   Time to defibrillation, min | 14.6 ± 3.0 | 14.0 ± 5.3 | 0.8 |
|   Defibrillation attempts | 3.6 ± 1.5 | 4.2 ± 1.3 | 0.29 |
|   Doses of epinephrine required | 2.3 ± 0.8 | 2.7 ± 0.7 | 0.16 |
| 8-minute CPR arterial blood gas results | | | |
|   pH | 6.98 ± 0.1 | 7.02 ± 0.2 | 0.77 |
|   PaCO$_2$ | 54 ± 20 | 42 ± 29 | 0.12 |
|   PaO$_2$ | 132 ± 77 | 120 ± 67 | 0.33 |
|   BE | −18 ± 3.4 | −20 ± 3.6 | 0.09 |
| Autopsy results | | | |
|   Atelectasis, n (%) | 10/13 (77) | 8/12 (66) | 0.67 |
|   Liver laceration, n (%) | 0/13 (0) | 0/12 (0) | N/A |
|   Epicardial hemorrhages, n (%) | 10/13 (77) | 4/12 (33) | 0.05 |
|   Hemothorax, n (%) | 3/13 (23) | 0/12 (0) | 0.12 |

Data are shown as mean ± SD unless otherwise specified. Percentages are in parentheses. BE = base excess; N/A = not applicable; PaCO$_2$ = arterial partial pressure of carbon dioxide; PaO$_2$ = arterial partial pressure of oxygen; ROSC = return of spontaneous circulation.