End-Tidal CO$_2$ Detection of an Audible Heart Rate During Neonatal Cardiopulmonary Resuscitation After Asystole in Asphyxiated Piglets

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ABSTRACT: Even brief interruption of cardiac compressions significantly reduces critical coronary perfusion pressure during cardiopulmonary resuscitation (CPR). End-tidal CO$_2$ (ETCO$_2$) monitoring may provide a continuous noninvasive method of assessing return of spontaneous circulation (ROSC) without stopping to auscultate for heart rate (HR). However, the ETCO$_2$ value that correlates with an audible HR is unknown. Our objective was to determine the threshold ETCO$_2$ that is associated with ROSC after asphyxia-induced asystole. Neonatal swine ($n = 46$) were progressively asphyxiated until asystole occurred. Resuscitation followed current neonatal guidelines with initial ventilation with 100% O$_2$ followed by cardiac compressions followed by epinephrine for continued asystole. HR was auscultated every 30 s, and ETCO$_2$ was continuously recorded. A receiver operator curve was generated using the calculated sensitivity and specificity for various ETCO$_2$ values, where a positive test was defined as the presence of HR >60 bpm by auscultation. An ETCO$_2$ cut-off value of 14 mm Hg is the most sensitive ETCO$_2$ value with the least false positives. When using ETCO$_2$ to guide uninterrupted CPR in this model of asphyxia-induced asystole, auscultative confirmation of return of an adequate HR should be performed when ETCO$_2$ $\geq$14 mm Hg is achieved. Correlation during human neonatal CPR needs further investigation. (*Pediatr Res* **69:** 401–405, 2011)

Although the need for neonatal cardiopulmonary resuscitation (CPR) in the delivery room is rare (1,2), morbidity and mortality rates are extremely high for newborns requiring CPR (3). During CPR, it is critical that adequate coronary perfusion should be achieved to establish return of spontaneous circulation (ROSC) (4–7). Adult clinical data and experimental models of ventricular fibrillation-induced cardiac arrest demonstrate that even brief interruption of compressions significantly reduces blood flow and coronary perfusion pressure and reduces ROSC and survival (8–10). No information is available from neonatal models of asphyxia-induced cardiac arrest.

Current adult CPR guidelines recommend a ratio of 30 compressions to 2 breaths for medical providers to limit interruptions of compressions (11) and even uninterrupted compression-only CPR for lay-providers in the field (12). Pediatric life support guidelines for medical providers emphasize a chest compression/ventilation ratio of 15:2 for all children except neonates (11). American Academy of Pediatrics/American Heart Association Neonatal Resuscitation Program (NRP) guidelines recommend a ratio of 3 compressions to 1 breath and pausing every 30 s to auscultate for return of a heart rate (HR) (13). Such frequent interruptions of compressions may limit the ability to achieve an adequate coronary perfusion pressure for ROSC.

End-tidal CO$_2$ (ETCO$_2$) monitoring is a noninvasive tool that has been shown to predict and demonstrate ROSC during experimental and human adult cardiac arrest (14–18). Carbon dioxide is produced by cellular metabolism and is subsequently transported by the venous system to the right heart, where it is pumped into the lungs and diffuses into the exhaled air where it can be measured as ETCO$_2$ (19). Thus, CO$_2$ production, alveolar ventilation, and pulmonary perfusion interact to determine ETCO$_2$. When CO$_2$ production and cardiac output are stable, ETCO$_2$ changes are typically due to changes in alveolar ventilation. During CPR, if ventilation is held constant and CO$_2$ production is assumed to be very low and thus constant, excretion of CO$_2$ through the lungs depends on pulmonary perfusion and therefore relates to cardiac output (14,20–22).

We hypothesized that ETCO$_2$ monitoring might provide a continuous noninvasive method of assessing ROSC without interrupting compressions during neonatal CPR. As a first step, we needed to determine whether there is a consistent threshold ETCO$_2$ that is associated with return of an audible HR >60 bpm after asphyxia-induced asystole. The infrequent and unexpected need for neonatal CPR coupled with the difficulty of obtaining informed consent for such studies has impeded the design and completion of rigorous delivery room CPR studies. Thus, we designed an animal study to determine

Abbreviations: CPR, cardiopulmonary resuscitation; **d,** distance; **ETCO$_2$,** end-tidal CO$_2$; **HR,** heart rate; **NRP,** Neonatal Resuscitation Program; **PPV,** positive pressure ventilation; **ROC,** receiver operator characteristic; **ROSC,** return of spontaneous circulation

the threshold $ETCO_2$ that is associated with ROSC during CPR in asphyxiated, asystolic neonatal piglets whose cardiopulmonary compromise parallels that of asphyxiated infants who require CPR at birth.

METHODS

This investigation was approved by the Institutional Review Board for Animal Research at The University of Texas Southwestern Medical Center at Dallas.

Surgical preparation. A convenience sample of 46 American domestic swine (mean $\pm$ SD: weight, 2.2 ± 0.6 kg; postnatal age, 8 ± 4 d) were studied. All piglets were administered ketamine (20 mg/kg i.m.) as premedication and then were instrumented under pentobarbital anesthesia of 20 mg/kg i.v. bolus followed by 10 mg/kg/h with additional boluses as needed to prevent spontaneous breathing. All surgical sites were infiltrated with 1% xylocaine (Steris Laboratories Inc., Phoenix, AZ). A tracheotomy was performed with placement of a 3.5-mm endotracheal tube. Piglets were ventilated (Harvard Apparatus Rodent Respirator, model 680; Millis, MA) with 70% nitrous oxide and 30% O_2 using rates of 60 breaths/min and tidal volume adjusted to achieve arterial partial pressure of CO_2 ($PaCO_2$) in the mid-40s mm Hg range during the stabilization period. Catheters were positioned by aseptic technique in the right and left external jugular vein, the left internal jugular vein, and the left common carotid artery and left femoral artery. After catheter placement, the inspired gas was changed to 70% nitrogen and 30% O_2. The piglet's body temperature was maintained between 38 and 39°C, using a thermal blanket wrapped around the body and circulating warm water (40–45°C) through the blanket.

Experimental protocol (Fig. 1). After instrumentation, animals were allowed to stabilize for 60 min before acquisition of baseline measurements. Asphyxia was induced by changing ventilatory gases to 7.5% CO_2 and 5.3% O_2, and the ventilator rate was reduced by 10 breaths/min for every 15 min until asystole occurred. Asystole was defined as mean arterial pressure = 0 mm Hg on the continuous blood pressure tracing and confirmed by auscultation of an absent HR. Resuscitation was implemented by a four-member NRP-trained resuscitation team. One team member was assigned to each of the following roles: 1) positive pressure ventilation (PPV) with a self-inflating bag, 2) manual chest compressions, 3) blood sampling and administration of i.v. medications, and 4) code supervisor, who coordinated the timing and sequence of resuscitation interventions as defined in the protocol (Table S1, http://links.lww.com/PDR/A67). Once asystole occurred, the initial steps of neonatal resuscitation (positioning, suctioning, and stimulation) were simulated for 30 s. Asphyxia was reversed by initiating resuscitation using PPV *via* a self-inflating anesthesia bag with 100% inspired O_2. Resuscitation continued with the initiation of manual cardiac compressions. Depth of compressions and compressor fatigue were assessed by real-time evaluation of the aortic compression pressures as displayed on the monitor. Our goals were to achieve an aortic compression pressure around 50–60 mm Hg. Compressions were followed by 0.01–0.03 mg/kg i.v. epinephrine doses in 3-min intervals in accordance with NRP guidelines until ROSC (defined as a HR $\geq$60 bpm) occurred. If there was no ROSC after 15 min of resuscitation, resuscitation efforts ceased. If ROSC was achieved, the piglet was maintained on the ventilator for 2 h without additional medications or interventions before euthanasia (using 200 mg/kg pentobarbital) unless death occurred early.

Measurements. HR and arterial blood pressure were recorded on either a 2-channel recorder (220; Gould, Oxnard, CA) or a Power Lab data acquisition system (model 16/30; AD Instruments, CO Springs, CO). Other measures, including O_2 saturation, HR, $ETCO_2$, and minute ventilation were recorded with a CO_2SMO Plus Respiratory Profile Monitor (Novametrix, Wallingford, CT). These vital signs and respiratory parameters were continuously monitored. Blood chemistries (arterial blood gas, hematocrit, lactate, and glucose) were obtained at control and subsequently every 15 min during asphyxia, every 3 min during the resuscitation phase, and every 30 min during the

postresuscitation phase. The arterial pH, PCO_2, and PO_2 were analyzed by an Instrumentation Laboratory Micro gas analyzer (15 μL of blood). The microhematocrit method was used to determine hematocrit. Serum glucose concentrations were measured using an Accu-Chek Advantage glucometer (Roche Diagnostics, Indianapolis, IN). The plasma concentration of lactic acid was determined by a quantitative enzymatic determination assay (Sigma Chemical Co., St. Louis, MO).

Statistical analysis. Data analysis was completed using Sigma Stat 11.0 (SPSS, Chicago, IL). The results are reported as the mean $\pm$ SD. Nonparametric analyses were used when indicated. A p-value $\leq$0.05 was considered statistically significant. A receiver operator characteristic (ROC) curve (a plot of the true positives against the false positives for different test cut-off points) was generated for various $ETCO_2$ values where a positive test was defined as an $ETCO_2$ value that was associated with return of a HR >60 bpm. The optimal $ETCO_2$ cut-off value on the curve was selected based on a combination of *a priori* criteria including 1) significant area under the curve compared with a 45° line of equality, 2) optimum sensitivity and specificity values, 3) maximum perpendicular distance (*d*) above the 45° line of equality, and 4) the highest proportion of correct predictions (accuracy).

RESULTS

At baseline before initiation of asphyxia, piglets had HR, pH, $PaCO_2$, $ETCO_2$, lactate, and glucose levels similar to healthy term neonates (Table 1). The mean time from initiation of asphyxia to asystole was 48 ± 13 min. As expected with asphyxiation, by the time asystole occurred, the piglets developed a severe mixed respiratory and metabolic acidosis similar to infants who require CPR in the delivery room (3). $ETCO_2$ levels had climbed concordant with the respiratory acidemia.

The actual mean ($\pm$SD) aortic compression (systolic) and relaxation (diastolic) pressures attained with this experimental neonatal CPR model were the following: 1) 1 min after initiation of CPR, the mean systolic compression pressure was 56 ± 8 mm Hg, with a diastolic pressure of 4 ± 2 mm Hg; 2) Immediately after the first dose of epinephrine, the mean systolic compression pressure remained 60 ± 11 mm Hg, with a diastolic pressure of 5 ± 3 mm Hg; 3) Immediately before ROSC, mean systolic compression pressure increased to 95 ± 9 mm Hg, with increased diastolic pressures of 19 ± 3 mm Hg.

A representative blood pressure/HR/$ETCO_2$ tracing is shown in Figure 2. Immediately before cardiac arrest, the high $ETCO_2$ values (due to asphyxia) drifted down as pulmonary blood flow became increasingly limited. After 30 s of PPV, the remaining CO_2 was ventilated off of the lung, and $ETCO_2$ decreased to near zero. When a small amount of pulmonary blood flow was reestablished by initiation of cardiac compressions, a slight increase in $ETCO_2$ was detected. A sudden increase in $ETCO_2$ was observed in all animals after ROSC (usually after epinephrine administration) as pulmonary blood
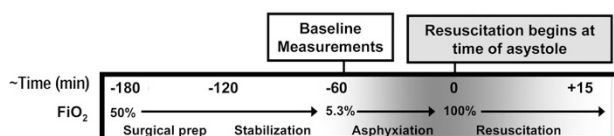

Figure 1. Experimental protocol. This model gradually induces asphyxia to create a biochemical profile similar to asphyxiated infants who require CPR in the delivery room. FiO_2, fraction of inspired O_2.

Table 1. *Piglet characteristics at baseline and asystole* (n = 46)

	Baseline	Asystole*
Heart rate	163 ± 26	0 ± 0
Mean arterial pressure (mm Hg)	78 ± 12	0 ± 0
Arterial pH	7.38 ± 0.05	6.84 ± 0.17
Arterial PCO_2 (mm Hg)	43 ± 5	96 ± 25
Arterial PO_2 (mm Hg)	192 ± 33	29 ± 12
$ETCO_2$ (mm Hg)	40 ± 4	70 ± 23
Glucose (mg%)	80 ± 23	114 ± 102
Hematocrit (%)	30 ± 5	30 ± 4

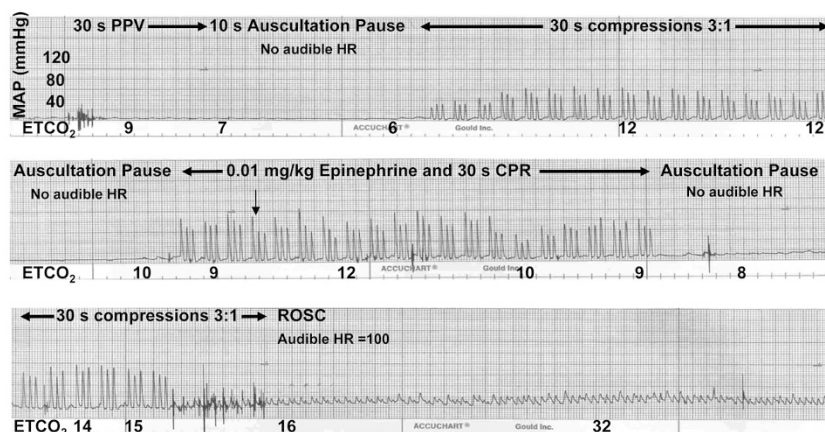* Measurements were obtained at the time of asystole before initiation of resuscitation.

Figure 2. Representative tracing of ETCO$_2$ and mean arterial pressure (MAP) during CPR. After initial PPV, ETCO$_2$ values decreased from asphyxia values to 6 mm Hg and then gradually increased as blood pressure increased with initiation of CPR. ETCO$_2$ values decreased during each 10 s pause to auscultate for HR, reflecting loss of blood flow with interruption of cardiac compressions. After epinephrine administration, blood pressure improved and ETCO$_2$ increased to 15 mm Hg, at which point ROSC occurred and an audible HR was detected. The hatch marks along the bottom of each frame represent 1 s.

Table 2. *ROC analysis for ETCO$_2$ corresponding to return of audible HR >60 bpm*

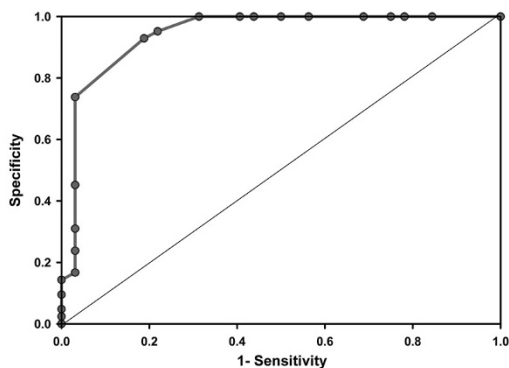| ETCO$_2$ cut-off value (mm Hg)	12	13	14	15
Sensitivity (%)	100	95	92	73
Specificity (%)	68	78	81	96
False negative (%)	0	4	6	24
False positive (%)	22	15	13	2
Likelihood ratio	3.20	4.35	4.95	23.62
Distance (*d*)	0.486	0.519	0.524	0.499
Correct predictions (%)	86	87	88	84

Figure 3. ROC curve for ETCO$_2$ detection of an audible HR after asystole. The sensitivity (true positive rate) was plotted against 1 − specificity (false-positive rate) for each ETCO$_2$ value. Area, 0.94; 95% CI, 0.88–1.00.

flow quickly improved with the resumption of the pumping action of the heart. ROSC was achieved in 42 of 46 piglets.

The sensitivity, specificity, false positive, false negative, positive likelihood ratio, and % correct prediction for return of an audible HR >60 bpm for a range of ETCO$_2$ values are seen in Table 2. The receiver operator curve is seen in Figure 3, and area under the curve statistics was significant at 0.94 (95% CI 0.88–1.00). An ETCO$_2$ cut-off >14 mm Hg had a sensitivity of 93%, specificity of 81%, positive likelihood ratio of 5, and 88% accuracy at predicting return of HR >60 bpm. The distance *d* calculated from the ROC analysis for the ETCO$_2$ critical value of 14 mm Hg or higher was 0.524.

DISCUSSION

In this neonatal model of asphyxia-induced asystole, increasing ETCO$_2$ values seem to correlate with ROSC and an

audible HR >60 bpm. Given the consistent threshold >14 mm Hg at which ETCO$_2$ correlates with return of an adequate HR, it may be useful to guide uninterrupted neonatal CPR. An ETCO$_2$ cut-off >14 mm Hg seems most useful for determining when to interrupt CPR to auscultate for a HR by providing the lowest combination of false positives and false negatives and the best fit with optimal calculated distance to an ideal curve using ROC analysis with a sensitivity of 93%, 81% specificity, and a positive likelihood ratio of 5.

The current NRP recommendation to interrupt cardiac compressions every 30 s for a 6 s auscultation pause to check for ROSC (13) may not be optimal. In an adult animal model, such breaks in cardiac compressions further delay reestablishment of adequate coronary perfusion pressure, which is very dependent on ongoing uninterrupted compressions (23). NRP also recommends checking for the presence or absence of a palpable pulse during the resuscitative effort to assess the adequacy of artificial perfusion during cardiac compressions (13); however, coronary perfusion pressure (which is calculated as the aortic diastolic blood pressure − the right atrial diastolic blood pressure) is not impacted by the difference in systolic and diastolic pressures represented by a palpable pulse but rather by the aortic diastolic pressure itself (24). Thus, monitoring ETCO$_2$ trends during CPR would allow uninterrupted cardiac compressions and might provide a better indicator of the effectiveness of perfusion during compression administration.

ETCO$_2$ is a measure of the P$_{CO_2}$ at the end of an exhaled breath and is mainly determined by alveolar ventilation, pulmonary perfusion (right cardiac output), and CO$_2$ production due to metabolism. During acutely low cardiac output states as in cardiac arrest, decreased pulmonary blood flow becomes the primary determinant of ETCO$_2$, resulting in low values (25,26). The concept of change in ETCO$_2$ reflecting the changes in pulmonary blood flow in the presence of constant cardiac compressions and ventilation has been used to assess circulatory status during cardiac arrest and resuscitation in adults (17). In experimental models of ventricular fibrillation-induced cardiac arrest, ETCO$_2$ concentration during ongoing CPR correlates with cardiac output, coronary perfusion pressure, and successful resuscitation from cardiac arrest (27,28).

Experimental animal adult studies of atraumatic cardiac arrest have reported increasing $ETCO_2$ to be also associated with ROSC (21). In such models, an $ETCO_2$ threshold of 15 mm Hg predicted ROSC with a positive predictive value 91% and negative predictive value of 91% (25).

In contrast to adult models of ventricular fibrillation, animal models of brief asphyxial pediatric cardiac arrest reported initially elevated $ETCO_2$ levels reflective of the high alveolar P_{CO_2} present at the time of asphyxial arrest. This was followed by a subsequent decrease in P_{CO_2} once ventilation was initiated (22,29) as the P_{CO_2} present in the lung at the time of arrest was ventilated off and no further CO_2 was brought to the lung due to arrested perfusion. In our neonatal model of asphyxia-induced asystole, we observed similar findings with high initial $ETCO_2$ at the time of asystole that decreased after 30 s of adequate PPV. This pattern of $ETCO_2$ changes is different from that observed in ventricular fibrillation arrest, because P_{CO_2} levels are typically normal at the time of cardiac arrest from ventricular fibrillation as opposed to very elevated at the time of asphyxial cardiac arrest. No previous study of asphyxial cardiac arrest has determined $ETCO_2$ values that correlate with return of an audible HR >60 bpm, which is the current clinical goal for stopping cardiac compressions after asphyxia-induced asystole in neonates.

A strength of this translational study is the use of a piglet asphyxia model that closely mimics delivery room events with gradual onset of severe asphyxia leading to asystole. The presence of a dedicated focused clinical resuscitation team with current NRP training, along with designated roles during the resuscitation, a supervisor leading the code and a recorder for accuracy of documentation, makes this piglet asphyxia model an ideally controlled mega code environment. We attempted to control for depth of compressions and compressor fatigue by real-time assessment and adjustment of the pulse pressures generated by the compressor. This controlled setting allowed us to generate an ROC curve related to the predictive values of $ETCO_2$, with minimum confounding variables.

The following limitations should be considered before general application of $ETCO_2$ guidance in future clinical neonatal resuscitation trials. The current model is one where the animals have already undergone fetal to neonatal transition and in addition are sedated/anesthetized. The findings are still relevant despite this limitation, because the distribution of cardiac output in the fetus and posttransitional neonate during asphyxial episodes are qualitatively similar (30–32). In addition, responsiveness and reactivity of the cerebral circulation to factors that modulate cerebral blood flow such as hypoxia qualitatively remain intact under barbiturate anesthesia (33,34). Another limitation is that manual ventilation and chest compressions could cause $ETCO_2$ to fluctuate with the effort of compression and rate of ventilation (20,35), so uniform compressions need to be delivered for $ETCO_2$ to be used as a predictor of ROSC. In addition, acute and chronic illness with comorbidities can result in a ventilation/perfusion mismatch, which can limit the accuracy of $ETCO_2$ (36). This is unlikely to be a problem in the post transitional neonatal piglet model currently used in this study. The effect of resuscitation medications such as epinephrine needs to be carefully re-corded and should also be taken into consideration. According to adult studies, $NaHCO_3$ can transiently increase $ETCO_2$, whereas epinephrine can lead to decreased levels (37). Finally, this model is based on HR assessment in term animals and does not include evaluation for pseudo-pulseless electrical activity, where there is no clinically palpable pulse but presence of blood flow. The model does not address issues of prematurity or low birth weight.

In conclusion, our study using this piglet model of asystole due to asphyxia demonstrates that capnometry can be used as a predictor of ROSC, and may be a useful substitute for frequent pauses in cardiac compressions to auscultate HR during neonatal CPR. Further investigation is needed to determine whether uninterrupted $ETCO_2$-guided CPR can improve time to ROSC and short- and long-term outcomes after neonatal resuscitation.

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