Continuous End-Tidal Carbon Dioxide Monitoring during Resuscitation of Asphyxiated Term Lambs

Praveen Kumar Chandrasekharan^a Munmun Rawat^a Jayasree Nair^a
Sylvia F. Gugino^{a, b} Carmon Koenigsnecht^a Daniel D. Swartz^{a, b} Payam Vali^a
Bobby Mathew^a Satyan Lakshminrusimha^a

^aDivision of Neonatology, Department of Pediatrics, and ^bDepartment of Physiology and Biophysics, University at Buffalo, Buffalo, N.Y., USA

Key Words

Capnography · Carbon dioxide · Carotid blood flow

Abstract

Background: The Neonatal Resuscitation Program (NRP) recommends close monitoring of oxygenation during the resuscitation of newborns using a pulse oximeter. However, there are no guidelines for monitoring carbon dioxide (CO₂) to assess ventilation. Considering that cerebral blood flow (CBF) correlates directly with PaCO₂, continuous capnography monitoring of end-tidal CO₂ (ETCO₂) may limit fluctuations in PaCO₂ and, therefore, CBF during resuscitation of asphyxiated infants. **Objective:** To evaluate whether continuous monitoring of ETCO₂ with capnography during resuscitation of asphyxiated term lambs with meconium aspiration will prevent fluctuations in PaCO₂ and carotid arterial blood flow (CABF). **Methods:** Fifty-four asphyxiated term lambs with meconium aspiration syndrome were mechanically ventilated from birth to 60 min of age. Ventilatory parameters were adjusted based on clinical observation (chest excursion) and frequent arterial blood gas analysis in 24 lambs (control group) and 30 lambs (capnography group)

received additional continuous ETCO₂ monitoring. Left CABF was monitored. We aimed to maintain PaCO₂ between 35 and 50 mm Hg and ETCO₂ between 30 and 45 mm Hg. **Results:** There was a significant correlation between ETCO₂ and PaCO₂ ($R = 0.7$, $p < 0.001$), between PaCO₂ and carotid flow ($R = 0.52$, $p < 0.001$) and between ETCO₂ and carotid flow ($R = 0.5$, $p < 0.001$). PaCO₂ and CABF during the first 60 min of age showed significantly higher fluctuation in the control group compared to the capnography group. **Conclusion:** Continuous monitoring of ETCO₂ using capnography with mechanical ventilation during and after resuscitation in asphyxiated term lambs with meconium aspiration limits fluctuations in PaCO₂ and CABF and may potentially limit brain injury.

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Introduction

Ventilation of the lungs is the single most important and effective step in resuscitation [1]. Approximately 5–10% of newborn infants require some degree of active resuscitation at birth [2] and approximately 1–10% of in-

infants born in hospital are reported to require assisted ventilation [1, 3], with few of these infants being intubated in the delivery room [4]. Clinically, the adequacy of ventilation is assessed by chest rise, auscultation and improving heart rate. The assessment of ventilation based on chest rise is unreliable [5, 6] and in instances when chest rise was used to determine the adequacy of ventilation, infants were hypocapnic at the time of admission [7]. Inaccurate clinical assessment of ventilation places newborns at risk for hypocapnia and/or hypercapnia. End-tidal capnography (end-tidal carbon dioxide, ETCO_2) provides a graphical assessment of the partial pressure of CO_2 during expiration and is being increasingly used in the neonatal intensive care unit (NICU) [8].

Extremes of PaCO_2 may prove detrimental in an asphyxiated infant by causing fluctuations in cerebral blood flow (CBF) [9]. Hypocapnia is associated with a decrease in brain tissue oxygen saturation during hyperventilation [10]. Cumulative exposure to hypocapnia ($\text{PaCO}_2 < 35$ mm Hg) has been associated with a higher rate of death or disability in infants with hypoxic-ischemic encephalopathy (HIE) [11]. Therefore, in addition to maintaining oxygenation during resuscitation and in the postresuscitation phase, it is crucial to avoid wide fluctuations in PaCO_2 in infants with perinatal asphyxia [12].

Frequent evaluation of PaCO_2 by blood gas analysis is not practical in the delivery room [13]. Studies have shown a positive correlation between ETCO_2 and PaCO_2 in the NICU [8, 14]. The reliability of ETCO_2 during the period of transition in the delivery room is not known. Monitoring ETCO_2 with waveform capnography during PPV in the delivery room may help avoid extreme fluctuations in PaCO_2 levels. We hypothesize that ETCO_2 correlates well with PaCO_2 during transition and continuous monitoring of ETCO_2 with capnography during resuscitation of asphyxiated term lambs with meconium aspiration will prevent fluctuations in PaCO_2 and CBF.

Methods

The Institutional Animal Care and Use Committee (IACUC) at the State University of New York at Buffalo approved this study. Near-term time-dated pregnant ewes (New Life Pastures, Attica, N.Y., USA) were sedated with intravenous ketamine and diazepam, intubated and ventilated with 21–30% oxygen and ~2% isoflurane. The fetal lambs were exteriorized. Jugular and carotid lines were placed on the right side for access, to draw preductal arterial blood gases and to monitor systemic blood pressure. Ultrasound probes (Transonic Systems, Ithaca, N.Y., USA) were placed around the left carotid artery and left pulmonary artery to measure blood flow. Systemic and pulmonary pressures were measured by trans-

ducing the right carotid and left pulmonary arteries. A catheter was placed in the left atrium to measure the pressures.

As previously described [15], approximately 1 g/kg of human meconium was added to warm amniotic fluid from the ewe's uterus (4 ml/kg lamb weight) to a total volume of 5 ml/kg estimated weight and homogenized to form a viscous 'thick' meconium solution. The solution was aspirated using an 18-gauge needle with a syringe. After draining the excess lung liquid, a funnel with meconium in the amniotic fluid was connected to the endotracheal tube. The meconium solution was layered over the fetal lung liquid in the endotracheal tube and maintained at a height whereby hydrostatic pressure did not force meconium into the lungs. The umbilical cord was occluded for 5 min (cord occlusion 1) using an inflatable vascular occluding device, resulting in approximately 10–15 gasps. Umbilical cord occlusion was released for 5 min to allow the lamb to recover and then occlusion was repeated for 5 more min (cord occlusion 2). Deep, gasping respirations aspirated meconium into the lung. At the end of this period, the endotracheal tube that was used to deliver the meconium was replaced. The umbilical cord was cut (delivery time) and the lamb was placed under a radiant warmer. Following this period, the lambs were delivered and resuscitated as per the Neonatal Resuscitation Program (NRP) guidelines. Preductal saturations were recorded using a Masimo Radical 7 pulse oximeter (Irvine, Calif., USA). To monitor ETCO_2 in the study group, side-stream capnography (SurgiVet 9004; Smith Medical, Mass., USA) was used. According to the manufacturer, SurgiVet 9004 has an accuracy of ± 2 mm Hg, with a display range of 0–100 mm Hg. The capnograph continuously displayed the ETCO_2 in millimeters of Hg with a waveform and respiratory rate.

Ventilation and Blood Gas Analyses

After delivery, the lambs were ventilated with the Siemens Servo 300A (Monet Medical, Salt Lake City, Utah, USA) using a pressure control mode of ventilation. Ventilation was initiated with a peak inspiratory pressure (PIP) of 30 cm H_2O and a PEEP of 5 cm H_2O . Arterial blood gases were drawn at birth and at 1 and 5 min after birth followed by every 5 min for the first 30 min and every 15 min for the next 30 min. The lambs were ventilated in the first hour in both groups with a preductal oxygen saturation range of 85–99%. The intervention group (capnography) was not randomized and was chosen based on the availability of capnography equipment.

In the control group (24 lambs), PaCO_2 was targeted between 35 and 50 mm Hg. PIP was adjusted by 2 cm H_2O (based on chest excursion) and subsequently the respiratory rate (by 5 breaths/min) in an attempt to maintain PaCO_2 within the target range. In the capnography group (30 lambs), in addition to maintaining PaCO_2 , ETCO_2 was targeted between 30 and 45 mm Hg as our preliminary data showed a variation of 5–10 mm Hg compared to PaCO_2 . Continuous monitoring of ETCO_2 with capnography with frequent ventilator adjustments based on ETCO_2 values in addition to PaCO_2 were performed in asphyxiated term lambs with meconium aspiration to limit fluctuations in PaCO_2 and CBF.

Data Collection and Calculations

Data were continuously recorded using AcqKnowledge Acquisition and Analysis Software (BIOPAC Systems, Goleta, Calif., USA). The variations in ETCO_2 , PaCO_2 and left carotid arterial blood flow (CABF) were compared from 5 to 60 min of age. Data

Fig. 1. PaO₂ (a), MBP (b) and PVR (c) are represented by graphs. Data from fetal baseline values, cord occlusion for asphyxiation, resuscitation and the first 60 min of postnatal period are shown in the graph. Data were analyzed from 5 to 60 min of life. PaO₂, MBP and PVR were similar between groups.

were compared after 5 min of age to allow pulmonary adaptation and transition to extrauterine life [16]. Pulmonary vascular resistance (PVR) was calculated by dividing the difference in mean pulmonary arterial pressure and left atrial pressure by left pulmonary blood flow per minute corrected for body weight.

Statistics

Sample Size and Power. The standard deviation (SD) of the fluctuation in PaCO₂ during the first 60 min in lambs with meconium aspiration is 11 mm Hg. To reduce this fluctuation (maximum PaCO₂ – minimum PaCO₂ in the first 60 min) by 10 mm Hg using capnography, we needed 20 lambs in each group with a type I error probability of 0.05 and a power of 0.8. With the current

sample size of 30 lambs in the capnography group and 24 control lambs, a probability (power) of 0.903 was achieved.

Statistical Methods. Pearson and Spearman correlations along with Bland-Altman plots were used in assessing ETCO₂ and PaCO₂ values. Normally distributed variables are presented as means ± SD and skewed variables as medians (with ranges). The proportion of PaCO₂ values outside the target range between the groups was compared by χ^2 test. The fluctuations (differences between minimum and maximum values during 5–60 min of age represented as bar graphs) in PaCO₂ and left CABF were analyzed by the unpaired t test. A p value of <0.05 was considered significant. Data were analyzed using SPSS 22 software (IBM, Armonk, N.Y., USA).

Fig. 2. a Scatter plot of ETCO₂ and PaCO₂ values from 5 to 60 min of age showed good correlation ($R = 0.73$, $\rho = 0.7$, $p < 0.001$). **b** The agreement between ETCO₂ and PaCO₂ is illustrated as a Bland-Altman plot. The ETCO₂ was lower than PaCO₂ with a mean bias of -11.7 ± 7.7 mm Hg, with a 95% confidence interval of -26.7 to 3.3 mm Hg.

Table 1. Baseline characteristics and blood gas values prior to onset of resuscitation

Parameters	Capnography (n = 30)	Control (n = 24)
Birth weight, g	3,460 ± 820	3,220 ± 780
Gestational age, days	141 ± 0.5	141 ± 0.8
Oxygenation index	18.6 ± 10	20.1 ± 9
SpO ₂ , %	49 ± 29	49 ± 25
pH	7.02 ± 0.10	6.9 ± 0.13
PaCO ₂ , mm Hg	102 ± 29	107 ± 25
Base excess, mEq/l	-8.7 ± 2.1	-10.4 ± 3.8

Values are means ± SD. SpO₂ = Preductal oxygen saturation; mEq = milliequivalent. Severe asphyxia induced by intermittent umbilical cord occlusion resulted in severe acidosis. The values represented in the table are at birth and were not different between groups.

Fig. 3. a Scatter plot of left CABF and PaCO₂ showed a moderate correlation ($R = 0.52$, $\rho = 0.31$, $p < 0.001$). **b** Scatter plot of left CABF and ETCO₂ showed a moderate correlation ($R = 0.48$, $\rho = 0.48$, $p < 0.001$). The left CABF is plotted on a logarithmic scale.

Results

Umbilical cord occlusion and meconium aspiration resulted in severe hypercarbia and acidosis at birth (table 1). The preductal oxygenation index (mean airway pressure in cm H₂O × FIO₂ × 100/preductal PaO₂) following meconium aspiration was 18.6 ± 10 and 20.1 ± 9 in the capnography and control groups, respectively. The partial pressure of oxygen in arterial blood (PaO₂), systemic mean blood pressure (MBP) and PVR between the groups were not different during the first postnatal hour (fig. 1). There were 274 simultaneous blood and ETCO₂ measures obtained from the 30 lambs in the capnography group. The ETCO₂ levels obtained during the first 2 min after birth were low compared to PaCO₂ values and were excluded from the correlation analysis. The correlation between ETCO₂ and PaCO₂ following the first 2 min after

Fig. 4. The variance of PaCO₂ (a) and left CABF (b) are depicted as box plots between the groups.

birth improved ($R = 0.64$, $\rho = 0.6$, $p = 0.01$). From 5–60 min after birth, the ET-CO₂ correlated well with PaCO₂ with a correlation coefficient $R = 0.73$ ($\rho = 0.7$, $p < 0.001$; fig. 2a). The agreement between ET-CO₂ and PaCO₂ is illustrated as a Bland-Altman plot [17]. The ET-CO₂ was lower than PaCO₂ with a mean bias of -11.7 ± 7.7 mm Hg, with a 95% confidence interval of -26.7 to 3.3 (fig. 2b). Left CABF had a modest correlation with PaCO₂ ($R = 0.52$, $\rho = 0.31$, $p < 0.001$; fig. 3a) and with ET-CO₂ ($R = 0.48$, $\rho = 0.48$, $p < 0.001$; fig. 3b). There was a mean 19% increase in CABF for each kilopascal increase in PaCO₂ (or 2.5% increase with an increase of 1 mm Hg in PaCO₂). The

respiratory rate (both spontaneous and ventilator setting of mandatory rate) during the entire study period did not correlate well with ET-CO₂ (0.13) or PaCO₂ (0.30). The percentage of PaCO₂ outside the target range in the control group (61%) was significantly greater than the capnography group (43%, $p = 0.002$). The variance of PaCO₂ and left CABF are depicted as box plots (fig. 4a, b) and the fluctuations as bar graphs (fig. 5a, b). The fluctuation of PaCO₂ (30.5 ± 18.9 vs. 20.0 ± 11.4 mm Hg, $p = 0.002$) and the fluctuation between the left CABF (25.8 ± 5.8 vs. 13.1 ± 2.1 ml/kg/min, $p = 0.008$) were significantly higher in the control group compared to the capnography group.

Fig. 5. a The fluctuations in PaCO₂ are depicted as bar diagrams in the capnography and control groups. The fluctuations (difference between the mean maximum and minimum values) were significantly different ($p = 0.002$). **b** The fluctuations in the left CABF are

depicted as bar diagrams between the groups. The fluctuations (difference between the mean maximum and minimum values) were significantly different ($p = 0.008$). * $p < 0.05$, significant difference.

The median PaCO₂ from 5–60 min of age was 40 (20–77) mm Hg in the capnography group and 40 (20–104) mm Hg in the control group. The median left CABF was 20 (3–59) ml/kg/min in the capnography group and 23 (5–90) ml/kg/min in the control group.

Discussion

Perinatal asphyxia is a major cause of HIE and is often associated with meconium aspiration syndrome [18, 19]. The initial delivery room management of an unstable newborn infant is important to ensure transition to extrauterine life and optimize lifelong neurodevelopmental outcome [20]. Birth asphyxia is associated with fluctuations in CBF in the early postresuscitation period [21]. Monitoring PaCO₂ is not only important to avoid fluctuations in CBF but also to maintain moderately elevated PaCO₂ during the first minutes of resuscitation to restore CBF [22, 23]. In addition elevated PaCO₂ may be beneficial and is associated with higher 5-min Apgar scores after moderate acidemia [24]. However, a persistent or excessive increase in brain perfusion during the postnatal period may be associated with reperfusion injury in HIE

[25]. Wide variations in arterial PaCO₂ values are common immediately following asphyxia and resuscitation [26] and may contribute to fluctuations in CBF. A recent retrospective study has shown severe abnormal neurodevelopmental outcomes to be associated with high PaCO₂ variability over 72 h in whole-body cooled HIE neonates [12]. Our study aimed at avoiding fluctuations in PaCO₂ and studying its impact on CABF in a term asphyxiated lamb model in the immediate transition phase.

Current NRP guidelines focus on maintaining normoxemia using a pulse oximeter in the delivery room [1]. However, hypercapnia even in the presence of normoxemia results in a significant increase in CBF in newborn piglets [27]. Severe hypercarbia is commonly seen immediately following asphyxia (table 1). Resuscitation with PPV can result in either overventilation with hypocapnia or underventilation with hypercapnia. In this study, we have demonstrated that capnography, when combined with blood gas monitoring, is a simple intervention that is superior to frequent blood gas sampling alone at the bedside in reducing fluctuations in PaCO₂.

Pryds et al. [28] have evaluated the effect of blood pressure and PaCO₂ on CBF in newborn infants with varying severity of HIE and compared them to normal

control infants. Following very severe asphyxial injury leading to an isoelectric EEG, vasoparalysis resulted in a pressure-passive cerebral circulation that is nonresponsive to PaCO_2 . However, CBF in neonates with severe asphyxial injury leading to burst suppression on EEG was pressure passive but was responsive to changes in PaCO_2 (~ 2% mean change in flow for every millimeter Hg change in PaCO_2 compared to 3.4% in control neonates without asphyxia) [28]. Carotid blood flow increased by 2.5% for every millimeter Hg increase in PaCO_2 in the current study – consistent with the published literature. Hence, in infants with moderate to severe asphyxia, avoiding hypocapnia and hypercapnia during and immediately after resuscitation and maintaining stable systemic blood pressure may be important in minimizing reperfusion injury.

We found poor correlation between ETCO_2 and PaCO_2 ($R = 0.11$) during the first 2 min of resuscitation. This is probably due to poor lung aeration secondary to alveolar fluid, poor access to alveolar gas, low pulmonary blood flow and severe lung disease. Hooper et al. [29] have similarly demonstrated that increasing ETCO_2 levels in newly born lambs and preterm rabbits are reflective of increasing tidal volume and improved lung aeration after birth. Similarly, Schmolzer et al. [16] have shown the relationship between ETCO_2 and establishing tidal volume during the first couple of minutes in human neonates. These findings suggest that ETCO_2 values may not correlate well with PaCO_2 in the first few minutes of resuscitation. In the presence of an increasing or stable heart rate, we recommend that adjustments to ventilation (such as decreasing PIP) should not be made based on ETCO_2 values during the first couple of minutes of resuscitation, prior to the establishment of lung aeration in asphyxiated neonates. An increasing ETCO_2 in the first couple of minutes may be a sign of better lung aeration and increasing pulmonary blood flow.

A good correlation between ETCO_2 and PaCO_2 has been demonstrated in NICU patients, including extremely low-birth-weight patients [14]. In the current study, we used a model of perinatal asphyxia with combined metabolic and respiratory acidosis, significant parenchymal lung disease and airway obstruction. In spite of the presence of parenchymal and airway disease, we found a good correlation between PaCO_2 and ETCO_2 . The presence of increased physiological dead space and the meconium aspiration in lambs could have contributed to the increased difference between PaCO_2 and ETCO_2 (mean of -11.7) in our study compared to previous studies (fig. 2b).

Term infants have much greater cerebrovascular sensitivity to PaCO_2 than preterm infants [30]. Wyatt et al. [30] calculated that the percentage change in cerebral blood volume increased per kilopascal change in PaCO_2 from 4% at 26 weeks to 25% at 40 weeks. We studied the effect of fluctuations of PaCO_2 on the left CABF in a controlled setting while maintaining normoxia with similar systemic pressure and PVR between the groups. Fluctuations in PaCO_2 outside the target range (35–50 mm Hg) could be considered clinically relevant, as hypocarbia and hypercarbia have been reported when clinical methods are used for ventilation. By reducing fluctuations in PaCO_2 , we were able to maintain the left CABF within a narrow range in the capnography group (fig. 5).

Strengths and Limitations

This study was conducted in a model of perinatal asphyxia and lung disease (meconium aspiration) with severe respiratory acidosis, a condition where variations in cerebral and pulmonary blood flows can influence outcome. An asphyxiated model with cardiac arrest would have provided more information on the effect of fluctuation of CO_2 on CBF. The use of hand bagging or a T-piece resuscitator instead of a ventilator for resuscitation may have yielded different results that are more pertinent to delivery room resuscitation. A wide target (35–50 mm Hg) for ETCO_2 was a limitation and could have contributed to fluctuation in the capnography group. Given the variability in ETCO_2 values, choosing a narrow target range (35–40 mm Hg) could have further reduced fluctuation in the capnography group. A major limitation of the current study is that it was unblinded and not randomized, where the lambs were assigned to the group based on the availability of capnography equipment in the laboratory animal-operating suite. Less frequent blood gas analysis (as seen in many clinical settings) may have yielded potentially increased fluctuation in CBF in the control group, leading to different results. Finally, we did not have access to volumetric data (tidal volume) in our capnograph instrument and access to this information may have helped us wean PIP and rate on the ventilator.

Potential Role of Monitoring ETCO_2 during Neonatal Resuscitation in the Delivery Room

We speculate that the use of capnography while providing PPV through an endotracheal tube will limit fluctuations in PaCO_2 and that maintaining normoxia may benefit asphyxiated, unstable term infants by avoiding

fluctuations of CBF. This may potentially lead to better outcomes in infants at risk for hypoxic injury. In addition, capnography may also be able to measure the effectiveness of chest compressions and identify the return of spontaneous circulation in patients with cardiac arrest [31]. It is also possible that in conditions with a marked increase in physiological dead space, a low ETCO_2 (with normal PaCO_2) may lead to hypoventilation. Caution must be exercised while interpreting ETCO_2 values during the first few minutes of resuscitation prior to the establishment of lung aeration. Periodic blood gas analysis and trending with ETCO_2 is recommended during prolonged resuscitation.

Conclusion

Based on our results, continuous ETCO_2 during and immediately after resuscitation is feasible and may limit fluctuations in PaCO_2 and CBF in an asphyxiated term infant with tracheal intubation. Further clinical and translational studies evaluating capnography with volumetric data during resuscitation and the postresuscitation phase with neurodevelopmental follow-up are needed before advocating its routine use in clinical practice.

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