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### Authors

Chandrasekharan, Praveen Kumar  
Rawat, Munmun  
Nair, Jayasree  
et al.

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

Praveen Kumar Chandrasekharan<sup>1</sup>, Munmun Rawat<sup>1</sup>, Jayasree Nair<sup>1</sup>, Sylvia F. Gugino<sup>1,2</sup>, Carmon Koenigschnekt<sup>1</sup>, Daniel D. Swartz<sup>1,2</sup>, Payam Vali<sup>1</sup>, Bobby Mathew<sup>1</sup>, and Satyan Lakshminrusimha<sup>1</sup>

<sup>1</sup>Division of Neonatology, Department of Pediatrics, University at Buffalo, Buffalo, New York

<sup>2</sup>Division of Physiology and Biophysics, University at Buffalo, Buffalo, New York

### 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 (CO<sub>2</sub>) to assess ventilation. Considering that cerebral blood flow (CBF) correlates directly with PaCO<sub>2</sub>, continuous capnography monitoring of end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) may limit fluctuations in PaCO<sub>2</sub> and, therefore, CBF during resuscitation of asphyxiated infants.

**Objective**—To evaluate if continuous monitoring of ETCO<sub>2</sub> with capnography during resuscitation of asphyxiated term lambs with meconium aspiration will prevent fluctuations in PaCO<sub>2</sub> 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 ETCO<sub>2</sub> monitoring. Left CABF was monitored. We aimed to maintain PaCO<sub>2</sub> between 35–50 mmHg and ETCO<sub>2</sub> between 30–45 mmHg.

**Results**—There was a significant correlation between ETCO<sub>2</sub> and PaCO<sub>2</sub> (R=0.7, p<0.001), between PaCO<sub>2</sub> and carotid flow (R=0.52, p<0.001), and between ETCO<sub>2</sub> and carotid flow (R=0.5, p<0.001). PaCO<sub>2</sub> and CABF during the first 60 minutes of age showed significantly higher fluctuation in the control group compared to the capnography group.

**Conclusion**—Continuous monitoring of ETCO<sub>2</sub> using capnography with mechanical ventilation during and after resuscitation in asphyxiated term lambs with meconium aspiration limits fluctuations in PaCO<sub>2</sub> and CABF, and may potentially limit brain injury.

### Keywords

capnography; carbon dioxide; carotid blood flow

## Introduction

Ventilation of the lungs is the single most important and effective step in resuscitation [1]. Approximately 5 to 10% of newborn infants require some degree of active resuscitation at birth [2] and approximately 1–10% of 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, 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 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 CO<sub>2</sub>, ETCO<sub>2</sub>) provides a graphical assessment of the partial pressure of carbon dioxide during expiration and is being increasingly used in the neonatal intensive care unit (NICU) [8].

Extremes of PaCO<sub>2</sub> may prove detrimental in an asphyxiated infant by causing fluctuations in CBF [9]. Hypocapnia is associated with a decrease in brain tissue oxygen saturation (PbtO<sub>2</sub>) during hyperventilation [10]. Cumulative exposure to hypocapnia (PaCO<sub>2</sub> <35 mmHg) 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 post-resuscitation phase, it is crucial to avoid wide fluctuations in PaCO<sub>2</sub> in infants with perinatal asphyxia [12].

Frequent evaluation of PaCO<sub>2</sub> by blood gas analysis is not practical in the delivery room [13]. Studies have shown positive correlation between ETCO<sub>2</sub> and PaCO<sub>2</sub> in the neonatal intensive care unit (NICU) [8,14]. The reliability of ETCO<sub>2</sub> during the period of transition in the delivery room is not known. Monitoring ETCO<sub>2</sub> with waveform capnography during PPV in the delivery room may help avoid extreme fluctuations in PaCO<sub>2</sub> levels. We hypothesize that ETCO<sub>2</sub> correlates well with PaCO<sub>2</sub> during transition and continuous monitoring of ETCO<sub>2</sub> with capnography during resuscitation of asphyxiated term lambs with meconium aspiration will prevent fluctuations in PaCO<sub>2</sub> 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 gestation fetal lambs from time-dated pregnant ewes (Newlife Pastures, Attica NY) 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 pre-ductal arterial blood gases (ABG) and to monitor systemic blood pressure. Ultrasound probes (Transonic systems, Ithaca, NY, USA) were placed around the left carotid artery and left pulmonary artery to measure blood flow. Systemic and pulmonary pressures were measured by transducing the right carotid and left pulmonary arteries. A catheter was placed in the left atrium to measure 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 18G needle with syringe. After draining excess lung liquid, a funnel with meconium in amniotic fluid was connected to the endotracheal tube. The meconium solution layered over the fetal lung liquid in the endotracheal tube and maintained at a height that 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 minutes (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 meconium was removed. The umbilical cord was cut (delivery time) and lamb was placed under a radiant warmer. Following this period, the lambs were delivered and resuscitated as per NRP guidelines. Preductal saturations were recorded using Masimo Radical 7 pulse oximeter (Irvine, CA, USA). To monitor ET $\text{CO}_2$  in the study group, a side stream capnography (SurgiVet 9004, Smith Medical, MA, USA) was used. According to the manufacturer, SurgiVet 9004 has an accuracy of  $\pm 2$  mmHg with a display range of 0 to 100 mmHg. The capnograph continuously displayed the ET $\text{CO}_2$  in mmHg with a waveform and respiratory rate.

### Ventilation and Blood Gas Analyses

After delivery, the lambs were ventilated with the Servo 300A (Siemens, Monet Medical, Utah) using a pressure control mode of ventilation. Ventilation was initiated with a peak inspiratory pressure (PIP) of 30 cm H $_2$ O and a PEEP of 5 cm H $_2$ O. Arterial blood gases were drawn at birth, 1 minute and 5 minutes after birth followed by every 5 minutes for the first 30 minutes and every 15 minutes for the next 30 minutes. The lambs were ventilated in the first hour in both groups with a preductal oxygen saturation (SpO $_2$ ) 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 35–50 mmHg. PIP was adjusted by 2 cm H $_2$ O based on chest excursion and subsequently the rate (by 5 breaths/min) in an attempt to maintain PaCO $_2$  in the target range. In the *capnography group* (30 lambs), in addition to maintaining PaCO $_2$ , ET $\text{CO}_2$  was targeted between 30–45 mmHg as our preliminary data showed a variation of 5–10 mmHg compared to PaCO $_2$ . Continuous monitoring of ET $\text{CO}_2$  with capnography with frequent ventilator adjustments based on ET $\text{CO}_2$  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 & Analysis Software (BIOPAC systems, CA, USA). The variations in ET $\text{CO}_2$ , PaCO $_2$  and left CABF were compared from 5 to 60 minutes of age. Data were compared after 5 minutes of age to allow pulmonary adaptation and transition to extra-uterine 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 of the fluctuation in PaCO<sub>2</sub> during the first 60 minutes in lambs with meconium aspiration is 11 mm Hg. To reduce this fluctuation (maximum PaCO<sub>2</sub> – minimum PaCO<sub>2</sub> in the first 60 minutes) by 10 mm Hg using capnography, we needed 20 lambs in each group with a type I error probability of 0.05 and 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 plot were used in assessing ETCO<sub>2</sub> and PaCO<sub>2</sub> values. Normally distributed variables are presented as mean  $\pm$  standard deviation and skewed variables as median (range) values. The proportion of PaCO<sub>2</sub> values outside the target range between the groups was compared by chi-square test. The fluctuation (difference between minimum and maximum values during 5 – 60 minutes of age represented as bar graphs) in PaCO<sub>2</sub> and left CABF were analyzed by unpaired t-test. A p-value of  $<0.05$  was considered significant.

**Software**—Data were analyzed using SPSS 22 software (IBM, Armonk, NY).

## Results

Umbilical cord occlusion and meconium aspiration resulted in severe hypercarbia and acidosis at birth (Table 1). The preductal oxygenation index (OI = mean airway pressure in cm H<sub>2</sub>O  $\times$  FIO<sub>2</sub>  $\times$  100  $\div$  preductal PaO<sub>2</sub>) following meconium aspiration was 18.6 $\pm$ 10 and 20.1 $\pm$ 9 in the capnography and control groups respectively. The partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), systemic mean blood pressure (MBP), PVR between the groups were not different during the first postnatal hour (Figure 1). There were 274 simultaneous blood and end-tidal CO<sub>2</sub> measures obtained from the 30 capnography group lambs. The ETCO<sub>2</sub> levels obtained during the first 2 minutes after birth were low compared to PaCO<sub>2</sub> values and were excluded from correlation analysis. The correlation between ETCO<sub>2</sub> and PaCO<sub>2</sub> following the first two minutes after birth improved, R=0.64 (rho=0.6, p=0.01). From 5 – 60 minutes after birth, the ETCO<sub>2</sub> correlated well with PaCO<sub>2</sub> with a correlation coefficient, R=0.73 (rho=0.7, p<0.001) (Figure 2A). The agreement between ETCO<sub>2</sub> and PaCO<sub>2</sub> is illustrated as a Bland-Altman plot [17]. The ETCO<sub>2</sub> was lower than PaCO<sub>2</sub> with a mean bias of  $-11.7\pm 7.7$  mm Hg with a 95% confidence interval of  $-26.7, 3.3$  (Figure 2B). Left CABF (ml/kg/min) had a modest correlation with PaCO<sub>2</sub>, R=0.52 (rho=0.31, p<0.001) (Figure 3A) and with ETCO<sub>2</sub>, R=0.48 (rho=0.48, p<0.0) (Figure 3B). There was a mean 19% increase in CABF for each KPa increase in PaCO<sub>2</sub> (or 2.5% increase with 1 mm Hg increase in PaCO<sub>2</sub>). The respiratory rate (both spontaneous and ventilator setting of mandatory rate) during the entire study period did not correlate well with ETCO<sub>2</sub> (0.13) or the PaCO<sub>2</sub> (0.30). The percentage of PaCO<sub>2</sub> outside the target range in the control group (61%) was significantly greater than the capnography group (43%) (P=0.002). The variance of PaCO<sub>2</sub> and left CABF are depicted as box plots (Figure 4A, 4B) and the fluctuations as bar graphs (Figure 5A, 5B). The fluctuation of PaCO<sub>2</sub> (30.5 $\pm$ 18.9 vs. 20.0 $\pm$ 11.4 mmHg, p=0.002) and the fluctuation between the left CABF (25.8 $\pm$ 5.8 vs. 13.1 $\pm$ 2.1ml/kg/min, p=0.008) were significantly higher in the control group compared to the capnography group.

The median (range) PaCO<sub>2</sub> from 5 – 60 minutes of age was 40 (20–77) mmHg in the capnography group and 40 (20–104) mmHg in the control group. Median (range) 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 extra uterine life and optimize lifelong neurodevelopmental outcome [20]. Birth asphyxia is associated with fluctuations in CBF in the early post-resuscitation period [21]. Monitoring PCO<sub>2</sub> is not only important to avoid fluctuations in CBF and but also to maintain moderately elevated PaCO<sub>2</sub> during the first minutes of resuscitation to restore CBF [22,23]. In addition elevated PCO<sub>2</sub> may be beneficial and is associated with higher 5 minute 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 PCO<sub>2</sub> 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 PaCO<sub>2</sub> variability over 72 hours in whole body cooled HIE neonates [12]. Our study aimed at avoiding fluctuations in PaCO<sub>2</sub> 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 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 over ventilation with hypocapnia or under ventilation 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 fluctuation in PaCO<sub>2</sub>.

Pryds et al have evaluated the effect of blood pressure and PaCO<sub>2</sub> 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 results in a pressure-passive cerebral circulation that is non-responsive to PaCO<sub>2</sub> [28]. However, CBF in neonates with severe asphyxial injury leading to burst-suppression on EEG was pressure-passive but was responsive to changes in PaCO<sub>2</sub> (~ 2% mean change in flow for every mmHg change in PaCO<sub>2</sub> compared to 3.4% in control neonates without asphyxia) [28]. Carotid blood flow increased by 2.5% for every mmHg increase in PaCO<sub>2</sub> in the current study consistent with 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  $\text{ETCO}_2$  and  $\text{PaCO}_2$  ( $R = 0.11$ ) during the first 2 minutes 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 have similarly demonstrated that increasing  $\text{ETCO}_2$  levels in newly born lambs, and preterm rabbits are reflective of increasing tidal volume and improved lung aeration after birth [29]. Similarly, Schmolzer et al have shown the relationship between  $\text{ETCO}_2$  and establishing tidal volume during the first couple of minutes in human neonates [16]. These findings suggest that  $\text{ETCO}_2$  values may not correlate well with  $\text{PaCO}_2$  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  $\text{ETCO}_2$  values during the first couple of minutes of resuscitation, prior to establishment of lung aeration in asphyxiated neonates. An increasing  $\text{ETCO}_2$  in the first couple of minutes may be a sign of better lung aeration and increasing pulmonary blood flow.

A good correlation between  $\text{ETCO}_2$  and  $\text{PaCO}_2$  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  $\text{PaCO}_2$  and  $\text{ETCO}_2$ . The presence of increased physiologic dead space and the meconium aspiration in lambs could have contributed to the increased difference between  $\text{PaCO}_2$  and  $\text{ETCO}_2$  (mean of  $-11.7$ ) in our study as compared to previous studies (Figure 2B).

Term infants have much greater cerebrovascular sensitivity to  $\text{PaCO}_2$  than preterm infants [30]. Wyatt et al calculated that the percentage change in cerebral blood volume increased per kilopascal change in  $\text{PaCO}_2$  from 4% at 26 weeks to 25% at 40 weeks [30]. We studied the effect of fluctuations of  $\text{PaCO}_2$  on the left CABF in a controlled setting while maintaining normoxia with similar systemic and PVR between the groups. Fluctuations in  $\text{PaCO}_2$  outside the target range (35–50 mmHg) could be considered clinically relevant, as hypocarbia and hypercarbia has been reported when clinical methods are used for ventilation. By reducing fluctuations in  $\text{PaCO}_2$ , we were able to maintain the left CABF in a narrow range in the capnography group (Figure 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  $\text{CO}_2$  on CBF. The use of hand bagging or T-piece resuscitator instead of ventilator for resuscitation may have yielded different results that are more pertinent to delivery room resuscitation. A wide target (35–50 mm Hg) for  $\text{ETCO}_2$  was a limitation and could have contributed to fluctuation in capnography group. Given the variability in  $\text{ETCO}_2$  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 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 cerebral blood flow 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<sub>2</sub> during neonatal resuscitation in the DR

We speculate that the use of capnography while providing PPV through an endotracheal tube will limit fluctuations in PaCO<sub>2</sub> 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 return of spontaneous circulation in patients with cardiac arrest [31]. It is also possible that in conditions with a marked increase in physiologic dead space, a low ETCO<sub>2</sub> (with normal PaCO<sub>2</sub>) may lead to hypoventilation. Caution must be exercised while interpreting ETCO<sub>2</sub> values during the first few minutes of resuscitation prior to establishment of lung aeration. Periodic blood gas analysis and trending with ETCO<sub>2</sub> is recommended during prolonged resuscitation.

### Conclusion

Based on our results, continuous end-tidal CO<sub>2</sub> during and immediately after resuscitation is feasible and may limit fluctuations in PaCO<sub>2</sub> and cerebral blood flow in an asphyxiated term infant with tracheal intubation. Further clinical and translational studies evaluating capnography with volumetric data during resuscitation and the post-resuscitation phases with neurodevelopmental follow-up are needed before advocating its routine use in clinical practice.

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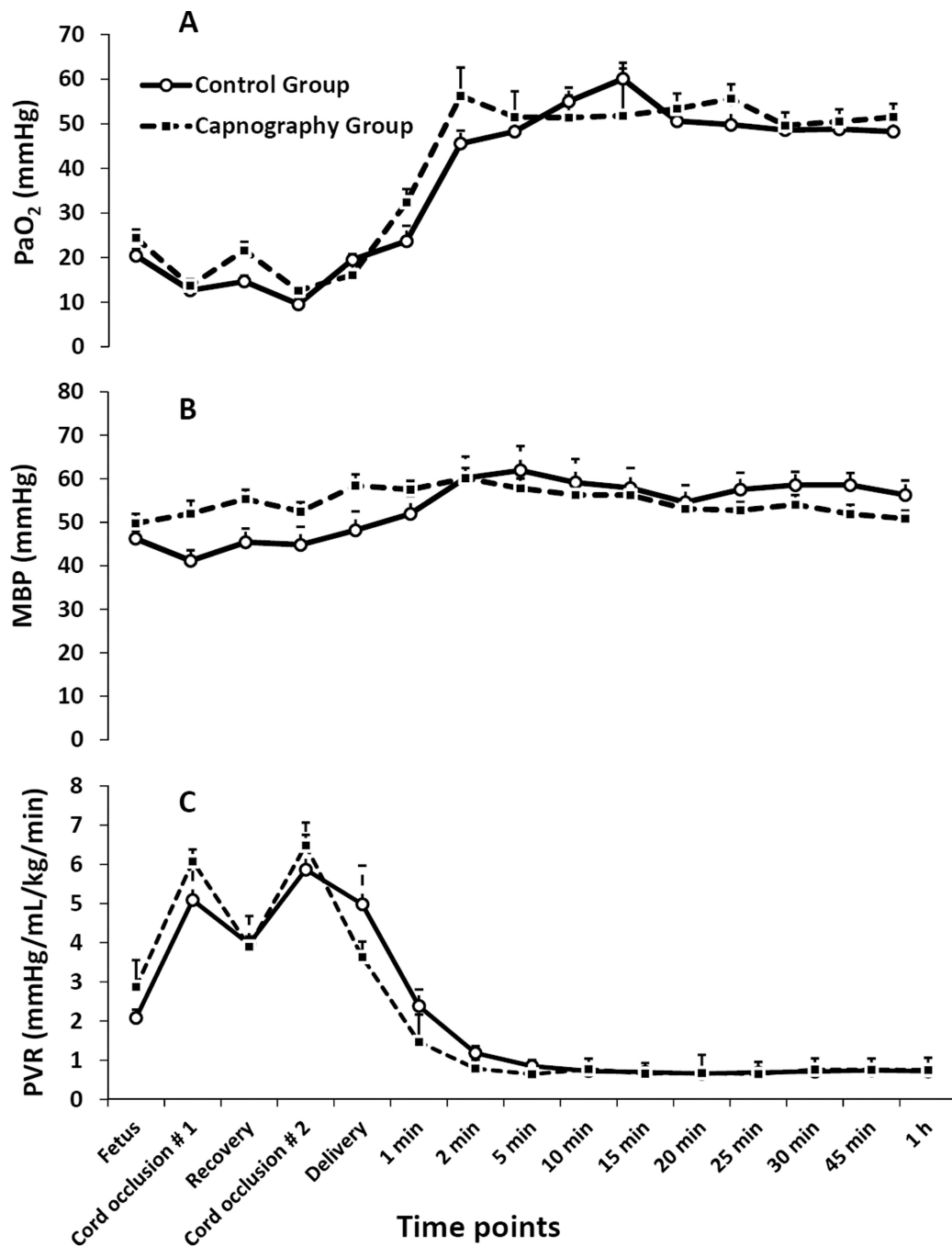
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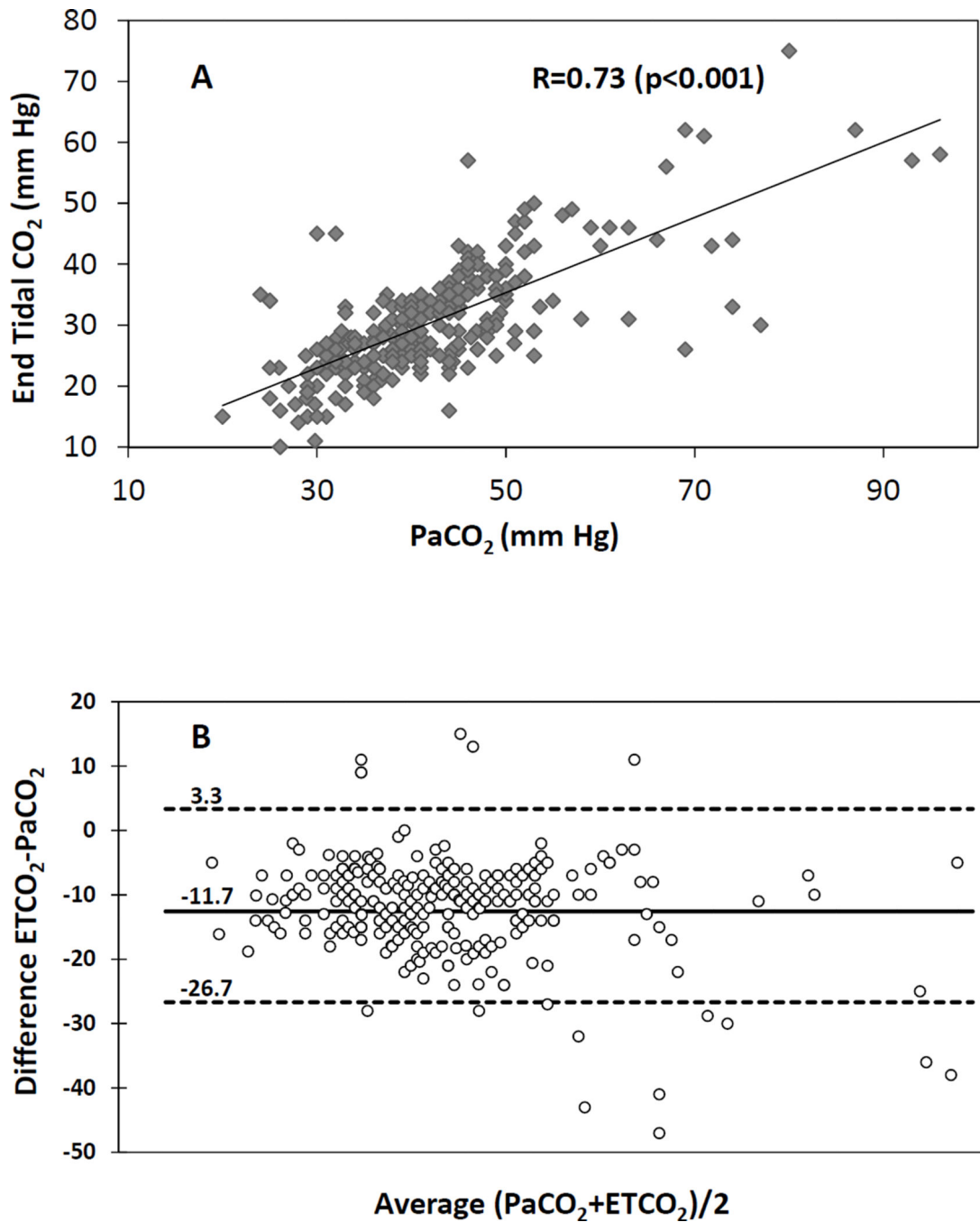


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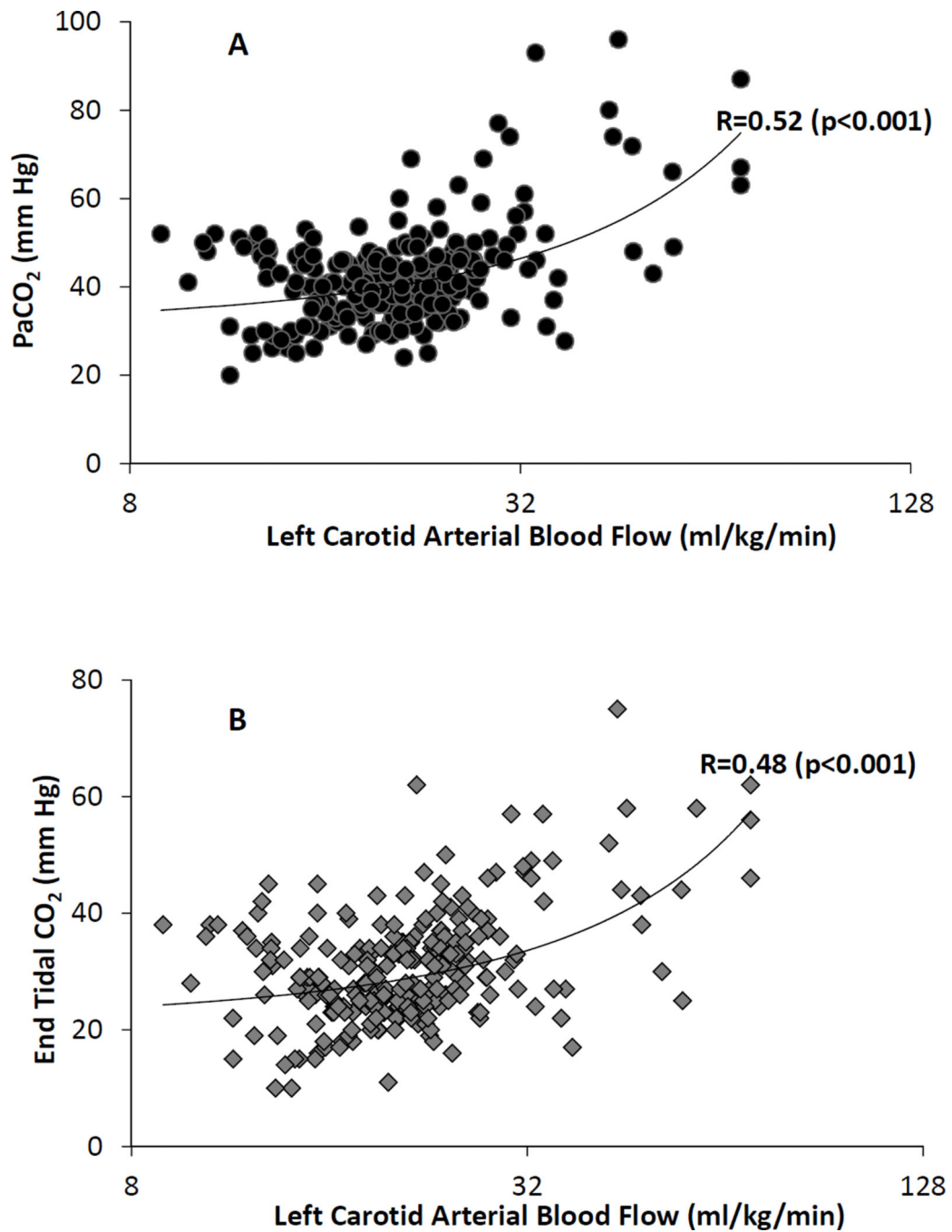


**Figure 1.** (A) Preductal arterial oxygen tension in mmHg (PaO<sub>2</sub>), (B) mean systemic blood pressure in mmHg (MBP) and (C) pulmonary vascular resistance (PVR) in mmHg/ml/kg/min are represented by graphs. Data from fetal baseline values, cord occlusion for asphyxiation, resuscitation and the first 60 minutes of postnatal period are shown in the graph. Data were analyzed from 5 to 60 minutes of life. PaO<sub>2</sub>, MBP and PVR were similar between groups.

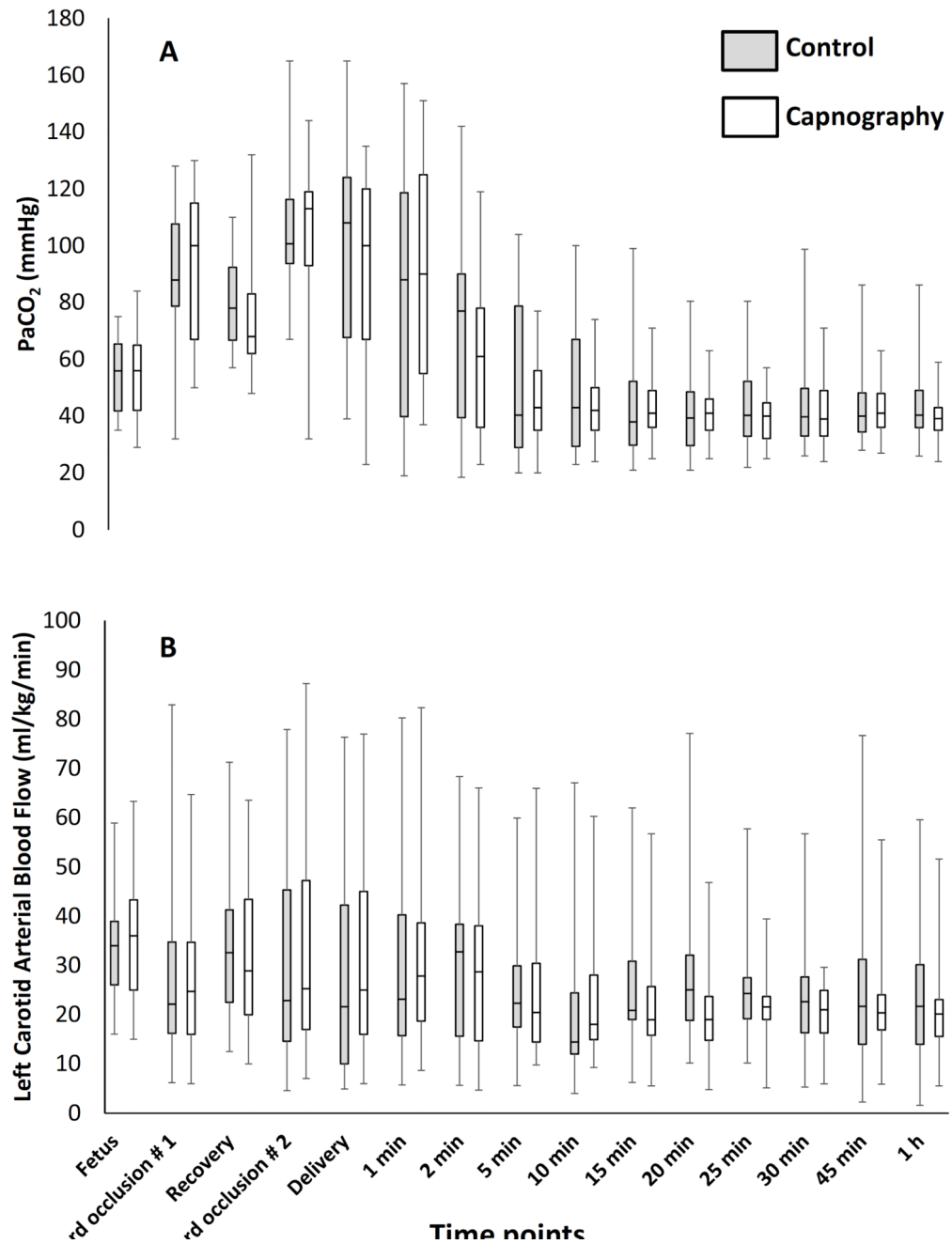


**Figure 2.**

(A) Scatter plot of end-tidal carbon dioxide (ETCO<sub>2</sub>) and arterial carbon dioxide (PaCO<sub>2</sub>) values from 5–60 minutes of age showed good correlation ( $r=0.73$ ,  $\rho=0.7$ ,  $p<0.001$ ). (B) The agreement between ETCO<sub>2</sub> and PaCO<sub>2</sub> is illustrated as Bland Altman plot. The ETCO<sub>2</sub> was lower than PaCO<sub>2</sub> with a mean bias of  $-11.7 \pm 7.7$  mm Hg with confidence interval of  $-26.7, 3.3$  mm Hg.

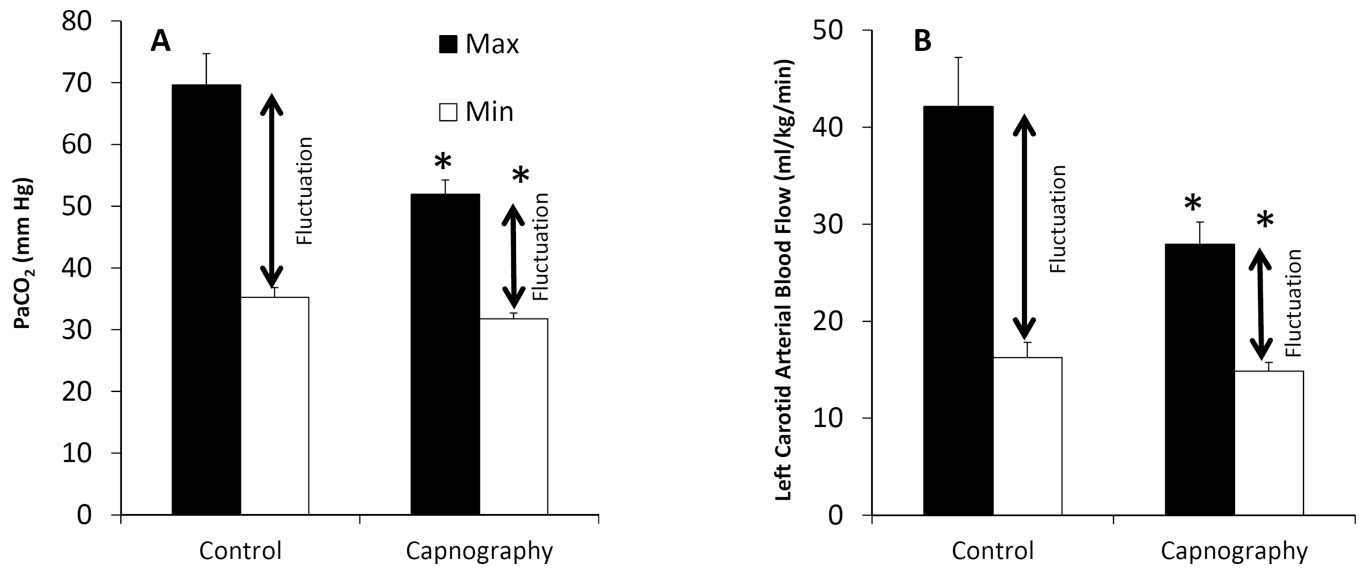


**Figure 3.** (A) Scatter plot of left carotid arterial blood flow and PaCO<sub>2</sub> showed a moderate correlation ( $R=0.52$ ,  $\rho=0.31$ ,  $p<0.001$ ). (B) Scatter plot of left carotid arterial blood flow and ETCO<sub>2</sub> showed a moderate correlation ( $r=0.48$ ,  $\rho=0.48$ ,  $p<0.001$ ). The left carotid arterial blood flow is plotted on a logarithmic scale.



**Figure 4.**

(A) The variance of PaCO<sub>2</sub> (mmHg) and (B) left carotid arterial blood flow are depicted as box plot between the groups.



**Figure 5.**

(A) The fluctuations in PaCO<sub>2</sub> (mmHg) is depicted as a bar diagram in the capnography group and control group. The amplitude of fluctuations (difference between the mean maximum and minimum values) were significantly different ( $p=0.002$ ). (B) The fluctuations in left carotid arterial blood flow (ml/kg/min) are depicted as bar diagrams between the groups. The fluctuations (difference between the mean maximum and minimum values) were significantly different ( $p=0.008$ ).



**Table 1**

Baseline characteristics and blood gas values prior to onset of resuscitation. Severe asphyxia induced by intermittent umbilical cord occlusion resulted in severe acidosis. The values represented in the table are at birth (mean±standard deviation) and were not different.

Parameters	Capnography (N=30)	Control (N=24)
Birth Weight (grams)	3460±820	3220±780
Gestational age (days)	141±0.5	141±0.8
Oxygenation index	18.6±10	20.1±9
SpO <sub>2</sub> (%)	49±29	49±25
pH	7.02±0.10	6.9±0.13
PaCO <sub>2</sub> (mmHg)	102±29	107±25
Base excess (mEq/L)	-8.7±2.1	-10.4±3.8