

## Arterial to End-Tidal Carbon Dioxide Tension Differences in Infants and Children

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### Abstract

**Background:** Several reports have demonstrated substantial mean differences between arterial carbon dioxide tension (PaCO<sub>2</sub>) and end-tidal carbon dioxide tension (ETCO<sub>2</sub>) in children under anesthesia.

**Aim:** We explored the importance of the (a-ET) PCO<sub>2</sub> gradient in a pediatric population receiving general anesthesia, with special attention to the relative effects of age and weight.

**Methods:** After induction of general anesthesia, 129 children, ASA I or II, and between 1 day and 15 years old, had an endotracheal tube placed and mechanical ventilation initiated. After reaching a steady-state ETCO<sub>2</sub>, an arterial blood sample was obtained and the PaCO<sub>2</sub> measured.

**Results:** The mean (a-ET) PCO<sub>2</sub> was 1.6 ± 4.3 mmHg for the entire pediatric population. There was a significant negative correlation between (a-ET) PCO<sub>2</sub> and age and weight ( $r = -0.42$ ,  $P < 0.0001$  and  $-0.44$ ,  $P < 0.0001$ , respectively). The calculated (a-ET) PCO<sub>2</sub> varied from 6.8 ± 6.9 mmHg in neonates to 4.8 ± 4.4 mmHg in children aged between 2 and 4 months. After 8 months, (a-ET) PCO<sub>2</sub> was less than 2 mmHg. A negative (a-ET) PCO<sub>2</sub> of -1.8 ± 1.4 mmHg was observed in 44 (34%) patients with an age range between 4 to 8 years.

**Conclusion:** Our results indicate that ETCO<sub>2</sub> gives an excellent value of the PaCO<sub>2</sub> in children more than 8 months. However, PaCO<sub>2</sub> cannot be extrapolated accurately from ETCO<sub>2</sub> in babies less than 4 months or weighing less than 5 kg who are mechanically ventilated via an endotracheal tube. Nevertheless, ETCO<sub>2</sub> remains a key monitoring as a trend monitor and mandatory to identify the tracheal position of the tube.

**Keywords:** Equipment; CO<sub>2</sub> analyzer; Lungs; Alveolar ventilation; Dead space; Mechanical ventilation; Anesthesia

### Introduction

End-tidal carbon dioxide pressure (ETCO<sub>2</sub>) is a reasonable indicator of arterial carbon dioxide pressure (PaCO<sub>2</sub>) in healthy anesthetized adults and children [1-4]. Nunn and Hill [1] suggested that the relationship of arterial to end-tidal CO<sub>2</sub> difference, (a-ET) PCO<sub>2</sub>, during anesthesia in healthy subjects is sufficiently constant such that the end-tidal values can be used for continuous direct assessment of arterial CO<sub>2</sub>. Age directly influences the (a-ET) PCO<sub>2</sub> gradient, which increases by 1.5 mmHg per decade [5]. In children, the (a-ET) PCO<sub>2</sub> is approximately 0.65 to 2.4 mmHg, compared to 4-5 mmHg in healthy adults and even higher in the elderly [6]. Over the last two decades, ETCO<sub>2</sub> monitoring has been extensively studied in children in a variety of intraoperative settings [2,3,7-10]. However, the exact effects of age and weight on the accuracy of using ETCO<sub>2</sub> measurements to estimate PaCO<sub>2</sub> in anesthetized infants and children remain unclear. Chhibber et al. [9] found no significant relationship of weight with ETCO<sub>2</sub> or PaCO<sub>2</sub> in infants weighing more than 10 kg. Badgwell et al. [8] showed that the (a-ET) PCO<sub>2</sub> was greater in anesthetized children <8 kg under positive pressure ventilation than in heavier children. However, Chhibber et al. [10] concluded that ETCO<sub>2</sub> is an accurate indicator of arterial PaCO<sub>2</sub> in infants weighing less than

10 kg who were mechanically ventilated via an endotracheal tube. The issue, therefore, needs further evaluation.

The aim of this study was to investigate the variation of the (a-ET) PCO<sub>2</sub> gradient in relation with age and weight during controlled ventilation in a pediatric population undergoing general anesthesia.

### Methods

A total of 129 children, ASA I or II, between 1 day and 15 years of age, who were undergoing elective abdominal or urological surgery were included in this study. Approval by the hospital ethics committee and informed parental consent was obtained. Children were excluded from the study if they suffered from right to left cardiac shunt, pulmonary disease, or abnormal airway anatomy. Patients fasted for 4 to 6 hours before the procedure. As premedication, patients received either midazolam 0.4 mg/kg rectally or alprazolam 0.25 mg orally, depending on their age.

Anesthetic management followed standard care at our institution. After anesthetic induction with inhalation of sevoflurane and air in oxygen and cannulation of a suitable vein, tracheal intubation was performed with an appropriately sized endotracheal tube (uncuffed and cuffed). In older children, anesthesia was induced intravenously with propofol, sufentanil and cisatracurium to facilitate intubation. Anesthesia was maintained with sevoflurane, sufentanil with or

without myorelaxant agent administered at the discretion of the attending anesthesiologist. The position of the endotracheal tube was confirmed by chest auscultation and  $\text{ETCO}_2$  detection. Several patients received regional anesthesia if considered necessary.

The lungs were ventilated in a standard fashion, using a Servo 900C ventilator (Siemens Elema, Nixdorff, Sweden) set to deliver a tidal volume of 8-10 ml/kg in a control mode at a rate of 14-35 breaths per min to provide an  $\text{ETCO}_2$  between 30-35 mmHg according to age. Rebreathing was avoided, as indicated by stable zero inspired carbon dioxide tension during inspiration as proposed by Lindahl et al. [11]. Peak airway pressure was maintained at less than 20 cm  $\text{H}_2\text{O}$ . No positive end expiratory pressure (PEEP) was applied. The pulse oxymeter hemoglobin saturation was maintained at >95% or between 90 to 95% for premature babies.

Gas samples for  $\text{ETCO}_2$  concentration were drawn from the sampling port of the connector between the proximal end of the endotracheal tube and the pediatric breathing circuit to allow greater accuracy of measurements in small subjects [3,8,12].  $\text{ETCO}_2$  was measured with a Capnomac Ultima infrared sidestream capnometer (Datex Instrument Corp., Helsinki, Finland), which was calibrated automatically. The sampling rate was 200 ml/min with a response time of less than 360 ms.

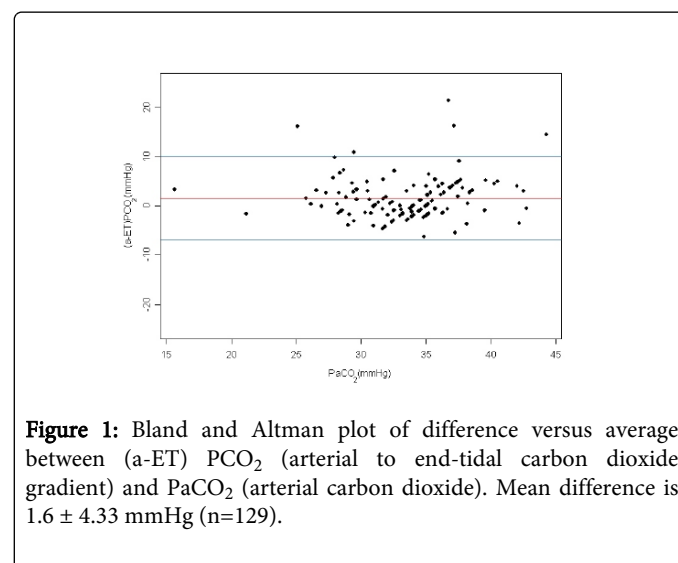
Once  $\text{ETCO}_2$  was stable following induction of anesthesia and after the patients were positioned for surgery and hemodynamically stable, an arterial blood sample was obtained from the radial artery by direct puncture with a 22G or 24 G butterfly needle fixed to a 1 ml syringe coated with heparin (Terumo, Belgium); the amount of blood necessary for the gas analysis was less than 0.5 ml. The  $\text{ETCO}_2$  was noted at the time point that blood was drawn. Blood gas and co-oximetry analyses were carried out immediately in a contiguous room using a gas analyzer at 37°C (Gem 3000, Instrumentation Laboratory 682, Lexington, Mass, USA). Body temperature (rectal) was maintained at approximately 37°C with a conventional air warmer (Gaymar, Romed, Belgium). All measurements were performed prior to surgery, and all patients were supine and horizontal throughout the study.

Data are expressed as mean  $\pm$  SD. The (a-ET)  $\text{PCO}_2$  gradient was calculated for each patient. Secondary comparison was performed according to the approach of Bland and Altman to define bias estimated by the mean difference and the standard deviation of the difference, and limits of agreement between arterial and end-tidal  $\text{PCO}_2$ [13]. The relationships between the different variables, i.e.,  $\text{PaCO}_2$ ,  $\text{ETCO}_2$ , gender, age and weight, and the (a-ET)  $\text{PCO}_2$  gradient were studied independently with a simple linear regression technique. Correlation was evaluated using Spearman's correlation coefficient ( $r$ ). To identify variables specifically associated with (a-ET)  $\text{PCO}_2$ , a multiple linear regression analysis was performed and the coefficient of determination ( $r^2$ ) was calculated. The coefficient of determination measures the strength of relationship between the different variables, not the agreement between them. All statistical calculations were carried out using the SAS package (SAS Institute, Cary, NC, version 6.12) using all available data. Results were considered to be significant at the 5% critical level ( $P < 0.05$ ).

## Results

Of the total 129 subjects, 80 (62%) were boys and 49 (38 %) were girls, weighing between 1 to 76 kg (mean  $12.2 \pm 11.1$  kg) and 1 day to 15 years of age (mean  $20 \pm 4$  months). The mean  $\text{ETCO}_2$  was  $32.8 \pm$

4.8 mmHg and was within the normal range. The expiratory capnograph showed a typical plateau configuration in all patients. The mean  $\text{PaCO}_2$  was  $34.4 \pm 5.0$  mmHg, and the calculated mean (a-ET)  $\text{PCO}_2$  was  $1.6 \pm 4.3$  mmHg. The  $\text{ETCO}_2$  was lower than the  $\text{PaCO}_2$  in 85 (66%) patients. Accordingly, a negative (a-ET)  $\text{PCO}_2$  of  $-1.8 \pm 1.4$  mmHg was observed in a substantial number of patients (44 patients, or 34%), predominantly in children between 4 to 8 years of age. Figure 1 shows the Bland and Altman plot of the difference versus average. The intraclass correlation coefficient was 0.58 (95% confidence interval). The relationship between  $\text{PaCO}_2$  and  $\text{ETCO}_2$  ( $r=0.66$ ,  $P < 0.0001$ ) is shown in Figure 2.



**Figure 1:** Bland and Altman plot of difference versus average between (a-ET)  $\text{PCO}_2$  (arterial to end-tidal carbon dioxide gradient) and  $\text{PaCO}_2$  (arterial carbon dioxide). Mean difference is  $1.6 \pm 4.33$  mmHg ( $n=129$ ).

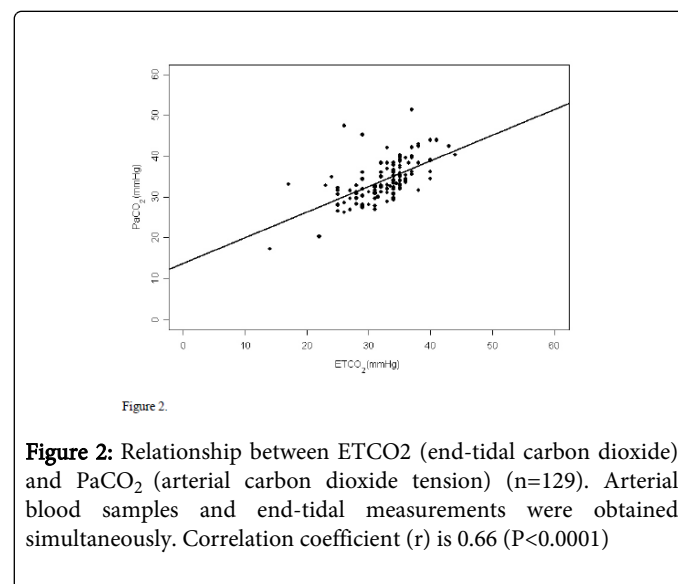
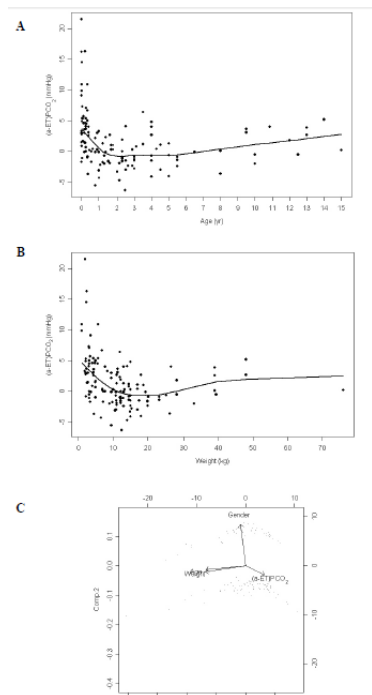


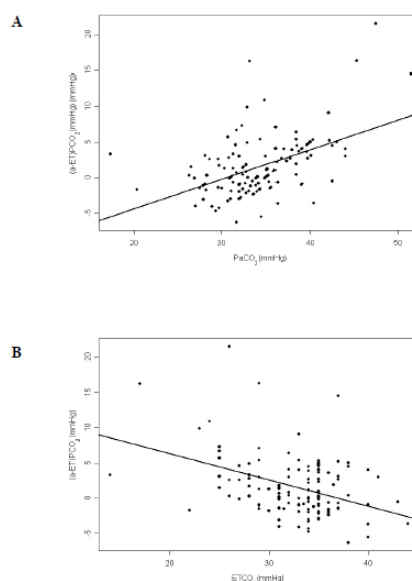
Figure 2.

**Figure 2:** Relationship between  $\text{ETCO}_2$  (end-tidal carbon dioxide) and  $\text{PaCO}_2$  (arterial carbon dioxide tension) ( $n=129$ ). Arterial blood samples and end-tidal measurements were obtained simultaneously. Correlation coefficient ( $r$ ) is 0.66 ( $P < 0.0001$ )



**Figure 3:** Relationship between (A) age and (B) weight and (a-ET) PCO<sub>2</sub> (arterial to end-tidal carbon dioxide gradient) (n=129). There was a significant correlation between (a-ET) PCO<sub>2</sub> and age ( $r=-0.42$ ,  $P<0.0001$ ), and between (a-ET) PCO<sub>2</sub> and weight ( $r=-0.44$ ,  $P<0.0001$ ). These results were confirmed by the multivariate analysis displayed in the (C) biplot graph (coefficient of determination  $R=0.30$ ). No relationship between (a-ET) PCO<sub>2</sub> and gender was detected ( $P=0.82$ ). Multiple linear regression analysis gave the following relationships:  $(aET)PCO_2 = -10 - 0.41 \times PaCO_2 - 0.39 \times weight + 0.00738 \times weight$  for females and  $(aET)PCO_2 = -7.04 + 0.4107 \times PaCO_2 - 0.802 \times weight + 0.0078 \times weight + 0.00263 \times age$  for males.

We found a significant negative correlation between (a-ET) PCO<sub>2</sub> and age ( $r = -0.42$ ,  $P<0.0001$ ) (Figure 3A), and between (a-ET) PCO<sub>2</sub> and weight ( $r=-0.44$ ,  $P<0.0001$ ) (Figure 3B). The (a-ET) PCO<sub>2</sub> gradient increased significantly in children under 4 months old or below 5 kg in weight ( $P<0.001$ ). The calculated (a-ET)PCO<sub>2</sub> varied from  $6.8 \pm 6.9$  mmHg in neonates to  $4.8 \pm 4.4$  mmHg in children between 2 and 4 months old. After 8 months, the calculated (a-ET) PCO<sub>2</sub> was less than 2 mmHg. No relationship between (a-ET) PCO<sub>2</sub> and gender was detected ( $P=0.82$ ). The results of the multivariate statistical analysis are summarized in Figure 3C. The coefficient of determination ( $r$ ) for (a-ET) PCO<sub>2</sub> was 0.30. The biplot graph confirms the negative correlation coefficient between (a-ET) PCO<sub>2</sub> and age or weight. We also observed that in our pediatric population, the (a-ET) PCO<sub>2</sub> gradient increased with PaCO<sub>2</sub> ( $r = 0.43$ ,  $P<0.0001$ ) but was negatively correlated with ETCO<sub>2</sub> ( $r=-0.31$ ,  $P=0.0004$ ) (Figures 4A and 4B).



**Figure 4:** Relationship between (A) (a-ET) PCO<sub>2</sub> (arterial to end-tidal carbon dioxide gradient) and PaCO<sub>2</sub> (arterial carbon dioxide tension) and between (B) (a-ET) PCO<sub>2</sub> and ETCO<sub>2</sub> (end-tidal carbon dioxide) (n=129). There was a significant correlation between (a-ET) PCO<sub>2</sub> and PaCO<sub>2</sub> ( $r=0.43$ ,  $P<0.0001$ ) and between (a-ET) PCO<sub>2</sub> and ETCO<sub>2</sub> ( $r=-0.31$ ,  $P=0.0004$ ).

## Discussion

The (a-ET) PCO<sub>2</sub> difference is considered to be lower in infants and smaller children than in adults, with ETCO<sub>2</sub> precisely reflecting the PaCO<sub>2</sub>. The mean (a-ET) PCO<sub>2</sub> gradient of  $1.6 \pm 4.3$  mmHg that we observed for the entire population shows good agreement between the two methods of CO<sub>2</sub> measurement and is consistent with previously published values [6]. The observed mean errors may be used as rough correction factors in clinical practice, although care should be taken when factors such as age, weight or breathing system differ. The probable multifactorial nature of the bias in measuring end-tidal CO<sub>2</sub> renders prediction of the bias in an individual patient difficult. Specially, results of the present study show that ETCO<sub>2</sub> markedly underestimates PaCO<sub>2</sub> values in very small children. We observed a clear relationship between the (a-ET) PCO<sub>2</sub> gradient and age or weight, with the (a-ET) PCO<sub>2</sub> gradient increasing inversely to age and weight in our pediatric population. The ETCO<sub>2</sub> data can, therefore, provide an accurate estimation of PaCO<sub>2</sub> only in anesthetized children above four months of age or 5 kg in weight.

Why the measured ETCO<sub>2</sub> underestimates the alveolar carbon dioxide tension in small children may be attributed to the low ratio of tidal volume to deadspace, high sampling rates by CO<sub>2</sub> analyzers, and high ventilatory rates with high fresh gas flows [8]. Gas samples for measuring the ETCO<sub>2</sub> concentration were drawn from the sampling port of the connector between the proximal end of the endotracheal tube and the pediatric breathing circuit, as proposed in previous studies [8,12,14]. Proximal site sampling is easy and carries minimal risk of blockage or contamination by secretions compared to distal site sampling using a catheter [14]. Badgwell et al. [8] showed that

measurements taken from the proximal end of the endotracheal tube accurately predicted PaCO<sub>2</sub> in infants weighing less than 8 kg when ventilated with a non-rebreathing system. In our study, we used controlled ventilation and a non-rebreathing pediatric system, which minimized variations in alveolar ventilation and rebreathing of expired gases. A dilution effect is enhanced when the expired volume is small [15]. In infants and small children, a sampling flow rate of 200 ml/min consistently yielded accurate estimates of PaCO<sub>2</sub> [16]. In our study, the sampling rate for the end-tidal gas monitor was 200 ml/min, which has been shown to ensure accurate estimates of the alveolar CO<sub>2</sub> content without entrapment of fresh gas [8,17,18].

The ability of a respiratory analyzer to respond to a change in PaCO<sub>2</sub> is determined by the response time of the optical system and can substantially affect the accuracy of the ETCO<sub>2</sub> measurement. At high respiratory rates, an increase of PCO<sub>2</sub> to its maximum may challenge the response of an instrument. A response time of less than 250 ms is usually considered adequate to reproduce clinical PCO<sub>2</sub> at respiratory rates up to 60 breaths per minute [19]. The Datex device used in this study has a response time of less than 360 ms and was tested for adequacy of response time; the apparatus was capable of reporting ETCO<sub>2</sub> to within 1 mmHg of the actual value at respiratory rates up to 60 breaths per minute [20].

As would be expected, PaCO<sub>2</sub> was greater than ETCO<sub>2</sub> in most cases. Nevertheless, the considerable number of negative (a-ET) PCO<sub>2</sub> values, i.e., in 44 patients aged 4 to 8 years in our study, is of interest. Negative (a-ET) PCO<sub>2</sub> values have been previously observed during anesthesia [1], and several mechanisms have been postulated to explain the observed (a-ET) PCO<sub>2</sub> differences during anesthesia. Theoretically, the alveolar CO<sub>2</sub> partial pressure is very close to the mixed venous PCO<sub>2</sub> and is higher than PaCO<sub>2</sub> [21], which could provide an explanation for a zero or negative (a-ET) PCO<sub>2</sub>. Rich and Sconzo (3) found a negative gradient in 50% of neonates under controlled ventilation that was related to an increase in CO<sub>2</sub> production and reduction of functional residual capacity. Negative gradients are likely related to larger than normal tidal volumes, which result in better ventilation of dependent and well-perfused alveoli. Ventilation with large tidal volumes and low frequencies results in (i) better ventilation of dependent well-perfused alveoli, which improves ventilation/perfusion matching, and (ii) gas emptying from slow alveoli to reach the mouth, instead of remaining in the airways if small frequent breaths are used. Under these circumstances, the low ventilation/perfusion areas (alveoli with higher PCO<sub>2</sub>) make a more substantial contribution to the gas exchange. The net effect of these factors is to enable the terminal phase III of the capnograph to exceed the mean PaCO<sub>2</sub>, resulting in a negative (a-ET) PCO<sub>2</sub> [22]. Since we did not specifically record tidal volume, we are unable to confirm the occurrence of this phenomenon in our subjects.

Recently, von Ungern-Sternberg et al. [23] examined the effects of neuromuscular blockade and PEEP on functional residual capacity (FRC) and ventilation inhomogeneity in infants and preschool age children with healthy lungs. While FRC at baseline was lower in young infants compared with preschool children, the impact of neuromuscular blockade was also significantly larger in infants compared with preschool children. Both effects were completely reversed upon use of 3 cm H<sub>2</sub>O PEEP. The increase in ventilation inhomogeneity in infants compared to preschool children was explained by partial airway collapse in the dependent regions of the lungs in the supine position [24]. Partially collapsed alveoli and less well-distended distal bronchi likely contribute to the results observed

in this study. In future studies, investigation of the effect of PEEP on the (a-ET) PCO<sub>2</sub> difference will be of further interest.

Overestimation of ETCO<sub>2</sub> may also result from the interference of water vapor in the measurement of CO<sub>2</sub> by an infrared analyzer [7]. The temperature difference between the patient's body temperature and the blood gas analyzer (37°C) might explain the approximately 2 mmHg decrease in PaCO<sub>2</sub> per °C decrease in temperature [5]. In this study, particular attention was taken to maintain body temperature as close as possible to 37°C. Hypermetabolic conditions cause greater CO<sub>2</sub> production [18] and may show a negative (a-ET) PCO<sub>2</sub> gradient. None of our patients exhibited a major temperature change at the time of arterial sampling.

We also observed intriguing correlations between (a-ET) PCO<sub>2</sub> with PaCO<sub>2</sub> and ETCO<sub>2</sub>. Of even greater concern, the two gas tensions, i.e., PaCO<sub>2</sub> and ETCO<sub>2</sub>, changed in opposite directions, consistent with previous observations by Wahba and Tessler [5]. The most likely reason is that one or more factors cause a marked change in cardiac output and pulmonary blood flow, resulting in changes in the ventilation/perfusion ratio [25].

In conclusion, in pediatric patients weighing less than 5 kg or under 4 months who are mechanically ventilated via an endotracheal tube, ETCO<sub>2</sub> is useful for a trend monitor but is not an accurate indicator of PaCO<sub>2</sub>. Even if ETCO<sub>2</sub> is mandatory to indicate the correct position of an endotracheal tube, caution should be used when utilizing capnometry to evaluate the adequacy of ventilation in very small patients.

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