Research Article

Arterial and end-tidal carbon dioxide difference in pediatric intensive care

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Abstract

Background and Aim: Arterial carbon dioxide tension ($PaCO_2$) is considered the gold standard for scrupulous monitoring in pediatric intensive care unit (PICU), but it is invasive, laborious, expensive, and intermittent. The study aims to explore when we can use end-tidal carbon dioxide tension ($P_{ET}CO_2$) as a reliable, continuous, and noninvasive monitor of arterial CO_2. **Materials and Methods:** Concurrent $P_{ET}CO_2$, fraction of inspired oxygen, $PaCO_2$, and arterial oxygen tension values of clinically stable children on mechanical ventilation were recorded. Children with extra-pulmonary ventriculoatrial shunts were excluded. The $P_{ET}CO_2$ and $PaCO_2$ difference and its variability and reproducibility were studied. **Results:** A total of 624 concurrent readings were obtained from 105 children (mean age [SD] 5.53 [5.43] years) requiring invasive bi-level positive airway pressure ventilation in the PICU. All had continuous $P_{ET}CO_2$ monitoring and an arterial line for blood gas measurement. The mean (SD) number of concurrent readings obtained from each child, 4-6 h apart was 6.0 (4.05). The $P_{ET}CO_2$ values were higher than $PaCO_2$ in 142 observations (22.7%). The $PaCO_2$–$P_{ET}CO_2$ difference was individual admission specific (ANOVA, $P < 0.001$). The $PaCO_2$–$P_{ET}CO_2$ difference correlated positively with the alveolar-arterial oxygen tension [$P(A\text{-}a)O_2$] difference ($\rho = 0.381$ $P < 0.0001$). There was a fixed bias between the $P_{ET}CO_2$ and $PaCO_2$ measuring methods, difference +0.66 KPa (95% confidence interval: +0.57 to +0.76). **Conclusions:** The $PaCO_2$–$P_{ET}CO_2$ difference was individual specific. It was not affected by the primary disorder leading to the ventilation.

Keywords: Capnography, carbon dioxide partial pressure, critical care, pediatrics

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Introduction

The measurement of partial pressure of carbon dioxide in arterial blood (arterial carbon dioxide tension [$PaCO_2$]) is an essential diagnostic and monitoring tool used in current clinical practice. However, its measurement remains invasive and intermittent.[1] The graphic display of CO_2 concentration (or partial pressure) during the respiratory cycle (capnography) has offered many uses in adult[2-4] and pediatric clinical practice.[5,6] The absolute numerical measurement of CO_2 concentration (or partial pressure) during the respiratory cycle has proved less useful. This is because the partial pressure of CO_2 at the end of exhalation (end-tidal carbon dioxide tension [$P_{ET}CO_2$]) does not reliably correlate with $PaCO_2$. Our study was designed to investigate the relationship between $P_{ET}CO_2$ and $PaCO_2$ in children during steady state mechanical ventilation in the pediatric intensive care unit (PICU).

Materials and Methods

All patients receiving treatment in our PICU have their vital signs data automatically recorded and saved in an electronic patient record system (MetaVision, iMD-Soft systems, Schiessstraße 55, 40549, Düsseldorf, Germany). The laboratory investigation results and blood gases are saved in the same record. Mechanically ventilated patients also have their fraction of inspired oxygen (FiO_2)

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and $P_{ET}CO_2$ measured concurrently and automatically recorded. The FiO_2 was measured by an oxygen electrode (calibrated daily) located at the inspiratory limb of the ventilator (Draeger Evita 4 XL ventilator, Drägerwerk AG & Co. KgaA, Moislinger Allee 53–55, 23558 Lübeck, Germany) whereas $P_{ET}CO_2$ was measured by micro-stream sampling (Philips server, model M3015A/B, attached to the Philips MP30 and MP70 IntelliVue monitors, calibrated with each device check, Philips Healthcare, P.O. Box 10.000, 5680 DA Best, The Netherlands).

We collected above data and clinical diagnoses of children who were mechanically ventilated in the PICU over a 12-month period (January–December 2012). Children who had (a) an end tidal CO_2 recording; (b) an arterial line for blood gas measurements and (c) were "clinically stable" (i.e, not in a resuscitation phase, and hemodynamically stable); and (d) on invasive bi-level positive airway pressure (BiPAP) ventilation were recruited. The maximum number of concurrent readings obtained from any single patient, if available, was capped to the first 16. All children had cuffed endotracheal tubes and minimal air leaks. A specific data collection form was used. They also had intermittent arterial blood gas measurements (corrected to 37°C) and continuous pulse oximetry (SpO_2). We retrieved concurrently recorded FiO_2, SpO_2, $P_{ET}CO_2$, $PaCO_2$, PaO_2, data every 4-6 h from all qualifying children using the "Metavision" electronic database. Children with suspected intracardiac shunting and/or poor cardiac output states were excluded. Furthermore, children on high-frequency oscillation (HFO) were excluded as they had no $P_{ET}CO_2$ measurement.

The standard alveolar-gas equation (Eq. 1) was used to calculate the alveolar oxygen tension (PAO_2).[7] The alveolar-arterial oxygen tension difference [$P(A\text{-}a)O_2$] was estimated by subtracting the concurrent measured PaO_2 from the calculated PAO_2 in mmHg.

Equation 1: The alveolar gas equation: PAO_2= alveolar oxygen tension in mmHg; FiO_2= fractional inspired oxygen concentration; P_{atm} = atmospheric pressure in mmHg; P_{H2O} = partial pressure of water (47 mmHg at 37°C); and R = 0.8

$$PAO_2 = (FiO_2 \times [P_{atm} - P_{H2O}]) - (PaCO_2 \div R) \quad (1)$$

Statistics

The $P(A\text{-}a)O_2$ difference was interpreted as indicative of the degree of intra-pulmonary shunt. Partial pressures were expressed in mmHg where necessary using a standard conversion (1 KPa = 7.5006 mmHg). The variability of the $P_{ET}CO_2$ and $PaCO_2$ difference (between children and between disorders) was studied using one-way ANOVA. The performance of $P_{ET}CO_2$ and $PaCO_2$ measurement methods were compared using a Bland-Altman plot.[8]

Ethics

This was an observational study of routinely monitored respiratory and hemodynamic parameters of children requiring mechanical ventilation in the PICU. There was neither any direct intervention in patient management nor a need to use any patient identifiable information. Therefore, according to local guidelines, an Ethics Committee review was not required. The study was registered as a service evaluation project.

Results

We obtained 624 concurrent readings from 105 children requiring invasive bi-level ventilation in the PICU. All children were in a clinically steady state and had an arterial line *in situ* for blood gas measurements and continuous $P_{ET}CO_2$ monitoring. The demographic data of the study population are shown in Table 1.

The $P_{ET}CO_2$ values recorded were higher than the concurrent $PaCO_2$ (i.e, $PaCO_2/P_{ET}CO_2$ ratio was <1) in 142 observations (22.7%). The proportions with $PaCO_2/P_{ET}CO_2$ ratio <1 in the subcategories were, liver disorder 26.0%, respiratory disorder 20.8%, central nervous system disorder 16.5%, septic shock (multiple organ failure) 33.3%, and others 26.7% respectively.

The $PaCO_2$–$P_{ET}CO_2$ difference was not significantly influenced by the disorders leading to mechanical ventilation (df 4, ANOVA, $P = 0.6$) [Table 1]. However, the mean $PaCO_2$–$P_{ET}CO_2$ difference was individual specific (df 103, ANOVA, $P < 0.0001$) [Figure 1]. This finding is limited by the fact that, in larger group analyses, ANOVA in SPSS (IBM United Kingdom Limited, PO Box 41, North

Table 1: Demographic data of the study population

Number of children		105
Age years (SD)		5.53 (5.43)
Total number of concurrent observations		624
Number of concurrent readings per patient		6.0 (4.05)
Number of observations in each disorder (proportion)		The mean KPa (SD) $PaCO_2$-$P_{ET}CO_2$ difference
Liver disorder	196 (31.4%)	0.61 (1.40)
Respiratory disorder	168 (26.9%)	0.79 (1.23)
CNS disorder	170 (27.2%)	0.49 (0.79)
Septic shock (MOF)	60 (9.6%)	0.65 (1.50)
Other	30 (4.8%)	0.63 (1.16)

Continuous variables are summarized as mean (SD) and categorical variables as count (percentage). SD: Standard deviation; CNS: Central nervous system; MOF: Multiple organ failure; $P_{ET}CO_2$: End-tidal carbon dioxide tension; $PaCO_2$: Arterial carbon dioxide tension

Harbour, Portsmouth , Hampshire, PO6 3AU) only tells you at least one group in the analysis is different from at least one other. For the confirmation of this finding follow-up data are needed in the same groups and this is obviously not realistic in our cohort.

The $PaCO_2$–$P_{ET}CO_2$ difference positively correlated with $P(A\text{-}a)O_2$ difference (two-tailed Pearson's correlation, $\rho = 0.381$, $P < 0.0001$) [Figure 2]. Please note scarcity of data at high FiO_2 concentrations. This is because these children were on HFO and excluded. The $PaCO_2$–$P_{ET}CO_2$ difference did not correlate with age when averaged.

We compared $PaCO_2$ and $P_{ET}CO_2$, without bias, using the Bland-Altman method.[8] We found that the average reading of $PaCO_2$ was consistently +0.66 KPa (95% confidence interval: +0.57 to +0.76) higher than that of $P_{ET}CO_2$ [Figure 3].

Discussion

$P_{ET}CO_2$ allows global evaluation of three main bodily functions: Metabolism, circulation, and ventilation.[9] Our study was designed to investigate the relationship of $P_{ET}CO_2$ and $PaCO_2$ in PICU patients, during different disease states. Circulation, ventilation and metabolic parameters were considered to be in a steady state whilst on invasive bi-level mechanical ventilation. We have shown that $PaCO_2$–$P_{ET}CO_2$ difference is consistent in each individual. Thus, in a clinically "steady" state of mechanical ventilation, the $P_{ET}CO_2$ and $PaCO_2$ difference can be expected to be static but unique to the individual in that setting. We also observed that the variability of $PaCO_2$–$P_{ET}CO_2$ was not affected by the primary disorder leading to the PICU admission.

The study demonstrates that in clinically stable children on mechanical ventilation, irrespective of their disease status, the $P_{ET}CO_2$ and $PaCO_2$ difference is consistent but individual specific. The corollary of this finding is that if an unstable difference between $PaCO_2$ and $P_{ET}CO_2$ becomes stable, this may suggest a clinical improvement as far as the ventilation/perfusion (V/Q) status of the lungs is concerned. Through attention to $PaCO_2$–$P_{ET}CO_2$ difference in PICU patients, unnecessary blood gas measurements can be avoided. A trend analysis of $PaCO_2$–$P_{ET}CO_2$ difference may therefore be valuable in the PICU setting.

Efforts to study $P_{ET}CO_2$ against $PaCO_2$ are not new. In order to have a noninvasive measure of $PaCO_2$, several authors have investigated the relationship between $PaCO_2$ and $P_{ET}CO_2$ with mixed results. Sharma found the $P_{ET}CO_2$-$PaCO_2$ mean difference to be stable and patient specific but variable between individuals.[10] Our findings go a step further. $P_{ET}CO_2$ alone is not sufficiently reliable to replace arterial blood sampling based measurements,[11] but becomes useful once the $PaCO_2$–$P_{ET}CO_2$ difference is known.

Capnography provides a numerical measurement of inspired and end tidal CO_2. Previous investigators have reported an average $P_{ET}CO_2$-$PaCO_2$ difference of 4-6 mmHg in patients with normal lungs.[11-15] In patients with respiratory failure, the average $PaCO_2$–$P_{ET}CO_2$ difference was 18 mmHg.[16] We noted a difference of 4.9 mmHg (0.66 KPa) in our study.

Intra-pulmonary shunting in lung disease due to alveolar collapse/consolidation and/or diffusion abnormalities minimally affects CO_2 elimination in the

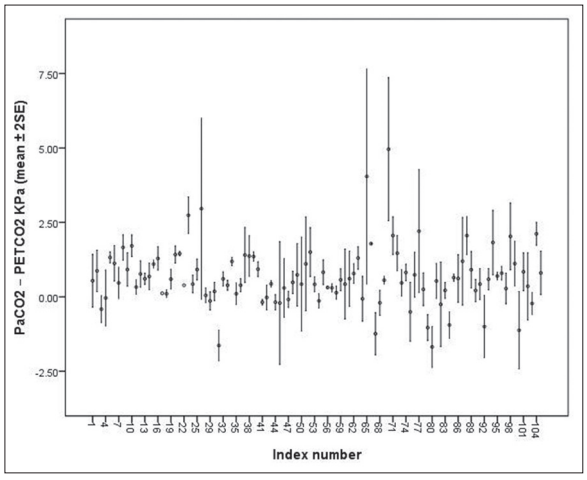

Figure 1: Individual variability of arterial carbon dioxide tension ($PaCO_2$)–end-tidal carbon dioxide tension ($P_{ET}CO_2$) difference during a single pediatric intensive care unit admission

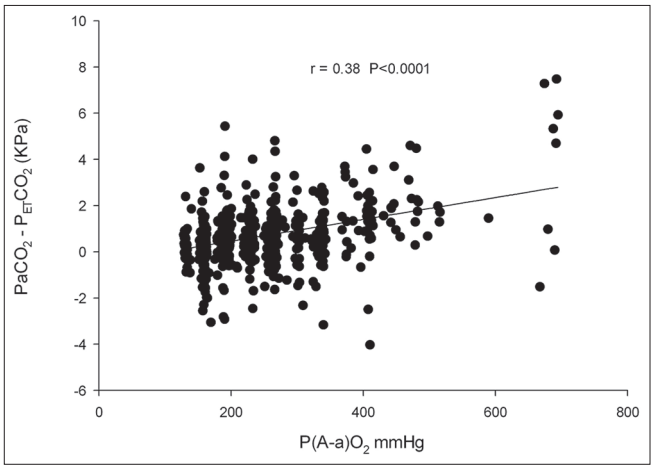

Figure 2: The arterial carbon dioxide tension ($PaCO_2$)–end-tidal carbon dioxide tension ($P_{ET}CO_2$) difference correlates positively with alveolar-arterial oxygen tension [$P(A\text{-}a)O_2$] difference (two-tailed Pearson correlation 0.381 $P < 0.0001$)

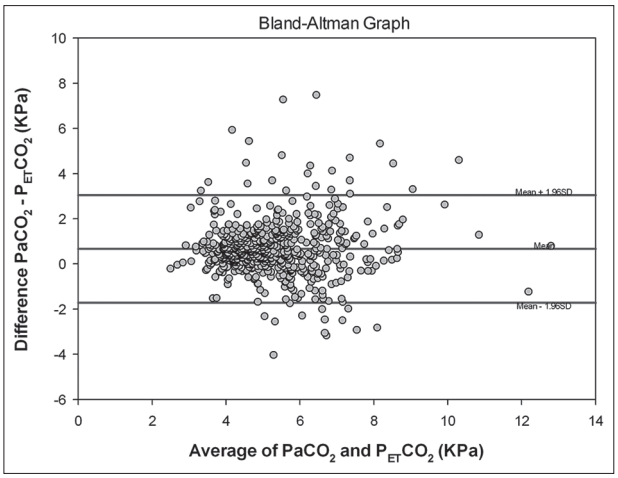

Figure 3: A Bland-Altman plot comparing concurrent arterial carbon dioxide tension ($PaCO_2$) and end-tidal carbon dioxide tension ($P_{ET}CO_2$) measurements (bias = 0.66, standard deviation = 1.22, limits of agreement = −1.72, 3.05, bias confidence interval [CI] 95% CI = 0.57-0.76, lower limit of agreement CI 95% CI = −1.89 to −1.56, upper limit of agreement CI 95% CI = 2.88–3.21)

early stages.[17] With worsening lung disease, right-to-left shunting increases and results in poor oxygenation and carbon dioxide elimination. Therefore, for any given degree of arterial oxygen de-saturation there is an associated and obligatory $PaCO_2$–$P_{ET}CO_2$ difference. Using the shunt equation, we have shown a positive correlation between the $PaCO_2$–$P_{ET}CO_2$ difference and the $P(A\text{-}a)O_2$ difference, and this provides an explanation to the above observations. As the FiO_2 requirement increases, the greater the $PaCO_2$–$P_{ET}CO_2$ difference.

Approximately 20% of our $P_{ET}CO_2$ values read higher than the concurrent $PaCO_2$ measurement, resulting in a negative $PaCO_2$–$P_{ET}CO_2$ difference. Similar negative $PaCO_2$–$P_{ET}CO_2$ differences have been observed more than 30 years ago by Nunn and Hill during anesthesia but no explanation was offered.[12] There does not appear to be any correlation between this negative difference and the primary disease. This suggests the factors contributing to this difference may be more technical and not related to the primary disease. For example, McSwain *et al*. has recently shown an increase in the $PaCO_2$–$P_{ET}CO_2$ difference with rising dead space/tidal volume ratio.[18] Fletcher and Jonson observed negative or zero $PaCO_2$–$P_{ET}CO_2$ values in 12% of normal subjects during intermittent positive pressure ventilation with large tidal volumes and low frequencies under anesthesia.[19] Negative $PaCO_2$–$P_{ET}CO_2$ values were also observed during anesthesia in 50% of pregnant subjects, in 8.1% of patients after postcardiac bypass and in 50% of infants.[20-25]

The following hypotheses may explain the observed negative $PaCO_2$–$P_{ET}CO_2$ differences. Low tidal volume and high frequency ventilation settings may result in poor ventilation of dependent but well-perfused alveoli, resulting in worse V/Q matching. The gas emptying from these slow alveoli may remain in the airways during small frequent breaths. Under these circumstances, the low V/Q areas (alveoli with higher PCO_2) make a higher contribution to overall gas exchange. The net effect of these factors is to enable the terminal part of phase III of the end tidal CO_2 wave to exceed mean $PaCO_2$, resulting in a negative $PaCO_2$–$P_{ET}CO_2$.

Alternatively, very elevated mixed venous PCO_2, as in exercise or septic shock, may contribute to a negative $PaCO_2$–$P_{ET}CO_2$ difference. In healthy adults, $PaCO_2$–$P_{ET}CO_2$ difference was shown to be inversely related to the frequency of breathing and directly related to tidal volume and CO_2 output.[26] A negative $PaCO_2$–$P_{ET}CO_2$ difference in pregnancy has been attributed to higher CO_2 production. The same explanation may hold true for children and infants with relatively higher metabolic rates. This study demonstrates that 33% of children in septic shock have negative $PaCO_2$–$P_{ET}CO_2$ observations.

The study had several limitations. For example, the standard alveolar gas equation is a simplification of the actual relationship between FiO_2, $PaCO_2$, and PaO_2 and may deviate up to 10 mmHg (when $FiO_2 = 1.0$) from the more rigorous, full calculation. In addition, values used in the equation may not be precisely known, particularly the value of respiratory quotient of 0.8 (*R*), which may shift depending upon the relative utilization of carbohydrate, protein, and fat. The breath-to-breath variability of respiratory rate or tidal volume that may occur during invasive BiPAP mode ventilation has also not been accounted for.

Conclusion

The $PaCO_2$–$P_{ET}CO_2$ difference is individual specific in mechanically ventilated children. It is not affected by the disorder leading to mechanical ventilation. The $P(A\text{-}a)O_2$ difference has a minor but a significant influence upon $PaCO_2$–$P_{ET}CO_2$ difference. In a "steady" state of mechanical ventilation the $PaCO_2$–$P_{ET}CO_2$ difference is static.

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