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ARTICLE

Effect of tidal volume and end tracheal tube leakage on end-tidal CO_2 in very low birth weight infants

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Abstract

Objective To examine the extents to which low tidal volume (VT) and endotracheal tube (ETT) leakeage influence the accuracy of $ETCO_2$ for estimating arterial PCO_2 ($PaCO_2$) in very low birth weight (VLBW) infants with mechanical ventilation.

Study design An observational study. We evaluated a total of 287 paired $ETCO_2$ and $PaCO_2$ values as well as VTs obtained from 22 VLBW infants with ventilation. Deming regression, quadratic discriminant analysis, and Bland–Altman analysis were performed.

Result $ETCO_2$ and $PaCO_2$ were correlated ($r^2 = 0.5897$, $p < 0.0001$). A quadratic discrimination analysis of the VT and the percentage of leak yielded 70.4% [95%CI, 65.1 to 75.7] discrimination for the agreement between $ETCO_2$ and $PaCO_2$. $ETCO_2$ was strongly correlated with $PaCO_2$ in the discriminant function $Z > 0$ group ($r^2 = 0.7234$, $p < 0.0001$).

Conclusion Our results indicate that $ETCO_2$ is a good surrogate for $PaCO_2$ when VT is high and ETT leak is low.

Introduction

The preterm lung is highly fragile because the lung is structurally immature and deficient in surfactant, and lung overdistension can cause pulmonary inflammation leading to lung injury. Therefore, careful monitoring of respiratory mechanics, including CO_2, is necessary during mechanical ventilation to prevent volutrauma and chronic lung disease [1, 2].

Capnography, which displays the level and waveform of CO_2 in expired breaths, is a simple and well-established standard monitoring technique that indicates arterial PCO_2 ($PaCO_2$) and provides information on cell metabolism, blood perfusion, and alveolar ventilation in adult and pediatric patients [3, 4]. The use of end-tidal CO_2 ($ETCO_2$) for monitoring and as a tool for verifying endotracheal tube (ETT) position is another standard technique [4–6].

Several investigators have demonstrated that $ETCO_2$ was in good correlation with $PaCO_2$ values in infants, including extremely low birth weight infants [7–12]. However, capnography has not been widely accepted by neonatologists for physiological and technical reasons, such as the weight of sensors or water droplets within circuits, dead space, and leakage from tracheal intubation tubes [13, 14]. Furthermore, the difficulty in acquiring adequate CO_2 waveforms due to tachypnea and ventilation–perfusion mismatch affects the accuracy of $ETCO_2$.

The main problem with capnography in infants is the low tidal volume (VT) and leakage from tracheal intubation, which is often observed when using uncuffed ETTs [15]. While the effects of ETT leakage on the monitoring of VT and respiratory mechanics have been well investigated, little is known about the extents to which low VTs and ETT leakage influence the agreement between $ETCO_2$ and $PaCO_2$. The aim of this study was to evaluate the accuracy of $ETCO_2$ for estimating $PaCO_2$ and examine the effects of different amounts of ETT leakage and inspiratory VTs on $ETCO_2$ measurements in very low birth weight (VLBW) infants requiring mechanical ventilation.

Materials and methods

This is an observational study and the study subjects consisted of 22 VLBW infants admitted to our Neonatal

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Intensive Care Unit at Fukuda Hospital, Kumamoto, Japan, and treated with mechanical ventilation during the period from March 2013 to February 2015. Data were excluded when waveform capnography was not available. Demographics, clinical features, and laboratory test result data for each subject were collected from medical charts.

The infants were mechanically ventilated with synchronized intermittent mandatory ventilation with pressure support (SIMV + PSV) using a time-cycled pressure-limited ventilator (Puritan Bennett^{TM} 840 ventilator®; Medtronic, Mansfield, MA, USA). The peak inspiratory pressure, support pressure, oxygen concentration, inspiratory time, positive end expiratory pressure, and respiratory rate were arranged to obtain the optimal arterial PaO_2 and $PaCO_2$ as determined by the physicians.

$ETCO_2$ was measured through a mainstream capnometer, which is lightweight (4 g) and has a low dead space (0.5 mL) airway adapter, connected to the proximal end of the endotracheal tube (cap-ONE®, TG-970P; Nihon-Kohden, Tokyo, Japan). Data were continuously recorded on a laptop computer using a software programmed by LabVIEW (National Instruments, Texas, USA) through a CO_2 monitor (OLG-2800; Nihon-Kohden, Tokyo, Japan) in each subjects. $ETCO_2$ varied appreciably from breath to breath in the presence of spontaneous breathing during mechanical ventilation. However, as previously described [8], there is a good correlation between $PaCO_2$ and maximum $ETCO_2$ of 20 s capnography. Therefore, the maximum $ETCO_2$ values were chosen based on the results of capnography for 20 s at the same time as the blood gas analysis.

The respiratory monitoring data, such as the VT and the leakage volume, were continuously downloaded from the ventilator by using a software 840 DCI (Medtronic, Mansfield, Massachusetts, USA) with a sampling rate of 6 s. These parameters were measured at the same time as the blood gas analysis. The percentage of ETT leakage was calculated using the following equation:

$$\begin{aligned}&\text{the percentage of ETT leakage}\\&= (\text{inspiratory VT} - \text{expiratory VT})/\text{inspiratory VT} \times 100.\end{aligned}$$

All the blood samples were drawn from indwelling arterial lines into a 0.1-mL heparinized syringe to prevent coagulation. $PaCO_2$ measurements were then made immediately using a bedside blood gas analytical instruments (ABL 700; Radiometer, Copenhagen, Denmark). All blood gas analyses were performed as part of the subject's evaluation (including PaO_2, $PaCO_2$, electrolytes, or lactate, etc.). Calibrations were performed automatically for the blood gas analyzer, and the accuracy of the capnography was examined using a 5% CO_2 gas cylinder. Zero calibration was also performed according to the operator's manual before the capnography device was connected to the respiration circuit.

Statistical analysis

All the statistical analyses were performed using MedCalc software version 16.8 (MedCalc Software bvba, Ostend, Belgium).

To determine whether $ETCO_2$ was representative of $PaCO_2$, the correlation between $ETCO_2$ and $PaCO_2$ was analyzed by Deming regression [16]. Deming regression is a preferred method for comparing two analytic methods or the same method at different time points. Because it considers both x- and y-axes to be subject to measurement error, it is less influenced by outliers. Bland–Altman plots [17] were conducted to assess the agreement between $ETCO_2$ and $PaCO_2$.

A quadratic discriminant analysis [18] was also used to assess whether the agreement between $ETCO_2$ and $PaCO_2$ was influenced by respiratory monitoring data about the VT and the percentage of ETT leakage. The quadratic discriminant function ($Z = 0$) is the boundary that separates into two groups; positive values of the discriminant function ($Z > 0$) are associated with the group that has an agreement between $ETCO_2$ and $PaCO_2$. And if the discriminant function is negative ($Z < 0$), there is no agreement between $ETCO_2$ and $PaCO_2$. We defined a bias ($ETCO_2$–$PaCO_2$) level of −6.74 mmHg as the acceptable lower limit for the difference between $ETCO_2$ and $PaCO_2$ based on our previous experiments examining $ETCO_2$ in rabbits [7], which showed that the limits of agreement were −6.74 to 4.99 mmHg based on Bland–Altman plots. Values of $p < 0.05$ were determined to be significant.

Statement of ethics

Informed consent was obtained from the subjects' guardians, and this study was performed under the control of the Ethics Committee of Medicine and Medical Care, Fukuda Hospital, Kumamoto, Japan.

Results

A total of 287 paired $ETCO_2$ and $PaCO_2$ values obtained from 22 VLBW infants were compared. The median gestational age, birth weight of subjects, and postnatal days at the measurement performed were 27 weeks (range 25–34 weeks), 944 g (range 643–1499 g) and 4 days (range 1–30 days), respectively. The median and range of VT were 8.9 mL (range 2.2 to 27.6 mL), and the percentage of ETT leak was 2.2% (range 0–60.7%).

Figure 1 shows the Deming regression analysis (left) and Bland-Altman plot (right). The correlation between $ETCO_2$ and $PaCO_2$ was statistically significant ($p < 0.0001$); however, these were not practically relevant ($r^2 = 0.5897$). In

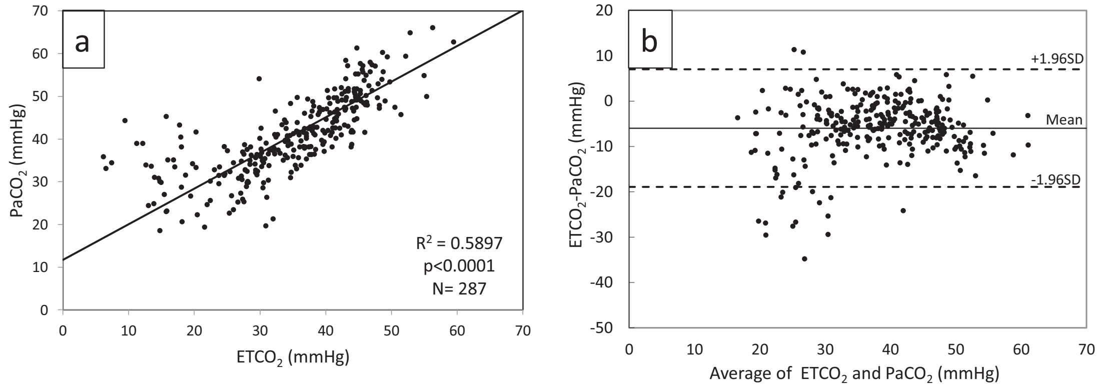

Fig. 1 Relationship and limits of agreement between $ETCO_2$ and $PaCO_2$ in VLBW infants. The correlation between $ETCO_2$ and $PaCO_2$ (**a**) was statistically significant ($p < 0.0001$); however, there is no practically relevant ($r^2 = 0.5897$). In the Bland–Altman plot test (**b**), the mean difference (bias) and the SD of the differences for $ETCO_2$ was -5.94 ± 6.63 mmHg (95% CI, -18.9 to 7.05 mmHg). The solid line and the dashed lines represent the mean and ±1.96 SD.

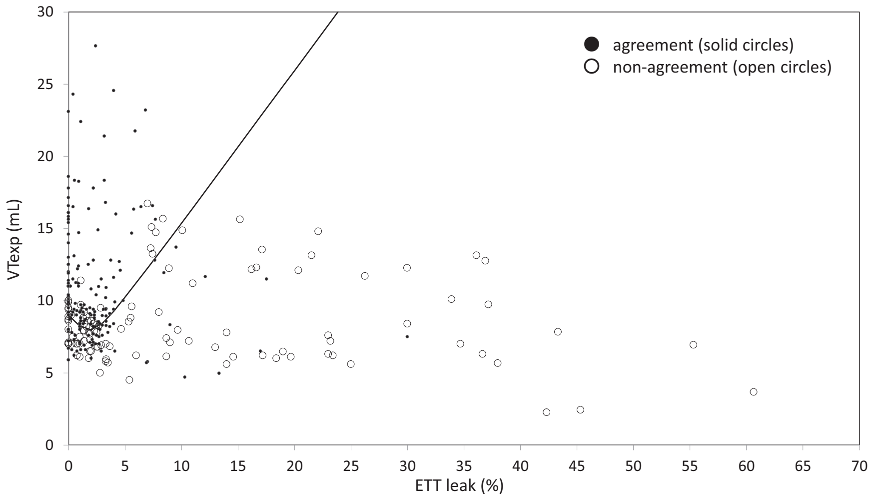

Fig. 2 Scatter plot of the tidal volume versus the percentage of leak in VLBW infants. The differences between $ETCO_2$ and $PaCO_2$ (bias) were compared to the bias of a previous study [7] to determine the degree of agreement between $ETCO_2$ and $PaCO_2$. The open circles represent measurements where the $ETCO_2$ and $PaCO_2$ measurements were not correlated; the solid circles represent measurements where the $ETCO_2$ measurement was correlated with the $PaCO_2$ measurement. A discrimination analysis for the tidal volume and the percentage of leak yielded 70.4% [95% CI, 65.1–75.7] discrimination for the agreement between $ETCO_2$ and $PaCO_2$. The solid line shows the discriminant function, which decides whether they agreed or not by a quadratic discrimination analysis of the VT and the percentage of the leak. This figure shows that the tidal volume and the percentage of leak provide independent information for evaluating the agreement between $ETCO_2$ and $PaCO_2$. VLBW: very low birth weight, ETT: end tracheal tube.

the Bland–Altman plot analysis, the mean difference (bias) and the standard deviation (SD) of the differences for $ETCO_2$ were -5.94 ± 6.63 mmHg [95% CI, -18.9 to 7.05]. In particular, $ETCO_2$ can be used to estimate $PaCO_2$ in the group with a TV of 8 mL or more and a ETT leak of 7% or less ($n = 156$, $r^2 = 0.7621$, $p < 0.0001$).

Figure 2 shows the quadratic discriminant analysis for VT and percentage of ETT leak. The differences between $ETCO_2$ and $PaCO_2$ (bias) were compared to the bias of a previous study [7] to determine the degree of agreement between $ETCO_2$ and $PaCO_2$. A discrimination analysis for the VT and the percentage of ETT leak yielded 70.4% [95% CI, 65.1 to 75.7] discrimination for the agreement between $ETCO_2$ and $PaCO_2$. The solid line shows the discriminant function, which decides whether they agreed or not by a quadratic discrimination analysis of the VT and the percentage of the ETT leak. This figure shows that the VT and the percentage of ETT leakage provide independent information for evaluating the agreement between $ETCO_2$ and $PaCO_2$.

We also classified the data into two groups, $Z < 0$ and $Z > 0$ groups, based on the results of a quadratic discriminant function. $ETCO_2$ was strongly correlated with $PaCO_2$ in the discriminant function $Z > 0$ group ($r^2 =$

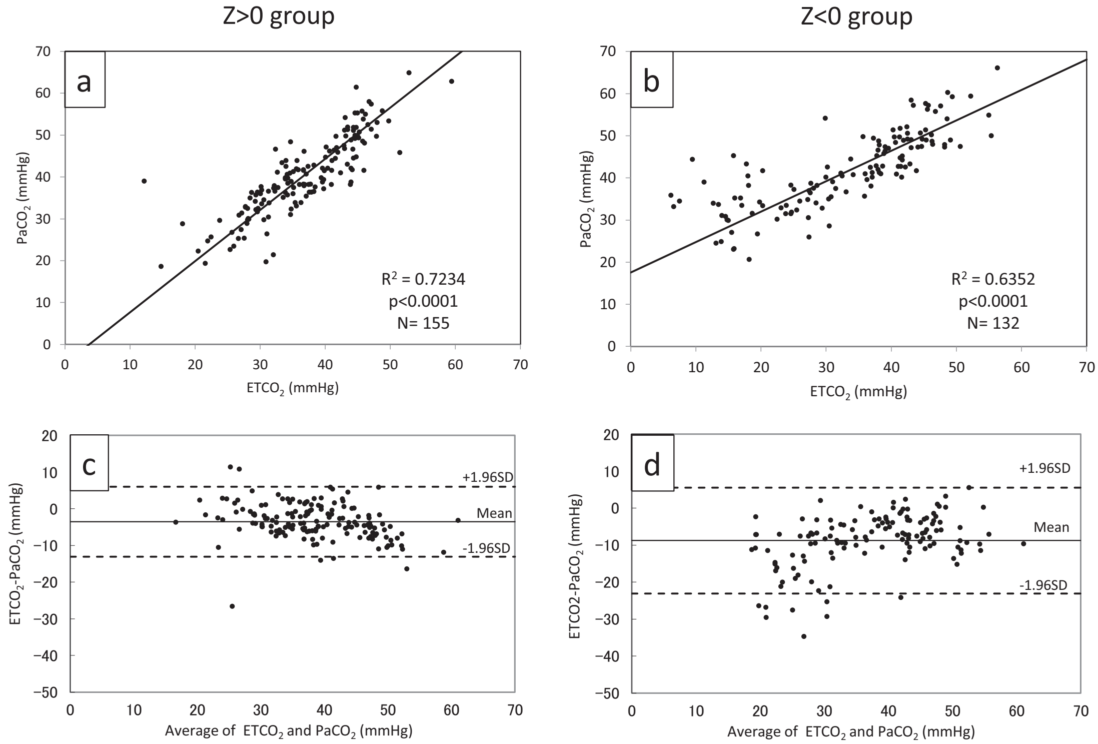

Fig. 3 Relationship between ETCO$_2$ and PaCO$_2$ (**a**, **b**) and a Bland-Altman plot showing the bias against average values of ETCO$_2$ and PaCO$_2$ (**c**, **d**) in the discriminant function Z > 0 (left panel) and Z < 0 (right panel) groups. ETCO$_2$ was strongly correlated with PaCO$_2$ in the discriminant function $Z > 0$ group ($r^2 = 0.7234$, $p < 0.0001$, **a**). The p-value is < 0.001 in the $Z < 0$ group as well; however, there is an only weak correlation ($r^2 = 0.6352$) between ETCO$_2$ and PaCO$_2$, respectively (**b**). The Bland-Altman analysis showed that ETCO$_2$ underestimated PaCO$_2$ by a mean difference (bias) of −3.52 ± 4.86 mmHg (95% CI, −13.0 to 6.00 mmHg) in the $Z > 0$ group (**c**) and −8.79 ± 7.29 mmHg (95% CI, −23.1 to 5.50 mmHg) in the $Z < 0$ group (**d**).

0.7234, $p < 0.0001$, Fig. 3a). The p value is less than 0.001 in the $Z < 0$ group as well; however, the correlation between ETCO$_2$ and PaCO$_2$ was weak ($r^2 = 0.6352$) (Fig. 3b).

The Bland–Altman analysis showed that ETCO$_2$ underestimated PaCO$_2$ by a mean difference (bias) of −3.52 ± 4.86 mmHg [95% CI, −13.4 to 6.00] in the $Z > 0$ group (Fig. 3c) and −8.79 ± 7.29 mmHg [95% CI, −23.07 to 5.50] in the $Z < 0$ group (Fig. 3d).

Discussion

We found that ETCO$_2$ measured using the mainstream capnometer cap-ONE® was an accurate and reliable non-invasive method for estimating PaCO$_2$ in VLBW infants. The Bland–Altman analysis showed the bias and SD of the differences between ETCO$_2$ and PaCO$_2$ of −5.94 ± 6.63 mmHg. In addition, our results imply that ETCO$_2$ and PaCO$_2$ are likely to correlate better if the tidal volume is larger and the ETT leak is lower; ETCO$_2$ can best be used to estimate PaCO$_2$ in the group with a VT of 8 mL or more and an ETT leak of 7% or less.

Uncuffed ETTs have been the standard of care for pediatric patients under 8 years old based on the presumption that complications such as airway mucosal injury and post-extubation stridor could occur with the use of cuffed ETTs [19, 20].

However, the use of uncuffed ETTs has several disadvantages, including excessive air leakage around the tube leading to unreliable respiratory mechanics, exhaled volumes, and end-expiratory gases, which may be especially important in the intensive care management of intubated pediatric and neonatal patients [21].

The apparatus dead space is of marked interest for capnography because it can lead to the rebreathing of exhaled CO$_2$, thereby causing false inspiratory and expiratory CO$_2$ measurements [22]. Although adapters with a small dead space of about 0.5 mL have become available, the problem regarding dead space remains, especially in preterm infants with low VTs. Furthermore, conventional high sampling flow to measure ETCO$_2$ like 150–200 mL/min using side-stream capnography, underestimates alveolar CO$_2$ concentration in neonatal patients.

ETT leaks reportedly occur in about 70–75% of ventilated infants [23, 24], and the effects of ETT leaks on the measurement of exhaled CO$_2$ are a worrisome problem for pediatric patients, especially for infants. According to the ventilated neonatal lung model study [25], at the end of expiration, when the patient flow is zero, an ETT leak can lead to reverse flow through the adapter, washing out the exhaled CO_2 and resulting in an $ETCO_2$ measurement close to zero. Leak-dependent CO_2 measurement errors depend on the shape of the CO_2 plateau in exhaled air. We previously reported a strong correlation between $ETCO_2$ and $PaCO_2$ when the VT/body weight was 10 mL/kg with a leakage rate of <60% in rabbits [7].

Healthcare providers need to know the minimum VT and maximum ETT leakage values that can be tolerated during $ETCO_2$ measurements in patients with ETT leaks. Greer et al. [26] reported that variations in VT could account for significant differences between $ETCO_2$ and $PaCO_2$. We found that both the VT and the percentage of ETT leak could be used to discriminate the agreement between $ETCO_2$ and $PaCO_2$. When evaluating all measures obtained with a similar degree of ETT leak (for example, 10% of ETT leak), $ETCO_2$ and $PaCO_2$ correlated well with large VTs but not well with smaller VTs. Furthermore, comparing agreement between $ETCO_2$ and $PaCO_2$ when a VT is held, there was a good correlation when the percentage of the ETT leak was small but not well with larger leakage. In particular, the lower the leakage, the more likely $ETCO_2$ and $PaCO_2$ correlate. In terms of the technical methodology, these results are easy to understand and very important.

$ETCO_2$ appears to underestimate $PaCO_2$ values, which could be potentially dangerous. Our results indicate that when estimating the $PaCO_2$ using $ETCO_2$ with a small VT in the presence of relatively small ETT leakage (even ETT leak <7%), the value of $ETCO_2$ might be lower than the actual CO_2 concentration, which clinicians need to be aware of.

In situations where the $ETCO_2$ is not correlated with the $PaCO_2$, $ETCO_2$ measurements can be used to confirm the placement of the ET tube in the trachea as long as the additional dead space created by the measurement does not affect the patient's respiration.

In the presence of ETT leaks, this difference between the displayed and actual VT becomes much more important. According to Vignaux et al., ventilators can underestimate VT in the presence of ETT leak during expiration [27].

In the present study, the VT might not have been accurate because many of the patients had ETT leakage. Besides, we used the VT values obtained from the ventilator; the measurement at the endotracheal tube adapter is more accurate [28]. Furthermore, blood gas measurements and ventilator adjustments were made at the discretion of the team, which innately introduces bias. Moreover, we have in no way accounted for what could potentially be multiple repeated measures in a single subject. Therefore, these issues should be studied in the future.

Conclusion

Our results indicate that $ETCO_2$ is a good surrogate for $PaCO_2$ when VT is high (over 8 mL) and ETT leak is low (<7%). As VT decrees and ETT leak increases, the agreement between the two decreases and reliability of $ETCO_2$ goes down; specifically, $ETCO_2$ underestimates $PaCO_2$.

Although the VTs and the percentage of ETT leaks obtained from the ventilator might not be accurate, such monitoring data could provide additional information for evaluating the accuracy of $ETCO_2$ estimations based on $PaCO_2$ measurements.

Author contributions DT conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Koko G. designed the data collection instruments, collected data, and reviewed and revised the manuscript. Kei G. conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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