Effect of tidal volume and end tracheal tube leakage on end-tidal CO2 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) leakage influence the accuracy of ETCO2 for estimating arterial PCO2 (PaCO2) in very low birth weight (VLBW) infants with mechanical ventilation.

Study design An observational study. We evaluated a total of 287 paired ETCO2 and PaCO2 values as well as VTs obtained from 22 VLBW infants with ventilation. Deming regression, quadratic discriminant analysis, and Bland–Altman analysis were performed.

Result ETCO2 and PaCO2 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 ETCO2 and PaCO2. ETCO2 was strongly correlated with PaCO2 in the discriminant function $Z > 0$ group ($r^2 = 0.7234, p < 0.0001$).

Conclusion Our results indicate that ETCO2 is a good surrogate for PaCO2 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 CO2, is necessary during mechanical ventilation to prevent volutrauma and chronic lung disease [1, 2].

Capnography, which displays the level and waveform of CO2 in expired breaths, is a simple and well-established standard monitoring technique that indicates arterial PCO2 (PaCO2) and provides information on cell metabolism, blood perfusion, and alveolar ventilation in adult and pediatric patients [3, 4]. The use of end-tidal CO2 (ETCO2) for monitoring and as a tool for verifying endotracheal tube (ETT) position is another standard technique [4–6].

Several investigators have demonstrated that ETCO2 was in good correlation with PaCO2 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 CO2 waveforms due to tachypnea and ventilation–perfusion mismatch affects the accuracy of ETCO2.

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 ETCO2 and PaCO2. The aim of this study was to evaluate the accuracy of ETCO2 for estimating PaCO2 and examine the effects of different amounts of ETT leakage and inspiratory VTs on ETCO2 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...
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™ 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 PaO2 and PaCO2 as determined by the physicians.

ETCO2 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 CO2 monitor (OLG-2800; Nihon-Kohden, Tokyo, Japan) in each subject. ETCO2 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 PaCO2 and maximum ETCO2 of 20 s capnography. Therefore, the maximum ETCO2 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:

\[
\text{the percentage of ETT leakage} = \frac{\text{inspiratory VT} – \text{expiratory VT}}{\text{inspiratory VT}} \times 100.
\]

All the blood samples were drawn from indwelling arterial lines into a 0.1-mL heparinized syringe to prevent coagulation. PaCO2 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 PaO2, PaCO2, electrolytes, or lactate, etc.). Calibrations were performed automatically for the blood gas analyzer, and the accuracy of the capnography was examined using a 5% CO2 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 ETCO2 was representative of PaCO2, the correlation between ETCO2 and PaCO2 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 ETCO2 and PaCO2.

A quadratic discriminant analysis [18] was also used to assess whether the agreement between ETCO2 and PaCO2 was influenced by respiratory monitoring data about the VT and the percentage of ETT leakage. The quadratic discriminant function 

\[
Z = a_1 X_1 + a_2 X_2 + \cdots + a_k X_k + b
\]

was in the form of

\[
Z = a_1 X_1 + a_2 X_2 + \cdots + a_k X_k + b
\]

where \(a_k\) is a coefficient, \(X_k\) is the parameter, and \(b\) is a constant. The discriminant function is negative (\(Z < 0\)) if the discriminant function is positive (\(Z > 0\)) if the discriminant function is zero (\(Z = 0\)).

###Results

A total of 287 paired ETCO2 and PaCO2 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 plots (right). The correlation between ETCO2 and PaCO2 was statistically significant \((p < 0.0001)\); however, these were not practically relevant \((r^2 = 0.5897)\). In
the Bland–Altman plot analysis, the mean difference (bias) and the standard deviation (SD) of the differences for ETCO2 were $-5.94 \pm 6.63 \text{ mmHg}$ [95% CI, $-18.9$ to $7.05 \text{ mmHg}$]. In the Bland–Altman plot test (b), the mean difference (bias) and the SD of the differences for ETCO2 was $-5.94 \pm 6.63 \text{ mmHg}$ [95% CI, $-18.9$ to $7.05 \text{ mmHg}$]. The solid line and the dashed lines represent the mean and $\pm 1.96 \text{ SD}$.

**Fig. 1** Relationship and limits of agreement between ETCO2 and PaCO2 in VLBW infants. The correlation between ETCO2 and PaCO2 (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 solid line and the dashed lines represent the mean and $\pm 1.96 \text{ SD}$. The open circles represent measurements where the ETCO2 and PaCO2 measurements were not correlated; the solid circles represent measurements where the ETCO2 measurement was correlated with the PaCO2 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 ETCO2 and PaCO2. 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 ETCO2 and PaCO2. VLBW: very low birth weight, ETT: end tracheal tube.

**Fig. 2** Scatter plot of the tidal volume versus the percentage of leak in VLBW infants. The differences between ETCO2 and PaCO2 (bias) were compared to the bias of a previous study [7] to determine the degree of agreement between ETCO2 and PaCO2. The open circles represent measurements where the ETCO2 and PaCO2 measurements were not correlated; the solid circles represent measurements where the ETCO2 measurement was correlated with the PaCO2 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 ETCO2 and PaCO2. 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 ETCO2 and PaCO2. VLBW: very low birth weight, ETT: end tracheal tube.
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 $-3.52 \pm 4.86$ mmHg (95% CI, $-13.0$ to $6.00$ mmHg) in the $Z > 0$ group (Fig. 3c) and $-8.79 \pm 7.29$ mmHg (95% CI, $-23.1$ to $5.50$ mmHg) 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 $-5.94 \pm 6.63$ 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

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**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 $-3.52 \pm 4.86$ mmHg (95% CI, $-13.0$ to $6.00$ mmHg) in the $Z > 0$ group (c) and $-8.79 \pm 7.29$ mmHg (95% CI, $-23.1$ to $5.50$ mmHg) in the $Z < 0$ group (d).
expansion, when the patient flow is zero, an ETT leak can lead to reverse flow through the adapter, washing out the exhaled CO\textsubscript{2} and resulting in an ETCO\textsubscript{2} measurement close to zero. Leak-dependent CO\textsubscript{2} measurement errors depend on the shape of the CO\textsubscript{2} plateau in exhaled air. We previously reported a strong correlation between ETCO\textsubscript{2} and PaCO\textsubscript{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\textsubscript{2} measurements in patients with ETT leaks. Greer et al. [26] reported that variations in VT could account for significant differences between ETCO\textsubscript{2} and PaCO\textsubscript{2}. We found that both the VT and the percentage of ETT leak could be used to discriminate the agreement between ETCO\textsubscript{2} and PaCO\textsubscript{2}. When evaluating all measures obtained with a similar degree of ETT leak (for example, 10% of ETT leak), ETCO\textsubscript{2} and PaCO\textsubscript{2} correlated well with large VTs but not well with smaller VTs. Furthermore, comparing agreement between ETCO\textsubscript{2} and PaCO\textsubscript{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\textsubscript{2} and PaCO\textsubscript{2} correlate. In terms of the technical methodology, these results are easy to understand and very important.

ETCO\textsubscript{2} appears to underestimate PaCO\textsubscript{2} values, which could be potentially dangerous. Our results indicate that when estimating the PaCO\textsubscript{2} using ETCO\textsubscript{2} with a small VT in the presence of relatively small ETT leakage (even ETT leak <7%), the value of ETCO\textsubscript{2} might be lower than the actual CO\textsubscript{2} concentration, which clinicians need to be aware of.

In situations where the ETCO\textsubscript{2} is not correlated with the PaCO\textsubscript{2}, ETCO\textsubscript{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\textsubscript{2} is a good surrogate for PaCO\textsubscript{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\textsubscript{2} goes down; specifically, ETCO\textsubscript{2} underestimates PaCO\textsubscript{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\textsubscript{2} estimations based on PaCO\textsubscript{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. 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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