Research and Reports in Neonatology

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METHODOLOGY

$P_{ET}CO_2$ measured by a new lightweight mainstream capnometer with very low dead space volume offers accurate and reliable noninvasive estimation of $PaCO_2$

This article was published in the following Dove Press journal:
Research and Reports in Neonatology
20 October 2011
Number of times this article has been viewed

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Objective: Although capnometers are widely used in adult and pediatric intensive care units, they are not widely used in neonatal intensive care units due to issues such as the weight of sensors, dead space, and leakage from tracheal intubation tubes. These authors developed a light and low dead space airway adaptor of end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and evaluated the correlations between $P_{ET}CO_2$ and partial CO_2 pressure ($PaCO_2$) in rabbits while changing tidal volume and leakage volume.

Methods: Firstly, Japanese rabbits weighing 2 kg were divided into three tidal volumes (6 mL/kg, 10 mL/kg, or 15 mL/kg), and $P_{ET}CO_2$ and $PaCO_2$ were measured. Secondly, the respiratory apparatus was set to a tidal volume/body weight ratio of 10 mL/kg, leakage rates were divided into seven groups, and $P_{ET}CO_2$ and $PaCO_2$ were measured.

Results: $P_{ET}CO_2$ and $PaCO_2$ were significantly correlated ($r^2 = 0.9099$, $P < 0.0001$) when there was no leakage in the tracheal intubation tubes. No significant differences were observed between $PaCO_2$ and $P_{ET}CO_2$ ($P_{a\text{-}ET}CO_2$) in the three tidal volume/body weight groups or for groups in which leakage rate was <60%, but significant deviations in $P_{a\text{-}ET}CO_2$ were noted in groups with leakage rate 60%.

Conclusion: There was a strong correlation between $P_{ET}CO_2$ and $PaCO_2$ when tidal volume/body weight ratio was 6–15 mL/kg with leakage rate <60%. Lightweight mainstream capnometer with a low amount of dead space airway adaptor might be useful in very low birth weight infants with small tidal volume.

Keywords: capnography, mainstream, neonate

Introduction

Advancements in the treatment of neonatal respiratory failure, including exogenous surfactant,[1,2] inhaled nitric oxide,[3,4] and a growing repertoire of assisted ventilation strategies,[5] have decreased morbidity and mortality rates. Patient monitoring has played a critical role in the safe and effective application of these advanced therapies.

Maintaining partial carbon dioxide pressure ($PaCO_2$) within the desired range by frequent arterial sampling can increase the need for multiple transfusions in the neonatal intensive care unit,[6] so methods for continuous noninvasive monitoring of CO_2 levels would prove extremely useful. Both hypocarbia and hypercarbia are detrimental to extremely low birth weight infants and have been implicated as causative factors in periventricular leukomalacia, intraventricular hemorrhage, and chronic lung disease.[7–9] Critical event analyses have documented hypoxemia secondary to depressed

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http://dx.doi.org/10.2147/RRN.S23987

respiratory activity as a principal risk factor for near misses and death.[10,11]

Capnography, which displays the level and waveform of CO_2 in exhaled air, provides information on cell metabolism, blood perfusion, and alveolar ventilation[12] with noninvasive indirect methods. Use of end-tidal CO_2 pressure ($P_{ET}CO_2$) for monitoring and as a tool for verifying endotracheal tube position is a common practice in the operating room and in adult and pediatric intensive care units.[12] However, so far capnometers are not used widely in neonates due to issues such as the weight of sensors and water droplets within circuits, dead space, and leakage from tracheal intubation tubes.

These authors developed a new light (6 g) and low dead space (1 mL) airway adapter (YG-213T; Nihon-Kohden Corporation, Tokyo, Japan) for mainstream capnography (Cap-ONE TG-970P; Nihon-Kohden). The objective of this study was to evaluate the correlations between $P_{ET}CO_2$ and $PaCO_2$ in rabbits while changing tidal volume (TV) and leakage volume with this device.

Material and methods

Ten adult Japanese rabbits weighing 2 kg were anesthetized by intramuscular injection of ketamine at 10 mg/kg and xylazine at 5 mg/kg, and a 24 G catheter (JELCO, Smiths Medical Italia Srl, Mirano, Italy) was placed in the ear vein for continuous intravenous infusion of anesthetic agents. Rabbits were placed in a supine position throughout the experiment. After tracheotomy, an endotracheal tube (internal diameter, 2.5 mm; Mallinkrodt, Inc, St Louis, MO) was inserted. A 24 G catheter was placed in the internal carotid artery to allow collection of samples for blood gas analysis and to monitor arterial blood pressure and heart rate using biomedical research system (LEG-1000; Nihon-Kohden). Anesthesia was provided by continuous intravenous infusion of ketamine (5 mg/kg/hour) and paralysis was maintained by continuous administration of pancuronium (0.1 mg/kg/hour). Animals were administered a mixture of 0.45% sterile saline and 10% glucose solution at 3 mL/kg/hour during the experiment. Body temperature was continuously monitored and maintained at 38.5°C–39.5°C using a heating pad.

Rabbits were ventilated mechanically with a time-cycled pressure-limited ventilator (Humming II; Metran Co, Ltd, Saitama, Japan) adjusted to: fraction of inhaled oxygen at 0.6; inspiratory time at 0.6 seconds; and positive end-expiratory pressure at 5 cmH_2O. Peak inspiratory pressure was settled at the TV maintained at TV/body weight (BW) ratios of 6 mL/kg, 7 mL/kg, 10 mL/kg, and 15 mL/kg, as measured by pneumotachography (ARFEL-VR; Aivision Corporation, Tokyo, Japan). Respiratory rate was adjusted to a level at which normocapnia was maintained (41.6 ± 3.8 mmHg). In the investigation of the effects on TV/BW, TV/BW was divided into three groups (6 mL/kg, 10 mL/kg, and 15 mL/kg), and $P_{ET}CO_2$ and $PaCO_2$ was measured.

$P_{ET}CO_2$ was monitored in intubated rabbits by mainstream capnography (Cap-One TG-970P; Nihon-Kohden). Mainstream $P_{ET}CO_2$ was measured via a capnograph connected to the proximal end of the endotracheal tube. Before each blood sampling, an adequate reading of $P_{ET}CO_2$ and a reliable waveform on the mainstream capnograph (continuous steady waveform of expired CO_2 throughout the ventilatory cycle) was taken. Data was continuously recorded on a laptop computer using the software programmed by LabVIEW (National Instruments Corporation, Austin, TX) for each rabbit. $PaCO_2$ was measured from samples withdrawn intermittently from intraarterial lines indwelling in the internal carotid artery (ABL700; Radiometer Medical ApS, Bronshoj, Denmark). The amount of leakage was adjusted by fixation of the tracheal intubation tubes. The leakage ratio was calculated using the following equation:

$$\text{Leakage ratio} = (\text{inspiratory TV} - \text{expiratory TV}) / \text{inspiratory TV } 100 \times 100$$

The end-tidal volume was measured by mainstream capnography (CO2SMO 8100, Fukuda Denshi, Tokyo, Japan) and also leakage rate was calculated with CO2SMO 8100. The respiratory apparatus was set to a TV/BW ratio of 10 mL/kg, then leakage rates were divided into seven groups (0%–10%, 10%–30%, 30%–50%, 50%–60%, 60%–70%, 70%–80%, and 80%–100%), and $P_{ET}CO_2$ and $PaCO_2$ were measured.

$PaCO_2$ was measured with the additional dead space caused by attachment of a CO_2 sensor and additional dead space in the setting of TV/BW ratios of 6 mL/kg, 7 mL/kg, and 10 mL/kg.

Statistical analyses were conducted using SPSS Statistics version 17.0 software (SPSS, Inc, Chicago, IL). To determine whether $P_{ET}CO_2$ values were representative of $PaCO_2$, the relationship between $P_{ET}CO_2$ and $PaCO_2$ was analyzed by simple linear regression. Bland–Altman plots, representing a visual assessment of agreement between two methods of measurement, were created to assess the measurement of $P_{ET}CO_2$. Bland–Altman plots demonstrate "good agreement" not only when differences between methods are consistent across all measurements but also when the differences are small. In a situation in which difference between the two measurements is expected to change based on a third variable, Bland–Altman plots lose importance. The precision of $P_{ET}CO_2$ measurements and agreement between $P_{ET}CO_2$ and $PaCO_2$ values were assessed by bias ($PaCO_2 - P_{ET}CO_2$), standard deviation, and 95% confidence interval (CI) for the bias. One-factor analysis of variance and the Mann–Whitney U test were used to compare differences between subgroups of TV/BW and leakage ratio. Values of $P < 0.05$ were considered significant. The present study was conducted with the approval of the Institutional Animal Care and Use Committee of Nagano Children's Hospital, Nagano, Japan.

Results

A total of 43 measurements of $P_{ET}CO_2$ and $PaCO_2$ were analyzed. Under conditions of no leakages in the tracheal intubation tubes, $P_{ET}CO_2$ and $PaCO_2$ were significantly correlated ($r^2 = 0.9099$, $P < 0.0001$; Figure 1) and the Bland–Altman plot test showed a mean difference (bias) for $P_{ET}CO_2$ of −0.876 mmHg (Figure 2). The 95% CI for this bias was −1.80–0.04 mmHg. The 95% CI of limits of agreement was −6.74–4.99 mmHg.

In the comparison of differences between $PaCO_2$ and $P_{ET}CO_2$, when setting the TV/BW to 6 mL/kg, 10 mL/kg or 15 mL/kg, no significant differences were observed between the three groups (Figure 3).

Figure 4 shows the effects of additional dead space on $PaCO_2$ under TV conditions of 12 mL, 14 mL, or 20 mL. Under TV conditions of 12 mL and 14 mL (6 mL/kg and 7 mL/kg, respectively), $PaCO_2$ was significantly increased by a dead space increase of only 1 mL, but under TV conditions of 20 mL (10 mL/kg), a dead space increase of 1 mL did not significantly increase $PaCO_2$. $PaCO_2$ thus seemed to be increased by dead space increases representing 7% of TV.

Figure 5 shows the effects of leakage rate on $PaCO_2/P_{ET}CO_2$ at a TV/BW of 10 mL/kg. For all leakage rates <60%, no significant differences were seen between $PaCO_2$ and $P_{ET}CO_2$ compared to the group with a leakage rate of 0%–10%. However, groups with leakage rate 60% showed significant deviations between $PaCO_2$ and $P_{ET}CO_2$.

Regarding the expiratory plateau phase, a relatively constant PCO_2 was maintained when alveolar mixed gas was expired, as shown by the capnogram for 10 mL/kg TV/BW and leakage ratio <60% (Figure 6).

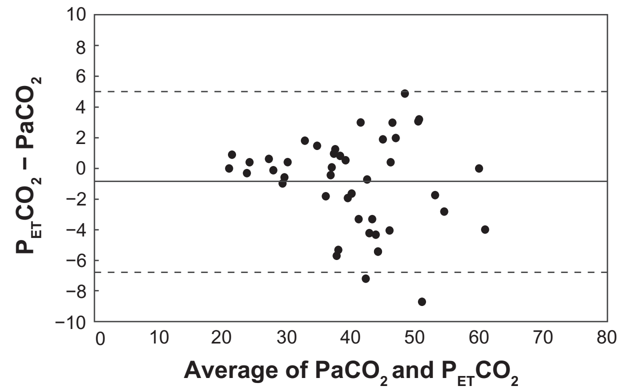

Figure 2 In the Bland–Altman plot test, the mean difference (bias) and standard deviation of differences for end-tidal carbon dioxide pressure ($P_{ET}CO_2$) was −0.876 ± 2.99 mmHg. The 95% confidence interval for bias was −6.74 to 4.99 mmHg.
Abbreviation: $PaCO_2$, partial CO_2 pressure.

Discussion

It was found that $P_{ET}CO_2$ measured by mainstream capnography cap-ONE was an accurate and reliable noninvasive method for estimating $PaCO_2$, showing a good correlation with $PaCO_2$ ($r^2 = 0.9099$, $P < 0.0001$), and there is no bias in the measurement (95% CI: −1.80–0.04 mmHg).

$P_{ET}CO_2$ can be feasibly measured by mainstream or sidestream capnography. Measuring $P_{ET}CO_2$ reportedly underestimates alveolar CO_2 due to the relatively low TVs and rapid respiratory rates of newborns.[13,14] The CO_2 waveform (capnogram) has been characterized for adult patients with normal and abnormal pulmonary function.[15,16] In newborns,

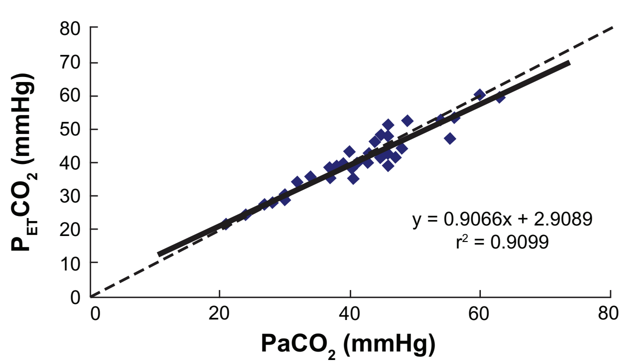

Figure 1 End-tidal carbon dioxide pressure ($P_{ET}CO_2$) and partial CO_2 pressure ($PaCO_2$) were significantly correlated ($r^2 = 0.9099$, $P < 0.0001$).
Note: Dotted line is the line of identity.

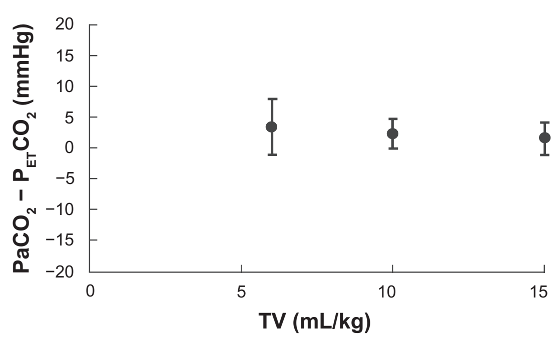

Figure 3 In the comparison of differences between end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and partial CO_2 pressure ($PaCO_2$), no significant differences were observed between the three groups with tidal volume (TV)/body weight ratio of 6 mL/kg, 10 mL/kg, and 15 mL/kg.

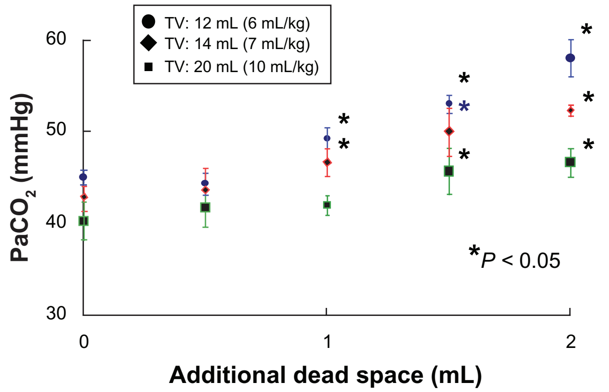

Figure 4 Effects of additional dead space on partial carbon dioxide pressure ($PaCO_2$) under conditions of 12 mL or 20 mL of tidal volume (TV). Under conditions of 12 mL of TV (6 mL/kg), $PaCO_2$ was significantly increased by a dead space increase of only 1 mL. Under conditions of 20 mL of TV (10 mL/kg), even a dead space increase of 1 mL did not significantly increase $PaCO_2$. $PaCO_2$ appears to be affected by a dead space increase of >7% of TV.

CO_2 waveform slurring (a spurious decrease in the slope of the ascending phase of the capnogram) occurs due to dilution of exhaled gas when small, rapid breath packets are measured in a relatively large sample cell.[17]

Condensed water and patient secretions may also impede both mainstream and sidestream technologies. Furthermore, relative inaccuracy is seen in conditions of ventilation-perfusion mismatch.[18,19]

Transcutaneous CO_2 monitoring is a noninvasive technique for measuring CO_2 levels. However, transcutaneous CO_2 monitoring is not tolerated in very low birth weight infants because of their fragile skin, and the technique is affected by acidosis and hypoxia.[20,21]

Mainstream capnography has been found to be more accurate,[22–24] but the sensor position used for mainstream capnography is connected inline between the proximal endotracheal tube and ventilator circuit. As a result, dead space is increased, the sensor competes for TV, and sensor weight may kink the endotracheal tube. When a flow sensor is connected to the endotracheal tube, use of mainstream capnography is even more cumbersome.[25] Given these limitations, most neonatal intensive care units do not routinely perform capnography to assess and manage ventilatory status. These problems might be reduced in measurement of $P_{ET}CO_2$ if the sensor is lightweight and the dead space is small.

In the comparison of differences between $PaCO_2$ and $P_{ET}CO_2$, when setting the TV/BW to 6 mL/kg, 10 mL/kg, or 15 mL/kg, no significant differences were observed between the three groups even at the 6 mL/kg setting. Conversely, Sakamoto et al reported a lower correlation between $PaCO_2$ and $P_{ET}CO_2$ with ≤6 mL/kg compared to >6 mL/kg in porcine neonates.[26] They measured $P_{ET}CO_2$ by sidestream capnography, so $P_{ET}CO_2$ might have been underestimated.

Figure 4 shows the effects of additional dead space on $PaCO_2$. Under conditions of 6 mL/kg of TV, $PaCO_2$ was significantly increased by a dead space increase of only 1 mL, representing >7% of TV. Figueras et al[27] reported that the introduction of the pneumotachometer, which has a dead space of 1.6 mL for 10 minutes, led to a transcutaneous PCO_2 increase of 5.40 ± 2.66 mmHg, from 39.76 ± 8.69 mmHg to 45.17 ± 9.22 mmHg ($P = 0.0000$) in newborn infants. However, they did not measure $PaCO_2$ directly, nor they did change the amount of dead space when measuring transcutaneous PCO_2.

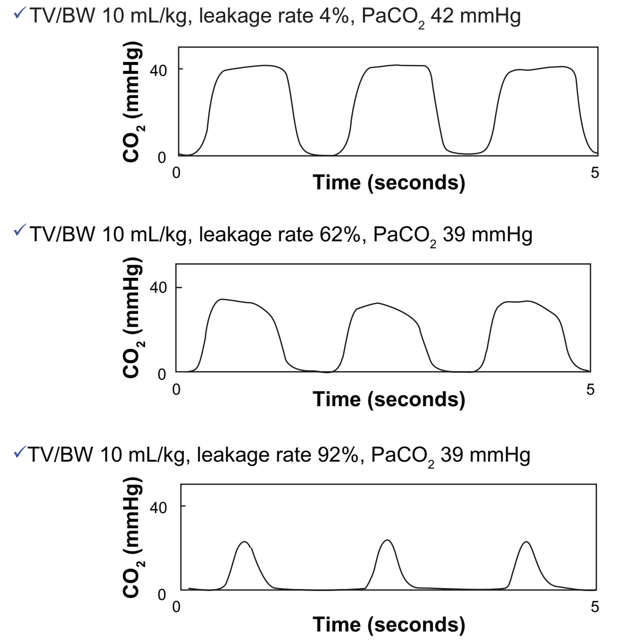

Figure 6 Regarding the expiratory plateau phase, when alveolar mixed gas was expired, a relatively constant partial CO_2 pressure ($PaCO_2$) was maintained, as shown by the capnogram for the >6 mL/kg tidal volume/body weight (TV/BW) group.

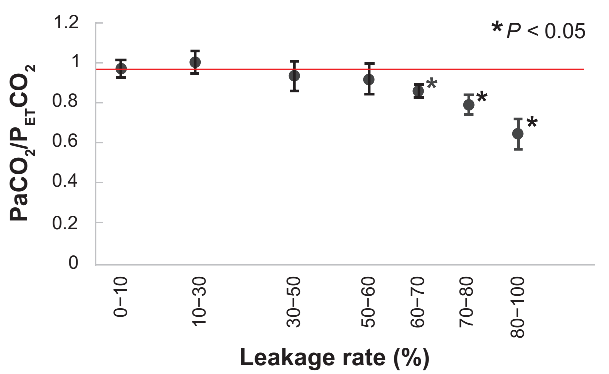

Figure 5 Effects of leakage rate on end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and partial CO_2 pressure ($PaCO_2$). When leakage rate was <60%, no significant differences were seen between $PaCO_2$ and $P_{ET}CO_2$ compared to the group in which the leakage rate was 0%–10%. However, groups with leakage rate 60% showed significant deviations between $PaCO_2$ and $P_{ET}CO_2$.

With respect to lung injury, too high volumes/pressures and/or too low positive end expiratory pressure promotes degradation of the lungs, so-called ventilator-induced lung injury, and is associated with high mortality.[28] Such injuries are known to result in local alterations in lung compliance and pulmonary edema secondary to capillary leakage and are important contributing factors to the pathogenesis of chronic lung disease in neonates.[29,30]

To the best of the authors' knowledge, no studies have described the effects of endotracheal tube leakage on $P_{ET}CO_2$. Leakage is more of a problem in children than in adults because of the use of uncuffed endotracheal tubes. Capnography offers direct monitoring of the inhaled and exhaled concentrations or partial pressure of CO_2. The amount of endotracheal tube leakage around an uncuffed endotracheal tube is thus larger, and significant differences between $PaCO_2$ and $P_{ET}CO_2$ might arise.

No significant differences were found between $PaCO_2$ and $P_{ET}CO_2$ when the leakage rate was $<60\%$, similar to the group in which leakage rate was 0%–10%. However, in groups with a leakage rate 60%, significant deviations were seen between $PaCO_2$ and $P_{ET}CO_2$.

Also, regarding the expiratory plateau phase, a relatively constant PCO_2 was maintained, as shown by the capnogram for 10 mL/kg TV/BW and leakage ratio $<60\%$ (Figure 6).

This analysis of rabbits weighing 2 kg revealed good correlation and agreement between $PaCO_2$ and $P_{ET}CO_2$. However, only deep anesthetized rabbits weighing 2 kg were used. In addition, $P_{ET}CO_2$ was measured in rabbits using the setting of limited mechanical ventilation. Further studies using different conditions are warranted to further elucidate this area.

Conclusion

A strong correlation was obtained and there was no bias between $P_{ET}CO_2$ and $PaCO_2$ when TV/BW was 6–15 mL/kg and the leakage rate was $<60\%$. Lightweight and low amounts of dead space capnometer may be used in very low birth weight infants with small TV.

Disclosure

The authors report no conflicts of interest in this work.

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