A lightweight mainstream capnometer with very low dead space volume is useful monitor for neonates with spontaneous and mechanical ventilation: Pilot study*

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ABSTRACT

Objects: The purpose of this study was to observe a correlation between PETCO2 and PaCO2 in intubated neonates under intermittent mandatory ventilation with spontaneous breathing. Material and methods: A total of 55 paired PETCO2 measured by mainstream capnometry and PaCO2 values were obtained from 4 intubated neonates in our neonatal intensive care units at Nagano Children’s Hospital, Nagano, Japan. Results: PETCO2 and PaCO2 were significantly correlated (r2 = 0.928, p < 0.0001). For samples in ventilated neonates with spontaneous breathing, maximum PETCO2 and mean PETCO2 correlated strongly with PaCO2 (maximum PETCO2: r2 = 0.9401, p < 0.0001; mean PETCO2: r2 = 0.8587, p < 0.0001). Although PaCO2 also correlated with minimum PETCO2 (r2 = 0.2884, p < 0.01) in ventilated infants with spontaneous breathing, a significant difference was seen with minimum PETCO2 (p < 0.05) and mean PETCO2 (p < 0.05) in the correlation coefficient r between PaCO2 and PETCO2. Conclusion: Present study showed that a good correlation exists between PETCO2 and PaCO2 in intubated neonates under intermittent mandatory ventilation with spontaneous breathing. Lightweight with low amounts of dead space mainstream capnometer can be used as noninvasive monitor in incubated neonates with spontaneous breathing.

Keywords: Capnography; Neonate

1. INTRODUCTION

Capnography, which displays the level and waveform of CO2 in exhaled air, is a simple technique that appears to accurately indicate arterial PCO2 (PaCO2) and provides information on cell metabolism, blood perfusion, and alveolar ventilation [1-3]. The use of end-tidal CO2 (PETCO2) for monitoring and as a tool for verifying endotracheal tube (ETT) position is another common practice in the operating room and in adult and pediatric intensive care units [3]. This procedure was also introduced to neonatal intensive care units (NICUs), but there are limitations of the technique in smaller babies, especially for extremely low birth weight infants due to issues such as the weight of sensors or water droplets within circuits, dead space, and leakage from tracheal intubation tubes. Recently, a lightweight mainstream capnometer was developed. We have previously reported a strong correlation between PETCO2 and PaCO2 under controlled ventilation when tidal volume/body weight (TV/BW) was 6 - 15 mL/kg and the leakage rate was <60% in rabbits. Furthermore, under conditions of 6 mL/kg of tidal volume (TV), PaCO2 was significantly increased by a dead space increase of only 1 mL, representing >7% of TV [4].

Capnometry is expected as one of the non-invasive monitor in NICUs. Although several investigators have demonstrated good relationships between values for PETCO2 and PaCO2 in infants [5-8], the value of capnometry in estimating PaCO2 has been questioned during anesthesia with spontaneous ventilation [9,10]. On the other hand, while TV is larger than spontaneous breaths, PETCO2 is close to the PaCO2 and to that observed with voluntary maximal expiration [11]. The purpose of this study was to observe a correlation between PETCO2 and PaCO2 in intubated neonates under intermittent mandatory ventilation (IMV) with spontaneous breathing.

2. MATERIAL AND METHODS

A total of 55 paired PETCO2 and PaCO2 values were obtained from the 4 neonates who had been admitted to the NICU at Nagano Children’s Hospital between April and July 2009. Neonates deemed as non-viable by the attending physician were excluded, as were those with
conditions such as acute shock, infection, or hemodynamic instability. Before enrollment into this study, informed consent was obtained from the parents or guardian of each infant. Study subjects comprised 4 neonates. Mean (±standard deviation (SD)) gestational age and birth weight were 36.7 ± 2.1 weeks and 2446 ± 487 g, respectively. Data on demographics, clinical characteristics, and laboratory findings for subjects were collected by referring to the clinical laboratory records.

The infants were ventilated mechanically using a time-cycled pressure-limited ventilator (Calliope®; Metran, Saitama, Japan). Peak inspiratory pressure (PIP), fraction of inhaled oxygen (FiO₂), inspiratory time, positive end expiratory pressure (PEEP) and respiratory rate were settled to provide the optimal arterial PaO₂ and PaCO₂ as defined by the neonatologists and were not manipulated for the purposes of the study.

Mainstream P ETCO₂ was measured via a capnograph connected to the proximal end of the endotracheal tube (Cap-One®; TG-970P, Nihon-Kohden, Tokyo, Japan). Data was continuously recorded on a laptop computer using the software programmed by LabVIEW (National Instruments, Texas, USA) through CO₂ monitor (OLG-2800; Nihon-Kohden, Tokyo, Japan) each patients. We distinguished between spontaneous breaths and ventilator breaths on the basis of capnography for 20 s at the time of blood gas analysis. For each 20-s sample period, we determined the maximum, mean and minimum values of PETCO₂ (Figure 1). Measurements of P ETCO₂ that did not show an alveolar plateau due to a large amount of leakage were excluded.

The tidal volume was measured by mainstream capnography (CO2SMO 8100, Fukuda Denshi, Tokyo, Japan). The leakage ratio was calculated using the following equation:

\[
\text{Leakage ratio} = \frac{\text{Inspiratory TV} - \text{Expiratory TV}}{\text{Inspiratory TV}} \times 100
\]

Blood samples were drawn from indwelling arterial lines into a 0.1 mL heparinized syringe to prevent coagulation. Blood sampling was performed by heel puncture when arterial line was not placed. Measurements were then immediately made using a bedside blood gas analyzer (ABL 700; Radiometer, Copenhagen, Denmark) for PaCO₂. Blood gas analysis was performed for the purposes of evaluation of the patient (including PaO₂, PaCO₂, electrolytes or lactate, etc.) only. Calibrations were performed automatically for the blood gas analyzer and the accuracy of the capnography was checked by 5% CO₂ gas cylinder.

All statistical analyses were conducted using SPSS Statistics version 17.0 (SPSS, Chicago, Illinois). To determine whether P ETCO₂ was representative of PaCO₂, the relationship between P ETCO₂ and PaCO₂ was analyzed by simple linear regression. The standard technique of Fisher’s Z transformation was performed to determine whether a significant difference existed in the correlation coefficient r between PaCO₂ and each group of P ETCO₂.

Furthermore, Bland-Altman plots were performed to assess measurements of P ETCO₂. 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 the difference between measurements is expected to change based on a third variable, Bland-Altman plots lose importance. Precision of P ETCO₂ and the agreement between PETCO₂ and PaCO₂ were assessed by bias, SD and calculating the 95% confidence interval (CI) for the bias (bias = P ETCO₂ – PaCO₂). Values of p < 0.05 were determined to be significant.

This study was carried out under the control of the Ethics Committee of Medicine and Medical Care, Nagano Children’s Hospital, Nagano, Japan.

3. RESULTS

Mean TV/BW and leakage ratio were 7.3 ± 1.7 mL/kg and 9.5% ± 12.0%, respectively (Table 1). All patients were treated using sedative drugs.

P ETCO₂ and PaCO₂ were significantly correlated (\( r^2 = 0.928, p < 0.0001 \)). In the Bland-Altman plot test, the mean difference (bias) and SD of the differences for
Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Inborn/Outborn</td>
<td></td>
</tr>
<tr>
<td>Inborn</td>
<td>3</td>
</tr>
<tr>
<td>Outborn</td>
<td>1</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Perioperative management</td>
<td>1</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36.7 ± 2.1</td>
</tr>
<tr>
<td>Range</td>
<td>34 - 39</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2446 ± 487</td>
</tr>
<tr>
<td>Range</td>
<td>1778 - 2894</td>
</tr>
<tr>
<td>Tidal volume/Body weight (mL/kg)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.3 ± 1.7</td>
</tr>
<tr>
<td>Range</td>
<td>4.8 - 8.6</td>
</tr>
<tr>
<td>Leakage ratio (%)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.5 ± 12.0</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 27</td>
</tr>
</tbody>
</table>

\( P_{ETCO_2} \) was \(-0.88 \pm 2.69 \text{ mmHg} \) (95% CI for the bias, \(-1.61 \text{ to } -0.16 \text{ mmHg}) (Figure 2). We chose the maximum for \( P_{ETCO_2} \) on the basis of capnograms for each 20 s period at the time of blood gas analysis.

Due to breath-to-breath variation, we evaluated three measurements of \( P_{ETCO_2} \) to determine which one most consistently and accurately predicted \( \text{PaCO}_2 \). From 55 measurements, we have selected 24 paired \( P_{ETCO_2} \) and \( \text{PaCO}_2 \) values which were obtained at the time when spontaneous breathing was present.

For samples in ventilated infants with spontaneous breathing, maximum \( P_{ETCO_2} \) and mean \( P_{ETCO_2} \) correlated strongly with \( \text{PaCO}_2 \) (maximum \( P_{ETCO_2}: r^2 = 0.9401, p < 0.0001 \); mean \( P_{ETCO_2}: r^2 = 0.8587, p < 0.0001 \)). Although \( \text{PaCO}_2 \) also correlated with minimum \( P_{ETCO_2} \) (\( r^2 = 0.2884, p < 0.01 \)) in ventilated infants with spontaneous breathing, a significant difference was seen with maximum \( P_{ETCO_2} \) (\( p < 0.05 \)) and mean \( P_{ETCO_2} \) (\( p < 0.05 \)) in the correlation coefficient \( r \) between \( \text{PaCO}_2 \) and \( P_{ETCO_2} \) (Figures 3(a)-(c)).

Bland-Altman analysis showed that \( P_{ETCO_2} \) underestimated \( \text{PaCO}_2 \) by a mean difference (bias) of \(-0.175 \pm 2.31 \text{ mmHg} \) (95% CI for the bias, \(-1.15 \text{ to } 0.799 \text{ mmHg}) in the maximum \( P_{ETCO_2}, -5.01 \pm 3.55 \text{ mmHg} \) (95% CI for the bias, \(-6.50 \text{ to } -3.51 \text{ mmHg}) in mean \( P_{ETCO_2} \), and \(-14.6 \pm 8.82 \text{ mmHg} \) (95% CI for the bias, \(-18.3 \text{ to } -10.9 \text{ mmHg}) in minimum \( P_{ETCO_2} \) (Figures 3(d)-(f)).

4. DISCUSSION

Advances in the treatment of neonatal respiratory failure, including exogenous surfactant [12,13], inhaled nitric oxide (iNO) [14,15], and a growing repertoire of assisted ventilation strategies [16] have decreased morbidity and mortality rates. Patient monitoring has played a critical role in the safe and effective application of these advanced therapies.

Pulse oximetry provides a noninvasive method of assessing oxygenation and continuous surveillance of the partial pressure of arterial oxygen [17]. Maintaining \( \text{PaCO}_2 \) within the desired range by frequent arterial sampling can increase the need for multiple transfusions in the NICU [18], highlighting the need for methods of continuous non-invasive monitoring of \( \text{CO}_2 \) levels. Both hypocarbia and hypercarbia are detrimental to extremely low birth weight infants and have been implicated as

\[
y = 0.9881x - 0.3335 \\
R^2 = 0.928
\]

Figure 2. The relationship between \( P_{ETCO_2} \) and \( \text{PaCO}_2 \) (a) and Bland-Altman plot shows bias against average values of \( P_{ETCO_2} \) and \( \text{PaCO}_2 \) in ventilated infants (b). \( P_{ETCO_2} \) and \( \text{PaCO}_2 \) were significantly correlated (\( r^2 = 0.928, p < 0.0001 \)).
Figure 3. The relationship between \( P_{\text{ETCO}_2} \) and \( \text{PaCO}_2 \) (a), (b) and (c) and Bland-Altman plot shows bias against average values of \( P_{\text{ETCO}_2} \) and \( \text{PaCO}_2 \) in ventilated infants with spontaneous breathing (d), (e) and (f). Maximum \( P_{\text{ETCO}_2} \) and mean \( P_{\text{ETCO}_2} \) correlated strongly with \( \text{PaCO}_2 \). Conversely, \( \text{PaCO}_2 \) did not correlate with minimum \( P_{\text{ETCO}_2} \).

Monitoring of \( P_{\text{ETCO}_2} \) is a simple and noninvasive technique that appears to accurately indicate \( \text{PaCO}_2 \) in a variety of clinical situations [1,24]. However, levels of \( P_{\text{ETCO}_2} \) and \( \text{PaCO}_2 \) depend on ventilation, cardiac output, \( \text{CO}_2 \) output, and pulmonary function; a change in any of these will cause a change in \( P_{\text{ETCO}_2} \) [25]. For instance, a growing degree of difference between \( P_{\text{ETCO}_2} \) and \( \text{PaCO}_2 \) can indicate the severity of pulmonary embolism [26] or even the effects of thrombolytic therapy [27].

\( P_{\text{ETCO}_2} \) varied appreciably from breath to breath. The reliability of this value under conditions of significant ventilation perfusion inequality or heterogeneous tidal volumes has thus been questioned [28]. In many cases, spontaneous breaths of variable tidal volumes far outnumbered ventilator breaths, but still contributed relatively little to alveolar minute ventilation. We found that maximum \( P_{\text{ETCO}_2} \) during each sampling period showed the best correlation with \( \text{PaCO}_2 \). A number of investigators have suggested that larger tidal volumes are necessary to measure \( P_{\text{ETCO}_2} \) accurately, as small (e.g., spontaneous) breaths may fail to “wash out” the anatomic dead space [11,29].

Weinger et al. [30] also found a wide range in differ-
ences between $P_{ET}$CO$_2$ and PaCO$_2$ over time. However, they measured mean peak $P_{ET}$CO$_2$ over a period of 8 min. Although averaging maximal $P_{ET}$CO$_2$ values over a longer time span might improve the stability and reliability of PaCO$_2$-$P_{ET}$CO$_2$, assessing the respiratory status to measure $P_{ET}$CO$_2$ over a long time would be difficult. The respiratory apparatus might change second to second.

Takahasi et al. [31] reported that reliable $P_{ET}$CO$_2$ was obtained when a vital capacity maneuver was performed on each nonintubated patient, indicating that full expiration to the maximal expiratory position is necessary for precise estimation of PaCO$_2$.

Comparison with spontaneous breathing, end tidal CO$_2$ measured from ventilated breath is close to the PaCO$_2$ and to that observed with a voluntary maximal expiration. This PCO$_2$ gradient between ventilator and spontaneous breathing indicates a large dead-space to tidal volume ratio; much of the expired CO$_2$ appearing with spontaneous breathing is diluted, with dead space air lowering the concentration at any point during expiration.

Although our prospective observational study revealed a good correlation and agreement between PaCO$_2$ and maximum $P_{ET}$CO$_2$, the present study included only a very small number of participants, and the conditions of patients were not constant. Furthermore, in children with congenital cyanotic heart disease, right-to-left intracardiac shunting reportedly causes an obligatory difference between PaCO$_2$ and $P_{ET}$CO$_2$ [32,33]. Our subjects included patients with congenital heart disease because they showed stable cardiorespiratory status in this study.

This study consisted of only a small number of participants, the statistical implications of repeated measurements in the same infants, and the conditions of the cases were not constant. In addition, we did not adjust for cardiac output their measurements, though differences in cardiac output are known to affect $P_{ET}$CO$_2$ measurements [25]. Therefore, we would like to study these issues in the future.

5. CONCLUSION

Our results indicate that a good correlation exists between $P_{ET}$CO$_2$ and PaCO$_2$ in intubated neonates under intermittent mandatory ventilation with spontaneous breathing. Furthermore, maximum $P_{ET}$CO$_2$ correlated strongly with PaCO$_2$ compared to minimum $P_{ET}$CO$_2$. Lightweight with low amounts of dead space mainstream capnometry can be used as noninvasive monitor in incubated neonates with spontaneous breathing.

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