End-tidal carbon dioxide and transcutaneous carbon dioxide monitoring during neonatal transport

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Key words: Infant newborn, Patient transportation, Carbon dioxide, Patient monitoring

Abbreviations:
CO₂, Carbon dioxide;
PaCO₂, Arterial partial pressure of carbon dioxide;
PtcCO₂, Transcutaneous partial pressure of carbon dioxide;
PetCO₂, End-tidal partial pressure of carbon dioxide;
NETS, Newborn Emergency Transport Service (Victoria);
NICU, Neonatal Intensive Care Unit;
PₐO₂/PₐO₂ ratio, alveolar-arterial ratio.
Abstract

Objective: To assess the accuracy of end-tidal carbon dioxide during neonatal transport compared with arterial and transcutaneous measurements.

Design: Paired end-tidal and transcutaneous carbon dioxide recordings were measured frequently during road transport of 21 ventilated neonates. The first paired carbon dioxide (CO₂) values were compared with an arterial blood gas. The differences between arterial CO₂ (PaCO₂), transcutaneous CO₂ (PtcCO₂) and end-tidal CO₂ (PetCO₂) (P(a-Tc)CO₂, P(a-Et)CO₂ and P(Tc-Et)CO₂) were analysed. The Bland-Altman method was used to assess bias and repeatability.

Results: PetCO₂ correlated strongly with PaCO₂ and PtcCO₂. However PetCO₂ underestimated PaCO₂ at a clinically unacceptable level (mean - 1.1 kPa [SD 0.70]) and did not trend reliably over time within individual subjects. The PetCO₂ bias was independent of the PaCO₂ and severity of lung disease.

Conclusions: End-tidal CO₂ had an unacceptable underrecording bias. Transcutaneous CO₂ should, currently, be considered the preferred method of non-invasive CO₂ monitoring for neonatal transport.
Introduction

Continuous non-invasive carbon dioxide (CO₂) monitoring has become an important bedside tool in neonatal intensive care. Transported sick neonates should receive full intensive care but frequent arterial blood gases are not possible. Assessing the efficacy of ventilation during neonatal transport is challenging. Continuous non-invasive CO₂ monitoring has been shown to increase the likelihood of arriving at the receiving hospital with a normal pH and partial pressure of CO₂ (PaCO₂).[1]

Transcutaneous CO₂ monitoring is the most frequently used non-invasive CO₂ monitoring system in neonatal intensive care and has been shown to accurately predict PaCO₂ and monitor CO₂ trends.[1][2] Calibrated TcCO₂ has been shown to reliably approximate PaCO₂ during neonatal transport and has been recommended as an alternative to frequent PaCO₂ measurements.¹ However PtcCO₂ devices are difficult to use,[3][4] bulky and weigh between 2 and 6 kg, thus limiting their use during neonatal transport.

End-tidal CO₂ (PetCO₂) monitors are lightweight and might indirectly monitor the PaCO₂.[5][6][7][8] Hence, PetCO₂ may have more utility in the transport environment than TcCO₂ monitoring. Studies of PetCO₂ monitoring in newborn infants have had mixed results, primarily due to the effects of ventilation perfusion mismatching on PetCO₂, failure to reach an expiratory plateau during rapid respiratory rates and technical limitations in PetCO₂ devices to interpret CO₂ in small tidal volume states.[2][5][9][10][11][12] Recent technological advances in PetCO₂ monitoring, such as smaller sample volumes and sample cells calibrated to neonatal tidal volumes, have attempted to overcome the limitations.[13] Some authors advocate PetCO₂ as an acceptable method of approximation of PaCO₂ trends in newborn infants.[10] [14][15][16]

The Newborn Emergency Transport Service of Victoria (NETS) is the largest neonatal transport service in Australasia. More than 900 infants per year are transported with approximately one third ventilated. PtcCO₂ and oxygen saturation monitoring have been standard practice for five years to indicate ventilation adequacy during transport and previous unpublished data have shown a close correlation between PtcCO₂ and PaCO₂.

Arterial blood gases and PtcCO₂ are commonly used to monitor ventilation. The aim of this study was to assess the accuracy and reliability of PetCO₂ monitoring during neonatal transport.

Methods

Ventilated infants requiring road transport to a level 3 NICU during March to August 2002 were recruited if the paediatrician involved in the transport was specifically trained to use both PetCO₂ and PtcCO₂ monitors, an arterial catheter was being used, endotracheal tube position could be confirmed by chest radiograph prior to transport and both PtcCO₂ and PetCO₂ monitoring could be started before the first arterial blood gas was measured by the NETS team. Due to the effects of barometric pressure on PetCO₂ infants transported by air were not studied.[5] Informed parental consent was obtained in each infant prior to transport.
Infants were not studied if they were older than 28 days, had a capillary refill time of greater than two seconds or PtcCO2 or PetCO2 readings could not be made or were lost during transport.

PtcCO2 was measured using the Microgas 7650™ system (weight 5.6kg) with Combi.M sensor 82 (Linde, Switzerland) applied to the skin of the anterior chest or abdomen. The manufacturers report that the Combi.M sensor 82, once calibrated, will remain accurate for up to four hours at one site. PetCO2 was measured using a side stream end-tidal analyser specifically designed for neonatal use (the Agilent Microstream™ system, Agilent Technologies, Andover, USA), a result was the highest of five consecutive measurements.[13] Arterial blood gases were analysed with the I-Stat portable clinical analyser (I-Stat cooperation, East Windsor, USA). Infants were ventilated using the Hoekloos Infant ventilator Mark 3 (Hoekloos, Amsterdam, Netherlands). The Australian Therapeutics Goods Administration has approved both devices for use in newborn infants. A specialist neonatal transport nurse and neonatal paediatrician escorted all infants.

After calibration of the PtcCO2 and PetCO2 monitors, paired CO2 measurements were recorded every 20 minutes, starting at stabilisation and continuing throughout the transport. The initial recordings were calibrated with a simultaneous PaCO2. The NETS team was not blinded to the PtcCO2 or PetCO2 values; any ventilator changes were based on the PtcCO2 or PaCO2 values.

The severity of each baby’s lung disease was determined by calculating the alveolar – arterial oxygen ratio (PaO2/PaO2 ratio). Severe lung disease was defined as a PaO2/PaO2 ratio <0.3. A PaO2/PaO2 ratio of <0.3 has been associated with less precision of PetCO2 measurements to estimate PaCO2.[15]

The parents of all infants enrolled in the study provided written and signed informed consent for their infants to be transported by NETS and this involved specific consent to the use of all devices used in the study. This study was discussed with the Royal Women's Hospital Ethics in Human Research Committee. It was decided that formal ethics approval was not required as the above written informed consent adequately informed the parents and addressed the ethical issues of the study.

**Statistics**

The differences between PaCO2, PtcCO2 and PetCO2 (expressed as P(a-Tc)CO2, P(a-Et)CO2 and P(Tc-Et)CO2 respectively) were analysed using a Student’s paired t test and their correlations (r) were calculated. The Bland-Altman technique was used to assess agreement and repeatability.[17] A bias of less than ±0.7 kPa was considered clinically acceptable. Intrasubject P(Tc-Et)CO2 variability over time was calculated.

**Results**

26 infants were enrolled and then five excluded because the PetCO2 could not be continuously measured in three, both PtcCO2 and PetCO2 could not be measured in another and in the fifth infant the initial blood gas was venous. The characteristics of the 21 infants are summarised in Table 1. A total of 21 P(a-Tc)CO2, P(a-Et)CO2 differences and 82 P(Tc-Et)CO2 differences (median recordings per subject 4.0 [range 2, 10]) were calculated.
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>35</td>
<td>26, 40</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2260</td>
<td>930, 4600</td>
</tr>
<tr>
<td>Age at enrolment (hours)</td>
<td>4.8</td>
<td>1.8, 61.2</td>
</tr>
<tr>
<td>Transportation time (minutes)</td>
<td>65</td>
<td>20, 180</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean [SD]</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.32 [0.12]</td>
<td>7.1, 7.55</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.52 [0.24]</td>
<td>0.21, 1.0</td>
</tr>
<tr>
<td>P_aO2/P_AO2 ratio¹</td>
<td>0.85 [1.3]</td>
<td>0.03, 5.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Number</th>
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<tbody>
<tr>
<td>Respiratory failure</td>
<td>15</td>
</tr>
<tr>
<td>Cyanotic heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of the newborn</td>
<td>1</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>1</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>1</td>
</tr>
<tr>
<td>Multiple congenital abnormalities</td>
<td>1</td>
</tr>
</tbody>
</table>

Definition of abbreviations: FIO2, Inspired oxygen fraction; P_aO2/P_AO2 ratio, alveolar-arterial ratio.

There was a linear relationship between PetCO₂, PaCO₂ and PtcCO₂. However PetCO₂ underestimated PaCO₂ by an average of 1.1 kPa (Table 2 and Figure 1). Only 48% of PetCO₂ recordings were within 1.0 kPa of the paired PaCO₂. The bias of the PetCO₂ values was independent of the PaCO₂.

Table 2. A comparison of CO₂ (kPa) measured in three different ways.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean [SD]</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_a(Tc)CO₂</td>
<td>21</td>
<td>-0.13 [0.71]</td>
<td>-0.46,0.19</td>
<td>0.4</td>
</tr>
<tr>
<td>P_a(Et)CO₂</td>
<td>21</td>
<td>1.04 [0.98]</td>
<td>0.59,1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P(Tc-Et)CO₂</td>
<td>82</td>
<td>-0.07 [0.84]</td>
<td>-0.26, 0.11</td>
<td>0.43</td>
</tr>
</tbody>
</table>

PtcCO₂ was closely related to PaCO₂, with no significant difference between the two measurements (Table 2). 67% of PtcCO₂ readings were within 0.7 kPa of the PaCO₂, and 81% of PtcCO₂ readings were within 1 kPa of the paired PaCO₂. There was not a significant change in the difference between PtcCO₂ and PaCO₂ as the CO₂ level changed (Figure 2).

When the initial PtcCO₂ and PetCO₂ values for each subject were calibrated to the original PaCO₂, there was a closer relationship between PetCO₂ and PtcCO₂, 64% of PetCO₂ values
were within 0.7 kPa of the paired PtcCO₂ value (Figure 3). Whilst P(Tc-Et)CO₂ difference was not statistically significant the variability, as demonstrated by Bland-Altman plot, was large (Table 2 and Figure 3).

There was no significant relationship between PetCO₂ accuracy and severity of lung disease (Table 3), although there was a non significant trend towards PetCO₂ values being more likely to reflect either PaCO₂ or PtcCO₂ in infants with a PaO₂/PAO₂ ratio >0.3. Muscle relaxation did not alter the reliability of PetCO₂ to trend with PtcCO₂.

Table 3. Relationship between PetCO₂ values and severity of lung disease

<table>
<thead>
<tr>
<th></th>
<th>Severe lung disease: PaO₂/PₐO₂ ratio &lt;0.3 (n=12)</th>
<th>Mild – moderate lung disease: PaO₂/PₐO₂ ratio ≥0.3 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(a-Et)CO₂</td>
<td>Mean [SD] 95% CI p value</td>
<td>Mean [SD] 95% CI p value</td>
</tr>
<tr>
<td>1.21 [0.76]</td>
<td>0.87,1.88 &lt;0.001</td>
<td>0.99 [1.16] -0.61,1.37 0.013</td>
</tr>
</tbody>
</table>

All CO₂ values in kPa

Discussion

This study demonstrates that in neonates requiring ventilation during transport, PtcCO₂ monitoring more accurately reflected PaCO₂ than PetCO₂ monitoring. Furthermore PetCO₂ monitoring should be used with caution. Both PetCO₂ and PtcCO₂ were linearly related to PaCO₂ and each other. However, a linear relationship alone, or correlation coefficients, the method used in many of the previous reports, do not adequately describe the agreement between two clinical measurement techniques.[2] [10] [18] Assessing agreement between two methods of clinical measurement is complex. The method described by Bland and Altman is a more informative technique to assess agreement, reliability and repeatability, and allows interpretation within a clinical context.[17] Using this technique PetCO₂ was neither as precise nor reliable method of assessing PaCO₂ during the transport of ventilated neonates, whilst PtcCO₂ provided a more reliable method. The degree of bias demonstrated between PetCO₂ and PaCO₂ (1.04 kPa) is clinically unacceptable.

Most of the infants involved in this study had mechanical ventilation instigated by the transport team; knowledge of any changes in the CO₂ is essential to safely deliver ventilation. Frequent PaCO₂ measurements are not practical during neonatal transport; a reliable non-invasive indicator of PaCO₂ is essential. Calibrated PtcCO₂ is an acceptable surrogate for PaCO₂ trends over time. Transcutaneous gas monitoring is an established and validated practice in neonatology.[3] Newborn infants are particularly suited to transcutaneous monitoring due to their thin skin. Although proper use is dependent on appropriate training and placement, the only practical limitations are skin perfusion (which may be altered by vasoconstrictive agents, hypovolaemia and oedema) and the temperature produced by the device. The response time of PtcCO₂ is too slow (30 to 50 seconds) to allow monitoring of the respiratory pattern.[19] PtcCO₂ monitoring has been previously evaluated in the neonatal transport setting and shown to result in improved ventilation on arrival at the receiving institution.[1] [20]
Many authors have reported a good correlation between PetCO₂, PtcCO₂ and PaCO₂ in newborn infants but in only three studies evaluating PetCO₂ was the relationship assessed using the Bland – Altman technique.[14][15] [21] Rozycki et al described a mean Pₐ(Et)CO₂ bias of 0.92 +/- 0.92 kPa in 45 newborn infants receiving mechanical ventilation with only 36.9% of PetCO₂ values falling within +/- 0.67 kPa of the PaCO₂. The authors concluded that despite the significant bias PetCO₂ provided a reliable estimate of PaCO₂ trends.[14] A similar mean Pₐ(Et)CO₂ difference of 0.91 +/- 0.68 kPa was reported by Tobias et al in 25 infants and toddlers (up to 48 months of age) receiving mechanical ventilation for respiratory failure, the Pₐ(Tc)CO₂ difference in this study was 0.31 +/- 0.18 kPa.[19] Sivan et al demonstrated a clinically acceptable Pₐ(Et)CO₂ result with a mean difference of 0.45 +/- 0.88 kPa in a study involving 134 children (2 days to 16 years) receiving mechanical ventilation. The mean Pₐ(Tc)CO₂ in this group was –0.17 +/- 0.96 kPa, the Pₐ(Tc)CO₂ bias was related to skin perfusion but remained clinically acceptable. Primary diagnosis was not described in this study, nor was the proportion of the population who were newborn infants, making inference to the neonatal population difficult.[15] Sivan and colleagues concluded that the degree of the Pₐ(Et)CO₂ bias was reduced in children with mild lung disease, as defined by the PaO₂/PaO₂ ratio being >0.3. In the cohort with severe lung disease the findings were similar to our data (mean Pₐ(Et)CO₂ 1.04 +/- 0.97 kPa).[15]

Parenchymal lung disease with ventilation perfusion (V/Q) mismatching and a PaO₂/PaO₂ <0.3 is a feature of most causes of neonatal respiratory failure. During our study only 2 infants did not require oxygen and nearly all had parenchymal lung disease. Our study was not designed to assess the relationship between degree of lung disease and PetCO₂ accuracy.

PetCO₂ monitoring has been validated in adult ventilated patients and healthy anaesthetised infants but the infants in our study had respiratory failure.[10] [18] PetCO₂ is dependant on alveolar CO₂ (PaCO₂) and the site of sampling. Non-uniform alveoli CO₂ emptying patterns in patients with large ventilation perfusion mismatching result in PaCO₂ underestimating PₐCO₂.[5][22][23]

Technical limitations of end-tidal analysis in patients with high rate, low tidal volume breathing would have contributed to the difference between PetCO₂ and PaCO₂. To account for the fresh inhaled gas admixture during proximal PetCO₂ sampling a minimum sampling flow rate of 150 ml.min⁻¹ is required.[5] The end-tidal analyser used in our study sampled at 50 ml.min⁻¹. Despite manufacturer assurances, this may have had an impact on our results. The response time of end-tidal analysers must be less than the respiratory cycle. The response time of the end-tidal analyser used was 190 milliseconds, which is adequate for the ventilation rates used during the study, although at high respiratory rates with a short expiratory time, all exhaled alveolar gas would not have migrated to a proximal end-tidal sampling site on completion of each respiratory cycle.[5]

The relationship between PtcCO₂ and PetCO₂ was not constant over time within individuals, even when both values were adjusted to PaCO₂. In our opinion PetCO₂ monitoring cannot be used to reliably monitor trends in PaCO₂ over time in newborn infants with lung disease.

Despite our findings, PetCO₂ monitoring may offer some benefits over PtcCO₂ monitoring. Primarily the ability to rapidly and reliably confirm endotracheal tube position within the trachea, with either a capnograph or colorimetric end-tidal CO₂ indicator, is of great benefit within the noisy environment of neonatal transport.[7] This study did not aim to assess the ability of PetCO₂ or PtcCO₂ to indicate endotracheal tube position. Inadvertent extubation is
not a common occurrence in our transport population and did not occur in any of the neonates involved in this study. Further study is required to determine the role of PetCO₂ in ensuring the endotracheal tube position during transport.

**Conclusions**

Due to the bias of approximately -1 kPa and lack of consistency in measuring PaCO₂ over time, PetCO₂ cannot be recommended during neonatal transport to monitor ventilation. PtcCO₂ monitoring was generally more precise, reliable and agreed with PaCO₂. PtcCO₂ monitoring is the preferred method of non-invasive CO₂ monitoring during neonatal transport.

**Competing interest statement**

There are no competing interests associated with this manuscript. David G Tingay is supported by a National Health and Medical Research Council (NHMRC) medical postgraduate research scholarship

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**Figure Legends**

**Figure 1**
Bland-Altman plot of the difference between PaCO₂ and PetCO₂ (P(a-Et)CO₂) against average CO₂.

**Figure 2**
Bland-Altman plot of the difference between PaCO₂ and PtcCO₂ (P(a-Tc)CO₂) against average CO₂.

**Figure 3**
Bland-Altman plot of the difference between PtcCO₂ and PetCO₂ (P(Tc-Et)CO₂) against average CO₂.
References


$^1$ Alveolar – Arterial oxygen gradient = PaO$_2$/PAO$_2$ (PAO$_2$ = [(Barometric pressure – 47)*(FiO$_2$-PaO$_2$)])
Figure 1. Bland-Altman plot of the difference between $P_{a, CO_2}$ and $P_{e, CO_2}$ ($P_{a-Et, CO_2}$) against average CO$_2$.
Figure 2. Bland-Altman plot of the difference between $P_{(a-Tc)}CO_2$ and $P_{(a-Tc)}CO_2$ against average $CO_2$. 
Figure 3. Bland-Altman plot of the difference between $P_{tc_{CO2}}$ and $Pet_{CO2}$ ($P_{(Tc-Et)CO2}$) against average CO$_2$.
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