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(Tc-Et)CO₂, P(a-Et)CO₂ and P(a-Tc)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 Pₐ(Tc)CO₂, Pₐ(Et)CO₂ and Pₜ(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 Pₜ(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 Pₐ(Tc)CO₂, Pₐ(Et)CO₂ differences and 82 Pₜ(Et)CO₂ differences (median recordings per subject 4.0 [range 2, 10]) were calculated.
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 21</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>21</td>
<td>35</td>
<td>26, 40</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2260</td>
<td>930, 4600</td>
<td></td>
</tr>
<tr>
<td>Age at enrolment (hours)</td>
<td>4.8</td>
<td>1.8, 61.2</td>
<td></td>
</tr>
<tr>
<td>Transportation time (minutes)</td>
<td>65</td>
<td>20, 180</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean [SD]</th>
<th>Range</th>
</tr>
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<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_{a}O_{2}/P_{A}O_{2} ratio</td>
<td>0.85 [1.3]</td>
<td>0.03, 5.9</td>
</tr>
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<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>
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</table>

Definition of abbreviations: FIO2, Inspired oxygen fraction; P_{a}O_{2}/P_{A}O_{2} ratio, alveolar-arterial ratio.

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

Table 2. A comparison of CO_{2} (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)}CO_{2}</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)}CO_{2}</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)}CO_{2}</td>
<td>82</td>
<td>-0.07 [0.84]</td>
<td>-0.26,0.11</td>
<td>0.43</td>
</tr>
</tbody>
</table>

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

When the initial PtcCO_{2} and PetCO_{2} values for each subject were calibrated to the original PaCO_{2}, there was a closer relationship between PetCO_{2} and PtcCO_{2}, 64% of PetCO_{2} values
were within 0.7 kPa of the paired PtcCO\textsubscript{2} value (Figure 3). Whilst P_{(Tc-Et)}CO\textsubscript{2} 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 PetCO\textsubscript{2} accuracy and severity of lung disease (Table 3), although there was a non significant trend towards PetCO\textsubscript{2} values being more likely to reflect either PaCO\textsubscript{2} or PtcCO\textsubscript{2} in infants with a PaO\textsubscript{2}/PAO\textsubscript{2} ratio >0.3. Muscle relaxation did not alter the reliability of PetCO\textsubscript{2} to trend with PtcCO\textsubscript{2}.

Table 3. Relationship between PetCO\textsubscript{2} values and severity of lung disease

<table>
<thead>
<tr>
<th></th>
<th>Severe lung disease: PaO\textsubscript{2}/P\textsubscript{A}O\textsubscript{2} ratio &lt;0.3 (n=12)</th>
<th>Mild – moderate lung disease: PaO\textsubscript{2}/P\textsubscript{A}O\textsubscript{2} ratio ≥0.3 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_{(a-Et)}CO\textsubscript{2}</td>
<td>Mean [SD] 1.21 [0.76] 95% CI 0.87,1.88 p value &lt;0.001</td>
<td>Mean [SD] 0.99 [1.16] 95% CI -0.61,1.37 p value 0.013</td>
</tr>
</tbody>
</table>

All CO\textsubscript{2} values in kPa

Discussion

This study demonstrates that in neonates requiring ventilation during transport, PtcCO\textsubscript{2} monitoring more accurately reflected PaCO\textsubscript{2} than PetCO\textsubscript{2} monitoring. Furthermore PetCO\textsubscript{2} monitoring should be used with caution. Both PetCO\textsubscript{2} and PtcCO\textsubscript{2} were linearly related to PaCO\textsubscript{2} 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 PetCO\textsubscript{2} was neither as precise nor reliable method of assessing PaCO\textsubscript{2} during the transport of ventilated neonates, whilst PtcCO\textsubscript{2} provided a more reliable method. The degree of bias demonstrated between PetCO\textsubscript{2} and PaCO\textsubscript{2} (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 CO\textsubscript{2} is essential to safely deliver ventilation. Frequent PaCO\textsubscript{2} measurements are not practical during neonatal transport; a reliable non-invasive indicator of PaCO\textsubscript{2} is essential. Calibrated PtcCO\textsubscript{2} is an acceptable surrogate for PaCO\textsubscript{2} 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 PtcCO\textsubscript{2} is too slow (30 to 50 seconds) to allow monitoring of the respiratory pattern.[19] PtcCO\textsubscript{2} 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 PetCO\textsubscript{2}, PtcCO\textsubscript{2} and PaCO\textsubscript{2} in newborn infants but in only three studies evaluating PetCO\textsubscript{2} was the relationship assessed using the Bland – Altman technique.[14][15] [21] Rozycki \textit{et al} described a mean P\textsubscript{(a-Et)}\textsubscript{CO}\textsubscript{2} bias of 0.92 +/- 0.92 kPa in 45 newborn infants receiving mechanical ventilation with only 36.9\% of PetCO\textsubscript{2} values falling within +/- 0.67 kPa of the PaCO\textsubscript{2}. The authors concluded that despite the significant bias PetCO\textsubscript{2} provided a reliable estimate of PaCO\textsubscript{2} trends.[14] A similar mean P\textsubscript{(a-Et)}\textsubscript{CO}\textsubscript{2} difference of 0.91 +/- 0.68 kPa was reported by Tobias \textit{et al} in 25 infants and toddlers (up to 48 months of age) receiving mechanical ventilation for respiratory failure, the P\textsubscript{(a-Tc)}\textsubscript{CO}\textsubscript{2} difference in this study was 0.31 +/- 0.18 kPa.[19] Sivan \textit{et al} demonstrated a clinically acceptable P\textsubscript{(a-Et)}\textsubscript{CO}\textsubscript{2} 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 P\textsubscript{(a-Tc)}\textsubscript{CO}\textsubscript{2} in this group was –0.17 +/- 0.96 kPa, the P\textsubscript{(a-Tc)}\textsubscript{CO}\textsubscript{2} 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 P\textsubscript{(a-Et)}\textsubscript{CO}\textsubscript{2} bias was reduced in children with mild lung disease, as defined by the PaO\textsubscript{2}/PAO\textsubscript{2} ratio being >0.3. In the cohort with severe lung disease the findings were similar to our data (mean P\textsubscript{(a-Et)}\textsubscript{CO}\textsubscript{2} 1.04 +/- 0.97 kPa).[15]

Parenchymal lung disease with ventilation perfusion (V/Q) mismatching and a PaO\textsubscript{2}/PAO\textsubscript{2} <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 PetCO\textsubscript{2} accuracy.

PetCO\textsubscript{2} monitoring has been validated in adult ventilated patients and healthy anaesthetised infants but the infants in our study had respiratory failure.[10] [18] PetCO\textsubscript{2} is dependant on alveolar CO\textsubscript{2} (P\textsubscript{A}CO\textsubscript{2}) and the site of sampling. Non-uniform alveoli CO\textsubscript{2} emptying patterns in patients with large ventilation perfusion mismatching result in P\textsubscript{A}CO\textsubscript{2} underestimating PaCO\textsubscript{2}.[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 PetCO\textsubscript{2} and PaCO\textsubscript{2}. To account for the fresh inhaled gas admixture during proximal PetCO\textsubscript{2} sampling a minimum sampling flow rate of 150 ml.min\textsuperscript{-1} is required.[5] The end-tidal analyser used in our study sampled at 50 ml.min\textsuperscript{-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 PtcCO\textsubscript{2} and PetCO\textsubscript{2} was not constant over time within individuals, even when both values were adjusted to PaCO\textsubscript{2}. In our opinion PetCO\textsubscript{2} monitoring cannot be used to reliably monitor trends in PaCO\textsubscript{2} over time in newborn infants with lung disease.

Despite our findings, PetCO\textsubscript{2} monitoring may offer some benefits over PtcCO\textsubscript{2} monitoring. Primarily the ability to rapidly and reliably confirm endotracheal tube position within the trachea, with either a capnograph or colorimetric end-tidal CO\textsubscript{2} indicator, is of great benefit within the noisy environment of neonatal transport.[7] This study did not aim to assess the ability of PetCO\textsubscript{2} or PtcCO\textsubscript{2} 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


\[ \text{Alveolar – Arterial oxygen gradient} = \frac{\text{PaO}_2}{\text{P}_{\text{A}}\text{O}_2} \text{ (P}_{\text{A}}\text{O}_2 = \text{[(Barometric pressure – 47)}* (F}_2\text{O}_2-\text{PaO}_2))] \]
Figure 1. Bland-Altman plot of the difference between $P_{(a-Et)}CO_2$ and $P_{aCO_2}$ and $Pet_{CO_2}$ against average $CO_2$.
Figure 2. Bland-Altman plot of the difference between $P_{(a-Tc)} CO_2$ vs $P_{(Tr-Eb)} CO_2$ against average $CO_2$. The plot includes lines for the mean difference (+2SD, mean of difference, mean difference -2SD).
Figure 3. Bland-Altman plot of the difference between $P_{c_{CO2}}$ and $P_{et_{CO2}}$ ($P_{(Tc-Et)} CO_2$) against average $CO_2$. 
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