Original Article: Neonatal Lung Disease

Weight-correction of carbon dioxide diffusion coefficient (DCO$_2$) reduces its inter-individual variability and improves its correlation with blood carbon dioxide levels in neonates receiving high-frequency oscillatory ventilation

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Key words: high-frequency oscillatory ventilation, hypercapnia, neonatal lung disease, normal range, pulmonary gas exchange, respiratory mechanics

Abbreviated title: Weight-corrected DCO$_2$ during HFOV
ABSTRACT

BACKGROUND: Carbon-dioxide elimination during high-frequency oscillatory ventilation (HFOV) is thought to be proportional to the carbon dioxide diffusion coefficient (DCO₂) which is calculated as frequency x (tidal volume)^2. DCO₂ can be used to as an indicator of CO₂ elimination but values obtained in different patients cannot be directly compared.

OBJECTIVES: To analyse the relationship between DCO₂, the weight-corrected DCO₂ (DCO₂corr) and blood gas PCO₂ values obtained from infants receiving HFOV.

METHODS: DCO₂ data were obtained from 14 infants at 1/sec sampling rate and the mean DCO₂ was determined over 10-minute periods preceding the time of the blood gas. DCO₂corr was calculated by dividing the DCO₂ by the square of the body weight in kg.

RESULTS: Weight-correction significantly reduced the inter-individual variability of DCO₂. When data from all the babies were combined, standard DCO₂ showed no correlation with PCO₂ but DCO₂corr showed a weak but statistically significant inverse correlation. The correlation was better when the endotracheal leak was <10%. There was significant inverse but weaker correlation between the HFOV tidal volume (VThf) and the PCO₂. In any baby, DCO₂corr >50 mL²/sec/kg² or VThf >2.5 mL/kg was rarely needed to avoid hypercapnia.

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CONCLUSION: Weight-correction of DCO₂ values improved its comparability between patients. Weight-corrected DCO₂ correlated better with PCO₂ than uncorrected DCO₂ but the correlation was weak.

INTRODUCTION

During high-frequency oscillatory ventilation (HFOV), CO₂ elimination is affected by the frequency (Hz) and tidal volume (VThf) of the oscillations. Unlike during conventional ventilation, during HFOV the relationship between tidal volume and CO₂ elimination is not linear but increases exponentially with the tidal volume. CO₂ removal is thought to be directly proportional to the carbon dioxide diffusion coefficient (DCO₂) which equals Hz x VThf. As frequency is expressed as Hz = 1/sec and tidal volume as mL, the unit of DCO₂ is mL²/sec.

From experience, DCO₂ values can be used as a trend during HFOV for individual babies to predict changes in the arterial CO₂ (PaCO₂) and help adjust ventilator settings. However, knowing the DCO₂ does not enable a neonatologist to predict a baby’s PaCO₂ and DCO₂ values from different infants cannot be compared because of differences in weight, pathophysiology and ventilator settings. We thought the limitation of using DCO₂ may, in part, be because the tidal volume used in the equation is expressed as mL and not...
normalized to the body weight. During conventional ventilation, tidal volumes are routinely expressed and compared as mL/kg and the same may be appropriate for HFOV. Several papers discussing HFOV also described VThf as mL/kg, but DCO₂ was not weight-corrected. To normalize DCO₂ to body weight it should be divided by the square of the weight as $\text{DCO}_2 = \text{Hz} \times \text{VThf}^2$, so weight-corrected DCO₂ ($\text{DCO}_2\text{corr}$) is expressed as $\text{mL}^2/\text{sec}/\text{kg}^2$. In this study we investigated the relationship between DCO₂, DCO₂corr and PCO₂ in newborn infants ventilated with HFOV.

METHODS

Patients

Ventilation data were obtained from the Babylog VN500 ventilator (Dräger, Lübeck, Germany) as part of a registered service evaluation project (authorized by the R & D department of Cambridge University Hospitals NHS Trust, registration number: 4572); therefore, individual participant consent or ethical approval was not required. The aim of the service evaluation was to assess ventilator alarms in babies on the Neonatal Intensive Care Unit. For this report we have re-analysed the data from the subset of infants who were ventilated with HFOV during the recordings. There were 18 recordings obtained from 14 infants, see Table 1 for details. Blood gas analyses were done routinely 6-8
hourly in these babies receiving HFOV. Additional blood gases were performed if the clinical team thought it justified. Blood gas measurements were done on a cobas b 221™ point of care blood gas system (Roche, Burgess Hill, United Kingdom).

Data retrieval and analysis

Tidal volumes of the high frequency oscillations (Vthf) are calculated by the ventilator from the flow measurements and are leak-compensated. The ventilator has a sampling frequency of one in 5.2 milliseconds with a low pass filter. VThf values are averaged by the ventilator’s internal computer over 1 second periods; these averaged values are displayed and updated every 1 second. DCO₂ values are calculated as frequency * Vthf² from the averaged VThf during the 1-second period. Ventilator data were anonymously downloaded with 1/sec sampling rate to a laptop computer via a cable attached to one of the communication ports of the ventilator using software obtained from Dräger. Data were exported into comma-separated value (.csv) text files. Arterial and capillary blood gas measurements were obtained from electronic clinical records.

Data analysis and visualisation was performed using Python (version 3.5.1, https://www.python.org) and its add-on packages: ipython (version 5.1.1, https://ipython.org), NumPy (version 1.10.4, http://www.numpy.org, pandas (version 0.18.0, http://pandas.pydata.org) and matplotlib (version 1.5.1,
http://matplotlib.org. All the software we used is open-source and freely available. We performed analysis on a personal computer (MacBook Pro 2014 version, 2.6 GHz i5 processor and 8 Gb RAM memory). Relationship between DCO$_2$ and PCO$_2$ was assessed by Pearson’s correlation analysis; p values <0.05 were considered statistically significant. Receiver-operating characteristic (ROC) analysis was performed and the optimal cutoff to predict risk of hypercapnia was determined using Youden’s J statistic$^9$. An iPython notebook containing all steps of data processing and statistical analysis can be viewed on GitHub (https://github.com/belteki/DCO2).

To use DCO$_2$ values which were more representative than single readings we calculated the mean of 600 DCO$_2$ values obtained during 10 minutes starting 12 minutes before and ending at 2 minutes before each blood gas measurement. We omitted the last two minutes before the gas analysis because the blood had already been collected and placed in the analyser during this period. We corrected DCO$_2$ data for the body weight by dividing by the square of the body weight in kilograms.

RESULTS

We obtained DCO$_2$ values from 18 recordings in 14 babies ventilated with HFOV. The combined duration of recordings was 952.5 hours (approximately
39.7 days), Table 1. There were 254 blood gas measurements during the recordings, of which, 106 (42%) were arterial.

When all the blood gases from all babies were considered together, uncorrected DCO$_2$ values showed no inverse correlation with PCO$_2$ data (Figure 1). The range of DCO$_2$ values was very wide (between 5.5 – 570 ml$^2$/sec) and DCO$_2$ readings from different patients “clustered” in different parts of the graph. This clustering and the lack of inverse correlation were also observed if only arterial blood gases were considered (E-Figure 1).

We then investigated whether weight-corrected DCO$_2$ (DCO$_2$corr) values showed better correlation with PCO$_2$ and less inter-individual variation. DCO$_2$corr values showed significantly (p<0.0001) less variability, the range was between 5.2 – 169 mL$^2$/sec/kg$^2$, (Figure 2). Unlike DCO$_2$, DCO$_2$corr from different patients showed an inverse correlation with PCO$_2$ values (Figure 3). This was weak (r = -0.3025, 95% confidence intervals: -0.4097, -0.1871) but statistically significant (p<0.001). Also, the graph shows less clustering of values from individual patients. When only arterial blood gas measurements were considered there was also an inverse correlation but it was not statistically significant because of the small numbers (E-Figure 2).

We analyzed the individual patient slopes of the correlation between DCO$_2$corr and PCO$_2$, where at least 10 blood gases were available (14 out of the 18 recordings). All except two showed an inverse correlation between DCO$_2$corr
and PCO$_2$ although it was statistically significant ($p<0.05$) in 6 out of 14 cases (Table 2 and see graphs in E-Figure 3). This is likely to be due to the smaller number of blood gas samples in individual cases. Also, weight-correction improved the inter-individual comparability of DCO$_2$ values. Therefore, a significant correlation on the whole cohort is still useful.

Analyses were done to determine whether DCO$_2$corr value could be used to predict avoidance of hypercapnia (PCO$_2$ >8 kPa or 60 mmHg). Receiver operating characteristic curve (ROC) analysis together with Youden’s statistic showed that the optimal cutoff was DCO$_2$ ≥50 mL$^2$/sec/kg$^2$ which predicted a PCO$_2$ ≤8 kPa with a positive predictive value of 0.886 and a negative predictive value of 0.278 (specificity = 0.825, sensitivity = 0.39, Youden score = 0.215, area under the curve = 0.638), see Figure 4. Moreover, of the 57 DCO$_2$corr values >60 mL$^2$/sec/kg$^2$ (from 9 patients), only 5 were associated with a PCO$_2$ value >8 kPa. Therefore, we suggest that DCO$_2$corr values >60 mL$^2$/sec/kg$^2$ should not be routinely targeted unless hypercapnia persists.

During ventilation through an un-cuffed endotracheal tube a gas leak can occur around the tube. We investigated the effect of leak on DCO$_2$corr. Leak was calculated, similarly to DCO$_2$, using the mean value of the 600 data points during 10 minutes before the blood gas was taken. Pragmatically, we divided the leak into two groups: <10% (209 blood gases) and ≥10% (45 blood gases). With <10% leak the correlation between DCO$_2$corr and PCO$_2$ improved ($r = -0.4342$, 95% confidence intervals: -0.5375, -0.3181 and $p<0.0001$)
compared to the total dataset (Figure 5), although the inverse correlation remained weak. In addition, the inverse correlation was statistically significant even when only arterial pCO$_2$ values were used (E-figure 4). In the subset with ≥10% leak there was no correlation between DCO$_2$corr or and PCO$_2$ or PaCO$_2$ (E-figure 5).

Previous reports have suggested a relationship between the VThf and PaCO$_2$ \cite{7} or transcutaneous CO$_2$ \cite{8}. We investigated if there was inverse correlation between VThf or the square of VThf and PCO$_2$. Interestingly, we found significant inverse correlation between both VThf and VThf$^2$ and DCO$_2$, although they were slightly weaker than between DCO$_2$corr and PCO$_2$. (E-Figure 6 & E-Figure 7). These data suggest that the VThf can also be used to target or predict normocapnia.

To investigate if time windows for DCO$_2$ averaging other than 10 minutes leads to better results, we performed the same analysis using different time windows between 2 and 20 minutes. DCO$_2$corr data obtained over 2, 5 and 15-minute windows also showed inverse correlation with PCO$_2$ albeit somewhat weaker than 10-minute data (data not shown). Data obtained with 20-minute time windows showed no inverse correlation.

DISCUSSION
There has been increasing interest in the tidal volumes delivered during neonatal HFOV (VThf), because modern ventilators now display this and it could give a better indication of ventilation than trying to assess chest wiggle \(^{10-12}\). Some new neonatal ventilators can deliver a targeted tidal volume during HFOV. Reports of volume-targeted HFOV found that VThf of 1.5 – 2.5 mL/kg is usually required to maintain PaCO\(_2\) within a normal range \(^4,6\). Importantly, if tidal volume-targeted HFOV is used then DCO\(_2\) changes from a measured parameter to a set parameter as both of its components (VThf and Hz) are set on the ventilator. This makes the clinical usefulness of the relationship between DCO\(_2\) and PCO\(_2\) even more important.

In this study, we found no correlation between uncorrected DCO\(_2\) and PCO\(_2\). However, if DCO\(_2\) was corrected to the square of body weight, there was a significant weak inverse correlation. When analysing gas exchange during HFOV in rabbits, Boynton et al, also used weight-corrected tidal volumes and found an inverse correlation between PaCO\(_2\) and DCO\(_2\) (see Figure 3 in reference 2). However, papers describing HFOV and DCO\(_2\) in neonates have not used weight-corrected tidal volumes \(^4-6\).

We found that if the DCO\(_2\)corr was >50 mL\(^2\)/sec/kg\(^2\) the probability of significant hypercapnia (PCO\(_2\) >8 kPa) was 17.5% and if DCO\(_2\)corr was >60 mL\(^2\)/sec/kg\(^2\) it was <10%. Therefore, when starting HFOV, clinician should not routinely use settings resulting in DCO\(_2\)corr >60 mL\(^2\)/sec/kg\(^2\). Moreover, we found an inverse correlation between VThf\(^2\) and even VThf and PCO\(_2\), even
though the HFOV frequency in our recordings varied between 7-12Hz. Despite using a different ventilator to deliver HFOV, our results are in line with the findings of Dimitriou et al\(^7\), suggesting that VThf >2.5 mL/kg are rarely needed to avoid hypercapnia.

Instead of relying on individual DCO\(_2\) values at the time of a blood gas measurement, we calculated the average of 600 DCO\(_2\) values obtained at (1 Hz over a 10-minute period. This is arguably better than recording a random DCO\(_2\) value just before the blood gas as our data showed significant variability even during a 10-minute period with a standard deviation of >10 mL\(^2\)/s/kg\(^2\) (data not shown). This variability has also been reported by others and it is likely due to the spontaneous breathing of the infant \(^{13}\).

The inverse correlation between DCO\(_2\)corr and PCO\(_2\) was weak, although it improved slightly if only those blood gas measurements were used when the endotracheal tube leak was <10%. There are several possible explanations for this. The DCO\(_2\) formula was originally developed on the basis animal experiments done in dog \(^1\), rabbits \(^2\) and mathematical calculations \(^{14}\). It is possible that the “true” DCO\(_2\) correlating with PCO\(_2\) volumes should be calculated as DCO\(_2\) = (Hz\(^x\) x (VThf\(^y\) where x and y are different from 1 and 2, respectively, and they may be fractions\(^{14,15}\). Moreover, x and y may be different for different oscillators to move the gas and can also vary between different patients depending on their weights or lung pathologies. The instrumental dead space and anatomical dead space account for approximately

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half the normal tidal volume which means that with VThf there will be a large proportion of expired CO\(_2\) that is not exhaled. A baby needing HFOV will have inhomogeneous alveolar ventilation and ventilation perfusion mismatching so it is expected that the correlation between DCO\(_2\) and PCO\(_2\) will not be good. The movement of gas in the lung is very different between conventional ventilation and HFOV and so this is likely to influence the relationship between VThf and PCO\(_2\) and the correlation with DCO\(_2\) where VThf is a major component of the DCO\(_2\).

The limitations to this study are that it was retrospective with a convenience cohort. The blood gas measurements were a mixture of arterial and arterialised capillary specimens, making this a pragmatic study reflecting what happens during neonatal intensive care. We analysed the effect of arterial or capillary blood gases separately and showed little difference in the efficacy of DCO\(_2\)corr.

Although using weight adjusted VThf and DCO\(_2\) would be preferable on neonatal ventilator displays this may not be practical without significant changes to ventilator “checks and balances“ to ensure that the correct weight is entered. However, when a particular DCO\(_2\) value is interpreted or targeted by clinicians, weight-correction using the square of the body weight should be used, as it is in conventional ventilation, when tidal volumes are interpreted as mL/kg. New research studies should report DCO\(_2\) as weight corrected.
In conclusion, we suggest that weight-corrected DCO$_2$ data over 10-minute epochs may be more informative about CO$_2$ elimination during HFOV than DCO$_2$. DCO$_2$corr values over 50 mL$^2$/sec/kg$^2$ are rarely needed to avoid hypercapnia.

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References


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TABLE LEGENDS:

Table 1: Characteristics of patients and recordings used in the analysis. Only recordings with more than 10 blood gases were used in the analysis and are shown in the table.

Table 2: Characteristics of the individual pCO₂ – corrected DCO₂ curves

FIGURE LEGENDS:

Figure 1: Lack of correlation between DCO₂ and PCO₂. Graph showing all blood gas PCO₂ (arterial and capillary) data plotted against uncorrected DCO₂. Data obtained from different patients are shown using different markers. There is no inverse correlation between DCO₂ and PCO₂, and data obtained from the individual patients tend to cluster. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

Figure 2: Boxplots of DCO₂ and weight-corrected DCO₂ corr values obtained from all patients. DCO₂ corr shows significantly less variability than uncorrected DCO₂.

Figure 3: Statistically significant inverse correlation between DCO₂ and PCO₂. Graph showing all blood gas PCO₂ (arterial and capillary) data plotted against DCO₂. Corrected for the square of the body weight. Data obtained from different
patients are shown using different markers. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

Figure 4: Receiver operating characteristic (ROC) analysis of DCO$_2$corr values to predict a PCO$_2$ less than 8 kPa. The optimal cut-off is shown at 50 mL/s/kg$^2$ (sensitivity: 0.390, specificity: 0.82, Youden score = 0.215).

Figure 5: Relationship between DCO$_2$corr and PCO$_2$ in blood gases when the endotracheal tube leak was less than 10%. The inverse correlation is stronger than when all gases were considered. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

SUPPLEMENTARY MATERIAL

E-Figure 1: No correlation between DCO$_2$ and arterial PaCO$_2$. In this graph only arterial PaCO$_2$ data are plotted against uncorrected DCO$_2$. Data obtained from different patients are shown using different markers. There is no inverse correlation between DCO$_2$ and PaCO$_2$. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

E-Figure 2: Inverse correlation between DCO$_2$ and arterial PaCO$_2$. In this graph only arterial PaCO$_2$ data are plotted against weight-corrected DCO$_2$. Data obtained from different patients are shown using different markers. There is inverse correlation between DCO$_2$ and PaCO$_2$. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

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E-Figure 3: Graphs showing the relationship between DCO$_2$ and PCO$_2$ in the individual patients. Only recordings where at least 10 blood gases were available are shown.

E-Figure 4: Relationship between DCO$_2$corr and arterial PaCO$_2$ in blood gases when the endotracheal tube leak was less than 10%. There is significant inverse correlation. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

E-Figure 5: Relationship between DCO$_2$corr and PCO$_2$ in blood gases when the endotracheal tube leak was more than 10%. There is no inverse correlation. “r” represents Pearson’s correlation coefficient with 95% confidence intervals.

E-Figure 6: VThf vs pCO$_2$: Relationship between tidal volume of high-frequency oscillations (VThf) and PCO$_2$. There is significant inverse correlation although slightly weaker than between DCO$_2$ and PCO$_2$.

E-Figure 7: Relationship between the square of tidal volume of high-frequency oscillations (VThf$^2$) and PCO$_2$. There is significant inverse correlation although slightly weaker than between DCO$_2$ and PCO$_2$.
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**Table 1: Characteristics of patients used in the analysis**

* I:E ratio was 1:1 in all cases

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<tr>
<td>DG018_1</td>
<td>$y=-0.0210x+7.5859$</td>
<td>r=-0.1894 (-0.5926 , 0.2897)</td>
<td>p=0.4373</td>
</tr>
<tr>
<td>DG020</td>
<td>$y=-0.0380x+10.8140$</td>
<td>r=-0.7170 (-0.9278 , -0.1593)</td>
<td>p=0.0196</td>
</tr>
<tr>
<td>DG022</td>
<td>$y=-0.0063x+10.8582$</td>
<td>r=-0.3180 (-0.6747 , 0.1593)</td>
<td>p=0.1846</td>
</tr>
<tr>
<td>DG025</td>
<td>$y=-0.4691x+10.9389$</td>
<td>r=-0.5458 (-0.8014 , -0.1218)</td>
<td>p=0.0156</td>
</tr>
<tr>
<td>DG032_2</td>
<td>$y=-0.0420x+10.2766$</td>
<td>r=-0.3346 (-0.7229 , 0.2144)</td>
<td>p=0.2229</td>
</tr>
<tr>
<td>DG038_1</td>
<td>$y=-0.0460x+9.3383$</td>
<td>r=-0.5297 (-0.7443 , -0.2159)</td>
<td>p=0.0022</td>
</tr>
<tr>
<td>DG038_2</td>
<td>$y=0.0127x+6.6313$</td>
<td>r=0.1438 (-0.3190 , 0.5513)</td>
<td>p=0.5452</td>
</tr>
<tr>
<td>DG040_1</td>
<td>$y=-0.0218x+4.9033$</td>
<td>r=-0.1893 (-0.5926 , 0.2898)</td>
<td>p=0.4375</td>
</tr>
<tr>
<td>DG040_2</td>
<td>$y=-0.1963x+11.5732$</td>
<td>r=-0.4855 (-0.7833 , -0.0063)</td>
<td>p=0.0482</td>
</tr>
<tr>
<td>DG046_1</td>
<td>$y=0.0592x+4.0290$</td>
<td>r=0.3173 (-0.2328 , 0.7136)</td>
<td>p=0.2491</td>
</tr>
</tbody>
</table>

* Pearson’s correlation coefficient with 95% confidence intervals

**Table 2: Characteristics of the individual pCO$_2$ – corrected DCO$_2$ curves**
Figure 1

Uncorrected DCO$_2$ - all gases

$y = 0.0038x + 6.6821$

$r = 0.1752 \ (0.0540, 0.2913)$

Figure 1
Figure 2

Figure 2
Figure 3

Weight-corrected DCO₂ - all gases

\[ y = -0.0210x + (7.9508) \]
\[ r = -0.3025 \pm (-0.4097, -0.1871) \]
\[ p < 0.001 \]
Figure 4

AUC = 0.638

Figure 5

Weight-corrected DCO₂ - leak<10%

y=-0.0292x+(8.5763)
r=-0.4342 (-0.5375 , -0.3181)
p<0.001

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Figure 5

Weight-corrected DCO₂ - leak < 10%

\[ y = -0.0292x + (8.5763) \]

\[ r = -0.4342 \] (-0.5375 , -0.3181)

\[ p < 0.001 \]
Author/s: Belteki, G; Lin, B; Morley, CJ

Title: Weight-correction of carbon dioxide diffusion coefficient (DCO2) reduces its inter-individual variability and improves its correlation with blood carbon dioxide levels in neonates receiving high-frequency oscillatory ventilation

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