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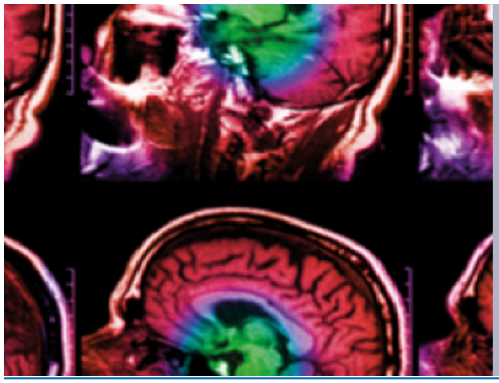

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Factors affecting the arterial to end-tidal carbon dioxide gradient in ventilated neonates

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Abstract

Objective. To determine factors which influenced the relationship between blood carbon dioxide (pCO_2) and end-tidal carbon dioxide ($EtCO_2$) values in ventilated, newborn infants. Furthermore, to assess whether pCO_2 levels could be predicted from continuous $EtCO_2$ monitoring. *Approach*. An observational study of routinely monitored newborn infants requiring mechanical ventilation in the first 28 d after birth was undertaken. Infants received standard clinical care. Daily pCO_2 and $EtCO_2$ levels were recorded and the difference (gradient: ΔP-$EtCO_2$) between the pairs were calculated. Ventilatory settings corresponding to the time of each blood gas assessment were noted. End-tidal capnography monitoring was performed using the Microstream sidestream Filterline H set capnograph. *Main results*. A total of 4697 blood gas results from one hundred and fifty infants were analysed. The infants had a median gestational age of 33.3 (range 22.3–42.0) weeks and birth weight of 1880 (395–5520) grams. Overall, there was moderate correlation between pCO_2 and $EtCO_2$ levels ($r = 0.65, p < 0.001$). The ΔP-$EtCO_2$ for infants born less than 32 weeks of gestation was significantly higher (1.4 kPa) compared to infants born at greater than 32 weeks of gestation (0.8 kPa) ($p < 0.001$). In infants born at less than 32 completed weeks of gestation, pCO_2 levels were independently associated with $EtCO_2$, day after birth, birthweight and fraction of inspired oxygen (FiO_2) (model $r^2 = 0.52, p < 0.001$). *Significance*. The results of end-tidal capnography monitoring have the potential to predict blood carbon dioxide values within the neonatal population.

Abbreviation LIST

BPD:	Bronchopulmonary dysplasia
CO_2:	Carbon dioxide
$EtCO_2$:	End-tidal carbon dioxide
FiO_2:	Fraction of inspired oxygen
NICE:	National Institute for Health and Care Excellence
pCO_2:	Blood carbon dioxide

1. Introduction

Carbon dioxide (CO_2) levels are routinely monitored on the neonatal unit, especially in those requiring invasive respiratory support as both hypercapnia and hypocapnia can have adverse effects on the developing brain (Wong *et al* 2021). The National Institute for Health and Care Excellence (NICE) has set out limits of CO_2 levels to target during the first 72 h and thereafter in mechanically ventilated prematurely born infants (NICE 2019).

The gold standard for measurement, blood gas analysis, is invasive and cannot be utilised to provide continuous values of CO_2, hence often leaving infants with periods of time during which CO_2 is unmonitored. Tidal capnography on the other hand allows for non-invasive, real-time continuous measurement of exhaled CO_2. Within the paediatric setting, non-invasive end-tidal CO_2 ($EtCO_2$) monitoring has been utilised to provide a reliable assessment of the effectiveness of mechanical ventilation (McDonald *et al* 2002).

The adoption of $EtCO_2$ as a surrogate for the partial pressure of blood (arterial/capillary) carbon dioxide (pCO_2) has, however, been questioned, especially for very low birth weight infants (Scrivens *et al* 2019). Concern has arisen within the neonatal population due to the often-reported poor agreement between pCO_2 and $EtCO_2$, especially in infants with severe lung disease (Trevisanuto *et al* 2012, Mehta *et al* 2014, Scrivens *et al* 2019, Williams *et al* 2020). Nevertheless, knowledge of the gradient between pCO_2 and $EtCO_2$ could provide valuable clinical information compared to standalone values of pCO_2 and $EtCO_2$. Indeed, the gradient has been utilised in adult intensive as an index of severity in acute respiratory distress syndrome (Yousuf *et al* 2017). A change in the observed $EtCO_2$ may either be secondary to a change in the pCO_2 value, or be reflective of a change in ventilatory factors affecting the gradient (Watkins and Weindling 1987). Furthermore, predictive models of pCO_2 from $EtCO_2$ values in children with varying degrees of respiratory failure have been described (Konca *et al* 2021). Reasons for discrepancies between pCO_2 and $EtCO_2$ values, however, have not been fully explored in neonates.

We aimed to determine factors which affected the relationship between pCO_2 and $EtCO_2$ in ventilated, newborn infants and whether pCO_2 levels could be predicted from the results of continuous $EtCO_2$ monitoring.

2. Methods

2.1. Subjects and protocol

This was an observational study of routinely monitored newborn infants requiring mechanical ventilation. Infants admitted to the neonatal intensive care unit at King's College Hospital NHS Foundation Trust between January 2020 and March 2021 were included if they required invasive mechanical ventilatory support during the first 28 d after birth. Newborn infants of all gestational ages were included and further categorised into extremely/very preterm (<32 weeks of gestational age) or moderate-late preterm or term (>32 weeks of gestational age) (World Health Organisation 2018).

Infants received standard clinical care. Mechanical ventilation was provided by the SLE6000 neonatal ventilator (Carefusion, UK) using pressure-controlled or volume-targeted time-cycled ventilation. As per local trust policy and guidelines, infants were intubated with Cole's shouldered endotracheal tubes. End-tidal capnography monitoring was performed using the Microstream sidestream Filterline H set capnograph (Phillips Medical Systems, Oridion Medical Ltd.) which was placed between the endotracheal tube and ventilator tubing and provided real-time continuous values of end-tidal carbon dioxide levels ($EtCO_2$) displayed on the ventilator screen. The nurses manually recorded the $EtCO_2$ levels as part of their hourly observations which were documented on the nursing charts. Arterial or capillary blood gases were routinely performed by medical and nursing staff and analysed utilising the ABL90 FLEX PLUS analyser (Radiometer Ltd., Denmark) with CO_2 (pCO_2) reported in kPa. Arterial and capillary CO_2 values have been shown to agree ($r = 0.93$) in newborn infants and hence can be used interchangeably (Yang *et al* 2002).

Demographic information were recorded for each infant. Data were collected for the first 28 d after birth only while infants were mechanically ventilated. For each day of mechanical ventilation, simultaneous blood carbon dioxide (pCO_2) and $EtCO_2$ levels were documented at the time of each blood gas analysis. The difference (gradient) between paired pCO_2 and $EtCO_2$ levels ($\Delta P\text{-}EtCO_2$) were calculated. Ventilatory settings corresponding to the time of each recorded blood gas were also noted. This included fraction of inspired oxygen (FiO_2), mean airway pressure, peak inspiratory pressure, positive end-expiratory pressure, generated expiratory tidal volume and trigger rate. The average of each of these parameters across each day of mechanical ventilation were calculated. Bronchopulmonary dysplasia development was defined according to the criteria agreed in the 2001 workshop led by Jobe and Bancalari (Jobe and Bancalari 2001).

2.2. Sample size

A previous study comparing pCO_2 and $EtCO_2$ values in a population of ventilated paediatric patients found a mean difference between blood $PaCO_2$ and end-tidal CO_2 levels of 4.8 mmHg (standard deviation 8.1 mmHg) (McDonald *et al* 2002). To detect a $\Delta P\text{-}EtCO_2$ of 4.8 mmHg (1.08 kPa) with 95% power at the 0.1% significance level, a minimum sample size of 138 infants was required.

Table 1. Demographic data and average ventilatory parameters over the first 28 d grouped by gestational age. Data displayed as median (range) or number (%).

	<32 weeks ($n = 66$)	>32 weeks ($n = 84$)	p value
Female gender	34 (51.5)	32 (38.1)	0.136
Gestational age (weeks)	26.0 (22.3–31.9)	37.7 (32.0–41.9)	<0.001
Birthweight (grams)	785 (395–1860)	3115 (1520–5520)	<0.001
Birthweight z-score	−0.5 (−2.8 to 1.3)	−0.2 (−3.8 to 5.6)	0.064
Days of mechanical ventilation (d)	13 (1–28)	4 (1–20)	<0.001
pCO_2 (kPa)	6.7 (3.7–12.4)	5.5 (3.4–10.7)	<0.001
$EtCO_2$ (kPa)	5.1 (0.5–8.9)	4.6 (1.9–7.9)	<0.001
FiO_2	0.3 (0.2–1.0)	0.3 (0.2–1.0)	<0.001
Mean airway pressure (cmH_2O)	10.7 (6.1–18.4)	8.5 (5.3–17.9)	<0.001
Peak inspiratory pressure (cmH_2O)	20.8 (8.6–31.9)	16.8 (8.7–45.7)	<0.001
Positive end-expiratory pressure (cmH_2O)	5.7 (3.6–14.3)	5.5 (4.0–8.4)	<0.001
Tidal volume ($ml\,kg^{-1}$)	6.8 (2.1–15.4) [$n = 61$]	5.6 (1.1–10.5) [$n = 84$]	<0.001
Trigger rate (per min)	20 (0–84)	26 (0–89)	0.123

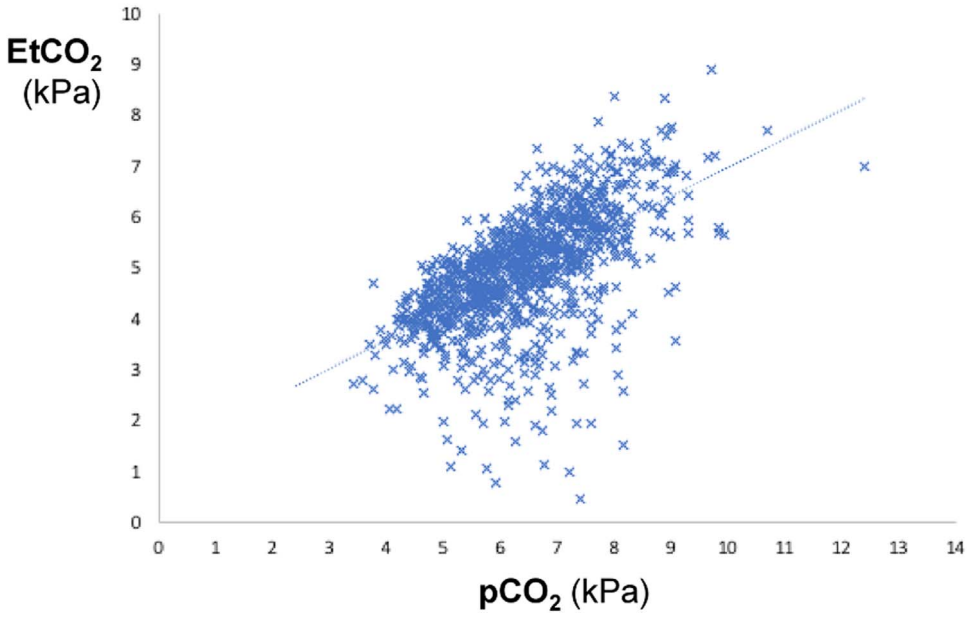

Figure 1. Correlation of pCO_2 and $EtCO_2$ across all gestations.

2.3. Statistical analysis

Data were tested for normality using the Kolmogorov–Smirnov test and found to be non-normally distributed. Non-parametric tests were therefore performed. Bland Altman analysis was performed alongside correlation analyses which were undertaken using Spearman Rho. Mann–Whitney U test assessed whether the differences between the two groups of infants as categorised by gestational age (less than or greater than 32 weeks of completed gestation) were statistically significant. Linear regression analysis was performed to define the ability of $EtCO_2$ to predict pCO_2 after adjusting for birthweight, day of life and FiO_2. In infants born at less than 32 weeks of gestational age, the ΔP-EtCO2 was compared in those who developed bronchopulmonary dysplasia (BPD) or those who required home oxygen compared to those who did not did not, using Mann Whitney U testing. Statistical analysis was undertaken with SPSS version 26.0 (SPSS Inc., Chicago, IL USA).

3. Results

A total of 4697 blood gases from one hundred and fifty infants who required invasive mechanical ventilation were included (84 male, 66 female). The infants had a median (range) gestational age of 33.3 (22.3–42.0) weeks and birth weight of 1880 (395–5520) grams [table 1]. Female infants were less mature (26.4 versus 28.2 weeks; $p < 0.001$) and of lower birthweight (0.79 versus 0.97 kg; $p < 0.001$) than their male counterparts. After correcting for this difference in gestational age, there was no significant difference in the pCO2-$EtCO_2$ gradient

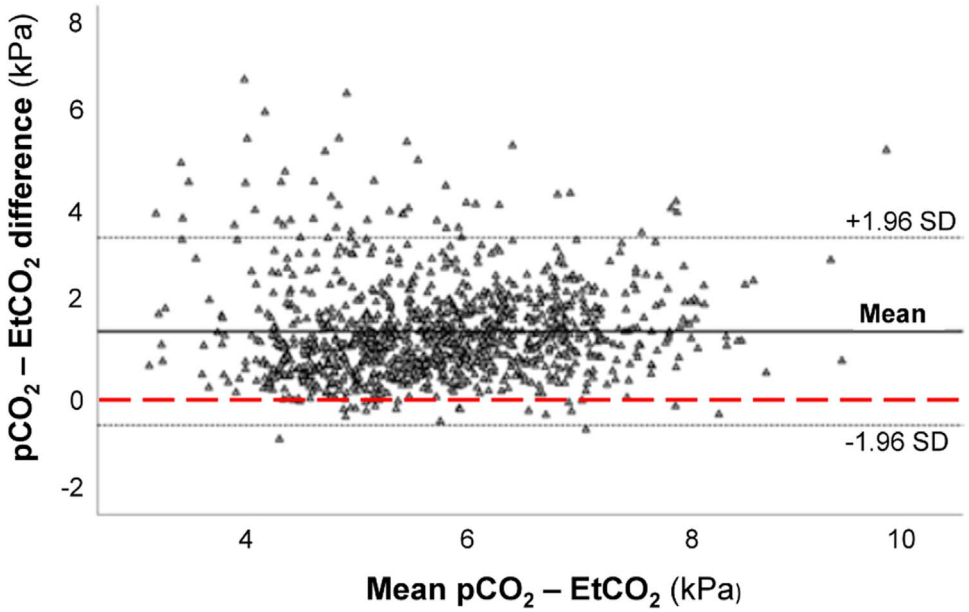

Figure 2. Bland Altman plot of the difference between pCO_2 and $EtCO_2$ versus the average of simultaneous measurements.

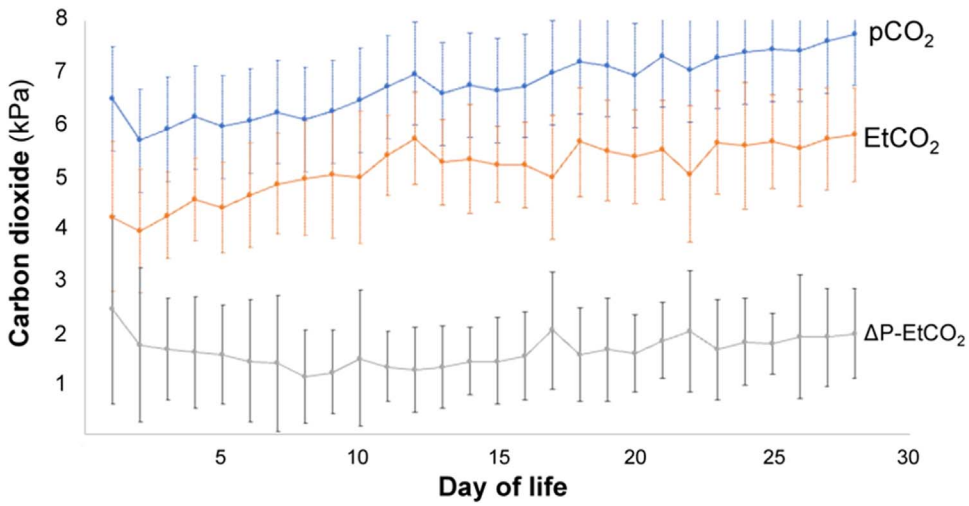

Figure 3. Temporal relationship between pCO_2 and $EtCO_2$ over the first 28 d of life in infants born at less than 32 weeks of gestation.

Table 2. Trend of $\Delta P\text{-}EtCO_2$ over the first ten days of life grouped by gestational age. Data are presented as mean (standard deviation).

Day	Gradient (kPa) <32 weeks	Gradient (kPa) > 32 weeks	*p* value
1	2.41 (1.81)	1.60 (1.09)	0.001
2	1.74 (1.48)	0.95 (0.66)	<0.001
3	1.65 (0.99)	0.86 (0.74)	0.186
4	1.59 (1.07)	0.62 (0.59)	0.062
5	1.55 (0.96)	0.61 (0.64)	0.045
6	1.42 (1.18)	0.88 (0.94)	0.302
7	1.38 (1.31)	0.77 (0.63)	0.207
8	1.13 (0.91)	0.67 (0.41)	0.036
9	1.21 (0.80)	0.98 (0.73)	0.626
10	1.48 (1.31)	1.10 (0.88)	0.609

Table 3. Correlation of demographic, temporal and respiratory state with the ΔP-$EtCO_2$ gradient, split by gestational age.

	ΔP-$EtCO_2$ < 32 weeks	ΔP-$EtCO_2$ > 32 weeks
Birthweight (kg)	$r = -0.26$ ($p < 0.001$)	$r = -0.004$ ($p = 0.943$)
Day of life	$r = 0.13$ ($p < 0.001$)	$r = -0.18$ (p=0.002)
FiO_2	$r = 0.44$ (<$p < 0.001$)	$r = 0.39$ ($p < 0.001$)

between the two sexes [females 1.36 kPa versus males 1.17 kPa; adjusted p value 0.15]. Overall pCO_2 and $EtCO_2$ correlated across all gestational ages ($r = 0.65$, $p < 0.001$) [figure 1], Bland Altman plot (figure 2). This correlation remained when grouping the data into infants <32 weeks of gestational age ($r = 0.64$, $p < 0.001$) and >32 weeks of gestational age ($r = 0.61$, $p < 0.001$).

The gradient value was assessed over the first 28 d after birth. The median (range) ΔP-$EtCO_2$ was 1.3 (−0.9 to 7.0) kPa in the whole study population. The average ΔP-$EtCO_2$ for infants born less than 32 weeks of gestation was significantly higher (1.4 kPa) compared to infants born at greater than 32 weeks of gestation (0.8 kPa) ($p < 0.001$). As only three infants more than 32 weeks of gestation were ventilated beyond ten days after birth, the trend in mean ΔP-$EtCO_2$ was reported only for the first ten days [table 2]. In infants less than 32 weeks of gestation, the temporal relationship between pCO_2 and $EtCO_2$ across the first 28 d after birth is shown in figure 3. The FiO_2 correlated with the ΔP-$EtCO_2$ in both less mature ($r = 0.44$, $p < 0.001$) and more mature infants ($r = 0.39$, $p < 0.001$) [table 3].

Following linear regression analysis, pCO_2 levels were independently associated with $EtCO_2$ ($p < 0.001$), day of life ($p < 0.001$), birthweight ($p < 0.001$) and FiO_2 ($p < 0.001$) in infants born at less than 32 completed weeks of gestation (model $r^2 = 0.52$, $p < 0.001$). In infants born at greater than 32 weeks of gestation, $EtCO_2$ ($p < 0.001$), day of life ($p < 0.001$) and FiO_2 ($p < 0.001$) were significantly associated with pCO_2 (model $r^2 = 0.53$, $p < 0.001$). A predictive equation therefore was calculated to estimate pCO_2 levels based on $EtCO_2$ levels and the factors affecting the ΔP-$EtCO_2$ gradient:

<32 weeks:

$$pCO_2 = 4.26\,(0.42 * EtCO_2) + (2.18 * FiO_2) + (0.02 * \text{day of life}) - (1.02 * \text{birthweight})$$

>32 weeks:

$$pCO_2 = 1.95 + (0.6 * EtCO_2) + (0.02 * FiO_2) + (0.03 * \text{day of life})$$

In infants born at less than 32 weeks of gestation ($n = 66$), 49 (74%) developed BPD. Infants that developed BPD had a higher average ΔP-$EtCO_2$ (1.44 kPa) during the first 28 d after birth than those infants who did not develop BPD (1.15 kPa) ($p = 0.007$). Furthermore, of those infants who developed BPD, 31 infants (63%) required supplemental oxygen on discharge home from the neonatal intensive care unit, of which 25 infants were born at less than 28 weeks of gestational age. Infants requiring home oxygen had a greater ΔP-$EtCO_2$ (1.48 kPa) compared to BPD infants not requiring supplemental oxygen (1.25 kPa) ($p = 0.002$).

4. Discussion

In ventilated newborn infants the partial pressure of the blood CO_2 correlated with end-tidal CO_2 both in term and preterm infants. The gradient between the two (ΔP-$EtCO_2$) was larger in less mature infants and those with higher oxygen requirements.

The moderate correlation between $EtCO_2$ and pCO_2, with the latter value being higher, agree with previously reported values in ventilated infants (Singh *et al* 2013, Williams *et al* 2020). Despite the values of $EtCO_2$ being lower than pCO_2, tidal capnography can provide continuous monitoring of CO_2 between intermittent invasive blood gas analyses. The larger gradient in those born at less than 32 weeks of gestation may be related to anatomical, developmental, or environmental factors. The larger relative anatomical and apparatus dead space in less mature infants can contribute to a larger ΔP-$EtCO_2$ gradient, as greater dilution of exhaled gas occurs (Ream *et al* 1995, McSwain *et al* 2010, Lin *et al* 2017, Williams *et al* 2022). Premature infants are born prior to completion of the alveolar stage of development and in theory have a reduced surface area for gas exchange to occur (Dassios *et al* 2018), which often can limit adequate diffusion of carbon dioxide across the alveolar blood gas barrier, hence increasing the ΔP-$EtCO_2$ gradient. Additionally, the necessary incubator

humidity for those born extremely preterm can cause droplets of water to build up within the capnography tubing, and thus potentially affecting the readings of $EtCO_2$ (Supkis 2011).

With respect to the temporal changes of carbon dioxide, values increase steadily during the first 28 d of mechanical ventilation (Ali *et al* 2019). After the initial period following delivery, clinicians may be more tolerant of higher values of carbon dioxide, in agreement with the higher accepted upper end range for pCO_2 as stated in recent guidance (NICE 2019). The $\Delta P\text{-}EtCO_2$ gradient however remains static as $EtCO_2$ also exhibits a rising trend, consistent with previous literature in paediatric intensive care that demonstrates a static gradient during steady state mechanical ventilation (Goonasekera *et al* 2014). The larger $\Delta P\text{-}EtCO_2$ gradient in infants with BPD and those who required home oxygen is likely due to the larger alveolar dead space volume and greater ventilation-perfusion mismatch in infants with pulmonary morbidity (Lopez *et al* 2011, Williams *et al* 2022). Indeed, in infants with BPD, parts of the lung may have cystic changes which become non-functioning for gas exchange and thus do not contribute to carbon dioxide elimination (Abman *et al* 2017). A rising gradient during the course of invasive ventilation may thus highlight infants with worsening chronic lung disease and identify those who may benefit from targeted postnatal therapies.

Regarding the relationship between inspired oxygen and the $\Delta P\text{-}EtCO_2$ gradient, it has previously been demonstrated in very low birth weight infants that FiO_2 affects the agreement of pCO_2 with $EtCO_2$ (Trevisanuto *et al* 2012). Poor oxygenation as a marker of increasing severity of pulmonary disease has also been associated with higher levels of $EtCO_2$ (Mehta *et al* 2014). The pathophysiological connection behind poor oxygenation and a higher gradient of CO_2 in severe respiratory disease might be increased intrapulmonary shunting which would cause a deterioration of oxygenation (and a greater FiO_2 requirement) with concomitant reduced clearance of carbon dioxide (increasing the $\Delta P\text{-}EtCO_2$ gradient) (Goonasekera *et al* 2014).

This study has strengths and some limitations. Many simultaneous readings of carbon dioxide values were analysed, including samples taken from extremely preterm infants. Many of the samples were from capillary gases which may be affected by alterations in perfusion and we acknowledge that agreement between arterial and capillary values is dependent upon individual patient characteristics. The poorer correlation between pCO_2 and $EtCO_2$ in those less than 32 weeks could be due to many factors both physiological and technical. An increase in the respiratory dead space will lower the $EtCO_2$ relative to the pCO_2. Furthermore, the faster neonatal breathing rate in such infants could capture the $EtCO_2$ prior to the end of expiration and hence give a falsely lower $EtCO_2$.The weak correlation of FiO_2 with $\Delta P\text{-}EtCO_2$, although statistically significant, may be due to the large number of gases analysed. Given the retrospective nature of the study, one limitation is that collecting manually recorded data from medical charts may be susceptible to observation bias, but this reflects clinical practice. The larger proportion of infants developing BPD in our study may be reflective of the inclusion of high number of infants born extremely prematurely, including those born at 22 weeks of gestation. One further limitation noted in our study is that sidestream capnography may function less well in extreme prematurity due to condensation from high incubator humidity accumulating in the circuit causing less reliable $EtCO_2$ values, and often requiring the capnography tubing to be replaced frequently which can be costly. The exact effect of differing levels of incubator humidity on the $\Delta P\text{-}EtCO_2$ gradient have however not yet been determined.

5. Conclusion

End-tidal capnography monitoring has the potential to predict blood carbon dioxide values within the neonatal population and thus provide clinicians with a tool for continuous non-invasive monitoring of invasive mechanical ventilation. The relationship between the partial pressure of CO_2 in the blood with end tidal CO_2 though is not static and is one which is affected by gestation at birth, postnatal age and oxygen requirement at the time of study. This monitoring tool, however, may be clinically beneficial in environments where blood gas testing is not readily available, such as in neonatal transport settings. Furthermore, the clinical care of infants may be enhanced if the frequency of blood sampling can be reduced in those born extremely prematurely, with respiratory status still being closely monitored by continuous non-invasive means.

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Conflict of interest

Carefusion provided the equipment but were not involved in the design or performance of the study, analysis of the results or production of this manuscript.

Ethical statement

The Health Research Authority (HRA) Toolkit of the National Health System (NHS), United Kingdom, confirmed the study would not need regulatory approval by a research ethics committee and hence the study was registered with the clinical governance department of King's College Hospital (KCH) NHS Foundation Trust.

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