Original Article

Arterial to end-tidal carbon dioxide difference in children undergoing mechanical ventilation of the lungs during general anaesthesia

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Summary

Capnography ($ETCO_2$) is routinely used as a non-invasive estimate of arterial carbon dioxide ($PaCO_2$) levels in order to modify ventilatory settings, whereby it is assumed that there is a positive gap between $PaCO_2$ and $ETCO_2$ of approximately 0.5 kPa. However, negative values ($ETCO_2 > PaCO_2$) can be observed. We retrospectively analysed arterial to end-tidal carbon dioxide differences in 799 children undergoing general anaesthesia with mechanical ventilation of the lungs in order to elucidate predictors for a negative gap. A total of 2452 blood gas analysis readings with complete vital sign monitoring, anaesthesia gas analysis and spirometry data were analysed. Mean arterial to end-tidal carbon dioxide difference was −0.18 kPa (limits of 95% agreement −1.10 to 0.74) and 71.2% of samples demonstrated negative values. The intercept model revealed $PaCO_2$ to be the strongest predictor for a negative $PaCO_2$-$ETCO_2$ difference. A decrease in $PaCO_2$ by 1 kPa resulted in a decrease in the $PaCO_2$-$ETCO_2$ difference by 0.23 kPa. This study demonstrates that $ETCO_2$ monitoring in children whose lungs are mechanically ventilated may paradoxically lead to overestimation of $ETCO_2$ ($ETCO_2 > PaCO_2$) with a subsequent risk of unrecognised hypocarbia.

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Introduction

Maintaining normocapnia during mechanical ventilation of the lungs in children undergoing general anaesthesia is highly recommended in order to avoid peri-operative central nervous system injury, particularly in younger patients and if combined with hypotension [1–3]. The gold standard in anaesthesia and intensive care units is intermittent determination of $PaCO_2$ by arterial blood gas analysis combined with continuous monitoring of end-tidal ($ETCO_2$) using capnography. Capnography provides a non-invasive estimate of arterial CO_2 levels and allows clinicians to modify mechanical ventilation settings in order to maintain normocapnia. Normally, a positive gap between arterial CO_2 and $ETCO_2$ of approximately 0.5 kPa is assumed in a healthy patient and ventilation settings are adjusted accordingly [4]. However, we have observed that the arterial to end-tidal carbon dioxide difference in children undergoing anaesthesia with mechanical ventilation of the lungs often resulted

in negative values ($ETCO_2 > PaCO_2$). We therefore decided to measure arterial to end-tidal carbon dioxide differences and to determine predictors for a negative gap in paediatric patients undergoing general anaesthesia with mechanical ventilation of the lungs.

Methods

Following local research ethics committee approval, children up to 18 years of age undergoing general anaesthesia with tracheal intubation, mechanical ventilation of the lungs and insertion of an in-dwelling arterial cannula for blood gas analysis were identified from a patient data management system (PDMS, deioRecorder™, deioWarehouse™ and deioAnalyzer™, Datex-Ohmeda, GE Healthcare, Helsinki, Finland). Patients with congenital cardiac abnormalities, those having surgical procedures that required cardiopulmonary bypass or patients with an uncuffed tracheal tube were not studied.

The retrospective analysis included paediatric patients anaesthetised between July 2009 and March 2015. The same arterial blood sampler syringe PICO 50 (Radiometer Medical ApS, Brønshøj, Denmark) and a single ABL 800 FLEX blood gas analysis machine (Radiometer Medical ApS, Brønshøj, Denmark) and were used for all arterial blood gas analyses. The ABL 800 FLEX blood gas analysis machine was regularly serviced and quality-checked by the hospital laboratory diagnostics department as well as the local distributor. The same anaesthetic machines with buit-in ventilator (Datex-Ohmeda GE Healthcare, Helsinki, Finland) with AS5 anaesthesia monitoring, including spirometry and side-stream capnography (GE Healthcare) were used in all patients. Side-stream $ETCO_2$ was sampled in a volume of 200 ± 20 $ml.min^{-1}$ by means of a sampling line connected to a heat- and moisture-exchanger (HME) filter (Pharma Systems, Knivsta, Sweden) or, when there were small-sized tracheal tubes, it was connected to a dead space adapter (Anandic Medical Systems AG, Feuerthalen, Switzerland).

Age, weight, sex, ASA physical status, cardiac abnormalities and cardiovascular diseases (such as pulmonary artery hypertension), as well as pulmonary diseases and respiratory infections, were recorded. The type of surgery and intra-operative prone or head-up position were also recorded from information provided on the anaesthetic charts. Blood gas analysis and oximetry data with time-related vital sign monitoring, anaesthesia gas analysis and spirometry data (at 1 min intervals) were retrieved from the anaesthesia archive. Arterial CO_2 values provided by the blood gas analysis machine were corrected for temperature (pH_{stat}).

All data were recorded using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Classical and modified Bland–Altman bias plots were used to compare $PaCO_2$ and $ETCO_2$. A random intercept model was run with the dependent variable $PaCO_2$-$ETCO_2$ difference and the fixed factors of sex, age, ASA physical status (1–2 vs. 3–5), type of surgery (with or without impact on perfusion/ventilation mismatch [5]), cardiovascular disease ('no' or 'yes'), respiratory disease ('no' or 'yes'), respiratory infection ('no' or 'yes'), $PaCO_2$, PaO_2, HCO^{3-}, SaO_2, arterial haemoglobin concentration (Hb), positive end-expiratory pressure, peak inspiratory pressure, respiratory rate, end-tidal nitrous oxide concentration, end-tidal oxygen concentration, end-tidal sevoflurane concentration, inspiratory CO_2 concentration and Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$). Apart from Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$), which already has a meaningful zero, all continuous predictors were centred at their mean. A reduced model was compared with the full model using a likelihood ratio test, which indicated that the reduced model was not worse than the full model. Interactions were tested but did not seem to improve the model. Regression analysis was performed using SPSS Version 20 (SPSS Inc, Chicago, IL, USA) software. A p value of < 0.05 was considered statistically significant.

Results

A total of 2409 patients with an indwelling arterial line were identified from 42,659 patient records. Of these, 1423 (59.1%) patients were not studied because of congenital cardiac abnormalities (296), the use of cardiopulmonary bypass (938) or tracheal intubation with an uncuffed tube (189). Of the remaining 986 patients, a total of 3164 arterial blood samples were taken. Of these, 712 were incomplete data sets and excluded. In total, 2452 blood gas analysis samples with complete vital sign monitoring, anaesthesia gas analysis and spirometry data sets from 799 patients were analysed

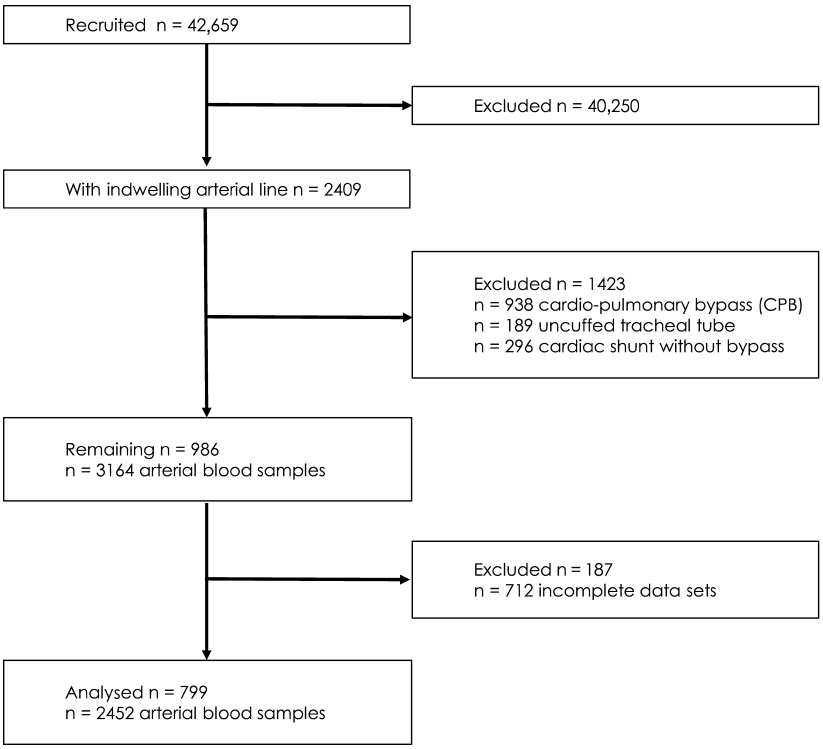

Figure 1 CONSORT flow diagram showing data from patients included in the study.

Table 1 Baseline characteristics and peri-operative data for the 799 patients included in the study. Values are number (proportion) or median (IQR [range]).

Sex; male	421 (53%)
Age; years	6.8 (1.8–12.2 [0.0–18.1])
Body weight; kg	19.9 (11.5–35.1 [2.7–93.0])
ASA physical status	
1	79 (9.9%)
2	310 (38.8%)
3	383 (47.9%)
4	26 (3.3%)
5	1 (0.1%)
Type of surgery	
No impact on ventilation	501 (62.7%)
Impact on ventilation	298 (37.3%)
Pulmonary arterial hypertension	18 (2.3%)
Respiratory disease	
Lung disease (obstructive, restrictive, others)	127 (15.9%)
Respiratory infection	67 (8.4%)

Surgery with an impact on ventilation: thoracotomy, laparotomy, laparoscopy, thoracoscopy, scoliosis surgery, neurosurgery, prone position.

(Fig. 1). Baseline patient characteristics and intra-operative data are shown in Table 1. Blood gas analysis and oximetry data, vital sign monitoring, anaesthesia gas analysis and spirometry data are summarised in Table 2.

Overall mean (SD) arterial to end-tidal carbon dioxide difference was −0.18 (0.46) for pH_{stat} assessment of $PaCO_2$ (limits of 95% agreement −1.10 to 0.74) and −0.26 (0.44) for $alpha_{stat}$ (temperature corrected) $PaCO_2$ measurement (limits of 95% agreement −1.14 to 0.62) (Fig. 2) with 71.2% of samples (82.4% of patients) demonstrating negative differences (pH_{stat} measurements). Arterial CO_2 values, bias and precision, as well as 95% limits of agreement for the comparison of $PaCO_2$ with $ETCO_2$ for different subgroups are shown in Table 3.

The intercept model revealed an expected mean $PaCO_2$-$ETCO_2$ difference of −0.24 kPa when all predictors are zero, that is, for the average patient in this sample of ASA physical status I–II, no respiratory tract infection, $F_iCO_2 < 0.01$ kPa and Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$) equal to zero. A decrease in $PaCO_2$ was the strongest predictor for a negative $PaCO_2$-$ETCO_2$ difference. A decrease in $PaCO_2$ by 1 kPa resulted in a decrease in the PaCO2-$ETCO_2$ difference by 0.23 kPa. Conversely, an increase in Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$)

Table 2 Blood gas, oximetry, vital sign, anaesthesia gas analysis and patient near spirometry parameters recorded from 2452 electronic anaesthesia patient data sets. Values are median (IQR [range]).

Parameter	
pH	7.37 (7.33–7.40 [7.03–7.60])
$PaCO_2$ (pH_{stat}); kPa	4.96 (4.63–5.38 [3.10–12.90])
$PaCO_2$ ($alpha_{stat}$); kPa	4.87 (4.55–5.30 [2.89–12.44])
Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$); kPa	0.04 (0.04–0.11 [−0.31–0.27])
PaO_2; kPa	27.00 (22.30–32.40 [6.96–99.30])
HCO^{3-}; mmol.l^{-1}	21.9 (20.4–23.4 [12.8–38.3])
Base excess; mmol.l^{-1}	−3.0 (−4.8 to 1.4 [−14.9 to 15.2])
Arterial oxygen saturation; %	100.0 (99.6–100.0 [85.5–100.0])
Arterial haemoglobin concentration; g.dl^{-1}	9.4 (8.3–10.7 [4.3–16.7])
SpO_2; %	99.7 (99.0–100.0 [88.8–100.0])
Body temperature; °C	36.7 (36.2–37.3 [35.0–39.4])
Positive end-expiratory pressure; cmH_2O	5.5 (5.2–6.1 [0.0–14.6])
Peak inspiratory pressure; cmH_2O	19.5 (17.5–22.1 [9.4–34.7])
Plateau pressure; cmH_2O	18.4 (16.3–20.8 [8.3–34.1])
Expiratory minute volume; l.min^{-1}	2.67 (2.00–3.59 [0.40–9.06])
Respiratory rate; min^{-1}	17 (13–22 [8–38])
Expiratory tidal volume; ml	158 (103–261 [13–660])
Inspiratory tidal volume; ml	169 (111–281 [16–672])
Δ Expiratory and inspiratory volume; ml	10 (6–18 [−163–120])
Expiratory tidal volume.kg^{-1}; ml.kg^{-1}	8.31 (7.36–9.30 [4.00–14.20])
Inspiratory tidal volume.kg^{-1}; ml.kg^{-1}	8.9 (7.9–10.0 [4.2–15.0])
Δ Expiratory and inspiratory volume.kg^{-1}; ml.kg^{-1}	0.56 (0.37–0.78 [−3.20 to 4.30])
Compliance; ml.$cm.^{-1}.H_2O^{-2}$	13.24 (7.67–22.19 [0.90–69.90])
End-tidal CO_2 concentration; kPa	5.16 (4.85–5.54 [2.20–10.80])
Inspiratory CO_2 concentration; kPa	0 (0.0–0.1 [0.0–0.7])
End-tidal N_2O concentration; %	0.04 (0.04–38.65 [0.00–80.60])
End-tidal O_2 concentration; %	39.64 (32.79–47.77 [17.40–95.80])
End-tidal sevoflurane concentration; %	1.55 (0.50–1.96 [0.00–3.70])

by 1 kPa resulted in a decrease in the $PaCO_2$-$ETCO_2$ difference of −0.23 kPa (Table 4).

The $PaCO_2$-$ETCO_2$ difference was 0.05 kPa lower in patients of ASA physical status 1–2 compared with ASA physical status 3–5, and 0.08 kPa lower in patients without a respiratory tract infection compared with those who had a respiratory tract infection. It was 0.07 kPa lower in patients with an $F_ICO_2 \geq 0.01$ kPa compared with those with an $F_ICO_2 < 0.01$ kPa. Finally, the $PaCO_2$-$ETCO_2$ difference became lower with decreasing ETO_2, HCO^{3-}, reduced inspiratory peak pressure and decreased respiratory rate (Table 4).

Discussion

End-tidal CO_2 monitoring during anaesthesia is mandatory and values obtained are used to adjust mechanical ventilator settings in patients whose lungs are ventilated. When making this adjustment, a $PaCO_2$-$ETCO_2$ difference of 0.5–0.7 kPa is assumed in healthy patients, potentially increasing in patients with lung pathology or a higher dead space/tidal volume ratio. This study clearly demonstrates that negative $PaCO_2$-$ETCO_2$ differences occur in paediatric patients. The most powerful predictor for a negative difference is a lower $PaCO_2$ value. To a lesser extent, an increasing Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$) also resulted in lower, or more negative, $PaCO_2$-$ETCO_2$ differences, but this is to be expected because the solubility of CO_2 in plasma is reduced at lower body temperatures.

Our findings are in agreement with those of other studies reporting negative $PaCO_2$-$ETCO_2$ differences, namely that a decrease in $PaCO_2$ is a strong predictor for a decrease in the $PaCO_2$-$ETCO_2$ difference [6, 7]. Negative $PaCO_2$-$ETCO_2$ differences have been reported to occur in up to 34% of patients in paediatric intensive care as well as anaesthetised patients [6–8]. They occur most frequently in children between 4 and 8 years of age [7], with decreasing $PaCO_2$ values [6, 7]

and with a dead space/tidal volume ratio of less than 0.4 [8]. There is no correlation between these negative differences and the child's primary disease and it has been suggested that this phenomenon is more methodological and technical rather than related to underlying pathology [6]. This is in agreement with our results, which showed that healthier patients (ASA physical status 1 or 2, no respiratory infection, surgery not influencing ventilation, lower etO_2 and reduced ventilation settings) had more negative $PaCO_2$-$ETCO_2$ differences. Negative $PaCO_2$-$ETCO_2$ differences are not only observed in paediatric patients but were also reported in adult patients many years ago [9–11].

It has been hypothesised that low tidal volumes and high respiratory rates may lead to inadequate ventilation of dependent, well perfused alveoli. This leads to accumulation of CO_2 in the lower airway and exhaled CO_2 in the terminal part of phase-3 capnography may exceed mean $PaCO_2$, resulting in a negative $PaCO_2$-$ETCO_2$ difference [6]. This may be aggravated by the fact that arterial CO_2 values vary cyclically between end-inspiration and end-expiration. The mixed blood from the heart and syringe, respectively, represents a spatial and temporal mean of $PaCO_2$ and may therefore be exceeded by $ETCO_2$ [10, 11]. An alternative explanation is that the highly elevated mixed venous return in patients with higher metabolic rates may lead to negative differences and that this may be typical for paediatric patients, septic patients and pregnant women [6, 9].

The overall mean $PaCO_2$-$ETCO_2$ difference (bias) reported in the study by Goonasekera et al. [6] was +0.66 kPa (95%CI+0.57 to +0.76), but up to 20% of samples demonstrated a negative PaCO2-$ETCO_2$ difference. However, our results revealed a bias of −0.18 kPa (−1.08 to +0.72 kPa) and 71.2% of samples revealed a negative difference. The negative differences were even present after excluding patients with potential V/Q mismatch due to surgery, patient positioning, lung disease or respiratory tract infections. Even samples where the $PaCO_2$ was normal (4.5 to 6.0 kPa), the mean $PaCO_2$-$ETCO_2$ difference (bias) was still −0.16 kPa (−0.92 to +0.60).

The reason for the relatively high rate of samples with a negative difference and with more negative bias in our study is explained by an incorrect setting in all anaesthesia gas analysis and capnography modules in our department to measure $ETCO_2$ as partial pressure (kPa). All gas analysis modules were set to measure gas samples at 'dry gas' conditions instead of 'wet gas' conditions. 'Wet gas' means gas analysis under body temperature pressure saturation (BTPS) conditions and allows measurement of $ETCO_2$ as partial pressure (kPa or mmHg) and volume per cent (vol%). 'Dry gas' corresponds

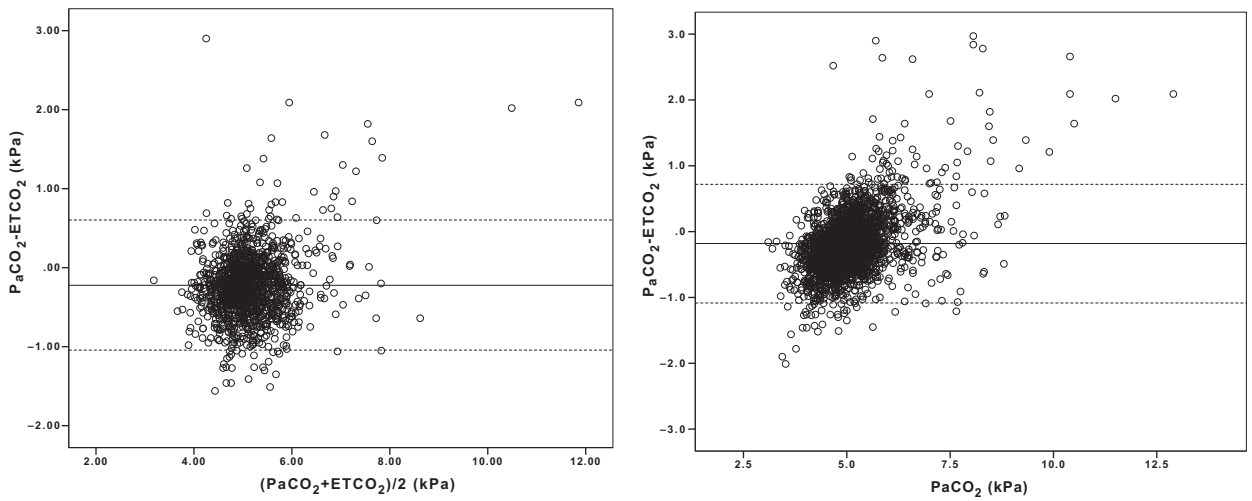

Figure 2 Classical (left) and modified (right) Bland Altman bias diagrams for the comparison of arterial ($PaCO_2$) (pHstat) and end-tidal ($ETCO_2$) carbon dioxide values (n = 799/2452 data sets).

Table 3 Bias (mean difference), precision (2 × SD of mean difference) and 95% limits of agreement for the comparison of arterial to end-tidal CO_2 difference for different subgroups.

Group	Number of samples (patients)	$PaCO_2$ (kPa) Median (IQR [range])	Bias; precision (kPa) pH_{stat} (% negative gaps) [% patients with negative gaps]	95% limits of agreement pH_{stat}	Bias; precision (kPa) $Alpha_{stat}$ (% negative gaps) [% patients with negative gaps]	95% limits of agreement $Alpha_{stat}$
Total	2452 (799)	4.96 (4.63–5.38 [3.10–12.90])	−0.18; 0.92 (71.2%) [82.5%]	−1.10 to 0.74	−0.26; 0.88 (71.5%) [83.4%]	−1.14 to 0.62
No surgical/ positional impact	1480 (505)	4.95 (4.62–5.32 [3.1–12.9])	−0.21; 0.88 (73.9%) [84.6%]	−1.09 to 0.67	−0.31; 0.84 (75.6%) [84.4%]	−1.15 to 0.53
No cardiovascular disease	2422 (781)	4.96 (4.63–5.37 [3.1–12.9])	−0.18; 0.92 (71.5%) [83.7%]	−1.1 to 0.74	−0.26; 0.86 (72.1%) [85.0%]	−1.12 to 0.60
No surgical/ positional impact No cardiovascular/ respiratory disease/respiratory tract infection	1317 (446)	4.94 (4.62–5.31 [3.1–12.9])	−0.22; 0.84 (75.4%) [85.4%]	−1.06 to 0.62	−0.33; 0.80 (77.5%) [85.9%]	−1.13 to 0.47
Patients with normal $PaCO_2$ (4.5–6.0 kPa) (pH_{stat})	1832 (669)	5.0 (4.8–5.3 [4.5–6.0])	−0.16; 0.76/ (70.1%)/ [80.0%]	−0.92 to 0.60	−0.26; 0.72 (73.4%) [83.4%]	−0.98 to 0.46

to gas analysis at ambient temperature pressure dry (ATPD) conditions and can only be used for measurement of $ETCO_2$ as volume per cent, and not as partial pressure. This means that $ETCO_2$ sampled in wet conditions and analysed as 'dry gas' results in falsely high $ETCO_2$ partial pressure values, exceeding the $PaCO_2$ values. According to our local GE equipment distributor, all anaesthesia gas and capnography modules are usually delivered worldwide in the 'dry gas' mode as the default setting. Neither a group of GE experts from Helsinki, Finland visiting our department to explore the problem, nor our local GE equipment distributor, were aware of this problem and the latter failed to identify it for a number of years. Therefore, it is not surprising that clinicians are unaware of this, nor that the anaesthesia gas and/or capnography modules are set to 'wet gas' mode when delivered by local distributors. Other manufacturers such as Draeger (Lubeck, Germany) only provide a 'wet gas' mode or, if the anaesthetic machine has both options, the equipment is delivered in 'wet gas' mode as the default setting. This allows the measurement of $ETCO_2$ as both volume percent and partial pressure independently of the 'gas setting'.

Our findings imply that in paediatric patients whose lungs are being ventilated, $ETCO_2$ monitoring can be considerably misleading even in, or particularly in, healthy patients undergoing surgery. The fact that an $ETCO_2$ value of 4.5 kPa could easily correspond to a $PaCO_2$ value of 3.6 kPa (95%CI) or, in extreme cases, even 2.5 kPa is worrying. Unfortunately, negative $PaCO_2$-$ETCO_2$ differences are more common at lower $PaCO_2$ values, further exacerbating the risk of hypocapnoea. Based on the information provided by our local distributor, GE capnography monitoring appears to have been delivered in the 'dry gas' mode and remained so for more than 20 years, potentially resulting in falsely high $ETCO_2$ partial pressure readings and consequently leading to hyperventilation of patients' lungs.

Other reasons for the higher number of samples with a negative $PaCO_2$-$ETCO_2$ difference could be measurement inaccuracy of both the blood gas and anaesthetic gas analysers, contamination or leaks in the measurement systems. However, none of these

Table 4 Estimates of fixed effects for the reduced random intercept model with $PaCO_2$-$ETCO_2$ difference as the dependent variable.

Parameter	Estimate	Standard error	t	95%CI	p value
Intercept	−0.241	0.016	−14.736	−0.273 to −0.209	0.000
ASA 3-5 vs. ASA 1-2	0.048	0.019	2.463	0.010 to 0.086	0.014
RTI vs. no RTI	0.080	0.035	2.174	0.007 to 0.145	0.000
$FiCO_2 \geq 0.01$ vs. < 0.01	−0.070	0.018	−3.947	−0.105 to −0.035	0.000
ETO_2	0.004	0.001	5.641	0.002 to 0.005	0.000
$PaCO_2$	0.233	0.011	20.656	0.211 to 0.256	0.000
HCO^{3-}	0.016	0.004	4.674	0.010 to 0.024	0.000
Δ $PaCO_2$ (pH_{stat}−$alpha_{stat}$)	−0.234	0.011	−21.307	−0.255 to −0.213	0.000
Peak inspiratory pressure	0.022	0.003	6.378	0.015 to 0.028	0.000
PaO_2 log	−0.099	0.030	−3.337	−0.157 to −0.041	0.001
Respiratory rate	−0.008	0.002	3.926	0.004 to 0.012	0.000

RTI, respiratory tract infection.

could explain the considerably high rate and degree of negative $PaCO_2$-$ETCO_2$ differences.

As a consequence of our findings, we propose that arterial or capillary blood gas analysis should be performed after tracheal intubation and establishment of steady state lung ventilation before adapting ventilator settings [12, 13]. Once the individual difference has been determined, it should remain constant and allow for safely maintaining normocapnoea, provided no changes in the dead space/tidal volume ratio occurs as this was not tested in the present study [6]. Transcutaneous monitoring to estimate $PaCO_2$ may be an alternative option, however, this has its own practical, physiological and technical limitations and may be most advantageous only in the smallest patients [14]. Industrial partners will hopefully investigate the phenomenon of negative $PaCO_2$-$ETCO_2$ differences through large prospective studies that include wide respiratory parameters.

In conclusion, $ETCO_2$ monitoring in paediatric patients whose lungs are ventilated may paradoxically lead to overestimation of $ETCO_2$ ($ETCO_2 > PaCO_2$) with the risk of hypocarbia and related deleterious effects on cerebral circulation. We encourage prospective studies, initiated by industrial partners, to elucidate predictors so as to improve their equipment. Until then, arterial or capillary blood gas testing should be performed, even during routine paediatric anaesthesia, in order to avoid iatrogenic hypocapnoea and associated peri-operative central nervous system injury to children.

Acknowledgements

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