

## ORIGINAL ARTICLE OPEN ACCESS

# End-Tidal Carbon Dioxide Monitoring in Neonates Receiving Therapeutic Hypothermia for Hypoxic-Ischemic Encephalopathy

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**Keywords:** end-tidal carbon dioxide | hypoxic-ischemic encephalopathy | therapeutic hypothermia

## ABSTRACT

**Introduction:** Primary aim was to assess the agreement between end-tidal carbon dioxide (etCO<sub>2</sub>) monitoring and arterial, capillary and venous PCO<sub>2</sub> values in mechanically ventilated patients receiving therapeutic hypothermia (TH) for hypoxic-ischemic encephalopathy (HIE). Secondary, to assess the percentage of time spent in predefined PCO<sub>2</sub> ranges based on continuous etCO<sub>2</sub> monitoring.

**Methods:** In this prospective observational single center trial, infants with moderate-to-severe HIE receiving conventional ventilation with sidestream capnography were enrolled. Blood gas measurements were performed based on clinical indication. The mean of 12,000 etCO<sub>2</sub> values obtained over 10 min before each corresponding blood gas was used for analysis. The agreement between mean etCO<sub>2</sub> and temperature corrected and uncorrected PCO<sub>2</sub> at 37°C were analyzed using Bland-Altman (BA) plots.

**Results:** A total of 262 paired PCO<sub>2</sub> and etCO<sub>2</sub> values were analyzed from 35 patients. The bias between temperature corrected arterial PCO<sub>2</sub> and etCO<sub>2</sub> ( $n = 116$ ) was 1.87 mmHg (SD 5.54) with -8.99 and 12.73 limits of agreement; whereas the bias between capillary PCO<sub>2</sub> and etCO<sub>2</sub> ( $n = 132$ ) was 7.22 mmHg (SD 6.08). EtCO<sub>2</sub> underestimated PCO<sub>2</sub> of any source at 37°C. Excluding patients with lung diseases from BA analysis did not show improvement in the agreement. Infants spent median 23.9% [IQR 8.5; 36.7] of monitoring time in etCO<sub>2</sub> range < 35 mmHg and median 75.0% [IQR 61.1; 87.7] in etCO<sub>2</sub> range of 35–55 mmHg.

**Conclusions:** EtCO<sub>2</sub> monitoring may be a valuable addition to neurocritical care of infants with HIE as it showed a strong level of agreement with temperature corrected arterial PCO<sub>2</sub>.

## 1 | Introduction

To date only therapeutic hypothermia (TH) has been proven to reduce the risk of death and unfavorable neurological outcomes

in infants with moderate-severe hypoxic-ischemic encephalopathy (HIE), which is one of the leading causes of neonatal morbidity and mortality, affecting approximately 1–4 cases in 1000 live births in high-resource settings [1, 2].

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Despite the effective treatment, nearly 30-50% of the infants with moderate-to-severe HIE either die, or suffer from long-term motor and/or cognitive disabilities [3, 4]. Over the last decades several pharmacological agents such as melatonin or erythropoietin have been tested but failed to show additional neuroprotective effects when combined with TH for the treatment of HIE [4]. Therefore, the optimization of intensive care including respiratory support can play a defining role to improve the long-term neurological outcomes [5, 6].

Secondary analysis of the CoolCap and NICHD (National Institute of Child Health and Human Development) randomized controlled trials for TH [7, 8] and multiple retrospective cohort studies [9–13] demonstrated the association between ventilation and oxygenation and neurodevelopmental outcomes in infants with HIE. Both hyperoxia and hypocapnia have been shown to be detrimental to the already injured brain [8–12]. Even a brief period of hyperoxia can trigger oxidative stress leading to secondary injury after hypoxia-ischemia [14]. Hypocapnia may worsen brain injury via multiple mechanisms including hypoperfusion via cerebral vasoconstriction, pro-inflammatory response, and increased neuronal excitability that may trigger seizure activity further increasing oxygen demand [15–17].

Since there has been a consistent association between hypocapnia and adverse long-term neurodevelopmental outcome, close monitoring of CO<sub>2</sub> levels should be encouraged. The gold standard arterial blood gas sampling (PaCO<sub>2</sub>) does not allow continuous monitoring of PCO<sub>2</sub> and may result in unnecessary blood loss [18]. Transcutaneous carbon dioxide (tcPCO<sub>2</sub>) monitoring during therapeutic hypothermia was tested in small-scale retrospective studies demonstrating from modest to poor agreement between PaCO<sub>2</sub> and tcPCO<sub>2</sub> [19, 20]. Prospective evaluation of the feasibility of tcPCO<sub>2</sub> under TH is currently underway (NCT04603547). End-tidal CO<sub>2</sub> (etCO<sub>2</sub>) monitoring with microstream sampling technique resulting in minimal instrumental dead space is a feasible option to continuously monitor CO<sub>2</sub> exchange.

A good agreement was demonstrated between PaCO<sub>2</sub> and etCO<sub>2</sub> in mechanically ventilated infants from a heterogeneous population, including both term and preterm infants, using both side, - and mainstream capnography [18, 21, 22]. A recent retrospective chart review of 58 mechanically ventilated patients under TH showed a reliable correlation between temperature corrected PaCO<sub>2</sub> and etCO<sub>2</sub> [23]. Notably, this retrospective study is the only one to date that has evaluated the agreement between etCO<sub>2</sub> and PCO<sub>2</sub> specifically in HIE patients.

The primary aim of this prospective observational study was to evaluate the agreement between etCO<sub>2</sub> and arterial, capillary and venous PCO<sub>2</sub> values in mechanically ventilated patients with HIE receiving TH. Secondary aim was to assess the percentage of time spent in predefined PCO<sub>2</sub> ranges based on the continuous etCO<sub>2</sub> monitoring. We hypothesized that etCO<sub>2</sub> would have a clinically acceptable agreement with the gold-standard arterial PCO<sub>2</sub>. Additionally, we expected that continuous etCO<sub>2</sub> monitoring would reveal that patients spend a substantial proportion of time outside the predefined optimal

PCO<sub>2</sub> ranges, highlighting the potential value of real-time CO<sub>2</sub> monitoring.

## 2 | Methods

### 2.1 | Patient Selection

In this prospective observational single center trial, we enrolled infants born between 2020 December and 2022 March, treated with therapeutic hypothermia for moderate-to-severe HIE according to the criteria of the international TOBY trial (Total Body Hypothermia for Neonatal Encephalopathy Trial) [24] at the Division of Neonatology, Pediatric Center, Semmelweis University. Ethical permission for data collection and analysis was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (IV/6161-1/2020/EKU). Consent was waived as the study involved no additional interventions beyond standard care and relied on deidentified data.

From this patient pool, we included all infants receiving conventional mechanical ventilation with sidestream capnography monitoring. Continuous etCO<sub>2</sub> data was linked to time-corresponding blood gas PCO<sub>2</sub> levels. Exclusion criteria were (a) major birth defects, (b) patients on palliative care, (c) respiratory morbidities treated with high-frequency oscillatory ventilation (HFOV) and/or inhaled nitric-oxide therapy as an indicator of severe persistent pulmonary hypertension.

Thompson encephalopathy score was utilized to assess the severity of HIE. Systematic evaluation of brain magnetic resonance images (MRI) was carried out using the scoring system published by Weeke et al. [25] Bayley Scales of Infant Development 2nd and 3rd Editions (Bayley-2 and Bayley-3, respectively) was performed at 18–22 months of age by trained examiners to evaluate neurodevelopmental outcome [26, 27]. Adverse neurodevelopmental outcome was defined as a score of < 70 on either the Mental Development Index (MDI) or the Psychomotor Development Index (PDI) in case of application of the Bayley-2 test, and < 85 on the Cognitive Language Composite scale (CLC) or the Motor Composite scale (MC) of Bayley-3 test. Neurodevelopmental impairment cutoff values were defined based on the recommendations of Jary et al. [28].

### 2.2 | End Tidal CO<sub>2</sub> Data Retrieval and Blood Gas PCO<sub>2</sub> Measurements

Neonates receiving TH were sedated (10 µg/kg/h continuous morphine infusion) and mechanically ventilated as per local protocol during the observational trial period. The etCO<sub>2</sub> level was monitored via Capnostream 35 portable respiratory monitor (Medtronic Plc, Minneapolis, MN, USA), using sidestream end tidal capnography with microstream sampling line (FilterLine® H Set CO<sub>2</sub> Sampling Line, Covidien, Medtronic) during hypothermia and rewarming. EtCO<sub>2</sub> monitoring was recommended if available during TH as per unit policy. EtCO<sub>2</sub> were registered and downloaded at a 20/s sampling rate.

Blood gas PCO<sub>2</sub> levels were measured from arterial, capillary and venous blood samples collected as part of routine care,

based on decisions of the attending physicians. Physicians were not blinded for the etCO<sub>2</sub> measurements. Blood gas measurements were done on a GEM Premier 3500 (Werfen, Barcelona, Spain) point of care blood gas system. PCO<sub>2</sub> levels were corrected for rectal temperature measured at the time of sample collection. The blood gas system generates both temperature-corrected PCO<sub>2</sub> values based on the entered rectal temperature, and uncorrected PCO<sub>2</sub> values, standardized to 37°C.

For every blood gas measurement, a corresponding time-matched etCO<sub>2</sub> values were linked using the following method: to create a representative etCO<sub>2</sub> value, we calculated the mean of 12,000 etCO<sub>2</sub> readings obtained over a 10 min period, starting 12 min before and ending 2 min before each blood gas measurement. We omitted the last 2 min before the gas analysis because the blood had already been collected and placed in the analyzer during this period. This approach was based on previously published data from Belteki et al. [29] Data points of etCO<sub>2</sub> were omitted before analysis if were < 20 mmHg or > 100 mmHg due to limited accuracy in extreme ranges.

## 2.3 | Outcomes

Primary outcome was the agreement between etCO<sub>2</sub> and temperature corrected and uncorrected PCO<sub>2</sub> at 37 °C from arterial, capillary and venous blood gas samples in infants with HIE during TH. In a subgroup analysis, infants with respiratory morbidities were excluded to assess the level of agreement in infants without lung pathology. Respiratory morbidities were defined as the following: meconium-aspiration syndrome (MAS) or respiratory distress syndrome (RDS) confirmed by chest X-ray and requiring surfactant replacement therapy or pneumothorax (PTX) requiring chest tube insertion.

Secondary outcome was the time spent in predefined etCO<sub>2</sub> ranges, namely hypocapnia (etCO<sub>2</sub> < 35 mmHg), normocapnia (35–55 mmHg) and hypercapnia (> 55 mmHg) in each patient.

## 2.4 | Statistical Analysis

Categorical variables are reported as absolute numbers and percentages, while continuous variables as median and 25th to 75th percentiles representing interquartile range [IQR].

Time stamped capnography measurements were downloaded from the respiratory monitor as comma separated value (.csv) text files. Blood gas measurements were entered manually into a research database (iSORT, Semmelweis University). The agreement between etCO<sub>2</sub> and temperature corrected and uncorrected PCO<sub>2</sub> at 37 °C from arterial, capillary and venous sources were analyzed. To assess agreement between the two measurement methods, a Bland-Altman (BA) analysis was planned. Previously published data [23] indicated that a median difference between arterial and end-tidal PaCO<sub>2</sub> was 3 units with an interquartile range of 0 to 7, thus the standard deviation of the differences was estimated at approximately 5.2. Assuming a desired 95% confidence interval width of ±3 units for the limits of agreement, the required minimum sample size was

calculated to be 35 subjects. We included multiple measurements from each subject to account for possible within-subject variability. Average difference (bias), standard deviation (SD) of the bias and 95% of limits of agreement were calculated.

The percentage of time spent in the predefined etCO<sub>2</sub> ranges was calculated by dividing the time spent within each range by the total duration of monitoring. The ranges were defined as follows: hypocapnia (etCO<sub>2</sub> < 35 mmHg), normocapnia (35–55 mmHg) and hypercapnia (> 55 mmHg). The Friedman test was used to compare the differences in the percentage of time spent in the three CO<sub>2</sub> ranges (hypocapnia, normocapnia, and hypercapnia). Dunn's test was then performed for pairwise multiple comparisons of the ranked data. Data were analyzed using IBM SPSS Statistics software version 23.0.0.0 (IBM Corporation, Armonk, NY, USA), GraphPad Prism version 9 for macOS (Boston, MA, USA), as well as R Statistical software 4.0.5. (R Core Team, Vienna, Austria).

## 3 | Results

Sixty-seven patients received TH over the 15 months study period. Out of the 67 patients 7 were ventilated with HFOV, 2 received inhaled nitric oxide treatment on conventional ventilation for severe pulmonary hypertension, 1 died within 12 h of life due to severe HIE associated with multi organ failure, the remaining 22 cases did not have prospectively recorded etCO<sub>2</sub> data. Altogether 35 patients on conventional ventilation with available etCO<sub>2</sub> recordings and corresponding blood gases were included in the analysis. Patients demographics, clinical and outcome data including MRI and Bayley test results are summarized in Table 1.

A total of 262 paired etCO<sub>2</sub> and PCO<sub>2</sub> values corrected for the rectal temperature and also analyzed at standard 37°C were evaluated including 116 arterial samples from 18 patients, 132 capillary samples from 29 patients, and 14 venous samples from 8 patients.

The etCO<sub>2</sub> monitoring started at median 10.9 [6.8; 20.6] hours of age and the length of observation was median 71.0 [62.5; 78.4] hours corresponding to the time of hypothermia and rewarming. No etCO<sub>2</sub> readings exceeded 100 mmHg, and only 0.9% of all etCO<sub>2</sub> data points (66,531 out of 7,367,926) were below 20 mmHg; these low values were excluded before analysis.

### 3.1 | Agreement Between PCO<sub>2</sub> and etCO<sub>2</sub> Values

The average difference (bias) between the temperature corrected arterial PaCO<sub>2</sub> and etCO<sub>2</sub> was 1.87 mmHg (SD 5.54) with -8.99 and 12.73 limits of agreement on 116 corresponding data points. The bias between the capillary PCO<sub>2</sub> and etCO<sub>2</sub> was 7.22 mmHg (SD 6.08) with -4.70 and 19.14 limits of agreement on 132 corresponding data points. Similarly, the bias between venous PCO<sub>2</sub> and etCO<sub>2</sub> was 8.07 mmHg with -2.53 and 18.67 limits of agreement, however the number of corresponding data points were low (n = 14) (Table 2). Figure 1 represents BA plots

**TABLE 1** | Baseline characteristics, clinical and outcome data.

Variable	Study cohort n = 35
Gestational age (week)	39 [37; 40]
Birth weight (g)	3060 [2490; 3500]
Apgar 1 min	2 [1; 3]
Apgar 5 min	5 [3; 6]
Apgar 10 min	6 [5; 7]
First postnatal pH	7.0 [6.9; 7.2]
First postnatal PCO <sub>2</sub> (mmHg)	44 [31; 70]
First postnatal base deficit (mmol/L)	4.7 [7.1; 2.1]
First postnatal lactate (mmol/L)	13 [11; 15]
Age at onset of hypothermia treatment (h)	2.5 [1.2; 3.6]
Thompson encephalopathy score <sup>a</sup>	7 [5; 12]
Length of invasive ventilation (days)	5 [4; 6]
<b>Respiratory morbidities<sup>b</sup></b>	
Respiratory distress syndrome, n (%)	4 (11.4%)
Meconium aspiration syndrome, n (%)	4 (11.4%)
Pneumothorax, n (%)	1 (2.9%)
Surfactant administration, n (%)	8 (22.9%)
<b>Short- and long-term outcomes</b>	
Length of NICU stay (days)	10.8 [8.7; 9.7]
MRI assessment <sup>c</sup>	
Age at MRI (day of life)	4.7 [3.5; 6.2]
Any brain injury, n (%)	30 (85.7%)
Grey matter injury, n (%)	16 (45.7%)
White matter injury, n (%)	30 (85.7%)
Cerebellum injury, n (%)	7 (20.0%)
IVH, n (%)	4 (11.4%)
SDH, n (%)	17 (48.6%)
Total score including MRS abnormalities	4 [1; 18]
Neurodevelopmental outcomes	
Lost to follow up, n (%)	3/35 (8.6%)
Severe neurodevelopmental delay <sup>d</sup> , n (%)	7/35 (20.0%)
Death during hospital stay <sup>d</sup> , n (%)	1/35 (2.8%)
Bayley test available <sup>e</sup> , n (%)	24/35 (68.6%)
Age at Bayley test (months)	19 [18; 25]
Adverse outcome on Bayley <sup>e</sup> , n (%)	0/24 (0%)

Note: Data are reported as median [IQR] for continuous variables and counts (percentages) for categorical variables.

Abbreviations: IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NICU, neonatal intensive care unit; SDH, subdural hematoma.

<sup>a</sup>Thompson score was available in 20 (56%) infants.

<sup>b</sup>Meconium-aspiration syndrome (MAS) and respiratory distress syndrome (RDS) confirmed by chest X-ray and received surfactant replacement therapy. Pneumothorax (PTX) requiring chest tube insertion.

<sup>c</sup>MRIs were assessed using scoring system of Weeke et al.

<sup>d</sup>Eight parents and/or health care providers of the infant were contacted via phone; seven of them reported severe neurodevelopmental delay requiring extensive neurodevelopmental treatment, one of them with severe HIE died subsequently in another hospital.

<sup>e</sup>Bayley test was available in 24 (68.6%) infants. Three infants were assessed by Bayley III test, otherwise Bayley II test was used. Adverse neurodevelopmental outcome defined as a score of < 70 on either the Mental Development Index or the Psychomotor Development Index in case of application of the Bayley-2 test, and < 85 on the Cognitive Language Composite scale or the Motor Composite scale of Bayley-3 test.

of temperature corrected arterial and capillary PCO<sub>2</sub> and etCO<sub>2</sub> values. Visual inspection of the BA plots could not identify a difference in precision in lower versus higher PCO<sub>2</sub> ranges, suggesting that the etCO<sub>2</sub> - PCO<sub>2</sub> agreement is similar in both hypocapnia and hypercapnia.

Compared to the temperature corrected blood gas values poor agreement found between uncorrected PCO<sub>2</sub> values analyzed at 37°C and corresponding etCO<sub>2</sub> measurements. Agreement between uncorrected blood gas values and etCO<sub>2</sub> data is summarized in Table 2.

Out of 35 infants, 4 (11.4%) presented with RDS, another 4 (11.4%) had MAS, all of them received surfactant replacement therapy. One patient had pneumothorax requiring chest tube insertion. Nine patients with significant pulmonary morbidities were excluded from BA analysis.

Excluding patients with respiratory morbidities from the Bland-Altman analysis did not improve the agreement between PaCO<sub>2</sub> and etCO<sub>2</sub> (n = 96, bias (SD): 1.37 (5.79); 95% limits of agreement: -9.99; 12.72) and capillary PCO<sub>2</sub> and etCO<sub>2</sub> (n = 81, bias (SD): 7.84 (6.53); 95% limits of agreement: -4.95; 20.63) (Table 2). Venous samples due to low number of data points (n = 3) were insufficient for analysis.

### 3.2 | Time Spent in Hypocapnia, Normocapnia and Hypercapnia Based on etCO<sub>2</sub> Monitoring

Infants spent median 23.9% [IQR 8.5; 36.7] of monitoring time in hypocapnia (etCO<sub>2</sub> range < 35 mmHg). Percentage of time spent in normocapnia (35–55 mmHg) was median 75.0% [IQR 61.1; 87.7]. Infants spent less than 1% [IQR 0.0; 0.1] in hypercapnia based on continuous etCO<sub>2</sub> measurements. Friedman test revealed that patients spent significantly less time in hypercapnia than in normocapnia or hypocapnia (*p*< 0.0001). Significant difference was found also in time spent in normocapnia and hypocapnia (*p* = 0.0257) (Figure 2).

## 4 | Discussion

We found a strong level of agreement between temperature corrected arterial PCO<sub>2</sub>, the gold standard measurement, and 10-min averaged high-frequency etCO<sub>2</sub> values in patients with HIE treated with TH. The agreement was modest between the temperature corrected capillary and venous PCO<sub>2</sub> and etCO<sub>2</sub> data. End-tidal CO<sub>2</sub> consistently underestimated PCO<sub>2</sub> from any source at 37°C but the level of bias was clinically unacceptable for venous and capillary samples. Excluding infants with pulmonary morbidities did not improve the level of agreement.

Several studies have assessed the accuracy of etCO<sub>2</sub> monitoring, primarily in preterm neonates, yielding controversial results and emphasizing the impact of underlying lung diseases [22, 30–32]. However, Kugelman et al. proved in a randomized, controlled multicenter study that continuous distal etCO<sub>2</sub> monitoring reduced the rate of intraventricular hemorrhage and periventricular leukomalacia in a group of patients where

**TABLE 2** | Agreement between temperature corrected and uncorrected arterial, capillary and venous PCO<sub>2</sub> and etCO<sub>2</sub> values in full cohort and in infants without pulmonary morbidities.

<b>Total patient population (n = 35)</b>				
<b>Agreement between temperature corrected PCO<sub>2</sub> and etCO<sub>2</sub> values</b>				
	All	Arterial	Capillary	Venous
# of corresponding values	262	116	132	14
Bias	4.90	1.87	7.22	8.07
SD of bias	6.39	5.54	6.08	5.41
95% Limits of Agreement				
From	-7.63	-8.99	-4.70	-2.53
To	17.43	12.73	19.14	18.67
<b>Agreement between PCO<sub>2</sub> at 37°C and etCO<sub>2</sub> values</b>				
Bias	12.18	8.64	14.88	16.04
SD of bias	7.59	6.48	7.39	5.61
95% Limits of Agreement				
From	-2.69	-4.07	0.40	5.05
To	27.04	21.35	29.35	27.03
<b>Infants without pulmonary morbidities (n = 26)</b>				
<b>Agreement between temperature corrected PCO<sub>2</sub> and etCO<sub>2</sub> values</b>				
# of corresponding values	180	96	81	3
Bias	4.31	1.37	7.84	n/a
SD of bias	6.91	5.79	6.53	n/a
95% Limits of Agreement				
From	-9.23	-9.99	-4.95	n/a
To	17.85	12.72	20.63	n/a
<b>Agreement between PCO<sub>2</sub> at 37°C and etCO<sub>2</sub> values</b>				
Bias	11.53	8.03	15.70	n/a
SD of bias	8.26	6.80	7.97	n/a
95% Limits of Agreement				
From	-4.65	-5.30	0.08	n/a
To	27.72	21.37	31.33	n/a

Note: The agreement between etCO<sub>2</sub> and temperature corrected and uncorrected at 37°C arterial, capillary and venous PCO<sub>2</sub> values were analyzed, using Bland-Altman (BA) plots. Average difference (bias), standard deviation (SD) of the bias and 95% of limits of agreement were defined.

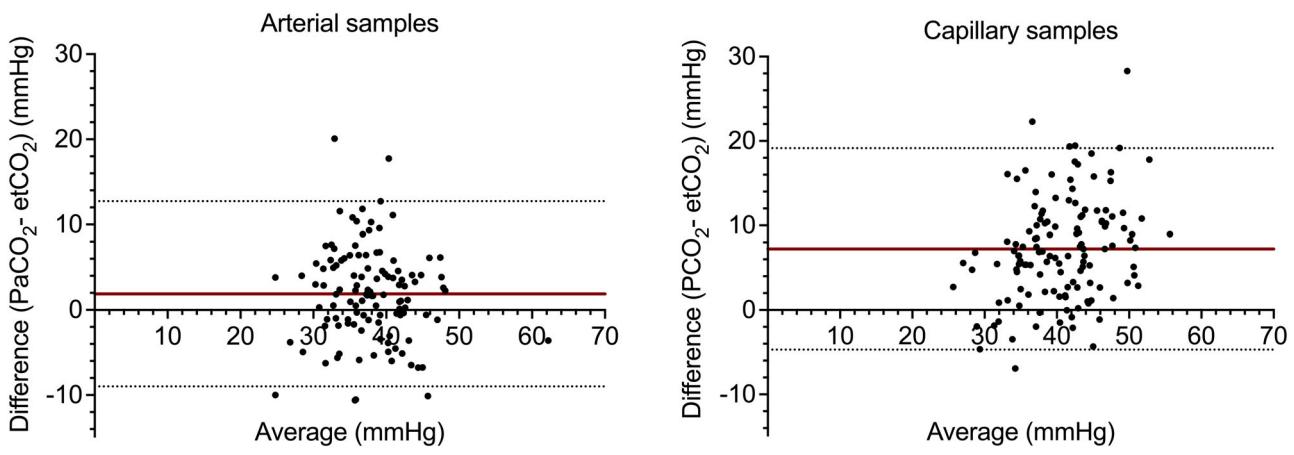
etCO<sub>2</sub> monitor was not masked and available for patient care comparing to a masked group [33]. A similar randomized controlled study is still awaited in infants with HIE with respect to long term outcomes.

To date, this is the second study—and the only prospective one—aimed at assessing the accuracy of etCO<sub>2</sub> measurement in infants undergoing therapeutic hypothermia. Similarly, to the present study Afzal et al. reported marginally lower etCO<sub>2</sub> compared to PaCO<sub>2</sub> (median difference of 3 mmHg; IQR, 0–7) based on 857 arterial samples from 58 patients. However, the method of processing etCO<sub>2</sub> data and whether side or mainstream capnography was used remained unclear in their paper [23].

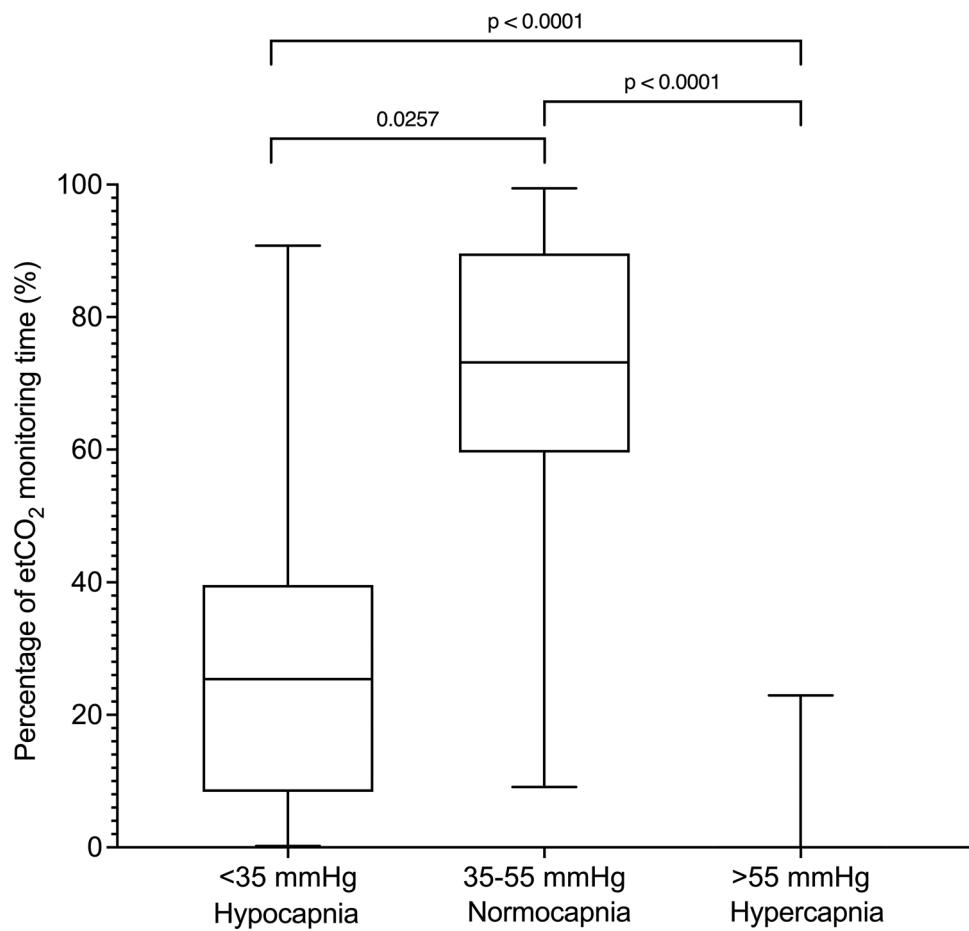
We propose that the computationally analyzed and averaged etCO<sub>2</sub> measurements, recorded 10 min before blood gas

sampling are more representative than any cross-sectional, single etCO<sub>2</sub> value, yielding a more reliable data agreement analysis.

It is well known that ventilation-perfusion mismatch, high respiratory rate, and the ratio of physiological dead space to tidal volume secondary lung disease negatively influence the correlation between etCO<sub>2</sub> and PCO<sub>2</sub> [18, 22, 31, 34]. Two research groups showed that etCO<sub>2</sub> correlated better with PaCO<sub>2</sub> in infants with less severe lung disease defined as the ratio of physiological dead space to tidal volume. Physiological dead space includes anatomical and alveolar dead space which increases with the disease severity [22, 31]. Of note, etCO<sub>2</sub> tends to underestimate PaCO<sub>2</sub> even in healthy lungs due to the contribution of physiological dead space, where alveolar CO<sub>2</sub> is diluted by CO<sub>2</sub>-free gas from the dead space [18].



**FIGURE 1** | Bland-Altman plots to assess the agreement between end-tidal CO<sub>2</sub> and arterial and capillary PCO<sub>2</sub>. For every blood gas measurement, the mean of 12,000 etCO<sub>2</sub> readings obtained over a 10 min period, starting 12 min before and ending 2 min before each blood gas measurement was calculated. To assess agreement between the two measurement methods, a Bland-Altman analysis was performed. See Table 2 for details.



**FIGURE 2** | Box plots of time spent in hypocapnia, normocapnia and hypercapnia based on etCO<sub>2</sub> monitoring. The ranges were defined as hypocapnia (etCO<sub>2</sub> < 35 mmHg), normocapnia (35–55 mmHg) and hypercapnia (> 55 mmHg). The Friedman test was used to compare the differences in the percentage of time spent in the three CO<sub>2</sub> ranges (hypocapnia, normocapnia, and hypercapnia). Dunn's test was then performed for pairwise multiple comparisons of the ranked data. See text for details.

We need to highlight that the correlation coefficient improved significantly more in very low birth weight infants (VLBW) comparing to non-VLBW infants utilizing the above detailed approach for defining lung disease [31]. In the present study excluding infants

with lung disease did not result in any improvement in the level of agreement. Of note, we did not use objective measures to define the severity of lung injury. Furthermore, the effect of physiological dead space may be more profound in preterm infants [31].

The partial pressures of gases and blood pH are temperature-dependent. At lower temperatures, gas solubility in plasma increases, leading to lower measured PO<sub>2</sub> and PCO<sub>2</sub>, and a higher pH.

To address this problem during intensive care, two acid-base management strategies, alpha-stat and pH-stat are available. Currently, it is unclear if alpha-stat or pH-stat management strategies should be preferred in neonates under hypothermia treatment. In pH-stat method PCO<sub>2</sub>, PO<sub>2</sub> and pH are corrected for the actual body temperature representing the true acid-base status of the patients; whereas alpha-stat management can overestimate PCO<sub>2</sub> and PO<sub>2</sub> and underestimate pH if partial tension of gases is analyzed at 37°C [35, 36]. Although further investigation is needed to answer which management is superior over the other, pediatric data and recommendation from CoolCap and NICHD hypothermia trial suggested to use temperature correction (pH-stat) [35, 37]. Based on our findings, etCO<sub>2</sub> estimates temperature corrected PCO<sub>2</sub> values considerably better than uncorrected PCO<sub>2</sub> values; further supporting the pH-stat management approach.

The secondary aim of our study was to determine the time spent in predefined PCO<sub>2</sub> ranges based on continuous etCO<sub>2</sub> measurements. It is well established that hypocapnia is common in the early hours of life, often resulting from compensatory hyperventilation due to metabolic acidosis and impaired cerebral energy metabolism. Additionally, therapeutic hypothermia further reduces metabolic rate, thereby decreasing CO<sub>2</sub> production and the amount of CO<sub>2</sub> available for exhalation [6]. Previous studies showed that hypocapnia occurred at least once in 57-89% of infants with HIE within the first few hours of life [7, 10, 38]. Furthermore, infants spent a median 15% of their first 24 h in hypocapnia defined as a PCO<sub>2</sub> level of ≤ 35 mmHg based on linear interpolation between blood gas sampling times [10]. Currently, we showed that patients spent median 24% of etCO<sub>2</sub> monitoring time in hypocapnia (< 35 mmHg) and median 75% of their time between 35 and 55 mmHg. It remains to be established whether continuously monitored etCO<sub>2</sub> values have any predictive value with respect to neurodevelopmental outcome. However, it may be inferred from our present data, that etCO<sub>2</sub> correlates more closely to actual arterial PCO<sub>2</sub> than capillary samples, thus the severity and duration of hypocapnia may be underestimated notoriously based on capillary blood gas sampling.

Some limitations of the study should be acknowledged. First, lung diseases were classified based on clinical diagnosis, without objective measures to assess severity. Second, the predefined normocapnia range of 35-55 mmHg is broader than the physiological standard of 35-45 mmHg. However, Wong et al. reported that PCO<sub>2</sub> levels between 5 and 7 kPa (37.5-52.5 mmHg) may be safe for neonates receiving ventilatory support [39]. Additionally, the percentage of leak around the uncuffed endotracheal tube was not recorded for analysis.

One key strength of our analysis is the high-frequency sampling rate of the etCO<sub>2</sub> monitor, allowing us to analyze 12,000 data points, rather than relying on a single reading of a dynamically changing value. Furthermore, arterial, capillary, and venous data were analyzed, recognizing that not all infants with HIE

have indwelling arterial catheters for blood draws. In addition, we suggest that the noninvasive method of PCO<sub>2</sub> monitoring may reduce blood loss in critically ill infants and lower the risk of infections.

## 5 | Conclusion

There was a strong agreement between temperature-corrected arterial PaCO<sub>2</sub> and etCO<sub>2</sub> values in infants with moderate-to-severe HIE. Given that nearly 50% of patients undergoing therapeutic hypothermia require mechanical ventilation, etCO<sub>2</sub> monitoring may be a valuable addition to respiratory and neurocritical care in this population [10, 40, 41]. Further studies are needed to evaluate whether end-tidal etCO<sub>2</sub> monitoring can mitigate extreme CO<sub>2</sub> levels and thereby improve neurodevelopmental outcomes in HIE.

## Author Contributions

**Mate Detar:** writing – original draft, project administration, data curation, investigation. **Barbara Szasz:** writing – original draft, writing – review and editing, data curation, visualization. **Hajnalka Barta:** writing – original draft, writing – review and editing, project administration. **Miklos Szabo:** supervision, writing – review and editing, resources. **Agnes Jermendy:** writing – review and editing, supervision, resources. **Eniko Szakmar:** writing – original draft, writing – review and editing, data curation, supervision, resources, visualization, methodology, conceptualization.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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