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CLINICAL RESEARCH ARTICLE

Transcutaneous carbon dioxide monitoring during therapeutic hypothermia for neonatal encephalopathy

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BACKGROUND: In neonates with post-asphyxial neonatal encephalopathy, further neuronal damage is prevented with therapeutic hypothermia (TH). In addition, fluctuations in carbon dioxide levels have been associated with poor neurodevelopmental outcome, demanding close monitoring. This study investigated the accuracy and clinical value of transcutaneous carbon dioxide ($tcPCO_2$) monitoring during TH.

METHODS: In this retrospective cohort study in neonates, agreement between arterial carbon dioxide ($PaCO_2$) values and $tcPCO_2$ measurements during TH was determined. $TcPCO_2$ levels during the first 24 h of hypothermia were tested for an association with ischemic brain injury on magnetic resonance imaging (MRI).

RESULTS: Thirty-four neonates were included. Agreement (bias (95% limits of agreement)) between $tcPCO_2$ and $PaCO_2$ levels was 3.9 (−12.4–20.2) mm Hg. No relation was found between the body temperature and $tcPCO_2$ levels. $TcPCO_2$ levels differed significantly between patients with considerable and minimal damage on MRI; after 6 h ($P = 0.02$) and 9 h ($P = 0.04$).

CONCLUSIONS: Although $tcPCO_2$ provided a limited estimation of $PaCO_2$, it can be used for trend monitoring during TH. $TcPCO_2$ levels after birth could provide an early indicator of ischemic brain injury. This relation should be investigated in large prospective studies, in which adjustments for confounders can be made.

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IMPACT:

- Transcutaneous carbon dioxide measurements during therapeutic hypothermia in neonates show limited accuracy similar to measurements reported in normothermic neonates and can be used for trend monitoring.
- Low transcutaneous carbon dioxide levels during the first 24 h were associated with considerable ischemic brain injury on MRI.
- The value of transcutaneous carbon dioxide measurements during the first 24 h as an indicator of considerable ischemic brain injury on MRI should be investigated in future studies, adjusting for confounders.
- Transcutaneous oxygen measurements during therapeutic hypothermia showed an inaccuracy that could not be related to a low body temperature.

INTRODUCTION

Perinatal asphyxia is defined as the occurrence of a hypoxic-ischemic event shortly before or during birth. The brain is the organ most prone to damage in these events, resulting in neonatal encephalopathy (NE). It has been known for some time that therapeutic hypothermia (TH) reduces mortality and extreme neurodevelopmental disability in asphyxiated term neonates with NE.[1,2] This reduction is achieved by inducing TH before the onset of the second phase in which reperfusion injury occurs from 6 h after birth.[3] Because of its neuroprotective effect, TH has been implemented as the standard of care treatment in neonates with NE after perinatal asphyxia.

TH affects tissue metabolism by reducing tissue carbon dioxide (CO_2) production and oxygen (O_2) consumption.[4] As a result, the required intensity of ventilation and oxygenation is decreased in comparison to normothermic neonates, demanding strategies tailored to TH patients. The arterial partial pressure of carbon dioxide ($PaCO_2$) plays an important role in the autoregulation of cerebral blood flow, causing cerebral vasoconstriction during hypocapnia.[5] In addition, fluctuations in $PaCO_2$ levels within the 72 h cooling period are associated with poor neurodevelopmental outcome.[6–9] Maintaining CO_2 and O_2 levels within the physiological range could aid in the prevention of further neuronal damage.[9]

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Continuous monitoring of CO_2 levels and O_2 levels in blood is recommended during TH, yet is often inaccurate. Underestimation of end-tidal CO_2 levels in neonates has frequently been reported.[10–15] Pulse oximetry values correspond to lower arterial partial pressures of oxygen (PaO_2) due to the effect of TH on the oxygen dissociation curve.[16] Intermittent blood gas analysis is currently the only reliable method for adjusting ventilation during TH.

Continuous transcutaneous monitoring of CO_2 is frequently used in neonatal care. The accuracy of transcutaneous blood gas monitoring has been investigated in various studies, showing an inaccuracy when compared to arterial blood gases, yet emphasizing the added-value of continuous CO_2 monitoring in preterm infants.[17,18] The accuracy and value during TH have never been investigated. This technology arterializes the skin microcirculation through local heating, increasing CO_2 and O_2 diffusion to approximate arterial values at the skin surface. However, during TH blood flow in the peripheral microcirculation is decreased.[19,20] It remains unclear whether sufficient arterialization can be achieved for valid measurements. This study aims to determine the accuracy of transcutaneous CO_2 monitoring and the effect of body temperature changes on measurements in neonates during TH. In addition, this study investigates whether transcutaneously monitored hypocapnia within the first 24 h of TH is associated with post-TH brain injury on magnetic resonance imaging (MRI). Secondary aims are to investigate the agreement of transcutaneous O_2 monitoring and the relation between the body temperature and transcutaneous O_2 monitoring.

MATERIALS AND METHODS

Population

Neonates with NE, admitted to a level III Neonatal Intensive Care Unit at Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands, between October 2015 and December 2019, were eligible for inclusion in this retrospective cohort study. In the first half of the study period, transcutaneous blood gas monitoring during TH was started on indication of the attending neonatologist. During the second half of the study period transcutaneous CO_2 monitoring was added to the department standard care protocol for CO_2 monitoring of neonates receiving invasive ventilation during TH. Neonates were included when treated with TH and simultaneously monitored with a body temperature sensor and a transcutaneous blood gas sensor. The study period was defined as the start of TH until 24 h after warming to a body temperature of 36.5 °C. The study protocol was reviewed and a waiver of approval (MEC-2018-1682) was provided by the medical ethics committee of Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands, in accordance with the Research Involving Human Subjects Act (WMO).

Definitions

Perinatal asphyxia was defined as the occurrence of at least three of the following six criteria: a 5 min Apgar ≤5; resuscitation; the need for mechanical ventilation after birth during 10 min or longer; pH <7.0; BE < −16 mmol/l or lactate >10.0 mmol/l, from either the umbilical cord or arterial, venous or capillary blood within 1 h after birth.

NE was defined as the presence of one or more of the following: a Thompson score higher than 7 at 1 h after birth and/or an aEEG pattern with a discontinuous normal voltage with a lower limit of 5 μV, burst suppression, continuous low voltage, flat trace or seizures.[21]

Therapeutic hypothermia

The indication for TH was based on the national recommendation with the following criteria: postnatal age of <6 h, gestational age of 36 0/7 weeks or older, presence of perinatal asphyxia and presence of NE. Contraindications were birth weight <1800 grams; postpartum age ≥6 h and gestational age <36 weeks. Neonates were actively whole-body cooled to a temperature of 33.5 °C for a period of 72 h using a CritiCool™ device (Belmont Instrument LLC, Billarica, MA, United States). After this cooling period, the body temperature was increased stepwise by 0.2 °C every 30 min until a temperature of 36.5 °C was reached. This body temperature was actively maintained for 24 h following the warming procedure.

As standard of care, ischemic brain injury was diagnosed using MRI between day 4 and day 8 after birth using T1, T2 and diffusion-weighted sequences. For this study, all MRIs were scored by a pediatric radiologist who was blinded to other study parameters. This MRI scoring system assesses brain injury in the first week of life in the deep gray matter, white matter or cortex, cerebellum and includes additional abnormalities.[22]

Respiratory monitoring

Target ranges of blood gas levels during TH, corrected to a temperature of 37.0 °C, were 45–58 mm Hg for $PaCO_2$, 60–100 mm Hg for PaO_2. Blood gas samples were analyzed at a temperature of 37.0 °C (ABL-800, Radiometer Medical ApS, Denmark), corrected for the input body temperature. The arterial O_2 saturation target was >93%. According to local protocol, transcutaneous sensors were heated to 42 or 43 °C (OxiVenT™ Sensor with software versions 01.57–01.58 and Sentec Digital Monitor with software versions 08.00.0–08.02.1 (Sentec Monitoring Board) and 06.00.00–06.02.00 (Multi Parameter Board), Sentec AG, Therwil, Switzerland). Sensors were calibrated every 3 h. When the site time elapsed, the sensor temperature was lowered automatically to 39 °C, awaiting sensor calibration. Transcutaneous blood gas values were also corrected to a temperature of 37 °C. Heating power was also included, indicating the amount of power (mW) needed to heat the sensor and maintain the set temperature.

Data collection

Patient characteristics were collected from the electronic patient information systems (PDMS, Picis Clinical Solutions, Wakefield, U.S.A; Hix, ChipSoft B.V., Amsterdam, The Netherlands). These included parameters related to perinatal asphyxia, the indication for TH, patient outcome and laboratory parameters sampled during the study period. Transcutaneous carbon dioxide ($tcPCO_2$) levels, transcutaneous oxygen ($tcPO_2$) levels and heating power values were logged at a 1 Hz rate (Raspberry Pi 2 or 3 model B, Raspberry Pi Foundation, U.K.). Body temperature and arterial pressures (1 Hz rate) (Dräger M540, Drägerwerk AG & Co. KGaA, Lübeck, Germany) were logged, as well as ventilation parameters, fraction of inspired oxygen (FiO_2) and the temperature setting of the CritiCool device.

Subgroup selection

For the determination of accuracy of transcutaneous blood gas measurements during TH, agreement with arterial blood gas samples was analyzed on a subgroup of neonates with an indwelling arterial catheter. The exact moment of arterial blood gas sampling was determined as the pressure peak following closure of the arterial line for blood withdrawal.[23] A subset, including neonates monitored during the warming procedure, was used to assess the effect of body temperature on transcutaneous blood gas monitoring. Another subset of the first 24 h of TH was used to evaluate the association between $tcPCO_2$ levels and ischemic brain injury on MRI. Patients were divided into two groups: with considerable and minimal ischemic brain injury on MRI. Injury in at least both the deep gray matter and white matter/cortex or cerebellum subscore was classified as considerable injury. All other patients were included in the minimal injury group.

Statistical analyses

Baseline characteristics are presented as median (interquartile range (IQR)) for continuous data or numbers (%) for categorical data. The Mann–Whitney U test and the Fisher's exact test, for continuous and categorical variables, were used to test significance between groups. Significance was set at a two-sided P value < 0.05. Missing data were excluded from analyses, as they were assumed to be missing completely at random.

To determine measurement accuracy of transcutaneous monitoring during TH, a Bland–Altman analysis was performed on all matched blood gas samples (A–B plot), correcting for multiple measurements per patient.[24] Data are presented as bias with 95% limits of agreement (LoA). To account for potential heteroscedasticity in the matched blood samples (a skewed relation between the difference between transcutaneous and arterial values and the mean value), accuracy was determined according to the method of Ludbrook,[25] with 95% confidence limits as presented by Bland.[26] Due to multiple measurements per patient, generalized least squares were modelled instead of ordinary least squares.

Median values were calculated over every half hour for all continuous parameters. Marginal models were fitted to analyze the temperature effect of TH on $tcPCO_2$, $tcPO_2$ and heating power using the nlme package for *R*.[27] When $tcPCO_2$ or $tcPO_2$ was the independent variable, body temperature and FiO_2 were included as fixed effects, in which nonlinearity was evaluated using natural splines. The FiO_2 was excluded as fixed effect when heating power was modelled as independent variable. Correlation between measurements was adjusted for in these models.

Median $tcPCO_2$ levels were calculated per hour to test for the consequences of asphyxia-induced hyperventilation. In addition, the standard deviations of $tcPCO_2$ levels were calculated per patient during these one-hour intervals to investigate fluctuations in $tcPCO_2$ levels during these intervals. $TcPCO_2$ values from patients with considerable and minimal ischemic brain injury on MRI after TH were compared at three-hour intervals during the first 24 h after start of TH using the Wilcoxon rank sum test.

Analyses were performed in *R* version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study cohort

A total of 38 neonates had continuous transcutaneous blood gas monitoring during TH. Due to incomplete data recordings four neonates were excluded from analyses, 34 neonates were included (Fig. 1). Baseline characteristics are presented in Table 1. The study cohort had an admission survival of ~85%. All neonates were invasively ventilated during the entire study period. The median (range) length of transcutaneous blood gas monitoring during the 72 h TH period was 37 (2–69) h. Noticeable was the extended time needed for stabilization of both $tcPCO_2$ and $tcPO_2$ measurements, which was excluded from every measurement interval during TH. A total of 364 measurements were started during the cooling period of which 219 (60.2%) continued a slow stabilization slope after the monitor determined the measurement to be stable. No skin burns were reported. Subgroup patient characteristics are presented in Online Supplemental Table 1.

Agreement of transcutaneous and arterial blood gas values

Out of the 34 included neonates, 26 had an indwelling arterial catheter and were selected for agreement analysis. The median $PaCO_2$ and PaO_2 levels during the 72 h of TH were 41.3 (36.0–47.3) mm Hg and 86.7 (61.7–117.8) mm Hg, respectively. The bias (95% LoA) between $tcPCO_2$ with $PaCO_2$ data pairs ($n = 145$) was 3.9 (−12.4–20.2 mm Hg (Fig. 2). Accuracy analysis of $tcPO_2$ and PaO_2 matched data pairs ($n = 144$) showed widening of the LoA and an increasing bias with an increase in mean O_2 levels (Online Supplemental Fig. 1).

Temperature effect on transcutaneous blood gas monitoring

To investigate the temperature effect of TH on the microcirculation, marginal models were fitted on a subgroup of 18 neonates during the warming period (Online Supplemental Table 1). Figure 3 illustrates the prediction of $tcPCO_2$ and heating power with the corresponding 95% confidence intervals with increasing temperature. $TcPCO_2$ changed minimally when the body temperature increased ($P = 0.58$) (Fig. 3a). FiO_2 was included as a fixed effect as it had a linear relation with $tcPCO_2$ (Online Supplemental Fig. 2). Body temperature was nonlinearly related to changes in heating power ($P < 0.001$) (Fig. 3b). No significant relation was found between $tcPO_2$ levels and the body temperature ($P = 0.85$) (Online Supplemental Table 1).

Transcutaneous carbon dioxide trends and MRI brain damage scoring

During the first 24 h of TH, 25 patients had transcutaneous blood gas monitoring, of which seven patients showed considerable ischemic brain injury on MRI with a median (range) total score of 21 (12–41), compared to patients with minimal to no brain injury on MRI with a median (range) total score of 0.5 (0–4) ($P < 0.001$) (Fig. 4a). No ischemic injury in the deep gray matter subscore was reported for the minimal to no brain injury on MRI group. No differences were seen in the baseline characteristics between these two groups (Table 2). As shown in Fig. 4b, $tcPCO_2$ levels (median (IQR)) were consistently lower in the first 9 h after birth in patients with considerable ischemic brain injury on MRI when compared to patients with minimal ischemic brain injury. $TcPCO_2$ values were $n = 6$, 32.1 (31.5–41.3) mm Hg and $n = 13$, 46.8 (40.1–51.0) mm Hg, $P = 0.02$ at 6 h, and $n = 6$, 35.0 (30.4–35.4) mm Hg and $n = 11$, 44.2 (39.1–52.2) mm Hg, $P = 0.04$ at 9 h in, respectively, the considerable and minimal brain injury groups. The median (IQR) standard deviations of $tcPCO_2$ during the 1 h periods are presented in Online Supplemental Table 3. In the period following the first 24 h of TH no differences were observed in $tcPCO_2$ levels and standard deviations between groups. Median (IQR) base deficit levels did not differ between the two groups during this 24 h period ($n = 15$, −13.1 (−14.1–9.85) mmol/l and $n = 7$,−7.7 (−9.3–6.6) mmol/l, $P = 0.05$).

DISCUSSION

This study investigated the accuracy and value of transcutaneous blood gas monitoring during TH. $TcPCO_2$ showed an inaccuracy when compared to $PaCO_2$ during TH. While the influence of body temperature on heating power was evident, changes in body temperature did not affect measured $tcPCO_2$ values. An interesting result was that $tcPCO_2$ monitoring showed hypocapnia in the

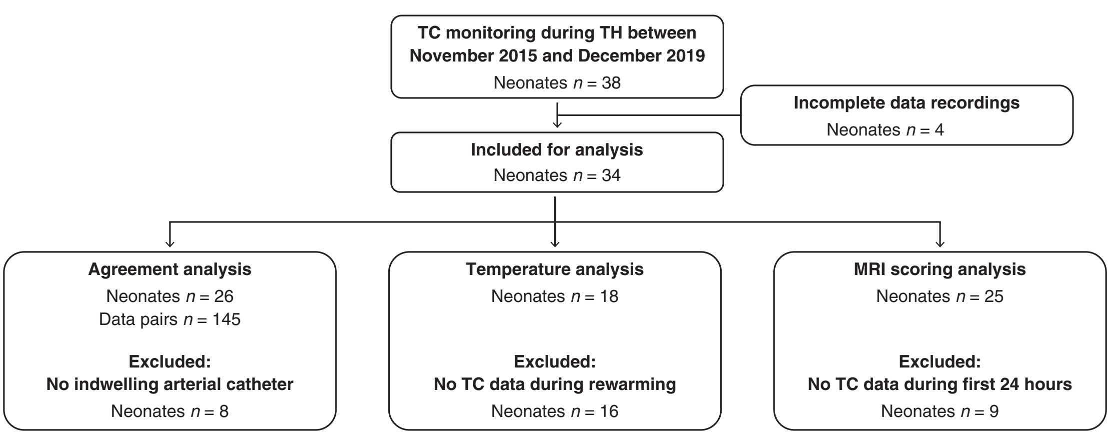

Fig. 1 Flowchart of inclusion and exclusion of neonates for analyses. TC transcutaneous blood gas monitoring, TH therapeutic hypothermia, MRI magnetic resonance imaging.

Table 1. Patient characteristics.

Post-asphyxial neonates (n)	***34***
GA (weeks)	38 6/7 (37 1/7–40 6/7)
Birth weight (grams)	3295 (2883–3636)
Sex (male)	19 (55.9)
Delivery method (C-section)	23 (67.6)
Apgar	
1 min[a]	1 (0–2)
5 min[a]	3 (1–4)
10 min[b]	4 (3–6)
Arterial umbilical cord pH[b]	6.98 (6.77–7.11)
Arterial umbilical cord base deficit (mmol/l)[d]	−15 (−25–−12)
PCO_2 level at 1 h (mm Hg)[a]	62 (52–83)
Thompson score at 1 h[c]	11 (9–13)
Inotropic administration	30 (88.2)
Admission survival	29 (85.3)

Values are presented as median (IQR) or n (%). Admission survival is defined as survival until discharge from the level III NICU.
GA gestational age, *PCO_2* pressure of carbon dioxide.
[a]Missing values $n = 2$.
[b]Missing $n = 4$.
[c]Missing $n = 6$.
[d]Missing values $n = 8$.

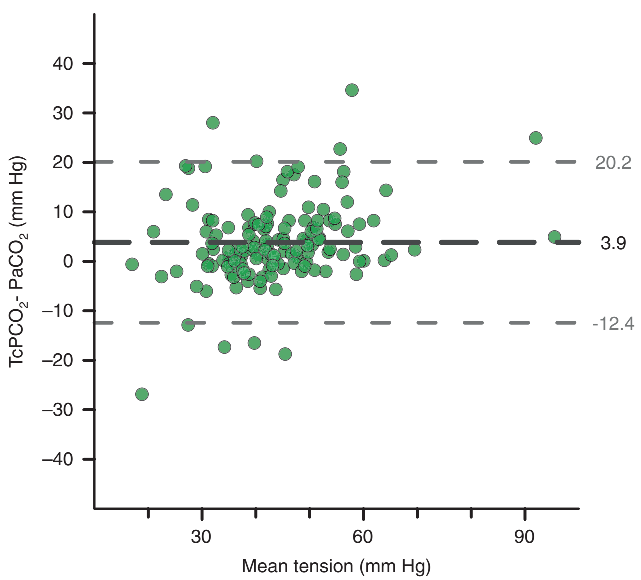

Fig. 2 Bland–Altman plot of agreement between $tcPCO_2$ and $PaCO_2$. $TcPCO_2$ transcutaneous carbon dioxide level, $PaCO_2$ arterial partial pressure of carbon dioxide.

first nine hours after the start of TH in patients with considerable ischemic brain injury on MRI. In addition, $tcPO_2$ showed poor agreement with PaO_2, which worsened with an increase in mean O_2 tension. No relation was found between body temperature and $tcPO_2$ levels.

Arterialization times of $tcPCO_2$ and $tcPO_2$ measurements were noticeably longer than at physiological body temperatures, indicated by a prolonged stabilization time. However, the agreement between $tcPCO_2$ and $PaCO_2$ found in this study is comparable to accuracy reported in normothermic preterm and term neonates.[17,18] This suggests that adequate arterialization could be achieved for acceptable $tcPCO_2$ measurements in patients undergoing TH. $TcPO_2$ persistently underestimated PaO_2, limiting its use in O_2 management during TH. This underestimation can be explained by a decreased O_2 diffusion capacity at lower temperatures[28,29] and a decreased capillary flow.[20] In addition, the majority of the included neonates were term, an age at which skin development can already affect the O_2 diffusion capacity.[30,31] The poor $tcPO_2$-PaO_2 agreement could also be a result of hyperoxygenation and the limit of the O_2 diffusion capacity during TH in this particular age group. When disregarding hyperoxygenated samples, agreement seems comparable to previous studies in neonates.[30,32,33] All these factors are only minimally affecting $tcPCO_2$, as illustrated in this study. It is, however, not unlikely that these same factors affect $tcPCO_2$ accuracy to a lesser extent. Although no relation was found between $tcPCO_2$ and body temperature in this study, the relation between the $tcPCO_2$-$PaCO_2$ difference and body temperature could be evident in study populations with impaired perfusion caused by for example shock.

Transcutaneous blood gas monitoring did not result in any burns or skin discoloration, despite a large temperature difference between sensor and skin. TH required ~25% higher heating power levels to maintain the set sensor temperatures and achieve adequate arterialization of the skin. Increases in body temperature were significantly associated with a decrease in heating power, providing stable measurements throughout the active warming period.

The MRI score applied in this study was used to classify post-TH brain injury on MRI.[22] This scoring system was chosen for its point-by-point scoring and validation for diffusion-weighted MRI's within the first week, directly following TH. It describes injury severity without grouping patterns of injury, reducing the influence of interpretation. There was a gap between the MRI scores of the two groups, which is most likely explained by the points scored simultaneously for damage in multiple brain regions. Although the gray matter subscore has been associated with adverse outcome at 2 years of age and school age,[22] no extensive analysis of the subscore could be performed in the current study as a limited number of patients had high MRI scores. Contrary to the cohort of Weeke et al.,[22] in our study cohort a high gray matter subscore did not always coincide with ischemic brain injury in other areas, and vice versa. To investigate all affected brain areas we chose to apply the total MRI score, instead of the gray matter subscore. Only neonates in the considerable ischemic injury on MRI group showed injury in the gray matter score. As previous research suggested that injury in the deep gray matter is related to an adverse outcome, low $tcPCO_2$ levels within the first 24 h of TH could potentially provide an early outcome indicator. Despite the association of low $tcPCO_2$ levels with severe ischemic brain injury on MRI, the expected neurodevelopmental outcome should be derived from the specific MRI findings. Future studies on transcutaneous carbon dioxide monitoring during TH should investigate the relation between $tcPCO_2$ levels and MRI-related outcome, including the potential predictive value.

Multiple studies have related hypocapnia in the first hours after perinatal asphyxia to poor neurodevelopmental outcome.[6–9,34] Hypocapnia could result in additional brain damage,[35] as cerebral blood flow is exponentially associated with deviations from normal CO_2 levels.[36] In our study, continuous transcutaneous monitoring showed a similar trend in CO_2 levels in patients with cerebral ischemia on MRI. Median standard deviations of $tcPCO_2$ levels over the one-hour periods were not higher than 2.45 mm Hg, indicating that the found differences were not based on short-term CO_2 fluctuations. Low $PaCO_2$ levels increase neuronal excitability, leading to seizures and additional neuronal damage.[37] Although this provides an additional indication of the association between hypocapnia shortly after birth and brain damage on MRI, the validity of this

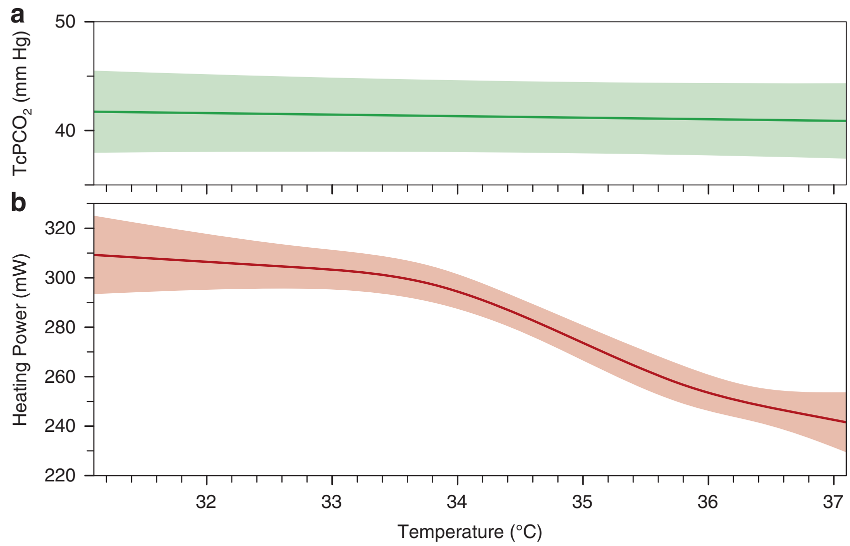

Fig. 3 Best fitted marginal models to determine the influence of temperature on $tcPCO_2$ and heating power. Prediction, including 95% confidence intervals, of (**a**) $tcPCO_2$ and (**b**) heating power are plotted against the body temperature. A relation with FiO_2 was included in the $tcPCO_2$ model. The nonlinear relation between the heating power and the body temperature is presented. $TcPCO_2$ transcutaneous carbon dioxide level, FiO_2 fraction of inspired oxygen.

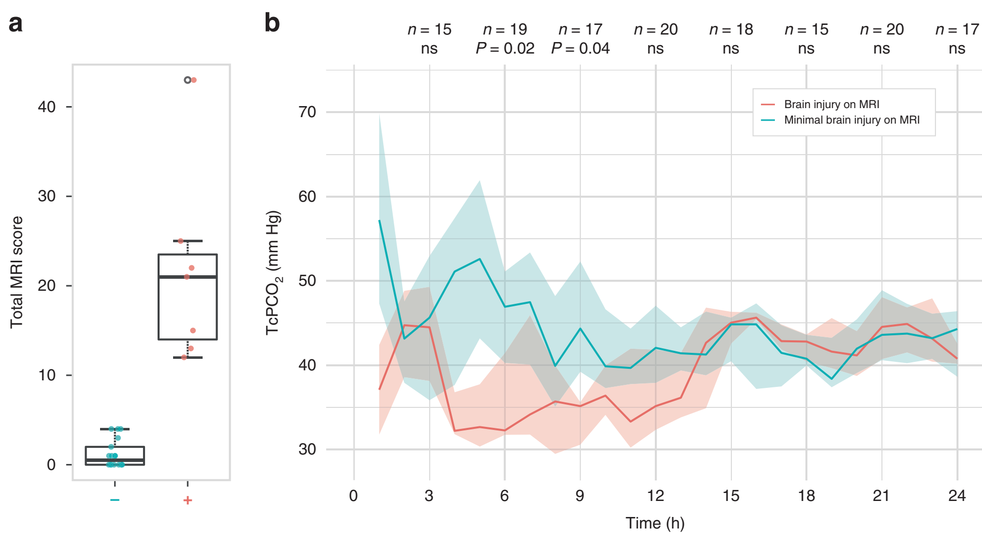

Fig. 4 $TcPCO_2$ levels in neonates with minimal and considerable brain injury on MRI during the first 24 hours of TH. a Boxplots of the total score of the MRI scoring system for neonates with ischemic brain injury (+) on MRI and with minimal brain injury (-). **b** Trend data of median (interquartile range) $tcPCO_2$ measurements during the first 24 h from the start of therapeutic hypothermia are presented for neonates who show ischemic injury on MRI and those who show minimal brain injury. Significant differences in the $tcPCO_2$ values are reported at 6 h and 9 h, after which $tcPCO_2$ values are comparable. $TcPCO_2$ transcutaneous carbon dioxide level, MRI magnetic resonance imaging.

method should be confirmed in a larger cohort. There are several options with regard to the etiology of the hypocapnic period, such as a decreased CO_2 production due to brain ischemia and reduced brain metabolism or reduced muscle tone due to sedation, potentially resulting in mechanical over-ventilation when applying standard settings on hypocapnic patients. However, as base deficit levels did not differ between groups, in our study hyperventilation could originate from the central chemoreceptors as a response to cerebral acidosis.[38,39]

This study has limitations that should be addressed in prospective studies. One is incomplete data on $tcPCO_2$ levels, arterial blood pressure or the body temperature, resulting in the need for subgroup analyses. Although agreement analysis and the relation between temperature and transcutaneous blood gas parameters are unaffected by selection bias, this might be a concern in the outcome-related analysis. As $tcPCO_2$ was only measured when neonates received invasive respiratory support, the presence of a similar transient hypocapnia in spontaneously breathing neonates or neonates on noninvasive ventilation during TH could not be investigated. Furthermore, ventilator respiratory rates were not recorded for all neonates during the study period. These rates could provide more insight into the extent to which respiratory support compensated for deviations of CO_2 levels from the set targets. Regardless, invasive respiratory support is unable to compensate for spontaneous hyperventilation. These respiratory parameters could clarify hypocapnic events during the initial 24 h of TH in patients who showed cerebral ischemia on MRI. As the association

Table 2. Patient characteristics of the MRI scoring groups.

Groups	***Considerable ischemic brain injury*** ***n* = 7**	***Minimal to no brain injury*** ***n* = 18**	***P value***
GA (weeks)	38 (36 4/7–39 1/7)	39 (38 5/7–41 1/7)	0.060
Birth weight (grams)	3000 (2805–3608)	3335 (3025–3500)	0.565
Sex (male)	2 (28.6)	12 (66.7)	0.203
Delivery method (C-section)	7 (100)	9 (50.0)	0.061
Apgar			
1 min	1 (0–1)[+]	1 (1–3)[+]	0.219
5 min	3 (2–4)	3 (2–4)[*]	0.785
10 min	4 (4–5)	5 (4–6)[*]	0.378
Arterial umbilical cord pH	6.79 (6.71–7.06)	7.01 (6.93–7.14)[#]	0.158
Arterial umbilical cord base deficit (mmol/l)	−24 (-30–−15)[+]	−13 (-16–−11)[±]	0.187
PCO_2 level at 1 h (mm Hg)	53 (45–69)	71 (56–88)[#]	0.204
Thompson score at 1 h	12 (10–13)[+]	10 (9–12)[^]	0.272
Inotropic administration	7 (100)	15 (83.3)	0.641
Total MRI score	21 (14–24)	1 (0–2)	<0.001
Admission survival	6 (85.7)	18 (100)	0.617

Values are presented as median (IQR) or n (%). Admission survival is defined as survival until discharge from the level III NICU.
GA gestational age, *PCO_2* pressure of carbon dioxide.
[+]Missing values $n = 1$.
[*]Missing values $n = 2$.
[#]Missing $n = 3$.
[^]Missing $n = 4$.
[±]Missing $n = 6$.

between $tcPCO_2$ levels and MRI score was a first exploratory analysis, providing insights for future prospective studies, it did not permit adjustment for confounders. Their effects should be investigated in regression analyses, for example by adjusting for GA at birth, severity of NE immediately after birth and respiration variables. No significant differences were found between the two groups, so we do not expect this to influence our presented results on the association. Remarkable was the fact that no difference was found in the Thompson scores, which can be a result of the investigated sample size or the limited value of the Thompson score immediately after birth.[40] The Sarnat classification should be included in future assessments.

Transcutaneous CO_2 monitoring provides the opportunity to closely monitor new therapeutic strategies in this population. Transcutaneous CO_2 monitoring is a continuous method for keeping values within the target range and managing the effects of asphyxia and TH.

CONCLUSIONS

$TcPCO_2$ monitoring during TH provides an estimation of $PaCO_2$ levels similar to accuracy reported in normothermic neonates, which is inaccurate according to the clinical practice guidelines. Arterial blood gas sampling remains the gold standard for CO_2 monitoring during TH, with $tcPCO_2$ levels providing information for trend monitoring. $TcPO_2$ measurements were not representative of PaO_2 levels. Continuous transcutaneous monitoring of hypocapnia after perinatal asphyxia can potentially provide an indication of ischemic brain injury on MRI.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Jacobs, S. E. et al. Cooling for Newborns with Hypoxic Ischaemic Encephalopathy. *Cochrane Database Syst. Rev.* **2013**, CD003311 (2013).
2. Abate, B. B. et al. Effects of Therapeutic Hypothermia on Death among Asphyxiated Neonates with Hypoxic-Ischemic Encephalopathy: a Systematic Review and Meta-Analysis of Randomized Control Trials. *PLOS ONE* **16**, e0247229 (2021).
3. Lorek, A. et al. Delayed ("Secondary") Cerebral Energy Failure after Acute Hypoxia-Ischemia in the Newborn Piglet: Continuous 48-Hour Studies by Phosphorus Magnetic Resonance Spectroscopy. *Pediatr. Res.* **36**, 699–706 (1994).
4. Al Zaabi, A., Rahmani, A. Y. & Souid, A. Optimal Temperature for Whole-Body Hypothermia in the Newborn: An in Vitro Study Using Foreskin Mitochondrial Oxygen Consumption. *J. Neonatal Perinat. Med.* **7**, 179–183 (2014).
5. Kety, S. S. & Schmidt, C. F. The Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output, and Blood Pressure of Normal Young Men. *J. Clin. Investig.* **25**, 107–119 (1946).
6. Lingappan, K., Kaiser, J. R., Srinivasan, C. & Gunn, A. J. Relationship between Pco2 and Unfavorable Outcome in Infants with Moderate-to-Severe Hypoxic Ischemic Encephalopathy. *Pediatr. Res.* **80**, 204–208 (2016).
7. Nadeem, M., Murray, D., Boylan, G., Dempsey, E. M. & Ryan, C. A. Blood Carbon Dioxide Levels and Adverse Outcome in Neonatal Hypoxic-Ischemic Encephalopathy. *Am. J. Perinatol.* **27**, 361–365 (2010).
8. Pappas, A. et al. Hypocarbia and Adverse Outcome in Neonatal Hypoxic-Ischemic Encephalopathy. *J. Pediatr.* **158**, 752–758 (2011). e751.
9. Klinger, G., Beyene, J., Shah, P. & Perlman, M. Do Hyperoxaemia and Hypocapnia Add to the Risk of Brain Injury after Intrapartum Asphyxia? *Arch. Dis. Child. - Fetal Neonatal Ed.* **90**, F49–F52 (2005).
10. Chandrakantan, A. et al. Transcutaneous Co(2) Versus End-Tidal Co(2) in neonates and infants undergoing surgery: a prospective study. *Med. Devices (Auckl.)* **12**, 165–172 (2019).
11. Hand, I. L., Shepard, E. K., Krauss, A. N. & Auld, P. A. Discrepancies between Transcutaneous and End-Tidal Carbon Dioxide Monitoring in the Critically Ill Neonate with Respiratory Distress Syndrome. *Crit. Care Med.* **17**, 556–559 (1989).
12. Kugelman, A. et al. Diagnostic Accuracy of Capnography During High-Frequency Ventilation in Neonatal Intensive Care Units. *Pediatr. Pulmonol.* **51**, 510–516 (2016).
13. Rozycki, H. J., Sysyn, G. D., Marshall, M. K., Malloy, R. & Wiswell, T. E. Mainstream End-Tidal Carbon Dioxide Monitoring in the Neonatal Intensive Care Unit. *Pediatrics* **101**, 648–653 (1998).

14. Sivan, Y., Eldadah, M. K., Cheah, T. E. & Newth, C. J. Estimation of Arterial Carbon Dioxide by End-Tidal and Transcutaneous Pco2 Measurements in Ventilated Children. *Pediatr. Pulmonol.* **12**, 153–157 (1992).
15. Tingay, D. G., Stewart, M. J. & Morley, C. J. Monitoring of End Tidal Carbon Dioxide and Transcutaneous Carbon Dioxide During Neonatal Transport. *Arch. Dis. Child Fetal Neonatal Ed.* **90**, F523–F526 (2005).
16. Afzal, B. et al. Monitoring Gas Exchange During Hypothermia for Hypoxic-Ischemic Encephalopathy. *Pediatr. Crit. Care Med.* **20**, 166–171 (2019).
17. Conway, A. et al. Accuracy and precision of transcutaneous carbon dioxide monitoring: a systematic review and meta-analysis. *Thorax* **74**, 157–163 (2019).
18. Hochwald, O. et al. Continuous noninvasive carbon dioxide monitoring in neonates: from theory to standard of care. *Pediatrics* **144** e20183640 (2019).
19. Ergenekon, E. et al. Peripheral Microcirculation Is Affected During Therapeutic Hypothermia in Newborns. *Arch. Dis. Child Fetal Neonatal. Ed.* **98**, F155–F157 (2013).
20. Fredly, S. et al. Noninvasive Assessments of Oxygen Delivery from the Microcirculation to Skin in Hypothermia-Treated Asphyxiated Newborn Infants. *Pediatr. Res.* **79**, 902–906 (2016).
21. Toet, M. C., Hellström-Westas, L., Groenendaal, F., Eken, P. & de Vries, L. S. Amplitude Integrated Eeg 3 and 6h after Birth in Full Term Neonates with Hypoxic-Ischaemic Encephalopathy. *Arch. Dis. Child Fetal Neonatal. Ed.* **81**, F19–F23 (1999).
22. Weeke, L. C. et al. A Novel Magnetic Resonance Imaging Score Predicts Neurodevelopmental Outcome after Perinatal Asphyxia and Therapeutic Hypothermia. *J. Pediatr.* **192**, 33–40 (2018). e32.
23. van Weteringen, W. et al. Validation of a New Transcutaneous Tcpo2/Tcpco2 Sensor with an Optical Oxygen Measurement in Preterm Neonates. *Neonatology*, **117**, 628–636 (2020).
24. Bland, J. M. & Altman, D. G. Agreement between Methods of Measurement with Multiple Observations Per Individual. *J. Biopharm. Stat.* **17**, 571–582 (2007).
25. Ludbrook, J. Confidence in Altman-Bland Plots: A Critical Review of the Method of Differences. *Clin. Exp. Pharm. Physiol.* **37**, 143–149 (2010).
26. Bland, M. How Do I Estimate Limits of Agreement When the Mean or Sd of Differences Is Not Constant? https://www-users.york.ac.uk/~mb55/meas/glucose.htm (2006).
27. Pinheiro J., B. D., DebRoy S., Sarkar D., R Core Team (2020). *Nlme: Linear and Nonlinear Mixed Effects Models. R Package Version 3.1-150*, https://CRAN.R-project.org/package=nlme (2020).
28. Hansen, J. E. & Sue, D. Y. Should Blood Gas Measurement Be Corrected for the Patient's Temperature? *N. Engl. J. Med.* **303**, 341 (1980).
29. Sidell, B. D. Intracellular oxygen diffusion: the roles of myoglobin and lipid at cold body temperature. *J. Exp. Biol.* **201**, 1119–1128 (1998).
30. Versmold, H. T., Holzmann, M., Linderkamp, O. & Riegel, K. P. Skin Oxygen Permeability in Premature Infants. *Pediatrics* **62**, 488–491 (1978).
31. Hamilton, P. A., Whitehead, M. D. & Reynolds, E. O. Underestimation of Arterial Oxygen Tension by Transcutaneous Electrode with Increasing Age in Infants. *Arch. Dis. Child* **60**, 1162–1165 (1985).
32. Huch, R., Lübbers, W. & Huch, A. Reliability of Transcutaneous Monitoring of Arterial Po2 in Newborn Infants. *Arch. Dis. Child* **49**, 213–218 (1974).
33. Palmisano, B. W. & Severinghaus, J. W. Transcutaneous Pco2 and Po2: A Multicenter Study of Accuracy. *J. Clin. Monit.* **6**, 189–195 (1990).
34. Lopez Laporte, M. A. et al. Association between Hypocapnia and Ventilation During the First Days of Life and Brain Injury in Asphyxiated Newborns Treated with Hypothermia. *J. Matern. Fetal Neonatal. Med.* **32**, 1312–1320 (2019).
35. Laffey, J. G. & Kavanagh, B. P. Hypocapnia. *N. Engl. J. Med.* **347**, 43–53 (2002).
36. Greisen, G. Autoregulation of Cerebral Blood Flow in Newborn Babies. *Early Hum. Dev.* **81**, 423–428 (2005).
37. Pospelov, A. S., Ala-Kurikka, T., Kurki, S., Voipio, J. & Kaila, K. Carbonic Anhydrase Inhibitors Suppress Seizures in a Rat Model of Birth Asphyxia. *Epilepsia* **62**, 1971–1984 (2021).
38. Darnall, R. A. The Role of Co(2) and Central Chemoreception in the Control of Breathing in the Fetus and the Neonate. *Respir. Physiol. Neurobiol.* **173**, 201–212 (2010).
39. Guyenet, P. G. & Bayliss, D. A. Neural Control of Breathing and Co2 Homeostasis. *Neuron* **87**, 946–961 (2015).
40. Mendler, M. R. et al. Predictive Value of Thompson-Score for Long-Term Neurological and Cognitive Outcome in Term Newborns with Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy Undergoing Controlled Hypothermia Treatment. *Neonatology* **114**, 341–347 (2018).

AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

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