Carbon dioxide reactivity in infants with neonatal encephalopathy

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Background and Aim

- Carbon dioxide is one of the most potent regulators of cerebral blood flow (CBF).
- Near infrared spectroscopy (NIRS) has been used in neonatal encephalopathy (NE) during therapeutic hypothermia (TH) to monitor regional cerebral oxygen saturation (rSO_2) that can be a proxy of CBF.
- Impaired cerebral autoregulation following severe hypoxic-ischemic brain injury has been associated with poor neurologic outcome.
- **The aim of this study was to evaluate the correlation between transcutaneous CO_2 and markers of cerebral oxygenation including cerebral oxygen saturation and fractional tissue oxygen extraction among infants with neonatal encephalopathy.**

Pryds O, et al. 1990. J Pediatr; Lemmers PM, et al. 2013. Pediatr Res.; Szakmar E, et al. 2021. J Perinatol.

Methods

- **This prospective observational trial** enrolled infants, who received TH for mild to severe NE between October 2019 and June 2022 at Brigham and Women's Hospital.
- The pattern of brain injury was evaluated according to an MRI grading system developed by Weeke et al. **We identified 2 groups of patients with and without any brain injury based on the assessment of MRI after rewarming.**
- **Transcutaneous CO_2 ($tcPCO_2$), rSO_2 and bedside physiological data were captured simultaneously by a real-time integrated neuromonitoring system** (CNS Monitor).
- Fractional tissue oxygen extraction was calculated as: $FTOE = (SpO_2 - rSO_2)/SpO_2$

Hypothermia
- Phase 1: 0-12 h
- Phase 2: >12- 24h
- Phase 3: >24- 36h
- Phase 4: >36- 48h
- Phase 5: >48- 60h
- Phase 6: >60- until the end of cooling

Phase 7: Rewarming

Phase 8: After rewarming

1. The median of $tcPCO_2$, SpO_2, rSO_2 and FTOE at each hour were calculated for each infant.
2. Using the median values at each hour, we calculated the median of all variables in each phase of TH for each infant.
3. Pearson correlation coefficients between median levels of $tcPCO_2$ and cerebral oxygenation (rSO_2 and FTOE) were computed within each phase .
4. Correlation between $tcPCO_2$ and oxygenation (rSO_2 and FTOE) across the study period by brain injury status was calculated using repeated measures correlation to take into account intra-individual correlation among medians of the different phases.

Results

Infants receiving hypothermia for NE
October 2019- June 2022
n=110

Enrolled n= 37

Serial measurement with CNS monitor n= 31

With brain injury n=16 (52%)

Without brain injury n=15 (48%)

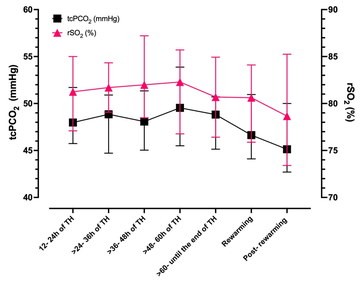
Table 1: Demographic and clinical data of the cohort

	With brain injury n= 16	Without brain injury n= 15	p values
Gestational age (week)	39 [37; 40]	40 [39; 40]	0.140
Birth weight (g)	3307 [2890; 3708]	3280 [2510; 3600]	0.358
Apgar 1 min	2 [2; 7]	1 [1; 3]	0.027
Apgar 5 min	8 [5; 8]	6 [5; 8]	0.232
Apgar 10 min	7 [6; 8]	8 [7; 8]	0.428
First postnatal pH	7.3 [7.2; 7.3]	7.3 [7.1; 7.3]	1.000
First postnatal BD (mmol/L)	8.8 [6.5; 11.7]	10.4 [6.9; 12.3]	0.560
First postnatal lactate (mmol/L)	8 [5; 9]	9 [6; 13]	0.220
Invasive ventilation, n (%)	5 (31 %)	4 (27 %)	1.000
Length of invasive ventilation (day)	1.0 [0.6; 17.0]	0.3 [0.06; 0.5]	0.003
Worst encephalopathy score within 12 h of life	7 [3; 11]	7 [4; 9]	0.870
Length of hospital stay (day)	7 [6; 11]	6 [5; 8]	0.401
MRI findings			
Age at brain MRI (day)	4 [4; 5]	4 [4; 4]	0.661
Total score of injury (min-max)	2 (2; 24)	n/a	n/a
Grey matter injury, n (%)	5 (31 %)	n/a	n/a
Cortex and white matter injury, n (%)	9 (56 %)	n/a	n/a
Cerebellar injury, n (%)	3 (19 %)	n/a	n/a

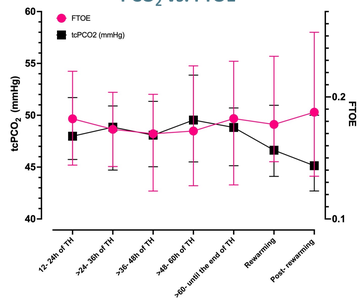
- 110 infants received TH during study period, out of those 37 infants were enrolled into this prospective study. Serial measurements from 31 patients were available for analysis. Sixteen (51.6%) infants had evidence of any brain injury on MRI.
- Integrated monitoring began at median 24 hours of life (min-max: 11-51) and ended at median 94 (min-max: 87-120) hours of life.

CO_2- reactivity throughout the phases of hypothermia and rewarming

PCO_2 vs. rSO_2



PCO_2 vs. FTOE

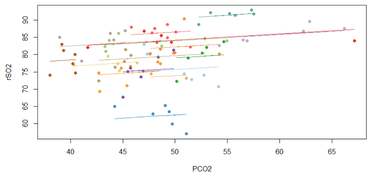


- Medians and interquartile ranges across each phase from hypothermia to post-rewarming are provided above for $tcPCO_2$, rSO_2, and FTOE. Pearson's r between $tcPCO_2$ and measures of oxygenation (rSO_2 and FTOE) were calculated within each phase of hypothermia, rewarming and post-rewarming phase.
- **Correlations between $tcPCO_2$ and measures of oxygenation were small throughout the phases of TH, with positive correlations with rSO_2 and negative with FTOE**

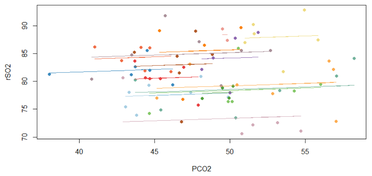
CO_2-reactivity in infants with and without brain injury

PCO_2 vs. rSO_2

With brain injury, r=0.19, 95% CI -0.04; 0.39

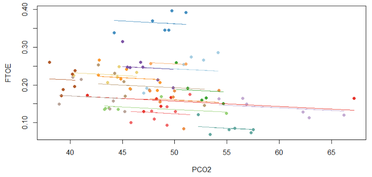


Without brain injury, r=0.08, 95% CI -0.17; 0.31

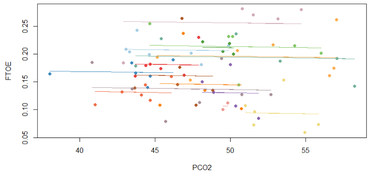


PCO_2 vs. FTOE

With brain injury, r=-0.15, 95% CI -0.39; 0.07



Without brain injury, r=-0.04, 95% CI -0.27; 0.21



- Correlation between $tcPCO_2$ and oxygenation (rSO_2 and FTOE) across the study period by brain injury status using repeated measures correlation to take into account intra-individual correlation among medians of the different phases. Separate parallel lines are fit to the data from each participant. The sign of the correlation coefficient is indicated by the direction of the common regression slope.
- **Though small in effect size, correlations were stronger among infants with brain injury, compared to those without brain injury on MRI.**

Conclusions

- **Correlations detected between CO_2 and cerebral oxygenation were modest with a positive correlation with rSO_2 and negative correlation with FTOE across the study period**.
- Though small in effect size, **the correlation between $tcPCO_2$ and cerebral oxygenation** (rSO_2 and FTOE) **over the study period was greater in magnitude among infants with brain injury compared to those without, among whom the correlation was close to zero.**
- These pilot results are needed to be interpreted with caution. Increasing sample size and further investigations are needed to confirm our findings.