# Impact of carbon dioxide on cerebral oxygenation 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

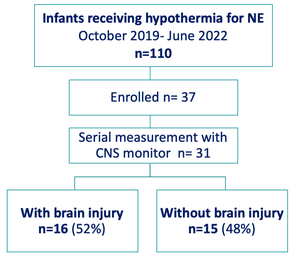



**Table 1: Demographic and clinical data of the cohort**

| | 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

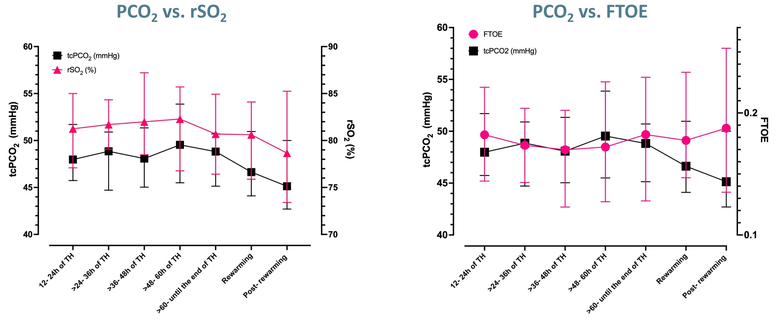



**Figure 1**: CO2- reactivity throughout the phases of hypothermia and rewarming

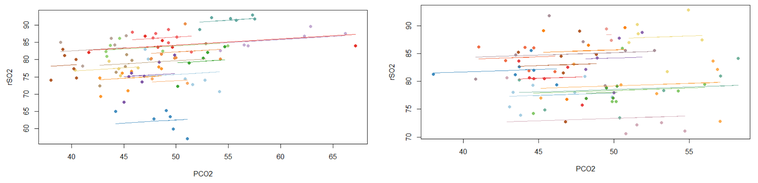
- Medians and interquartile ranges across each phase from hypothermia to post-rewarming are provided above for $tcPCO_2$, $rSO_2$, and FTOE. Pearson's r between $tcPCO_2$ and measures of oxygenation ($rSO_2$ and FTOE) were calculated within each phase of hypothermia, rewarming and post-rewarming phase.
- **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

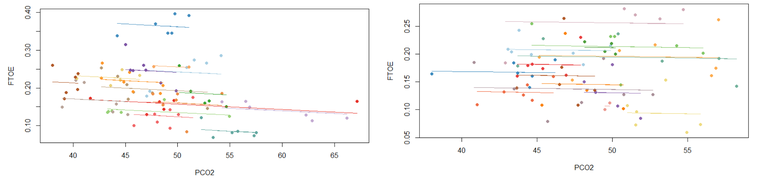



**Figure 2**. CO2- reactivity in infants presented with and without brain injury across the study period

- 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.**
- **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.