Brain Health in Preterm Infants: Cerebral Metabolic Rate of Oxygen (CMRO2) Using Advanced MRI

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Introduction

Approximately every 1 in 10 babies are born preterm. About 50% display cognitive, motor, and behavioural problems long-term. Improving the capacity to understand neonatal brain health is a major focus of neonatal medicine and can aid the development of optimized treatments.

- Oxygen metabolism in the brain is an important indicator of neonatal brain health, as cerebral hypoxia and ischemia are associated with neurodisability. However, it has historically been difficult to measure in neonates. Most clinical measurements of oxygen metabolism only determine the level of oxygen delivery, for example, cerebral venous oxygen saturation (SvO2), and not full oxygen metabolism such as cerebral metabolic rate of oxygen (CMRO2).
- Measurements of CMRO2 can provide information with greater clinical relevance including the balance of neonatal cerebral oxygen delivery and demand. Previous studies measuring neonatal CMRO2 often use methods that have limitations.
- Recent advances in magnetic resonance imaging (MRI) such as quantitative susceptibility mapping (QSM) may be a safe, precise, and non-invasive method of quantifying CMRO2.

Study Aims

- Assess feasibility of measuring CMRO2 at term equivalent age (TEA) in neonates born very preterm using advanced MRI techniques.
- Evaluate the relationships between CMRO2 and clinical risk factors.

Study Population

N=20 preterm neonates <33 weeks gestation cared for in the neonatal intensive care unit (NICU) at BC Women's Hospital. Exclusion criteria: major congenital malformation or syndrome, TORCH infection, and ultrasound evidence of significant brain injury.

Methods

Data collection: Preterm neonates discharged from the NICU returned to the facility for scanning when they are at term equivalent age (37 to 42 weeks post menstrual age). MRI scans are acquired at the BC Children's Hospital MRI Research Facility via a specialized research broadband GE 3T MRI system. Infants are fed, swaddled, and placed in an MRI compatible incubator with a built-in neonatal imaging coil. Molded foam and ear plugs will be provided to minimize head movement and noise. A research nurse monitors the neonates throughout the scan using and heart rate and arterial oxygen saturation will be monitored through a toe-attached pulse-oximeter.

Data collection (cont'd): The MRI scanning sequence is conducted as listed. The total scan time is estimated to be 30-60 minutes.

1. T1-weighted spin echo imaging;
2. T2-weighted imaging,
3. CBF will be measured using ASL and a 3D fast spin echo (FSE) sequence; estimated scan time = 4 mins.
4. QSM from a flow-compensated 3D multi-echo spoiled gradient echo (GRE) sequence with five equally spaced echoes; estimated scan time = 5 mins.
5. Diffusion Tensor Imaging
6. Diffusion Tensor Imaging Blip-down

Image and Data Analysis: MRI data from the scans is analyzed using FSL and ANTS software. The data is organized as per the Brain Imaging Data Structure (BIDS). The data is then processed through the dHCP structural pipeline to extract a structural analysis. The cerebral blood flow of grey matter is derived from ASL using the following equation:

$$CBF = 6000 * \lambda \frac{\left(1-\exp\left(-\frac{ST(s)}{T_{1t}(s)}\right)\right)\exp\left(\frac{PLD(s)}{T_{1b}(s)}\right)}{2T_{1b}(s)\left(1-\exp\left(-\frac{LT(s)}{T_{1b}(s)}\right)\right)\varepsilon * NEX_{PW}} \left(\frac{PW}{SF_{pw}PD}\right)$$

Variable	Description
λ	Partition coefficient
T_{1b}	Longitudinal relaxation time of blood
T_{1t}	Longitudinal relaxation time of tissue
ST	Saturation time
LT	Labeling duration
PLD	Post labeling delay
ε	Efficiency
NEX_{pw}	Number of excitations for PW images
SF_{pw}	Scaling factor of PW sequence
PW	Perfusion weighted image
PD	Proton density image

QSM data is post-processed using an algorithm from https://github.com/kamesy/QSM.m to produce a magnetic susceptibility map. The cerebral venous oxygen saturationSvO2 is then calculated using the following equation:

$$SvO_2 = 1 - \left(\Delta\chi_{\text{blood}} - \Delta\chi_{oxy} * Hct\right) / \left(\Delta\chi_{do} * Hct\right)$$

Variable	Description
Hct	Hematocrit
ΔXblood	Susceptibility difference between blood and water
Δxoxy	Constant susceptibility shift of fully oxygenated blood relative to water
ΔXdo	Susceptibility difference between fully oxygenated and fully deoxygenated blood

CMRO2 is then solved using the following equation:

$$CMRO_2 = OE \times CBF \times [HbT] = (sO_{2,a} - sO_{2,v}) \times CBF \times [HbT]$$

Variable	Description
sO2,a	Arterial oxygen saturation
sO2,v	Cerebral venous oxygen saturation
CBF	Cerebral blood flow
HbT	Hemoglobin concentration

Statistical Analysis: A partial correlation will be performed using statistical software R to determine the relationship between CMRO2 and clinical measures of respiratory health. As both CMRO2 and health are expected to relate to age, gestational age will act as a control random variable.

Preliminary Results

Currently, CMRO2 values for three subjects have been calculated. The CMRO2 values are as follows:

Subject	CMRO2 Value
Subject 1	38.47
Subject 2	26.88
Subject 3	27.29

These preliminary results agree with the literature standards of CMRO2 in preterm neonates at term equivalent age which range from 20-45umol/100g/min.

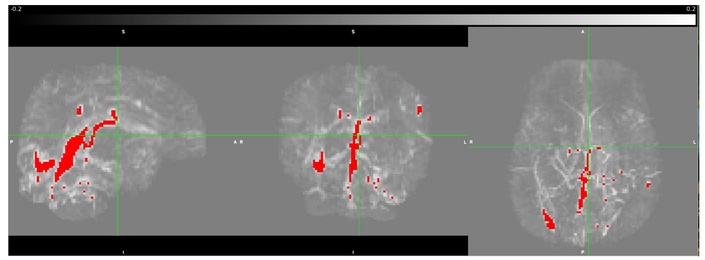

Figure 1. Processed QSM scan as underlay with a vessel mask projected in red at maximum intensity by thresholding the QSM image at 0.15ppm. The views from left to right are sagittal, coronal, and axial.

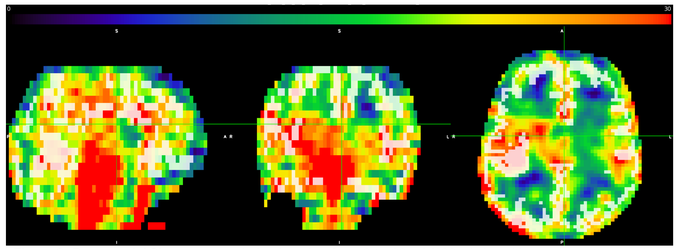

Figure 2. Processed ASL scan as underlay in color, from 0 to 30 mL/100 g/min, with a grey matter mask as overlay in slightly transparent white. The views from left to right are sagittal, coronal, and axial.

Discussion

This study will provide preliminary data to establish the feasibility of a non-invasive and precise advanced MRI technique in determining neonatal brain health and oxygen metabolism. This may be clinically relevant in further aiding and optimizing the development of therapies for brain injured neonates.