Quantitative assessment of cerebral metabolism rate of oxygen in neonates

Peiying Liu[1], Hao Huang[1], Nancy Rollins[2], Tina Jeon[1], Lina Chalak[3], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [2]*Department of Radiology, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [3]*Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas, United States*

INTRODUCTION: In recent years, advanced MRI techniques such as DTI, functional connectivity MRI, and ASL have been increasingly used in neonatal brain imaging to better understand brain development and brain disorders. However, the relationship between these biomarkers and brain function is indirect at best. The brain's energy "budget", denoted by cerebral metabolic rate of oxygen ($CMRO_2$), is thought to be a more direct index of neural activity. Unfortunately, *in vivo* measurement of $CMRO_2$ has proven challenging. This is particularly the case for neonatal population in whom the gold standard PET methods that are potentially available for adults are not applicable due to radiation concerns. There have been occasional reports in the literature using Near Infrared Spectroscopy (NIRS) approaches (1-3), but none has been widely used since their development. The purpose of our study is to fill this gap and develop a global $CMRO_2$ method that is non-invasive (no exogenous agent), fast (<5 min), and can be used in any facility with a standard MRI scanner. An adult version of the technique has been previously reported (4-5) and is currently undergoing multi-site testing (6).

THEORY: Our method is based on the Fick Principle (Fig. 1), in which global $CMRO_2$ can be quantified from arterio-venous difference in oxygen content, i.e., $CMRO_2=CBF\cdot(Y_a-Y_v)\cdot C_a$, where CBF is cerebral blood flow, Y_a and Y_v are oxygen saturation fraction in arterial and venous blood, respectively; C_a is the amount of oxygen molecules that a unit volume of blood can carry and is well established in physiology literature (8.97μmol O_2/100ml blood) (7). Thus, once Y_a, Y_v and CBF are experimentally determined, $CMRO_2$ in units of μmol O_2/min/100g brain tissue can be calculated. Of the three parameters, Y_v measurement is the most challenging component. Recently, we have developed a T2-Relaxation-Under-Spin-Tagging (TRUST) technique that is capable of measuring Y_v in the sagittal sinus with a scan duration of 1.2 min (8). Y_a is measured with pulse oximetry. Global CBF is measured by applying Phase-contrast (PC) MRI in the four feeding arteries of the brain, left/right internal carotid arteries (ICA) and left/right vertebral arteries (VA).

METHODS: *Participants*: 6 neonates (Gestational age at birth: 31.9±2.4 wk, Gestational age at scan: 35.4±0.8 wk) were scanned on a 3T scanner (Philips) without sedation. Demographic information of each subject is listed in Table 1. These neonates were pre-term but had no brain pathology as confirmed by clinical MR images. Vital signs including body temperature, heart rate, and Y_a were monitored throughout the study. Scan session was repeated for one subject following a 12-day interval. *$CMRO_2$ measurement:* Fig. 2 shows the protocol of the neonatal $CMRO_2$ technique, including the duration of each sequence. Scans in blue were for Y_v measurement and those in red were for CBF measurement. The experiment started with a mid-sagittal PC MRI which provided a quantitative map of venous flow velocity in the superior sagittal sinus (Fig. 3a). This information was then used by an automated algorithm to compute the labeling offset and thickness (Fig. 3a) in the TRUST sequence. For CBF determination, a TOF angiogram was placed around magnum foramen (Fig. 3d) and the resulted images allowed visualization of the feeding arteries (Fig 3e). Four PC MRIs were then positioned on these images, each optimized for one artery (Fig. 3e).

RESULTS and DISCUSSION: Fig. 3a illustrates the location of imaging slice (yellow) and labeling slab (green) in TRUST MRI. Fig. 3b shows the corresponding TRUST images. The control and label images are largely similar in visual inspection, but their subtraction highlighted the venous signal, which is most prominent in the sagittal sinus (bottom row in Fig. 3b). The image intensity was modulated by increasing T2 weighting (from left to right in bottom row of Fig. 3b). Fig. 3c plots signal as a function of TE. A mono-exponential fitting (Fig. 3c) yielded T2 value of the venous blood, which was in turn converted to Y_v using a calibration plot established previously (9). Y_v values of individual subjects are listed in Table 1.

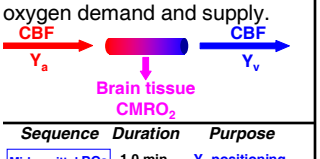
Fig. 3e shows slice positions of the four PC MRI scans. The resulting flow-velocity maps are displayed in the corresponding corners. The targeted arteries are clearly visible in the center of each image. Summation of flow in all arteries yielded the total blood supply to the brain. It was found that the ICA provided 69.5±12.6% of the total supply to the brain and the VA provided the rest. This percentage was similar to those of adults (data not shown). The total blood flow was normalized with the whole-brain volume to obtain CBF per unit tissue (in ml/100g/min), which is listed in Table 1.

$CMRO_2$ was calculated from CBF, Y_v, and Y_a (from vital signs) and the data are summarized in Table 1. The mean $CMRO_2$ of the whole sample was 26.2±14.9 μmol/100g/min (for reference, $CMRO_2$ in adults is 150-200 μmol/100g/min (5)). A total of four previous reports (1 using PET (10) and 3 using NIRS (1-3)) have quantified $CMRO_2$ in neonates and the values ranged from 2.7 to 68.2 μmol/100g/min. So our values are in general agreement with this scarce and highly variable literature. The relatively large variations in our data were partly attributed to the age spread in our sample. Importantly, it is expected that $CMRO_2$ increases quickly in first few weeks after birth. Indeed, we found a positive correlation between $CMRO_2$ and age across our subjects (cc=0.6). Furthermore, in the subject who was scanned twice with a 12-day interval, we found a $CMRO_2$ increase of 52%, again suggesting a rapid increase of $CMRO_2$ with age. We emphasize that, in these $CMRO_2$-vs-age comparisons, the brain volume growth has been accounted for. Thus, our findings cannot be simply explained by brain growth. It is also interesting to note that neonates have Y_v and Y_a values similar to those in adults, but their CBF value was much lower. Thus, Y_v of ~65% seems to be a critical target value for tissue function and the brain seems to have a system to adjust its blood supply to meet this target regardless the age.

In summary, we proposed a technique to measure global $CMRO_2$ in neonates. Preliminary testings in six subjects have shown great promises of this approach. Although it is a global measure and lacks regional information, several features of this technique (no exogenous agent, <5 min in scan duration, available on a standard 3T) make it a potentially important tool in functional assessment of neonatal population.

REFERENCES: 1) Skov et al, Pediatr Res 33:52, 1993; 2) Yoxall et al, Pediatr Res 44:283, 1988; 3) Elwell et al, Adv Exp Med Biol 566:263, 2005; 4) Xu et al, MRM 62:141, 2009; 5) Lu et al, Cereb Cortex 21:1426, 2011; 6) Liu et al, ISMRM submitted, 2013; 7) Guyton and Hall, Textbook of medical physiology, 2005; 8) Lu and Ge, MRM 60:357, 2008; 9) Lu et al, MRM 67:42, 2011; 10) Altman et al, Pediatrics 92:99, 1993.

Fig. 1: Relationship among physiologic parameters in oxygen demand and supply.



Sequence	Duration	Purpose
Mid-sagittal PCs	1.0 min	Y_v positioning
Angiogram	0.3 min	CBF positioning
TRUST MRI	1.2 min	Y_v measurement
PC on left ICA	0.5 min	CBF Measurement
PC on right ICA	0.5 min	CBF Measurement
PC on left VA	0.5 min	CBF Measurement
PC on right VA	0.5 min	CBF Measurement

Table 1: Results of the $CMRO_2$ measurements in all neonates.

sub #	Sex	GA at scan (wk)	Weight (kg)	Hct (%)	Y_a (%)	Y_v (%)	CBF(ml/ 100g/min)	$CMRO_2$(umol /100g/min)
1	M	36.1	2.55	48.5	**97.5**	**72.6**	**11.0**	**27.0**
2	M	34.9	2.96	29.7	**96.0**	**66.5**	**8.3**	**14.8**
3	M	35.7	1.92	37.0	**97.0**	**61.9**	**5.3**	**14.0**
4	F	34.7	2.01	28.7	**92.0**	**60.5**	**9.6**	**17.7**
5	F	34.7	1.82	30.4	**95.0**	**63.9**	**15.7**	**30.3**
6	M	36.4	1.88	52.2	**96.0**	**64.4**	**15.9**	**53.5**
mean		35.4	2.19	37.7	**95.6**	**65.0**	**11.0**	**26.2**
SD		0.8	0.46	10.3	**2.0**	**4.3**	**4.2**	**14.9**

Fig. 2 (left): The MRI procedure for a complete neonatal $CMRO_2$ dataset.

Fig. 3: MR images from a representative subject. (a-c) Positioning and the resulted TRUST images and T2 fitting. (d-e) Positioning and the resulted phase-contrast images.