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 'bucket', 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 (Y$_v$-Y$_i$)C$_i$, where CBF is cerebral blood flow, Y$_v$ and Y$_i$ are oxygen saturation fraction in arterial and venous blood, respectively; C$_i$ is the amount of oxygen molecules that a unit volume of blood can carry and is well established in physiology literature (8.97 μmol O$_2$/100ml blood) (7). Thus, once Y$_v$, Y$_i$, 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$_i$ measurement is the most challenging component. Recently, we have developed a T2-Relaxation-Under-Spin-Tagging (TRUST) technique that is capable of measuring Y$_i$ in the sagittal sinus with a scan duration of 1.2 min (8). Y$_v$ 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. An adult version of the technique has been previously reported (4-5) and is currently undergoing multi-site testing (6). 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 (Y$_v$-Y$_i$)C$_i$, where CBF is cerebral blood flow, Y$_v$ and Y$_i$ are oxygen saturation fraction in arterial and venous blood, respectively; C$_i$ is the amount of oxygen molecules that a unit volume of blood can carry and is well established in physiology literature (8.97 μmol O$_2$/100ml blood) (7). Thus, once Y$_v$, Y$_i$, 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$_i$ measurement is the most challenging component. Recently, we have developed a T2-Relaxation-Under-Spin-Tagging (TRUST) technique that is capable of measuring Y$_i$ in the sagittal sinus with a scan duration of 1.2 min (8). Y$_v$ 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).

RESULTS AND DISCUSSION: Table 1 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$_i$ using a calibration plot established previously (9). Y$_i$ 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 coroners. 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$_i$, and Y$_v$ (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$_2$ 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$_i$ values similar to those in adults, but their CBF value was much lower. Thus, Y$_i$ 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 of the age.

In summary, we proposed a technique to measure global CMRO$_2$ in neonates. Preliminary testing 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.