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Non-invasive Assessment of Neonatal Brain Oxygen Metabolism: A Review of Newly Available Techniques

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Abstract

Because oxidative metabolism is the primary form of energy production in the brain, the amount of oxygen consumed by the brain, denoted by a physiological parameter termed cerebral metabolic rate of oxygen (CMRO2), represents a key marker for tissue viability and brain function. Quantitative assessment of cerebral oxygen metabolism in the neonate may provide an important marker in better understanding normal brain development and in making diagnosis and treatment decisions in neonatal brain injuries. Measurement of CMRO2 in human has been a challenging task, particularly in neonates. Recently, several promising techniques have been proposed to quantify neonatal CMRO2 and the purpose of this article is to provide a technical review of these techniques. Among these, we will focus the review on the NIRS optic based methods and MRI methods which are non-invasive, have been applied in normal and sick newborns and show great potentials. Potential clinical prospects of CMRO2 techniques are discussed in the context of their advantages, challenges and limitations.

Keywords

Cerebral oxygen metabolism; cerebral metabolic rate of oxygen; neonates; near-infrared spectroscopy; magnetic resonance imaging

Conflict of interest statement The authors declare that there are no conflicts of interest.

Introduction

Brain is a big energy consumer and most of its energy is generated by oxidative metabolism, because anaerobic metabolism is inefficient and the produced lactate can cause further injury[1]. In neonates, cerebral oxidative metabolism is thought to play a particularly critical role in the early development of the brain. Starting from the third trimester and continuing until several months after birth, the energy source of the human brain shifts from anaerobic glycolysis to the more energy-efficient aerobic metabolism, in order to meet the escalating cerebral energy demands for the complex structural and functional maturational processes[2]. Consequently, disruption of oxygen supply and metabolism at this stage is highly detrimental. Several cerebral injuries have been associated with abnormal cerebral oxidative metabolism, such as hypoxic-ischemic encephalopathy, stroke, and metabolic disorders, all of which may lead to long-term neurologic deficits[3–5]. Therefore, quantitative assessment of cerebral oxygen metabolism in the neonate may provide a much needed tool to diagnose brain injuries, to provide mechanistic insights into the disease course, and to guide therapy on an individual basis.

However, measurement of cerebral oxygen metabolism, denoted by cerebral metabolic rate of oxygen (CMRO2), is particularly challenging in neonates, compared to other physiologic parameters such as perfusion and diffusion. Several CMRO2 measurement techniques have been developed in adults, but so far only a few of them have been shown to be feasible in neonates.

General principle underlying CMRO2 measurement techniques

Most CMRO2 measurement techniques are based on a simple principle called the Fick's principle. Basically, the amount of O2 consumed by the brain equals the difference between the amount delivered on the arterial side and the amount drained on the venous side. As illustrated in Fig. 1, arterial blood has an oxygenation level of Y_a and delivers oxygen to the brain. The flow rate is indicated by CBF. When the blood reaches brain tissue, a portion of the carried oxygen is extracted by the tissue for its metabolism, and this rate is referred to as CMRO2. The blood leaving the tissue is venous blood and has an oxygenation level of Y_v. The flow rate of the venous blood is the same as that of the arterial blood, CBF. Thus, CMRO2 (in unit of μmol/100g/min) can be quantified from arterio-venous difference in oxygen content according to the Fick Principle[6]:

$$\mathrm{CMRO2}=\mathrm{CBF}\bullet(\mathrm{Y_a}-\mathrm{Y_v})\bullet\mathrm{C_h},\quad \text{Eq. [1]}$$

where C_h is the amount of O2 molecules that a unit volume of blood can carry and is proportional to hematocrit (8.97μmol O2/100 ml blood at Hct=0.44)[7]. The ratio of arterio-venous difference to the artery oxygenation is known as oxygen extraction fraction (OEF), i.e., $OEF=(Y_a-Y_v)/Y_a$.

Thus, once Y_a, Y_v and CBF are experimentally determined, CMRO2 can be calculated. Different modalities and techniques can be used to measure these parameters for CMRO2 quantification.

Available CMRO2 techniques

Positron Emission Tomography (PET) is considered the gold standard method to measure brain metabolism in adults[8]. In this technique, CBF, OEF and CMRO2 are measured with the infusion and inhaling of ^{15}O- labeled radiotracers (i.e., H $^{15}_2$O, C^{15}O and $^{15}O_2$). In addition, repeated arterial blood sampling and on-site cyclotron for the production of ^{15}O tracers are required. The need of ionized radiation is the primary impediment when applying this technique in pediatric population. Additional issues include complexity of the procedure and the need of special equipment in ^{15}O-PET. To date, there were few studies that reported CMRO2 measurement in neonates using this technique[9], despite much broader applications in adults.

Near-infrared spectroscopy (NIRS) as a bed-side tool has been used to measure CMRO2 in adults[10]. It estimates oxyhemoglobin and deoxyhemoglobin concentrations (and thus Y_a and Y_v) by detecting the absorption and attenuation of NIR lights in brain tissue. Different techniques (both optical and non-optical) have been proposed to measure CBF[11–13]. Because of its low-cost and bed-side access, there have been increasing number of reports that used NIRS methods to measure CMRO2 in the neonate[12–16] (see more details below).

Magnetic resonance imaging (MRI) techniques that do not involve exogenous tracer have been developed more recently to measure CMRO2 in adults[17–21]. CBF is usually measured by phase-contrast MRI[20, 22–26] or arterial spin labeling (ASL) MRI[27–32]. Arterial oxygenation, Y_a, is usually measured by pulse oximetry[20, 24, 32], or assigned an assumed value given the highly oxygen content and small variation in arterial blood[18, 19]. The main difference among these MRI-based CMRO2 techniques is the approach by which venous oxygenation, Y_v, is determined. Based on the Y_v measurement methods, these techniques can be divided into four categories: susceptibility effect in extravascular tissue[17], phase angle in intravascular blood signal[18], gas-inhalation modulated fMRI signal[21], and transverse relaxation time (T2) of blood signal[20, 32]. Among these four categories, two blood T2-based CMRO2 method[24, 32] and a phase angle-based method[33] have been shown to be feasible to apply in the neonate, which will be discussed later.

Other techniques, such as nuclear magnetic resonance (NMR) methods using ^{13}C and ^{17}O as exogenous tracers[34, 35], have been developed to measure CMRO2 in adults, but have not been applied to neonatal brain yet.

NIRS measurement of CMRO2 in the neonate

In NIRS measurement, the optical probes are placed on the scalp at the region of interest. The transmitted NIR light in the brain is absorbed mainly by oxyhemoglobin, deoxyhemoglobin and water while it is scattered mainly due to red blood cells. The light absorption rates of oxyhemoglobin, deoxyhemoglobin and water varies at different wavelengths. Therefore, by measuring the differential changes of the received light intensity at multiple wavelengths, the concentrations of oxyhemoglobin and deoxyhemoglobin can be estimated.

Oxygenation measurements using NIRS are particularly successful in neonates because of their thin skulls. Early studies used continuous wave NIRS to measure oxyhemoglobin and deoxyhemoglobin concentrations, which give relative oxygen saturation[12–14]. In order to obtain absolute values of venous oxygenation, ratio of arterial and venous cerebral blood volume (CBV) is either assumed[12], or estimated from blood volume changes induced by either head-down tilt maneuver[13] or partial jugular venous compression[14]. Optical imaging technologies are continuingly evolving. A recent technique called frequency domain NIRS (FDNIRS) has shown great promises in absolute quantification of oxygenation saturation and CBV[15, 16] (Fig. 2).

Another challenging part for the optical methods is the quantitative measurement of cerebral blood flow (CBF). Some studies used non-optical methods as alternative for CBF quantification, such as the ^{133}Xe clearance technique[13]. Other studies used the diffuse correlation spectroscopy (DCS) to measure microvascular blood flow non-invasively without exogenous tracers[15, 16, 36]. DCS provides measurement of an index of cerebral blood flow, and in combination with oxygen saturation, provides an index of CMRO2 ($CMRO2_i$, [mol/dl·mm^2/second])[15, 16].

In 1992, using NIRS combined with ^{133}Xe injection and head tilting, Skov et al. reported a mean CMRO2 of 44.7±17.9 μmol/100g/min from 9 preterm neonates with respiratory distress syndrome and a mean CMRO2 of 62.6±35.8 μmol/100g/min from 10 asphyxiated, term neonates, but noted a 59% success rate using their technique[13]. Later in 1998, Yoxall et al. used NIRS with partial jugular venous occlusion for CBV estimation, and reported CMRO2 values varied between 23.2 and 78.7 μmol/100g/min from 20 neonates under intensive care aged between 24 and 41 gestational weeks, with 8 neonates under sedation during measurement, and 3 taking medication for seizure treatment[14]. More recently, Elwell et al. reported CMRO2 of 30.8 to 68.4 μmol/100g/min from 9 sick neonates between 23 to 37 gestational weeks using NIRS with assumed venous CBV and modeling[12]. Comparison of the NIRS-measured CMRO2 and other modalities are listed in Table 1.

It has been showed that relative CMRO2, or index of CMRO2 ($CMRO2_i$), measured by FDNIRS and DCS, could also be an effective indicator to monitor brain metabolism. Roche-Labarbe et al demonstrated the $CMRO2_i$ increases by 40% during the first six weeks of life (Fig. 2D)[16]. Dehaes et al reported that neonates with hypoxic ischemic encephalopathy (HIE) has lower $CMRO2_i$ during hypothermia treatment comparing to post-treatment ($p<0.01$) and healthy controls ($p<0.00001$)[15].

NIRS approaches of CMRO2 assessment have the advantages of low-cost and bedside access. However, absolute quantification of CMRO2 with this method is not yet straightforward, primarily because of the need to make assumptions on arterio-venous volume ratio and the difficulty in determining penetration depth.

MRI measurements of CMRO2 in the neonate

With the advances in technologies that are originally developed in adults, MRI methods for absolute CMRO2 quantification in the neonates are emerging[15, 24, 32]. Techniques for quantitative and non-invasive measurements of CBF, including phase-contrast MRI and

ASL MRI, are being adapted and optimized in neonates[22, 24, 32]. The feasibility of measuring oxygenation non-invasively using MRI has also been demonstrated by recent studies[15, 24, 32]. Two of such techniques measure venous blood oxygenation based on the transverse relaxation time of blood spins in magnetic field (i.e., T2 of blood)[24, 32]. The other technique is named as MR susceptometry, which measures the phase-angle induced by the blood's susceptibility[33].

T2-based CMRO2 measurement

T2-based measurements of Y_v rely on the principle that T2 relaxation time of the blood has a well-known and calibratable relationship with Y_v, thus one can measure pure blood T2 and then convert T2 to Y_v using a calibration plot[37].

One recently developed technique that can determine Y_v from blood T2 is T2-Relaxation-Under-Spin-Tagging (TRUST) MRI[37–39]. A unique aspect of TRUST MRI is that this method isolates pure venous blood by magnetically labeling the venous blood (using the principle similar to that in ASL MRI), thereby effectively minimizing confounding effects due to partial voluming of surrounding tissue and cerebrospinal fluid[38]. For T2 determination, the sequence applies various numbers of flow-insensitive T2-preparation pulses, thus the blood signal is modulate with different T2 weightings. The monoexponential fitting of the blood signal to the T2-preparation duration then gives the T2 value of the venous blood, which is then converted to Y_v via T2-Y_v calibration plot (Fig. 3A). The combination of Y_v measurement by TRUST at the large draining vein (superior sagittal sinus, Fig. 3A) and CBF measurement by phase-contrast MRI at the brain's feeding arteries (Fig. 3B), provides a whole-brain CMRO2 measurement technique to quantify global CMRO2[24, 39]. This technique is completely non-invasive (no need for any exogenous agents), rapid (<5 min scan time), and reliable (coefficient of variation, CoV<4% in adults) [19]. It has been validated in adults[37]. More recently, Liu et al. successfully applied this method to neonatal population, and reported an average CMRO2 of 38.3±17.7 μmol/100g/min in 10 healthy and non-sedated neonates aged between 35–42 gestational weeks[24]. It was found that CMRO2 increased rapidly during this period, as manifested by a positively correlation with age (p=0.007, slope 5.2 μmol/100g/min per week) (Fig. 3C). Test-retest studies showed a coefficient of variation of 5.8±2.2 % between repeated CMRO2 measurements using the technique[24].

More recently, another technique was reported to measure T2-based Y_v in neonates using a sequence called “T2 prepared tissue relaxation inversion recovery” (T2-TRIR)[32]. In this method, blood signal in superior sagittal sinus was detected by suppressing the static surrounding tissue. Similar to TRUST, the blood signal was modulated with different T2 weightings and then fitted for its T2 value (Fig. 4). ASL MRI was used to obtain whole brain CBF. The whole brain CMRO2 was then calculated according to Eq. [1]. Using this method, De Vis et al. reported the averaged CMRO2 of 30±12 μmol/100g/min in 10 healthy neonates (38–40 gestational weeks), which is significantly higher (p<0.01) than that of 24 μmol/100g/min measured in 9 HIE neonates(34–41 gestational weeks)[32].

MR susceptometry-based CMRO2 measurement

MR susceptometry measurement of Y_v relies on the relative magnetic susceptibility difference between intravascular blood and surrounding tissue[18]. This susceptibility difference affects the intravascular water protons, which results in a phase-shift of the MR signal that is correlated with the intravascular blood oxygenation (Fig. 5A and B). In combination with phase-contrast MRI for CBF measurement (Fig. 5C and D), this technique also provides rapid whole brain CMRO2 estimation with 5 minutes[18].

Jain et al demonstrated the feasibility of applying this technique in neonates with congenital heart disease (CHD)[33]. In 32 anesthetized full term neonates with CHD, they found a median CMRO2 of 23.2 μmol/100g/min, which is lower than the CMRO2 of healthy neonates in other literature reports at this age (Table 1). They also compared the MRI-measured CMRO2 with that measured by optics method (diffuse optical spectroscopy and diffuse correlation spectroscopy). Their results demonstrated a strong linear correlation between the MRI-method and optics method[33].

Clinical applications of CMRO2 measurement

Due to the increasing demand of energy in early brain development after birth, CMRO2 as a measure of oxygen supply and metabolism is a particularly important biomarker of neonatal brain health. Measurement of CMRO2 may be used to diagnose brain injuries, to provide mechanistic insights into the disease course, and to guide therapy on an individual basis.

Studies in normal healthy neonates using both NIRS and MRI methods revealed that CMRO2 increases quickly with age[16, 24], demonstrated the escalating cerebral energy demands for the complex structural and functional development at this stage. Using NIRS measurements, Roche-Labarbe et al reported an up-to-40% increase in relative CMRO2 during the first six weeks of life[16]. Using the MRI method with absolute CMRO2 quantification, Liu et al found that CMRO2 increases with gestational age at a rate of 5.2 μmol/100g/min per week, although the highest CMRO2 value in this age range was still less than half of the adult level[24]. This rate of increase during early brain development is in line with previous PET literature which showed that cerebral metabolism continues to increase from the third trimester until 4 years old, and then gradually reduces with age afterwards[40, 41].

Abnormal CMRO2 values are expected in neonates with brain injuries and other diseases. For instance, Jain et al. reported that CMRO2 in full-term newborn infants diagnosed with cyanotic heart disease was lower than literature reports for healthy term neonates while similar to the previously reported values for premature infants[33].

Biological plausibility supports that disruption of oxygen supply and metabolism would be detrimental in newborns. A specific example in newborns is HIE, caused by a hypoxic ischemic injury, resulting in acute mortality and chronic neurological disability in survivors. A very recent study this year reported that HIE neonates have lower CMRO2 comparing to healthy neonates (24 vs. 30 μmol/100g/min)[32], suggesting decreased neural activity as a result of brain tissue damage in HIE. Previous literature also showed that the cerebral

oxidative metabolism derangement at the first week of life in neonates with birth asphyxia might predict their neurodevelopmental outcome at 4 years old[42]. Thus, monitoring CMRO2 in neonatal patients and along their growth could improve the assessment of disease course and treatment outcomes.

Hypothermia is the only currently available neuroprotective therapy for HIE. One of the hypothesized mechanism by which hypothermia works is that it reduces brain metabolic rate and thus preserves high-energy phosphate compound (e.g. ATP) and prevent lactate production and tissue acidosis. Dehaes et al. using FDNIRS and DCS systems recently showed that cerebral oxygen metabolism ($CMRO2_i$) in HIE neonates during hypothermia treatment was significantly lower than post-hypothermia and age-matched healthy controls[15]. Since it is now practical to transport to the MRI scanner[43] with ongoing hypothermia therapy, quantification of CMRO2 with MR techniques may provide in situ valuable information.

Measuring CMRO2 in real time during hypothermia will allow to confirm mechanisms of neuroprotection and to establish likelihood of therapeutic responses in real time, rather than current status of knowledge where one needs to wait 18–24 months. Similarly, future randomized neuroprotective trials [44–46] could benefit from an insight into mechanisms of therapeutic responses via measurement of CMRO2.

Conclusion

Disruptions in oxygen supply and metabolism has been associated with several cerebral injuries, such as HIE, stroke and metabolic disorders, all of which may lead to long-term neurologic deficits. Application of CMRO2 measurements in these diseases would provide a better understanding of the etiology of these neonatal brain injuries, as well as for the diagnosis and treatment assessment of these injuries on an individual basis. Fortunately, several emerging CMRO2 techniques that are suitable for neonates may be able to fill this gap by providing an quantitative index of brain function.

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Research Directions

- The above mentioned techniques are still research based and not ready for clinical implementation into practice.
- Further development of accurate and reliable techniques to measure CMRO2 in neonates non-invasively.
- Clinical applications of CMRO2 measurement in neonatal brain injuries.

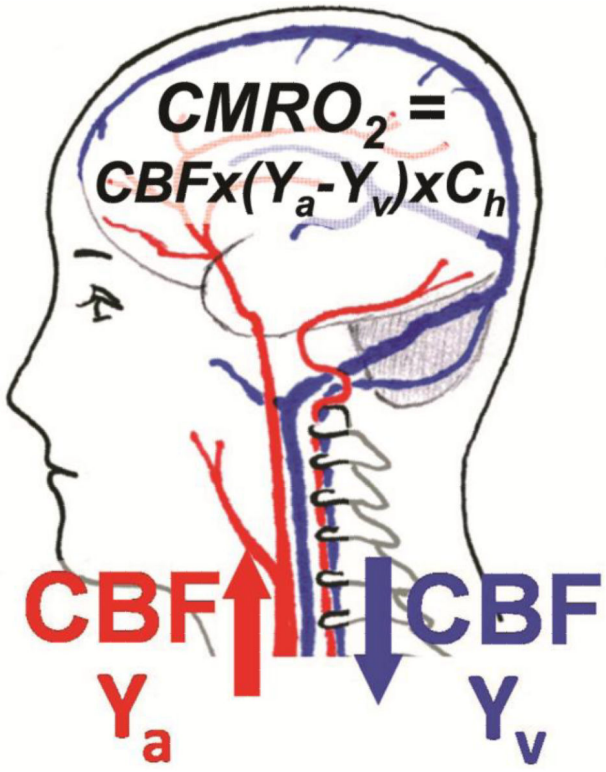

Figure 1.
Illustration of the relationship among different physiologic parameters associated with oxygen demand and supply of the brain.

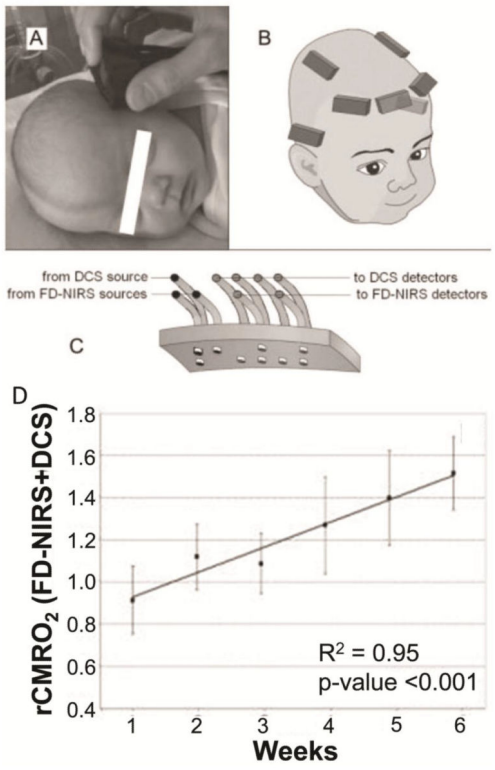

Figure 2.

Illustration of relative CMRO2 measurement using FD-NIRS and DCS[16]. (A) Picture of a subject during a measurement. (B) Locations of optical probes on a subject. (C) Schema of the optical probe. (D) Resulted relative CMRO2 (rCMRO2) increases quickly with age after birth.

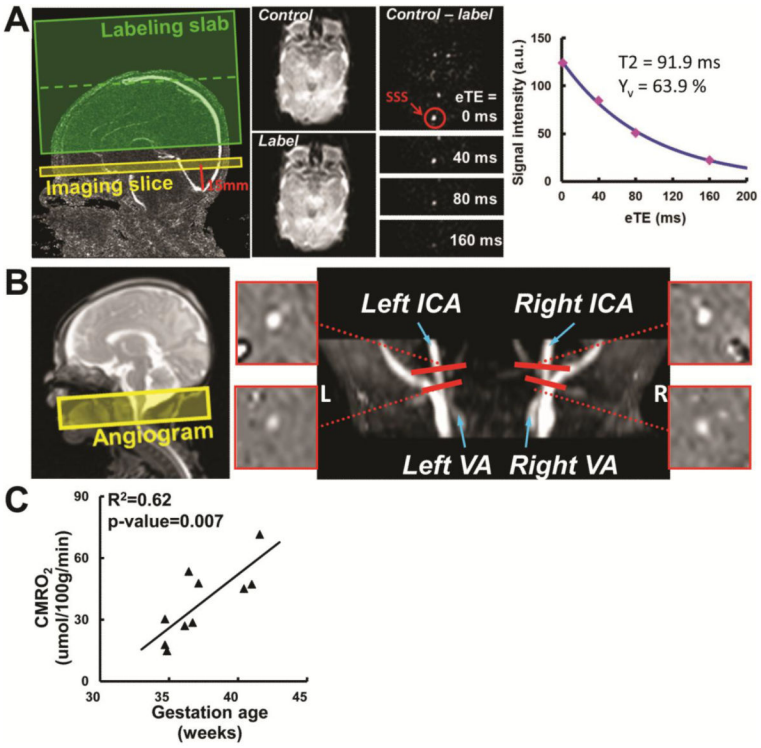

Figure 3.

TRUST-based CMRO2 measurement on a representative neonate. (A) Measurement of venous oxygenation (Y_v) using T_2-Relaxation-Under-Spin-Tagging (TRUST) MRI. SSS, superior sagittal sinus. (B) Measurement of cerebral blood flow (CBF) using Phase-Contrast (PC) MRI on the feeding arteries. ICA, internal carotid artery. VA, vertebral artery. (C) Resulted CMRO2 increases quickly with gestational age (at the time of scan).

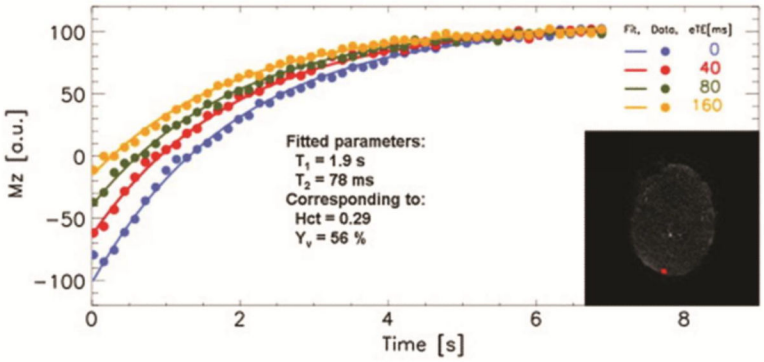

Figure 4.

T2-TRIR measurement of Y_v at superior sagittal sinus[32]. Four inversion recovery curves of blood signal from sagittal sinus with different T2-weighting are shown. Insert: The brain tissue is saturated, while only inflowing blood within the sagittal sinus is visible.

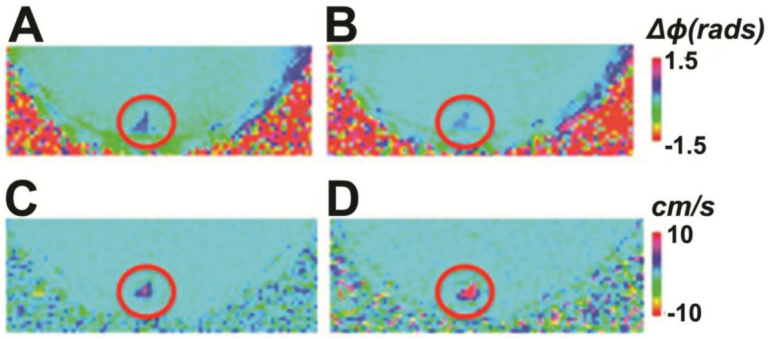

Figure 5.

MR susceptometry-based CMRO2 measurement in a typical subject[33]. MR images during room air breathing (A, C) and during hypercapnia breathing (B,D) are shown. (A, B) Phase-difference images used for calculating Y_v. (C, D) Velocity maps used for calculating CBF. Both acquired in the superior sagittal sinus (SSS, red circle).

Table 1

$CMRO_2$ values reported in literature.

Study	Method	Number of subjects	Gestational age (weeks)	Subject condition	Y_v (%)	CBF (ml/100g/min)	$CMRO_2$ (μmol/100g/min)
Skov et al, 1993 [13]	NIRS	32	26 – 39	Asphyxiated; RDS	53.44±15.36 (preterm) 67.30±9.38 (term)	12.6±6.4 (preterm) 26.5±17.9 (term)	44.7±17.9 (preterm) 62.6±35.8 (term)
Altman et al, 1993 [9]	PET	11	26 – 41	HIE and other conditions	-	21.6±21.0	21.4±16.4
Yoxall and weindling, 1998 [14]	NIRS	20	24 – 41	Seizure and other conditions	64.6 (76.1 – 46.8)	9.3 (4.5 – 28.3)	23.1 (8.6 – 78.5)
Elwell et al, 2005 [12]	NIRS	9	23 – 37	Ventilatory support	-	-	45.9±12.3
Liu et al, 2014[24]	MRI	12	35 – 42	Healthy	62.6±8.3	13.4±4.2	38.3±17.7
Jain et al, 2014[33]	MRI	33	38 – 40	CHD	55.2 (49.3 – 60.2)	9.7 (7.5 – 15.1)	23.2 (17.8 – 35.2)
De Vis et al, 2014[32]	MRI	51	28 – 52	Healthy, HIE and other diagnosis	52±12 (healthy) 65±13 (HIE)	14±3 (healthy) 12±4 (HIE)	30±6 (healthy) 24±12 (HIE)

NIRS, near infrared spectroscopy; PET, positron emission tomography; MRJ, magnetic resonance imaging; RDS, Respiratory distress syndrome; HIE, Hypoxic-ischemic encephalopathy; CHD, Congenital heart disease.