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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 ($CMRO_2$), 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 $CMRO_2$ in humans has been a challenging task, particularly in neonates. Recently, several promising techniques have been proposed to quantify neonatal $CMRO_2$ 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 $CMRO_2$ techniques are discussed in the context of their advantages, challenges and limitations.

1. 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, a 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, the measurement of cerebral oxygen metabolism, denoted by cerebral metabolic rate of oxygen ($CMRO_2$), is particularly challenging in neonates, compared to other physiologic parameters such as perfusion and diffusion. Several $CMRO_2$ measurement techniques have been developed in adults, but so far only a few of them have been shown to be feasible in neonates.

2. General principle underlying $CMRO_2$ measurement techniques

Most $CMRO_2$ measurement techniques are based on a simple principle called the Fick's principle. Basically, the amount of O_2 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 $CMRO_2$. 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, $CMRO_2$ (in unit of μmol/100 g/min) can be quantified from arterio-venous difference in oxygen content according to the Fick Principle [6]:

$$CMRO2 = CBF \bullet (Y_a - Y_v) \bullet C_h, \quad (1)$$

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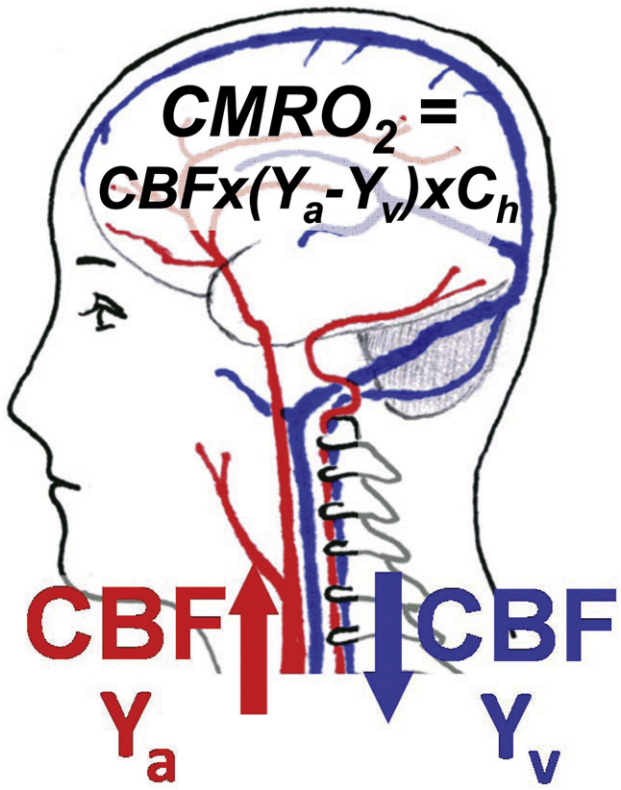

Fig. 1. Illustration of the relationship among different physiologic parameters associated with oxygen demand and supply of the brain.

where C_h is the amount of O_2 molecules that a unit volume of blood can carry and is proportional to hematocrit (8.97 μmol 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, $CMRO_2$ can be calculated. Different modalities and techniques can be used to measure these parameters for $CMRO_2$ quantification.

3. Available $CMRO_2$ techniques

Positron Emission Tomography (PET) is considered the gold standard method to measure brain metabolism in adults [8]. In this technique, CBF, OEF and $CMRO_2$ are measured with the infusion and inhaling of ^{15}O- labeled radiotracers (i.e., $H_2^{15}O$, $C^{15}O$ 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 $CMRO_2$ 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 $CMRO_2$ 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 has been an increasing number of reports that used NIRS methods to measure $CMRO_2$ 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 $CMRO_2$ 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 $CMRO_2$ 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 $CMRO_2$ 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 $CMRO_2$ in adults, but have not been applied to neonatal brain yet.

4. NIRS measurement of $CMRO_2$ 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 vary 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, the 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 $CMRO_2$ ($CMRO_{2i}$, [mol/dl · mm^2/s]) [15,16].

In 1992, using NIRS combined with ^{133}Xe injection and head tilting, Skov et al. reported a mean $CMRO_2$ of 44.7 ± 17.9 μmol/100 g/min from 9 preterm neonates with respiratory distress syndrome and a mean $CMRO_2$ of 62.6 ± 35.8 μmol/100 g/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 $CMRO_2$ values varied between 23.2 and 78.7 μmol/100 g/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 $CMRO_2$ of 30.8 to 68.4 μmol/100 g/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 $CMRO_2$ and other modalities are listed in Table 1.