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Non-invasive MRI measurements of venous oxygenation, oxygen extraction fraction and oxygen consumption in neonates ☆

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ABSTRACT

Background and purpose: Brain oxygen consumption reflects neuronal activity and can therefore be used to investigate brain development or neuronal injury in neonates. In this paper we present the first results of a non-invasive MRI method to evaluate whole brain oxygen consumption in neonates.
Materials and methods: For this study 51 neonates were included. The T_1 and T_2 of blood in the sagittal sinus were fitted using the 'T2 prepared tissue relaxation inversion recovery' pulse sequence (T2-TRIR). From the T_1 and the T_2 of blood, the venous oxygenation and the oxygen extraction fraction (OEF) were calculated. The cerebral metabolic rate of oxygen ($CMRO_2$) was the resultant of the venous oxygenation and arterial spin labeling whole brain cerebral blood flow (CBF) measurements.
Results: Venous oxygenation was 59 ± 14% (mean ± sd), OEF was 40 ± 14%, CBF was 14 ± 5 ml/100 g/min and $CMRO_2$ was 30 ± 12 μmol/100 g/min. The OEF in preterms at term-equivalent age was higher than in the preterms and in the infants with hypoxic–ischemic encephalopathy ($p < 0.01$). The OEF, CBF and $CMRO_2$ increased ($p < 0.01$, <0.05 and <0.01, respectively) with postnatal age.
Conclusion: We presented an MRI technique to evaluate whole-brain oxygen consumption in neonates non-invasively. The measured values are in line with reference values found by invasive measurement techniques. Preterms and infants with HIE demonstrated significant lower oxygen extraction fraction than the preterms at term-equivalent age. This could be due to decreased neuronal activity as a reflection of brain development or as a result of tissue damage, increased cerebral blood flow due to immature or impaired autoregulation, or could be caused by differences in postnatal age.

Introduction

Brain growth (Kretschmann et al., 1986) and myelinisation are at their maximum postnatal (Bourgeois and Rakic, 1993) which makes this period of brain development most vulnerable. Both myelinisation and increases in capillary density are known to be energy demanding (Altman et al., 1988) and therefore monitoring the energy consumption of the brain can be used to evaluate brain development. Due to technical advances in neonatal intensive care an increasing number of infants are born preterm. Preterm infants are at risk for cerebral injury such as hypoxia–ischemia, stroke and periventricular leukomalacia causing neurological deficits (Kiechl-Kohlendorfer et al., 2009). Hemodynamic instability may be the cause of these injuries necessitating the need for hemodynamic monitoring of the brain. In 2 per 1000 term live births hypoxic–ischemic encephalopathy occurs (Himmelmann et al., 2005). The majority of these infants suffer from the reperfusion phenomenon in which autoregulation is lost causing hyperperfusion (Pryds et al.,

Abbreviations: ASL, arterial spin labeling; C_a, oxygen carrying capacity of blood; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; Hct, hematocrit; HIE, hypoxic–ischemic encephalopathy; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; OEF, oxygen extraction fraction; PASL, pulsed arterial spin labeling; PMA_b, postmenstrual age at birth; PMA_s, postmenstrual age at the time of MR imaging; PNA, postnatal age; sd, Standard deviation; StO_2, tissue oxygen saturation; T_{1b}, longitudinal relaxation time of blood; T_{2b}, transverse relaxation time of blood; T2-TRIR, T2 prepared tissue relaxation inversion recovery; PT-TEA, Preterm at term-equivalent age; TRUST-MRI, T2-relaxation under spin tagging MRI; Y_a, arterial oxygen saturation; Y_v, venous oxygen saturation.

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1990) which restores the high energy phosphates and can lead to delayed cell death (Grant and Yu, 2006). Brain hemodynamic evaluation may detect this hyperperfusion stage (Shi et al., 2012) and could then be used to initiate and evaluate neuroprotective therapies. Quantitative estimates of the brain oxygen consumption can be obtained with oxygen-15 positron emission tomography (Mintun et al., 1984). Alternatively, the xenon clearance technique can measure the cerebral blood flow and provides a measurement of the brain oxygen consumption when the oxygenation in the jugular vein is evaluated (Skov et al., 1993). Unfortunately, both techniques are invasive as they require the use of ionizing radiation which limits their usability in neonates. An upcoming non-invasive tool to evaluate brain hemodynamics is near infrared spectroscopy (NIRS). This technique relies on the attenuation of near-infrared light (~650–950 nm) when it permeates biological tissue. Deoxygenated and oxygenated hemoglobin contribute to this attenuation. Therefore, NIRS can be used to estimate changes in deoxyhemoglobin and oxyhemoglobin (Wray et al., 1988) allowing for an evaluation of the oxygen saturation of the tissue (StO_2). This technique is advantageous as it allows for a non-invasive continuous monitoring at the bedside. However, NIRS is limited to the evaluation of the overall tissue oxygen saturation and not the oxygen extraction fraction, and therefore, the technique does not allow for the evaluation of the oxygen consumption. In addition, it only provides regional evaluation at the location where the probe is positioned and the sensitivity of NIRS is limited to the superficial brain tissue as the penetration depth of near-infrared light is limited (Boas et al., 2004). Non-invasive methods which can evaluate whole brain oxygen consumption are currently under investigation. A combined approach of non-invasive venous oxygenation measurements in the sagittal sinus, using T_2-relaxation–under-spin-tagging magnetic resonance imaging (TRUST-MRI) (Lu and Ge, 2008), and flow measurements with phase-contrast MR angiography has been used to evaluate whole brain oxygen consumption in adults (Xu et al., 2009) and the feasibility of this technique within neonates has been investigated (Liu et al., 2014). Another non-invasive MRI technique to evaluate venous oxygenation and oxygen consumption in the brain combines MR susceptometry, to evaluate the venous oxygenation in the sagittal sinus, with phase-contrast MR angiography (Jain et al., 2011). Venous oxygenation and brain oxygen consumption measurements, obtained in neonates with this technique, were shown to correlate well to results obtained by means of diffuse optical and correlation spectroscopies (Jain et al., 2013).

In this paper we present a newly developed non-invasive approach to investigate whole brain oxygen consumption in neonates. The 'T2 Prepared Tissue Relaxation Inversion Recovery' (T2-TRIR) MRI pulse sequence (Petersen et al., 2012) is used to measure the transverse and longitudinal relaxation rate of blood (T_{2b} and T_{1b}) in the sagittal sinus. The venous oxygenation is subsequently derived from the T_{2b} and the T_{1b}-derived hematocrit (Lu et al., 2012). Arterial oxygenation is measured with pulse oximetry allowing for a calculation of the oxygen extraction fraction. Pulsed arterial spin labeling (ASL) perfusion MRI is used to measure whole brain cerebral blood flow. By combining information of venous oxygenation, arterial oxygenation and whole brain cerebral blood flow a non-invasive MRI measurement of the brain oxygen consumption is obtained. In order to investigate the validity of this new non-invasive approach we compare the obtained results to previous reported reference values (Altman et al., 1993), investigate if the technique detects changes related to postnatal age, as was earlier found by NIRS studies (Franceschini et al., 2007; Roche-Labarbe et al., 2012) and are thought to be related to the decline in hematocrit after birth (Palis and Segel, 1998), and we evaluate if the technique can detect differences in between categories of neonates which can be contributed to differences in neuronal activity. For the latter, results obtained in preterm neonates and in neonates with hypoxic–ischemic encephalopathy are compared to the results of neonates at term-equivalent age.

Materials and methods

Subjects

The present study was approved by our institutional review board and the requirement to obtain written parental informed consent was waived. Fifty-one neonates who underwent MRI for clinical reasons were included: 5 preterm infants, 17 preterms with MR imaging at term-equivalent age (PT-TEA), 19 infants with hypoxic–ischemic encephalopathy (HIE) and 9 infants with another diagnosis (others). Mean postmenstrual age at the time of MR imaging was 29 weeks for preterms (range: 28–29 weeks), 39 weeks for PT-TEA (range: 38–40 weeks), 38 weeks for HIE (range: 34–41 weeks) and 39 weeks for the infants with another diagnosis (range: 33–52 weeks). HIE was diagnosed in infants having altered alertness, abnormal tone, feeding difficulties or seizures with at least three of the following criteria: 1) late decelerations on fetal monitoring or meconium staining, 2) delayed onset of respiration, 3) arterial cord blood pH < 7.10, 4) Apgar scores <7 at 5 min, and 5) multi-organ failure (van Rooij et al., 2010). The baseline characteristics – postmenstrual age at birth, postmenstrual age at the time of MR imaging, postnatal age and reason for MRI – for all groups are shown in Table 1.

MR imaging

MR imaging was performed on a 3.0 Tesla Philips Achieva System (Philips Medical Systems, Best, The Netherlands) with a quadrature body coil for transmission and an 8-element phased-array SENSE head coil as a signal receiver. Prior to MR imaging infants were sedated; either by oral administration of chloral hydrate (50 to 60 ml per kilogram body

Table 1
Baseline characteristics.

	n	PMA_b (in weeks)	PMA_s (in weeks)	PNA (in days)	Reason for MRI	n
Preterm	5	26 (24–28)	29 (28–29)	21 (7–38)	PMA_b < 28 wks	5
PT-TEA	18	27 (24–31)	39 (38–40)	79 (37–106)	PMA_b < 28 wks	15
					PHVD	2
					Enlarged ventricles on US	1
HIE	19	37 (34–40)	38 (34–41)	5 (2–7)	Hypoxic–ischemic encephalopathy	19
Others	9	35 (32–39)	39 (33–52)	24 (1–93)	Stroke	6
					Ischemic lesions on US	1
					Post-surgery	1
					Suspected for neuromuscular disease	1

PMA_b = postmenstrual age at birth, mean (range); PMA_s = postmenstrual age at the time of MR imaging, mean (range); PNA = postnatal age, mean (range); PT-TEA = preterm born infants with MR imaging at term-equivalent age; PHVD = posthemorrhagic ventricular dilatation; HIE = infants with hypoxic–ischemic encephalopathy; US = ultrasound.
The category 'others' comprises all infants who did not fit in any of the other categories.