NeuroImage 85 (2014) 279–286

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Somatosensory evoked changes in cerebral oxygen consumption measured non-invasively in premature neonates

Nadege Roche-Labarbe [a,b,*], Angela Fenoglio [c], Harsha Radhakrishnan [a], Marcia Kocienski-Filip [d], Stefan A. Carp [a], Jay Dubb [a], David A. Boas [a], P. Ellen Grant [c,d], Maria Angela Franceschini [a]

[a] A.A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
[b] Laboratoire Psychologie des Actions Langagières et Motrices, Université de Caen Basse-Normandie, France
[c] Fetal-Neonatal Neuroimaging & Developmental Science Center, Children's Hospital Boston, MA, USA
[d] Newborn Medicine, Brigham and Women's Hospital, Boston, MA, USA

ARTICLE INFO

Available online 28 January 2013

Keywords:
Oxygen metabolism
Functional activation
Premature neonates
Somatosensory cortex
Near infrared spectroscopy
Diffusion correlation spectroscopy

ABSTRACT

The hemodynamic functional response is used as a reliable marker of neuronal activity in countless studies of brain function and cognition. In newborns and infants, however, conflicting results have appeared in the literature concerning the typical response, and there is little information on brain metabolism and functional activation. Measurement of all hemodynamic components and oxygen metabolism is critical for understanding neurovascular coupling in the developing brain.

To this end, we combined multiple near infrared spectroscopy techniques to measure oxy- and deoxy-hemoglobin concentrations, cerebral blood volume (CBV), and relative cerebral blood flow (CBF) in the somatosensory cortex of 6 preterm neonates during passive tactile stimulation of the hand. By combining these measures we estimated relative changes in the cerebral metabolic rate of oxygen consumption ($rCMRO_2$).

CBF starts increasing immediately after stimulus onset, and returns to baseline before blood volume. This is consistent with the model of pre-capillary arteriole active dilation driving the CBF response, with a subsequent CBV increase influenced by capillaries and veins dilating passively to accommodate the extra blood. $rCMRO_2$ estimated using the steady-state formulation shows a biphasic pattern: an increase immediately after stimulus onset, followed by a post-stimulus undershoot due to blood flow returning faster to baseline than oxygenation. However, assuming a longer mean transit time from the arterial to the venous compartment, due to the immature vascular system of premature infants, reduces the post-stimulus undershoot and increases the flow/consumption ratio to values closer to adult values reported in the literature.

We are the first to report changes in local rCBF and $rCMRO_2$ during functional activation in preterm infants. The ability to measure these variables in addition to hemoglobin concentration changes is critical for understanding neurovascular coupling in the developing brain, and for using this coupling as a reliable functional imaging marker in neonates.

Introduction

The mature brain's functional response to stimulation involves an increase in oxygen metabolism and an even greater hemodynamic response (Fox and Raichle, 1986). This disproportionate increase in blood flow over oxygen consumption leads to an increased blood volume (CBV) and oxygenation (SO_2) signal in functional near-infrared spectroscopy (fNIRS) and blood oxygen level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI). This positive functional response is used as a reliable marker of neuronal activity in countless studies of brain function and cognition. In newborns and infants, however, there is little information about brain metabolism and functional activation, though both may differ from those in adults. Unexplained negative functional responses, as well as positive and biphasic responses, have been reported (see Seghier et al. (2006), Lloyd-Fox et al. (2009), Wolf and Greisen (2009) for a review). This is a major obstacle in fundamental and clinical studies of early brain function and cognition.

In order to clarify the functional response in newborns and infants, it is necessary to measure all hemodynamic components and oxygen metabolism. To this end, we combined multiple NIRS techniques to obtain safe and noninvasive measures of functional changes in blood flow, blood volume, oxygenation, and oxygen metabolism in premature infants. In particular, we used diffuse correlation spectroscopy (DCS) to measure relative cerebral blood flow changes (rCBF) (Boas et al., 1995; Durduran et al., 2004), frequency-domain near-infrared spectroscopy (FDNIRS) to measure baseline hemoglobin concentration and saturation (Franceschini et al., 2007), and continuous-wave near-infrared spectroscopy (CWNIRS) to measure hemoglobin concentration and

* Corresponding author at: Lab. PALM, MRSH, SH018, Université de Caen, Campus 1, Esplanade de la Paix, 14000 CAEN, France.
E-mail address: nadege.roche@unicaen.fr (N. Roche-Labarbe).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.01.035

saturation changes. By combining all of these measures we report the relative change in the cerebral metabolic rate of oxygen ($rCMRO_2$) in the somatosensory cortex of preterm newborns during a tactile stimulus. While baseline regional CBF and $CMRO_2$ have been previously measured in neonates using this method (Durduran et al., 2010; Roche-Labarbe et al., 2010) or other optical methods (Edwards et al., 1988; Elwell et al., 2005; Noone et al., 2003; Patel et al., 1998), we are the first to report functional changes in $CMRO_2$.

We first calculated $CMRO_2$ using the steady-state formulation. This common approach simply combines relative changes in blood flow and oxygenation. We then tested two dynamic models. The first model, proposed by Mayhew et al. (2001) and used in rats by Jones et al. (2001) and Dunn et al. (2005), allows us to assign different fractions of functional changes versus baseline values of HbR and HbT concentrations in the venous compartment with respect to the total volume fractions. This is done to compensate for the fact that the NIRS measurements average the hemoglobin changes over the arterial, capillary, and venous compartments and do not provide a direct measure of the changes in the venous compartment alone. The second model, derived from Buxton et al. (1998) and Hoge et al. (2005), allows us to test the influence of the blood transit time from the arterial to venous compartment on the oxygen extraction fraction. While in the steady-state formulation transit time is considered equal to zero, it is possible that low blood flow in infants has a non-negligible effect on oxygen extraction from the blood during transit from arteries to veins. Our results provide the first account of oxygen metabolism during brain activity in neonates.

Methods

Subjects

Between October 2010 and June 2011 in the neonatal ICU at Brigham and Women's Hospital, we recruited 6 neonates born at 33 or 34 weeks GA (2 females), with no known neurological or cardio-respiratory issues. All had APGAR scores ≥ 8 after 5 min, with the exception of subject 5, who scored 5 at 5 min but reached 8 after 10 min. Subjects were not under respiratory support or medication that would modify their vigilance or brain function. Measurements were performed during post-feeding sleep. Only subject 4 had SaO_2 monitoring, which was stable between 97 and 100%. We performed functional measurements within the first 2.5 weeks of life and four infants (subjects 1, 2, 3, and 5) were measured twice in this time period. Data from the first measurement session on subject 3 were discarded due to poor DCS signals. Our Institutional Review Board approved the study and parents provided informed consent.

Techniques and acquisition protocol

To assess relative changes in $CMRO_2$ we combined three NIRS modalities: frequency-domain near-infrared spectroscopy, continuous-wave near-infrared spectroscopy, and diffusion correlation spectroscopy. In particular, for FDNIRS we used a customized commercial frequency-domain oximeter from ISS, Inc. (Champaign IL, USA, www.iss.com) (Franceschini et al., 2007), for CWNIRS we used a CW6 8×8 system made by TechEn, Inc. (Milford, MA, USA, www.techen.com) (Franceschini et al., 2006; Wilcox et al., 2012), and for DCS we used a custom-built device similar to the system developed by Drs. Arjun Yodh and Turgut Durduran at the University of Pennsylvania (Cheung et al., 2001; Durduran et al., 2004; Li et al., 2005). We have previously used these devices in measurements in infants and technical details are reported in several papers (Franceschini et al., 2007; Grant et al., 2009; Roche-Labarbe et al., 2010; Zimmermann et al., 2012). For the present study, the three devices were contained in a small cart, controlled by the same laptop computer, and operated in sequence (Fig. 1).

We could have used FDNIRS to measure relative changes during functional measurements, but the availability in our lab of a CW system with a larger number of channels, higher acquisition rate and better signal-to-noise ratio prompted us to use CWNIRS for the functional measurements.

The FDNIRS measurements were performed at the beginning of the session to obtain baseline optical properties at 6 wavelengths ranging from 660 to 830 nm; from these we fit the hemoglobin absorption spectrum to obtain concentration values (Franceschini et al., 2007). We used a rigid handheld probe with sources and detector fibers arranged in a row and separated by 1, 1.5, 2, and 2.5 cm distances, as described by Roche-Labarbe et al. (2010). These small distances are optimal for premature neonates, whose head is about half the size of a 6 months old infant's with much thinner scalp and skull, as shown by experimental results in layered phantoms and Monte Carlo simulations in 3D segmented MRI of a neonate's head (Dehaes et al., 2011; Fabbri et al., 2004; Franceschini et al., 1998). The FDNIRS probe was kept in place over the left somatosensory cortex (position C3 in the 10–20 system) for sixteen seconds of data acquisition. The measurement was repeated five times, with the probe repositioned to account for local inhomogeneities such as hair and superficial large vessels and thus to ensure that the measurement was representative of the underlying brain region. Measurements were averaged to obtain absolute baseline values.

The CWNIRS and DCS measurements were performed during functional stimulation to measure evoked changes in hemoglobin oxygenation and blood flow. For the CWNIRS measurements we used three source pairs (two lasers each emitting at 690 and 830 nm) and four APD detectors, all coupled to glass fiber bundles. Data from all sources and detectors was simultaneously acquired at 25 Hz. We arranged the three source fibers in a row in a flexible black rubber probe ($5\times3\times0.5$ cm^3) and the four detectors in an X pattern around the central source, with source-detector distances of 1.5 cm (Fig. 1). This distance is adequate for a depth penetration of about 0.8–1 cm, which includes the cerebral cortex in preterm neonates (Dehaes et al., 2011). Besides, peripheric channels show a much smaller response than central channels (located over the region of interest), ensuring that we are not measuring systemic changes (Supplementary Fig. 1). For the DCS we used a long coherence length solid state laser emitting at 785 nm coupled to a multimode silica fiber and 4 photon counting APD detectors coupled to single mode fibers. The intensity autocorrelation function of each detector channel was computed by a digital correlator (Correlator.com, Bridgewater, NJ), and an autocorrelation curve was acquired every second over a delay time range of 200 ns to 0.5 s.

For the DCS, the source fiber was set next to the central CWNIRS source, with the detectors arranged in an X pattern next to the CWNIRS detectors, maintaining the same source-detector distances (Fig. 2).

The CWNIRS-DCS probe was then strapped over the same cortical area measured with the FDNIRS probe, with the central source located over the C3 position. Continuous CWNIRS and DCS measurements were performed alternatively in 5 min long functional runs. We acquired up to 6 functional runs per session (3 CWNIRS and 3 DCS), during which we stimulated the infant's right hand by gently stroking it with a toothbrush. During each run 10 stimuli, 5 s long, were presented pseudo-randomly every 20–30 s. Total examination time was 60 min, while subjects were asleep.

Data processing

Frequency-domain near-infrared spectroscopy

To analyze the FDNIRS data in a standardized fashion we used an automated data analysis routine, which includes data quality assessment and data rejection based on previously established statistical criteria (Franceschini et al., 2007). We used the amplitude and phase data collected at four distances to determine absorption and scattering