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Dual role of cerebral blood flow in regional brain temperature control in the healthy newborn infant

Sachiko Iwata[a,b], Ilias Tachtsidis[c], Sachio Takashima[d], Toyojiro Matsuishi[a], Nicola J. Robertson[b], Osuke Iwata[a,b,*]

[a] Centre for Developmental and Cognitive Neuroscience, Department of Paediatrics and Child Health, Kurume University School of Medicine, Kurume, Fukuoka, Japan
[b] Institute for Women's Health, University College London, London, UK
[c] Department of Medical Physics and Bioengineering, University College London, London, UK
[d] Yanagawa Institute for Developmental Disabilities, International University of Health and Welfare, Fukuoka, Japan

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ABSTRACT

Small shifts in brain temperature after hypoxia–ischaemia affect cell viability. The main determinants of brain temperature are cerebral metabolism, which contributes to local heat production, and brain perfusion, which removes heat. However, few studies have addressed the effect of cerebral metabolism and perfusion on regional brain temperature in human neonates because of the lack of non-invasive cot-side monitors. This study aimed (i) to determine non-invasive monitoring tools of cerebral metabolism and perfusion by combining near-infrared spectroscopy and echocardiography, and (ii) to investigate the dependence of brain temperature on cerebral metabolism and perfusion in unsedated newborn infants.

Thirty-two healthy newborn infants were recruited. They were studied with cerebral near-infrared spectroscopy, echocardiography, and a zero-heat flux tissue thermometer. A surrogate of cerebral blood flow (CBF) was measured using superior vena cava flow adjusted for cerebral volume (rSVC flow). The tissue oxygenation index, fractional oxygen extraction (FOE), and the cerebral metabolic rate of oxygen relative to rSVC flow ($CMRO_2$ index) were also estimated.

A greater rSVC flow was positively associated with higher brain temperatures, particularly for superficial structures. The $CMRO_2$ index and rSVC flow were positively coupled. However, brain temperature was independent of FOE and the $CMRO_2$ index. A cooler ambient temperature was associated with a greater temperature gradient between the scalp surface and the body core.

Cerebral oxygen metabolism and perfusion were monitored in newborn infants without using tracers. In these healthy newborn infants, cerebral perfusion and ambient temperature were significant independent variables of brain temperature. CBF has primarily been associated with heat removal from the brain. However, our results suggest that CBF is likely to deliver heat specifically to the superficial brain. Further studies are required to assess the effect of cerebral metabolism and perfusion on regional brain temperature in low-cardiac output conditions, fever, and with therapeutic hypothermia.

1. Introduction

Therapeutic hypothermia is safe and provides significant protection for one in six to seven neonates with moderate to severe neonatal encephalopathy (Edwards et al., 2010; Jacobs et al., 2013). Small shifts in brain temperature are known to affect neuronal death following hypoxia–ischaemia (Ginsberg et al., 1992; Laptook et al., 2008). Therefore, the importance of monitoring and controlling brain temperature in sick infants is increasingly recognised. Brain temperature is determined by the balance between local heat production and heat removal. Local heat production is represented by cerebral metabolism, whereas heat removal depends on cerebral

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate of oxygen; FOE, fractional oxygen extraction; Hb, haemoglobin; LVO, left ventricular output; NIRS, near-infrared spectroscopy; rSVC flow, superior vena cava flow corrected to 100 g of brain mass; SaO_2, arterial blood oxygen haemoglobin saturation; SVC, superior vena cava; SvO_2, cerebral venous oxygen saturation; TOI, tissue oxygenation index.

* Corresponding author at: Centre for Developmental and Cognitive Neuroscience, Department of Paediatrics and Child Health, Kurume University School of Medicine, Asahimachi, Kurume, Fukuoka 830-0011, Japan. Tel.: +81 942 31 7565; fax: +81 942 38 1792.
E-mail addresses: o.iwata@ucl.ac.uk, oiwata@med.kurume-u.ac.jp (O. Iwata).

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blood flow (CBF) and heat dissipation through the scalp (Sukstanskii and Yablonskiy, 2006). Previous pre-clinical and clinical studies have identified factors that determine body/brain temperature in newborn infants, such as ambient temperature and humidity, and maturity and body size (Karlsson et al., 1995; Simbruner et al., 2005; Iwata et al., 2006). However, associations between brain temperature, metabolism, and perfusion have not been fully investigated.

Near-infrared spectroscopy (NIRS) has been used to assess brain oxygenation and haemodynamic changes non-invasively in newborn infants (Wyatt et al., 1986). Using tracers, such as oxygen and indocyanine green, NIRS can also provide information on cerebral perfusion (Edwards et al., 1988; Patel et al., 1998). However, the oxygen bolus technique cannot be performed when infants are already on 100% oxygen or are well saturated in air. Intravenous infusion of indocyanine dye may be burdensome to some critically ill infants. Eventually, most clinical studies of NIRS were performed without using tracers. Because simple NIRS measures are unable to distinguish contributions of tissue oxygen delivery and consumption, findings were often difficult to translate. Further techniques have been developed to allow the absolute quantification of brain tissue oxygenation and estimation of oxygen metabolism without using tracers (Boas et al., 2003; Roche-Labarbe et al., 2010). However, these techniques are available only in limited institutions.

Ultrasound Doppler velocimetry has also been proposed as an alternative non-invasive CBF marker (Scheel et al., 2000; Schoning and Hartig, 1996). Monitoring of superior vena cava (SVC) flow is accepted, based on its correlation with the flow velocity of cerebral arteries, cerebral tissue oxygenation, and the incidence of intraventricular haemorrhage in preterm infants (Evans et al., 2002; Moran et al., 2009; Takami et al., 2010).

This study aimed to investigate the associations among cerebral metabolism, perfusion, and body/brain temperatures in healthy newborn infants. To assess the correlations between these variables, we also aimed to determine novel cot-side markers of cerebral perfusion and metabolism by combining non-invasive techniques of NIRS and echocardiography.

2. Materials and methods

This study was conducted under the approval of the ethics committee of Kurume University School of Medicine with written informed consent from a parent of each participating newborn infant.

2.1. Study population

Thirty-two newborn infants without major cerebral lesions or congenital heart diseases (12 males and 20 females; postnatal age, 21 ± 17 days; postconceptional age, 38.3 ± 2.6 weeks; body weight, 2616 ± 515 g; mean ± standard deviation) were recruited from the special care unit of a tertiary neonatal intensive care unit (Kurume University Hospital, Fukuoka, Japan). These newborn infants initially required medical care because of preterm birth (n = 18), transient feeding problems (n = 5), transient neonatal tachypnoea (n = 4), gestational diabetes mellitus of the mother (n = 3), hypoglycaemia (n = 1), and multiple minor anomalies (n = 1). However, by the time of the study, all newborn infants were stable and healthy, and were cared for in an open cot with an ambient temperature of approximately 25–26 °C. A cotton blanket was placed over the limbs and the trunk in all newborn infants.

2.2. Data collection

We examined the newborn infants approximately 1 h after feeding when they were either asleep or calmly awake. To minimise technical bias, data collection was conducted in the same order, and was completed within 20 min.

2.2.1. Temperature measurements

Scalp temperature (T_{scalp}) was measured three times (median values used) at the centre of the forehead using a non-contacting infrared thermometer (Thermofocus Pro, Technimed, Varese, Italy). To measure brain temperature, two thermal-compensation thermistor probes connected to a dual-channel zero-heat-flow tissue-core thermometer (Coretemp, Terumo, Tokyo, Japan) were simultaneously applied to the centre of the forehead ($T_{brain\text{-}15}$, 15 mm in diameter) and the anterior fontanelle ($T_{brain\text{-}25}$, 25 mm in diameter) for approximately 5–10 min until the temperature readings equilibrated with a drift of <0.05 °C over 1 min. The diameter of the probe theoretically corresponds to the depth of the tissue, which the temperature reading reflects (Yamakage and Namiki, 2003). The rectal temperature (T_{rectal}) was measured at 3 cm from the anal margin (C202, Terumo, Tokyo, Japan). The ambient temperature was also measured beside the newborn infant's cot (605-H1 Mini, Testo, Yokohama, Japan). For the analysis of brain and scalp temperatures, values were corrected to T_{rectal} ($T_{brain\text{-}25} - T_{rectal}$, $T_{brain\text{-}15} - T_{rectal}$, and $T_{scalp} - T_{rectal}$) to self-correct for inter-patient T_{rectal} variation (see Online Supplementary Tables 2 and 3 for alternative analysis performed using uncorrected brain/scalp temperatures).

2.2.2. Echocardiographic measurements

Echocardiographic data were obtained by the same examiner (S.I.) using an ultrasound scanner (iE33, Philips, Amsterdam, The Netherlands) and an 8–13-MHz vector array transducer. SVC flow was measured by an established method (Evans et al., 2002) using the following formula:

$$\text{SVC flow} = V_{svc} \cdot \text{HR} \cdot \pi \cdot \frac{\Phi_{svc}^2}{4}$$

where

V_{svc} = velocity time integral of SVC in cm
HR = heart rate per minute
Φ_{svc} = mean SVC diameter in cm

To minimise the effect of spontaneous breathing, the flow profile was measured when the patients were calm and regularly breathing, and the flow velocity was averaged for at least 10 consecutive cardiac cycles. SVC flow was corrected to 100 g of brain mass (rSVC flow). Brain weight was estimated from the head circumference using an equation proposed by Dobbing and Sands (1978).

2.2.3. NIRS data acquisition

At the same time as the echocardiographic examination, another examiner (O.I.) acquired a NIRS temporal profile data using a time-resolved NIRS system (TRS-10, Hamamatsu Photonics, Hamamatsu, Japan). This system uses three pulsed-laser diodes (761, 791, and 836 nm), which generate light pulses with a pulse width of approximately 100 ps, a pulse rate of 5 MHz, and an average power of 30 μW. A photomultiplier tube for high sensitive detection and a signal processing circuit based on a time-correlated single photon counting method were used. The observed temporal profiles were fitted into a photon diffusion equation using the nonlinear least square fitting method (Ohmae et al., 2006). The reduced scattering and absorption coefficients for the three wavelengths were calculated, and the absolute cerebral tissue oxy-, deoxy-, and total haemoglobin (Hb) concentrations were obtained. Ten-second data acquisition was repeated five times by repositioning the probe each time to give mean values. The data quality was inspected retrospectively for their fitting into the photon diffusion equation and reproducibility before/after repositioning. The tissue oxygenation index (TOI) and cerebral blood volume (CBV) were further calculated using the following formulas:

$$\text{TOI} = \frac{[\text{oxy-Hb}]}{[\text{oxy-Hb}] + [\text{deoxy-Hb}]}$$

$$\text{CBV} = \frac{([\text{oxy-Hb}] + [\text{deoxy-Hb}]) \cdot \text{MW}_{\text{HB}} \times 10^{-6}}{10 \cdot \text{tHb} \times 10^{-2} \cdot D_t}$$

where

[] indicates Hb concentrations in μM
MW_{Hb} = molecular weight of Hb (64,500)
tHb = blood Hb concentration (g/dL)
D_t = brain tissue density (1.05 g/mL)

A pulse-oxymeter (Rad-8, Masimo, Irvine, CA, USA) was recorded for approximation of arterial blood oxygen saturation (SaO_2) at the beginning, in the middle, and at the end of NIRS data acquisition, and the mean value was used for analysis. Cerebral venous oxygen saturation (SvO_2) was estimated using the method proposed by Tichauer et al. (2006). This method assumes that the relative contribution of venous and arterial blood to the total blood volume in the brain is approximately 3:1 (Phelps et al., 1979).

$$SvO_2 = 4/3 \cdot \text{TOI} - 1/3 \cdot SaO_2$$

As surrogate markers for cerebral metabolism, we also calculated fractional oxygen extraction (FOE) and the cerebral metabolic rate index ($CMRO_2$ index) using the equations below. We used rSVC flow as a surrogate marker of CBF, based on the assumption that the fraction of total brain perfusion to total SVC flow is of limited variation between newborn infants.

$$\text{FOE} = (SaO_2 - SvO_2)/SaO_2$$

$$CMRO_2 \text{ index} = 1.34 \cdot \text{tHb} \cdot 10^{-2} \cdot \text{rSVC flow} \cdot (SaO_2 - SvO_2)$$