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

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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.

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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.

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

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

Table 1
Data profile.

	Mean	SD
Clinical background variables		
Post-natal age (d)	21.0	17.8
Post-conceptional age (weeks)	38.1	2.6
Body weight (g)	2556	503
Brain weight (g)	324	56
Temperature measures (°C)		
Ambient temperature	25.7	0.9
T_{rectal}	37.0	0.2
$T_{brain\text{-}25}$	36.7	0.2
$T_{brain\text{-}15}$	36.2	0.2
T_{scalp}	34.7	0.3
$T_{brain\text{-}25} - T_{rectal}$	−0.3	0.2
$T_{brain\text{-}15} - T_{rectal}$	−0.8	0.3
$T_{scalp} - T_{rectal}$	−2.3	0.3
Hb concentration, blood flow and derivatives		
Blood Hb (g/dL)	14.0	3.6
rSVC flow (mL/100 g/min)	72.7	26.1
Oxy-Hb (μM)	34.7	6.4
Deoxy-Hb (μM)	18.2	2.7
TOI	0.65	0.03
CBV (mL/100 g)	2.4	0.5
FOE	0.45	0.05
$CMRO_2$ index (mL/100 g/min)	5.7	2.1

Abbreviations: SD, standard deviation; T_{rectal}, rectal temperature; $T_{brain\text{-}25}$ and $T_{brain\text{-}15}$, brain temperatures measured using a zero-heat flux thermometer with probe diameters of 25 mm and 15 mm, respectively; T_{scalp}, forehead scalp skin temperature measured using non-contacting infrared thermometer; Hb, haemoglobin; rSVC flow, relative blood flow of the superior vena cava; TOI, tissue oxygenation index; CBV, cerebral blood volume; FOE, fractional oxygen extraction; $CMRO_2$, cerebral metabolic rate of oxygen.

where 1.34 (mL), oxygen-binding capacity of haemoglobin per g.

2.2.4. Clinical information

Gestational age, body weight, postnatal age, head circumference at the time of the study, and tHb assessed within 3 days of the study were obtained from the patient's record.

2.3. Data analysis

Exploratory analysis was first performed to understand characteristics of the variables. Temperature values were compared between different sites using the paired *t*-test. Linear regression analysis was used to assess (i) dependence of variables on the postnatal/postconceptional age and body weight, (ii) relationships between temperature values, and (iii) relationships among rSVC flow, the $CMRO_2$ index, and CBV. The *p* values obtained from this exploratory analysis were corrected for multiple comparisons using Bonferroni correction.

Primary analysis was then performed using univariate linear regression analysis, where dependence of temperature on rSVC flow, the TOI, CBV, FOE, and the $CMRO_2$ index were assessed. For multivariate models, which explained the temperature, we assigned up to four independent variables based on (i) our hypothesis that body/brain temperature is determined by cerebral perfusion and metabolism (the $CMRO_2$ index was not included because of significant collinearity with rSVC flow), and (ii) the results of univariate analysis (independent variables with uncorrected *p* values <0.05 were considered). Independent variables for the final model were determined by backward elimination. For the final model, *p* values were not corrected for multiple comparisons because the primary analysis was performed using restricted variables based on a priori hypotheses.

3. Results

Data are shown as mean ± standard deviation unless otherwise described. Data from three newborn infants were excluded because of poor fitting of NIRS data into the photon diffusion equation.

3.1. Temperature profiles

$T_{brain\text{-}25} - T_{rectal}$ was higher than $T_{brain\text{-}15} - T_{rectal}$, and $T_{brain\text{-}15} - T_{rectal}$ was higher than $T_{scalp} - T_{rectal}$ (both $p < 0.002$; Bonferroni correction; Table 1). A higher T_{rectal} was associated with a greater postnatal age and body weight ($p = 0.006$ and 0.009, respectively; Online Supplementary Table 1). T_{rectal} was most closely correlated with $T_{brain\text{-}25}$, which was followed by $T_{brain\text{-}15}$ and then T_{scalp} ($p = 0.009$, 0.015 and 0.033, respectively; Bonferroni correction; Online Supplementary Table 2). $T_{brain\text{-}25} - T_{rectal}$ was linearly correlated with $T_{brain\text{-}15} - T_{rectal}$ and $T_{scalp} - T_{rectal}$ ($p = 0.004$ and 0.002, respectively), and $T_{brain\text{-}15} - T_{rectal}$ was associated with $T_{scalp} - T_{rectal}$ ($p < 0.002$; Bonferroni correction; Online Supplementary Table 2).

3.2. Echocardiographic observations

SVC flow relative to body weight was 93.1 ± 35.6 mL/kg/min. None of the newborn infants showed critically low SVC flow < 40 mL/kg/min (Kluckow and Evans, 2000). The rSVC flow was not associated with any background clinical variables.

3.3. Haemoglobin and its derivative indices

A greater postnatal age was associated with lower tHb ($p < 0.003$), cerebral oxy-Hb ($p < 0.003$), the TOI ($p = 0.006$), and the $CMRO_2$ index ($p = 0.045$), and greater CBV ($p < 0.003$) and FOE ($p < 0.003$) (Online Supplementary Table 1; Bonferroni-corrected for comparisons over three independent variables). A greater body weight showed weak correlations with greater deoxy-Hb ($p = 0.036$; Bonferroni-corrected for comparisons over three independent variables; Online Supplementary Table 1).

No significant association was observed between rSVC flow and CBV. The $CMRO_2$ index was positively correlated with rSVC flow and was negatively correlated with CBV ($p < 0.006$ and $p = 0.018$, respectively). FOE was not associated with rSVC flow or CBV (Bonferroni-corrected for six comparisons; Online Supplementary Figure 1).

3.4. Associations between cerebral temperature, perfusion, and metabolism

3.4.1. Univariate analysis

A lower T_{rectal} was associated with a higher TOI, smaller CBV, and smaller FOE ($p = 0.006$, 0.004 and 0.005, respectively; Online Supplementary Table 3). Greater $T_{brain\text{-}25} - T_{rectal}$, $T_{brain\text{-}15} - T_{rectal}$, and $T_{scalp} - T_{rectal}$ were associated with the higher ambient temperature ($p = 0.044$, 0.010, and 0.023, respectively). Greater $T_{brain\text{-}15} - T_{rectal}$ and $T_{scalp} - T_{rectal}$ were associated with a higher rSVC flow ($p = 0.040$ and 0.002, respectively; Table 2 and Fig. 1).

3.4.2. Multivariate analysis

Greater $T_{brain\text{-}15} - T_{rectal}$ and $T_{scalp} - T_{rectal}$ were associated with a higher ambient temperature ($p = 0.034$ and 0.030, respectively). Greater $T_{scalp} - T_{rectal}$ was associated with a higher rSVC flow ($p = 0.004$; Table 2).

4. Discussion

In this study, cerebral metabolism and perfusion were quantified in healthy newborn infants using two non-invasive bedside techniques of NIRS and echocardiography. We found that variation in cerebral metabolism had no significant effect on regional brain temperature. However, brain temperature was associated with cerebral perfusion, particularly in the superficial brain. CBF has been predominantly linked with heat removal from deep brain tissue (Sukstanskii and Yablonskiy, 2006). However, our data suggest that CBF has an alternative role in delivering heat to the superficial brain. Further investigations of independent variables for regional brain temperatures may help accomplish optimal temperature control in critically ill newborn infants.

Table 2
Relationships among cerebral perfusion, metabolism, and temperature.

Variables	$T_{brain-25} - T_{rectal}$		$T_{brain-15} - T_{rectal}$		$T_{scalp} - T_{rectal}$	
	Coefficient	p	Coefficient	p	Coefficient	p
Univariate analysis						
Ambient temperature	0.38	0.044	0.47	0.010	0.42	0.023
rSVC flow	0.34	–	0.38	0.040	0.55	0.002
TOI	0.16	–	0.23	–	0.20	–
CBV	−0.21	–	−0.16	–	0.05	–
FOE	−0.22	–	−0.21	–	−0.23	–
$CMRO_2$ index	0.31	–	0.18	–	0.21	–
Multivariate analysis						
Ambient temperature	0.30	–	0.40	0.034	0.36	0.030
rSVC flow	0.25	–	0.29	–	0.50	0.004
CBV	−0.08	–	−0.01	–	0.24	–
FOE	−0.08	–	−0.05	–	−0.09	–

Independent variables for multivariate models were assigned based on our a priori hypothesis and the results of univariate analysis (see Section 2.3 for detail). *P* values are corrected for multiple comparisons over three relative temperatures using the Bonferroni correction. Abbreviations: T_{rectal}, rectal temperature; $T_{brain-25}$ and $T_{brain-15}$, brain temperatures measured using a zero-heat flux thermometer with probe diameters of 25 mm and 15 mm, respectively. T_{scalp}, forehead scalp skin temperature measured using non-contacting infrared thermometer; Hb, haemoglobin; rSVC flow, relative blood flow of the superior vena cava; TOI, tissue oxygenation index; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate of oxygen.

4.1. Non-invasive bedside monitoring of cerebral metabolism and perfusion

Among the newly introduced biophysical probes for cerebral metabolism and perfusion, NIRS has an advantage in its repetitive bedside use. Previous studies have identified regulatory factors of cerebral metabolism and perfusion in sick newborn infants using the tracer-bolus technique (Edwards et al., 1988; Patel et al., 1998). However, presumably because of practical and ethical concerns in using clinically unnecessary tracers, NIRS has predominantly been applied without using tracers (Goff et al., 2010), where the contribution of oxygen delivery and consumption could not be divided between the two (Tisdall et al., 2009). In our study, using NIRS and echocardiography, we developed a technique that estimates individual contributions of cerebral metabolism and perfusion separately. To accomplish this without using tracers, we assumed that the fraction of CBF relative to SVC flow is similar between patients. According to a study on newborn infants, which used indocyanine green pulse dye densitometry, the relationship between left ventricular output (LVO) and CBF was estimated as: CBF = 0.03·LVO + 8.7 (Kusaka et al., 2005). Based on the fact that SVC flow is approximately 52% of LVO in term infants (Kluckow and Evans, 2000), CBF in our study population was estimated as 12.9 ± 1.5 mL/(100 g of brain weight)/min, the value and deviation of which correspond to reported CBF values in newborn infants (Edwards et al., 1988; Kusaka et al., 2005; Altman et al., 1988). Our data suggested a postnatal decrease in oxy-Hb and TOI, and an increase in CBV and FOE. These findings highlight the effect of a growth-related increase in the cerebral venous blood pool and postnatal progress in anaemia (Franceschini et al., 2007). In contrast, the $CMRO_2$ index showed a weak negative association with postnatal age. Previous studies, which compared cerebral metabolism in infants and children of 1–16 years old, suggested a gradual increase in oxygen and glucose consumption with age (Franceschini et al., 2007; Takahashi et al., 1999; Chugani and Phelps, 1986). However, an age-related alteration in cerebral metabolism was not observed when the study period was restricted within 2 months of age (Franceschini et al., 2007; Chugani and Phelps, 1986), suggesting that metabolic changes are different or too small to detect during the first month of age.

In our study, we used time-resolved NIRS, which instantly provides absolute Hb concentrations and CBV. Several studies have proposed the estimation of CBF from CBV using the formula: $(CBV/CBV_0) = (CBF/CBF_0)^G$, where G is the Grubb's exponent, and

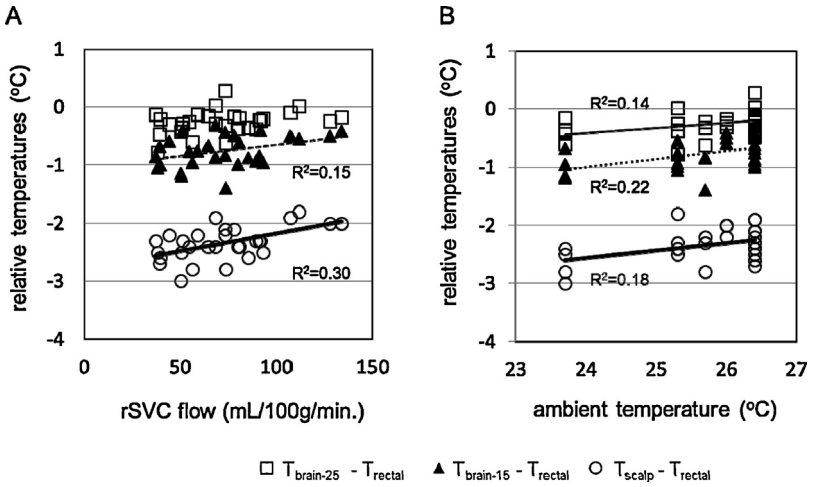

Fig. 1. Independent variables associated with relative brain temperatures. (A) Greater $T_{brain-15} - T_{rectal}$ and $T_{scalp} - T_{rectal}$ were associated with a higher rSVC flow ($p < 0.05$ and $p < 0.01$, respectively). (B) Greater $T_{brain-25} - T_{rectal}$, $T_{brain-15} - T_{rectal}$, and $T_{scalp} - T_{rectal}$ were associated with a lower ambient temperature (all $p < 0.05$). Regression lines are from univariate analysis with $p < .05$ for $T_{brain-25} - T_{rectal}$ (solid), $T_{brain-15} - T_{rectal}$ (broken) and $T_{scalp} - T_{rectal}$ (bold). Abbreviations: rSVC flow, relative flow of the superior vena cava; T_{scalp}, scalp temperature; T_{rectal}, rectal temperature; $T_{brain-15}$ and $T_{brain-25}$, brain temperatures obtained using a zero-heat-flow tissue-core thermometer at the forehead and the anterior fontanelle, respectively.

CBV_0 and CBF_0 are baseline values. In the current study, we did not observe any association between rSVC flow and CBV. However, estimation of CBF using Grubb's exponent has been validated for induced CBF changes from 20% to 240% of baseline levels (Cheung et al., 2001; Grubb et al., 1974). Roche-Labarbe et al. (2010) observed in young infants that physiological changes in CBF extrapolated from CBV and Grubb's exponent did not reflect those given by diffusion correlation spectroscopy. These previous studies and our findings suggest that subtle intra-patient differences in CBF may not be extrapolated from CBV.

4.2. Non-invasive monitoring of brain temperature

Zero-heat-flux core temperature monitoring using a temperature probe covered by a piece of heat insulator is widely accepted as a reliable surrogate marker for invasive methods (Simbruner et al., 2005, 1994; van der Spek et al., 2009). Fox and Solman (1971) further improved this technique using a heater and a thermal flux transducer, the accuracy of which has been validated in a range of body locations and clinical situations in reference to jugular vein and other body core temperatures (Yamakage and Namiki, 2003; Kimberger et al., 2009; Akata et al., 2007; Ball et al., 1973). Matsukawa et al. (1996) validated the same system with ours, but with a full-size sensor element (43 mm in diameter), and reported that the temperature reflected tissue 18–38 mm from the surface. Considering the head size of newborn infants, we used small-sized probes, expecting to monitor the temperature of superficial brain tissue with approximately 10–20-mm depths. This assumption was relevant to the findings that temperature showed a gradual reduction from T_{rectal} to $T_{brain\text{-}25}$, $T_{brain\text{-}15}$, and then T_{scalp}, and that the linear association with T_{rectal} was strongest for $T_{brain\text{-}25}$, followed by $T_{brain\text{-}15}$, and then T_{scalp}. As in previous studies, which investigated determination factors of brain temperature, we corrected temperature values by T_{rectal}, which allowed us to assess the effect of physiological and environmental variables without further considerations for variations in T_{rectal}.

4.3. Effect of brain metabolism and perfusion on brain temperature

Thermogenic responses to cold stress have been well described in newborn species (Smales and Hull, 1978). However, the regulatory relationships between body/brain temperature, cerebral metabolism, and perfusion have not been fully investigated (Simbruner et al., 1994). In our study, to minimise the number of variables, we studied stable newborn infants cared for at thermo-neutral conditions. However, we still observed positive correlations between ambient temperature and brain temperature. In contrast, an association between cerebral metabolism and brain temperature was not recognised. This might be relevant under physiological conditions, where the effect of cerebral metabolism on brain temperature is considered to be small (Kauppinen et al., 2008). Instead, rSVC flow was observed as the primary independent variable for brain temperature in our patients; the greater the cerebral perfusion, the greater the brain temperature. This finding may be initially counterintuitive because blood temperature is higher in the jugular vein than in the carotid artery (Nunneley and Nelson, 1994); therefore, cerebral perfusion generally contributes to heat removal from brain tissue (Sukstanskii and Yablonskiy, 2006; Simbruner et al., 1994; Kauppinen et al., 2008). However, the superficial brain is spontaneously cooled by the environment, and is cooler than arterial blood. This suggests that, under physiological conditions, an increase in CBF may lead to an increase in superficial brain temperature and a simultaneous decrease in deep brain temperature. In the current study, a positive association between brain temperature and rSVC flow became weaker from the scalp surface towards deeper brain structures, supporting the presence of paradoxical dependence of brain temperatures on CBF. Depth-depended correlations between brain temperature and rSVC flow might also be explained if zero-heat flux temperature measurement is much less reliable than the direct scalp-skin temperature measurement using infrared light. However, closest correlations with T_{rectal} were observed for $T_{brain\text{-}25}$ and $T_{brain\text{-}15}$ but not T_{scalp}, suggesting that $T_{brain\text{-}15}$ and $T_{brain\text{-}25}$ are likely to reflect the temperature of deeper brain tissue than T_{scalp} does.

A similar phenomenon to ours, where an increase in CBF is associated with higher regional brain temperature, has been suggested from a mathematical model and in a small animal model (Sukstanskii and Yablonskiy, 2006). Although we speculated that brain temperature depends on cerebral perfusion, regional CBF to cooler brain tissue might be restricted in meeting its relatively smaller oxygen demands. This possibility is supported by the finding by Laptook et al. (2001) who observed a superficial brain-dominant reduction in CBF under selective head cooling in a piglet model.

4.4. Limitations and future studies

For technical and ethical reasons we were not able to undergo repeated measures within the same patients. Therefore, our current findings were extrapolated from inter-patient correlations of variables. To minimise technical bias, data collection was performed when newborn infants were calm over a sufficient acquisition time to obtain reliable representative values. By combining NIRS and echocardiography, we were able to assess the potential correlations between physiological variables, and to identify the individual contribution of cerebral perfusion and metabolism to brain temperature. However, as previously discussed, our technique is based on several assumptions that haemodynamic information derived from NIRS is predominantly obtained from intra-cerebral blood flow, and that regional CBF distribution is consistent or of limited variation between patients. Finally, our method estimated global CBF, which would not be suitable for identifying spatially heterogeneous CBF distribution (Volpe et al., 1983). The use of tracer bolus technique may provide region-specific CBF information. However, NIRS predominantly reflects signals from superficial cranial contents, whereas our study aimed to correlate brain perfusion and metabolism with brain temperatures of different depths. A three-dimensional NIRS system may enable direct comparisons between regional brain perfusion, metabolism and temperature (Austin et al., 2006). These limitations must be noted in interpreting our current findings for clinical practice. Future studies need to confirm the relevance and accuracy of our technique using invasive methods in translational large-animal models (Iwata et al., 2006), and more advanced NIRS techniques, such as diffuse correlation spectroscopy in clinical settings (Goff et al., 2010; Verdecchia et al., 2013).

5. Conclusions

In this study, cerebral oxygen metabolism and perfusion were monitored non-invasively in newborn infants without using tracers. This study shows that the effect of cerebral metabolism on brain temperature is negligible in healthy newborn infants. In addition, brain temperature is positively correlated with cerebral perfusion and ambient temperature. An increase in CBF has been linked with overall heat removal from the brain. However, our results highlight the possibility that CBF delivers heat specifically to the superficial part of the brain. Further studies are required to identify relationships between regional brain metabolism, perfusion, and temperature by incorporating a range of clinical variables, such as

therapeutic hypothermia, fever, optic stimuli, and anaesthesia. This information may help provide the optimal local brain temperature for particular pathological conditions.

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

Sachiko Iwata: Dr S Iwata conceptualised and designed the study, collected data, performed statistical analysis, contributed to the interpretation of the results, drafted the initial manuscript, and approved the final manuscript as submitted.

Ilias Tachtsidis: Dr Tachtsidis contributed to the interpretation of the results, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Sachio Takashima: Dr Takashima conceptualised and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Toyojiro Matsuishi: Dr Matsuishi conceptualised the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Nicola J. Robertson: Dr Robertson conceptualised the study, contributed to the interpretation of the results, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Osuke Iwata: Dr. O Iwata conceptualised and designed the study, participated in the collection of data and the statistical analysis, contributed to the interpretation of the results and manuscript writing, and approved the final manuscript as submitted.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijdevneu.2014.05.010.

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