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Multimodal measurements of brain tissue metabolism and perfusion in a neonatal model of hypoxic-ischaemic injury

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ABSTRACT

This is the first multimodal study of cerebral tissue metabolism and perfusion post-hypoxic-ischaemic (HI) brain injury with broadband near-infrared spectroscopy (bNIRS), diffuse correlation spectroscopy (DCS), positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). In 5 piglet models of HI, we measured cerebral tissue saturation (StO_2), cerebral blood flow (CBF), cerebral oxygen metabolism ($CMRO_2$), changes in the mitochondrial oxidation state of cytochrome-c-oxidase (oxCCO), cerebral glucose metabolism (CMRglc), and tissue biochemistry (Lac+Thr/tNAA). At baseline, the parameters measured were: 64±6 % StO_2, 35±11 ml/100g/min CBF, and 2.0±0.4 μmol/100g/min $CMRO_2$. After HI the parameters measured were: 68±6% StO_2, 35±6 ml/100g/min CBF, 1.3±0.1 μmol/100g/min $CMRO_2$, 0.4±0.2 Lac+Thr/tNAA, and 9.5±2.0 CMRglc. This study demonstrates the capacity of a multimodal set up to interrogate the pathophysiology of HIE using a combination of optical methods, MRS, and PET.

Keywords: broadband near-infrared spectroscopy, diffuse correlation spectroscopy, cytochrome-c-oxidase, multimodal

1. INTRODUCTION

Neonatal hypoxic-ischaemic encephalopathy (HIE) is a relatively common (1-3/1000 term births[1]) and potentially fatal (44-53% of infants with HIE die or suffer disabilities[1]) healthcare problem. Magnetic resonance imaging and spectroscopy (MRI and MRS) are the imaging and prognostic modalities of choice, but they cannot provide continuous or cotside measurements of brain injury severity, perfusion, or metabolism. Optical devices such as near-infrared spectroscopy (NIRS) for cerebral haemodynamics or diffuse correlation spectroscopy (DCS) for cerebral blood flow (CBF) give the opportunity for non-invasive, continuous, bedside monitoring, and have been demonstrated in neonatal intensive care units (NICU) to study HIE[2,3]. Using broadband NIRS (bNIRS), it is also possible to obtain a measurement of cellular metabolism via changes in oxidised cytochrome-c-oxidase (oxCCO, see review by Bale et al.[4]) and measure tissue saturation (StO_2) via broadband fitting[5]. The aim of this study is to demonstrate the capacity of a multimodal set up to interrogate the pathophysiology of HIE.

2. METHODS

2.1 Animal Model

Newborn piglets (<48 hours old) were anesthetized, tracheotomized, and mechanically ventilated. Arterial oxygen saturation (SaO_2) was measured via a pulse oximeter attached to the piglet's right forelimb. DCS and bNIRS probes were secured to the left side of the head, avoiding the sagittal sinus, using an in-house 3D-printed probe holder. Hypoxic-ischaemic (HI) insult was induced by inflating occluders around the carotid arteries, followed by reducing the inspired oxygen from 21% to 8%. HI was maintained for 10 to 20 minutes. At the end of the insult, recovery was initiated by deflating the carotid occluders and returning oxygen supply to baseline levels. Figure 1 shows the protocol schematic.

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2.2 Multimodal Monitoring

The optical system, a hybrid bNIRS and DCS device, has been fully described previously[6]. To avoid crosstalk between the systems, a shutter-based multiplexing approach was used. To obtain an absolute measurement of CBF in ml/100g/min, a dynamic contrast-enhanced (DCE) bNIRS procedure using an indocyanine green (ICG) tracer was performed at the end of the optical measurements. After the optical measurement, the piglets were transferred to a PET-MRI scanner. FDG PET and ^{1}H MRS were performed to obtain cerebral metabolic rate of glucose (CMRglc) and the ratio to lactate and threonine to total NAA (Lac+Thr/tNAA) which is a surrogate marker of injury severity.

DCS and bNIRS measurements were analysed using MATLAB to yield oxy- and deoxy-haemolgobin (HbO_2 and HHb) changes, oxCCO changes, cerebral oxygen saturation (StO_2), CBF, and cerebral metabolic rate of oxygen ($CMRO_2$) (for details, see Rajaram et al.6). Recovery fractions of the optical signals were calculated as the ratio of the difference between the recovered signal and nadir of HI with the baseline signal and nadir of HI (equation in Table 1 caption).

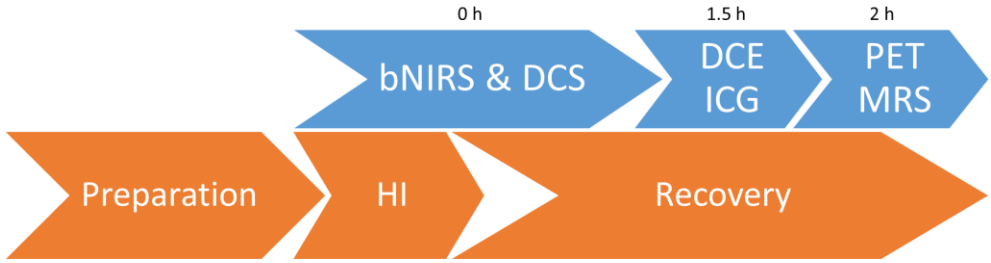
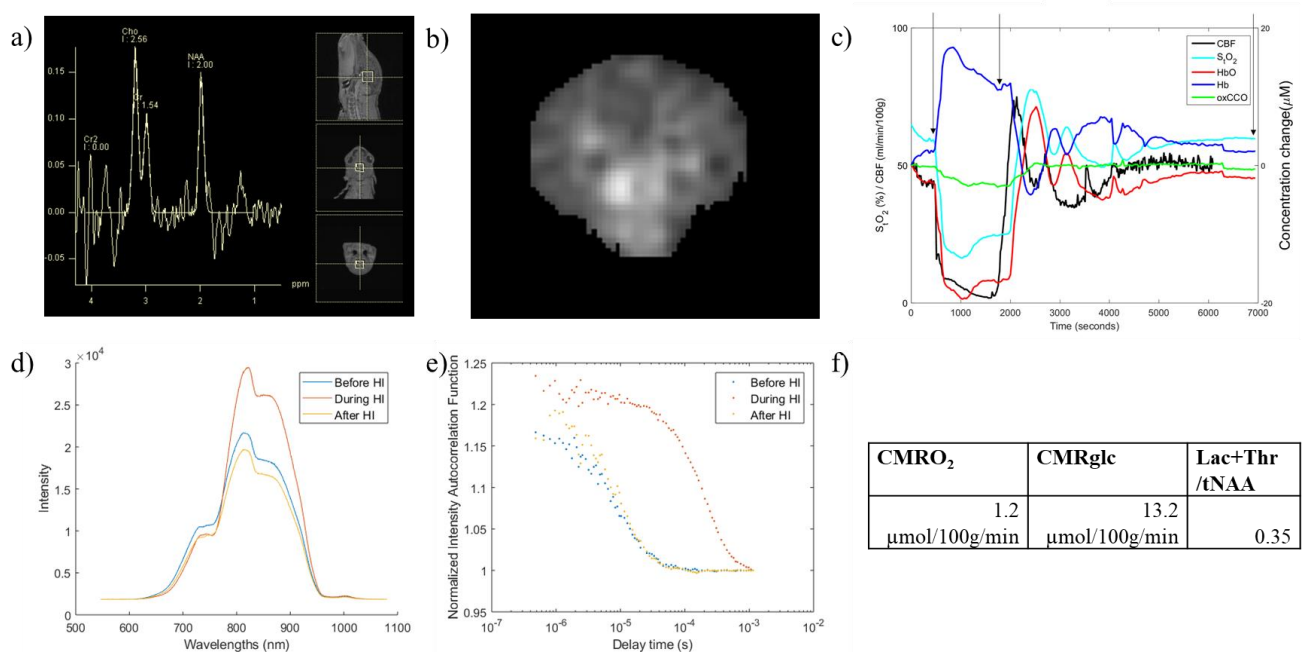


Figure 1. Schematic of measurement protocol and modalities with timings post-HI.

3. RESULTS



$CMRO_2$	CMRglc	Lac+Thr /tNAA
1.2 μmol/100g/min	13.2 μmol/100g/min	0.35

Figure 2. Examples of data collected from all modalities in one piglet (piglet 26): a) basal ^{1}H MRS spectra and voxel location, b) FDG PET glucose map, c) bNIRS and DCS signals during HI; arrows indicate start and end of HI, and final measurement for RF, d) NIRS intensity spectra before, during and after HI, e) DCS normalized intensity autocorrelation functions before, during and after HI, f) results obtained from all modalities after HI.

Measurements on 5 piglets post-HI (2 females, age 23±10 h, weight 1.6±0.2 kg) of HbO_2, HHb, oxCCO, StO_2, CBF, $CMRO_2$, Lac+Thr/tNAA and CMRglc were collected (see Table 1 for details). At baseline the parameters measured were: 64±6 % StO_2, 35±11 ml/100g/min CBF, and 2.0±0.4 μmol/100g/min $CMRO_2$. After HI the parameters measured were: 68±6% StO_2, 35±6 ml/100g/min CBF, 1.3±0.1 μmol/100g/min $CMRO_2$, 0.4±0.2 Lac+Thr/tNAA, and 9.5±2.0 CMRglc. Figure 2 shows examples of the multimodal data collected and the optical data recorded continuously for one piglet.

Table 1. Details of piglets studied with all variables measured after HI. Age is postnatal age at experiment start. CBF measured in ml/100g/minute, $CMRO_2$ and CMRglc measured in μmol/100g/min. Recovery fractions of optical signals in %: RF = recovery – nadir/baseline-nadir x 100%. *Note that the Lac+Thr/tNAA for piglet 31 was measured in the left cortex.

Pig	Age (h)	Weight (kg)	Sex	HI (mins)	StO_2 (%)	CBF	$CMRO_2$	CMRglc	Lac	HbO_2 (%)	HHb (%)	oxCCO (%)	StO_2 (%)	CBF (%)
22	23	1.2	F	10	70.4	35.7	1.2	8.6	0.11	103	98	105	100	101
23	10	1.6	M	20	71.7	39.2	1.4	7.0	0.57	109	94	108	106	86
26	24	1.5	M	20	64.1	42.0	1.2	13.2	0.35	105	91	110	114	94
30	20	1.8	M	20	75.4	30.8	1.4	9.6	0.39	116	90	136	121	198
31	40	1.7	F	20	59.0	26.6	1.3	9.1	*0.45	140	77	168	114	73

4. DISCUSSION

This is the first multimodal study of cerebral tissue metabolism and perfusion post-HI with optics, PET and MRS. This multimodal configuration allows us to investigate pathophysiology during HIE. It should be noted these measurements were not simultaneous, with optical measurements recorded before the PET and MRS measurements. Further, the low number of animals and small range of injury severity (determined by lactate ratio) means it is not possible at this stage to identify biomarkers or relationships between measurements. Tissue saturation is the most commonly used optical cerebral monitor in the NICU; the addition of bNIRS and DCS to the optical instrumentation gives insight into the cerebral metabolism ($CMRO_2$ and oxCCO) and perfusion continuously during treatment.

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