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Cerebral Near-Infrared Spectroscopy Analysis in Preterm Infants with Intraventricular Hemorrhage

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***Abstract*—Near-infrared spectroscopy (NIRS) for cerebral circulation monitoring has gained popularity in the neonatal intensive care setting, with studies showing the possibility of identifying preterm infants with intraventricular hemorrhage (IVH) by transfer function analysis of arterial blood pressure (BP) and NIRS measures. In this study, we examined a number of NIRS-derived measures in a cohort of preterm infants with IVH (n = 5) and without IVH (n = 12) within 1-3 hours after birth. The IVH infants were found to have significantly higher tissue oxygenation index (TOI), lower fractional tissue oxygen extraction (FTOE) and lower coherence between arterial BP and deoxygenated hemoglobin (HHb) in the very low frequency range (VLF, 0.02-0.04 Hz). Further studies with larger sample size are warranted for a more complete understanding of the clinical utility of these NIRS measures for early identification of IVH infants.**

I. Introduction

Preterm infants with very low birth weight (VLBW; birth weight ≤1500 g) suffer from a high risk of intra-ventricular hemorrhage (IVH). Even for those VLBW infants who survive, they still have a strong possibility of developing long-term neurodevelopmental disabilities [1, 2]. The ability to identify preterm infants with IVH at an early stage is of great importance in terms of minimizing mortality and morbidity in the neonatal intensive care setting.

One popular technique for monitoring cerebral circulation in preterm infants is near-infrared spectroscopy (NIRS). NIRS provides measures of cerebral oxygenation and hemoglobin content, including oxygenated hemoglobin (HbO_2) content, deoxygenated hemoglobin (HHb) content, tissue oxygenation index (TOI) (which is ratio of HbO_2 to total hemoglobin HbO_2+HHb), and the fractional tissue oxygen extraction (FTOE) (which is the ratio of cerebral oxygen consumption to oxygen delivery). Some of these NIRS measures have been used as surrogates of cerebral blood flow (CBF), for example TOI can reflect CBF variations during reduction in perfusion pressure, under the conditions of constant arterial oxygen saturation and cerebral oxygen consumption [3]. Some investigators also derived the Hb difference (HbD = HbO_2 – HHb), which was found to be correlated with CBF during hypotensive episodes [4].

Cross-spectral transfer function analysis can provide information in relation to the regulation of CBF by cerebral autoregulation mechanisms, by examining the relationship between arterial blood pressure (BP) and CBF fluctuations in the frequency domain [5]. The transfer function analysis of BP and cerebral NIRS measures has demonstrated that alterations in dynamic cerebral autoregulation properties, such as higher coherence or transfer gain, are linked with IVH or other mortality risk factors [6-9]. It has been suggested that the higher gain or coherence in the cerebral pressure-flow relationship could reflect impairment of CBF control by cerebral autoregulation, thus potentially linked with brain injury such as IVH.

In this study, we examined whether the various parameters derived from cross-spectral transfer function analysis of arterial BP and cerebral NIRS, including gain, phase and coherence, could demonstrate significant difference between preterm infants with and without IVH. In contrast to previous studies which adopted a single NIRS measure (TOI or HbD) as a surrogate of CBF, we examined the transfer function relationships of arterial BP to a number of NIRS measures including HbO_2, HHb, HbD and TOI, to understand which of the measures might be more useful for the detection of IVH. In addition, we also compared the mean values of the NIRS-derived TOI and FTOE between the two groups of infants.

II. Methods

A. Subjects

All the data were collected in the neonatal ICU at the Nepean Hospital in Sydney, Australia. The study was approved by the Sydney West Area Health Service Human Research and Ethics Committee, and informed parental consent was obtained in all cases. The study cohort comprised a convenience sample of 17 early low birth weight infants with gestational age <30 wks, without significant congenital anomalies who survived at least 2 hours. The demographic and clinical characteristics of the infants are as follows (mean±SD): 10 males 7 females, gestational age 26±2 wks (range 24-29 wks), birth weight 1024±351 g (range 552-1929 g). Out of the 17 infants, 16 infants were mechanically

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ventilated, 5 infants suffered from IVH and 1 infant died eventually.

B. Measurement and protocol

All physiological data were collected from the infants within 1-3 hours after birth. Electrocardiogram (ECG), arterial BP waveform and arterial oxygen saturation (SaO_2) were acquired via a bedside patient monitor (Philips Agilent Systems, Philip Healthcare, North Ryde, Australia). Intra-arterial BP was continuously measured via an umbilical or peripheral arterial catheter connected to a transducer calibrated to atmospheric barometric pressure and zeroed to the midaxillary point. Cerebral near-infrared spectroscopy data were measured by the NIRO-300 system (Hamamatsu Photonics, Hamamatsu City, Japan), with the sensor probe placed over the skin of the temporoparietal region on the head of the infant. The device provides measurement of the changes in relative concentration of oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb), the tissue oxygenation index (TOI) which is given as the ratio of HbO_2 to the total haemoglobin (HbO2 + HHb) expressed in percentage, and also the fractional tissue oxygen extraction (FTOE) which is the ratio of cerebral oxygen consumption to oxygen delivery, i.e. (SaO_2-TOI)/SaO_2. Hb difference (HbD) was computed as HbO_2 – HHb [4, 6-8].

ECG, arterial BP, SaO_2 and NIRS signals were collected by a data acquisition system (ADInstruments, Sydney, Australia) at a sampling rate of 1 kHz. The LabChart software (ADInstruments, Sydney, Australia) provided automatic beat-to-beat detection of R-waves from the ECG for the computation of R-R interval (RRi) and also the computation of systolic BP (SBP) and mean arterial pressure (MAP) from the arterial BP waveform.

C. Spectral analysis

10-minutes of data (obtained within the 1-3 hours after birth) for each infant were processed in Matlab (Natick, MA, USA). These data were without noticeable corruption by artefacts. The MAP time series was converted to evenly spaced samples at 8 Hz using a previously proposed method to obtain the blood pressure variability (BPV) signal [10]. The HbO_2, HHb and TOI signals were also resampled to 8 Hz, by performing moving averaging (0.25 s window) with a sampling interval of 0.125 s. Linear detrending was performed on the resampled signals prior to spectral analysis. The power spectral density (PSD) of each signal was computed by the Welch method – this involved dividing each of the 10 min segments into 4 min sections with 75% overlap, multiplying each section with a Hanning window, performing a 2048-pt fast Fourier transform (FFT) then squaring and scaling the magnitude to give the auto power spectrum (modified periodogram), and finally averaging the power spectra of all segments to get the PSD of the signal.

Cross-spectral analysis was performed on MAP-HbO_2, MAP-HHb, MAP-HbD and MAP-TOI using the Welch method to provide information about cerebral autoregulation [6-9]. With the auto power spectra of signals x and y defined as $P_{xx}(f)$ and $P_{yy}(f)$ respectively (f represents frequency) and the cross power spectrum of x-y as $P_{xy}(f)$, the transfer function of x-y (from x to y) was computed as $H(f) = P_{xy}(f)/P_{xx}(f)$ and the magnitude and phase angle of the transfer function could be obtained accordingly. The magnitude-squared coherence function was defined as $\gamma^2(f) = |P_{xy}(f)|^2/P_{xx}(f)P_{yy}(f)$. The coherence assesses the linear correlation between spectral components in the two signals, with a value ranging from 0 (lack of linear correlation) to 1 (perfect linear relationship).

The frequency spectra of the infants were divided into two bands, similar to those described previously [9, 11]: the very low frequency band (VLF, 0.02–0.04 Hz) and the low frequency band (LF, 0.04–0.15 Hz). Within each band, the spectral power was obtained by integrating the power spectrum over the given frequency range. The transfer function parameters (gain, phase and coherence) in each band were computed by averaging values at frequencies with coherence ≥ 0.5, or from the frequency with the maximum coherence if coherence < 0.5 (as this represented the frequency at which the signals were most strongly correlated) [12, 13]. In addition, the average coherence of the whole band was computed by averaging all values within each band.

D. Data analysis

The results for the IVH and non-IVH infants were presented as mean ± SEM. Logarithmic transformation was performed on the transfer gain parameters as they do not follow a normal distribution. Differences between two groups were compared with the Student's t test. A P value of <0.05 was considered significant.

TABLE I

PHYSIOLOGICAL VARIABLES IN THE COHORT OF PRETERM INFANTS

	IVH	Non-IVH	P Value
RRi (ms)	441±11	423±6	0.160
SBP (mmHg)	44±5	43±2	0.760
MAP (mmHg)	33±3	35±1	0.695
TOI (%)	76±5	63±2	0.011*
SaO_2 (%)	95±5	95±1	0.863
FTOE (%)	20±6	34±2	0.015*

Values are mean ± SEM. IVH, intraventricular hemorrhage; RRi, R-R interval; SBP, systolic blood pressure; MAP, mean arterial pressure; TOI, tissue oxygenation index; SaO_2, arterial oxygen saturation; FTOE, fractional tissue oxygen extraction. * $P < 0.05$.

III. RESULTS

The mean values of the physiological variables are shown in table I. TOI was significantly higher and FTOE was significantly lower in the IVH infants compared with the non-IVH infants (P value = 0.011 and 0.015 respectively). No significant difference was found between the IVH and non-IVH infants for the transfer function parameters derived from HbO_2, HbD or TOI, but the VLF coherence of MAP-HHb was significantly lower in the IVH compared with the non-IVH infants (P =0.049). Similar results were obtained

TABLE II

TRANSFER FUNCTION ANALYSIS OF MEAN ARTERIAL PRESSURE (MAP) AND NEAR-INFRARED SPECTROSCOPY (NIRS) PARAMETERS IN THE COHORT OF PRETERM INFANTS.

		IVH		Non-IVH		*P* value	
		VLF	LF	VLF	LF	VLF	LF
MAP- HbD	Gain	- 0.44±0.11	- 0.71±0.12	- 0.40±0.06	- 0.51±0.10	0.719	0.266
	Phase	0.67±0.69	- 1.12±0.09	- 0.41±0.42	- 0.62±0.27	0.190	0.252
	Coh	0.49±0.06	0.68±0.02	0.63±0.05	0.64±0.03	0.111	0.353
	Coh_{AV}	0.32±0.07	0.44±0.05	0.45±0.06	0.37±0.04	0.245	0.357
MAP- HbO_2	Gain	-0.45±0.15	- 0.61±0.17	- 0.38±0.05	- 0.45±0.09	0.559	0.355
	Phase	0.74±0.69	- 1.17±0.15	- 0.01±0.51	- 0.44±0.30	0.428	0.149
	Coh	0.49±0.08	0.67±0.03	0.62±0.04	0.67±0.02	0.128	0.892
	Coh_{AV}	0.32±0.09	0.45±0.06	0.45±0.05	0.43±0.04	0.181	0.824
MAP- TOI	Gain	- 0.35±0.19	-0.19±0.15	- 0.40±0.11	- 0.19±0.12	0.804	0.979
	Phase	-1.48±0.61	-0.67±0.47	- 0.10±0.48	0.57±0.20	0.119	0.831
	Coh	0.54±0.04	0.62±0.02	0.56±0.03	0.62±0.01	0.691	0.784
	Coh_{AV}	0.27±0.03	0.27±0.04	0.31±0.04	0.30±0.02	0.596	0.428
MAP- HHb	Gain	- 0.90±0.16	- 0.88±0.26	- 0.69±0.08	- 0.73±0.11	0.201	0.547
	Phase	- 0.05±0.69	- 0.28±0.17	- 0.48±0.59	- 0.23±0.29	0.679	0.293
	Coh	0.46±0.08	0.65±0.04	0.62±0.04	0.65±0.01	0.049*	0.834
	Coh_{AV}	0.23±0.04	0.38±0.05	0.46±0.05	0.38±0.03	0.015*	0.983

Values are mean ± SEM. HbD, haemoglobin difference; HbO_2, oxygenated haemoglobin; TOI, tissue oxygenation index; HHb, deoxygenated haemoglobin; VLF, very low frequency (0.02-0.04 Hz); LF, low frequency (0.04-0.15 Hz); Gain, transfer gain after logarithmic transformation; Phase, transfer phase in rad; Coh, coherence; Coh_{AV}, average coherence of whole band. * $P < 0.05$.

from the use of average coherence within the VLF band (P =0.015). The time series of MAP, HbO_2 and HHb of an IVH infant with low MAP-HHb coherence in the VLF range and a non-IVH infant with high coherence were illustrated in Fig 1 and 2.

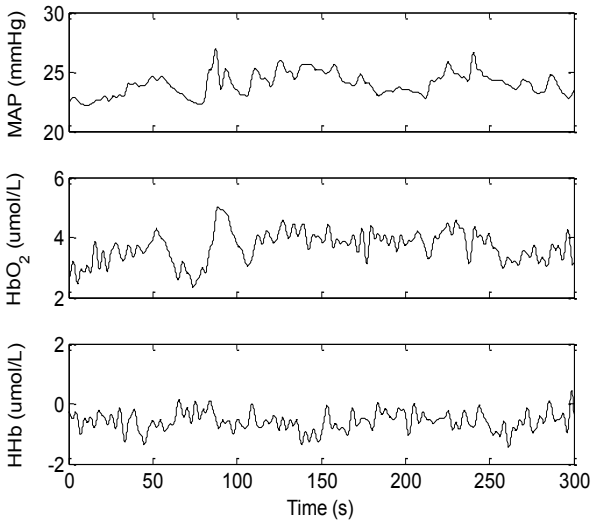

Fig. 1. Time series of MAP and relative concentrations of HbO_2 and HHb in a preterm infant with IVH. Note the highly similar fluctuations in the very low frequency (VLF) range (25-50 s cycle period) in MAP and HbO_2, which were absent in HHb. This IVH infant had a low MAP-HHb coherence of 0.36 in the VLF range.

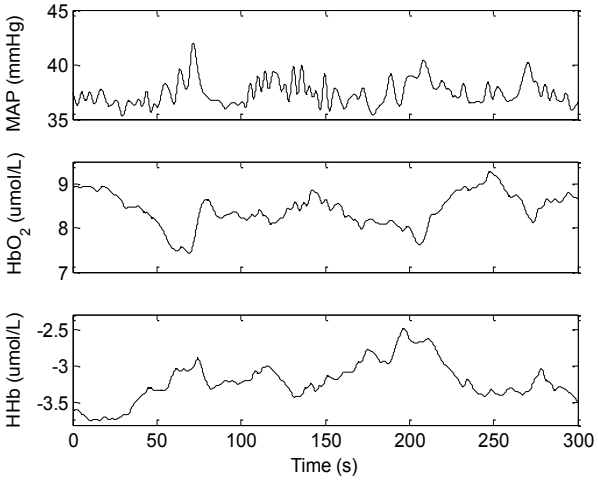

Fig. 2. Time series of MAP and relative concentrations of HbO_2 and HHb in a preterm infant without IVH. Note the highly correlated fluctuations in the VLF range (25-50 s cycle period) in MAP, HbO_2 and HHb. This non-IVH infant had a high MAP-HHb coherence of 0.86 in the VLF range.

IV. DISCUSSION AND CONCLUSION

The main finding of this study was that IVH infants had lower VLF coherence between BP and cerebral HHb derived from NIRS, along with higher TOI and lower FTOE. Parameters derived from transfer function analysis of HbO_2, HbD and TOI, however, did not show any significant

difference between the two groups. While our results were seemingly at odds with the expectation that IVH infants should have higher coherence [7-9] or gain [6] between BP and NIRS measures due to impairment in cerebral autoregulation as postulated by previous studies, there were two major methodological differences that should not be neglected. First, our findings were derived from the deoxygenated hemoglobin HHb, which had not been examined in the past. Second, studies which found association between high coherence and incidences of IVH [7, 8] were based on the investigation of the very slow trend or the ultra-low frequency (ULF) component (<0.02 Hz) using longer measurements (30 min), whereas our results were obtained from the VLF component using shorter term measurements (10 min). These differences likely accounted for the contrasting results.

Moreover, our findings could be explained based on the physiological conditions of the preterm infants. The IVH infants had both higher TOI and lower FTOE than the non-IVH. The higher level of cerebral oxygenation in the IVH cases should not be seen as a positive sign, as it could well be a consequence of impaired oxygen extraction capability. In fact, a recent study also showed that cerebral oxygenation on the first day of life was higher in very preterm infants compared with healthy term newborns, with the higher TOI again coinciding with lower FTOE in the preterm cases [14]. The reduced oxygen extraction was very likely to have an impact on the relationship between arterial BP and HHb, as the generation of HHb fluctuation was not only dependent on the BP-driven blood flow, but also on the oxygen consumption rate in the cerebral capillaries which governed the conversion of HbO_2 to HHb. It was of interest to note that the two IVH infants who had the lowest BP-HHb VLF coherence (0.19 and 0.36) also had rather low FTOE (15% and 8%), suggesting a possible link between the two conditions.

In conclusion, cerebral NIRS measurement was able to provide a number of parameters that were potentially useful for distinguishing between preterm infants with or without brain hemorrhage. Specifically, IVH infants were found to have significantly higher cerebral oxygenation level, lower cerebral oxygen extraction rate and lower VLF coherence between arterial BP and deoxygenated hemoglobin. Further studies with larger sample size are warranted for a more complete understanding of the clinical utility of these NIRS measures for early identification of IVH infants.

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