Chapter 6
Assessment of the Myogenic and Metabolic Mechanism Influence in Cerebral Autoregulation Using Near-Infrared Spectroscopy

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1 Introduction

Cerebral autoregulation is a complex process that refers to the maintenance of a constant cerebral blood flow (CBF) over a broad range of arterial blood pressures. This process avoids damage in the brain due to hemorrhagic brain injury and ischemia. Several mechanisms are involved in this process. So far, evidence of the myogenic, metabolic, and neurogenic ones has been described in the literature [1]. Cerebral autoregulation can be assessed by analyzing the relation between mean arterial blood pressure (MABP) and CBF, which can be measured continuously. The similarity in the dynamics of both signals has been quantified so far by means of correlation (partial) coherence [2–4], among other methods. However, the role of other variables in cerebral autoregulation, such as partial pressure of carbon dioxide (pCO_2) and partial pressure of oxygen (pO_2), has not been well explored in clinical studies.

In this chapter, we examine how well the myogenic and the metabolic mechanisms involved in cerebral autoregulation can be assessed by mean of transfer

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function analysis and near-infrared spectroscopy (NIRS) signals. Moreover, we study how these derived measures are related to the long- and short-term clinical outcome in premature infants.

2 Data

The study was performed in 42 infants from the University Hospital Zurich (Switzerland), with a gestational age of 28.1 ± 2.27 weeks and a birth weight of $1{,}155 \pm 467$ g. In all infants, the pCO_2 was measured by a transcutaneous monitor, peripheral oxygen saturation (SaO_2) was measured continuously by pulse oximetry, and MABP by an indwelling arterial catheter. With NIRS, the cerebral intravascular oxygenation (HbD) was continuously and noninvasively recorded using the Critikon Cerebral RedOx Monitor from Johnson & Johnson Medical. MABP, SaO_2, and NIRS signals were simultaneously measured during the first 3 days of life and downsampled at 0.333 Hz.

3 Methods

Signal Analysis. Artifacts shorter than 30 s were removed and corrected by interpolation using robust least squares support vector machines for function estimation [5]. Artifacts longer than 30 s were truncated. Remaining artifacts, if any, were removed manually. Hence, a single continuous measurement was replaced by a set of continuous artifact-free segments. Moreover, only the segments with variations of SaO_2 lower than 5% were included in the analysis. The resulting signals were filtered with a mean average filter and then downsampled to 0.333 Hz in order to obtain a common sampling frequency and minimize the loss of information.

Mathematical Tools. Assessment of the myogenic mechanism in cerebral autoregulation was done via analysis of the MABP/HbD transfer function; the metabolic mechanism was assessed by analysis of the pCO_2/HbD transfer function. After preprocessing, the signals were divided into segments of 20 min with the maximum overlap (step size: one sample). For each segment, the transfer function gain and phase coefficients were calculated. The transfer function was estimated by means of the following equation

$$H(f) = \frac{G_{\mathrm{io}}(f)}{G_{\mathrm{ii}}(f)}$$

where $G_{\mathrm{io}}(f)$ represents the input–output cross-power spectrum and $G_{\mathrm{ii}}(f)$ represents the input auto-power spectrum. The Welch method was used for the calculation

of the respective cross-power and auto-power spectral densities. This method involves a further segmentation of the signals into 10-min epochs with an overlap of 7.5 min. The average of the coefficients in the frequency ranges 0.003–0.02 Hz (very low frequency range: VLF), 0.02–0.05 Hz (low frequency range: LF), and 0.05–0.1 Hz (high frequency range: HF) were calculated [3] for further analysis. Moreover, in order to study the influence of different frequencies in autoregulation assessment, the values of the gain and the phase in all frequencies were also analyzed.

With respect to clinical outcomes, infants were classified as abnormal for short term or long term according to their clinical scores. For short-term outcomes, infants were classified as abnormal whenever bleedings, periventricular leukomalacia (PVL), intra-ventricular hemorrhage (IVH), or death occurred; otherwise they were classified as normal. For long-term clinical outcomes classification, the Bayley scores (Mental and Physicomotor Development Index: MDI and PDI, respectively) were used. Infants were classified as normal if MDI and PDI > 85, otherwise they were classified as abnormal. In addition, in order to study the relation between birth weight (BW) and autoregulation state, the scores of infants with very low birth weight (BW < 1,200 g)[1] were group-wise compared to those with a BW > 1,200 g.

Statistical Analysis. To assess whether the concordance scores were predictive for outcome (normal or abnormal) the nonparametric Kruskal–Wallis test was applied, due to the lack of normality in the data distributions. The statistical analysis was performed using the statistics toolbox from MATLAB. All reported p-values were two-tailed and a nominal p-value < 0.05 was considered as statistically significant.

4 Results

Table 6.1 presents the median, minimum, and maximum values of the gain and phase scores, calculated in the VLF, LF, and HF frequency ranges for the normal and abnormal population according to the short- and long-term classification criteria. In the short-term outcome analysis, there were 23 infants classified as normal and 19 infants classified as abnormal, while in the long-term analysis 8 infants were classified as normal and 34 infants as abnormal. Statistically significant differences between the groups were found only in the gain score for the HF range, with a median value of 0.43 and 0.20 for the normal and abnormal classes (p-value 0.02). All other scores did not differ significantly between the normal and abnormal subgroups.

Figure 6.1 shows the high- and low-pass filter characteristic behavior for the gain median values. However, for the myogenic mechanism (MABP-HbD) it seems that

[1] Clinically, low birth weight is defined for babies with BW < 1,500 g; however, due to the small population with BW > 1,500 g in this dataset, this criterion was modified to BW < 1,200 g.

Therefore, better statistics can be computed.

Table 6.1 Comparison between normal and abnormal population scores for short- and long-term outcomes using the gain and the phase scores

Outcome	Frequency range	Scores	Normal median (min:max)	Abnormal median (min:max)	*p*-Value
Short-term (23 normal, 19 abnormal infants)	VLF	Gain			
		MABP-HbD	0.79 (0.37:2.04)	0.55 (0.34:2.43)	0.07
		pCO_2-HbD	15.30 (7.03:66.52)	14.61 (6.21:28.05)	0.55
		Phase			
		MABP-HbD	−0.15 (−1.08:0.45)	−0.06 (−0.68:0.77)	0.71
		pCO_2-HbD	0.01 (−0.40:0.30)	−0.06 (−0.54:0.32)	0.45
	LF	Gain			
		MABP-HbD	0.48 (0.19:4.45)	0.39 (0.15:5.23)	0.07
		pCO_2-HbD	17.03 (9.00:43.13)	13.72 (4.94:41.43)	0.24
		Phase			
		MABP-HbD	−0.08 (−1.0:0.32)	−0.07 (−0.58:0.67)	0.71
		pCO_2-HbD	0.02 (−0.20:0.28)	−0.02 (−0.23:0.20)	0.31
	HF	Gain			
		MABP-HbD	0.43 (0.11:10.02)	0.20 (0.09:14.74)	**0.02**
		pCO_2-HbD	9.28 (3.02:42.48)	6.72 (2.08:45.12)	0.14
		Phase			
		MABP-HbD	0.005 (−0.42:1.39)	−0.005(−0.27:0.26)	0.81
		pCO_2-HbD	−0.01(−0.15:0.14)	−0.01(−0.17:0.16)	0.79

Long-term (8 normal, 34 abnormal infants)	VLF	Gain			
		MABP-HbD	0.80 (0.43:1.78)	0.66 (0.34:2.43)	0.22
		pCO_2-HbD	14.57 (8.75:66.52)	15.44 (6.21:56.54)	0.79
		Phase			
		MABP-HbD	−0.21 (−1.08:0.29)	−0.09 (−0.76:0.77)	0.40
		pCO_2-HbD	−0.01 (−0.54:0.23)	−0.03 (−0.43:0.32)	0.70
	LF	Gain			
		MABP-HbD	0.45 (0.32:1.63)	0.39 (0.15:5.23)	0.35
		pCO_2-HbD	16.65 (11.78:23.23)	14.02 (4.94:43.13)	0.50
		Phase			
		MABP-HbD	−0.07 (−0.67:0.32)	−0.18 (−1.00:0.67)	0.77
		pCO_2-HbD	−0.03 (−0.23:0.20)	0.014 (−0.20:0.28)	0.46
	HF	Gain			
		MABP-HbD	0.45 (0.21:4.00)	0.23 (0.09:14.74)	0.23
		pCO_2-HbD	9.62 (6.35:12.08)	7.95 (2.08:45.12)	0.54
		Phase			
		MABP-HbD	0.17 (−0.42:1.39)	−0.03 (−0.32:0.26)	0.09
		pCO_2-HbD	−0.04 (−0.09:0.14)	−0.013 (−0.17:0.16)	0.92

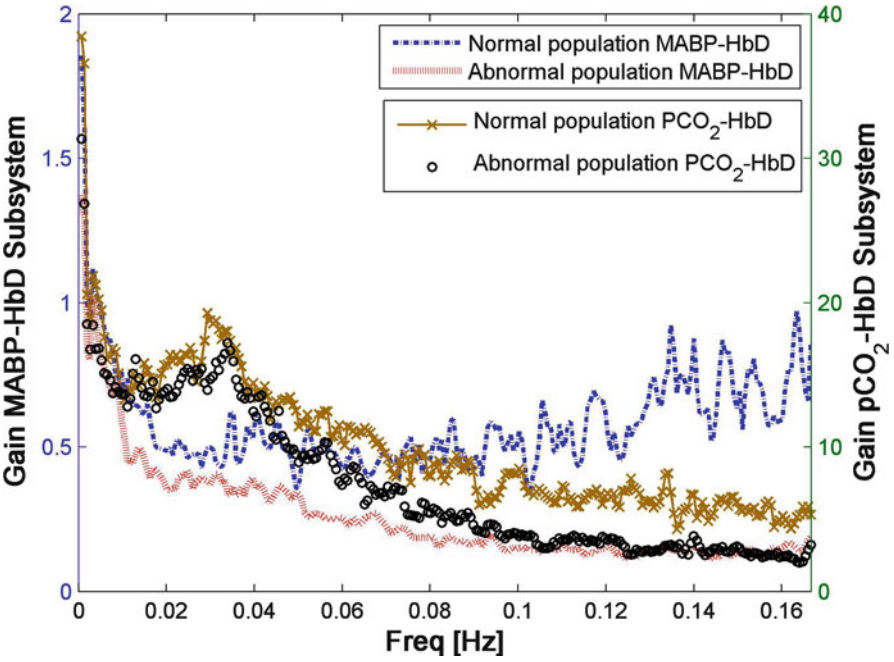

Fig. 6.1 Median values of the gain frequency response for the MABP/HbD and the pCO_2/HbD subsystems

the high-pass filter behavior is only present in the normal population. The metabolic (pCO_2-HbD) subsystem presents a low-pass filter behavior in both classes. The area under the curves was compared for the normal and the abnormal population. The areas for the median gain values for the myogenic mechanism were 0.096 and 0.043 μmol Hz/mmHg L for the normal and abnormal population, respectively; for the metabolic mechanism, the areas were 1.67 and 1.23 μmol Hz/mmHg L. Those areas were statistically different between normal and abnormal populations with *p*-values 0.022 and 0.042 for the myogenic and metabolic mechanism, respectively.

Figure 6.2 presents the *p*-values from the Kruskal–Wallis test performed for the gain values of the metabolic subsystem (pCO_2-HbD) in frequency domain for the BW analysis. In this analysis, 15 infants were classified as abnormal with BW < 1,200 g and 27 infants classified as normal with BW > 1,200 g. The differences between the median values in the normal and abnormal subgroups are statistically more significant in the VLF frequencies. As frequency increases, the gain scores in both populations are similar.

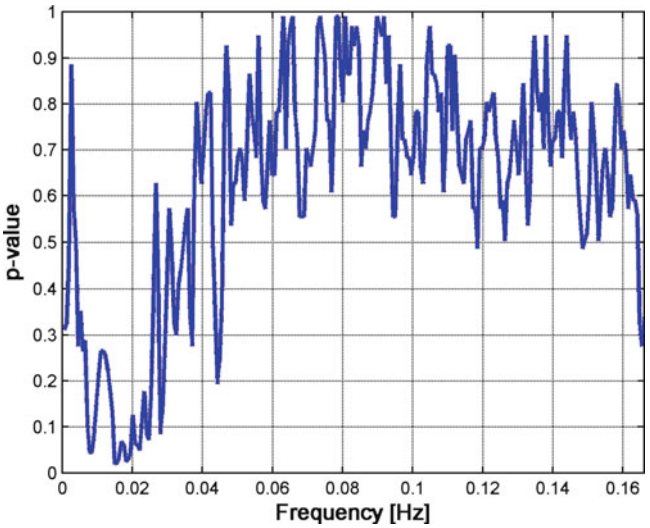

Fig. 6.2 *p*-Values from the Kruskal–Wallis test performed for each gain value (pCO_2-HbD) in frequency domain

5 Discussion

Cerebral autoregulation is a property of the brain and is regulated by three different mechanisms, namely: a myogenic, metabolic, and neurogenic one. On the one hand, the myogenic mechanism is in charge of minimizing the impact of the variations in MABP in the CBF. This mechanism is hypothesized to behave as a high-pass filter [1] where the slow oscillations in MABP are damped but the fast oscillations are reflected in the CBF. This hypothesis appears to be correct according to the results shown in Fig. 6.1. However, this high-pass characteristic was only found outside the normal frequency ranges where autoregulation is normally explored and is absent in the abnormal population. If only the VLF, LF, and HF ranges are analyzed the system behavior reflects a low-pass filter characteristic. This can be due to the disturbances included for the pCO_2 in the MABP and CBF in the VLF. The coupled dynamics between MABP and pCO_2 have not been studied in this chapter; therefore, further investigation is needed to prove this claim.

On the other hand, the metabolic mechanism is hypothesized to behave as a low-pass filter [1]. In this system, the slow variations in pCO_2 are reflected in the CBF while the fast variations are neglected. This is consistent with the results shown in Fig. 6.1. This behavior can be attributed to the time constant involved in the metabolic mechanism to adjust the muscular tone around the vascular wall. Thus, fast changes in pCO_2 are of too short duration to produce big changes in CBF.

We use the gain and phase values in the myogenic and the metabolic subsystems present in cerebral autoregulation to classify between normal and abnormal infants

based on different criteria. Only infants with abnormal short-term outcomes presented statistically different gain scores for the myogenic mechanism. All the other gain and phase scores given in Table 6.1 did not present statistically significant differences between the normal and abnormal population. Moreover, the scores were higher in the normal population compared to the abnormal population, contrary to what was expected. Indeed, according to the literature, higher gain values are expected in the abnormal population as this population should present a stronger link in dynamics compared to the normal infants. Nevertheless, important trends could be observed. As given in Table 6.1, all median values of the gain score were higher in the normal than the abnormal population. Moreover, Fig. 6.1 shows that the difference in median values for the normal and abnormal population becomes more pronounced as frequency increases. The results presented in this chapter point out the importance of the frequency range selected for cerebral autoregulation assessment. Moreover, the frequency response shown in Fig. 6.1 suggests that the metabolic mechanism can be acting as a modulator of the myogenic mechanism in the VLF. This hypothesis should be proven in a more extensive study where more babies, and with more critical outcomes, are included.

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