Cerebral Autoregulation Assessment in Premature Infants: Clinical Relevance

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***Abstract*—Cerebral auto-regulation was assessed in premature infants by the analysis of the common dynamics between the Cerebral Blood Flow (CBF) and Mean Arterial Blood Pressure (MABP). Changes in cerebral intravascular oxygenation (HbD), regional cerebral oxygen saturation (rSO_2), and cerebral tissue oxygenation (TOI), all recorded with Near-Infrared Spectroscopy (NIRS), were used as an indirect measurement that reflects changes in CBF. Correlation, (partial) coherence and transfer function analysis scores were compared with normal and abnormal population in order to establish the importance of cerebral auto-regulation in clinical practice.**

***Index Terms*—blood pressure, cerebral blood flow, monitoring, auto-regulation**

I. Introduction

Cerebral autoregulation refers to the maintenance of a constant CBF over a broad range of arterial blood pressures. This process avoids damage in the brain due to hemorrhagic brain injury and ischemia. Evidence of impaired cerebral autoregulation in preterm infants has been found in the literature [1]; however, its clinical relevance is uncertain [2].

Cerebral autoregulation can be assessed by analyzing the relation between Mean Arterial Blood Pressure (MABP) and Cerebral Blood Flow (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 and transfer function analysis [1] [3], among other methods. Intervals with a correlation, (partial) coherence coefficient $>$ 0.5 or high gain and positive phase are considered to present impaired autoregulation.

MABP can be measured continuously by classical clinical monitors, in premature babies normally an umbilical catheter is used. Cerebral blood flow however is difficult to measure continuously. By means of Near-Infrared Spectroscopy (NIRS), changes in hemoglobin difference (HbD) can be measured, which reflect changes in CBF [4] [5] in case of constant arterial oxygen saturation (SaO_2). The CBF also correlates with the Tissue Oxygenation Index (TOI) and the regional Arterial oxygen Saturation (rSO_2) [6]. Clinical outcomes in preterm infants are normally assessed by the use of birth weight and gestational age. However, other variables have been proven to be more sensitive to the prediction of some clinical outcomes in the neonates, such as the CRIB score. Although this score has given good results in the prediction of neonatal mortality [7] no conclusive information exist related to other outcomes; one of the causes, is that this score is calculated based on the clinical information of the baby at birth and doesn't take into account the evolution in time of the patient. Therefore, short-term clinical outcomes such as the presence of bleedings, PVL (Periventricular Leukomalacia) and IVH (IntraVentricular Hemorrhage) have not been proven to be directly related to this score.

In this paper we examine by means of a multicentric study how well cerebral autoregulation as quantified by correlation, (partial) coherence, transfer function analysis and derived measures, is related to the short-term clinical outcomes of premature infants, and hence we evaluate its usefulness in neonatal monitoring.

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II. Data

The study was performed in 100 infants from three different centers. 38 infants were admitted at the University Medical Center Utrecht (The Netherlands), they presented mean gestational age of 28.9 $\pm$ 1.8 weeks and a birth weight of 1120 $\pm$ 509 grams. A second set of 20 infants from the University Hospital Leuven (Belgium) was included, having a mean gestational age of 28.4 $\pm$ 3.5 weeks and a birth weight of 1113 $\pm$ 499 grams. Finally, 42 infants from the University Hospital Zurich (Switzerland), with a gestational age of 28.1 $\pm$ 2.27 weeks and a birth weight of 1155 $\pm$ 467 grams were also included. In all infants the peripheral oxygen saturation SaO_2 was measured continuously by pulse oximetry, and MABP by an indwelling arterial catheter. With NIRS, the HbD and the tissue oxygenation index (TOI) were continuously and non-invasively recorded using the NIRO 300 from *Hamamatsu* (Leuven data) and the Critikon Cerebral Monitor (Zurich data), and in Utrecht the regional cerebral oxygen saturation (rSO_2) was recorded using the INVOS4100 from *Somanetics*. MABP, SaO_2 and NIRS signals were simultaneously measured during the first three days of life and downsampled at 0.333Hz. Figure 1 shows a representative sample of the recorded signals.

III. Methods

Signal Preprocessing. Artifacts shorter than 30 seconds were removed and corrected by interpolation using robust least-squares support vector machines for function estimation [8]. Artifacts longer than 30 seconds were truncated. Remaining

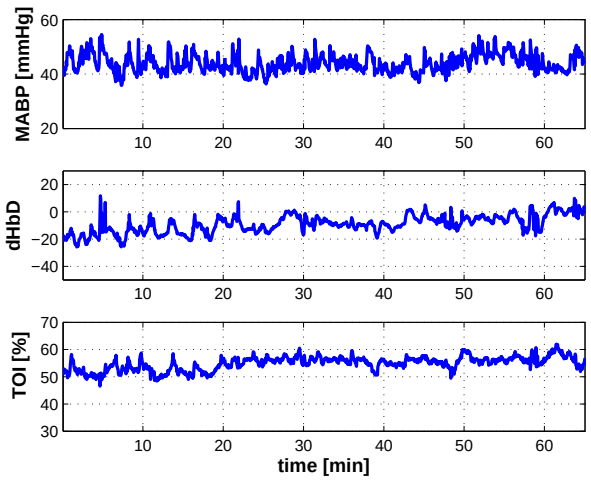


Fig. 1. Example of the MABP, HbD and TOI signals preprocessed from the Leuven dataset.

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 0.333Hz in order to obtain a common sampling frequency and avoid the loss of information in the new downsampled signal.

Mathematical Tools. Assessment of autoregulation was done via analysis of the following pairs of signals: MABP-HbD and MABP-TOI (Leuven data), MABP-HbD (Zurich data) and MABP- rSO_2 (Utrecht data). After preprocessing, the signals were divided into segments of 20 minutes. For each segment, the correlation (CORR), coherence (COH), partial coherence (PACOH) [3] [4] and transfer function gain and phase coefficients were calculated. For the (partial) coherence and the transfer function analysis, 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-minute epochs with an overlap of 7.5 minutes. The transfer function was estimated by means of the following equation:

$$H(f) = \frac{G_{io}(f)}{G_{ii}(f)} \tag{1}$$

where G_{io} represents the input-output cross-power spectrum and $G_{ii}(f)$ represents the input auto-power spectrum. The gain is calculated as the absolute value of the transfer function $H(f)$ and the phase as the phase of the same transfer function.

The average of the coefficients in the frequency range 0.003Hz-0.04 Hz is then calculated, according to [4]. This procedure was applied to all 20-minute length segments and a time series with the corresponding coefficients was obtained. Then, a score equal to the mean value of this time series was assigned to each child.

With respect to clinical outcomes, infants were classified as abnormal whenever bleedings, PVL (Periventricular Leukomalacia) and/or IVH (IntraVentricular Hemorrhage) occurred, else they were classified as normal.

Statistical Analysis. To assess whether the concordance scores were predictive for outcome (normal or abnormal), the non-parametric Kruskal-Wallis test was applied. 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.

IV. Results

Table I shows the results for the three data sets used. The mean and standard deviation for the correlation, coherence and partial coherence scores calculated for the normal and abnormal population are given in percentage, while the gains scores are dimensionless, and the phase values are given in radians. The Leuven dataset contains two different measurements that reflects the CBF, namely TOI and the HbD. The analysis was performed separately for each parameter.

In the Leuven dataset 45% (9/20) of the infants had a bad outcome. In the analysis done based on the signal pair MABP vs TOI the COH and the PCOH scores presented differences which are statistically significant between the normal and abnormal population (p-values 0.02 and 0.05 respectively). However, the median value of the COH and PCOH scores were higher in the normal population than the abnormal population: 21.33 versus 17.82 for the COH and 22.09 versus 18.70 for the PCOH. When the analysis was performed in the other signal pair MABP vs HbD signal the CORR score presents differences which are statistically significant between the normal and abnormal population (p-value 0.03). However, also in this case, the median CORR values for normal children are higher than the ones for abnormal children: 25.83 vs 17.15. The other parameters didn't show statistically significant differences.

In the Utrecht dataset 34% (13/38) of the infants had a bad outcome. In this dataset only the CORR score showed statistically significant differences between normal and abnormal population (p-value 0.04). Moreover, the median value of the scores value for the normal population was lower than the one for the abnormal population: 20.24 vs 26.57. This is consistent with the expectations as confirmed in the literature [4] [5]. In the other cases the differences were not statistically significant.

In the Zurich dataset 45% (19/42) of the infants had a bad outcome. In this dataset the gain score shows statistically significant differences (p-value 0.05). The median value of the gain for the normal population was higher than the one for the abnormal population: 0.82 vs 0.56. The other parameters didn't show statistically significant differences.

On the other hand, although the phase values didn't show differences statistically significant between both populations, it is important to note that the median values for the abnormal population were higher than the ones for the normal population in all the centers.

V. Discussion

Impaired cerebral autoregulation is considered a risk factor for brain injury in the sick, premature infant [1] [4] [5] and has been associated with mortality in this population. Continuous measurements of MABP and CBF are thus of interest to

assess cerebral autoregulation due to its importance in neonatal monitoring.

TABLE I
CONCORDANCE SCORES STRATIFIED BY CENTER AND BABY'S OUTCOME: NORMAL AND ABNORMAL.

Center	Method	Normal	Abnormal	p-value
Leuven	**Correlation**			
MABP-HbD	*median*	25.83	17.15	0.03
	min-max	17.41-45.60	11.16-39.86	
	Coherence			
	median	27.22	21.72	0.42
	min-max	19.98-55.83	16.23-32.27	
	Partial Coh			
	median	27.26	21.53	0.18
	min-max	18.98-42.36	19.31-34.44	
	Gain			
	median	1.22	0.79	0.08
	min-max	0.53-2.34	0.48-2.72	
	Phase			
	median	-0.40	-0.36	0.56
	min-max	-0.74-0.42	-0.63-0.50	
Leuven	**Correlation**			
MABP-TOI	*median*	22.06	14.87	0.10
	min-max	14.56-44.01	10.86-25.67	
	Coherence			
	median	21.33	17.82	0.02
	min-max	17.01-30.14	14.33-26.35	
	Partial Coh			
	median	22.09	18.70	0.05
	min-max	14.56-31.70	14.08-23.42	
	Gain			
	median	0.31	0.32	0.90
	min-max	0.18-0.58	0.20-0.45	
	Phase			
	median	-0.30	-0.20	0.51
	min-max	-0.59-0.21	-0.39-0.20	
Utrecht	**Correlation**			
MABP-rSO_2	*median*	20.24	26.57	0.04
	min-max	11.94-34.69	16.16-46.45	
	Coherence			
	median	36.68	38.44	0.33
	min-max	32.42-45.75	32.58-47.18	
	Partial Coh			
	median	37.01	37.60	0.70
	min-max	32.70-45.07	33.38-47.75	
	Gain			
	median	0.48	0.45	0.74
	min-max	0.27-0.87	0.23-1.83	
	Phase			
	median	-0.40	-0.35	0.81
	min-max	-1.09-0.17	-0.85-0.97	
Zurich	**Correlation**			
MABP-HbD	*median*	24.55	24.45	0.85
	min-max	9.81-47.94	7.79-44.99	
	Coherence			
	median	36.48	37.45	0.96
	min-max	29.06-59.77	28.09-48.62	
	Partial Coh			
	median	38.24	37.95	0.96
	min-max	27.94-55.80	29.18-45.80	
	Gain			
	median	0.82	0.56	0.05
	min-max	0.35-3.62	0.34-2.44	
	Phase			
	median	-0.20	0.17	0.28
	min-max	-0.68-0.78	-1.08-0.53	

Autoregulation assessment can be done by means of correlation, coherence, partial coherence and transfer function analysis. Normally, high CORR, COH, PCOH, and gain scores point out a strong link between the dynamics of the MABP and the CBF signals, thereby, indicating a failure in the autoregulative mechanism in the infant. According to the results shown in the table I the Utrecht dataset is consistent with this statement, however, the Leuven and the Zurich dataset show contradictory results. For the COH, PCOH and transfer function scores, these differences can be explained by the frequency range selected to average the scores, another frequency range can lead to different results.

On the other hand, the phase values for the normal population were smaller than the values for the abnormal population, this suggests that the reaction time between the changes produced in MABP and CBF is longer in normal infants than abnormal infants in the frequency range explored. Moreover, the negative values in the phase indicate that the autoregulative process is lead by changes in MABP and followed by changes in CBF. However, in some infants this relation was inverse, this can indicate the presence of impaired autoregulation, further studies will be needed in order to prove this hypothesis.

Cerebral autoregulation is a dynamic process, hence a transition between impaired and paired autoregulation can be expected. If the periods where impaired autoregulation is present are shorter than the periods with paired or intact autoregulation the median value will not be a representative score due to the dominant influence of normal episodes over the all measurement period. There are several approaches that can be taken into account to address this problem. First of all, scores that include a description of the evolution in time for the CORR, COH, PCOH and transfer function analysis values per patient can be be used; however, such scores require large datasets in order to produce reliable information. Another possibility is to include in the analysis only those segments that present variations in MABP large enough to alter the autoregulative mechanism in the infant; however, there is not agrement so far on how autoregulation can be most effectively assessed in this population. Finally, a better selection of the population including more critical outcomes can elucidate which scores are most predictive with respect to clinical outcome.

VI. CONCLUSIONS

Several parameters that evaluate the state of the autoregulative mechanism in the brain of infants have been exposed. Although the scores show not statistical evidence of a relationship between impaired cerebral autoregulation and the clinical outcomes a trend was observed. However, the CORR, COH, PCOH and gain scores showed contradictory information between the different dataset. On the other hand, the phase was lower in the normal population than in the abnormal population in all the cases. This can indicate that the phase should be a better parameter in order to monitor the mechanism responsible for the autoregulative process of the brain in infants. But, due to its high intra variability among the normal and the abnormal population, further refinements are needed.

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