Differences in the Cerebral Hemodynamics Regulation Mechanisms of Premature Infants with Intra-Ventricular Hemorrhage Assessed by Means of Phase Rectified Signal Averaging

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***Abstract*— Cerebral hemodynamics regulation consists of several mechanisms that try to keep brain homeostasis. In premature infants, due to the immaturity of their cerebral vascular bed, these mechanisms might be impaired exposing their brain to damage. The status of the cerebral regulation mechanism is classically assessed by measuring the coupling between some systemic variables, such as Mean arterial blood pressure (MABP) and concentration of blood gases, with surrogate measurements for cerebral blood flow, such as brain tissue oxygenation ($rScO_2$) measured by means of Near-infrared Spectroscopy. We hypothesized that the coupled dynamics between systemic variables and $rScO_2$ is different in premature infants that suffered from brain damage than in those with a favorable clinical outcome. Therefore, we explore the use of phase rectified signal averaging (PRSA) and bi-variate PRSA (BPRSA) in order to identify these differences. We found that the coupled dynamics between changes in MABP and cerebral oxygenation was different in premature infants that suffered III-IV grade intra-ventricular haemorrhage (IVH), when compared to control subjects.**

I. INTRODUCTION

Cerebral hemodynamics regulation is one of the most important regulation mechanisms in the brain. It tries to keep the brain homeostasis by supplying the sufficient amount of substrate to sustain brain metabolism, whilst reducing the effects of systemic variables on cerebral hemodynamics. In premature infants, due to immaturity, this mechanism is likely to be impaired exposing their brain to damage caused by systemic or hemodynamic instability [1]. Therefore, monitoring of cerebral hemodynamics regulation in this population is paramount in order to avoid brain damage.

In the literature there exist several methodologies that have been developed in order to monitor the status of the brain regulative mechanisms [2], [3], [4]. These methodologies estimate the coupling between the variations in some systemic variables, such as heart rate (HR), mean arterial blood pressure (MABP), and blood gases concentrations, and brain hemodynamic variables such as brain tissue oxygenation ($rScO_2$), cerebral blood flow (CBF), and cerebral blood volume. When used in premature infants, non-invasive technologies for the measurement of brain hemodynamic variables are preferred due to their fragility. In this context near-infrared spectroscopy (NIRS) represents an attractive technology that measures the changes in oxy- and deoxy-hemoglobin concentration using light [5].

Phase rectified signal averaging is a methodology that was developed in order to analyze quasi-stationary oscillations [6], [7]. This methodology has been extended to the bivariate PRSA (BPRSA) in order to study the inter-relations between two or more signals measured simultaneously [8]. PRSA, as well as BPRSA, summarizes the dynamic information of the signal(s) in a single template that represents the average persistent dynamic behavior in the signal, or in the coupling between the signals. In the monitoring of cerebral hemodynamics regulation, one of the main challenges is the presence of non-linear, and non-stationary relations between the variables under analysis. Since PRSA and BPRSA can mitigate these effects, its use in this field is appropriate.

In this study, we hypothesize that premature infants that suffer from an intra-ventricular hemorrhage (IVH) might present a different dynamic relation between systemic and cerebral hemodynamic variables, than premature infants that do not experience brain damage. We use BPRSA in order to study these differences.

The paper is organized as follows. In section II the PRSA and BPRSA algorithms, as well as the data used in this study, are described. In section III the results obtained from both methodologies are shown. Finally, in section IV we discuss the results and their clinical relevance.

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II. METHODS

A. Phase Rectified Signal Averaging

Phase rectified signal averaging (PRSA) is a method that was developed in order to study quasi-periodic oscillations in signals that might be contaminated by nonstationarities and noise [6]. One of the strengths of PRSA lies in its ability to identify differences in dynamics due to increases or decreases in the signal under analysis. Given a signal $\mathbf{x} = \{x_i\}_{i=1}^{N}$ where N is the number of observations, the analysis of $\mathbf{x}$ using PRSA is as follows. First, the anchor points in $\mathbf{x}$ are identified. An increasing anchor point is identified when $x_i > x_{i-1}$; alternatively, a decreasing anchor point can also be defined and it is identified when $x_i < x_{i-1}$. Once an anchor point is located, a segment, s, of length $(2L)$ is extracted from the signal $\mathbf{x}$ around the anchor point as follows $s = \{x_{i-L}, \ldots, x_i, \ldots, x_{i+L}\}$. This procedure is repeated for all the anchor points found in $\mathbf{x}$. When all the segments, s, for each anchor point are obtained the PRSA curve is computed as follows:

$$\bar{\mathbf{x}} = \frac{1}{M} \sum_{k=1}^{M} s_k, \tag{1}$$

where M represents the number of segments extracted from the signal.

The PRSA curve, $\bar{\mathbf{x}}$, contains the average information related to the dynamics of the signal. In case of selecting increasing anchor points, $\bar{\mathbf{x}}$ will indicate the average dynamics in $\mathbf{x}$ related to its increments, whilst, in case of selecting decreasing anchor points, $\bar{\mathbf{x}}$ will indicate the average behavior in $\mathbf{x}$ due to decrements in its value. Since all the segments, s, are aligned prior to averaging, changes in phase of the quasi-periodic oscillations are corrected. In addition, the averaging procedure mitigates the effects of nonstationarities and noise, preserving only the persistent information about the system dynamics.

Additionally, it is important to take into account that the value L should be larger than the slowest oscillation expected in the signal under analysis.

B. Bi-variate Phase Rectified Signal Averaging

Originally PRSA was developed for the analysis of quasi-periodic oscillations. However, it has also been extended in order to study the interrelations between 2 different signals recorded simultaneously [8]. The generalization of PRSA, called bi-variate PRSA (BPRSA), includes a slight modification to the original PRSA algorithm. Consider a set of measurements $(\mathbf{x}, \mathbf{y}) = \{x_i, y_i\}_{i=1}^{N}$, where N represents the number of observations, x is considered as an independent variable called the trigger signal, and y is assumed to depend on x, y is called the target signal. In order to identify the profile of the coupling between these 2 signals, BPRSA is used as follows. First, the anchor points in the trigger signal, $\mathbf{x}$, are identified using the criteria described in the previous section. Once these anchor points have been selected, a segment, s, of length $(2L+1)$ is extracted from the target signal, $\mathbf{y}$, around the anchor point, such that $s = \{y_{i-L}, \ldots, y_i, \ldots, y_{i+L}\}$. When all the anchor points have been selected, the BPRSA curve is computed as follows:

$$BPRSA^{\uparrow}_{\mathbf{x}\to\mathbf{y}} = \frac{1}{M} \sum_{k=1}^{M} s_k, \tag{2}$$

where M represents the number of segments extracted from the signal $\mathbf{y}$, and $BPRSA^{\uparrow}_{\mathbf{x}\to\mathbf{y}}$ is the BPRSA curve of $\mathbf{y}$ due to the increments in $\mathbf{x}$. Alternatively, the response in $\mathbf{y}$ due to decrements in $\mathbf{x}$, $BPRSA^{\downarrow}_{\mathbf{x}\to\mathbf{y}}$, can be found using equation (2) by defining decreasing anchor points.

The obtained BPRSA curves contain the information related to the dynamics in the target signal, $\mathbf{y}$, caused by changes in the trigger signal, $\mathbf{x}$. In case of decoupled dynamics between the signals, the BPRSA curve should converge to zero. However, in case of dependence, the BPRSA curves will converge to the dynamic response in $\mathbf{y}$ caused by a change in $\mathbf{x}$. Additionally, the separate analysis of the responses in the target signal due to the increments or decrements in the trigger signal are useful to identify the presence of non-linear coupling between the signals, i.e. in case of a linear relation $BPRSA^{\uparrow}_{\mathbf{x}\to\mathbf{y}} = -BPRSA^{\downarrow}_{\mathbf{x}\to\mathbf{y}}$, any deviation from this equality indicates the presence of a nonlinear behavior.

C. Data

Measurements from 9 premature infants, with a gestational age lower than 32 weeks, during the first three days of life were included in this study. From these 9 subjects, 5 presented III-IV grade of intra-ventricular hemorrhage (IVH), diagnosed by means of cranial ultrasound. The remaining 4 patients were used as control and were matched by gestational age, birth weight and sex. Concomitant measurements of HR, MABP measured with an indwelling arterial catheter, arterial oxygen saturation SaO_2 measured by a pulse oxymeter, and $rScO_2$ measured by (INVOS 4100-5100; Somanetics, Troy, Michigan) were recorded and stored in a personal computer for offline analysis using Poly 5 (Inspector Research Systems, Amsterdam, The Netherlands) with a sampling frequency of 1Hz. Cranial ultrasound was performed at least daily and it was used to determine neonatal outcome. The grade for IVH was given based on the classification presented in [9], where III-IV grade is considered as a severe IVH. This data is part of a large data collection presented in [10].

The signals were filtered using a median filter of 7 samples, the length for this filter was found empirically and was selected based on the visual inspection of the filtered signal. Additionally, artifacts were detected manually and corrected as follows. If the artifact duration was shorter than 10 seconds, the data was corrected using a linear interpolation, otherwise the data within the artifact was erased and replaced by the symbol 'NaN', indicating missing data-points. In order to deal with missing points, the mean in equations (1) and (2) was computed using only the available data. This artifact correction scheme was used in order to avoid alterations in the PRSA and BPRSA curves due to other

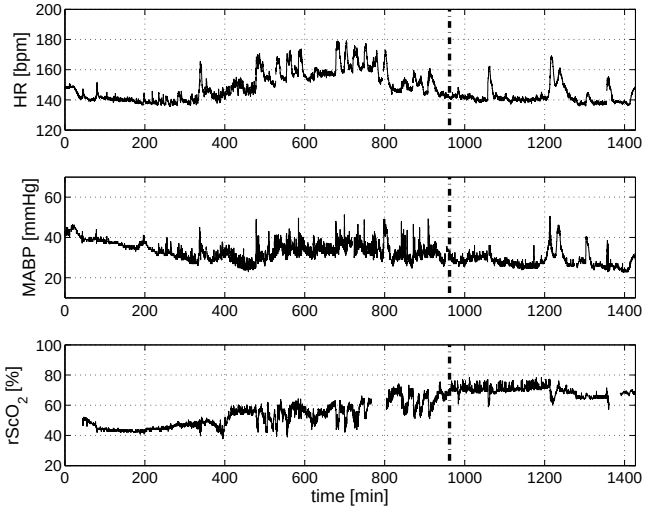


Fig. 1. Data collected from one subject that suffered a IV-grade IVH. From top to bottom, measurements of HR, MABP and $rScO_2$. The black dashed vertical line represent the time when the last ultrasound with favorable outcome was performed. This indicates that the hemorrhage occurred during the last interval of the displayed data.

type of interpolation. Data from one of the subjects that suffered IVH is shown in Fig. 1, where the time at which the last ultrasound with favorable outcome was performed is indicated.

For the analysis, we computed the BPRSA between (HR, $rScO_2$) and (MABP, $rScO_2$), and the PRSA curve for the $rScO_2$. Additionally, for each premature infant with IVH the analysis was performed using the data from the start of the measurements until the diagnosis of IVH. In order to compare the results with the controls, the analysis in the respective matched controls was performed using the same amount of data samples. A value of $L = 300$ samples was selected for the analysis, indicating a segment, s, with length 601 samples. This value was used in order to be able to assess dynamics with a period of 5 minutes before and after the anchor point [11].

III. RESULTS

The results from the PRSA and BPRSA analysis are shown in Fig. **??**. The figure displays the average responses on the target signal, $rScO_2$, due to an increase or decrease in the trigger signals, HR and MABP, for the control group and the group of premature infants that suffered and IVH, in black and gray respectively. From the results we can observe that $BPRSA^{\uparrow}_{\mathbf{HR\rightarrow rScO_2}} \neq -BPRSA^{\downarrow}_{\mathbf{HR\rightarrow rScO_2}}$, and $BPRSA^{\uparrow}_{\mathbf{MABP\rightarrow rScO_2}} \neq -BPRSA^{\downarrow}_{\mathbf{MABP\rightarrow rScO_2}}$, which indicates the presence of a non-linear relation between the variables. In addition, the BPRSA curves for the control subjects converge faster to zero than the curves for the subjects with brain injury. Furthermore, no changes were observed in the PRSA curves obtained from the $rScO_2$.

IV. DISCUSSION

The results obtained from the BPRSA analysis indicate the presence of a nonlinear behavior in the mechanisms that regulate cerebral hemodynamics, especially, in the relation between MABP and $rScO_2$ for increasing as well as decreasing anchor points. This relation is important since premature infants are likely to suffer of hypotension. Therefore, in order to avoid brain damage due to an insufficient perfusion it is common practice to treat this population with drugs to increase their blood pressure. However, increasing blood pressure might be dangerous for these infants due to the fragility of their cerebral vascular bed. In this particular case, we observed that in premature infants that experience an IVH an increment in MABP causes a large increase in $rScO_2$, this might indicate an increasing cerebral blood flow or cerebral blood volume, which in combination with a fragile cerebral vascular bed can lead to hemorrhage. Additionally, it was also observed that a decrement in MABP leads to a large decrease in $rScO_2$ values exposing the brain to hypoxic damage.

When comparing the time profile of the BPRSA curves after the anchor point, it can be observed that in the control population the variations converge towards zero. This might be due to the regulatory mechanism that reacts to changes in MABP and counteract its influence in order to keep brain homeostasis. In contrast, patients with brain injury did not present this profile, indicating a depressed regulatory mechanism.

Additionally, responses due to decelerations in HR do not differ significantly between both groups, which indicates that the influence of the vagal activity on the cerebral hemodynamic regulation mechanisms between the groups is similar. Interestingly enough, changes between the groups can be observed in the accelerations of the HR, indicating a different coupling between sympathetic mediated activity and $rScO_2$ in both groups. This effect might be a sign of a difference in maturation between the infants in both populations. In [12], it was found that in very low birth weight premature infants the effect of maturation is seen on the HR variability analysis as an increment in the power contained in the low frequency band. This suggests that in more mature infants the sympathetic activity is larger, which can lead to a more effective regulation of cerebral hemodynamics. This is in agreement with some previous work where we also found that blockade of α_1 adrenergic receptors, due to the use of Labetalol, results on a reduction of the influence of the low frequencies of HR on the cerebral hemodynamics regulation [13].

Finally, PRSA does not provide differences in the dynamic profiles for changes in $rScO_2$ between both groups. This result is not surprising, since variations in $rScO_2$ are expected to be caused by external regulation mechanisms and not self-regulation.

In conclusion, the results from this preliminary work can be summarized as follows. First, BPRSA exposes a nonlinear behavior in the cerebral hemodynamic regulation mechanisms. Second, even though the control and III-IV grade IVH population were matched by gestational age, birth weight and sex, BPRSA suggests a difference in maturation. These results are of high clinical impact, since they might

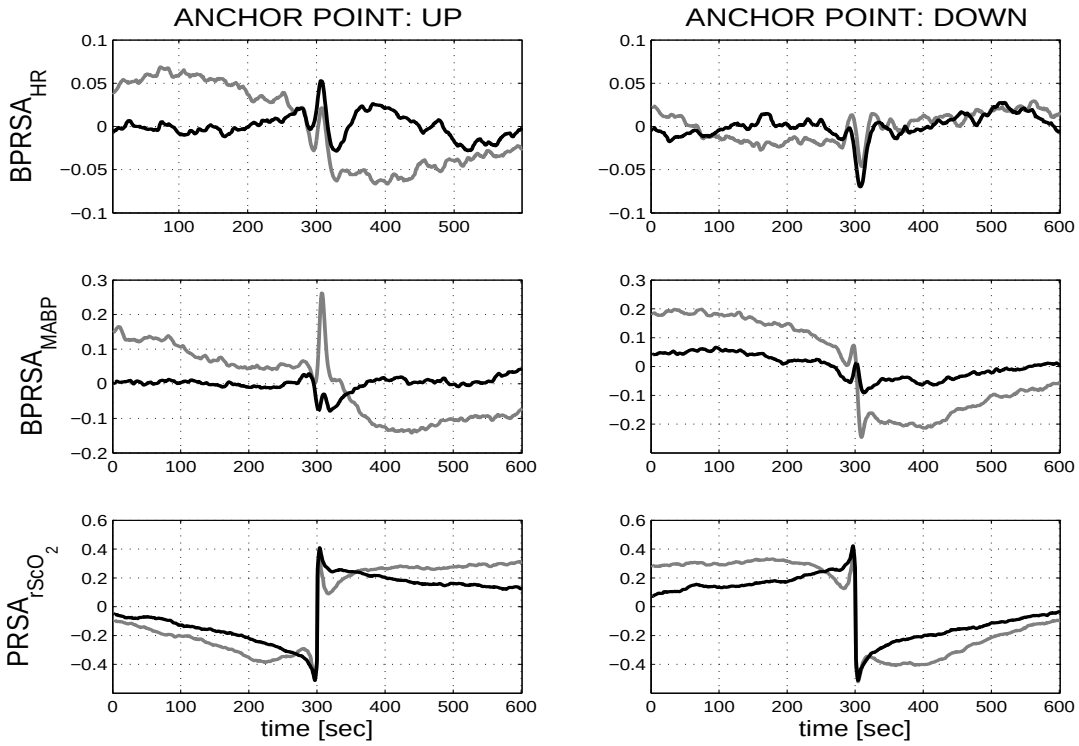


Fig. 2. Results from the PRSA and BPRSA algorithms. The solid black lines represent the average responses for the control group, while the solid gray lines represent the average response for the premature infants that suffered an IVH. In the left column the results using increasing anchor points are displayed. The right column shows the results for decreasing anchor points. The upper and middle row present the results from the BPRSA analysis or $rScO_2$ using the HR and the MABP as trigger signal, respectively. The results for the PRSA analysis in the $rScO_2$ are depicted on the lower row. The anchor point is located at 300 seconds.

indicate that even if an infant is premature he might be mature enough to preserve brain homeostasis without the need of treatment [14]. These preliminary results highlight the uses of BPRSA in the field of cerebral hemodynamics monitoring; however, a larger validation study is needed.

REFERENCES

[1] M. Tsuji, J. P. Saul, A. du Plessis, E. Eichenwald, J. Sobh, R. Crocker, and J. J. Volpe, "Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants," *Pediatrics*, vol. 106, no. 4, pp. 625–632, 2000.

[2] T. Peng, A. B. Rowley, P. N. Ainslie, M. J. Poulin, and S. J. Payne, "Multivariate system identification for cerebral autoregulation," *Annals of Biomedical Engineering*, vol. 36, no. 2, pp. 308–320, 2008.

[3] F. Y. Wong, T. S. Leung, T. Austin, M. Wilkinson, J. H. Meek, J. S. Wyatt, and A. M. Walker, "Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy," *Pediatrics*, vol. 121, no. 3, pp. e604–e611, 2008.

[4] A. Caicedo, M. D. Papademetriou, C. E. Elwell, A. Hoskote, M. J. Elliott, S. Van Huffel, and I. Tachtsidis, "Canonical correlation analysis in the study of cerebral and peripheral haemodynamics interrelations with systemic variables in neonates supported on ecmo," *Advances in Experimental Medicine and Biology*, vol. 765, pp. 23–29, 2013.

[5] M. Wolf, M. Ferrari, and V. Quaresima, "Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications," *Journal of biomedical optics*, vol. 12, no. 6, pp. 062 104–062 104, 2007.

[6] A. Bauer, J. W. Kantelhardt, A. Bunde, P. Barthel, R. Schneider, M. Malik, and G. Schmidt, "Phase-rectified signal averaging detects quasi-periodicities in non-stationary data," *Physica A: Statistical Mechanics and its Applications*, vol. 364, pp. 423–434, 2006.

[7] J. W. Kantelhardt, A. Bauer, A. Y. Schumann, P. Barthel, R. Schneider, M. Malik, and G. Schmidt, "Phase-rectified signal averaging for the detection of quasi-periodicities and the prediction of cardiovascular risk," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 17, no. 1, p. 015112, 2007.

[8] A. Y. Schumann, J. W. Kantelhardt, A. Bauer, and G. Schmidt, "Bivariate phase-rectified signal averaging," *Physica A: Statistical Mechanics and its Applications*, vol. 387, no. 21, pp. 5091–5100, 2008.

[9] L.-A. Papile, G. Munsick-Bruno, and A. Schaefer, "Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps," *The Journal of pediatrics*, vol. 103, no. 2, pp. 273–277, 1983.

[10] T. Alderliesten, P. Lemmers, J. J. Smarius, R. E. van de Vosse, W. Baerts, and F. van Bel, "Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage," *The Journal of pediatrics*, vol. 162, no. 4, pp. 698–704, 2013.

[11] A. Caicedo, G. Naulaers, P. Lemmers, F. van Bel, M. Wolf, and S. Van Huffel, "Detection of cerebral autoregulation by near-infrared spectroscopy in neonates: performance analysis of measurement methods," *Journal of biomedical optics*, vol. 17, no. 11, pp. 117 003–117 003, 2012.

[12] A. Z. Khattak, N. S. Padhye, A. L. Williams, R. E. Lasky, F. R. Moya, and M. T. Verklan, "Longitudinal assessment of heart rate variability in very low birth weight infants during their nicu stay," *Early human development*, vol. 83, no. 6, pp. 361–366, 2007.

[13] A. Caicedo, L. Thewissen, G. Naulaers, P. Lemmers, F. Van Bel, and S. Van Huffel, "Effect of maternal use of labetalol on the cerebral autoregulation in premature infants," *Advances in Experimental Medicine and Biology*, vol. 789, pp. 105–111, 2013.

[14] T. Alderliesten, P. Lemmers, I. C. van Haastert, L. S. de Vries, H. J. Bonestroo, W. Baerts, and F. van Bel, "Hypotension in preterm neonates: Low blood pressure alone does not affect neurodevelopmental outcome," *The Journal of Pediatrics*, 2014.