Impaired Cerebral Autoregulation Using Near-Infrared Spectroscopy and its Relation to Clinical Outcomes in Premature Infants

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Abstract The concordance between the change in the Mean Arterial Blood Pressure (MABP) and the Cerebral Blood Flow (CBF) is studied using the Correlation, Coherence and Partial Coherence methods in order to detect Impaired Cerebral Autoregulation in Neonates. The presence of impaired autoregulation is assessed by the use of the Critical Percentage of Recording Time (CPRT). The changes in CBF are reflected by the measurement of changes in cerebral intravascular oxygenation (HbD), regional cerebral oxygen saturation (rSO_2), and cerebral tissue oxygenation (TOI), as measured by Near-Infrared Spectroscopy (NIRS) (INVOS4100 and NIRO300). The relation between impaired autoregulation and long term clinical outcomes in premature infants is studied.

1 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 relation with clinical outcomes 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 [1] [3], among other methods. Intervals with a correlation, (partial) coherence coefficient > 0.5 are considered to present impaired autoregulation. In order to include all this information in a single value, two scores have been used: the Pressure Passive Index (PPI) [4], defined as the percentage of 10-min epochs with impaired autoregulation, and the Critical Percentage of Recording Time (CPRT), which represents the percentage of

the total measuring time during which impaired cerebral autoregulation is detected [5].

MABP can be measured continuously by classical clinical monitors. 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 [6] [7] 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) [8].

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 the clinical outcomes in the neonates such as the CRIB score [9]. Moreover, long-term development of infants with regard to mental and psychomotor development is assessed by the Bayley and the Griffith scores

In this paper we examine by means of a multicentric study how well cerebral autoregulation as quantified by correlation, (partial) coherence and derived measures, is related to the long-term clinical outcomes of premature infants, as quantified by the above-mentioned scores.

2 Data

The study was performed in 33 infants, admitted at the University Medical Center Utrecht (The Netherlands), mean gestational age of 28.9±1.8 weeks and a birth weight of 1120 ± 509 grams. Another 20 infants from the University Hospital Leuven (Belgium), with a gestational age of 28.4±3.5 weeks and a birth weight of 1113±499 grams were 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 (Hamamatsu) (Leuven data), and in Utrecht the regional cerebral oxygen saturation (rSO_2) was recorded using the INVOS4100 (Somanetics). MABP, SaO_2 and NIRS signals were simultaneously measured during the first three days of life and downsampled at 0.333Hz. The total length of the recordings was 50-70 hours for the Utrecht data and 6-9 hours for the Leuven data.

3 Methods

Signal Analysis. In the data preprocessing artifacts <1.5 seconds were removed and corrected by interpolation. Artifacts > 1.5 seconds were truncated. Hence, a single continuous measurement was replaced by a set of continuous artifact-free segments. Then, the signals were filtered and downsampled to 0.333Hz in order to obtain a common sampling frequency. Assessment of autoregulation was done by analysis of MABP-HbD and MABP-TOI signals (Leuven data) and analysis of MABP- rSO_2 signals (Utrecht data). After preprocessing, the signals were divided into segments of 20 minutes. For each segment, the correlation (CORR), coherence (COH) and partial

coherence (PACOH) coefficients were calculated. For the (partial) coherence the Welch method was used for the assessment of the respective cross-power and auto-power spectra densities. This method involves a further segmentation of the signals into 10-minute epochs with an overlap of 7.5 minutes. The average of the coefficients in the frequency range 0.003Hz-0.1 Hz is then calculated [7]. This procedure was applied to all 20-minute length segments and a time series with the corresponding coefficients was obtained. This time series, together with a Critical Score Value (CSV) of 0.5, were used to derive the CPRT score for the corresponding infant.

With respect to clinical outcomes, infants were classified as normal, suspicious or abnormal according to their clinical scores. The CRIB score was measured in the first 12 hours after birth. Infants with score < 3 or > 3 were classified as normal or abnormal, respectively. The Bayley score was calculated at the age of 12 and 24 months for infants with a gestational age < 30 weeks for Leuven and Utrecht respectively. The Bayley score is based upon the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) and is 100 ± 15 in case of good outcome. Hence, patients were classified as normal if MDI and PDI > 85, as suspicious if MDI or PDI < 85 or as abnormal if MDI and PDI < 85. The Griffith score is similar to the Bayley score but is used only for babies with a gestational age $>$ 30 weeks.

Statistical Analysis was performed using the SAS System, version 9.1, SAS Institute Inc., Cary, NC, USA. The concordance scores computed from TOI versus MABP and from HbD versus MABP, using the recordings from Leuven, can be considered as two measurements from the same underlying process. Therefore, the paired t-test was applied in order to test the difference between these concordance scores computed in two ways as mentioned above: mean as well as CPRT values derived from the COR, COH and PACOH concordance scores. To assess whether the concordance scores were predictive for outcome (normal, 'suspicious', abnormal) in the Utrecht data, the non-parametric Kruskal-Wallis test was applied. Least squares regression analysis was applied to investigate the relation between the concordance scores and the CRIB score. All reported p-values were two-tailed and a nominal p-value < 0.05 was considered as statistically significant.

4 Results

Table 1 presents the difference in concordance scores for the Leuven data, i.e. HbD versus MABP compared to TOI versus MABP. The difference in the mean COR scores did not reach statistical significance, implying that both methods might be used interchangeably. Similarly the CPRT COH and PACOH scores from TOI-MABP were not statistically significantly different from those obtained with HbD-MABP. Nevertheless, the mean COH or mean PACOH scores computed from TOI-MABP were significantly smaller than mean COH or mean PACOH based on HbD-MABP, although these differences are relatively small, e.g. mean COH: 36.2% TOI-MABP compared to 41.1% HbD-MABP (p-value <0.01) or in other words an absolute difference of 4.9%.

In Leuven, 30% (6/20) of the infants had an abnormal outcome. Nevertheless no statistical evidence could be found for the predictive value of the concordance scores

with respect to clinical outcome (normal/abnormal). However, CPRT CORR seemed to be predictive for the CRIB score: higher values of CPRT CORR were associated with higher values of the CRIB score (R-square of 0.27) (Figure 1).

Table 1 - Comparison between TOI-MABP and HbD-MABP in Leuven (N=20)

Score	Method	Mean TOI-MABP	Mean HbD-MABP	p-value
Mean	COR mean ± st dev median (min-max)	23.5±8.8 23.8 (10.7 – 51.5)	27.9±10.3 25.1 (16.0 – 49.0)	0.06
	COH mean ± st dev median (min-max)	36.2±3.7 35.3 (31.6 – 43.2)	41.1±6.3 40.6 (33.6 – 61.8)	<0.01
	PCOH mean ± stdev median (min-max)	36.4±3.7 36.2 (32.7 – 47.7)	40.8±4.8 39.9 (35.1 – 43.7)	<0.01
CPRT	COR mean ± stdev median (min-max)	5.8±10.9 0.4 (0 – 48)	12.2±18 1.4 (0 – 59.0)	0.04
	COH mean ± st dev median (min-max)	4.0±6.12 3.5 (0 – 19.8)	14.0±22.9 6.3 (0 – 100)	0.06
	PCOH mean ± st dev median (min-max)	4.6±6.6 1.2 (0 – 24)	13.9±20.4 6.3 (0 – 85)	0.05

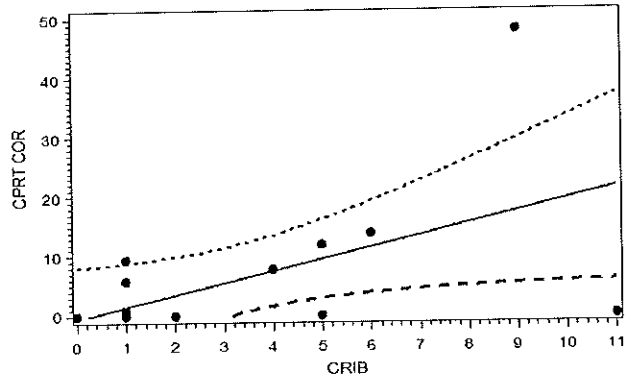


Figure 1 – Regression plot of CPRT CORR versus the CRIB score (the solid line presents the regression line, the dashed lines present the 95% confidence bounds).

Of the 33 babies from Utrecht, 20 (61%) had normal outcome, 9 (27%) 'suspicious' and 4 (12%) abnormal. Table 2 shows the COR, COH and PACOH stratified by the baby's outcome. No trend reached statistical significance, likely related to the underpowered sample size as we have only 4 cases with an abnormal outcome. Nevertheless, the obtained values are encouraging, e.g. median CPRT COH is 3.5% in the normal cases, 6.0% in the 'suspicious' cases and 17.2% in the abnormal cases (p-value 0.08).

Table 2 – Concordance score stratified by the baby's outcome: normal, suspicious or abnormal

Score	Method	Normal (N=20)	Suspicious (N=9)	Abnormal (N=4)	p-value
Mean	COR				
	mean ± st dev	24.3±8.6	22.7±6.4	23.8±8.1	0.95
	median (min-max)	24.4 (11.9-46.4)	20.7 (12.0-31.1)	22.8 (15.0-34.7)	
	COH				
	mean ± st dev	37.3±3.4	38.8±2.6	40.1±5.0	0.27
	median (min-max)	36.7(32.4-47.2)	38.4 (34.2-42.7)	39.9 (34.8-45.7)	
	PCOH				
	mean ± st dev	37.0±3.5	39.7±2.4	39.1±5.1	0.09
	median (min-max)	36.2(32.7-47.7)	39.9 (35.1-43.7)	38.3 (34.6-45.1)	
CPRT	COR				
	mean ± st dev	8.1±10.4	5.2±6.3	9.7±8.7	0.5
	median (min-max)	4.0(0-38)	3.0 (0-18)	7.4 (2-22)	
	COH				
	mean ± st dev	5.3±7.4	8.8±7.0	19.4±18.3	0.08
	median (min-max)	3.5 (0-29)	6.0 (0-21)	17.2 (0-43)	
	PCOH				
	mean ± st dev	5.2±8.1	10.3±8.4	12.3±14.6	0.23
	median (min-max)	3 (0-34)	11.0 (0-27)	10.0 (0-29)	

5. Discussion

Cerebral autoregulation is a dynamic process that refers to the maintenance of a constant CBF over a broad range of perfusion pressures (MABP). Impaired cerebral autoregulation is considered a risk factor for brain injury in the sick, premature infant [1] [6] [7]. Continuous measurements of MABP and CBF are thus of interest to assess cerebral autoregulation. With NIRS, changes in HbD can be continuously measured, which represent changes in CBF [1] [6]. For the analysis of cerebral autoregulation, the relation between MABP and CBF or HbD can then be assessed by the correlation, coherence and partial coherence method.

The COH method has been applied to continuous measurements of MABP and HbD to detect impaired cerebral autoregulation [1] [6] and [10]. HbD however is an unstable parameter, which is strongly affected by movement artefacts. Wong et al. [7] first described the use of TOI instead of HbD for measuring autoregulation in a clinical setting.

We found similar scores for the mean COR, the CPRT COH and the CPRT PACOH, between MABP-HbD and MABP-TOI. However, the mean COH and PACOH scores for MABP-TOI were statistically smaller than those obtained for MABP-HbD. However these differences are small and within the normal variation of these parameters, therefore they are considered as clinically not relevant. From these important findings we infer that HbD and TOI are interchangeable parameters for the assessment of (impaired) cerebral autoregulation.

Impaired autoregulation has been associated with mortality in sick infants, although a correlation with clinical outcomes that are based upon mental and psychomotor development, such as the CRIB score, Bayley score or Griffith score, could not yet be proven. Because of our small study population, we were not able to

prove a statistically significant association between these clinical scores and the mean or CPRT of the CORR/COH/PACOH scores computed from MABP-versus NIRS-measured TOI or rSO_2, although the CPRT index, calculated using the CORR methods, seems to be predictive for the CRIB score: a trend of higher CPRT values with higher CRIB scores (i.e. worse clinical outcome) was observed. In order to statistically prove this, further research is recommended, based upon a larger study population, including more infants with a bad clinical outcome and infants with higher variations in MABP. Our results imply that by means of NIRS and optimal signal processing, dynamic autoregulation and its relation to clinical outcome can be assessed.

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