New Time-Frequency Method for Cerebral Autoregulation in Newborns: Predictive Capacity for Clinical Outcomes

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Objective To describe an alternative analysis in the frequency-domain of the temporal relationship between 2 biological signals and evaluate the method's predictive capacity for classifying infants at risk for an adverse outcome.

Study design We studied 54 infants (mean gestational age 27 weeks) with invasive mean arterial blood pressure monitoring. The bivariate autoregressive spectral coherence (BiAR-COH) method and the spectral coherence methods were used to analyze the relationship between spontaneous changes in mean arterial blood pressure and the near-infrared tissue oxygenation index.

Results The mean postnatal age at the beginning and end of the autoregulation study was 6.0 (3.0) and 29.0 (7.5) hours, respectively. The BiAR-COH was superior to the spectral coherence in predicting low superior vena cava (SVC) flow (≤41 mL/kg per minute), with an area under the receiver operating characteristic curve of 0.84 (95% CI, 0.77-0.90; $P < .001$). The BiAR-COH threshold for identifying low SVC flow was 0.577, with 0.8 sensitivity and 0.76 specificity. After adjusting for the repeated measures effect (multiple epochs) in a given patient, the averaged BiAR-COH per patient and averaged COH per patient were calculated as the average value per patient. The pBiAR-COH (but not the pCOH) was associated with intraventricular hemorrhage grades 3 and 4 and predicted mortality.

Conclusions The BiAR-COH classifier identifies low SVC flow infants who are at risk for brain hypoperfusion. The BiAR-COH is superior to frequency domain methods in predicting adverse outcomes in infants. *(J Pediatr 2014;165:897-902)*.

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Cerebral pressure autoregulation is defined as the capacity of the brain to maintain cerebral blood flow unaltered over a range of arterial blood pressures. This range is narrowed with impaired autoregulation, which is important because cerebral blood flow fluctuations are considered a major determinant of cerebral injury and death.[1-3]

Cerebral autoregulation is a developmentally regulated process that is still not well characterized for neonates for various reasons. First, a number of factors interact with the vascular smooth muscle cells regulating arterial tone, such as the sympathetic nervous system, the partial pressure of carbon dioxide and oxygen, endocrine and paracrine substances, the flow-metabolism coupling (infant's activity), disease states, and medications.[4] Autoregulation is, therefore, complex and multifactorial. Second, the relationship between spontaneous blood pressure changes and a near-infrared spectroscopy (NIRS) variable was proposed as a suitable tool for exploring dynamic autoregulation.[2,5,6] Correlation and coherence function methods have been applied for this purpose.[2,5,7,8] However, these methods merely describe instances when pairs of structures are in synchrony. The strength of the relationship between signals can be derived by using transfer function gain.[6,9] None of these methods provide information about how 2 signals are time related. For these reasons, these methods might not accurately identify populations at high risk of brain injury and unfavorable outcomes.

Echocardiography-Doppler-derived superior vena cava (SVC) flow has been proposed as a key biomarker of cerebral perfusion.[10] Low SVC flow was associated with late intraventricular hemorrhage (IVH), impaired neurodevelopment, and death.[11,12] It is assumed that 70%-80%

AUC	Area under the receiver operating characteristic curve
BiAR	Bivariate autoregressive
BiAR-COH	Bivariate autoregressive spectral coherence
COH	Spectral coherence
GA	Gestational age
IVH	Intraventricular hemorrhage
MABP	Mean arterial blood pressure
NIRS	Near-infrared spectroscopy
SaO_2	Peripheral arterial oxygen saturation
SVC	Superior vena cava
TOI	Tissue oxygenation index

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of flow into the SVC comes from the brain.[13] SVC flow correlates with a NIRS-derived surrogate variable of cerebral perfusion-oxygenation.[14] However, the integrity of cerebral autoregulation capacity and its relationship with SVC flow has not been explored.

Our aim was to develop an alternative method of analysis for cerebral autoregulation capacity during the transitional circulation that improves the predictive capacity against variables of adverse outcome in the preterm infant. The analysis in the frequency domain of the temporal relationship between 2 biological signals would provide information about the mutual dependence of the signals. In addition, we aim to explore the relationship between the proposed method and a surrogate measure of the actual cerebral perfusion, the SVC flow.

Methods

All infants born before 31 weeks who were on ventilator support (mean airway pressure ≥4 cm H_2O or fraction of inspired oxygen ≥0.3) were prospectively assessed for SVC flow from birth to 96 hours. Those infants who had invasive blood pressure monitoring were eligible for the cerebral autoregulation capacity studies. The exclusion criteria were major congenital malformations, postnatal age over 12 hours at screening, or no informed consent. The study protocol was approved by the Ethics Committee for Human Studies at La Paz University Hospital of Madrid (Spain) and the Spanish Medicines Agency at the National Ministry of Health (European Union Drug Regulating Authorities Clinical Trials-EurodraCT 2009-010901-35).

The infants had early (first 12 hours of life) SVC flow measurements (a minimum of 2 evaluations, 60 minutes apart) and were included in an interventional placebo-controlled trial of dobutamine if their SVC flow was ≤41 mL/kg per minute at any time during the first 24 hours (step-increase in dobutamine dose infusion [5-10-15-20 μg/kg per minute] or equal volume of placebo [5% water dextrose]). The management of blood pressure was in accord with the unit's current policy, following a standardized protocol that did not include dobutamine.[15] Intensive SVC flow follow-up continued during the drug escalation period until SVC flow stabilized above 41 mL/kg per minute (intervention period). Beyond that period, SVC flow was measured at 24, 48, 72, and 96 hours of postnatal life. To reduce the influence of inter-individual variability on the results, the longitudinal monitoring changes in a given infant were performed by the same investigator for most studies. The images were stored and reviewed off-line by a single investigator (M.B.) who approved or rejected the scans after a systematic quality assessment. Simultaneous mean arterial blood pressure (MABP) and NIRS recordings were started during the first echocardiographic assessment, which continued for at least 120 minutes in infants with normal SVC flow, and for the whole intervention period for those infants with low SVC flow. The recordings were restarted at the 24 hours study time point, coinciding with the SVC flow assessment. Standard cranial ultrasound imaging to evaluate brain injury was conducted as early as possible during the first 24 hours after birth, at postnatal day 4, 7, and 14, and at 36 weeks' gestation. Additional scans were performed if clinically indicated. Major cranial ultrasound diagnoses were classified according to a previously reported system.[15]

Physiologic and Near-Infrared Data Recordings

Patients were monitored continuously for intravascular arterial blood pressure and peripheral arterial oxygen saturation (SaO_2) (IntelliVue MP50; Phillips, Best, The Netherlands). Cerebral perfusion-oxygenation was assessed using the NIRO-200NX oximeter (Hamamatsu Photonics, Fukuoka, Japan), with the sensor placed at the frontal-parietal level. The tissue oxygenation index (TOI), representing the absolute ratio of oxyhemoglobin to total hemoglobin, was recorded by the monitor. The research team developed a real-time, simultaneous, time-locked data acquisition system (BioAcSys software; La Paz University Hospital Research Foundation) for the physiological variables and the NIRS-derived TOI. The recording frequency for SaO_2, MABP, and TOI was 2 Hz. Signal disruption periods because of infant manipulations or interventions were manually marked. Disruption-free zones were automatically segmented into nonoverlapping 30-minute epochs if SaO_2 was stable (less than 5% variation). Each epoch was filtered with a linear high order low-pass finite impulse response filter at 0.095 Hz and resampled at 0.2 Hz. The mean of the signal was subtracted. Epochs that satisfied the conditions of stationarity (covariance stationarity) and that had at least 3% variation were selected for analyses. An in-house Matlab toolbox (MathWorks, Inc, Natick, Massachusetts) enabled the selection of epochs. Stationarity was tested using the Augmented Dickey-Fuller and Kwiatkowski-Philips-Schmidt-Shin tests,[16,17] which were applied separately for the MABP and TOI epoch waveforms.

Data Analyses

The bivariate autoregressive spectral coherence (BiAR-COH) method and the spectral coherence (COH) method were used to analyze the relationship between MABP and TOI. The description of the analytical model is included in the **Appendix** (available at www.jpeds.com).

The principle behind BiAR-COH is that each sample of signals can be predicted using the past samples of a given signal and samples from related signals. This process can be modeled as a bivariate autoregressive (BiAR) model. The number of past samples to be considered is automatically calculated using the Akaike information criterion[18] and the Bayesian information criterion,[19] taking the lowest value (between 3 and 25 samples).

To derive the frequency domain interpretation of the BiAR, the coherence analysis is applied to the BiAR coefficients, leading to the BiAR-COH.

In the COH method, epochs were subdivided into 10-minute segments with 50% overlap; the Hamming window to minimize spectral leakage was applied to both methods.

The BiAR-COH and COH were averaged over the frequency bands of 0.003-0.04 Hz (very low frequency band). An example of the method's application is shown (**Figure 1**).