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Original Article

Cerebral Hemodynamics in Asphyxiated Newborns Undergoing Hypothermia Therapy: Pilot Findings Using a Multiple-Time-Scale Analysis

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ABSTRACT

BACKGROUND: Improved quantitative assessment of cerebral hemodynamics in newborns might enable us to optimize cerebral perfusion. Our objective was to develop an approach to assess cerebral hemodynamics across multiple time scales during the first 72 hours of life in newborns during hypothermia therapy. **METHODS:** Spontaneous oscillations in mean arterial pressure and regional cerebral tissue oxygen saturation were analyzed using a moving window correlation method with time scales ranging from 0.15 to 8 hours in this pilot methodology study. Abnormal neurodevelopmental outcome was defined by Bayley III scores and/or cerebral palsy by age 24 months using receiver operating curve. **RESULTS:** Multiple-time-scale correlations between the mean arterial pressure and regional cerebral tissue oxygen saturation oscillations were tested in 10 asphyxiated newborns undergoing hypothermia therapy. Large noninduced fluctuations in the blood pressure were observed during cooling in all five infants with abnormal outcomes. Notably, these infants had two distinct patterns of correlation: a positive in-phase correlation at the short time scales (15 minutes) and/or a negative antiphase correlations observed at long time scales (4 hours.). Both the in-phase (area under the curve 0.6, [95% confidence interval 0.2-0.95]) and antiphase correlations (area under the curve 0.75, [95% confidence interval 0.4-0.95]) appeared to be related to an abnormal outcome. **CONCLUSIONS:** Our observations suggest that the time scale is an important factor that needs to be standardized in the assessment of neonatal cerebral hemodynamics.

Keywords: neonate, hypoxic-ischemic encephalopathy (HIE), hypothermia, cerebral hemodynamics, near infrared spectroscopy (NIRS)

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Introduction

The healthy brain is protected by cerebral autoregulation, which maintains cerebral blood flow relatively constant across a wide range of changes in perfusion pressure.[1] In asphyxiated newborns, positron emission tomography studies have reported impairment of cerebral hemodynamics with impaired cerebral vasomotor control associated with death and abnormal outcomes.[2] Although hypothermia therapy provides neuroprotection via reduction in cerebral metabolism as well as cerebral blood flow,[3-5] a significant knowledge gap exists regarding how to quantify hemodynamics in real time during this therapy. Since approximately 40% of asphyxiated newborns still have neurodevelopmental abnormalities at age 24 months despite hypothermia therapy,[6-8] a better real-time understanding of pathophysiologic mechanisms of brain injury is essential to identify those in need of the additional neuroprotective strategies.

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Cerebral autoregulation is dynamic and possesses multiple-time-scale properties.[9,10] Assessment of cerebral autoregulation in neonates must be noninvasive and allow for the application of external perturbations, which are often used and have proven helpful in the study of cerebral autoregulation in adults.[11] The heterogeneity and complexity of associated confounding factors in these sick newborns with hypoxic-ischemic encephalopathy (HIE) represents a challenge to the conventional fixed scales that have been previously used in other patient populations.[12,13] The primary aim of this pilot study was to test a multiple-time-scale approach in order to assess the most optimal time in which to measure cerebral hemodynamics of newborns with neonatal encephalopathy during hypothermia in the first 72 hours of life. Spontaneous oscillations in mean arterial pressure (MAP) from an indwelling umbilical arterial catheter and regional cerebral tissue oxygen saturation ($Scto_2$) by near-infrared spectroscopy (NIRS) were measured. A time domain moving window correlation (MWC) method was employed to quantify the relationship between changes in MAP and $Scto_2$ across multiple time scales.

Methods

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, and informed consent was obtained from parents before enrollment. Inborn infants ≥36 weeks of gestation and birth weight ≥1800 g who were admitted to the neonatal intensive care unit at the Parkland Hospital of Dallas from June 2010 to January 2012 with perinatal asphyxia or metabolic acidosis and a clinical examination showing moderate to severe encephalopathy in the first 6 hours were cooled according to the published protocols as defined by the National Institute of Child Health and Human Development Neonatal Research Network study of whole-body hypothermia.[14] Infants undergoing cooling who had an indwelling arterial catheter in order to allow continuous recording were included. Exclusion criteria included the presence of congenital anomalies, unstable oxygenation status due to pulmonary hypertension, imminent death, or transfer to another facility. Whole-body hypothermia was started within 6 hours after birth and achieved by placing the newborn on a cooling blanket (Blanketrol II, Cincinnati Sub-Zero) and maintaining the esophageal temperature at 33.5°C by the blanket servomechanism for 72 hours. Afterward, rewarming was obtained by 0.5°C per hour with incremental changes per published protocols.[14] Magnetic resonance imaging (MRI) studies (3T, Philips Healthcare Systems) were performed between 5 and 8 days of life for evidence of neurological abnormalities and injuries. Outpatient neurodevelopmental follow-up assessments were performed at age 24 months as specified by our protocol.[15] Neurodevelopmental delay was identified by a Bayley-III score ≤ 85 in any of the domains listed (motor, cognitive, or language) or documentation of cerebral palsy by the developmental pediatrician at the follow-up assessment.[14,16]

Continuous monitoring of cerebral hemodynamics

MAP was measured continuously from an indwelling umbilical arterial catheter. Regional $Scto_2$ was measured using a spatially resolved NIRS cerebral oximeter (INVOS 4100-5100; Somanetics Corporation, Troy, MI). The probe (neonatal, Soma Sensor) was placed on the left frontoparietal side of the infant's head. Both MAP and $Scto_2$ data were recorded simultaneously with a Vital Sync system (Somanetics Corporation). In addition, a pulse oximeter (Massimo Corporation, Irvine, CA) was used to measure arterial oxygen saturation (Sao_2) and was set to maximal sensitivity with 2-second averaging of measurements. Blood pressure variance range was calculated by averaging the maximum and minimum values. Recordings of Sao_2 were synchronized with those of MAP and $Scto_2$. Fractional tissue O_2 extraction, defined as $FTOE = (Sao_2 - Scto_2)/Sao_2$, was calculated to reflect oxygen utilization of regional brain tissue.[17] Electroencephalography using standard montage was obtained starting day 1 and continued until the end of the hypothermia therapy. Fourteen channels of scalp electroencephalography data were referentially recorded using Stellate Harmonia acquisition systems sampling at 200 Hz, using the international 10–20 and modified combinatorial nomenclature system of electrode placement.

Multiple-time-scale correlation analysis

A schematic diagram of multiple-time-scale MWC data processing and analysis procedures is shown in Fig 1. First, both MAP and $Scto_2$ time series were inspected by an author (FT) who was blinded to clinical outcomes, through a spike-detection algorithm to identify outliers that were defined as a transient swing of 15% or larger from the baseline. The spike-like outliers usually resulted from body movements or other technical artifacts, and, therefore, were replaced with the values linearly interpolated from the nearest data points. The Pearson's correlation coefficients (R) between MAP and $Scto_2$ were calculated based on the MWC method with the sizes of the moving window (i.e., the time scales) over 1/8, 1/4, 1/2, 1, 2, 4, 6, and 8 hours. To evaluate the overall extent of correlation between MAP and $Scto_2$ at each time scale, we defined *a priori* a cerebral hemodynamic index (CH index) as the percentage of data points with significant $R < -0.4$ or $R > 0.4$ over the entire data.[18-21]

Data were analyzed during steady-state changes in arterial partial pressure of CO_2 ($Paco_2$, 40-50 mm Hg) and hemoglobin level (12-15 mg/dL) and normal blood glucose concentrations. Therefore, the actual length of data processed was less than 72 hours in some instances. Clinically unstable patients, with less than 48 hours of continuous recording, were further excluded from the multiple-time-scale data analysis. Patients with a constant $Scto_2$ ≥95% for 6 hours or more were excluded by convention as oscillations cannot be recorded in such infants. The latter high $Scto_2$ have already been studied and correlated with abnormal outcomes, so there is no need to measure a hemodynamic index in these scenarios.[11,22]

Statistical analysis

Since multiple-time-scale assessment of cerebral autoregulation in newborns undergoing hypothermia therapy have not been described in prior literature, an empirical sample size of sequentially cooled newborns was used in this pilot study. One author (FT) was blinded to clinical outcomes and determined the 10 infants whose tracing met the predefined criteria for MWC analysis. Data were summarized as means ± S.D. or as median and ranges where appropriate. Differences in patient characteristics between neonates with adverse and favorable outcomes were compared using Student t test, χ^2 test, or Fisher exact test where appropriate, and predictive values as well as likelihood ratios were calculated. A receiver operator characteristic curve was generated for various time scale measures in order to assess the sensitivity and specificity of these measures in detecting abnormal neurodevelopmental outcomes. The optimal time scale cut-off value was selected based on the area under the receiver operator characteristic curve compared with a 45-degree line of equality ($P < 0.05$).

Results

Cohort characteristics in cooled newborns

During the study period, 20 newborns received whole-body hypothermia therapy for 72 hours, of which 10 met the entry criteria and were recruited for the study. Subjects were excluded for clinical instability with hypoxia and pulmonary hypertension (n = 3), NIRS signal ≥ 95 (n = 4), use of pressors (n = 2), and lack of continuous arterial recording (n = 1). Infants had an average gestational age of 39 ± 2 weeks and all were in our institution. All had umbilical arterial evidence of severe fetal acidosis with multiple organ involvement and moderate (n = 8) or severe