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Wavelet coherence analysis of dynamic cerebral autoregulation in neonatal hypoxic–ischemic encephalopathy

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ABSTRACT

Cerebral autoregulation represents the physiological mechanisms that keep brain perfusion relatively constant in the face of changes in blood pressure and thus plays an essential role in normal brain function. This study assessed cerebral autoregulation in nine newborns with moderate-to-severe hypoxic–ischemic encephalopathy (HIE). These neonates received hypothermic therapy during the first 72 h of life while mean arterial pressure (MAP) and cerebral tissue oxygenation saturation ($S_{ct}O_2$) were continuously recorded. Wavelet coherence analysis, which is a time-frequency domain approach, was used to characterize the dynamic relationship between spontaneous oscillations in MAP and $S_{ct}O_2$. Wavelet-based metrics of phase, coherence and gain were derived for quantitative evaluation of cerebral autoregulation. We found cerebral autoregulation in neonates with HIE was time-scale-dependent in nature. Specifically, the spontaneous changes in MAP and $S_{ct}O_2$ had in-phase coherence at time scales of less than 80 min (<0.0002 Hz in frequency), whereas they showed anti-phase coherence at time scales of around 2.5 h (~0.0001 Hz in frequency). Both the in-phase and anti-phase coherence appeared to be related to worse clinical outcomes. These findings suggest the potential clinical use of wavelet coherence analysis to assess dynamic cerebral autoregulation in neonatal HIE during hypothermia.

1. Introduction

Birth asphyxia is a global burden in clinical neonatal care (Levene et al., 1985). Every year four million newborns are affected worldwide, of which one million die and another million are left with disabilities. Hypothermia is a neuroprotective therapy to improve clinical outcomes by reducing body temperature of newborns for a specific duration of time (Shankaran et al., 2005). However, even following the introduction of hypothermic therapy for neonatal hypoxic–ischemic encephalopathy (HIE), approximately 40% of newborns still have neurodevelopmental abnormalities at 24 months of age (Zonta et al., 2003; Bryce et al., 2005; Higgins et al., 2011). A better understanding of pathophysiological mechanisms of HIE-related brain injury is essential for developing new effective interventions to improve clinical outcomes.

The healthy brain is protected by the mechanisms of cerebral autoregulation, which maintains cerebral blood flow (CBF) at a relatively constant rate across a wide range of arterial blood pressures. In asphyxiated newborns, invasive positron emission tomography (PET) studies reported impairment of cerebral autoregulation with associated vasoparalysis (Pryds et al., 1990). However, it remains unknown whether hypothermic therapy in asphyxiated newborns alters cerebral autoregulation. In addition, there is a lack of methodology that can quantify cerebral autoregulation non-invasively and reliably at the bedside.

In the last decade, significant progress has been made in developing methods to assess cerebral autoregulation based on spontaneous oscillations in blood pressure, CBF, and cerebral oxygenation (Panerai, 1998). Both CBF and cerebral oxygenation can be measured with non-invasive techniques. Specifically, blood flow velocity in the basal cerebral arteries can be measured using transcranial Doppler (TCD) ultrasonography (Aaslid et al., 1982), and cerebral oxygenation can be measured with near-infrared spectroscopy (NIRS) represented as either the difference between the oxygenated and deoxygenated hemoglobin (HbD = HbO_2 − Hb) (Tsuji et al., 2000; Soul et al., 2007; Govindan et al., 2014) or cerebral tissue oxygen saturation ($S_{ct}O_2$) (Caicedo et al., 2011a; Caicedo et al., 2011b; Gilmore et al., 2011; Wong et al., 2012). Both variables are reliable surrogates for changes in CBF as demonstrated in animal models (Tsuji et al., 1998; Brady et al., 2007; Brady et al., 2008; Hahn et al., 2011; Lee et al., 2011; Lee et al., 2012). In particular, $S_{ct}O_2$ is less prone to the movement artifacts during continuous, long-term measurements as compared with HbD (van Bel et al., 2008; Caicedo et al., 2011a).

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To assess cerebral autoregulation in the face of dynamic changes in blood pressure, referred to as dynamic cerebral autoregulation, transfer function (Zhang et al., 1998) and other analysis methods for dynamic systems have been developed (Liu et al., 2015). These methods are often based on an assumption that changes in blood pressure and cerebral hemodynamics are stationary, that is, assuming the statistical properties of these variables do not change with time. In reality, blood pressure and cerebral hemodynamics are non-stationary in nature, particularly under pathophysiological conditions (Panerai, 2014). Hence, better tools are needed to characterize the non-stationary aspects of cerebral autoregulation.

Continuous wavelet transform (CWT) is a powerful mathematical tool for time-frequency domain analysis of stationary and non-stationary time series (Torrence and Compo, 1998; Mallat, 1999). Wavelet coherence analysis, based on CWT, characterizes intermittent cross-correlations between two time series at multiple time scales (Grinsted et al., 2004), which makes no assumption about the stationarity of input signals. In this study, we introduced wavelet coherence analysis to assess dynamic cerebral autoregulation in newborns with HIE. All hemodynamic data, including mean arterial pressure (MAP) and $S_{ct}O_2$, were recorded continuously during the first 72 h of life under hypothermic therapy. Wavelet coherence analysis was performed to quantify the spectral power and the dynamic relationship between spontaneous oscillations in MAP and $S_{ct}O_2$. Wavelet-based metrics of phase, coherence and gain were derived for quantitative evaluation of cerebral autoregulation. Potential prognostic values of these metrics for clinical magnetic resonance imaging (MRI) and neurodevelopmental outcomes were explored to reveal short- and long-term neurologic complications in HIE patients.

2. Materials and methods

2.1. Subjects, clinical care and outcome evaluations

This study included newborn infants at ≥36 weeks of gestation with a birth weight of ≥1800 g who were admitted to the neonatal intensive care unit at Parkland Hospital, Dallas, TX, from January 2011 to January 2012. These newborns had perinatal asphyxia or metabolic acidosis, including a clinical symptom of moderate to severe encephalopathy within the first six hours of birth. 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.

Perinatal acidemia was determined by blood gases measured from umbilical arterial blood during delivery. The criteria included a pH of 7.0 or less, a base deficit of 16 mEq/L or greater in umbilical artery blood, or any postnatal blood sample within one hour of life. In order to establish the diagnosis of encephalopathy, a neurological examination was performed within six hours of birth according to the National Institute of Child Health and Human Development (NICHD) classification for modified Sarnat staging (Sarnat and Sarnat, 1976), which assessed 1) level of consciousness, 2) spontaneous activity, 3) posture, 4) tone, 5) primitive reflexes, and 6) autonomic nervous system. Newborns that were diagnosed with moderate or severe encephalopathy for at least three of the six categories were abnormal and would receive hypothermic therapy (Shankaran et al., 2005). Whole-body hypothermia was initiated within six hours after birth and achieved by placing the newborns on a cooling blanket (Blanketrol II, Cincinnati Sub-Zero). The esophageal temperature was maintained at 33.5 °C by the blanket servomechanism for 72 h. Then whole-body rewarming was initiated by increasing the temperature of the blanket by 0.5 °C per hour using the previously published protocols (Shankaran et al., 2005).

Clinical outcome of the hypothermic therapy was evaluated in two stages: First, 3-Tesla MRI (Philips Healthcare Systems, TX) was performed on each HIE survivor within 5–8 days of age for evidence of neurological abnormalities and injuries. MRI findings were scored for abnormalities by an experienced pediatric neuro-radiologist based on the NICHD summary classification, which has been validated in this population to predict outcomes following hypothermia (Chalak et al., 2014b; Rollins et al., 2014). Second, outpatient neurodevelopmental follow-ups were performed at 18 to 24 months of age using the previously published protocol (Chalak et al., 2014a). Bayley-III scales of neurodevelopment were rated in three domains: cognitive, language and motor. Neurodevelopmental delay was identified by at least one Bayley-III scale <85 or cerebral palsy.

2.2. Blood pressure and NIRS monitoring

Intra-arterial blood pressure was continuously measured from an indwelling umbilical arterial catheter. Regional $S_{ct}O_2$ was measured on the frontoparietal side of the neonate's head using an INVOS™ 4100–5100 oximetry (Somanetics, Troy, MI) and a neonatal sensor. Both MAP and $S_{ct}O_2$ data were sampled at a rate of two data points per minute and recorded synchronously with a Vital Sync™ system (Somanetics Corporation, Troy, Michigan).

The MAP and $S_{ct}O_2$ data were collected only under clinically stable conditions (pCO_2 between 40 to 50 mm Hg and hemoglobin level between 12 to 15 mg/dl). Therefore, the actual length of recorded data was less than 72 h and varied case by case. Neonates were selected only if they did not require any vasopressor medications, to avoid potential drug effects on cerebral autoregulation.

2.3. Data preprocessing

Both the MAP and $S_{ct}O_2$ data were first inspected to identify artifacts that were defined as a sharp change of signals greater than 15% from the baseline. These spikes were removed by linear interpolation. Then a second-order polynomial detrending was applied to remove the slow drifts from each time series.

2.4. Wavelet coherence analysis

Wavelet coherence analysis is based on CWT, which decomposes a time series in time-frequency domain by successively convolving the time series with the scaled and translated versions of a mother wavelet function ψ_0 (Mallat, 1999). The continuous wavelet transform of a time series $x(n)$ of length N, which is sampled from a continuous signal at a time step of Δt, is defined as:

$$W^X(n,s) = \sqrt{\frac{\Delta t}{s}} \sum_{n'-n}^{N} x(n)_0^* \left[(n'-n) \left(\frac{\Delta t}{s} \right) \right] \quad (1)$$

where n is a time index, s denotes the time scale that is in inverse proportion to frequency, and * indicates the complex conjugate.

In analogy to Fourier analysis, a wavelet power spectrum of $x(n)$ can be defined as the wavelet transformation of its autocorrelation function, which is implemented as follows:

$$W^{XX}(n,s) = W^X(n,s) W^{X^*}(n,s). \quad (2)$$

The auto-wavelet power spectrum $W^{XX}(n,s)$ is a real function, which describes the power of $x(n)$ in the time-frequency domain.

Similarly, the cross-wavelet transform of two time series, $x(n)$ and $y(n)$, is defined as:

$$W^{XX}(n,s) = W^X(n,s) W^{Y^*}(n,s). \quad (3)$$

The modulus $|W^{XY}(n,s)|$ represents the amount of joint power between $x(n)$ and $y(n)$, and the complex argument $\Delta\varphi(n,s) = \tan^{-1}\left\{\frac{Im[W^{XY}(n,s)]}{Re[W^{XY}(n,s)]}\right\}$ represents the relative phase between $x(n)$ and $y(n)$.