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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 (MAP) and regional cerebral tissue oxygen saturation ($S_{ct}O_2$) were analyzed using a moving window correlation (MWC) 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 24 months of age using receiver operating curve (ROC).

Results—Multiple-time-scale correlations between MAP and $S_{ct}O_2$ oscillations were tested in 10 asphyxiated newborns undergoing hypothermia therapy. Large non induced 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 min), and/or a negative anti-phase correlations observed at long time scales (4

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hrs.). Both the in-phase (AUC 0.6, [95% CI 0.2–0.95]) and anti-phase correlations (AUC 0.75, [95% CI 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)

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, invasive positron emission tomography studies have reported impairment of cerebral hemodynamics with impaired cerebral vasomotor control associated with death and abnormal outcomes. [2] While hypothermic 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 24 months of age despite hypothermia therapy,[6–8] a better real-time understanding of pathophysiological mechanisms of brain injury is essential to identify those in need of the additional neuroprotective strategies.

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. [21] The heterogeneity and complexity of associated confounding factors in these sick newborns with HIE represents a challenge to the conventional fixed scales which have been previously used in other patient populations. [11,12] 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 ($S_{ct}O_2$) 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 $S_{ct}O_2$ 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 grams who were admitted to the neonatal intensive care unit (NICU) at the Parkland Hospital of Dallas from June 2010 to January 2012 with perinatal asphyxia or metabolic acidosis, and a clinical exam showing moderate to severe encephalopathy in the first six hours were cooled

according to the published protocols as defined by the NICHD Neonatal Research Network study of whole body hypothermia.[13] 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 degrees per hour with incremental changes per published protocols. [13] Magnetic resonance imaging (MRI) studies (3T, Philips Healthcare Systems) were performed between five and eight days of life for evidence of neurological abnormalities and injuries. Out-patient neurodevelopmental follow-up assessments were performed at 24 months of age as specified by our protocol.

[14] Neurodevelopmental delay was identified by a Bayley-III equal or less 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.[13,15]

Continuous monitoring of cerebral hemodynamics

Continuous MAP was measured from an indwelling umbilical arterial catheter. Regional $S_{ct}O_2$ was measured using a spatially resolved NIRS cerebral oximeter (INVOS 4100–5100; Somanetics, Troy, MI). The probe (neonatal, Soma Sensor) was placed on the left frontoparietal side of the infant's head. Both MAP and $S_{ct}O_2$ data were recorded simultaneously with a Vital Sync™ system (Somanetics Corporation, Troy, Michigan). Additionally, a pulse oximeter (Massimo Corporation, Irvine, CA) was used to measure arterial oxygen saturation (S_aO_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 $FTOE = (S_aO_2 - S_{ct}O_2)/S_aO_2$, was calculated to reflect oxygen utilization of regional brain tissue. [16] EEG using standard montage was obtained starting day 1 and continued until the end of the hypothermia therapy. Fourteen channels of scalp EEG 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 Figure 1. First, both MAP and $S_{ct}O_2$ 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 $S_{ct}O_2$ 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

$S_{ct}O_2$ 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.[17–20]

Data were analyzed during steady-state changes in arterial partial pressure 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 $S_{ct}O_2$ ≥95% for six hours or more were excluded by convention as oscillations cannot be recorded in such infants. The latter high $S_{ct}O_2$ have already been studied and correlated with abnormal outcomes, so there is no need to measure a hemodynamic index in these scenarios.[21,22]

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 (TF) was blinded to clinical outcomes and determined the 10 infants whose tracing met the predefined criteria for MWC analysis. Data were summarized as means ± SD or as median and ranges where appropriate. Differences in patient characteristics between neonates with adverse and favorable outcomes were compared using Student's t-test, Chi-squared test or Fisher's exact test where appropriate and predictive values as well as likelihood ratios were calculated. A receiver operator characteristic (ROC) 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 ROC curve compared with a 45° line of equality ($p<0.05$).

RESULTS

Cohort Characteristics in cooled newborns

During the pilot 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), 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 encephalopathy (n=2). None of the infants studied had seizures during the duration of hypothermia (Table 1).

MWC analysis was done on all eligible 10 patients. No differences were seen in the general characteristics of the selected 10 infants for the MWC analysis, when compared to the overall cohort of cooled infants. All enrolled infants survived to NICU discharge. MRI was available on all patients and was performed at a median age of 7 days. The MRI was abnormal in 5 (50%) neonates, and all had evidence of diffuse white matter injury. In addition, one also had imaging abnormalities involving the basal ganglia. Abnormal Bayley III scores occurred in 5 (50%) of the cooled infants. Of the five infants with an abnormal

outcome, all had cognitive scores < 70, while two had scores 70–85 in the motor domains and one additional infant had a severe cerebral palsy.

Key findings were presence of the large intermittent spontaneous fluctuations in the blood pressure with a variance range of 30± 4 mmHg, which were observed during hypothermia. Notably, these swings in blood pressure were observed during steady state without influences from medications, activity, seizures or pressors infusions. Figure 2 illustrates in two newborns the presence of different patterns of correlations between MAP and $S_{ct}O_2$ which were both observed in the patients with abnormal outcomes. Positive correlations were observed at short time scale of 7 minutes ($R > 0.4$ during 32% of the individual patient total recording time). Conversely, predominantly negative correlations were observed in another patient at the long time-scale 4 hours ($R < -0.4$ during 39% of the individual patient total recording time). The infants with normal outcomes all had CH_{index} <10% at any of the time scales studied, when compared to infants with abnormal outcomes (Figure 3) below. Infants with abnormal outcomes were best detected either by a positive CH_{index} using the conventionally utilized 7.5 minutes short time scale, i.e. window at 1/8 hrs. (AUC 0.6, [95% CI 0.2–0.95]), or alternatively by a negative CH_{index} at the long 4 hour time scale (AUC 0.75, [95% CI 0.4–0.95]).

In further analyses, we inspected the dependence of MAP-$S_{ct}O_2$ correlation on the range of MAP by measuring the binned averages of *R* against MAP at each of selected time scales. Most infants optimal MAP was found to be around 50 to 55 mm HG in all time scales studied, while the amount of time from the total recording, which included this critical MAP, greatly varied amongst patients. Secondary analyses were also performed following initiation rewarming, by comparing data to the 12 preceding hours of hypothermia respectively. Significant hemodynamic differences were seen during rewarming with respect to heart rate (122 ±15 versus. 103 ±12, p 0.002), and MAP (50 ±2 versus. 56 ± 8, p 002). No infants had any documented hypotension or fluid bolus need. No differences were seen in NIRS $S_{ct}O_2$ (80 ±8 versus. 80 ± 7, p 0.7) or fractional tissue oxygen extraction (18±11 vs. 19±7, p 0.8) during rewarming vs hypothermia. However, fractional tissue oxygen extraction was lower in the infants with abnormal outcomes as compared to the normal outcomes (13± 4% vs. 21±5%).

Discussion

In this pilot study, large non induced fluctuations in the blood pressure and multiple-time-scale correlations between MAP and $S_{ct}O_2$ oscillations were observed in the asphyxiated newborns undergoing hypothermia therapy. This is the first report to highlight that infants with abnormal outcomes despite cooling had two different patterns of impaired cerebral hemodynamics during hypothermia, depending on the time scale studied. In addition to the well reported positive correlation between changes in MAP and $S_{ct}O_2$ at short time scales of 10 minutes, *w*e observed negative correlations at the larger time scales of 4 hours which were also associated with abnormal neurodevelopmental outcomes. These findings would suggest that cerebral hemodynamics is a time-scale-dependent phenomenon, potentially associated with abnormal outcomes at 18–24 months. Since prior studies have only utilized a short time scale window of correlation, the new findings at larger time scales emphasize

the need of standardized methodology assessing different time scales in specific patient populations.

Asphyxia starts with a fetal insult due to ischemia that impairs cerebral blood flow regulation as a consequence of a substantial interruption of maternal and/or fetal placental blood flow and gas exchange.[23] The timing, severity, pattern and duration of the fetal insult as well as the degree of recovery via fetal adaptive mechanisms determine the spectrum of disease, outcomes and possibly the responses to the hypothermia therapy. Cerebral autoregulation represents a key physiological mechanism essential to maintaining a relatively constant brain perfusion in the face of changing arterial blood pressure. Invasive methodology in animal and previous clinical studies reported impaired autoregulation in the face of hypoxia[24], hypercarbia[25], and acidosis[26], all of which are integral components of HIE. For example, a linear relationship between cerebral blood flow and arterial blood pressure indicating an impaired autoregulation was observed in asphyxiated newborns with the Xenon clearance method.[27–28] Such a loss of cerebral autoregulation was reported also using a PET scan [2] or arterial spin labeling MRI.[29] Recent non- invasive NIRS studies showed that high $S_{ct}O_2$ was associated with abnormal outcomes in HIE prior to [21–22] and following hypothermia therapy. [30,31] These studies demonstrated high $S_{ct}O_2$ with low FTOE indicative of a luxury brain perfusion associated with a complete cerebral vasoparalysis to be related abnormal outcomes. [30,31] Our studies are different in that we include the blood pressure to evaluate hemodynamics, rather than isolated NIRS values. Moreover we have excluded the infants with high $S_{ct}O_2$, from our MWC analysis as these infants have already been studied and by convention, it is not possible to record oscillatory hemodynamics on a saturated NIRS signal. We focused on early recognition of spontaneous oscillations in blood pressure; as such infants have not been studied, and if recognized early, might benefit from added stabilizing neuro-vascular interventions.

The observed blood pressure variability in our newborns with HIE, without medications or surgical interventions, and in the absence of seizures, is in agreement with studies on preterm infants where blood pressure variability was also found to exceed the autoregulatory capacity. [32]

A recent study of asphyxiated newborns by Howlett et al.[33] reported median optimal MAP to be around 50 mmHg during hypothermia, and neonates with MRI injury spent a greater proportion of time with MAP below that cutoff than neonates with no or mild injury. Our findings of an optimal range MAP of 50–55 mmHg associated with the CH index concur with above study. Variations in the time spent within an optimal MAP range during cooling were reported in both studies and further emphasize the importance of using continuous, real-time autoregulation monitoring to individualize hemodynamic goals.

Other researchers have studied preterm newborns non-invasively by quantifying frequency domain coherence between oscillations in MAP and NIRS oxy/deoxy-hemoglobin difference (HbD). [11,1234] Such studies have used a time scale of moving window correlation fixed at 10 min and reported a pressure-passive status of impaired cerebral autoregulation, with a positive correlation between these two variables. [11,12] The observed positive correlation in newborns with HIE at the small time scales are consistent with above previous

studies done in preterm newborns using NIRS HbD. In the present study, we elected to use NIRS SctO2 rather than HbD as an index of cerebral blood flow hemodynamics, because such food and drug administration (FDA) approved sensors are less sensitive to movement artifact,[35,36] and can be easily integrated in the clinical care. NIRS SctO2 have also been correlated to HbD[37], as well as to MRI arterial spin label cerebral blood flow in the setting of HIE[38]. Our findings of negative correlations between changes in MAP and $S_{ct}O_2$ within the time scales of 4 hours are new and have not been done prior with neither NIRS SctO2 or HbD signals. We speculate that the underlying mechanisms for the observed negative correlations are related to large blood pressure variability. Changes in $S_{ct}O_2$ in reality represent changes in blood oxygenation from the arterioles, capillary vascular beds, and post-capillary venues, [16,39] It is possible that after a decreased blood pressure, redistribution of oxygenated blood among the arterioles, capillary vascular beds, and venules, can result in an increase in $S_{ct}O_2$, at the long time scale studied. The changes still need to be studied in larger clinical settings to understand their role in the observed abnormal outcomes. Overall the mean value of FTOE was reduced in the above newborns indicating greater severity of injury as reported in other studies. [28,29]

Limitations of this study include a small sample size, which limits our ability to separately analyze moderate and severe encephalopathy, and other confounders of outcomes. We emphasize that these findings are very preliminary, and their predictive values will need to be studied in larger groups of patients.

We do not know whether these findings would apply in settings using other type of NIRS sensors.[40] Alternative measures of CBF, such as Doppler flow velocity, were not measured, as they are not recommended for long term monitoring. The effects of rewarming, vasoactive infusions or seizures on autoregulation were not examined, as these patients were excluded in order to validate the MTS methodology in a steady state, without external modifiers. Strengths of this study include a follow-up of clinical outcomes at 18–24 months, continuous monitoring of MAP and $S_{ct}O_2$ during the first 72 hours of life in newborns during hypothermia therapy, and testing the effect of multiple time scales on cerebral hemodynamics. Future studies should also be performed in patients prior to initiation of cooling to distinguish the effects of hypothermia from the severity of the asphyxia insult. [41]

In summary, we report the presence of multiple-time-scale correlations between oscillations in MAP and $S_{ct}O_2$ in the first 72 hours of life during hypothermic therapy which suggest impairment of cerebral hemodynamics in newborns with HIE. Preliminary findings of this study highlight the significance of development of rigorous approaches to assess early impairment of cerebral autoregulation in real time in order to guide future neuroprotective interventions in newborns with HIE.

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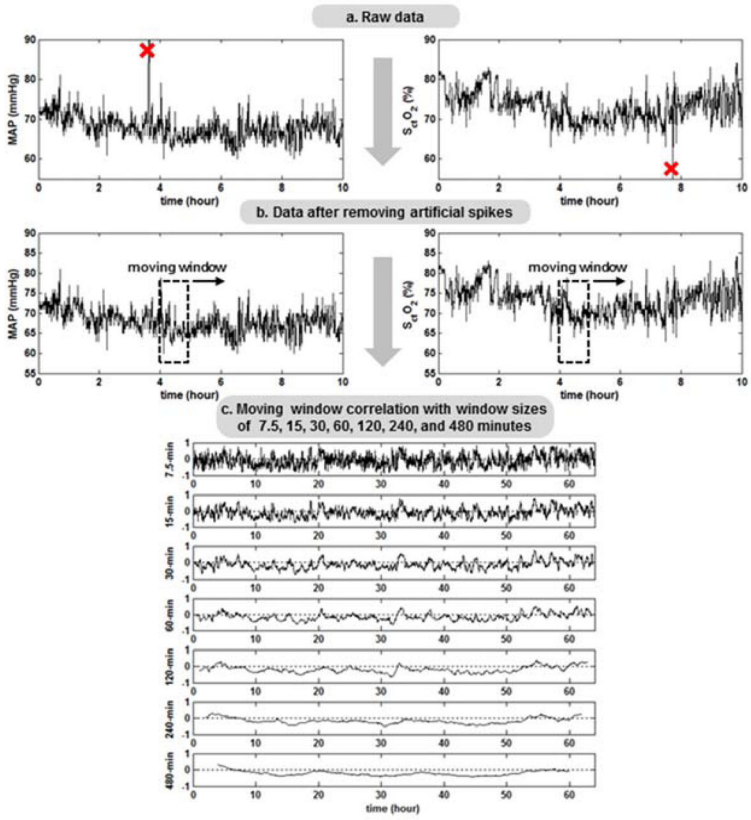

Figure 1.

a. Data processing and analysis procedures. Mean arterial pressure (MAP) and cerebral tissue oxygen saturation ($S_{ct}O_2$) were recorded every 30 seconds. The raw data were inspected through a spike-detection algorithm to identify any measurement artifacts. 1b. Spike-like data points were replaced with linearly interpolated values from their nearest neighbors. 1c. Pearson's correlation coefficient (*R*) between MAP and $S_{ct}O_2$ was computed within a moving window. The window size increased over time scales of 1/8, 1/4, 1/2, 1, 2, 4, and 8 hours.

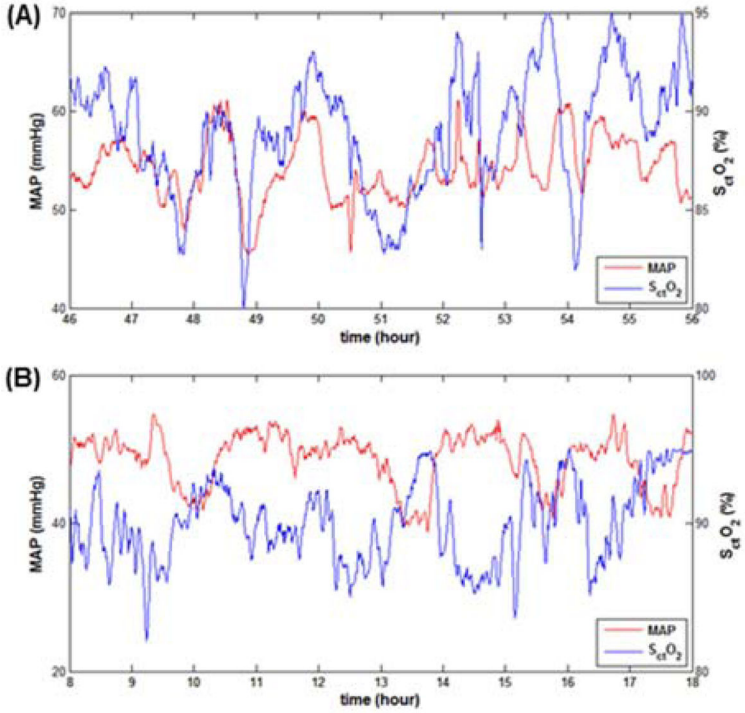

Figure 2.

Examples of the different patterns of hemodynamics noted during cooling in infants with abnormal outcomes. Mean arterial pressure (MAP) and cerebral tissue oxygen saturation ($S_{ct}O_2$) are depicted on the y axis, time on the x axis in: (2a.) newborn with positive correlation, and (2b.) newborn with negative correlation both of whom had abnormal outcomes.

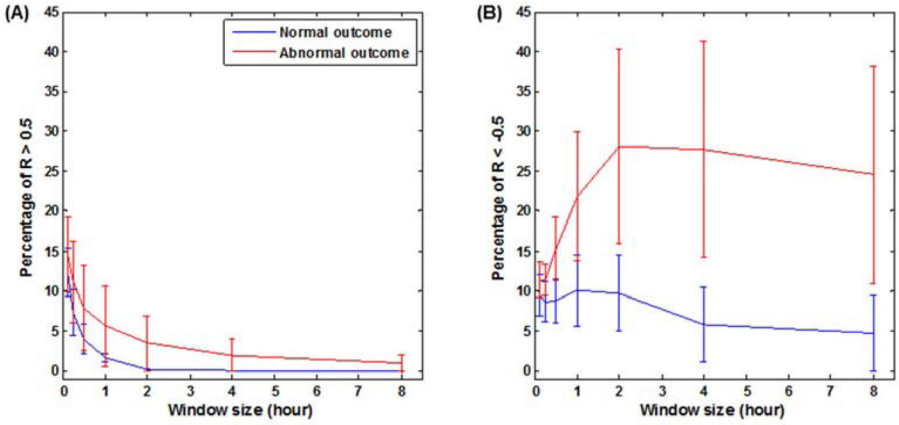

Figure 3.

Cerebral hemodynamics index (CH index) derived from the multiple-time-scale correlation analysis. The CH index values in the selected 10 newborns are plotted against the five time scales of 7min, 15min, 30 min, 1hr, 2hr, 4hr and 8 hr. At each time scale, the CH index was calculated for significant correlation coefficient $R>0.5$ (left) and $R< -0.5$ (right).

Table 1

Patient Characteristics

Maternal age (years)	27± 6
Mode of Delivery	
C/section Emergent	12 (60%)
C/section Elective	5 (25%)
Vaginal Delivery	3 (15%)
Weight (gm)	3025 ± 520
Gestational age	39 ± 2
Race	Hispanic 75%
	Black 14%
Sex	14 (70%) M 6 (30%) F
Apgar Score 1 min	2 (2–3)
Apgar Score 5 min	6 (5–7)
Umbilical Arterial pH at birth	6.98 ± 0.09
O_2 (mmHg)	16 (11–20)
CO_2 (mmHg)	77 (66–99)
Base deficit (mmHg)	19 ± 6
Mechanical Ventilation	12 (60%)
Days in hospital	24 (10–50)

Data presented as mean ± SD or median and IQR.