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Autonomic nervous system depression at term in neurologically normal premature infants

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ABSTRACT

Background: Premature infants are vulnerable to destructive brain injury and disturbed neurological development. Prematurity may alter maturation of the central autonomic nervous system (ANS).

Aims: To compare ANS function (using heart rate variability; HRV) between preterm infants with normal neuroimaging at term equivalent age and low-risk term controls.

Study design, subjects.

We performed a case-control study of preterm infants born ≤28 weeks gestational age that had normal brain imaging and archived continuous EKG data at term equivalent age. We documented other factors thought to influence ANS maturation (e.g. infection, ventilation days, and postnatal steroids). Controls were low-risk term gestational age newborns from uncomplicated pregnancies/deliveries. We characterized HRV metrics using frequency-(Welch periodogram) and time-domain (detrended fluctuation) analyses. Sympathetic tone was characterized by α_1, root mean square analysis (RMS_1 and RMS_2), low-frequency (LF) power, and normalized LF (nLF) and parasympathetic tone was characterized by high-frequency (HF) power and normalized HF (nHF). α_2 characterized ultraslow changes in heart rate. We used ANCOVA to compare HRV metrics between groups.

Outcome measures, results.

HRV from 26 preterm infants were compared to 55 controls. Analyzed HRV data for preterm infants were recorded at median (range) gestational age of 39 (36–39) weeks and for controls at 39 (37–41) weeks gestational age. α_1, RMS_2, LF and HF were significantly higher in control infants and remained significant after controlling for infection, ventilator days, and postnatal steroids ($P < .005$).

Conclusions: Autonomic maturation is impaired in a premature extrauterine environment. In the absence of destructive brain injury, our data suggest an important role for disturbed programming in this impaired autonomic development.

1. Introduction

In premature newborns, the central autonomic nervous system (ANS) is immature and may be inadequately prepared for the demands of cardiorespiratory transition at birth [1]. About 25% of premature infants develop brain injury [2] which may further impact ANS maturation and function [3]. The sympathetic system develops earlier than the parasympathetic system with the latter undergoing accelerated

Abbreviations: ANS, autonomic nervous system; EKG, electrocardiogram; GA, gestational age; HF, high-frequency; HR, heart rate; HRV, heart rate variability; IVH, intraventricular hemorrhage; LF, low-frequency; MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; nHF, normalized high-frequency; nLF, normalized low-frequency; RMS, root mean square; US, ultrasound

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maturation at 25–30 weeks gestation, a time period when premature newborns may already be ex utero and undergoing transition [4,5]. In addition to prematurity itself, multiple clinical and caregiving exposures in the neonatal intensive care unit (NICU) such as oxygenation disturbances, mechanical ventilation, hemodynamic instability, infections, pain, and surgery may impede normal maturation of the ANS. This premature engagement of the ANS under the condition of premature birth may result in "*dysmaturation*", or a shift in the temporal program of ANS maturation due to aberrant programming [6,7].

ANS function can be measured in the infant non-invasively from physiologic signals of heart rate (HR), respiratory rate, and blood pressure. HR variability (HRV), or the fluctuation in the length of time between successive heart beats (R-R intervals), provides a measure of sympathetic and parasympathetic function and therefore ANS maturation [8,9]. As the ANS matures, there should be increased parasympathetic function [10]. HRV can be measured by the frequency domain. High-frequency variability reflects parasympathetic function and is influenced by the respiratory rate, while low-frequency variability is due to a combination of sympathetic and parasympathetic inputs and baroreflex-induced changes in HR. [11] HRV may also be measured by time-domain analysis which evaluates short- and long-term variability in the HR. Long-term variability is influenced by both the sympathetic and parasympathetic nervous systems, meanwhile short-term variability is influenced more by the parasympathetic nervous system based on rapid ANS needs [12].

HRV measures of autonomic tone are dampened in premature infants compared to infants born at term [13]. However, prior studies include infants with neurologic complications of prematurity such as brain injury (i.e. white matter injury or intraventricular hemorrhage [IVH]), which impact HRV and ANS maturation in premature infants [3,14,15]. To exclude the role of direct brain injury on ANS development, preterm infants included in this study had no brain injury by term-equivalent neuroimaging. The objective of this study was to evaluate ANS function through HRV analysis in preterm infants that have normal neuroimaging at term-equivalent age compared to term control infants.

2. Materials and methods

2.1. Participants

Premature infants with birth gestational age (GA) < 29 weeks who survived to discharge from the NICU in 2014 at Children's National Health System, Washington, D.C. and had quality archived physiologic data were studied retrospectively following Institutional Review Board approval. All infants had a normal or near-normal term-equivalent neuroimaging study (brain magnetic resonance imaging [MRI] and/or cranial ultrasound [US]) and no clinical neurologic problems including seizures during their NICU hospitalization. Some infants were part of a separate Institutional Review Board approved protocol and underwent an unsedated term-equivalent brain MRI prior to hospital discharge. Brain MRI findings considered "near-normal" included minimal susceptibility weighted change consistent with prior grade I IVH, minimal punctate area(s) of T1 hyper-intensity in the white matter, or small punctate area(s) of susceptibility weighted change in the cerebellum. Infants were excluded if they had grade II IVH or greater (on cranial US or MRI) or more significant brain MRI findings. The medical record was reviewed to determine other risk factors for abnormal ANS maturation such as infection, necrotizing enterocolitis (NEC), postnatal steroids, surgical ligation of patent ductus arteriosus, and duration of mechanical ventilator support [15–17].

Low-risk controls were term newborns prospectively enrolled within three days of birth following Institutional Review Board approval and informed consent at Inova Women and Children's Hospital, Fairfax, Virginia. Eligible newborns were from uncomplicated pregnancies and deliveries, without significant maternal illness, uncomplicated labor and delivery, ≥37 weeks GA at birth, with a normal birth weight (10th - 90th percentile for GA), and without postnatal infection. None of the low-risk controls had neuroimaging. All were discharged home from the birth hospital at the time of their mother.

2.2. Data collection

The medical history of the infants was ascribed from the clinical database and included 1) gender, 2) GA at birth (born < 26 weeks GA [0] or between 27 and 28 weeks GA [1] or born at term GA (37–41 weeks), [2], 3) any infection developed and if respiratory, blood, or urine culture was positive, 4) developed infection and/or NEC, 5) patent ductus arteriosus ligation, 6) number of days on assisted oxygen support, 7) receipt of postnatal steroids, and 8) caffeine treatment and date of discontinuation. All infants were off caffeine or other centrally-acting medications at the time of the retrieved electrocardiogram (EKG) data for at least 7 days prior to the HRV recording.

Within the preterm infant group, EKGs were retrieved from an institutional Research Data Export archive (IntelliVue Information Center, Philips Healthcare, Andover, MA, USA). We used data from the same hour (6 pm–7 pm) at term-equivalent age from all infants except two, for which we used their data from 36 weeks GA due to timing of NICU discharge. The sampling rate of the EKG retrieved from Research Data Export was 125 Hz. For the term control infants, we obtained EKG data using the EGI physiological input box (Electrical Geodesics, Inc. EGI: www.egi.com, Eugene, OR, USA). The sampling rate of the EKG measured using EGI- physiological input box was 1000 Hz. The duration of the study for term infants was between 45 and 60 min.

2.3. EKG processing

EKG was bandpass filtered between 0.5 and 70 Hz to attenuate the baseline drift and the R-wave (the wave with the dominant amplitude in each cardiac cycle) was identified using a recently proposed method [18]. Beat-to-beat interval (RRi) was calculated. Artifacts such as missed and/or extra beats were removed through an automatic approach [19]. The RRi were partitioned into non-overlapping 10-min epochs. For spectral analysis, the RRi were converted into evenly sampled data using a cubic spline interpolation technique with a sampling rate of 5 Hz.

2.4. Detrended fluctuation analysis – time domain characterization

Detrended fluctuation analysis is a modified root mean square (RMS) analysis approach [20]. This approach involves the following four steps: 1) remove the average value of the data and calculate the profile function as the cumulative sum of the data; 2) partition the profile into windows containing 's' number of beats; 3) fit the profile inside each window using a 4th order polynomial and calculate the local fluctuation function as the RMS of the deviation of the profile from the best polynomial fits; 4) calculate the global fluctuation function as the median of all the local fluctuations. Repeat steps 2 to 4 for different values of 's'. Using the global function the following metrics were calculated: RMS_1 as the maximum value of the global fluctuation function for 's' between 15 and 50 beats; RMS_2 was calculated as the maximum of the global fluctuation function for 's' between 100 and 150 beats [21]. We also calculated α exponent from the slope of global fluctuation function versus 's' in double logarithmic representation. α_1 was obtained from the region 15–30 beats (short time scale) and α_2 was obtained from the region 35–150 beats (long time scale/ultralow frequency) [21]. The α metrics characterize the autocorrelation in the RRi whereas the RMS characterizes the variability in the RRi. The α metrics are dimensionless quantities. The RMS metrics are in units of seconds (*sec*).