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Effects of regional brain injury on the newborn autonomic nervous system

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ABSTRACT

Objective: Cerebral mapping of central autonomic nervous system (ANS)[1] function in mature animals and humans lateralizes sympathetic and parasympathetic influence predominantly to the right and left cerebral hemispheres, respectively. Spectral analysis of heart rate variability (HRV)[2] is an established measure of ANS function. We examined whether such lateralization is present in the term newborn.

Methods: We retrospectively reviewed records of infants >36 weeks of gestation diagnosed with hypoxic ischemic encephalopathy (HIE).[3] We included infants with neonatal EEG and regional injury on brain MRI, which was scored using a schema. We extracted ECG signals from the EEG recording, but excluded periods of electrographic seizure activity to eliminate possible seizure influence on HRV. HRV was evaluated by spectral analysis in the high frequency (HF[4]; 0.3–1 Hz) and low frequency (LF[5]; 0.05–0.25 Hz) ranges, and the LF/HF ratio was examined to assess sympatho-vagal balance. The relation between the injured brain regions and HRV was studied using multiple linear regression models.

Results: We studied 40 neonates with HIE. Injury to the right cerebral cortex ($p = 0.009$) and right cerebellum ($p = 0.041$) predicted a decreased LF/HF ratio. Injury to the left cerebral cortex ($p = 0.035$) and left cerebellum ($p = 0.041$) was associated with an increased LF/HF ratio. The association between brain injury location and the individual LF or HF spectral powers of brain injury did not reach significance.

Conclusions: Our data suggest that a functional lateralization for cerebral autonomic influence is established by term gestation.

1. Introduction

The autonomic nervous system (ANS) is critical for fetal adaptation to stress, successful transition from fetal to extrauterine life, and appropriate neonatal responses to internal and external environmental signals [1,2]. Mediation of cardiovascular and respiratory coordination is an important ANS function. Heart rate variability (HRV) indices and spectral HRV analysis are an established method to assess autonomic function as they reflect the ANS's components (e.g., parasympathetic and sympathetic function) and their different contributions to the overall heart-rate patterns [1,3,4]. Specifically, variability in the high frequency (HF) range represents parasympathetic activity and low frequency (LF) range variability is attributed to mainly sympathetic activity (with parasympathetic contribution). The LF/HF ratio thus serves as an indicator of sympathovagal balance [1,3].

HRV increases with gestational age [2] and with postnatal age in infancy [4], which reflects ANS maturation. Previous studies in fetuses and in neonates have linked decreased HRV to adverse outcome in various disease states [3–8] and to a worse long-term neurodevelopmental outcome [9–12].

Central influences on the ANS are well known from neuropsychological studies [13] and from studies showing different visceral responses to regional electric stimulation of the cerebral cortex [14,15]. Furthermore, mature animal studies using retroviral labeling, as well as adult human brain stimulation and imaging studies, have implicated forebrain structures in the central control of the ANS [14–18]. Some of these cortical regions exhibit a laterality in which the left regions appear to modulate parasympathetic cardiovascular effects, while the right

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[1] ANS—autonomic nervous system.
[2] HRV—heart rate variability.
[3] HIE—hypoxic ischemic encephalopathy.
[4] HF—high frequency.
[5] LF—low Frequency.

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regions seem to have more significant sympathetic influence [19]. To date, there have been few reports on premature and term neonatal brain injury and decreased HRV [7,8,20]. The regionally specific effect of cortical brain injury in the developing brain on the ANS is not well understood.

Our goal in the current study was to test whether we could identify cerebral lateralization for ANS function in the newborn. To do so we compared the association between the regional distribution of neonatal brain injury (by brain magnetic resonance imaging, MRI) and the spectral characteristics of HRV (by electrocardiogram [ECG]). We hypothesized that this approach would show that functional cerebral lateralization for ANS function similar to that described in adults was present as early as term gestation.

2. Methods

Data were acquired retrospectively from the neonatal intensive care units of two tertiary centers in Boston, namely Boston Children's Hospital and the Brigham and Women's Hospital. Medical records of newborn infants were reviewed to identify infants (i) who were >36 weeks of gestational age at birth; (ii) who were diagnosed with hypoxic–ischemic encephalopathy (HIE); (iii) who underwent electroencephalography (EEG) studies during the first 72 h after birth; and (iv) who underwent brain magnetic resonance imaging (MRI) during the neonatal period. Exclusion criteria included infants with (i) brain malformations; (ii) congenital anomalies suggestive of a genetic syndrome; and (iii) abnormal chromosome studies or an inherited metabolic disorder.

Maternal, prenatal, perinatal, and neonatal data were obtained by detailed review of the maternal and infant's medical charts and abstracted into a database.

All study EEGs were reviewed by a pediatric neurologist (YZE) and the timing of EEG seizure activity was carefully documented. Files containing seizures were excluded to eliminate possible seizure influence on heart rate and HRV measures.

A single-channel ECG was part of the EEG montage. All the signals were sampled at 256 Hz and archived in the clinical database. These recordings were retrieved from the clinical database and exported into MATLAB (MathWorks, Inc., MA, USA) for further processing. ECG was bandpass filtered between 0.05 and 80 Hz and the R-wave was identified using an adaptive Hilbert transform approach [21]. The heart rate was calculated as 60 divided by the time between successive R waves expressed in seconds. For spectral analysis, the heart rate was then converted into uniformly sampled data using cubic spline interpolation with a sample rate of 4 Hz. Availability of at least 20 min of heart rate devoid of seizure periods was used in this study.

For each eligible patient, the first 20 min of heart-rate readings was divided into four 5-minute epochs. Spectral decomposition of heart rate was done using the Welch periodogram approach and the relative HF and LF ranges were defined as 0.3–1.0 Hz and 0.05–0.25 Hz, respectively. The average HRV spectral power for both ranges, as well as the LF/HF ratio in all four epochs, was determined for each patient.

MRI images were scored by a pediatric neurologist (AdP) according to a brain injury location schema that divided the brain into 13 regions. Regions 1–6 signify the cortex, with regions 1, 3 and 5 representing the cortical areas supplied by the right anterior, middle and posterior cerebral arteries, respectively, and regions 2, 4 and 6 representing their left counterparts, respectively. Regions 7 and 8 signify left and right white matter, 9 left and 10 right basal ganglia, 11 the left and 12 the right cerebellum and 13 the brainstem (Fig. 1). Each region was marked as either injured or preserved. When more than one MRI was available for a patient, the last study within the neonatal period (first 30 days of life) was selected.

The study was approved by the Boston Children's Hospital and Brigham and Women's Hospital institutional review boards.

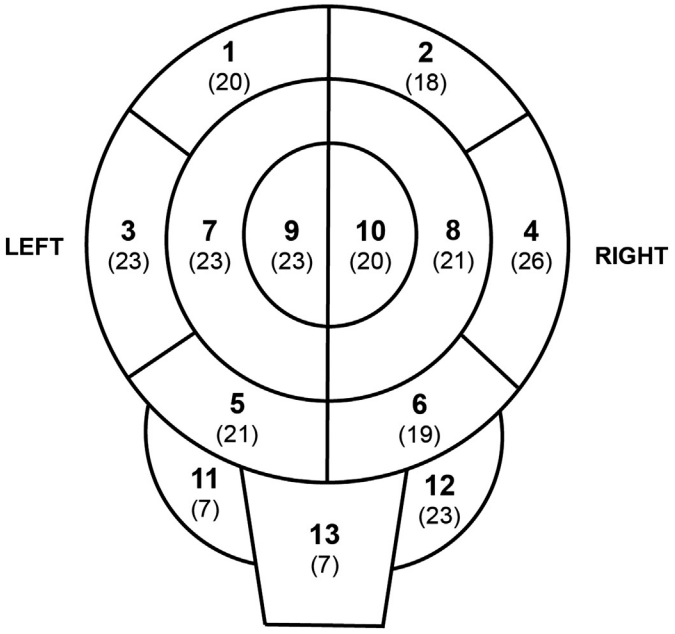

Fig. 1. Number of injuries per brain region according to brain schema. Region numeral (n).

2.1. Statistical analysis

Statistical analysis of patient demographics and clinical characteristics utilized standard measures of central tendency and variability for continuous data and frequencies for categorical variables. The relation between the injured brain regions and HRV was studied by multiple linear regressions using StataCorp LP, TX, USA, which yielded a single coefficient for each region. The statistical significance of the model was assessed using F-statistics. A value of $p < 0.05$ was considered statistically significant. The coefficients were plotted on the regional brain schema as a contour plot.

3. Results

Fifty-one subjects had (i) ECG data in a format amenable to MATLAB processing and (ii) MRIs showing regional brain injury. Eleven of these subjects lacked 20 min of seizure-free data and were excluded from the HRV analysis. Forty subjects formed our study group. Nearly all (98%) were singletons. Patient demographics and characteristics are described in Table 1.

Table 1
Patient demographics and clinical characteristics.

Clinical/demographic data	N = 40
Male, n (%)	22 (55)
Birth weight, g, mean ± SD	3358 ± 529
Gestational age, weeks, mean ± SD	39.4 ± 1.5
Cesarean delivery, n (%)	19 (48)
Apgar 1 min[a]	Range: 0–7, median 2
Apgar 5 min[a]	Range: 0–9, median 4
Ventilation support required, n (%)	32 (80)
Cardiac resuscitation, n (%)	22 (55)
Cord blood pH, median (range)[b]	6.98 (range: 6.7–7.28).
First hemoglobin, g/dL, mean ± SD	14.6 g/dL ± 3.5
First hematocrit, %, mean ± SD	44 ± 12 SD
Clinical seizures, n (%)	33 (82)
Anti-epileptic drug treatment, n (%)	38 (95)

[a] Apgar scores available for 39 subjects.
[b] Cord blood pH available for only 15 (38%) subjects.