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Reduced respiratory sinus arrhythmia in adults born at extremely low birth weight: Evidence of premature parasympathetic decline?

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ABSTRACT

Individuals born at extremely low birth weight (ELBW; <1000 g) are exposed to early adversity in multiple forms. Given that substantial development of the autonomic nervous system (ANS) occurs during the third trimester of gestation, ANS functioning may be altered in adults who were born before reaching 28 weeks of gestational age. The aims of the study were to: 1) determine whether two indices of ANS functioning [resting heart period (HP) and respiratory sinus arrhythmia (RSA)], differed between adult ELBW survivors and normal birth weight (NBW) controls, and 2) ascertain whether ANS functioning was differentially vulnerable to age-related decline in the ELBW participants. Resting HP and RSA (reflecting cardiac efficiency and responsive cardiac control, respectively) were assessed in 30 non-impaired ELBW survivors and 47 NBW controls at ages 22–26 and again at 30–35 years. At each assessment, resting RSA was significantly lower in the ELBW group than in the NBW comparison group. In addition, individual differences in RSA within the ELBW group were poorly preserved over time. These findings are suggestive of a premature decline in parasympathetic functioning in some adult ELBW survivors.

1. Introduction

Infants born at extremely low birth weight (ELBW; <1000 g) are among the tiniest, most vulnerable babies, but medical advances made in the last few decades have enabled the first generation of ELBW survivors to reach adulthood (Fanaroff et al., 2003). Adult ELBW survivors provide a unique opportunity to investigate the consequences of significant prenatal and perinatal adversity for major physiological regulatory systems in humans.

Although it is possible to be born at term, and yet, have very low birth weight, most individuals born at ELBW are also born preterm (<37 weeks' gestation). These infants are exposed to early adversity in multiple forms, including the stresses that contribute to their premature delivery, insufficient time to develop prior to birth, and exposure to medical procedures aimed at improving their odds of survival in the post-natal period. Because substantial development of the autonomic nervous system (ANS) occurs during the third trimester of pregnancy (Van Leeuwen et al., 1999), ANS functioning may be altered in individuals born prior to 28 weeks of gestation. Indeed, preterm birth has been linked to alterations in the development of the vasculature (Norman, 2008), ANS functioning (Yiallourou et al., 2013), and cardiac rhythmicity (Wolfenstetter et al., 2012). Preterm birth also has been associated with higher blood pressure in adults (Bergvall et al., 2007; Dalziel et al., 2007) and lower heart rate variability (HRV) in children (Rakow et al., 2013), especially if the children experienced growth-restriction in utero (Schneider et al., 2006). It is noteworthy that both high blood pressure and low heart rate variability are associated with cardiovascular morbidity later in life.

1.1. Heart rate variability

Resting heart rate is characterized by substantial variability in healthy young adults. High-frequency heart rate variability (HF) (and its natural log equivalent, respiratory sinus arrhythmia [RSA]) reflect a healthy irregularity in the cardiac signal that is primarily due to the activity of the parasympathetic nervous system (90%; Randall et al., 1991) and is commonly used to index phasic vagal cardiac control in humans (Berntson et al., 1997). The parasympathetic contribution to autonomic regulation is of critical importance (Reyes del Paso et al., 2013). Whereas resting heart rate indexes general cardiac efficiency, evidence from across the lifespan suggests that higher resting HRV indexes more responsive cardiovascular adaptation to changing environmental demands, more effective behavioral and emotional self-regulation (e.g.,

Abbreviations: ELBW, extremely low birth weight; NBW, normal birth weight; SGA, small for gestational age; AGA, average for gestational age; ANS, autonomic nervous system; HP, heart period; HRV, heart rate variability; HF, high frequency heart rate variability; RSA, respiratory sinus arrhythmia; BMI, body mass index.

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Thayer et al., 2009), and a lower risk for cardiovascular disease (Dekker et al., 2000). After the attainment of peak levels in the late teen years, resting RSA declines with increased age (Korkushko et al., 1991). Resting RSA is also sensitive to the effects of physical deconditioning, ill health, and the use of some medications. Notwithstanding these contextual effects, individual differences in resting RSA are reported to be substantial, and in adults, appear to be stable over time (Pitzalis et al., 1996).

1.2. Prematurity and increased risk for reduced heart rate variability

At birth, heart rate variability is lower in preterm than term infants (Patural et al., 2008). Furthermore, as compared to term infants, maturation of RSA in preterm infants exhibits a 2–3-fold reduction in magnitude during the first 6 months of life, suggesting that maturation of parasympathetic control may be suppressed in these individuals (Yiallourou et al., 2013). Results from both of these studies intimate that autonomic development does not "catch up" between birth and term-equivalent age. Accordingly, cardiac reactivity to stressors may be enhanced, i.e., poorly regulated, in these infants (Cohen et al., 2008). As well, myelination of the vagus nerve increases significantly between 33 and 35 weeks' gestation, with the number of myelinated vagal nerve fibers reaching adolescent levels by full term (Sachis et al., 1982). The vagus nerve is the principal mediator of parasympathetic outflow to the heart, and critical to effecting rapid changes in heart rate. Importantly, its myelinated branch is involved in social communication processes and the implementation of calm behavioral states (Porges, 2007). Additional evidence suggests that the effects of preterm birth on autonomic regulatory systems may be enduring and not easily compensated, as the detrimental influence of preterm birth on RSA appears to be maintained into middle childhood in those born either preterm or small for gestational age (SGA; <10th percentile of birth weight for gestational age) (Rakow et al., 2013).

1.3. The present study

While the effects of preterm birth on RSA may persist from infancy into childhood, whether these effects extend beyond these developmental stages is not known. Accordingly, the first goal of this study was to determine whether being born at ELBW was associated with adverse effects on RSA in young adulthood. Given the life-long role of resting RSA as an index of efficient cardiovascular adaptability, a second goal was to compare age-related decline in mean levels of resting RSA in the ELBW group relative to NBW controls.

Autonomic measures (RSA and heart period (HP), the inverse of heart rate) in ELBW and NBW participants were examined on two occasions, once at ages 22–26, and again at ages 30–35. Resting RSA was expected to be lower in adult ELBW survivors than in NBW controls at each assessment. Although both groups were expected to exhibit RSA decrements with increasing age, the mean decline was expected to be greater in the ELBW group. In addition, individual differences in RSA were examined at each assessment to ascertain whether age-related decline was consistent within each group, or whether decline in some individuals was greater than in others.

2. Materials and method

2.1. Cohort and participants

The cohort comprised ELBW survivors recruited at birth and a group of NBW controls recruited when both ELBW participants and controls were 8 years of age. Originally, the ELBW group included 397 mainly Caucasian infants who were born at extremely low birth weight between 1977 and 1982 within a geographically-defined area in southwestern Ontario, Canada. Gestational ages for the ELBW participants in this study ranged from 23 to 34 weeks. These infants weighed between 500 and 1000 g at birth and have been followed longitudinally since, with assessments at ages 3, 5, 8, 14, 22–26 and 30–35 years. Of the original cohort, 179 (45%) survived to hospital discharge, and 13 more children died subsequently. Of these 166 survivors, 142 participated in the young adulthood assessment (ages 22–26) (see Saigal et al., 2006). At the young adult assessment, a subset of 71/142 right-handed ELBW participants free of neurosensory impairments was tested in the Child Emotion Laboratory at McMaster University (Schmidt et al., 2008). Electrocardiogram (ECG) data were obtained from 67/71 (94%) of these non-impaired ELBW participants at 22–26 years of age and from 34/71 (48%) at ages 30–35.

The age-, sex-, and socioeconomic status-matched control group consisting of 145 children born at normal birth weight (NBW, birth weight ≥ 2500 g) has been assessed in tandem with the ELBW cohort at ages 8, 14, 22–26, and 30–35. Of these 145 NBW controls, 133 participated at ages 22–26. From this group, a subset of 83/133 right-handed, control participants was tested in our laboratory. ECG data were obtained from 80/83 (96%) of these NBW control participants at ages 22–26 and 48/83 (58%) at the current sweep (ages 30–35).

As we wished to examine autonomic functioning at ages 22–26 and also at 30–35, all analyses were restricted to those participants for whom a complete set of ECG measures was available from both assessments. Applying this criterion reduced the pool of available participants, with losses deriving about equally from both time periods. In a few cases, losses were due to equipment difficulty or excessive artifact in the ECG recordings (6.0% at ages 22–26, 7.3% at ages 30–35). In all, complete ECG data were available from 30 non-impaired ELBW participants, and 47 non-impaired NBW controls.

2.2. Procedure

At each assessment, participants were introduced to the laboratory and briefed about the study procedures. After obtaining written consent, regional electroencephalogram (EEG) and ECG measures were collected. The EEG measures were collected using a lycra stretch cap (Electro-cap, Inc., Eaton, OH) as part of a larger study and are not presented herein. Following each assessment, participants received nominal remuneration for their participation. All laboratory procedures were approved by the participating university and hospital research ethics boards.

2.3. ECG collection and measures

2.3.1. ECG recording

At the 22–26 year assessment, ECG was continuously recorded during 2 min of rest via two disposable ECG electrodes placed on the medial forearms, while the participant sat quietly in a comfortable chair. At the 30–35 year assessment, baseline recordings were extended to 6 min and ECG electrodes were placed below the right clavicle and on the lower left rib area in a modified lead II con. Although a recording of 1 min is sufficient to assess RSA, recordings of 5 min are recommended for comparison of short recordings across studies (Task Force, 1996). As well, respiration rate was not monitored in this study. While statistical control of respiration may be implemented to ensure that respiration rate does not influence RSA, spontaneous respiration rates during seated rest are generally slow enough to avoid any undue influence of respiration on RSA (Berntson et al., 1997; Denver et al., 2007). ECG signals were recorded at each assessment, amplified by an individual SA Instrumentation Bioamplifier, filtered between 0.1 Hz (high pass) and 1000 Hz (low pass), and digitized at a sampling rate of 512 Hz. The acquisition software at ages 22–26 was Snapshot-Snapstream (HEM Data Corp., Southfield, MI), and at ages 30–35, SnapMaster (HEM Data Corp., Southfield, MI).