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A Longitudinal Description of Heart Rate Variability in 28–34-Week-Old Preterm Infants

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Abstract

The purpose of this study was to longitudinally describe changes in heart rate variability (HRV) from 28 to 34 weeks postmenstrual age (PMA). A convenience sample of 31 low-risk preterm infants participated. HRV was quantified using a spectral analysis of heart periods and recorded during seven weekly test sessions from an electrocardiogram (ECG) signal. The total range of frequency components (0.04–2.0 Hz), high-frequency (HF) components (0.30–1.3 Hz), and ratio of low-to-high frequency (LF/HF) components (0.04–0.20/0.30–1.3 Hz) were measured. A mixed general linear model analysis revealed no significant change over weekly test sessions for the total, the high, and the ratio of LF/HF components. A significant interaction effect was, however, noted in the HF components for test session $\times$ gender ($df = 1$; $F = 4.85$; $p = .030$). With increasing age, the HF components for females increased or displayed a pattern of HRV indicative of a more mature autonomic nervous system (ANS). Study findings warrant further investigation of the impact of gender on normative descriptions of HRV.

Keywords

autonomic nervous system; gender; heart rate variability; preterm infant; spectral analysis

Of the two primary branches of the autonomic nervous system (ANS), the increasing influence of the parasympathetic branch is now used to characterize maturation of the ANS in the fetus and the preterm infant (Chatow, Davidson, Reichman, & Akselrod, 1995; Kotini et al., 2001; Oppenheimer & Lewinsky, 1994; Verklan & Padhye, 2004). Measures used by researchers to characterize maturational trends are as follows: the total/entire range of heart rate variability (HRV); the high-frequency (HF) components affected by the respiratory system, which reflects parasympathetic control of HRV; and the ratio of low-to-high frequency (LF/HF), which reflects a balance between sympathetic and parasympathetic control of HRV. The objective of this study was to provide a longitudinal description of these measures of HRV (total range of frequencies, HF, and ratio of LF/HF) from 28 to 34 weeks postmenstrual age (PMA) in the preterm infant.

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Declaration of Conflicting Interests

Current Descriptions of Normative Trends

Most current descriptions of normative trends in HRV have compared cohorts of preterm (born prior to completion of 37th gestational week) infants to term (40 weeks postmenstrual age [PMA]) infants, grouped across several developmental weeks. One exception is a longitudinal description of HRV across 23 to 38 weeks PMA in which study findings are confounded by occurrence of a painful event (Khattak et al., 2007). Comparisons of HRV in preterm and term infants have largely identified an increase in HF, with a coinciding decrease in the ratio of LF/HF components (Chatow et al., 1995; Clairambault, Curzi-Dascalova, Kauffmann, Medigue, & Leffler, 1992; Hunt, 2006; Khattak et al., 2007; Longin, Gerstner, Schaible, Lenz, & König, 2006). Clairambault et al. (1992), Hunt (2006), and Khattak et al. (2007) all found a general increase in HF between preterm and term infants, and the same trend was found to be statistically significant by Chatow et al. (1995) and Longin et al. (2006). The authors concluded that between preterm birth and term age, the infants' ANS nervous system control of HRV matured, particularly the parasympathetic control of HRV.

A more specific look at preterm infants grouped in cohorts older than 33 weeks PMA has revealed findings related to the HF components similar to that noted when comparisons were made between older preterm and term infants. Hunt (2006) found a general increase in HF between infants 33–36 and >37 weeks PMA. A similar, significant increase in HF was found by Sahni et al. (2000) in infants 32–38 weeks PMA grouped in cohorts across 2–3 weeks. The general increase in HF, along with a coinciding decrease in the ratio of LF/HF, was concluded to reflect a greater balance of parasympathetic control of HRV (or maturation of the ANS) with increasing age of the preterm infant. This normative trend, however, was demonstrated using cohorts, making it difficult to discern when longitudinally the increase in HF and decrease in the ratio of LF/HF occurred (Cairns, 1986).

In contrast to normative trends identified for the older preterm infant, the longitudinal measures of HRV in the younger preterm infant are more frequently described as general trends because they have not reached a level of statistical significance ($p < .05$), and cohorts more regularly include a combination of low- and high-risk infants.

Clairambault et al. (1992) described changes in HRV using low-risk cohorts grouped by 2–5 gestational weeks across 31–41 weeks of age. A general increasing trend in HF was reported that was not significant. Differences in HF and the ratio LF/HF by sleep–wake state were significant ($p < .01$), with infants in a quiet state displaying lower levels than those in an active state. This same trend in 33–35-week PMA infants was noted by Doussard-Rossevelt, Porges, and McClenny (1996) in that no significant findings were reported but a general increasing trend in HF was discussed. More convincingly, Longin et al. (2006) compared cohorts of low-risk infants by age and gender (<32 weeks to those >32 weeks and term infants). Although no gender differences were noted, the HF and total frequency components increased significantly ($p < .001$) from the <32 (2.47; 43.71 ms) to the >32 week cohorts (8.13; 96.58 ms), respectively.

Using a mix of low- and high-risk infants with apgars less than 5 at 5 min, Mazursky et al. (1998) noted a general (but not significant) decrease in the ratio of LF/HF from initiation of the study at 28 weeks PMA to study closure at 40 weeks PMA. Using 2-week cohorts, Smith, Doig, and Dudley (2004) reported changes in measures of HRV using a small sample size of infants 28–34 weeks PMA undergoing assisted ventilation. A Tukey-Kramer post hoc analysis revealed a general increase ($p = .06$) in HF from 28–29 weeks PMA ($n = 4$; 6.15 ms²) to 32–34 weeks PMA ($n = 3$; 11.12 ms²). This same finding was further

substantiated by Khattak et al. (2007) using a larger sample ($N = 38$) of preterm infants who were largely undergoing assisted ventilation on initiation in the study at 23 weeks PMA.

Previous research suggests there is a general increase in HF with a coinciding decrease in the ratio of LF/HF components beginning sometime near 32 weeks of age. This trend is the same for both males and females. However, in the previous research upon which this observation is based, infants were grouped into cohorts (sometimes combined across as many as 5–6 gestational weeks), and in some studies, researchers used a mix of low- and high-risk infants. This mix of low- and high-risk infants is further complicated by variations in HRV and the incidence of infection and death in neonates (Griffin et al., 2003) and, potentially, the occurrence of intraventricular hemorrhage in preterm infants (Krueger, Gyland, & Theriaque, In press). In the study reported here, a description of normative, weekly changes in HRV in low-risk preterm infants grouped by gender is provided to more clearly describe the longitudinal changes during 28–34 weeks PMA. Given previous findings, we hypothesized no differences by gender and a delayed increase occurring near 32 weeks of age in the total range of frequencies and HF components with a respective decrease in the ratio of LF/HF across the study time period.

Methods and Materials

Setting and Sample

A convenience sample of 31 low-risk preterm infants (admitted to a neonatal intensive care unit [NICU] in the Southeast) was recruited, following parental informed consent (see Table 1).

Infants enrolled in the study reported here also participated in a larger study, Heart Rate Variability and Learning in the 28–34-Week Premie (NIH/NINR P20 NR07791), in which they were randomly assigned using SAS software (v8, Cary, NC) in blocks of four to Group 1 or Group 2. Groups listened to a CD recording of a nursery rhyme recited by their mothers twice a day either from 28 to 34 weeks PMA (Group 1) or from 32 to 34 weeks PMA (Group 2). All procedures involving participation in this larger ongoing study took place directly following procedures for the study reported here. The target age for admission was 27–28 weeks PMA, determined from the mother's last menstrual period. Exclusion criteria consisted of the following: (a) abnormal head ultrasound, (b) sensorineural hearing loss, (c) confirmed prenatally transmitted viral/bacterial infections, and (d) cardiac abnormalities.

A chart review was also performed on discharge to determine the infants' level of risk using a neonatal assessment tool. The tool chosen was Brazy's Nursery Neurobiological Risk Score (NBRS). This tool has been demonstrated to effectively differentiate among the general risk statuses in preterm infants, with a score of 7 indicating high risk (Brazy, Eckerman, Oehler, Goldstein, & O'Rand, 1991). The overall mean NBRS score for the infants participating in the study was 2.98 ($SD = 2.49$), with 2 males and 1 female receiving NBRS scores of 7. Participant 12 (male) received ventilatory assistance for >7 days and developed meningitis with positive blood cultures. Participant 30 (male) received >28 days of ventilatory assistance and suffered a cardiopulmonary arrest (not at birth). Participant 37 (female) was diagnosed with hydrocephalus and positive blood cultures for infection.

The mean maternal age was 25.3 (range 18–38 years). Of the 38 mothers initially enrolled, 64% reported White ethnicity, 27% African American, and 9% Hispanic. The majority of mothers had completed some form of higher education (46%), 33% had graduated from high school, and 21% had not completed high school.

Power Analysis

A power analysis was performed on completion of data collection to determine whether there was adequate power to detect differences in measures of HRV (Maxwell & Delaney, 1990). Although several different test session means and standard deviations could have been used in the determination of effect size, due to the unknown nature of what the longitudinal changes in HRV would be, we chose to use the final test session as a first approximation. Given a .75 effect size (difference between means = 0.22 Hz; males = 0.16 Hz; $SD = 0.22$ Hz; females = 0.38 Hz; $SD = 0.40$ Hz) and six levels (28–34 weeks of age), a minimum sample size of 11 per group was determined to achieve .80 power ($\alpha = .05$, two-sided).

Data Lost

With the 38 infants initially enrolled in the study, a maximum of 266 test sessions (7 sessions for each infant) were possible; however, only 139 test sessions (52%) were actually used. Reasons for not analyzing sessions included (a) detection of exclusion criteria in 7 participants following admission into the study (49); (b) failure of infants to meet the criteria for sleep–wake state (26); (c) equipment-related problems (9); (d) instability of infants during the day of testing (8); (e) a need to conduct procedures unrelated to the study such as a head ultrasound/surgery (7); or (f) a transfer from NICU to another hospital prior to completing participation in the study (28). Although any missing observations are a concern, we believe these were missed at random.

Materials and Procedure

Cardiac data collection system—The electrocardiogram (ECG) signal was sampled at equal intervals for 300 s at a rate of 500 Hz and transferred (using ECG electrodes attached in the standard three-lead manner via an RS232 interface and software) from an Agilent Neonatal monitor (model #1092A) to a Dell Inspiron 8100 laptop. A Matlab program was used to filter, or smooth, the signal by removing noise components and baseline wander. The filtered signal was then passed through a QRS detection algorithm (also implemented in Matlab), resulting in a time series of R-R intervals or heart periods.

Spectral analysis of heart periods—Spectral analysis of the heart periods was performed offline using a Lomb procedure. This method was chosen because the interval between consecutive samples is not required to be uniform (Lomb, 1976), which is the case with consecutive heart periods. The total or entire spectrum (0.04–2.0 Hz) was examined except for very low frequencies (0.0–0.04 Hz), because these components are typically produced by slow-trend artifacts (or noise). The HF components (0.30–1.30 Hz), occurring in response to respirations and controlled only by the parasympathetic nervous system, were measured. In addition, the ratio of LF/HF components (0.04–0.20/0.30–1.30 Hz), reflecting the balance between sympathetic and parasympathetic tone, was measured (Akselrod et al., 1981; Chatow et al., 1995; Denver, Reed, & Porges, 2007; Pomeranz et al., 1985).

Sleep–wake criteria—Sleeping and waking states involve clusters of behaviors that tend to occur together and reflect underlying neural activity (Thoman, 1990). In the preterm infant, the behaviors typically evaluated include movement (body and eye), respirations, and facial expressions. The electroencephalography (EEG) may also be used as a criterion for state determination (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004). Several behavioral sleep–wake states have been identified in the preterm infant (quiet waking, active waking, sleep–wake transitions, active sleep, and quiet sleep; Holditch-Davis, 1990; Thoman, 1990). Because the preterm infant spends the most time in active sleep, this state was selected for use in this study, making it more likely that data collection occurred while

the infants were in a consistent sleep–wake state. Behavioral criteria used to determine participants were in an active sleep state were (a) irregular respirations, (b) the absence of body movement, and (c) closed eyes (Holditch-Davis, 1990; Holditch-Davis et al., 2004; Thoman, 1990).

Evaluation of sleep–wake criteria was conducted at the initiation of each test session and confirmed post hoc by also assessing the infant's range of short-term HRV (Nijhuis, 1995; Nijhuis, Prechtl, Martin, & Bots, 1982). The addition of short-term HRV (> 5 beats per min) as a criterion for sleep–wake state was made due to known variations in HRV depending on the fetal and preterm infant sleep–wake state (Doussard-Rossevelt et al., 1996; Nijhuis, 1995).

Interrater reliability in behavioral state detection at the initiation of each test session was maintained at 90% agreement. All infant test sessions that did not meet the behavioral criteria and pass the post hoc screening of HRV (> 5 beats per min) were excluded from the final analysis ($n = 26$).

Procedure—Seven weekly test sessions were performed from 28 to 34 weeks PMA. Sampling of infants' heart periods from the ECG signal lasted for 300 s and was performed while infants remained in their assigned NICU incubator beds. Data collection was not initiated until at least 15 min following a meal and the infant was determined to be in an active sleep state. To control for potential circadian influences on heart rate patterns and movements (Arduini, Rizzo, & Romanini, 1995), ECG recordings occurred at approximately the same time of day for each infant (10 a.m.–12 p.m.).

Statistical Analyses

General descriptive statistics and a general linear mixed model (GLMM) analysis were used to analyze changes in HRV over time. The GLMM was chosen because this type of statistical analysis models for group means as fixed effects while simultaneously modeling for individual participants as random effects (Edwards, 2000; Holditch-Davis, Edwards, & Helms, 1998; Krueger & Tian, 2004). The fixed effects were test session (or PMA), gender, group assignment, and all two-way interactions between these fixed effects. The only random effect was the class variable identifying the individual participants. An autoregressive structure was used; the correlation coefficient within a participant declined exponentially with the time between sessions (Singer, 1998). The test session independent variable was centered, so Week 28 was coded as -3 , Week 29 as -2 , up to Week 34 as $+3$.

Results

Total Frequencies (0.04–2.0 Hz)

No significant effect by test session, gender, or group assignment was noted for the total range of frequency components (see Table 2).

HF Components (0.30–1.3 Hz)

The effects of test session and group assignment were not significant for HF components. A test session $\times$ gender interaction was significant ($df = 1$; $F = 4.85$; $p = .030$; see Table 3). While males began the study with higher levels of HF (male $M = 0.14$, $SD = 0.11$; female $M = 0.12$, $SD = 0.06$), this trend shifted at 31 weeks of age or Test Session 4 (male $M = 0.09$, $SD = 0.11$; female $M = 0.22$, $SD = 0.24$). From 31 weeks of age onward, females maintained higher levels of HF (see Figure 1).

Ratio of LF/HF Components (0.04–0.20/0.30–1.3 Hz)

No significant effect for test session, gender, or group assignment was noted for the ratio of LF/HF components (see Table 2).

Discussion

In general, minimal change was noted across the study period in the total and HF components and in the ratio of LF/HF components. Unexpectedly, a closer examination of the weekly trends during this developmental time period, however, revealed differences between males and females. While the HF for males displayed minimal change over time, from 31 weeks of age onward, females maintained higher levels of HF or displayed a pattern of HRV indicative of a more mature ANS.

As with only the females in this study, a significant increasing trend in HF with a coinciding decrease in the ratio of LF/HF has been demonstrated in a mix of male and female fetuses from 28 to 34 weeks of age (Kotini et al., 2001) and in the older preterm infant (Chatow et al., 1995; Clairambault et al., 1992; Khattak et al., 2007; Longin et al., 2006). A likely reason for this trend is that from 28 to 34 weeks, the relative influence of the parasympathetic branch of the ANS on cardiac activity has been shown to increase linearly for the fetus (Kotini et al., 2001), and behavioral studies report that cardiac reactions elicited by fetal movement (Gagnon, 1989) and loud sounds (Kisilevsky, Muir, & Low, 1992) occur reliably only after about 32 weeks' gestation. Thus, ANS control of cardiac activity, movement, and HRV is maturing significantly during this time (DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996; Groome, Loizou, Holland, Smith, & Hoff, 1999; Holmes, 1986).

In contrast to females, measures of HRV for males in this study were dissimilar to those reported with fetuses in a developmentally appropriate environment (womb) and to those reported for older, or >32-week PMA, preterm infants. Males demonstrated minimal change over 28–34 weeks PMA. One possible explanation for differences between males and females in measures of HRV is that the ANS is differentially affected by gender with an early birth.

Although previous descriptions of HRV that have examined gender have not identified differences in HRV (Longin et al., 2006), greater levels of parasympathetic control of HRV (HF) for females is consistent with retrospective studies identifying higher survival rates in female preterm graduates of the NICU (Morse et al., 2006; Roth et al., 1993). Recently, it was reported that males experience more episodes of nursing care at discharge compared to females (Thomas, Tsai, & Brown, 2008). Following participation in the study reported here, more males (2) than females (1) went on to develop NBRS risk scores indicating high-risk status. In addition, variations in HRV have been found to be correlated with sudden infant death syndrome, with the diagnosis occurring 50% more in males than females (Mage & Donner, 2004, 2006). Mage and Donner (2004, 2006) further suggest that this gender difference may also occur in additional respiratory disorders. At present, we do not know why this occurs. Taken together with the findings reported here, females may acquire the ability to establish a homeostatic relationship with their environment earlier than males, thereby requiring less intensive care while in the NICU. It is possible, as with the sensory systems, that the ANS of preterm infants is affected by the altered environment of the NICU (vs. normal environment of womb; Gottlieb, 1971, 1991; Lickliter, 2000a, 2000b; Turkewitz & Kenny, 1985) and that this impact varies by gender.

Infants in this study also participated in a larger study in which they were exposed daily to a CD recording of their mothers reciting a nursery rhyme (Group 1 from 28 to 34 weeks PMA

and Group 2 from 32 to 34 weeks PMA). Although the larger study is ongoing, no significant differences by group assignment were noted and, due to the imbalance of males and females between groups, we cannot state at this time whether regular exposure to CD recordings of maternal voice directly affected HRV.

A limitation of the study was that nine infants were transferred from the NICU prior to completion of the study at 34 weeks of age (loss of a total of 28 test sessions). A systematic bias may have been introduced because it is possible that the most stable infants underwent transfers to smaller, less intensive nurseries, leaving the less stable infants to complete the study. In the future, it will be important to allow for continuation of the study at outlying hospitals where the majority of infants were transferred.

In conclusion, study findings warrant further investigation of the impact of gender on normative descriptions of HRV and other factors affecting the preterm infants' time spent in the NICU. The final trimester of fetal gestation and early preterm infant development has challenged researchers since technology has allowed us to access this unique developmental time period (DiPietro et al., 1996, 2004; Groome et al., 1999; Philbin, Lickliter, & Graven, 2000). Given previous studies that have demonstrated the usefulness of HRV to describe maturation of the ANS (Chatow et al., 1995; Oppenheimer & Lewinsky, 1994; Verklan & Padhye, 2004), risk status (Griffin et al., 2003; Krueger et al., In press) and differences in mortality rates between males and females (Mage & Donner, 2004, 2006), future studies investigating HRV during this important developmental time period are needed.

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References

- Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectral analysis of heart rate fluctuation: A quantitative probe of beat to beat cardiovascular control. *Science*. 1981; 213:220–222. [PubMed: 6166045]
- Arduini, D.; Rizzo, G.; Romanini, C. Fetal behavioral states and behavioral transitions in normal and compromised fetuses. In: Lecanuet, JP.; Fifer, W.; Krasnegor, N.; Smotherman, W., editors. *Fetal development: A psychobiological perspective*. Hillsdale, NJ: Erlbaum; 1995. p. 83-99.
- Brazy J, Eckerman C, Oehler J, Goldstein R, O'Rand A. Nursery neurobiologic risk score: Important factors in predicting outcome in very low birth weight infants. *Journal of Pediatrics*. 1991; 118:783–792. [PubMed: 2019935]
- Cairns, R. Phenomena lost: Issues in the study of development. In: Balsiner, J., editor. *Individual subject and scientific psychology*. New York: Plenum; 1986. p. 97-111.
- Chatow U, Davidson S, Reichman B, Akselrod S. Development and maturation of the autonomic nervous system in premature and term infants using spectral analysis of heart rate fluctuations. *Pediatric Research*. 1995; 37:294–302. [PubMed: 7784138]
- Clairambault J, Curzi-Dascalova L, Kauffmann F, Medigue C, Leffler C. Heart rate variability in normal sleeping full-term and preterm neonates. *Early Human Development*. 1992; 28:169–183. [PubMed: 1587227]
- Denver JW, Reed SF, Porges SW. Methodological issues in the quantification of respiratory sinus arrhythmia. *Biological Psychology*. 2007; 74:286–294. [PubMed: 17067734]
- DiPietro JA, Caulfield L, Costigan KA, Meriardi M, Nguyen RH, Zavale N, et al. Fetal neurobehavioral development: A tale of two cities. *Developmental Psychology*. 2004; 40:445–456. [PubMed: 15122969]
- DiPietro JA, Hodgson D, Costigan K, Hilton S, Johnson T. Fetal neurobehavioral development. *Child Development*. 1996; 67:2553–2567. [PubMed: 9022256]

- Doussard-Rossevelt J, Porges S, McClenny B. Behavioral sleep states in very low birth weight preterm neonates: Relation to neonatal health and vagal maturation. *Journal of Pediatric Psychology*. 1996; 21:785–802. [PubMed: 8990724]
- Edwards L. Modern statistical techniques for the analysis of longitudinal data in biomedical research. *Pediatric Pulmonology*. 2000; 30:330–344. [PubMed: 11015135]
- Gagnon R. Stimulation of human fetuses with sound and vibration. *Seminars in Perinatology*. 1989; 13:393–402. [PubMed: 2683110]
- Gottlieb, G. Ontogenesis of sensory function in bird and mammals. In: Tobach, E.; Aronson, L.; Shaw, E., editors. *The biopsychology of development*. New York: Academic Press; 1971. p. 67-128.
- Gottlieb, G. *Individual development and evolution*. New York: Oxford; 1991.
- Griffin M, O'Shea T, Bissonette E, Harrel F Jr, Lake D, Moorman J. Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. *Pediatric Research*. 2003; 53:920–926. [PubMed: 12646726]
- Groome L, Loizou P, Holland S, Smith L, Hoff C. High vagal tone is associated with more efficient regulation of homeostasis in low-risk fetuses. *Developmental Psychobiology*. 1999; 35:25–34. [PubMed: 10397893]
- Holditch-Davis D. The development of sleeping and waking states in high-risk preterm infants. *Infant Behavior and Development*. 1990; 13:513–531.
- Holditch-Davis D, Edwards L, Helms R. Modeling development of sleep–wake behaviors: I. Using the mixed general linear model. *Physiology & Behavior*. 1998; 63:311–318. [PubMed: 9469721]
- Holditch-Davis D, Scher M, Schwartz T, Hudson-Barr D. Sleeping and waking state development in preterm infants. *Early Human Development*. 2004; 80:43–64. [PubMed: 15363838]
- Holmes G. Morphological and physiological maturation of brain in neonate and children. *Journal of Clinical Neurophysiology*. 1986; 3:209–238. [PubMed: 3722369]
- Hunt C. Ontogeny of autonomic regulation in late preterm infants born at 34–37 weeks postmenstrual age. *Seminars in Perinatology*. 2006; 30:73–76. [PubMed: 16731280]
- Khattak A, Padhye N, Williams A, Lasky R, Moya F, Verklan M. Longitudinal assessment of heart rate variability in very low birth weight infants during their NICU stay. *Early Human Development*. 2007; 83:361–366. [PubMed: 16978804]
- Kisilevsky B, Muir D, Low J. Maturation of human fetal responses to vibroacoustic stimulation. *Child Development*. 1992; 63:1497–1508. [PubMed: 1446565]
- Kotini A, Anninos P, Adamopoulos A, Avgidou K, Galazios G, Anastasiadis P. Linear analysis of fetal magnetocardiogram recordings in normal pregnancies at various gestational ages. *Journal of Obstetrics and Gynaecology*. 2001; 21:154–157. [PubMed: 12521885]
- Krueger C, Gyland E, Theriaque D. Neonatal heart rate variability and intraventricular hemorrhage: A case study. *Pediatric Nursing*. (In press).
- Krueger C, Tian L. A comparison of the general linear mixed model and repeated measures ANOVA using a data set with multiple missing data points. *Biological Research for Nursing*. 2004; 6:151–157. [PubMed: 15388912]
- Lickliter R. Atypical perinatal sensory stimulation and early perceptual development: Insights from developmental psychobiology. *Journal of Perinatology*. 2000a; 20:S45–S54. [PubMed: 11190700]
- Lickliter R. The role of sensory stimulation in perinatal development: Insights from comparative research for care of the high-risk infant. *Journal of Developmental and Behavioral Pediatrics*. 2000b; 21:437–447. [PubMed: 11132796]
- Lomb NR. Least-squares frequency analysis of unequally spaced out data. *Astrophysics and Space Science*. 1976; 39:447–462.
- Longin E, Gerstner T, Schaible T, Lenz T, Konig S. Maturation of the autonomic nervous system: Differences in heart rate variability in premature vs term infants. *Journal of Perinatology in Medicine*. 2006; 34:303–308.
- Mage D, Donner M. The X-linkage hypotheses for SIDS and the male excess in infant mortality. *Medical Hypotheses*. 2004; 62:564–567. [PubMed: 15050108]

- Mage D, Donner M. Female resistance to hypoxia: Does it explain sex differences in mortality rate? *Journal of Womens Health*. 2006; 15:786–794.
- Maxwell, S.; Delaney, H. *Designing experiments and analyzing data: A model comparison perspective*. Pacific Grove, CA: Brooks/Cole; 1990.
- Mazursky J, Clay L, Birkett K, Bedell A, Ben-Haim S, Segar J. Development of baroreflex influences on heart rate variability in preterm infants. *Early Human Development*. 1998; 53:37–52. [PubMed: 10193925]
- Morse SB, Wu SS, Ma C, Ariet M, Resnick M, Roth J. Racial and gender differences in the viability of extremely low birth weight infants: A population-based study. *Pediatrics*. 2006; 117:e106–e112. [PubMed: 16396844]
- Nijhuis, JG. Physiological and clinical consequences in relation to the development of fetal behavior and fetal behavioral states. In: Lecanuet, J-P.; Fifer, WP.; Krasnegor, NA.; Smotherman, WP., editors. *Fetal development: A psychobiological perspective*. Hillsdale, NJ: Earlbaum; 1995. p. 67-82.
- Nijhuis J, Prechtl H, Martin C, Bots R. Are there behavioural states in the human fetus? *Early Human Development*. 1982; 6:177–195. [PubMed: 7094856]
- Oppenheimer L, Lewinsky R. Power spectral analysis of the fetal heart rate. *Baillieres Clinics of Obstetrics and Gynaecology*. 1994; 8:643–661.
- Philbin M, Lickliter R, Graven S. Sensory experience and the developing organism: A history of ideas and view to the future. *Journal of Perinatology*. 2000; 20:S2–S5. [PubMed: 11190696]
- Pomeranz B, Macauley R, Caudil M, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *American Journal of Physiology*. 1985; 17:H151–H153. [PubMed: 3970172]
- Roth J, Resnick MB, Ariet M, Carter CL, Eitzman DV, Curran JS, et al. Changes in survival patterns of very low-birth-weight infants from 1980 to 1993. *Archives of Pediatric and Adolescent Medicine*. 1993; 149:1311–1317.
- Sahni R, Schulze K, Kashyap S, Ohira-Kist K, Fifer W, Myers M. Maturational changes in heart rate and heart rate variability in low birth weight infants. *Developmental Psychobiology*. 2000; 37:73–81. [PubMed: 10954832]
- Singer J. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and growth models. *Journal of Educational and Behavioral Statistics*. 1998; 24:323–355.
- Smith S, Doig A, Dudley W. Characteristics of heart period variability in intubated very low birth weight infants with respiratory disease. *Biology of the Neonate*. 2004; 86:269–274. [PubMed: 15297789]
- Thoman E. Sleeping and waking states in infancy: A functional perspective. *Neuroscience and Behavioural Reviews*. 1990; 14:93–107.
- Thomas K, Tsai S, Brown S. State change in preterm infants in response to nursing caregiving: Possible gender effects. *Neonatal Network*. 2008; 27:15–22. [PubMed: 18232587]
- Turkewitz G, Kenny PA. The role of developmental limitations of sensory input on sensory/perceptual organization. *Journal of Developmental and Behavioral Pediatrics*. 1985; 6:302–306. [PubMed: 3905863]
- Verklan MT, Padhye NS. Spectral analysis of heart rate variability: An emerging tool for assessing stability during transition to extrauterine life. *Journal of Obstetric, Gynecologic and Neonatal Nursing*. 2004; 33:256–265.

Figure 1.

High-frequency (HF) changes in heart rate variability. For the overall group, minimal change was noted across 28 to 34 weeks PMA. The trend for females was not consistent with this trend. A general increase in HF was noted for females and, from 31 weeks of age onward, females maintained higher levels of HF than males ($F = 4.19$, $df = 1/105$, $p < .05$).

Table 1

Characteristics of Preterm Infant Participants

Participant	Group Assignment	Birth Weight (g)	Delivery Type	Apgar Score	
				1 Min	5 Min
Males (n = 14)					
2	1	1,250	SVD	6	8
3	2	1,200	SVD	6	6
9	1	1,175	C/S	4	7
11	2	1,133	C/S	6	8
12	1	1,225	SVD	8	8
13	2	861	C/S	3	8
18	2	1,135	C/S	7	8
22	1	925	SVD	7	9
25	2	1,146	C/S	9	9
30	2	880	C/S	1	5
32	2	1,470	C/S	4	8
33	2	1,095	C/S	5	7
34	2	1,090	C/S	5	7
35	1	1,102	SVD	8	8
Mean (SD)		1,120.50 (158.23)		5.64 (2.17)	7.57 (1.08)
Females (n = 17)					
5	2	1,192	C/S	8	9
6	1	950	C/S	2	5
7	2	1,235	C/S	4	7
10	2	943	C/S	5	7
14	1	1,290	C/S	6	7
15	1	1,270	SVD	8	9
16	2	780	C/S	1	5
17	1	1,359	C/S	5	7
19	1	1,200	C/S	6	5
20	2	1,135	C/S	8	9

Participant	Group Assignment	Birth Weight (g)	Delivery Type	Apgar Score	
				1 Min	5 Min
26	1	1,080	SVD	8	5
27	1	1,090	SVD	7	8
28	2	654	C/S	6	7
29	1	880	C/S	6	8
31	1	970	SVD	9	9
36	1	1,000	C/S	6	8
38	1	1,000	SVD	7	9
Mean (SD)		1,001.69 (310.13)		6.07 (2.11)	7.18 (1.52)

NOTE: Seven infants did not contribute data for the statistical analyses because they developed exclusion criteria (Participants 4, 8, 21, 23, 24, and 37) or gestational age was not confirmed following birth (Participant 1). C/S = cesarean delivery; SVD = spontaneous vaginal delivery.

Table 2

Descriptive Statistics

Measure	Overall			Group 1			Group 2			Male			Female		
	N	M	SD	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Session 1															
Total	15	0.47	0.14	7	0.48	0.11	8	0.47	0.17	7	0.44	0.16	8	0.51	0.13
High	15	0.13	0.08	7	0.12	0.11	8	0.13	0.07	7	0.14	0.11	8	0.12	0.06
Ratio	15	26.74	22.21	7	35.05	29.92	8	19.47	9.47	7	26.17	25.93	8	27.24	20.25
Session 2															
Total	23	0.49	0.22	12	0.58	0.17	11	0.39	0.23	10	0.46	0.24	13	0.50	0.21
High	23	0.13	0.12	12	0.14	0.12	11	0.12	0.12	10	0.17	0.16	13	0.10	0.05
Ratio	23	26.46	24.60	12	31.94	31.20	11	20.49	13.62	10	18.62	12.84	13	32.49	29.92
Session 3															
Total	21	0.48	0.25	12	0.46	0.22	9	0.51	0.29	7	0.62	0.19	14	0.41	0.25
High	21	0.17	0.23	12	0.19	0.27	9	0.16	0.18	7	0.26	0.27	14	0.13	0.21
Ratio	21	29.34	25.04	12	33.76	30.27	9	23.45	15.48	7	28.59	26.77	14	29.71	25.17
Session 4															
Total	25	0.47	0.28	14	0.48	0.33	11	0.46	0.21	11	0.38	0.20	14	0.54	0.31
High	25	0.16	0.20	14	0.15	0.20	11	0.19	0.21	11	0.09	0.11	14	0.22	0.24
Ratio	25	28.33	22.99	14	33.13	26.50	11	22.22	16.79	11	29.28	15.71	14	27.59	28.01
Session 5															
Total	18	0.47	0.26	9	0.45	0.14	9	0.49	0.35	6	0.35	0.17	12	0.55	0.29
High	18	0.23	0.40	9	0.19	0.13	9	0.26	0.57	6	0.10	0.08	12	0.29	0.48
Ratio	18	21.73	17.41	9	14.67	11.42	9	28.78	20.05	6	28.21	23.49	12	18.48	13.54
Session 6															
Total	20	0.42	0.26	11	0.40	0.28	9	0.44	0.24	6	0.35	0.22	14	0.45	0.27
High	20	0.11	0.12	11	0.09	0.12	9	0.13	0.12	6	0.05	0.04	14	0.13	0.13
Ratio	20	36.37	32.81	11	36.95	23.37	9	35.65	43.27	6	49.84	35.55	14	30.59	31.10
Session 7															
Total	17	0.50	0.41	9	0.61	0.33	8	0.38	0.48	7	0.36	0.32	10	0.61	0.45
High	17	0.29	0.35	9	0.34	0.31	8	0.23	0.40	7	0.16	0.22	10	0.38	0.40

		Overall			Group 1			Group 2			Male			Female		
		<i>N</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>
Measure		17	19.71	17.54	9	17.27	18.47	8	22.45	17.24	7	23.18	17.70	10	17.28	17.95
Ratio																

NOTE: Group 1 listened to a CD recording of a nursery rhyme recited by their mothers twice a day from 28 to 34 weeks postmenstrual age and Group 2 from 32 to 34 weeks. High = high-frequency tone; ratio = ratio of low-to-high frequency tone; total = total tone.

Table 3

Mixed General Linear Model Effects: High Frequency

Effect	Numerator <i>df</i>	Denominator <i>df</i>	<i>F</i>	<i>Pr</i> > <i>F</i>
Gender	1	27	1.68	.2060
Group	1	27	0.00	.9516
Gender × Group	1	27	2.62	.1171
Session	1	105	1.26	.2635
Session × Gender	1	105	4.85	.0298*
Session × Group	1	105	0.03	.8692

*
 $p < .05$.