Characteristics of Heart Period Variability in Intubated Very Low Birth Weight Infants with Respiratory Disease

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Abstract:

Background: Heart period variability provides a measure of balance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Since the PNS develops during the final weeks of gestation, premature infants have an overriding SNS. Spectral power analysis of heart period variability reveals two main frequency regions, the low frequency region (LF) representing primarily SNS activity and the high frequency region (HF) representing PNS activity.
Objectives: To identify the characteristics of heart period power in the LF and HF regions in very low birth weight (VLBW) infants in the neonatal intensive care unit across gestational age groups and between sleep and awake states.
Methods: Data were collected from 16 intubated and mechanically ventilated VLBW infants with respiratory disease. Using spectral analysis techniques, heart period power in the two main frequency regions was extracted.
Results: HF power did not improve with gestational age as expected. LF power did increase with age, albeit nonsignificantly. LF and HF power were not significantly different between awake and sleep states.
Conclusions: The results of this preliminary study suggest that PNS tone does not improve with gestational age in VLBW infants with respiratory disease. The intensive care environment may stimulate a sympathetic response in these infants and disrupt normal PNS development.
Key Words: Heart period variability • Very low birth weight infant • Low frequency power . High frequency power

Article:

INTRODUCTION

Environmental stressors that heighten sympathetic nervous system (SNS) activity present significant challenges to the health of premature intubated very low birth weight (VLBW) infants [1-3]. The negative effects of stress observed in these infants include temperature fluctuations, acute changes in heart and respiratory rates, hypoxemia, and increased metabolic rate [2, 4-6]. Physiological stability, as measured by the balance between the SNS and parasympathetic nervous system (PNS) branches of the autonomic nervous system (ANS), is paramount to the development and growth of the critically ill infant in the neonatal intensive care unit (NICU). Previous research has shown that premature infants possess an overriding SNS, and balance between the SNS and PNS varies with disease severity [7-11]. Increased SNS

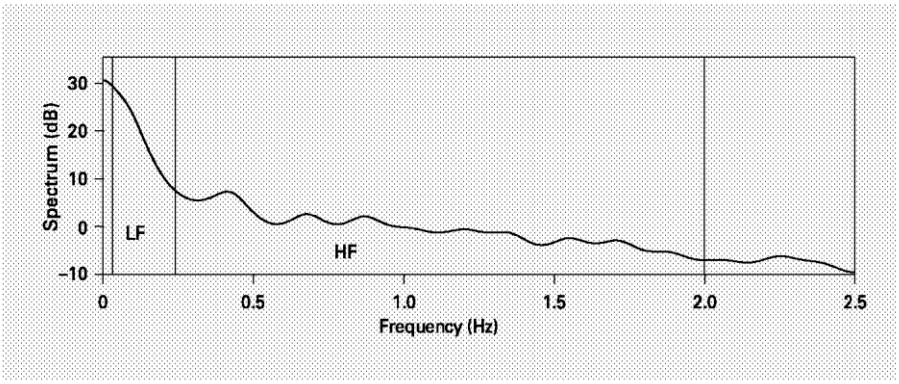

Fig. 1. Spectral density graph of baby 9 using AR(30) yule-walker. The low frequency (LF) region is from 0.02 up to 0.2 Hz and the high frequency (HF) region is from 0.2 to 2.0 Hz.

activity is indicative of a stress response whereas enhancement of the PNS promotes rest and restoration [8]. Therefore, promotion of PNS maturation would enhance recovery from illness and promote growth in these vulnerable infants [12]. The majority of studies to date have focused on the ANS response in healthy full-term and low birth weight preterm infants [7, 9, 13, 14]. There are few studies that attempt to quantify ANS balance in intubated VLBW infant [15].

Heart rate and the number of bradycardic events are gross measures of physiological stability, but lack the sensitivity to evaluate the underlying capacity for ANS adaptation. Heart period (inter-beat interval or R—R) variability (HPV) is a precise and sensitive measure of the balance between the SNS and PNS branches of the ANS and is useful for determining the infant's ability to adapt to external events, maintain homeostasis, and conserve energy which is necessary for growth and recovery from illness [12].

Power spectral analysis, a statistical technique that plots physiological rhythms of different frequencies characteristic of HPV, provides an appraisal of SNS/PNS balance [16]. Examination of heart period power reveals two main frequency regions of heart period activity (fig. 1). Low frequency (LF) heart period power represents SNS activity with some vagal influence, while high frequency (HF) heart period power represents PNS (vagal) activity [17, 18]. The ratio of LF:HF power reflects the balance between sympathetic and parasympathetic tone. The balance between the SNS and PNS via heart period power is a central physiologic measure for research concerning stress responses and growth promotion in this vulnerable population.

The relationship between the sleep state and HPV has not been well defined in the VLBW population. In studies involving full-term and healthy low birth weight infants, power in the HF region increased during quiet sleep while power in the LF region increased during active sleep [7, 10]. Clairambault et al. [7] also reported significant differences in the LF region between quiet and active sleep states. Power in the HF and LF region during sleep and awake states in the intubated VLBW infant has not been described in the literature.

In summary, analysis of the mean heart rate in critically ill, intubated VLBW infants may not be a sensitive enough measure of ANS balance for research or clinical purposes. In this study, the amount of power within the LF and HF regions are identified in intubated VLBW infants with

respiratory disease across a range of gestational ages and birth weights. The objectives of this study were to identify the characteristics of heart period power in the LF and HF regions in intubated VLBW infants in the incubator and to describe the effects of sleep on these parameters.

MATERIALS AND METHODS

Study Design

The parent study for this exploratory secondary analysis was an experimental, interrupted time series, crossover protocol comparing the effects of incubator care and maternal skin-to-skin holding. Although this particular analysis was not a component of the original study, National Institute of Health funding was obtained to retrospectively examine these aspects of the data (NHLBI R01 HL71920- 01). Further detail regarding design and data acquisition for the parent study has been described by Smith [19]. Heart period data acquired from October 1997 to December 1998 from the infants enrolled in the original protocol were used in this secondary analysis. The original and secondary analysis protocols were approved by the Institutional Review Board and informed consent was obtained from the infant's mothers.

Subjects

Heart period data from 16 intubated and mechanically ventilated VLBW infants were included in this secondary analysis. Due to significant differences in heart period during holding compared to post- holding ($F(1,13) = 11.15$, $p = 0.005$), only heart period indices acquired during incubator care were included in this analysis. Infants were included in the study if they were medically stable as defined by weaning or stable ventilator settings. Detailed exclusion criteria have been described by Smith [19].

Heart Period Power

Detailed procedures for heart period data acquisition in the parent study have been described elsewhere [19, 20]. After the heart period epochs during maternal holding were removed, a total of 645 heart period epochs were available from 16 infants. These data were submitted to power spectral analysis in the first phase of statistical analysis, as described in the statistical analysis section.

Power spectra, derived from heart period time series, are statistically useful in determining the balance between the SNS and PNS branches of the ANS. These power spectra have been divided into LF and HF regions of activity, each region being influenced by different physiological phenomenon [7-9, 18]. For the purposes of this study, the mutually exclusive LF and HF regions as defined by Chatow et al. [8] were used. The LF region ranges from 0.02 Hz up to, but not including 0.2 Hz.. The HF region begins at 0.2 Hz and ranges up to and including 2.0 Hz. Frequencies below 0.02 and above 2.0 Hz are generally considered to be artifact or noise. The mean heart period power in the LF and HF regions, and the ratio of LF to HF power were the variables of interest for this study.

The amount of power in the LF and HF regions is obtained from the power spectral densities by integrating the power within the LF and HF regions. In essence, power spectral density analysis provides an estimate of the variance within specific frequency regions (LF and HF) of the heart period data [21]. For the purposes of this research, natural power/variance units (ms2) will be used. Recall that the power value within each frequency region is specific to the sympathetic and

parasympathetic branches of the ANS so that the ratio of these values can be computed for each infant to determine SNS/PNS balance.

Sleep

Infant state was assessed using a modified Anderson Behavioral State Scoring System (ABSSS) during the acquisition of each HPV epoch [22]. Inter-rater reliability of the ABSSS was established among the research assistants prior to data collection (Kappa = 0.75). For the purposes of this research, the 12 behavioral states of the ABSSS were collapsed to asleep or awake states. Infants in this study were predominantly in an irregular sleep state described as irregular respirations with occasional small movements or jerking movements of the limbs. When infants were awake they had eyes open.

Statistical Analysis

Heart rate variability data were collected beyond the 256 s needed for analysis to allow for cleaning and deletion of aberrant data caused by signal interruption or electronic noise which was visually identified during data collection. Time series graphs for each raw heart period file were examined for aberrant R—R data points after data collection was complete as recommended by Kamath and Fallen [23]. The average amount of aberrant data in all files was 1.1%, well below the 20% threshold [24]. Heart period data from the

Table 1. Characteristics of 16 intubated and mechanically ventilated VLBW infants with chronic lung disease participating in the heart period variability study

Characteristic	Mean ± SD	Range
Birth weight, g	763.7 ± 160.7	600–1,121
Weight at study entry, g	983.8 ± 209.7	763–1,409
Gestational age at birth, weeks	25.8 ± 1.6	24–29
Gestational age at study entry, weeks	30.4 ± 1.5	28–34
Ventilator PIP	18.6 ± 2.5	15–25
Ventilator PEEP	5.4 ± 0.8	4–6.5
Ventilator rate	26.0 ± 7.0	17–42

PIP = Peak inspiratory pressure; PEEP = positive end expiratory pressure.

645 epochs were subsequently analyzed using SPLUS 6.0 for Windows (Insightful, Seattle, Wash., USA) and SAS 8.02 (SAS, Cary, N.C., USA). After data cleaning, power in the LF and HF regions was extracted using spectral analysis. Exploratory data analysis was used to examine the distribution of the LF and HF power regions. The tests for normality indicated that the distributions deviated significantly from normal, thus the recommendations of Hines and O'Hara-Hines [25] were employed to use power transformations. These transformations yielded distributions that were not significantly different from normal and could thus be analyzed using standard parametric analyses.

Measures of central tendency and dispersion were computed. Due to the differences in maturation across gestational ages, infants were further stratified into gestational age groups as follows: 28-29 weeks (n = 4); 30-31 weeks (n = 9), and 32-34 weeks (n = 3). Using a one-way analysis of variance, differences in LF, HF, and the ratio of LF:HF power among the gestational age groups were tested to explore whether PNS development in the critically ill VLBW infant follows expected patterns of maturation.

RESULTS

Sample Characteristics

All infants were orally intubated and receiving mechanical ventilation for lung disease of prematurity. Mean birth gestational age was 25.8 ± 1.6 weeks and mean corrected gestational age (CGA) at study entry was 30.4 ± 1.5) (range 28-34) weeks. General sample characteristics are presented in table 1.

LF Power, HF Power, and LF:HF Ratio

LF power, HF power, and the LF:HF power ratio were calculated for all infants and for each gestational age group. The mean LF power was 57.80 ± 86.30 ms², the

Table 2. Heart period power in the low and high frequency regions and the low to high frequency ratio during sleep amd awake stated in 16 VLBW infants

Group/state[a]	Low frequency[b]	High frequency[b]	Low to high frequency ratio
28–29 weeks (n = 4)			
Sleeping	41.24 ± 23.19	5.96 ± 2.53	6.03 ± 1.65
Awake	85.11 ± 113.95	6.34 ± 3.40	11.36 ± 13.15
30–31 weeks (n = 9)			
Sleeping	51.98 ± 33.00	5.63 ± 1.50	7.57 ± 2.78
Awake	85.56 ± 52.38	7.01 ± 1.86	10.08 ± 4.41
32–34 weeks (n = 3)			
Sleeping	69.02 ± 33.02	7.67 ± 1.79	7.02 ± 2.78
Awake	154.54 ± 168.36	14.56 ± 12.05	9.11 ± 4.37

All values reported are the mean ± standard deviation.

[a] Groups were based upon corrected gestational age. State is awake or sleeping.

[b] Power in ms².

mean HF power was 6.14 ± 4.64 ms² and the mean LF:HF ratio was 7.77 ± 6.10. No significant differences in LF power ($F(^2, 13) = 1.09$, $p = 0.36$), and ratio of LF:HF power ($F(^2, 13) = 0.43$, $p = 0.66$) were found among the gestational age groups. A significant difference was found in the HF power ($F(^2, 13) = 3.75$, $p = 0.05$) among the gestational age groups. Tukey-Kramer post hoc analysis for HF power revealed no significant pair-wise differences among the 3 gestational age groups. However the 32- to 34-week infants had a somewhat higher mean HF power of 11.12 ms² when compared to a mean HF power of 6.32 ms² for the 30- to 31-week infants and 6.15 ms² for the 28- to 29-week infants ($p = 0.06$).

LF power, the indicator of SNS tone, had a wide variability among all 3 gestational age groups. The LF power ranged from 23.39 ± 24.93 to 65.42 ± 56.95 ms² in the 28- to 29-week gestation

infants, from 22.39 ± 30.28 to 100.12 ± 98.60 ms² in the 30- to 31-week gestation infants, and from 36.70 ± 45.36 to 121.85 ± 148.93 ms² in the 32- to 24-week gestation infants.

HF power, the indicator of PNS tone, was also variable among the gestational age groups. The HF power ranged from 4.26 ± 3.04 to 7.19 ± 4.59 ms² in the 28- to 29- week gestation infants, from 3.94 ± 2.11 to 7.84 ± 6.40 ms² in the 30- to 31-week gestation infants, and from 5.66 ± 4.13 to 10.66 ± 9.06 ms² in the 32- to 34-week gestation infants.

Sleep

Infant state was visually scored with each HPV epoch as asleep or awake. Infants were asleep 79% of the time. There were no significant differences in LF, HF, or LF:HF power ratio between awake and asleep states. The mean LF power was 52.49 ± 30.37 ms² during sleep and 98.38 ± 92.82 ms² during the awake state. The mean HF power was 6.09 ± 1.88 ms² during sleep and 8.26 ± 5.78 ms² during the awake state. The mean LF:HF power ratio was 7.08 ± 2.48 ms² during sleep and 10.22 ± 6.94 ms² during the awake state.

Due to gestational age differences LF, HF, and LF:HF ratio by sleep state were computed for each gestational age group. As seen in table 2, the mean LF power is higher during the awake state than during the sleep state for the infants at 30-31 and 32-34 weeks of gestation which is expected as sympathetic tone would be anticipated to be higher during the awake states. Interestingly, the LF power in the 28- to 29-week gestation infants was higher during sleep than during awake periods suggesting an overriding SNS in these younger infants. HF power for these infants was similar during awake and sleep states. The 32- to 34-week gestation infants had higher HF power during sleep and awake states compared to the 28- to 29- and 30- to 31-week gestation infants. Again, this suggests that parasympathetic tone is increasing as the infants increase in age.

DISCUSSION

LF and HF region power represents an estimate of the variance in each of these regions. An examination of power isolates the effects of SNS and PNS activity on heart rate variability. A demonstration of PNS maturation in older infants, represented by an increase in HF power, was expected. Although HF power was significantly different among the 3 gestational age groups, post hoc analysis revealed a nonsignificant increase in HF power despite the noted increase in HF power in the 32- to 34- week gestation infants. These results may be due to the small sample size in each gestational age group. A decrease in the ratio of LF:HF power would have represented improvement in the balance between the two branches of the ANS. In this sample, this ratio was relatively constant. Does PNS maturation for the VLBW preterm infant naturally plateau at this early age or do environmental stressors hamper PNS development? The primary reason for the lack of improvement in this ratio with chronologic maturation was that LF power increased more dramatically than HF power, as did its variability. Does the NICU environment with the many medical and nursing disruptions influence the development of the ANS? Is the maturation of the PNS delayed or some how disrupted by the intensive care environment such that the SNS is constantly on alert? A larger sample may be able provide more definitive analysis of ANS maturation and the effects of care in the NICU environment on ANS maturation.

Wide variation in the amount of power in the LF region (>_0.02 to <0.2 Hz) and the HF region (0.2 to 2.0 Hz) used in this study suggests inter-individual differences that may be due to a number of factors. The use of sedation may have an effect on the ANS which may be reflected in the LF and HF power; however, this has not been investigated. Methylxanthines may also influence heart period power. Kibblewhite and Sleigh [26] reported a significant increase in HF power after methylxanthine dosing, particularly in infants with a higher severity of illness. We did not test for this effect, however 12 of the 16 infants in this study were receiving either caffeine (n = 1), theophylline (n = 8), or albuterol nebulizer treatments (n = 9). All of the infants that received theophylline were also receiving the albuterol nebulizer treatments. Two of the 4 infants who did not receive methylxanthine therapy had higher HF power than the other infants, which may suggest improved PNS tone. However, a larger number of infants who have not received methylxanthines is necessary to properly test this speculation.

Sleep is a time of rest and restoration and improved parasympathetic tone was anticipated, however these data do not support this hypothesis. This study suggests that the more premature infants do have an overriding SNS as reported elsewhere and that PNS tone is not enhanced during sleep as expected [7]. These results are limited by the manner with which sleep was measured. A more precise measure of sleep, such as EEG would strengthen the analysis and provide a measure that could be used to correlate sleep state with LF and HF power.

This secondary analysis of heart period data from a small homogeneous group of intubated VLBW infants is a first step in establishing characteristic heart period power values. Although establishment of normative values is difficult in a critically ill population due to physiologic instability, VLBW infants often share common problems such as chronic lung disease, metabolic disturbances, and cardiovascular complications. A large sample, with adequate representation from the continuum of gestational ages and disease severity, could provide clinicians and researchers with comparative data. Data from this study could be used to estimate sample sizes necessary for future research in this area.

Limitations

This study is the first step in identifying characteristic values in HP power in intubated VLBW infants, but is limited by several factors. First, the small sample size does not allow adequate statistical power for definitive testing of gestational age differences. However, these findings are useful in establishing a model for research with a larger sample of intubated VLBW infants. Second, the meaning of these heart period values is unknown with regard to infant stability and response to stressors. Future work will need to incorporate measures of heart period power during sleep and during nursing/medical interventions. A longitudinal study would also strengthen these results as maturation may not become evident until after the infant is discharged from the NICU. Third, there are many measures of LF and HF power including ms^2, dB, and others as reported by Porges [12]. This lack of standardization leads to difficulty in comparing results across studies and in applying these results to the clinical setting.

In conclusion, HPV data, in the form of LF and HF heart period power, may be useful to neonatal clinicians interested in the balance between the SNS and PNS. More data from a larger sample of intubated VLBW infants is needed to provide an accurate estimate of normative characteristics for heart period power. Reference data will also be helpful to researchers

investigating interventions to minimize stress and promote healthy growth in this vulnerable infant population.

REFERENCES

1 Gorski PA, Hole WT, Leonard CL, Martin JA: Direct computer recording of premature infants and nursery care: Distress following two interventions. Pediatrics 1983;72:198-202.

2 Mok Q, Bass CA, Ducher DA, McIntosh N: Temperature instability during nursing procedures in preterm neonates. Arch Dis Child 1991;66:783-786.

3 Peters K: Bathing premature infants: Physiological and behavioral consequences. Am J Crit Care 1998;7:90-100.

4 Billeaud C, Piedboeuf B, Chessex P: Energy expenditure and severity of respiratory disease in very-low-birthweight infants receiving longterm ventilatory support. J Pediatr 1992;120: 461-464.

5 Peters K: Does routine nursing care complicate the physiologic status of the premature neonate with respiratory distress syndrome? J Perinat Neonatal Nurs 1992;6:67-84.

6 Zahr LK, Balian S: Responses of premature infants to routine nursing interventions and noise in the NICU. Nurs Res 1995;44:179185.

7 Clairambault J, Curzi-Dascalova L, Kauffmann F, Médigue C, Leffler C: Heart rate variability in normal sleeping full-term and preterm neonates. Early Hum Dev 1992;28:169183.

8 Chatow U, Davidson S, Reichman BL, Akselrod S: Development and maturation of the autonomic nervous system in premature and full-term infants using spectral analysis of heart rate fluctuations. Pediatr Res 1995;37:294302.

9 Cabal LA, Siassi B, Zanini B, Hodgman JE, Hon E: Factors affecting heart rate variability in preterm infants. Pediatrics 1980;65:50-56.

10 Sahni R, Schulze KF, Kashyap S, Ohira-Kist K: Maturational changes in heart rate and heart rate variability in low birth weight infants. Dev Psychobiol 2000;37:73-81.

11 Fox NA: Maturation of autonomic control in preterm infants. Dev Psychbiol 1983;16:495504.

12 Porges SW: Cardiac vagal tone: A physiologic index of stress. Neurosci Biobehav Rev 1995; 19:225-233.

13 Massin MM, Withofs N, Maeyns K, Ravet F: The influence of fetal and postnatal growth on heart rate variability in young infants. Cardio- ¯logy 2001;95:80-83.

14 Veerappan S, Harel R, Craelius W, Curcie D, Hiatt M, Hegyi T: Spectral analysis of heart rate variability in premature infants with feeding bradycardia. Pediatr Res 2000;47:659662.

15 Jenkins JG, Reid MM, McClure BG: Study of heart rate variability in sick newborn infants. Acta Paediatr Scand 1980;69:393-396.

16 Burr RL, Cowan MJ: Autoregressive spectral models of heart rate variability. J Electrocardiol 1992;25(suppl):224-233.

17 Kamath MV, Fallen EL: Power spectral analysis of HRV: A noninvasive signature of cardiac autonomic functions. Crit Rev Biomed Eng 1993;21:245-311.

18 Giddens DP, Kitney RI: Neonatal heart rate variability and its relation to respiration. J The- or Biol 1985;113:759-780.

19 Smith SL: Physiologic stability of intubated VLBW infants during skin-to-skin care and incubator care. Adv Neonatal Care 2001;1:2848.

20 Smith SL: Heart period variability of intubated very-low-birth-weight infants during incubator care and maternal holding. Am J Crit Care 2003;12:54-64.

21 Warner RM: Spectral Analysis of Time Series Data. New York, Guilford Press, 1998.

22 Gill NE, Behnke M, Conlon M, McNeely JB, Anderson GC: Effect of nonnutritive sucking on behavioral state in preterm infants before feeding. Nurs Res 1988;37:347-350.
23 Kamath MV, Fallen EL: Correction of the heart rate variability signal for ectopics and missing beats; in Malik M, Camm AJ (eds): Heart Rate Variability. Armonk, Futura, 1995, pp 75-85.
24 Kleiger RE, Miller JP, Bigger JT, Moss AJ, Multicenter Post-Infarction Research Group: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256262.
25 Hines WGS, O'Hara-Hines RJ: Quick graphical power-law transformations. Am Statist 1987;41:21-24.
26 Kibblewhite DP, Sleigh JW: Heart rate variability in premature neonates pre- and post-methylxanthine administration. Paediatr Anesth 1996;6:399-403.