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Heart rate variability as a feeding intervention outcome measure in the preterm infant

Britt F. Pados, PhD, RN, NNP-BC [Assistant Professor],

School of Nursing, Boston College, Chestnut Hill, MA

Suzanne M. Thoyre, PhD, RN, FAAN,

Francis Hill Fox Distinguished Term Professor, School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC

George J. Knafl, PhD [Professor], and

School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC

W. Brant Nix, BMET, BA

Medical Laboratory Technologist & Lab Manager, Biobehavioral Laboratory, School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Background—Feeding interventions for preterm infants aim to reduce the physiologic stress of feeding to promote growth. Heart rate variability (HRV) is a potential non-invasive measure of physiologic stress that may be useful for evaluating efficacy of feeding interventions.

Purpose—To evaluate whether HRV is a sensitive measure of physiologic stress compared to standard physiologic outcomes in the context of a feeding intervention study.

Methods—This was secondary analysis of a within-subjects, cross-over design study comparing usual care feeding to a gentle, co-regulated feeding approach (CoReg) in 14 infants born < 35 weeks post-menstrual age. HRV indices were calculated from electrocardiogram data and compared to standard physiologic outcomes, including oxygen saturation (SpO₂), respiratory rate (RR), apnea, heart rate (HR), and bradycardia. Data were analyzed using linear mixed modeling.

Results—Infants fed using the CoReg approach had fewer apneic events and higher RR, suggesting they were able to breathe more during feeding. No statistically significant differences were found in SpO₂, HR, bradycardia, or high frequency power (the most commonly-reported measure of HRV). Infants fed using the usual care approach had significantly higher SD12, a measure of HRV indicating randomness in the HR, which is a potential indicator of elevated stress.

Contact information for Corresponding Author: Britt F. Pados, Boston College, William F. Connell School of Nursing, Maloney Hall, 140 Commonwealth Ave., Chestnut Hill, MA 02467, britt.frisk.1@bc.edu.

Institution where the work occurred: University of North Carolina at Chapel Hill, School of Nursing, Chapel Hill, NC, United States of America

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Implications for Practice—SD12 was more sensitive to stress than SpO₂, HR, and bradycardia. The utility of HRV as a measure of feeding outcomes in clinical practice needs further exploration.

Implications for Research—Further exploration of HRV as an intervention outcome measure is needed, particularly evaluating non-linear indices, such as SD12.

Keywords

Feeding Methods; Bottle Feeding; Preterm Infant; Autonomic Nervous System; Physiological Stress; Heart Rate Variability

Feeding is a physiologically challenging event for the preterm infant. Research on the physiologic effect of feeding interventions typically report the following physiologic measures: heart rate (HR), respiratory rate (RR), and oxygen saturation measured by pulse oximetry (SpO₂).^{1–3} These measures are non-invasive and provide important information about the infant's physiologic response to the work of feeding.^{1–3} While these measures are generally accepted, they may not be the most sensitive measures, or alterations in their values may be late indicators of distress. Heart rate variability (HRV) is an additional non-invasive measure that can be used to evaluate the adaptability of the autonomic nervous system to respond to the physiologic stress of feeding. Feeding has been shown to produce changes in HRV.^{4–6} It is theorized that HRV may be a more sensitive measure of physiologic stress or provide important information about infant response to feeding in addition to these traditional measures. It remains unknown whether HRV is a useful outcome measure of physiologic stress in intervention studies where the intervention aims to change the level of stress experienced by the infant.

Heart Rate Variability

HRV is the rhythmic variation in HR that results from the dynamic influences of the autonomic nervous system.⁷ Key terms and definitions related to HRV are provided in Table 1. Contraction of the heart is initiated by an electrical impulse in the sinoatrial node located in the right atrium.⁸ The sinoatrial node is innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system via the vagus nerve.⁹ The sympathetic and parasympathetic divisions have opposing effects on the HR. Sympathetic input results in release of noradrenaline, which increases HR, while parasympathetic input results in release of acetylcholine, which slows HR.⁹ The interaction of sympathetic and parasympathetic input is determined by the autonomic nervous system to maintain physiologic homeostasis in response to internal and external demands.⁹

The variation that occurs in HR to produce HRV results from the complex interaction of sympathetic and parasympathetic input and is measured by variations in the time period between normal heartbeat complexes, specifically R waves (Figure 1).⁷ The variation in intervals between R waves (R to R interval) has a cyclical pattern with some cyclical changes occurring infrequently or at low frequencies (LF) and some occurring frequently or at high frequencies (HF).

Since there are connections within the vagus nerve between the heart and other physiologic systems, input from the sympathetic nervous system and parasympathetic nervous system is mediated by other cyclical rhythms in the body. Fluctuations in blood pressure and thermoregulation contribute to LF rhythms in HRV.⁹ Rhythmic alterations in HR that coincide with respiration contribute to HF rhythms in HRV.⁹ It is generally accepted that HF components of HRV may be interpreted as a measure of parasympathetic nervous system influences.¹⁰ The interpretation of the LF component remains controversial;¹⁰ it is likely a result of mixed effects of the parasympathetic and sympathetic nervous systems and its significance remains to be determined.¹¹

The HF rhythm associated with respiration, whereby the HR accelerates during inspiration and decelerates during expiration, is often referred to as respiratory sinus arrhythmia.¹² The frequency range of HRV that respiratory sinus arrhythmia occupies is dependent on the RR of the individual. In human neonates, the RR ranges generally from 20 to 80 breaths per minute. Frequency is measured in Hertz (Hz) as the number of cycles per second. Therefore, a RR of 20 to 80 breaths per minute is equal to a frequency range of 0.3–1.33 Hz (i.e., breaths per second).¹³

There are several methods of HRV analysis, including time domain, frequency domain, and non-linear analyses. Time domain methods are preferred for long-term studies of HRV (e.g., 24 hours), while frequency domain methods are preferred for short-term evaluation of HRV (e.g., less than 5 minutes), such as used in this study.¹⁰ Frequency domain measures of HRV include LF Power (ms^2), HF Power (ms^2), and LF/HF ratio. As mentioned previously, the appropriate interpretation of LF is yet to be determined, and therefore LF Power and LF/HF ratio are not interpretable measures of HRV at this time. When evaluating frequency domain HRV indices, it is necessary to compare epochs (i.e., samples of data) of the same length because epoch length affects the accuracy with which the frequency components are estimated.¹⁰

Non-linear analysis of HRV is a relatively new technique, which is in the early stages of development, but may contribute to the interpretation of frequency and time domain analysis by distinguishing between sinus arrhythmia of respiratory and non-respiratory origin.¹⁴ One method of non-linear analysis is the creation of a Poincaré plot (or recurrence map) (Figure 2), where the interval between a pair of heart beats (e.g., R wave 1 and R wave 2) is plotted against the interval between the next two heart beats (e.g., R wave 2 and R wave 3).¹⁵ Poincaré plots may be qualitatively analyzed for the shape and dispersion of the intervals or quantitatively analyzed for the degree of randomness in the heart rate pattern.¹⁵ Quantitatively, the index SD12 provides information about the shape of the Poincaré plot by giving the ratio of the length of the transverse axis (SD1) and longitudinal axis (SD2) of the ellipse.¹⁵ SD1 is an indicator of short-term variability of the HR and SD2 is an indicator of intermediate-term variability of the HR.¹⁵ Low SD12 indicates high correlation between interbeat intervals while high SD12 indicates low correlation or increased randomness in interbeat intervals (Figure 3). SD12 has been found to be a strong non-linear predictor of mortality in patients with cardiovascular disease by identifying patients with increased randomness in the heart rate from non-respiratory sinus arrhythmia in 24 hour monitoring (i.e., high SD12).^{15,16}

Theoretical Framework

Polyvagal Theory¹⁷ was used in this study to guide selection of outcome measures and conceptualize the infant response to the challenge of feeding as a function of the two pathways of the vagus nerve: the myelinated nucleus ambiguus and the unmyelinated dorsal motor nucleus (Figure 4). Polyvagal Theory suggests when feeding is associated with low stress, there is primarily input from the highly-evolved nucleus ambiguus, which results in conservation of metabolic resources for growth and restoration, as evidenced by low HR and high HF HRV; increased tone of the structures of the face and ears for social interaction; and increased tone of the pharyngeal and laryngeal muscles for coordination of sucking, swallowing, and breathing during feeding.^{18,19} Improved coordination of sucking, swallowing, and breathing may allow the infant to maintain SpO₂ and RR closer to that during non-feeding times. At the same time, minimal input from the dorsal motor nucleus during times of low stress encourages digestion and absorption of nutrients from the gastrointestinal tract.²⁰

Alternatively, if feeding is highly stressful, there is withdrawal of input from the nucleus ambiguus and up-regulation of the sympathetic nervous system, which responds by increasing HR, decreasing HF HRV, activating the stress response system of the hypothalamic pituitary axis (e.g., release of cortisol), stimulating the immune system (e.g., release of cytokines), and diverting blood away from the gastrointestinal tract to the more vital organs such as the heart, brain, and lungs.^{21,22} If these responses still do not meet the demands of the feeding and the level of stress is perceived as being life-threatening, the dorsal motor nucleus is activated to conserve resources resulting in disengagement, hypotonia, apnea, and bradycardia.¹⁸ Bradycardic events resulting from this dorsal motor nucleus response result in sinus arrhythmia of non-respiratory origin, and may therefore result in increased SD12.

Feeding and Heart Rate Variability

Eleven published studies have measured HRV during active oral feeding of infants.^{4–6,23–30} The majority of these have been descriptive studies of the changes that occur in HRV measures as infants develop over time^{4,24–26,29} or how birth characteristics, such as birth weight, gestational age, or congenital heart disease, affect HRV responses to feeding.^{23–25,28,30} Consistent with Polyvagal Theory, Portales,²⁷ McCain,⁶ and Suess²⁸ all found that HF HRV decreased during feeding.

The only feeding intervention study that measured HRV as an intervention outcome was McCain's⁵ study of a semi-demand protocol for healthy preterm infants, which included a protocol that used infant cues to discontinue feeding and did not "encourage" the infant to consume the prescribed volume of feeding. Theoretically, this protocol could decrease the amount of physiologic stress experienced by the infant by not pushing the infant to continue feeding beyond the point they become fatigued or stressed. This study found that during feeding, the experimental group had higher HF power, suggesting lower physiologic stress.⁵ The experimental and usual care groups were similar in terms of mean HR and feeding bradycardia episodes, suggesting that these outcome measures may be less sensitive than

HRV.⁵ The research done to date utilizing HRV during feeding has been supportive of the theoretical changes that occur within the autonomic nervous system during a physiologic challenge such as oral feeding and supports the use of this measure during feeding. None of the studies mentioned have explored the use of nonlinear HRV indices, such as SD12, during feeding.

Purpose

The purpose of this study was to evaluate whether HRV is a sensitive measure of physiologic stress compared to standard physiologic outcomes in the context of a feeding intervention study that was expected to reduce the physiologic stress of feeding. The specific aims of this study were to 1) determine whether infants fed with a usual care approach were fed in a significantly different manner than those fed using a gentle, co-regulated approach (CoReg) so that physiologic stress would be expected to be different, 2) evaluate the effect of the feeding intervention on standard physiologic outcomes, and 3) evaluate the effect of the feeding intervention on linear and non-linear HRV outcomes, specifically HF HRV and SD12.

Methods

Setting and Sample

This secondary analysis of de-identified data was deemed exempt by the Institutional Review Board. The setting of the original data collection was a Level III Neonatal Intensive Care Unit in North Carolina. The original sample was 20 preterm infants who were born at less than 35 weeks gestation weighing less than 1500 grams. At the time of the original study, they were less than or equal to 37 weeks post-menstrual age (PMA) and had been orally feeding at least once per day for 3 consecutive days.³ Infants may have been receiving supplemental oxygen. Infants were excluded from the study if they had a history of Grade IV intraventricular hemorrhage (IVH), congenital disorders that may have interfered with sucking (e.g., cleft palate, Down Syndrome, congenital hydrocephalus, or microcephaly), symptoms from substance exposure, or a mother less than 15 years of age. Infant feeding data were excluded from this secondary analysis if active feeding episodes with the bottle in the infant's mouth were $\leq$ 2 minutes, if the HR data were of poor quality and not analyzable for HRV, or if the infant had frequent ectopic beats (e.g., premature ventricular contractions).

Procedure

The data collection procedures that are described refer to the procedures carried out in the original study.³ The HRV analysis methods describe the procedures carried out in this secondary analysis. The original study was a within-subjects, cross-over design study of a gentle, co-regulated approach (CoReg) to feeding preterm infants. CoReg feedings were provided by a trained research team member and included a head elevated, side-lying position; minimal oral and tactile stimulation; and enhanced auditory assessment of sucking, swallowing, and breathing with the use of a microphone placed on the infant's neck to allow for feeder co-regulation of swallowing and breathing. Additional information about the CoReg protocol is available elsewhere.³ The CoReg approach was compared to usual care

feeding by the infant's nurse who was unaware of the intervention protocol. Infants were studied during two feedings per day for two days (one CoReg and one usual care feeding each day). The order of the conditions was randomized without replacement.

Feedings were video recorded and The Observer XT (Noldus Information Technology, Asheville, NC) was used to code the videos for the following feeder actions: positioning of the infant (side-lying or other), number of times the feeder stimulated the infant to suck, number of times the feeder gave the infant a pause by tipping the bottle back or stopping milk flow, and number of times the feeder gave the infant a rest period by removing the nipple. Positioning of the infant was calculated as the percent of the feeding the infant was in side-lying. A co-regulation score was created and defined as the number of times the feeder provided a rest period for the infant plus the number of times the feeder cued the infant to pause feeding by tipping the bottle back or stopping milk flow. To account for differences in the length of feedings, frequency of feeder action events were divided by the number of minutes the bottle was in the infant's mouth. The observational data was used to evaluate fidelity to the CoReg protocol and to describe the feeding method used during usual care in order to determine whether the feeding methods were in fact different and whether physiologic stress should be expected to be different.

In order to compare HRV outcomes to traditional physiologic outcomes used in evaluating feeding interventions, the following measures were assessed during feeding: mean SpO₂, mean RR, number of apneic events, HR, and number of seconds of bradycardia. These measures were chosen based on the expected infant responses to the challenge of feeding as described by Polyvagal Theory.^{17,19}

Two methods were used to assess respiratory function during feeding. SpO₂ was collected using a pulse oximeter (Ohmeda, Boulder, CO) placed on the infant's foot. SpO₂ data was sampled using a 2 second averaging window and cleaned of artifact. Mean SpO₂ during feeding was calculated. Respiration data were collected using respiratory inductance plethysmography bands placed around the infant's chest and abdomen (Respirace, Ambulatory Monitoring Ind., Ardsley, NY). Electrocardiogram (ECG) data were collected from a three-lead ECG monitor (Gould Electronics, Valley View, Ohio). Physiologic data (SpO₂, RR, and HR) were collected at a sampling rate of 1,000 samples per second, digitized by an A-D converter, and stored on a computer using Windaq Data Acquisition software (Dataq Instruments Inc., Akron, OH).

Respiratory waveform data were imported into Windaq Waveform Browser (Dataq Instruments Inc., Akron, OH), marked using an algorithm within the program, and confirmed for accuracy by the investigators. Respiratory waveform data were used to calculate mean RR and number of episodes of apnea (defined as absence of breath for more than 4 seconds [sec]).³¹ Number of episodes of apnea were divided by the total length of feeding to account for variation in length of feedings.

Digitized ECG data were imported into MindWare HRV (MindWare Technologies LTD, Gahanna, OH) for review and analysis. MindWare HRV uses an algorithm to mark each R wave peak of the QRS heartbeat complex and to calculate the interbeat interval. Artifact is

identified by interbeat interval that is inconsistent with those intervals before and after. The investigator manually reviewed the data to confirm accuracy of the R wave peak detection. ECG data were used to calculate HR (in beats per minute [bpm]) and number of seconds of bradycardia (defined as HR < 100 bpm).³² Mean HR was calculated for each two-minute bottle-in period. ECG data were also used for HRV analyses.

Frequency domain analysis of HRV was performed using two-minute epochs of artifact-free data to calculate HF power (in ms²). Power spectral analysis with Hamming windowing function was executed with the frequency bandwidths set for HF: 0.3–1.33 Hz. Two minutes was chosen as the epoch for comparison because this is the minimum acceptable epoch length for frequency domain measurement^{10,33} and it is a reasonable amount of time to expect vulnerable preterm infants to be able to feed without having the bottle removed from the mouth. Only data collected when the bottle was in the infant's mouth were analyzed. In some cases, the infant required prolonged breaks with the bottle out of the mouth. Since this study aimed to evaluate HRV during feeding, only data during active feeding were analyzed. Data for active feeding periods that were not two minutes in length were excluded.

Non-linear analysis of HRV was conducted by combining all two-minute epochs of artifact-free data during each feeding. Kubios HRV version 2.0 (Kuopio, Finland) was used to create a single Poincaré plot for each feeding and to calculate SD12.

Sample

The sample included fourteen infants and 34 feedings. Of the 75 original feedings, 22 were excluded because the data were collected at a sampling rate of only 50 samples per second, which is not sufficient for HRV analysis; 14 were excluded because there were no active feeding periods of at least 2 minutes; 21 were excluded because of poor ECG data or no artifact-free segments of active oral feeding; and 4 (all from the same infant) were excluded because of abnormal cardiac rhythm, specifically frequent premature ventricular contractions. All 14 infants included in the study had a usual care feeding that was included in the analysis. Ten of the infants had at least one of each feeding type that was analyzed.

Statistical Analysis

Linear mixed modeling was used to analyze these repeated-measures data for effects of feeding method (Usual care vs. CoReg) using appropriate covariance structures to account for correlation between feedings within the same infant and within the same feeding over time, as well as variances possibly changing over time. The order effect of feeding method and the effect of baseline physiologic data was tested and included in the model, when appropriate. Frequency domain measures of HRV have been found to have skewed distributions.⁷ These data were assessed for skewness and transformed, if needed. An alpha of 0.05 was used for all tests of statistical significance.

Results

There were 22 usual care feedings and 12 CoReg feedings analyzed. Table 2 provides information about the demographic and clinical data of the infants and feedings included in the study. The sample of infants that had a usual care feeding analyzed ($n=14$) was similar to

the sample of infants that had an intervention feeding analyzed ($n=10$) in terms of birth weight (996 vs. 992 grams), PMA (28.6 vs. 28.8 weeks), and chronic lung disease (79% vs. 80%). The sample of feedings that were included for usual care ($n=22$) and CoReg ($n=12$) were also similar in terms of the age of the infant at the time of the feeding (36.4 vs. 36.9 weeks), oxygen use on the day of the study (64% vs. 67%), and number of days of feeding experience the infant had at the time of the study feeding (13 vs. 13).

Feeder Actions

As expected, the CoReg and usual care feedings were significantly different from one another in terms of feeder actions (Table 3). Taking into account correlation between feedings of the same infant, CoReg feedings were performed with the infant in a side-lying position significantly more than usual care feedings ($F_{1,9}=117$, $p<.01$) and the feeder stimulated the infant to suck significantly less during CoReg feedings ($F_{1,9}=6.8$, $p=.03$). The CoReg and usual care feedings were not significantly different in terms of the co-regulation score ($F_{1,9}=.07$, $p=.80$).

Standard physiologic measures

Accounting for order of study feedings and correlation within feedings of the same infant, there were no significant differences between the two feeding methods for mean SpO₂ ($F_{1,17}=1.35$, $p=.26$) or number of seconds of bradycardia during feeding ($F_{1,16}=2.91$, $p=.11$) (Table 4). Baseline SpO₂ was used as a covariate in the analysis to evaluate mean SpO₂ during feeding. There was also no difference between the groups for HR during feeding ($F_{1,9}=.84$, $p=.38$), accounting for order of feedings and correlation between feedings of the same infant and between measurements within the same feeding.

Infants fed using the CoReg method had significantly fewer feeding-related apneas ($F_{1,9}=5.92$, $p=.04$). This analysis also took into account order of study feedings and correlation within feedings of the same infant. Infants fed using the CoReg method also had significantly higher RR during feeding than infants fed using usual care ($F_{1,18}=5.33$, $p=.03$), accounting for baseline RR, correlation within feedings of the same infant, and order of study feedings.

Heart rate variability measures

Taking into account correlations between feedings of the same infant and between measurements within the same feeding, as well as taking into account the order of study feedings, there was no statistically significant difference in HF Power (ms²) ($F_{1,22}=1.30$, $p=.26$) between feeding methods (Table 4). Infants fed with the usual care technique had a significantly higher SD12 than infants fed with the CoReg approach ($F_{1,9}=5.70$, $p=.04$).

Discussion

Feeding is a physiologically-challenging event for many preterm infants as they attempt to coordinate sucking, swallowing, and breathing. Feeding interventions aim to reduce the stress of feeding for these fragile infants in order to promote growth and facilitate development of feeding skills for discharge home. Polyvagal Theory¹⁷ provides a theoretical

framework to understand the degree of stress perceived by the infant and resultant changes in physiology and behavior, based on dominant nervous system activity (Figure 4). HRV is a non-invasive measure that provides insight into the infant's response to the stress of feeding and may be more sensitive than standard physiologic measures (e.g., HR and SpO₂).

This study was the first to compare standard physiologic measures to linear and non-linear indices of HRV in the context of a feeding intervention study to measure the degree of physiologic stress experienced by the infant. A gentle, co-regulated approach to feeding involving side-lying positioning, decreased stimulation, and enhancement of auditory assessment of sucking, swallowing, and breathing was found to significantly reduce the number of apneic events during feeding and to allow the infants to breathe more during feeding, as evidenced by higher RR. The results of the standard physiologic measures suggested that the intervention feeding method reduced the physiologic stress of feeding somewhat for this group of preterm infants, however there was no significant difference in SpO₂, bradycardia, or HR. No significant difference was found between the feeding methods for HF HRV, suggesting that feeding remained highly stressful for these fragile infants even when fed with a gentle, co-regulated approach.

The non-linear HRV index of SD12 was the only HRV measure that revealed a significant difference between the feeding methods and was more sensitive to feeding stress than the standard physiologic measures of SpO₂ and HR. Infants fed with the usual care technique were found to have significantly higher SD12 than infants fed with the CoReg technique. Increased SD12 indicates increased randomness of the heart rate, or sinus arrhythmia of non-respiratory origin as opposed to respiratory sinus arrhythmia (RSA).^{14,15} Frequency domain analyses, which are used to calculate HF HRV, are unable to differentiate variability in the heart rate from these two sources, which is important because increased variability from respiratory origin is considered an indicator of lower risk, while increased variability from non-respiratory origin is an indicator of higher risk.¹⁴

Higher SD12 in the infants fed with the usual care technique suggests that those infants experienced more stress during feeding than infants fed with the CoReg technique, but the interpretation of this finding is limited by relatively little data on SD12 in neonates. It is speculated that transient decreases in the heart rate from baseline, such a change in heart rate from 160 beats per minute to 110 beats per minute lasting less than 10 seconds, may have contributed to the elevation in SD12 in the usual care group. A change in heart rate like this would not have met criteria for a bradycardic event, which was defined in this study as heart rate less than 100 beats per minute, but these transient changes in heart rate may reflect dorsal motor nucleus activity and may be significant in our understanding of infant stress during feeding. Although bradycardia is a key indicator of dorsal motor nucleus activity in Polyvagal Theory, the definition of neonatal bradycardia for this purpose is unclear. The significance of these transient changes in heart rate from baseline needs further exploration. In the context of this feeding intervention study, SD12 was more sensitive to the physiologic stress of feeding in the preterm infant than HF HRV and was more sensitive than the standard physiologic measures of SpO₂, HR, and bradycardia.

Limitations

The sample size for this secondary analysis was small because only artifact-free data could be used. This study was an exploration of a new application for heart rate variability as a feeding intervention outcome measure and provides preliminary findings to support future work with a larger sample. Additionally, this study was limited to examining the HRV response during feeding. Examining the recovery of HRV after feeding would provide additional information about the infant's response to feeding and should be considered in future studies.

Implications for Practice

The utility of HRV as a clinical assessment for feeding remains to be determined. The results of this study suggest that SD12 may be more sensitive to stress during feeding than the standard physiologic measures of SpO₂, HR, and bradycardia, supporting the need for further research. Bedside HRV monitoring is available and has been used for other purposes in neonates, such as monitoring of neonatal sepsis³⁴ and necrotizing enterocolitis.³⁵ If HRV is found to be a useful measure for evaluating stress during feeding in future research, the use of bedside HRV monitoring during feeding may be worth exploring. Bedside HRV monitoring also has the potential for being useful for measuring autonomic nervous system response in infants in the neonatal intensive care unit related to other stressors (e.g., procedural pain) and interventions intended to reduce stress (e.g., skin-to-skin care).

Implications for Research

Further exploration of HRV as a feeding intervention outcome with a larger sample is warranted and both linear and non-linear HRV measures should be considered. The significance of nonlinear HRV measures is yet to be fully defined, especially in infants, although it was the only HRV index in this study to find a statistically significant difference between feeding methods in this study. Infants, particularly preterm infants, are more likely to experience bradycardia, or transient decreases in HR, as a result of stress compared to adults. The impact of this physiologic difference between infants and adults on HRV outcomes needs further clarification. Nonlinear HRV may be particularly useful for evaluation of HRV in this population.

Future research may consider exploring the use of HRV for identification of readiness for oral feeding in preterm infants, recovery from feeding, or as a predictor of feeding progression. The combination of HRV with other measures, such as cortisol, cytokines, galvanic skin response, and/or near infrared spectroscopy of abdominal tissue oxygenation may provide a more comprehensive evaluation of stress during feeding and would be worth exploring.

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What this Study Adds

- An exploration of a non-invasive measure of stress for evaluation of feeding interventions.
- Comparison of heart rate variability findings to standard physiologic measures in the context of a feeding intervention.
- Support for further exploration of heart rate variability, particularly non-linear indices, as a feeding intervention outcome measure.

Figure 1.

Electrocardiogram (ECG) tracing. The + indicates the peak of the R wave in the QRS complex of the heart beat. The red line between two R waves indicates the R to R interval, or distance between R waves. Image courtesy of Britt Pados.

Figure 2. Poincaré plot with SD1 (red) and SD2 (green). SD12 is the ratio of SD1 to SD2. Image courtesy of Britt Pados.

Figure 3.

Poincaré plot examples of low SD12 (left) and high SD12 (right). Low SD12 indicates high correlation between interbeat intervals. High SD12 indicates low correlation, or increased randomness, in interbeat intervals. Images courtesy of Britt Pados.

Figure 4.

Infant responses to feeding based on level of perceived stress (i.e., low, high, or life-threatening) and dominant nervous system activity, as guided by Polyvagal Theory^{17–22,27,28,37} and research on non-linear HRV indices^{14–16}

Table 1**Key Terms and Definitions**

Term	Definition
Autonomic nervous system	Branch of the peripheral nervous system that provides motor and sensory innervation to the organs under involuntary control (e.g., heart). Two divisions: sympathetic and parasympathetic. ³⁶
Co-regulated feeding method (CoReg)	Involved head elevated, side-lying position, minimal oral and tactile stimulation, and enhanced auditory assessment of sucking, swallowing, and breathing by a small microphone on the neck of the infant.
Dorsal motor nucleus	Most primitive, unmyelinated circuit of the vagus and the first to develop in the human fetus. Responsible for immobilization response to life-threatening stress (e.g., vasovagal syncope). ³⁷
Heart rate variability (HRV)	Variation in HR resulting from influences of the autonomic nervous system and cyclical rhythms of other systems (e.g., respiration). ⁷
High frequency (HF) HRV	HRV associated with respiratory sinus arrhythmia. HF HRV is a measure of parasympathetic activity. Higher HF HRV is better. ⁹
Low frequency (LF) HRV	HRV associated with infrequent cyclical rhythms (e.g., blood pressure); ¹⁰ measure of mixed parasympathetic and sympathetic activity. ¹¹
Nucleus ambiguus	Most highly evolved, myelinated circuit of the vagus and last to develop in the human fetus. Responsible for social communication and coordination of sucking, swallowing, and breathing. ³⁷
Parasympathetic nervous system	The division of the autonomic nervous system responsible for conserving and restoring energy during times of low stress. ³⁶
Poincaré plot	Plot of the interval between a pair of heart beats (e.g., R wave 1 and R wave 2) plotted on the x-axis against the interval between the next two heart beats (e.g., R wave 2 and R wave 3) on the y-axis (see Figure 2). An ellipse is fit to the data to quantify SD1 and SD2.
SD1	Length of the transverse axis of the ellipse plotted on the Poincaré plot (Figure 2); a measure of short-term variability in HR.
SD2	Length of the longitudinal axis of the ellipse plotted on the Poincaré plot (Figure 2); a measure of the intermediate-term variability in HR.
SD12	Ratio of SD1 to SD2; a measure of correlation between interbeat intervals. High SD12 indicates low correlation or randomness in the heart rate from non-respiratory origin (associated with elevated risk). ^{15,16} (Figure 3).
Sinoatrial node	The “pacemaker of the heart”; electrical impulses resulting in cardiac contraction arise from the sinoatrial node. ³⁶
Sympathetic nervous system	The division of the autonomic nervous system responsible for responding to stress (i.e., the fight or flight response). ³⁶
Vagus or vagal nerve	Cranial nerve X; innervates a variety of structures in the body - soft palate, pharynx, larynx, epiglottis, ear, thoracic and abdominal organs (heart, lungs, and gastrointestinal tract). Two motor branches of the vagal nerve originate from two nuclei in the medulla of the brain: the nucleus ambiguus and dorsal motor nucleus. ^{17,37}

Table 2**Demographic and Clinical Data**

Parameter	Usual Care (n=14 ^a)	CoReg (n=10 ^a)
Birth weight in grams (mean, range)	996 (713 – 1390)	992 (713 – 1390)
Birth PMA in weeks (mean, range)	28.6 (24.6 – 32.3)	28.8 (24.6 – 32.3)
Gender (n, %)		
Female	11 (79%)	8 (80%)
Male	3 (21%)	2 (20%)
Race (n, %)		
African-American	4 (29%)	2 (20%)
Euro-American	8 (57%)	6 (60%)
Other	2 (14%)	2 (20%)
NBRS	3 (0 – 10)	3 (0 – 10)
Lung Disease (n, %)		
None	0	0
RDS	3 (21%)	2 (20%)
CLD	11 (79%)	8 (80%)
IVH (n, %)		
None	9 (64%)	7 (70%)
Grade 1	4 (29%)	2 (20%)
Grade 2	0	0
Grade 3	1 (7%)	1 (10%)
	Usual Care (n=22 ^b)	CoReg (n=12 ^b)
Study PMA in weeks (mean, range)	36.4 (33.9 – 40.3)	36.9 (34 – 40.3)
O ₂ Day of Study (n, %)	14 (64%)	8 (67%)
O ₂ During Feeding (n, %)	15 (68%)	10 (83%)
Feeding Experience in days (mean, range)	13 (2 – 39)	13 (2 – 39)

Note. Parameters are presented as mean (minimum - maximum) unless otherwise noted. NBRS = Neurobiologic Risk Score³⁸; RDS = Respiratory Distress Syndrome; CLD = Chronic Lung Disease; IVH = Intraventricular Hemorrhage; PMA = Post-menstrual age; Birth PMA = PMA at birth; Study PMA = PMA on day of study; O₂ = Oxygen;

^a = Sample size of infants;

^b = Sample size of feedings

Table 3

Feeder Actions

	Usual Care	CoReg	<i>p</i>
Side-lying	10.14%	100%	<.01 [*]
Stimulation to Suck	1.71	0.15	.03 [*]
Co-regulation score	1.88	2.09	.80

Note. Side-lying = Percent of time during feeding the infant was held in a side-lying position. Stimulation to suck = number of events per minute where feeder stimulated the infant to suck. Co-regulation score = number of events per minute where feeder gave a rest period or cued the infant to pause feeding.

^{*} $p < .05$; computed with linear mixed models while accounting for correlation between feedings of the same infant.

Table 4

Standard Physiologic and Heart Rate Variability Results

	Usual Care Mean (SD)	CoReg Mean (SD)	<i>p</i>
<i>Standard Measures</i>			
SpO ₂	91.7% (2.03)	92.1% (2.56)	.26
RR	62	70	.03 *
Apnea	0.68	0.17	.04 *
HR	159.4	157.1	.38
Bradycardia	0.59	0.43	.11
<i>HRV Measures</i>			
HF Power (ms ²)	22.92	6.80	.26
SD12	0.26	0.19	.04 *

Note. SpO₂ = mean oxygen saturation during feeding. RR = respiratory rate (breaths/min) during feeding. Apnea = number of apneic events per minute during feeding. HR = mean heart rate during feeding. Bradycardia = number of seconds of bradycardia per minute of feeding. HRV = heart rate variability. HF = high frequency. ms² = milliseconds squared. SD12 = ratio of the length of the transverse axis (SD1) and longitudinal axis (SD2) of the ellipse (Figure 2).

* *p* < .05; computed with linear mixed models while accounting for order of study feedings, baseline physiologic data, and/or multiple measurements within the same infant or feeding, as appropriate. HRV Measures data were log-transformed.

Table 5**Summary of Recommendations**

What we know:

- Heart rate variability is a potential non-invasive measure of physiologic stress during feeding.
- This is the first study to compare heart rate variability outcomes to standard physiologic outcomes in the context of a feeding intervention for preterm infants.
- Infants fed using a usual care approach had higher SD12 compared to those fed using a gentle, co-regulated approach, which indicates increased randomness in the heart rate of non-respiratory origin and has been associated with adverse outcomes in other populations.

What needs to be studied:

- Additional research with larger sample sizes is needed to evaluate heart rate variability as an intervention outcome measure during feeding.
- Both linear and non-linear indices of heart rate variability need to be explored.
- The effect of bradycardia and transient decreases in heart rate in the preterm population on heart rate variability indices needs to be explored.
- Heart rate variability as a measure of feeding readiness or predictor of feeding progression in preterm infants may be worth investigating.

What we can do today:

- Recognize that feeding is a stressful event for the preterm infant and provide feeding support to reduce stress.
 - Support preterm infants during feeding by utilizing a gentle, co-regulated approach to feeding, including a head-elevated, side-lying position and minimal tactile and oral stimulation.
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