A pilot study: the role of the autonomic nervous system in cardiorespiratory regulation in infant feeding

Emily Zimmerman (e.zimmerman@neu.edu), Kelsey Thompson
Department of Communication Sciences & Disorders, Northeastern University, Boston, MA, USA

Keywords
Electrodermal activity, Feeding, Heart rate variability, Respiratory rate

Correspondence
E. Zimmerman, Department of Communication Sciences & Disorders, Northeastern University, 228C Forsyth Building, 360 Huntington Ave, Boston, MA 02115, USA.
Tel: +1617-373-5140 | Fax: +1617-373-2239 | Email: e.zimmerman@neu.edu

ABSTRACT
Aim: The purpose of this pilot study was to examine the interplay between the parasympathetic (PNS) and sympathetic nervous systems’ (SNS) contributions to prefeeding, feeding and satiation in young, healthy infants.
Method: This prospective study was completed on eleven full-term infants, less than 6 months old. Respiratory rate, heart rate, heart rate variability (HRV), electrodermal activity and low-frequency/high-frequency heart rate variability ratio were sampled from the infant during prefeeding, feeding and satiation periods.
Results: A repeated-measures ANOVA revealed a significant difference in respiratory patterning during the three feeding phases ($p = .049$); however, none of the other physiological measures reached significance. An emerging trend across physiological measures suggests that the feeding phase was influenced by the SNS with increasing respiratory rate, heart rate, low-frequency HRV, electrodermal activity and decreasing high-frequency HRV compared to the prefeeding and satiation phases, which were influenced predominantly by the PNS.
Conclusion: Respiration rate increased significantly during the feeding phase compared to prefeeding and postfeeding phases. Emerging trends indicate a pattern of alternating relative tone in PNS versus SNS across feeding phases – with SNS predominating the feeding phase. More clinical research examining the SNS and PNS contributions to feeding should be completed across patient populations.

INTRODUCTION
Every year, approximately 15 million babies are born preterm and this number is rising (1). It is estimated that between 40% and 70% of premature infants experience feeding difficulties (2). With premature births on the rise, it is important to find more objective, quantitative, and physiologically governed measures to assess feeding readiness and feeding behaviours in infants. Understanding the role of the autonomic nervous system (ANS) during feeding in term infants is an essential first step in this process, with the overarching goal of subsequently improving diagnosis and treatment of infants with feeding issues.

The ANS is composed of the parasympathetic and sympathetic nervous systems. The parasympathetic nervous system (PNS) prepares the organism for the ‘rest-and-digest’ functions and regulates activities that occur while the body is at rest, whereas the sympathetic nervous system (SNS) prepares the organism for the ‘fight-or-flight’ response and regulates activities geared towards mobilization of the body. The act of feeding has been shown to have clear autonomic responses in both pre-term and full-term infant cohorts (3,4).

Key notes
- This study examined the parasympathetic (PNS) and sympathetic nervous systems’ (SNS) contributions to feeding phases in infants.
- A significant increase in respiration rate during the feeding phase was evident compared to prefeeding and postfeeding phases. Emerging trends across physiological measures indicate more SNS tone during the feed.
- Understanding the interplay of the SNS and PNS that underlies the physiology of infant feeding is essential to understand normal growth and development.
Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. The low-frequency HRV (Low HRV) spectra likely reflects a complex interaction between the PNS and SNS (5), although recent reports suggest that Low HRV may in fact reflect predominately PNS activity (6). The high-frequency HRV (High HRV) spectra represent ventilatory modulation and efferent impulses (5). Previous studies have shown that the act of feeding to be signalled by a decrease in High HRV (i.e. a decrease in PNS activity) (3) and an increase in heart rate (HR) (i.e. an increase in SNS activity) (7). These feeding-mediated HRV and HR responses have been shown to remain stable during the first 6 months of life (3).

Knowledge of the contributions of the PNS and SNS across multiple physiological domains throughout the feeding process is still emerging. Previous researchers have examined a small number of physiological measures to gain insights into the complex PNS and SNS interactions, but often these studies have not sampled enough physiological measures to gain a more complete understanding of the PNS versus SNS contributions during feeding. Lappi et al. (2007) examined the long-term variability in HR, which reflects sympathetic tone, and found that sympathetic tone decreased during feeding, demonstrating a reduction in sympathetic regulation. A study by Brown (4) in 2007 showed a decrease or no change in Low HRV power during feeding compared to prefeeding and postfeeding. A unique aspect of the current study is the sampling of electrodermal activity (EDA), which is a measure of SNS activity, as well as the use of HRV spectrum analyses in addition to respiratory rate and HR sensors sampled throughout the feeding phases. The sampling of six physiological measures will help to elucidate the interplay between the PNS and SNS’ contributions to prefeeding, feeding and satiation in young, healthy infants.

METHODS

Participants
Eleven, healthy, full-term infants less than 6 months of age were enrolled in this prospective pilot study, see Table 1 for participant details. Exclusion criteria included serious medical diagnoses, and/or diagnosed feeding problems. Mother/infant dyads were recruited via posted fliers and postings in local mom groups/blogs. The institutional review board approved this study, and parental consent was received prior to the start of the study.

Procedures
Mothers were asked to bring their infant to the laboratory approximately one hour before their infant’s scheduled feed. When they arrived, each mother completed a questionnaire regarding her pregnancy (pregnancy/delivery complications), her infant’s medical information (birth-weight, growth patterns) and her infant’s typical mode of feeding (bottle or breast). Every attempt was made to mimic the typical feeding experience the mother described during the study session.

Next, mothers were asked to change their infant’s diaper and during this time the infant was fitted with the necessary study sensors. Neonatal electrodes, connected to an ADInstruments BioAmp (Bella Vista, Australia), were used to measure HR as well as HRV. Two neonatal electrodes were placed on the infant’s upper chest and one on the lower right side. These specialized neonatal electrodes (Conmed Softrace Cloth) are frequently used with infants in medical settings and are made with a soft fabric material and mild conductive adhesive that provides secure, comfortable electrode contact. The conductive adhesive gel is latex- and PVC-free and did not dry or irritate the infant’s skin. A Piezo Respiratory Belt Transducer (ADInstruments) was used to measure respiratory rate (RR). The Piezo Respiratory Belt Transducer is appropriate for use with humans of all sizes and is a solid-state device that requires no excitation. The transducer was wrapped around the infant’s abdomen under his/her clothing or over a thin onesie. After the infant was dressed, the Q Sensor was placed around the infant’s wrist and secured with medical wrap.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Sex</th>
<th>Birthweight (g)</th>
<th>Oxygen after birth</th>
<th>Current PMA (weeks)</th>
<th>Current weight (g)</th>
<th>Feed: bottle or breast*</th>
<th>Feed: schedule or on demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-01</td>
<td>Female</td>
<td>3147</td>
<td>No</td>
<td>15</td>
<td>7258</td>
<td>Breast</td>
<td>Schedule</td>
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<tr>
<td>A-02</td>
<td>Male</td>
<td>3147</td>
<td>Yes</td>
<td>8</td>
<td>5443</td>
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<td>Schedule</td>
</tr>
<tr>
<td>A-03</td>
<td>Female</td>
<td>4026</td>
<td>No</td>
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<td>7484</td>
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<td>Demand</td>
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<td>Male</td>
<td>3657</td>
<td>No</td>
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<td>3629</td>
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<tr>
<td>A-05</td>
<td>Male</td>
<td>3374</td>
<td>No</td>
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<tr>
<td>A-06</td>
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<td>3430</td>
<td>No</td>
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<td>Demand</td>
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<td>No</td>
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<td>4990</td>
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<tr>
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<td>20</td>
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<tr>
<td>A-11</td>
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<td>No</td>
<td>9</td>
<td>6690</td>
<td>Breast</td>
<td>Demand</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6F:5M</td>
<td>3512.9 (±400.8)</td>
<td>11.41 (±5.2)</td>
<td>6030.7 (±1150.5)</td>
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</tbody>
</table>

*Note that during the study, only infant A_02 was bottle fed, all other infants were fed by breast.
After the infant was fitted with the respective sensors, the infant’s RR and HR sensor output cords were attached to the ADInstruments PowerLab 16/35 Data Acquisition Device. The sampling rate for both RR and HR was set for 1000/sec. The RR range was set for 200 mV and the HR/HRV range for 5 mV. RR, HR and HRV data were filtered by a Mains filter to reduce electrical noise. A high pass filter of 0.3 Hz was applied to the HR data during data collection on all participants to reduce movement artifact. High-versus-Low HRV was determined by the power spectra energy pre-set by LabChart Pro Software (ADInstruments, Bella Vista, Australia) using the HRV 2.0 Add-On with the cut-off of 0.15–0.45 Hz for High HRV and 0–0.15 Hz for Low HRV.

While the study was being completed, the mother was encouraged to interact with her infant as she typically would at home. When the mother felt like her infant was ready to feed (i.e. showing their typical feeding cues), the mother would commence either bottle or breastfeeding. All mothers held their infant in a semi-inclined developmentally supportive position during the feed. When the infant was done feeding, the mother was asked to continue normal interaction with her infant for an additional two minutes. Before and after the feed, the infant would sit on mother’s lap upright and this positioning was consistent across participants. Data analysis was completed for the entire feeding period, 2 minutes before feeding (prefeeding) and 2 minutes after feeding (satiation).

**Measures**

HR beats per minute (HR BPM) and HRV (ms²) data were extracted from three neonatal electrodes using commercially available software (LabChart Pro Software using the HRV 2.0 Add-On; ADInstruments). HRV was calculated using a beat-to-beat (R) interval analysis through the ADInstruments LabChart Pro Software. This system automatically detects beats by finding the R wave in the ECG signal, and then classifying beats into normal or ectopic, the latter of which are excluded. After analysis, results are displayed for the selected time period in a frequency domain of a low-frequency band (0.04–0.15 Hz) and high-frequency band (0.15–0.45 Hz). Numerous studies, on both adults and infants, have used these settings (8–10). In fact, a recent study utilized the PowerLab HRV system as a reference gold standard (11).

Skin conductance level was measured in microSiemens (µS) using Ag-AgCl electrodes. Skin conductance changes are a result of SNS activity, and have been shown to be an objective measure of emotional and/or behavioural state because it is not influenced by temperature or circulatory changes (12,13). While skin conductance is primarily measured on the palmar surfaces of the hand and the bottom of the feet, it can also be detected on the distal forearm (13,14). Measuring these sites ensures that the sweating is related to emotional stimuli (cognitive, sensory, affective, stress, pain, anxiety, concentration) rather than heat or pain (13,14). Skin conductance has been reported to be an objective, noninvasive, and valid measure of pain, stress and behavioural state in both full-term and preterm infants (12). The key reason behind using skin conductance in neonates lies in the fact that it is unaffected by cardiorespiratory status, areas that may be variable or compromised in at-risk infants. Because EDA values vary widely for each person based on the individual’s hydration status, eccrine sweat gland density and CNS difference; there is no generally recognised average or standard value (15). For this study, individual EDA measurements (see Table 2) were examined on the basis of an increase or decrease in EDA compared across feeding phases.

**RESULTS**

Of the eleven infants who completed the study, one infant did not tolerate the ECG sensors, and therefore, we do not have HRV or HR data for that infant. With consultation from two computational behaviour science laboratory fellows with experience in interpreting EDA, only six of the eleven EDA recordings were deemed valid for analysis and interpretation. The EDA data that were not valid for analysis were primarily due to excess movement artifact, with occasional instances of interrupted electrode contact.

Repeated-measures ANOVA was completed for each of the dependent variables (RR, BPM, HR, High HRV, Low HRV, EDA) to compare these measures across each of the

<table>
<thead>
<tr>
<th>Table 2 The physiological measures sampled from the infants’ prefeed, feed and satiation phases.</th>
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<tbody>
<tr>
<td><strong>Physiologic measure</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>RR (BPM)</td>
</tr>
<tr>
<td>HR (BPM)</td>
</tr>
<tr>
<td>High-frequency HRV (ms²)</td>
</tr>
<tr>
<td>Low-frequency HRV (ms²)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
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<tr>
<td>EDA (µS)</td>
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</table>

The mean (SD) data for all infants (except LF/HF, which is denoted as a ratio), as well as p-value from the repeated-measures ANOVA are included. PNS or SNS indicates whether dependent variable was controlled by either the parasympathetic or sympathetic nervous system. Data represent eleven infants’ respiratory rate, ten infants’ HRV/HR and six infants’ EDA.
feeding phases (Table 2), please note that a Bonferonni adjustment was used to adjust for multiple comparisons. For each repeated-measures ANOVA, if Mauchly’s test was not significant, sphericity was assumed. If it was significant, then departures from sphericity were measured using the Greenhouse–Geisser. The repeated-measures ANOVA revealed a significant difference in respiratory patterning across the feeding phases (p = .049); however, none of the other physiological measures reached significance.

For each of the physiological measures, we examined the parasympathetic and sympathetic contributions by examining if there was an increase or decrease in the infant’s physiological response, see Table 2. From this table, the emerging trends suggest that the feeding phase was predominantly affected by the SNS with an increase in RR, HR, Low HRV, EDA and a decrease in High HRV compared to the prefeeding and satiation phases, which appear to be affected predominantly by the PNS. The ratio between the LF/HF HRV (balance of the SNS to PNS) was highest during the feeding.

**DISCUSSION**

Overall, this pilot study reveals a significant increase in respiration rate during feeding phase compared to prefeeding and postfeeding phases. Emerging data suggest a pattern of switching of relative tone in the PNS before and after the feed and SNS control during the feed.

Respiratory rate, as measured by breaths per minute (RR BPM), was the only physiologic measure that significantly changed across the three feeding phases (p < .05). Infants had lowest RR during the prefeeding phase (41.64 ± 26.42) and fastest RR during the feeding phase (66.39 ± 26.12), with satiation RR between the two phases (48.38 ± 24.55). RR increased during feeding compared to prefeeding, with a large effect size (1.08) and decreased from feeding to satiation with a medium effect size of 0.70. Faster respiratory rate is associated with higher levels of sympathetic traffic (16). Thus, the increase in RR evident during the feeding phase may indicate more SNS involvement. Our RR results are in contrast to previous studies, which report a decrease in RR during feeding in preterm and full-term infants (17–19). We speculate that this discrepancy in respiratory results is mainly due to the age of the participants. The previous research examined preterm infants as well as full-term infants who were less than 4 days old, whereas our infants were, on average, 11 weeks old when they completed the study. The range of ages in this study likely represents the broad continuum of infant suck–swallow–breathe development and an older population that has rarely been studied with regards to the study outcomes. One finding that was common among previous studies and the present study was the variability found in the infants’ RR. Respiratory rhythms for feeding continue to develop as the infants mature. In fact, breathing is one of the last mechanisms to fully mature in feeding (19,20). For example, the phase relation between swallowing and respiration continues to stabilize with an increase in postmenstrual age (PMA) (19). Lau (21) has noted that the close temporal relation between swallow duration compared to respiratory cycle leaves little time for the successful and safe integration of respiration. As infants mature, swallowing occurs at a safer time during respiration (i.e. start of inspiration or end of expiration) (21). Gewolb and colleagues have used instrumental measures to demonstrate these developmental changes. They found that breathing rate was reduced in term infants at the onset of feeding and the pattern of airflow became more irregular. There is a great degree of variation in respiration in both term (17) and preterm (19) infants. Future studies examining respiration should focus on a more narrow age window for participants.

On average, infants in our study demonstrated an increase in HR and a decrease in High HRV during feeding compared to the prefeed, although this was not statistically significant. This finding is consistent with previous feeding studies (3,7,22) and suggests that during nutritive sucking there is a reduction in parasympathetic control to allow for decreased vagal input to the sinus node via the ANS, resulting in an increase in sympathetic control in an effort to maintain performance level throughout the feed (3,4). Additionally, the decrease in High HRV during feeding is thought to be an adaptive response to stimulation that requires increased attention or metabolic output (23), such as the arduous task of feeding or digesting a bolus.

The LF/HF ratio revealed there to be more Low HRV power throughout all of the feeding phases, but a nearly two-fold increase in this ratio during feeding. However, the fact that Low HRV power was more present than High HRV power may be attributed to the fact that in the first 6 months of life there is a predominance of the sympathetic component of the autonomic nervous system (24).

Our study contained one physiologic measure governed chiefly by the SNS, EDA. Overall, EDA increased from prefeed to feed, indicating more SNS engagement. This finding is not surprising as the infant is likely in a more ‘fight or flight’, or sympathetic response, when he/she is hungry, highly alert and ready to feed. However, this finding is in contrast to previous research that found sympathetic tone decreased during feeding, as measured by long-term variability in HR (3). Our findings are unique in the sampling of EDA, which solely examines the SNS, and reiterates the notion that there appears to be a reduction in vagal input during the feed resulting in an increase in sympathetic control. It is important to note that EDA measures may be impacted by technical difficulties and a small sample size, and further studies are needed to examine this measure in more detail.

Understanding the contributions of the SNS vs. PNS during prefeeding, feeding and satiation in healthy full-term newborns will allow us to translate these results to infants at-risk for feeding delays. This will be especially important for infants born prematurely who often have more difficulty achieving the balanced stimulation of sympathetic and parasympathetic pathways (25) needed for adequate cardiorespiratory stability. In fact, low-risk premature infants have higher HR and reduced HRV compared to full-term
infants (26). This has detrimental effects for preterm infants, as infants with higher HRV variability are more likely to exhibit adaptive autonomic reactivity as well as emotional and behavioural responses to internal and external changes or demands (27), which are all essential skills for early learning and development.

The relatively small sample size in this study was due to the investigators’ goal of ensuring clinically relevant and accurate physiologic measures and outcomes before pursuing a larger trial. Due the small sample size, there remained considerable variability across physiologic measures. Throughout the study, we did not denote how many infants used pacifiers during the prefeeding or satiation phases and we estimate it was approximately fifty percent. Previous research has shown mixed results in regard to HRV and non-nutritive suck (NNS), one study found that NNS resulted in a higher LF/HF ratio (28) and another study found no effect on HRV during NNS (3). With only eleven infants in this study and approximately half using a pacifier, there may not have been enough subjects to show a difference, but this should be controlled for in subsequent studies.

In conclusion, the present study revealed that respiratory rate increased significantly during the feeding phase compared to prefeeding and postfeeding phases. Emerging trends indicate that as the infant begins a feeding there is a reduction in PNS control and an increase in SNS control in an effort to maintain performance level throughout the feed. Further research examining the sympathetic and parasympathetic contributions to feeding should be completed with a larger number of subjects as well as comparing full-term vs. preterm cohorts.

ACKNOWLEDGEMENTS
We would like to thank the mothers and infants who participated in this research study. We would also like to thank Dr. Mathew Goodwin and his laboratory for letting us use the Q Sensor in this study and for their support with EDA data interpretation.

CONFLICT OF INTEREST STATEMENT
Authors have reported no relevant financial and/or personal relationship with other people or organisations that could inappropriately influence their work.

References


