

## ORIGINAL ARTICLE

## Impaired parasympathetic response to feeding in ventilated preterm babies

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Arch Dis Child Fetal Neonatal Ed 2005;90:F505-F508. doi: 10.1136/adc.2004.070334

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Accepted 20 May 2005  
Published Online First 7 June 2005

**Background:** Premature very low birthweight (VLBW) infants are born with an underdeveloped parasympathetic nervous system (PNS) which may limit their ability to respond adequately to feeding and may limit their capacities for extrauterine growth and development.

**Objectives:** To describe the patterns of autonomic response to feeding and identify relationships between change in heart period variability measures over time with selected infant characteristics.

**Methods:** Individual growth curve analysis techniques were used to describe the patterns of change over time in sympathetic and parasympathetic tone as measured by low and high frequency heart period power.

**Results:** Sixteen mechanically ventilated VLBW infants with a mean corrected gestational age of 30.4 weeks participated in the study. The low frequency (LF) power slope was  $-17.67$  ( $p=0.0002$ ) and the high frequency (HF) power slope was  $-0.92$  ( $0.0003$ ). There was a significant relationship between HF slope and birth gestational age ( $r=-0.49$ ,  $p=0.05$ ).

**Conclusions:** HF power, representing primarily parasympathetic activity, did not increase with enteral feeding as anticipated. LF power, an indicator of sympathetic tone, decreased during and after feeding suggesting the anticipated effect of inhibition of the sympathetic nervous system in response to the gut stimulus. Critically ill VLBW infants possess an overriding sympathetic response, but may not have adequate PNS tone development.

Autonomic control of cardiac and other involuntary tissues is not fully developed until 37–38 weeks gestation.<sup>1–5</sup> Studies of intrauterine activity show that the early fetus has a predominantly sympathetic nervous system (SNS) and that parasympathetic nervous system (PNS) control gradually increases with post-conceptual age.<sup>6</sup> Fleisher *et al* showed that healthy fetuses demonstrated increasing heart period variability (HPV) consistent with improved SNS/PNS balance between 20 and 36 gestational weeks.<sup>7</sup>

Research on autonomic nervous system (ANS) development in the preterm infant has described interindividual HPV across gestational age groups and the corresponding ANS response to stress. In the healthy preterm infant, as with the fetus in utero, sympathetic tone predominates and parasympathetic tone gradually increases as the infant matures.<sup>8–10</sup> One of the physiological consequences of extremely premature birth is a PNS that may not adequately respond to environmental stimuli such as feeding and may not be active enough to promote balanced homeostasis, growth, and development. It is unclear whether the patterns of ANS development in the intubated very low birthweight (VLBW) infant are similar to those observed in the fetus in utero and the healthier premature infants in the aforementioned studies.

In this study, we examined how the introduction of a parasympathetic stimulus, in this case feeding, was associated with the PNS response of intubated VLBW infants (24–32 weeks corrected gestational age (CGA)). Based on previous HPV research in fetal and other premature infant populations, it was anticipated that infants of older gestational age would demonstrate improved parasympathetic response to this stimulus.

Heart rate and number of bradycardic events are general indicators of autonomic control but do not discriminate between the underlying components of the ANS. Power

spectral analysis of HPV reveals two frequency regions, each under the primary influence of a separate branch of the ANS.<sup>11</sup> The low frequency (LF) heart period power region, representing sympathetic activity with some parasympathetic influence, ranges from 0.02 Hz up to, but not including, 0.2 Hz. The high frequency (HF) heart period power region, representing primarily parasympathetic activity, begins at 0.2 Hz and ranges up to and includes 2.0 Hz.<sup>12–13</sup>

Examination of heart period power provides a mechanism for analysing the balance between sympathetic and parasympathetic tone. Increased sympathetic activity is often caused by physiological stress, while enhanced parasympathetic tone can indicate an increase in digestive and other parasympathetic activities.<sup>9</sup> Promoting PNS tone in premature infants has been shown to promote growth and development, as well as recovery from illness.<sup>2</sup> Heart period power is therefore a valuable clinical and research measure of the autonomic responses and capabilities in this critically ill infant population. Change in HPV across time, during various environmental fluctuations, may be indicative of the infant's ability to adapt. Our previous results from this sample of VLBW infants suggested that overall parasympathetic tone did not improve significantly with age while the infants were in the neonatal intensive care unit (NICU) environment.<sup>14</sup> The goal of this analysis was to determine if the PNS of these extremely immature infants was capable of responding to a basic gut stimulus. We hypothesised that feeding would increase parasympathetic activity, as measured by an increase in HF power during and after feeding. All nasogastric tube feedings took place while the infants were in the incubator,

**Abbreviations:** ANS, autonomic nervous system; CGA, corrected gestational age; HF, high frequency; HPV, heart period variability; LF, low frequency; NICU, neonatal intensive care unit; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; VLBW, very low birthweight

**Table 1** Slope and intercept of low frequency and high frequency power in 16 intubated VLBW infants around feeding

Effect	Estimate	Error	df	t	p
Low frequency					
Intercept	56.26	8.18	15	6.88	0.0001
Slope	-17.67	3.65	15	-4.84	0.0002
High frequency					
Intercept	6.08	0.49	15	13.56	0.0001
Slope	-0.92	0.20	16	-4.63	0.0003

an environment that was not particularly chaotic or stressful to the infant.

In the current study, individual change over time is conceptualised as following a trajectory that reflects some underlying biological process. With more than two measurement occasions, one can estimate slope for each research participant with a statistical technique known as individual growth curve analysis.<sup>15-17</sup> In the current study, this focus on the slope or pattern of change within the individual is consistent with a dynamic model of change in which the infant adapts (or fails to adapt) to changes in the environment, specifically feeding.

We hypothesised that the slope in the HF region of HPV would increase with stimulation of the gut by enteral feeding. The power in the HF region would be lower prior to feeding, increase with feeding, and remain elevated after feeding. Conversely, the power in the LF region, the region primarily influenced by the SNS, would be suppressed during and after feeding and thus show a negative slope. The specific aims of this study were to categorise patterns of intra-individual heart period power over time, specifically around enteral feeding, describe changes in HPV in relation to feeding, and correlate trends in HPV over time with selected infant characteristics.

**METHODS**

**Study design**

Individual growth curve analysis was performed on data collected for a study that compared infant physiological responses during maternal skin to skin holding and routine incubator care. During the incubator care phase, the infant was in the incubator and received nursing care every 3 h around a feed, which is the standard of care at the study site NICU. Details regarding the design and data collection protocols of the parent study are described elsewhere.<sup>18</sup> National Institutes of Health funding was obtained to perform two secondary analyses: (i) describe normative values for heart period power across gestational age and

**Table 2** Correlations of selected characteristics of 16 intubated VLBW infants with the slope of low frequency and high frequency power

Characteristic	LF slope		HF slope	
	r	p	r	p
Birth GA	-0.23	NS	-0.49	0.05
Corrected GA	0.02	NS	-0.32	NS
Birth weight (g)	-0.29	NS	-0.48	0.06
Study entry weight (g)	-0.04	NS	-0.29	NS
Study entry DOL	0.31	NS	0.27	NS

DOL, day of life; GA, gestational age.

other infant characteristics,<sup>14</sup> and (ii) describe patterns of change in heart period power using growth curve analysis (reported in this paper). Institutional Review Board approval was obtained for all analyses and informed consent was obtained from the infants' mothers for the original protocol.

**Subjects**

Data from 16 intubated and mechanically ventilated VLBW infants with respiratory disease were included in this study. Heart period data acquired during maternal skin to skin holding were excluded from the secondary analysis due to significant differences when compared to routine incubator care ( $F_{1,13} = 11.15, p = 0.005$ ). All infants were medically stable on the ventilator or were in the process of being weaned, and were on full enteral feedings administered by nasogastric tube. Other inclusion and exclusion criteria are described by Smith.<sup>18</sup>

**Heart period power**

Heart period (r-r interval) data were computer acquired 5 times per second in 5 min epochs scheduled around three infant feeding times throughout each 8 h study day. A total of 4 days of data per infant were obtained. Procedures for physiological data acquisition are described elsewhere.<sup>18, 19</sup>

Power spectral analyses of heart period data were performed to extract the power within the regions of high and low frequency as described by Smith *et al.*<sup>14</sup> The HF power and LF power data were then submitted to individual growth curve analyses to study individual trajectories of change over time as a way of examining the infants' response to PNS stimuli. Within this individual growth curve model of change, we anticipated that the slopes in the HF region would be positive, thus indicating an increase in PNS tone during feeding.

**Statistical analysis**

Individual growth curve analyses were conducted on the HF and LF power data using the processes recommended by Singer and Willett.<sup>20, 21</sup> For the following analyses, data were aggregated into three measurement occasions: pre-feeding, feeding, and post-feeding times. HF and LF data for each infant were plotted over these three times of measurement. This exploratory technique provided a visual indication of the shape and direction of individual changes over time. For each infant, linear regression lines were fit for each of 4 days. Polynomial models for each infant were estimated in which the data were centred around the feeding time, which was the mid-point of the data. The nature of the model is as follows:

$$Y_{it} = \pi_{0i} + \pi_{1i}[\text{TIME}]_{it} + R_{it}$$

where  $Y_{it}$  represents the level of HF or LF power for each individual (i) at time (t); t represents the time of measurement centred about feeding and thus took on three values, -1, 0, and 1;  $\pi_{0i}$  represents each individual's intercept, which occurs at the feeding time point;  $\pi_{1i}[\text{TIME}]_{it}$  represents the linear rate of change over time (that is, the slope); and  $R_{it}$  is an i by t matrix of model residuals at time t for individual i.

When implemented within statistical software SAS PROC MIXED (SAS 8.02, Cary, NC), this polynomial form of linear change allows for quantification of an individual trajectory (intercept and slope) for every case in the study. An advantage of PROC MIXED is that the form of the covariance matrix of the individual residuals can be specified by the user. The unstructured form provided the best fit and was employed in the analyses reported below. In addition to the overall fit, the analyses provide individual parameters (intercept and slope for each infant) in the HF and LF power

variables. In this study we focus on the slope. These individual slope parameters were then correlated with individual characteristics, using the Pearson product moment correlation.

## RESULTS

### Sample characteristics

At the time of data collection, all 16 VLBW infants were mechanically ventilated for respiratory disease of prematurity. Mean birth gestational age was 25.8 weeks (SD 1.6, range 24–29) and mean CGA age when the infants entered the study was 30.4 weeks (SD 1.5, range 28–34). Mean birth weight was 763.7 g (SD 160.7, range 600–1121) and mean weight at study entry was 983.8 g (SD 209.7, range 763–1409).

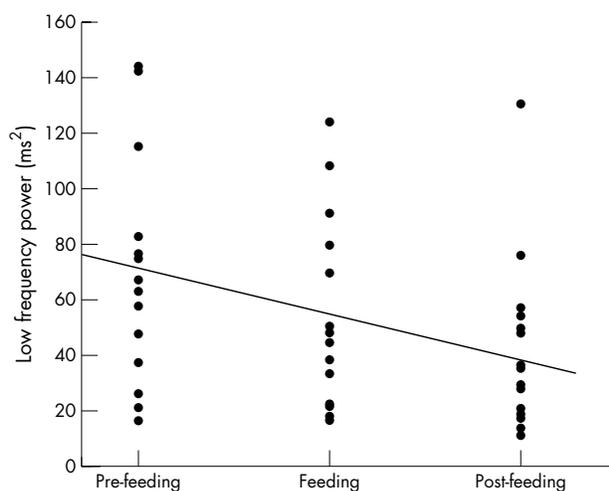
### Individual growth curve analysis

Two individual growth curve models were fit to the LF and HF power data. The slopes of HF power and LF power were negative, and both were significantly different from zero. The negative slope of LF power was much steeper than that of HF power, which was relatively flat. The results from these models are shown in table 1.

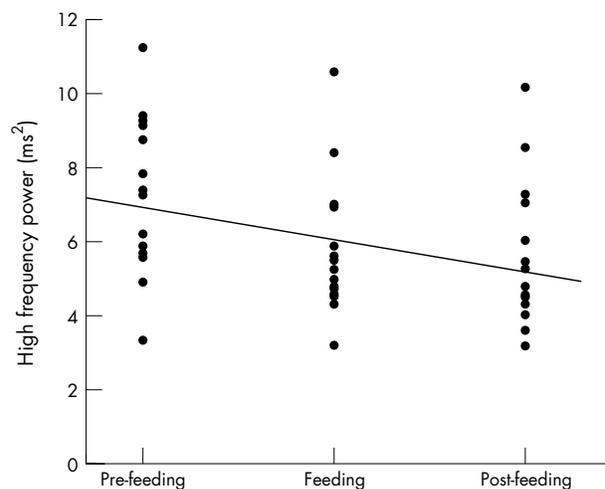
There were no significant correlations between selected infant characteristics and the LF slope. Gender was not significantly correlated with either HF or LF slope. There was a significant relationship between HF slope and birth gestational age (table 2). No other significant relationships were detected; however, the relationship between HF slope and birth weight is nearly significant.

## DISCUSSION

The slope of the HF power (SNS activity) was expected to increase during and after enteral feeding; however, this was not the case. In fact, the slope of change in HF power was negative, a response contrary to what was expected with stimulation of the gut. Inhibition of SNS activity would also be expected with an enteric stimulus. In fact, the slope of change in LF power (SNS activity) decreased with feeding as anticipated. In this study, stimulation of the gut did not appear to stimulate the PNS, but there is strong evidence of SNS suppression. As seen in the graphic display (figs 1 and 2), the LF and HF slopes were both negative, suggesting that stimulation of one branch of the ANS has no effect on the



**Figure 1** Average of the within subject linear growth curve models of low frequency power for 16 mechanically ventilated VLBW infants before, during, and after enteral feeding.



**Figure 2** Average of the within subject linear growth curve models of HF power for 16 mechanically ventilated VLBW infants before, during, and after enteral feeding.

other branch of the ANS in these infants. These results are congruent with prior research that demonstrated autonomic imbalances in premature infants evidenced by overriding SNS activity.<sup>8–10</sup>

The negative relationship between birth gestational age and birth weight with HF slope was another unexpected finding. This result suggests that the PNS response to feeding is reduced in the gestationally older and heavier infants and appears to be contrary to what researchers of gestationally older, healthier premature populations have found.<sup>8–10</sup> Possible explanations for this unexpected finding could be that the gestationally older infant is able to mobilise the SNS in response to a chaotic environment in a more organised fashion. One could also speculate that these older infants who are intubated and mechanically ventilated are on constant sympathetic alert because of their degree of illness.

Although not statistically significant, the negative correlation of CGA with the slope of HF power is also contrary to what would be expected. In this study, the more gestationally mature infants exhibited a weaker PNS response. Parasympathetic activity is necessary for normal digestive function and plays a role in restorative function, growth, and development in premature infants.<sup>2</sup> The findings in this study suggest that elements in the NICU environment may impair PNS maturation that should be occurring during the infant's hospitalisation.

### Limitations

The limitations of this study include limited statistical power due to the small sample size. In addition, these data were previously acquired in a separate study thus limiting the ability to control for the NICU environment. The number of time points was constrained to three and thus we have modelled only straight line trajectories. This, in conjunction with the small sample size ( $n = 16$ ) has limited our ability to model more complex non-linear processes of change. Finally, the NICU study site has been redesigned since these data were acquired, with significant changes in the physical environment including semiprivate rooms within the nursery, acoustic tiles, and low level lighting. With these improvements in the physical environment, a study of similar infants in these new surroundings may provide different results.

### What is already known on this topic

- The parasympathetic nervous system develops later in gestation
- The premature infant has an overriding sympathetic nervous system

### What this study adds

- Promoting PNS tone is difficult to accomplish even with stimulation of the PNS
- Intubated very low birthweight infants may be on constant sympathetic alert, thus attenuating PNS development and maturation

### CONCLUSIONS

Heart period power is a precise measure of ANS responses to various stimuli. Intubated VLBW infants in this exploratory study failed to demonstrate improved PNS tone in response to enteral feeding; nor did the infants' PNS tone improve with gestational age. Study of a larger cohort of VLBW infants with respiratory disease could provide the necessary statistical power to detect differences in ANS maturation and identify factors affecting the maturation process in these critically ill infants. Longitudinal research to quantify the amount of stimulus to promote ANS development in the NICU environment may help to isolate the factors inhibiting PNS maturation in these infants.

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This study was funded by a grant from the National Heart, Lung, and Blood Institute at the National Institutes of Health (NHLBI R01 HL71920-01)

Competing interests: none declared

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