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Autonomic Nervous System Function in Infants with Transposition of the Great Arteries

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Abstract

The ability to maintain homeostasis and respond to challenges to homeostasis is primarily a function of the autonomic nervous system (ANS) and may be impaired in infants with complex congenital heart defects. This study described change in ANS function before and after surgical correction in infants with transposition of the great arteries (TGA) and in healthy infants. Fifteen newborn infants with TGA were matched with 16 healthy infants on age, gender, and feeding type. ANS function was measured using heart rate variability (HRV). Data were collected pre-operatively in the first week of life and post-operatively before, during, and after feeding at two weeks and two months of age. At baseline, infants with TGA demonstrated significantly lower high frequency and low frequency HRV pre-operatively (p <.001) when compared with healthy infants. At two weeks, infants with TGA were less likely than healthy infants to demonstrate adaptive changes in high frequency HRV during-feeding (Wald Z = 2.002, p = .045), and at two months, 40% of TGA infants exhibited delayed post-feeding recovery. Further research is needed to more thoroughly describe mechanisms of a physiologically adaptive response to feeding and to develop nursing interventions supportive of these high risk infants.

Keywords

congenital heart defects; heart rate variability; infant feeding

Introduction

Infants with complex congenital heart defects (CCHD) requiring repair or palliation within the first days or weeks of life demonstrate impaired ability to regulate physiologic processes such as feeding (Jadcherla, Vijayapal, & Leuthner, 2009; Limperopoulos et al., 1999; Limperopoulos et al., 2000). Impaired ability to regulate physiologic processes may be associated with the compromised growth seen in this population (Pillo-Blocka et al., 2004; Varan, Tokel, & Yilmaz, 1999) and may affect subsequent regulation of social and emotional behavior (Doussard-Roosevelt, McClenny, & Porges, 2001). Regulation of physiologic processes is largely controlled by the autonomic nervous system (ANS). The purpose of this study was to compare ANS function before surgical correction and in response to the challenge of feeding after surgical correction in infants with transposition of the great arteries (TGA) and a matched group of healthy infants.

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ANS function

The ANS, through the sympathetic and parasympathetic divisions, is largely responsible for regulation of physiologic processes. This physiologic regulation serves to maintain an optimum state of functioning for growth and development (i.e., homeostasis, primarily controlled by parasympathetic function), and to effectively respond to internal and external challenges to homeostasis (i.e., stress, primarily controlled by sympathetic function). Function of the ANS is reflected, physiologically, in the modulation of heart rate (De Jong & Randall, 2005; Ohuchi, et al., 2003; Verklan, 2002). Regulation of heart rate is characterized by changes in sequential beat-to-beat intervals reflecting precise and constant interaction between effects of parasympathetic and sympathetic divisions of the ANS. These minute changes in the interval between heart beats are known as heart rate variability (HRV), and analysis of the rhythms and frequency of beat-to-beat changes provides a measure of autonomic control of the heart (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). In general, higher levels of variability reflect a healthy, responsive system able to finely regulate physiologic processes; lower levels of variability reflect an ANS that is less responsive to changing conditions (Pumprla, Howorka, Groves, Chester, & Nolan, 2002).

Vagal and sympathetic fibers, as well as neurohormonal influences, affect heart rate through processes operating at different frequencies that can be identified and quantified (Pumprla et al., 2002). Variations of heart rate occurring in the ultra-low frequency range (0.00 – .003 Hz) reflect circadian rhythm; variations in very low frequency (0.003 – 0.04 Hz) reflect the effects of thermoregulation and neurohormones; variations in low frequency (0.04 – 0.15 Hz) reflect the effects of both sympathetic and vagal influences; variations in high frequency (0.15 – 0.4 Hz) reflect primarily parasympathetic (vagal) influences (Pumprla et al.; Schumacher, 2004). The effect of the vagus nerve on heart rate varies with the respiratory cycle: with inspiration, heart rate increases; with expiration, heart rate decreases (Hayano & Yasuma, 2003). Thus, the effect of the vagus nerve on heart rate is expressed within the frequency band of respiration, and during infancy the band width is adjusted based on respiratory rate. These various frequencies are referred to in terms of power which refers to the amount of variance in modulation of heart rate attributable to a particular frequency range (Buchman, Stein, & Goldstein, 2002; Schumacher, 2004). Ratios of LF power to HF power are considered by some to be markers of change in the relative balance between sympathetic and parasympathetic activity (Malliani, Pagani, & Lombardi, 1994; Montano et al., 1994). However, the validity of conclusions related to specific changes in sympathetic or parasympathetic activity is controversial (Berntson et al., 1997; Eckberg, 2000; Kleiger, Stein, & Bigger, 2005; Schumacher, 2004).

Regulation of physiologic systems is a dynamic process wherein physiologic parameters are maintained within functional ranges during homeostasis and in response to challenges to homeostasis (Porges, 1996). Thus, analysis of the quality of physiologic regulation includes measures of baseline (homeostasis), change (reactivity), and return to baseline (recovery). One approach to examining autonomic function during states of homeostasis and in response to stress or challenge is to assess HF power (Calkins, Graziano, & Keane, 2007; Porges, 1996; 2001), an accepted marker for parasympathetic activity (Berntson et al., 1997; Kleiger et al., 2005; Task Force, 1996). Adaptive regulation of physiologic processes is marked by the ability to respond to internal or external stressors by withdrawing parasympathetic activity, allowing sympathetic activity to dominate, followed by a resumption of parasympathetic dominance after the stress is relieved (Porges, 1992; 1996; 2001). Consistent with the view of parasympathetic function as a marker of stress response, the focus of this paper will be HF power. Relevant data on LF power and LF/HF ratios will be provided for completeness.

ANS function and CCHD

Although little is known about ANS function in infants with CCHD, changes in the function of the ANS, specifically sympathetic activation and parasympathetic withdrawal, are known to occur in adults with acquired cardiac disease (Stein, Domitrovich, Huikuri, & Kleiger, 2005). For example, adults with coronary artery disease (CAD) undergoing coronary bypass surgery have significantly reduced HF power, reflecting a reduced ability to regulate physiologic functions. In one study, these reductions reached a nadir 3 to 6 days after surgery when compared to pre-surgery levels, and returned to presurgical levels within 30 to 60 days (Soares, Moreno, Cravo, & Nobrega, 2005). LF power and LF/HF ratios were increased postoperatively with a return to the lower preoperative values within 60 days. At all three time points, HRV indices were significantly lower in the adults with CAD when compared with a healthy control group.

Similar to findings in the adult population, parasympathetic withdrawal was demonstrated in preoperative recordings in infants and children with a variety of CCHDs when compared with age-matched controls (Heragu & Scott, 1999). Additionally, HF, LF, and LF/HF ratios were all significantly lower in the post-operative period when compared with preoperative values. A longitudinal assessment of HRV in infants with different types of cardiac defects made pre-operatively, 2 weeks post-operatively, and at routine follow-up 3 to 6 months later revealed consistent increases in LF and HF power over time with the most marked increase found between the post-operative and the follow-up time points (Kaltman et al., 2006). A lower two week post-operative LF/HF ratio was predictive of longer hospital stay.

These studies provide evidence for compromised ANS function in infants and children with CCHD. However, in most of these studies, children of different ages and with different cardiac defects have been treated as one group. Additionally, none of these studies assessed autonomic response and recovery to physiologic challenge. In the current study, ANS function in infants with a common diagnosis, TGA, was examined both at baseline and in response to challenge. Infants with TGA have corrective surgery and are discharged within fairly uniform time frames (Mussatto & Wernovsky, 2005), creating a more homogeneous sample. Importantly, although infants with TGA have good cardiac outcomes with long term survival rates as high as 96.7% (DiBardino, Allison, Vaughn, McKenzie, & Fraser, 2004), infants with TGA experience growth impairment in the first few months of life that often does not normalize until 12 months of age (Rosti et al., 2002) and can be below standardized norms up to four years of age (Schuurmans et al., 1998). With cardiac function comparable to healthy infants and children (Mussatto & Wernovsky, 2005), it is important to identify differences in physiologic processes that may affect growth in children with TGA, including impaired ANS function.

ANS function and the Challenge of Feeding

During infancy, feeding is a challenge to homeostasis (DiPietro & Porges, 1991). Reductions in parasympathetic activity (as measured by HF power) during the metabolically demanding coordination of sucking, swallowing, and breathing with ingestion of food has been demonstrated in healthy infants (Lappi et al., 2007) and in premature infants (Brown, 2007; Porges & Lipsitt, 1993; Portales et al., 1997). When the feeding is finished, parasympathetic activity (i.e. HF power) increases in a recovery of conditions supportive of growth and restorative processes, i.e. homeostasis (Porges, 1996).

Mothers report feeding as one of the most difficult and time consuming aspects of caring for infants with CCHD (Imms, 2000; Svavarsdottir & McCubbin, 1996). Evidence of difficulty regulating the physiologic process of feeding has been found in infants with different types of CCHDs, including more vomiting, more breathlessness, and reduced growth when

compared to a healthy control group (Clemente et al., 2001). These problems were found regardless of stage of treatment, i.e., mothers of infants who had had a complete repair were just as likely to report these difficulties as mothers of infants awaiting repair. The role of the ANS in dysregulated feeding and in the high metabolic requirements observed in infants with CCHD has received little attention.

In one sample of 10 one-month-old infants with a variety of CCHDs, HF power demonstrated little change across phases of feeding (Winters et al., 2006). In an earlier publication drawn from our larger study, two week old infants with TGA demonstrated significantly lower HF power pre-feeding and post-feeding and significantly higher HF power during-feeding when compared with healthy infants of the same age (Harrison, 2009). However, we found no differences in HF power by phase of feeding at two months of age. Knowledge of an infant's ability to respond to stress is important in order to identify infants who may require more support from caregivers, such as alterations in position, timing, and environment during feedings.

Our specific aims in this study were to provide a more complete assessment of infant response to stress by comparing infants with TGA with healthy infants in regards to: (1) HRV indices before surgical correction and postoperatively with each phase of feeding (pre-feeding, during feeding, and post-feeding), (2) likelihood of reductions in HF power between pre- and during-feeding phases and increases between during- and post-feeding phases, and (3) time to recovery to pre-feeding HF power values after the feeding was completed.

Methods

This study was a component of a larger exploratory study investigating the effect of maternal behavior on physiologic and arousal regulation in a sample of infants with TGA and healthy infants.

Sample

Eligible infants with TGA were recruited from three metropolitan children's hospitals in the Midwest over 15 consecutive months. Inclusion criteria included: (a) full-term infants (≥ 37 weeks gestational age) diagnosed with TGA either prenatally or after birth, with no co-morbidities and (b) English-speaking mothers at least 18 years of age or who were legally emancipated, and who would be the primary caregiver. Infants were excluded if had spent time at home prior to admission for corrective surgery. In order to obtain closely equivalent groups, a comparison group of healthy infants was recruited from a birth center affiliated with one of the children's hospitals and matched with infants in the TGA group on three variables that could potentially affect the measure of HF power: gender (Silvetti, Drago, & Ragonese, 2001), age (Massin et al., 2001), and feeding type (breast or bottle; Marino, O'Brien, & LoRe, 1995). One healthy infant matched for breastfeeding was retained in the study when the mother stopped breastfeeding before data collection was complete. The final sample consisted of 15 infants with TGA and 16 healthy infants.

Instruments and Procedures

Subject Procedures—After obtaining the mother's written informed consent, a three channel ECG recording was made using seven neonatal electrodes. The channel 1 positive electrode was placed at the 5th intercostal space at the left axillary line and the negative electrode at the right clavicle lateral to the sternum. The channel 2 positive electrode was placed at the 4th intercostal space at the right sternal edge and the negative electrode at the left clavicle lateral to the sternum. The channel 3 positive electrode was placed equidistant

between the positive channel 1 and channel 3 electrodes and the negative electrode mid-sternum at the level of the clavicles. The ground electrode was placed at the lower right chest wall.

For presurgical data collection for TGA infants, a continuous four hour ECG recording was made to provide a baseline of average modulations of the power spectra. Prior to surgery, infants with TGA are hospitalized in an intensive care setting for hemodynamic and respiratory support. Most infants with cardiac defects are not given oral feedings prior to surgical correction (Kogan et al., 2007). Therefore, measures relating to feeding were not collected at this time point. A four hour time period was chosen when few interruptions were expected. The infants were asleep except for unavoidable arousals associated with medical and nursing care. Four hour recordings of matched healthy infants were collected in the home with the exception of three infants who were in the birth center. According to parent-completed activity logs, all but one infant was asleep for the duration of the recording, wakening only for feedings.

For post-surgical data collection, shorter ECG recordings were used to examine autonomic response to feeding: 30 minutes prior to feeding, for the duration of the feeding, and for 60 minutes after the feeding was completed. Short recordings provide more detailed information about modulation of HRV in response to internal and external demands. Positioning and activity pre- and post- feeding were monitored, but not controlled. Mothers held their infants in their arms during feeding.

For the TGA group, Time 1 data collection took place in the hospital prior to surgery; Time 2 took place in the hospital after surgery just prior to discharge. For the comparison group, Times 1 took place in the hospital or home and Time 2 in the home with infant age in days consistent with matched TGA participant. For both groups, Time 3 data collection took place in the home six weeks after Time 2 (see Figure 1). The study was approved by human subjects review boards in each of the participating hospitals and academic institutions.

Waveform processing—A Marquette Seer MC Holter Recorder and a MARS 5000R Ambulatory ECG Analysis and Editing System (General Electric, Inc.) were used for collection and processing of the ECG. Data were initially sampled at 250 Hz and then filtered to 125 Hz for R wave detection. The R waves were detected with a template pattern-matching method and patterns were updated in real-time. The upcoming new potential R waves were matched with the templates, and the matched R waves were then classified to its closest template group. A pattern-matching method of detecting the R waves allows accurate detection of R waves without increasing noise level (an issue with higher sampling frequencies). Each ECG complex was identified and characterized with regard to morphology by the computer software. This preliminary analysis was then overread and edited to assure that proper identification had occurred. Artifact and ectopic beats were excluded from analysis. Final calculations were based solely on normal sinoatrial node initiated complexes and are referred to as N-N (Normal to Normal) intervals in this paper. HRV was calculated using frequency domain measures, determined by fast Fourier transformation with Hanning window weighting to produce an interval function defined continuously in time and resampled at equal spacing to produce 1024 samples of the N-N interval function for every 300 seconds.

Two frequency domains were quantified: LF and HF. The low frequency band width was calculated at 0.04 – 0.15 Hz. The high frequency band is typically calculated based on an adult respiratory rate of 15 breaths per minute, yielding a band width of 0.15 to 0.40 Hz. However, infants with CCHD often have high respiratory rates. In order to properly identify the correct frequency for HF power, the HF band was calculated separately for each infant

based on average respiratory rate. The lower end of the band was defined at 0.15 Hz. The upper end of the band ranged from 0.4 to 1.707 Hz with a mean (SD) of .924 (.236).

LF and HF power and LF/HF ratios were calculated for the total four hour epoch pre-surgery and in five minute epochs for the post-surgery observations. The HRV value for each epoch was the average interval between heart beats for that epoch expressed in milliseconds, squared. For post-surgical analysis, these five minute epochs were averaged over the duration of each of the three feeding phases (pre-feeding, during-feeding, and post-feeding). Post feeding HF power was further analyzed using one minute epochs to examine recovery to pre-feeding HF power levels. Because frequency domain measures have skewed distributions (Kleiger et al., 2005), the data were log transformed to normalize the distribution and are reported as the natural log of milliseconds, squared [ln (ms^2)].

Data Analysis—To address Aim 1, HRV indices were compared using two-sample Mann-Whitney tests. To address Aim 2, fixed occasions, multiple condition, logistic regression analysis (Diggle, Liang, & Zeger, 1994; Goldstein, 1986; Yang, Heath, & Goldstein, 2000) was used to address likelihood of change in HF power between feeding phases. Two dependent variables were calculated based on one measure of HF power taken at each of three phases of feeding and at two different points in time, i.e. pre-feeding, during-feeding, and post-feeding at Time 2 (approximately 14 days after surgery) and Time 3 (six weeks after Time 2). These dichotomous outcome variables, Pre-During Change and During-Post Change, indicated the presence or absence of an adaptive physiologic response to feeding (i.e. a reduction in HF power during feeding followed by a return to pre-feeding HF power values after the feeding was complete).

Because HF power fluctuates over consecutive short epochs of time, a conservative method of defining change was used to avoid overestimating change. First, HF power values for the five minute epochs within each phase of feeding were examined. Values more than one standard deviation from the mean for each feeding phase were excluded in order to provide a value most reflective of overall phase HF power. Next, to determine if change in the direction of lower HF power had occurred during feeding compared to pre-feeding, the lowest value of HF power in the pre-feeding phase was compared with the mean value of HF power in the during-feeding phase. The comparison for this Pre-During Change variable was scored dichotomously with 0 = during-feeding mean value was not lower than pre-feeding lowest value (i.e. no change observed) and 1 = during-feeding mean value was lower than pre-feeding lowest value (i.e. change was observed).

Finally, to determine if change in the direction of higher HF power had occurred post-feeding compared to during-feeding, the highest value of HF power in the during-feeding phase was compared with the mean value of HF power in the post-feeding phase. The comparison was scored dichotomously with 0 = post-feeding mean value was not higher than during-feeding highest value (i.e. no change observed) and 1 = post-feeding mean value was higher than during-feeding highest value (i.e. change was observed).

Thus, the Change Model included two outcome variables, Pre-During Change and During-Post Change and one predictor variable, Group (dummy coded 0 = healthy infants and 1 = infants with TGA). Using MLwiN Version 2.02 (Rasbash, Browne, Healy, Cameron, & Charlton, June 2005), these equations were examined simultaneously for each dependent variable at each of the two times of assessment. By modeling the dependent variables at each of the two times of assessment, covariation between the dependent variables and between the two time points could be controlled. Coefficients for the predictor group were interpreted as the probability of the infants with TGA being in the group whose HF power

changed. Given the exploratory nature of this study, alpha level for all significance tests was set at .05. Coefficients were tested using approximate Wald statistics (Goldstein, 1995).

To address Aim 3, event history analysis (Tabachnick & Fidell, 2001) was used to analyze the length of time in minutes for infants to return to pre-feeding HR power values after the feeding was completed. For this analysis, one-minute epochs of HF power were recorded and compared with the pre-feeding HF power median values for each infant. Median values were used for this analysis to obtain a closer measure of central tendency (Tabachnik & Fiddell, 2001). Visual inspection of the data by two researchers was used to identify criteria indicating sustained recovery of HF power. Data indicated that the first minute post-feeding in which the HF power remained at or above the pre-feeding median value for five consecutive one-minute epochs was a reasonable indicator of sustained recovery. Two variables were created for each time point. The first variable (time to criterion) marked the point at which post-feeding HF power remained at or above the pre-feeding HF power median value for five consecutive minutes. The number of minutes into the post-feeding phase when the first minute of this five minute sequence appeared was selected as the value for this variable (see Figure 2 for example).

The second variable was a dichotomous value indicating whether or not the infant had reached pre-feeding median HF power during the 60 minute post-feeding observation with 0 = no recovery before end of the observation and 1 = recovery before end of the observation. This variable was the censored variable (i.e. recovery time was unknown). The Kaplan-Meier survival function was then run using NCSS software (Hintze, 2004). Exact Logrank tests were used to test for significant differences between groups.

Results

The sample of mothers was primarily non-Hispanic, non-Latino White, 28 to 29 years old, with some college education. Median income of mothers of infants with TGA was higher than median income of mothers of healthy infants ($75,001–100,000 and $30,001–50,000 respectively). The TGA infants were primarily male (n = 9), bottle feeding (n = 10), with a mean (SD) weight of 3484.1 (482.5) grams. Mean (SD) age in days at data collection were Time 1: 4.27 (1.83); Time 2: 17.13 (3.94); Time 3: 59.07 (4.4). Surgery was done at a mean (SD) age of 6.8 (2.98) days and the infants were discharged at mean (SD) age of 20.13 (6.05) days. Due to equipment malfunction, two healthy infants were without pre-feeding ECG data at Time 2 and one TGA infant was without during-feeding data at Time 3. At Time 1, one infant with TGA had a 702 beat run of supraventricular tachycardia which was excluded from analysis. Correlations between mean N-N intervals and SDNN (standard deviation of all N-N intervals, a measure of total power) were modest (see Table 1). Mean (SD) minutes pre-feeding data collection time was 23.08 (7.71); post-feeding 57.02 (5.90). One infant at Time 2 received full nasogastric (NG) feedings so During-Feeding and Post-Feeding data from this infant were not included in analysis. Partial NG feedings were received by five infants at Time 2 and one infant at Time 3. This passive receipt of nutrients was analyzed as part of the Post-Feeding phase. Because only five infants with TGA were breastfed, separate analysis by feeding type was not possible. Variations in positioning and sleep and wake states pre- and post- feeding were similar between groups. For feeding, all mothers held their infants in their arms in a semi-reclined position.

Variability in HF power was similar between groups at Time 1 (see Figure 3). At Time 2 healthy infants demonstrated less variability as well as adaptive reductions in mean and median values during feeding whereas infants with TGA demonstrated wide variability and little mean change across feeding. By Time 3, both groups showed adaptive reductions during-feeding. However, variability during feeding was greater for infants with TGA.

For Aim 1, comparisons of HRV indices between groups at baseline and at each feeding phase are presented in Table 2 and Figure 4. HF power in infants with TGA was significantly lower than healthy infants prior to surgery ($U = 218.0$, $p = .001$), but was not different by feeding phase at either time post-operatively. LF power was significantly lower at baseline and during all three feeding phases at Time 2, but not Time 3. LF/HF ratios did not differ between groups.

For Aim 2, the Change Model revealed that at Time 2, infants with TGA were significantly less likely than healthy infants to demonstrate reductions in HF power during-feeding (see Table 3). At Time 3, no significant differences between groups in HF power change between feeding phase were found.

In examining recovery after feeding at Time 2 (Aim 3), 50% of both healthy infants and infants with TGA had recovered to pre-feeding HF power levels within 6 minutes post feeding (see Figure 5). From this point, there was a separation between infants with TGA and healthy infants. Eighty-six percent of healthy infants had recovered by 37 minutes and the remaining 14% had not reached pre-feeding values by the end of the 60 minute observation. Approximately 93% of the infants with TGA recovered by 29 minutes and the remaining 7% had not recovered by the end of the 60 minute observation. At Time 3, 50% of the healthy infants recovered within the first 6 minutes, 81% had recovered by 37 minutes, and the remaining 19% did not recover by the end of the 60 minute observation (see Figure 5). Among infants with TGA, 53% had recovered within 2 minutes post-feeding and 60% within 5 minutes. However, the remaining 40% did not recover pre-feeding HF power by the end of the 60 minute observation. Differences between groups were not significant at either time point (Log rank: Time 2 $p = .46$; Time 3 $p = .65$).

Discussion

In this study, HRV before and after surgical correction and across three phases of feeding at two points in time was examined in order to compare ANS function in infants with surgically corrected TGA with a matched group of healthy infants. Consistent with previous literature (Heragu & Scott, 1999; Kaltman et al., 2006), infants with TGA demonstrated significantly lower HF power prior to surgery and increasing values postoperatively until by age two months significant differences were not found. The study extended knowledge of ANS function by demonstrating that infants with TGA responded differently to the challenge of feeding than healthy infants. Specifically, adaptive reductions in HF power between pre-feeding and during-feeding were less likely in infants early after surgical correction for TGA than in matched healthy infants, and LF power in each phase of feeding was significantly lower. Additionally, two months after surgical correction, a subgroup of infants with TGA had delayed recovery from the physiological challenge of feeding when compared with healthy infants.

The underlying mechanisms for altered ANS function in infants before and early after corrective surgery for CCHD when compared with healthy infants have not been investigated. Several possible mechanisms are proposed. First, the initial comparison of this study was made before the infants with TGA had had corrective surgery. ANS function as measured by LF and HF power was significantly lower in infants with uncorrected TGA when compared with healthy infants in the first few days of life. Infants undergoing neonatal surgery to repair CCHD are in some degree of heart failure prior to surgery (Kaltman, et al., 2006). The impaired function of the heart in the presence of a complex defect reduces tissue perfusion and the body responds by increasing neuorhormones such as norepinephrine, vasopressin, and renin in an attempt to improve perfusion (Packer, 1988). These

neurohormones, along with changes in baroreflex control, lead to sympathetic activation and parasympathetic withdrawal (Packer).

Second, the physical stress of undergoing and recovering from surgery may result in changes in ANS function post-operatively. Specifically, the increased metabolic demand required to manage the healing processes of responding to inflammation and re-building tissue could be reflected in enhanced sympathetic and withdrawn parasympathetic activity. Adults undergoing non-cardiac general surgery were assessed for changes in HRV measures the day before surgery and one day and seven days after surgery (Ushiyama et al., 2008). Indices of HRV were reduced on the first post-operative day when compared with pre-operative levels and had returned to pre-operative levels within seven days. A different type of analysis for HRV was used (time domain measures rather than the frequency domain measures used in this study), but the reductions in indices of HRV demonstrated in this study were consistent with autonomic response to surgical stress expressed in reductions in parasympathetic function. The effect of surgical recovery on ANS function clearly needs further investigation to elucidate mechanisms for reductions in HRV in populations of high-risk infants who have undergone major surgery.

Third, differences in HRV in infants with surgically corrected TGA when compared with healthy infants may be related to the environment at the time of the early observations. Factors of the hospital environment that may affect regulation of physiologic processes include invasive diagnostic or therapeutic treatments (Gunnar et al., 1995; Lindh et al., 1999; Lindh et al., 2000; Oberlander et al., 2005), receiving care from multiple professionals (Sander, 1975), and being separated from the mother (Hofer, 1994; Lehman, Stohr, & Feldon, 2000; Winberg, 2005).

Finally, in healthy infants, parasympathetic withdrawal during feeding is considered to be an adaptive response (Lappi et al., 2007). An adaptive response to the challenge of feeding in infants recovering from cardiac surgery is not known. Perhaps, for these infants, maintaining relatively steady parasympathetic function is useful in preventing a potentially overwhelming sympathetic response. Consistent with Porges' premise that examining parasympathetic function provides sufficient information for assessing response to stress (1992; 1996; 2001), sympathetic activity was not specifically measured in this study. However, analysis of parasympathetic function alone may not be adequate when prolonged physical challenges, such as recovery from major surgery, are experienced. Analyzing sympathetic activity through measures such as cardiac pre-ejection period (Cacioppo, Uchino, & Berntson, 1994) and analyzing complexity and structure of HRV using non-linear measures of variability (Stein et al., 2005) may be useful in more completely describing ANS function in this early post-operative time period.

By two months of age, the infants were in their home environment and tissue repair processes were likely complete. Baseline HRV and likelihood of adaptive changes in HF power during-feeding did not differ between groups at this time. Group differences in post-feeding recovery were seen, although these differences did not reach significance, possibly a function of sample size. Failure to recover to pre-feeding HF power levels at this time point may reveal subtle differences in physiologic regulation for a subgroup of these infants. Recovery from challenge may be a better indicator of adaptive physiologic regulation than absolute HF power values. This is an area that deserves additional research.

Limitations of the study

Because this was viewed as an initial, primarily exploratory study, possible relationships between the major variables were identified theoretically and examined with the goal of detecting areas for subsequent investigation. Choosing to examine a homogeneous sample of

infants with a common heart defect was useful in controlling for the unique functional and physiologic characteristics of different cardiac defects. However, this strategy limited the number of potential participants. A larger sample size may have demonstrated more significant differences between the two groups of infants. In future studies, strategies for increasing sample sizes need to be undertaken in order to allow variance contributed by confounding variables to be partialled out. These strategies may include large, multi-site studies of infants and children with one particular defect as well as developing a method for grouping infants with different congenital heart defects that are similar enough physiologically to yield valid and more generalizable results.

Conducting the study in naturalistic settings was useful in describing ANS function in realistic situations. However, this approach made it difficult to control potential external influences on the measurements, particularly in the hospital setting. In spite of attempts to schedule data collection during times when procedures or activities were not planned, infants prior to surgery and infants recovering from surgery experienced activities that could potentially have affected the measurement of HRV. Other factors that could have affected HRV were ventilatory support (Kaltman et al., 2006) at Time 1 (n = 7) and antiarrhythmic medications (Fei, 1995) at Times 2 and 3 (n = 4 at each time point). Because of the limited number of infants with TGA in the study, the infants with these conditions were included in the analysis, but their inclusion could have affected results.

HRV is also sensitive to differences in infant state (Rosenstock, Cassuto, & Zmora, 1999) and position (Malliani, 1995). Infant position during feeding was consistent (cradled), but the pre-feeding and post-feeding position and state varied. Some infants were sleeping quietly prior to feedings; others were awake and alert. Likewise, some infants fell asleep after feeding while others remained awake and alert. These differences in state and position may have yielded different measurements of HRV. It is not known how significant these differences may be, but healthy infants and infants with TGA had similar variability in state and position.

Nursing implications

Findings in this study suggest potential areas for nursing practice. Infants with a complex congenital heart defect, such as TGA, may be less able to respond adaptively to all phases of feeding and, thus, may require support not only during the actual feeding, but through the post-feeding time as well. Work with other high risk infants suggests that the types of support that may be useful include assisting mothers in identifying and supporting infant strengths, developing strategies to support infant behavioral organization during feeding, and reducing environmental stress during and after feedings (Als et al., 2004).

Conclusions and Future Research

In this study, the effect of correction of this defect on ANS function as compared with ANS function healthy infants was examined with this question in mind: Did correction of this cardiac defect result in ANS function comparable to that of healthy infants? Overall, these findings suggest that infants with TGA differ from healthy infants in their ability to regulate the challenge of feeding in the early weeks following surgical correction. By two months of age, the majority of these differences were no longer apparent. However, the prolonged recovery time observed in infants with TGA at two months raises questions about the equivalence of these groups. Further research in this area is needed to describe mechanisms involved in the physiologic response to feeding and its development over time. Questions that need to be answered include: (a) What measures or group of measures of ANS are most informative for assessing regulation of feeding in infants? (b) What are normative post-feeding HF power recovery times for healthy infants and for infants with surgically

corrected cardiac defects? (c) What characteristics differentiate infants who recover from infants who do not recover in a time frame similar to healthy infants? (d) How might these results differ in a population of infants with different types of CCHDs?

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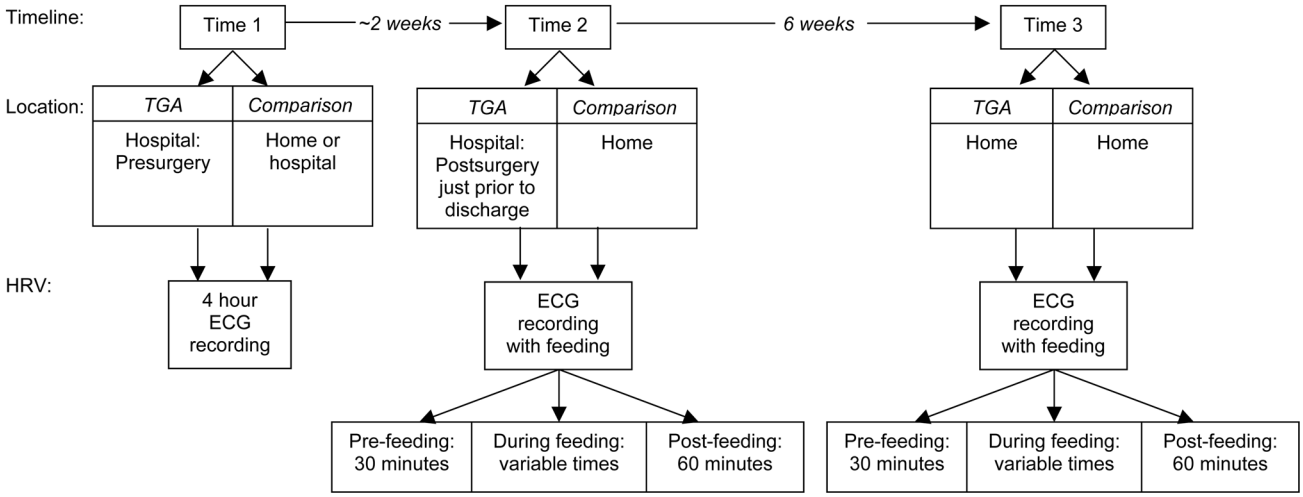

Figure 1.
Diagram of data collection design with timing, location, and type of ECG recording obtained.

Calculation for Time to Recovery to Pre-feeding HF power

Minutes post feeding	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Achieved	X	X	–	–	–	–	X	–	–	–	–	X	X	X	X	X	–	–	–	X

Figure 2.

Calculation of post-feeding recovery time variable. Numbers indicate the number of minutes post-feeding. X indicates each minute during which the infant has achieved HF power post-feeding value at or above median HF power pre-feeding value. The post-feeding recovery time variable is calculated as the first minute of the first occurrence of at least five consecutive one-minute epochs at or above the median HF power pre-feeding value for that infant. See arrow. Time to recovery in this example is 12 minutes.

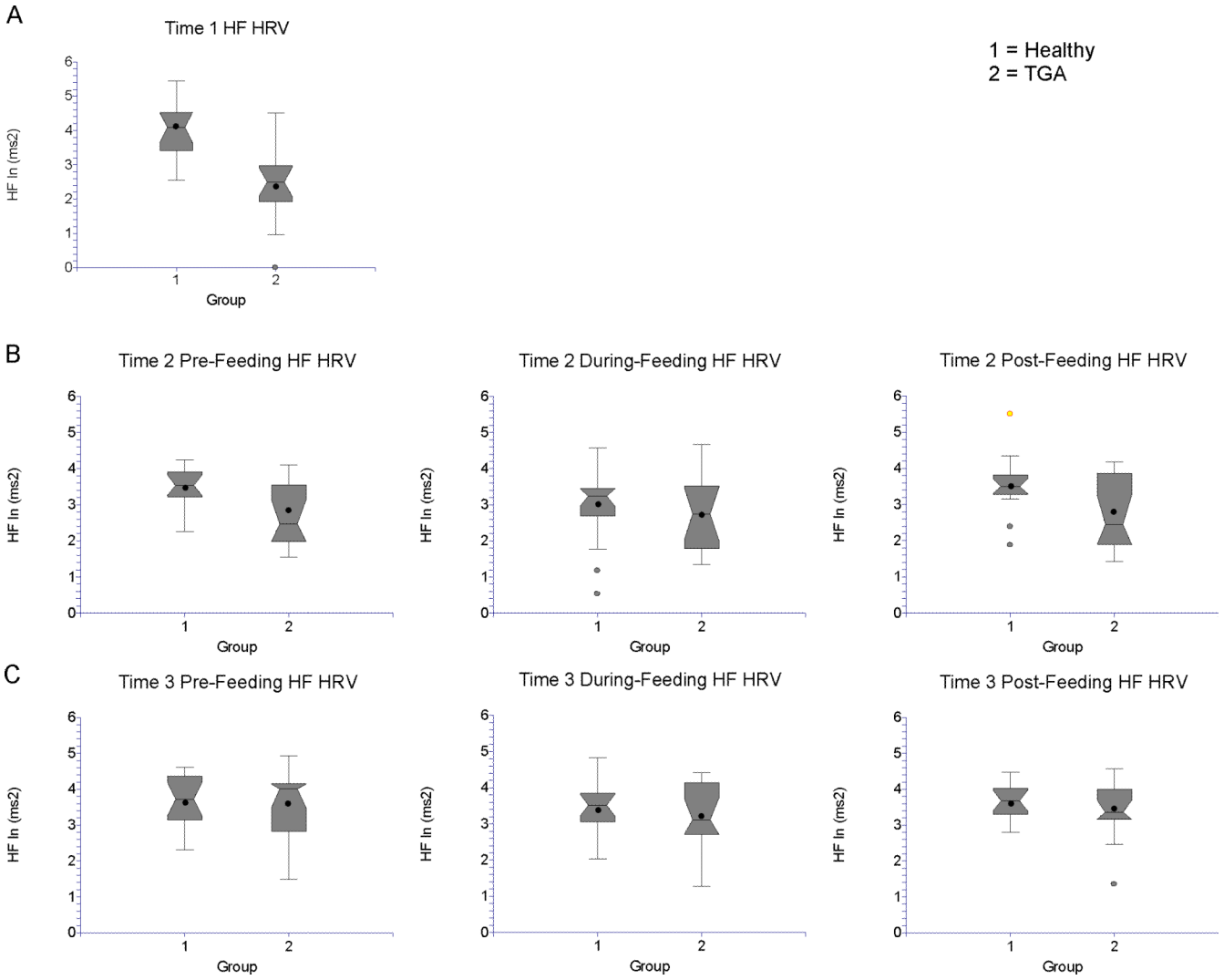

Figure 3.

HF power box plots at Time 1 baseline and Times 2 and 3 across feeding by group. Top border of box plot indicates 75th percentile, lower border 25th percentile. The box itself represents the interquartile range containing 50% of the values. Solid line in body of box plot indicates median value; solid dot indicates mean value. Whiskers above and below box indicate 1.5 times the interquartile range above and below 75th and 25th percentile respectively. Outliers are designated with open circles.

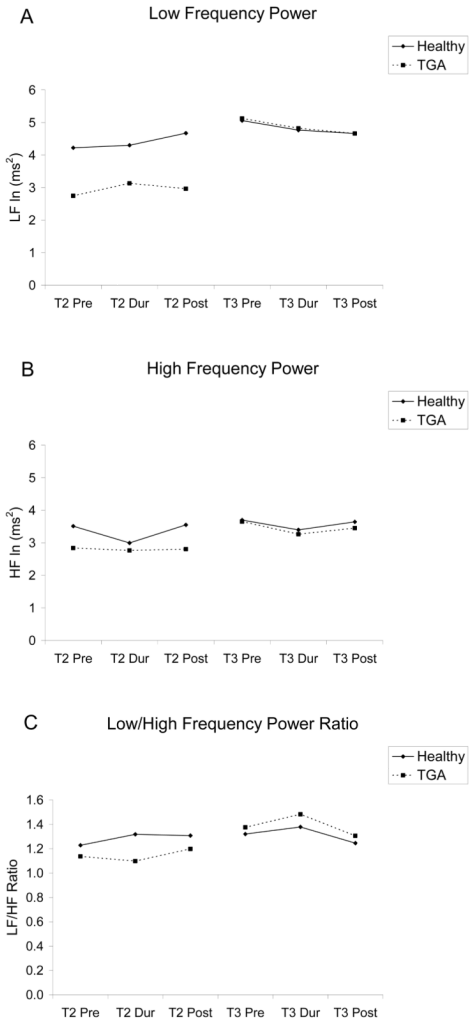

Figure 4.
HRV indices pre-, during-, and post-feeding at two points in time by group. (A) LF = low frequency power (sympathetic and parasympathetic activity), (B) HF = high frequency power (parasympathetic activity), (C) LF/HF ratio = low/high frequency power ratio.

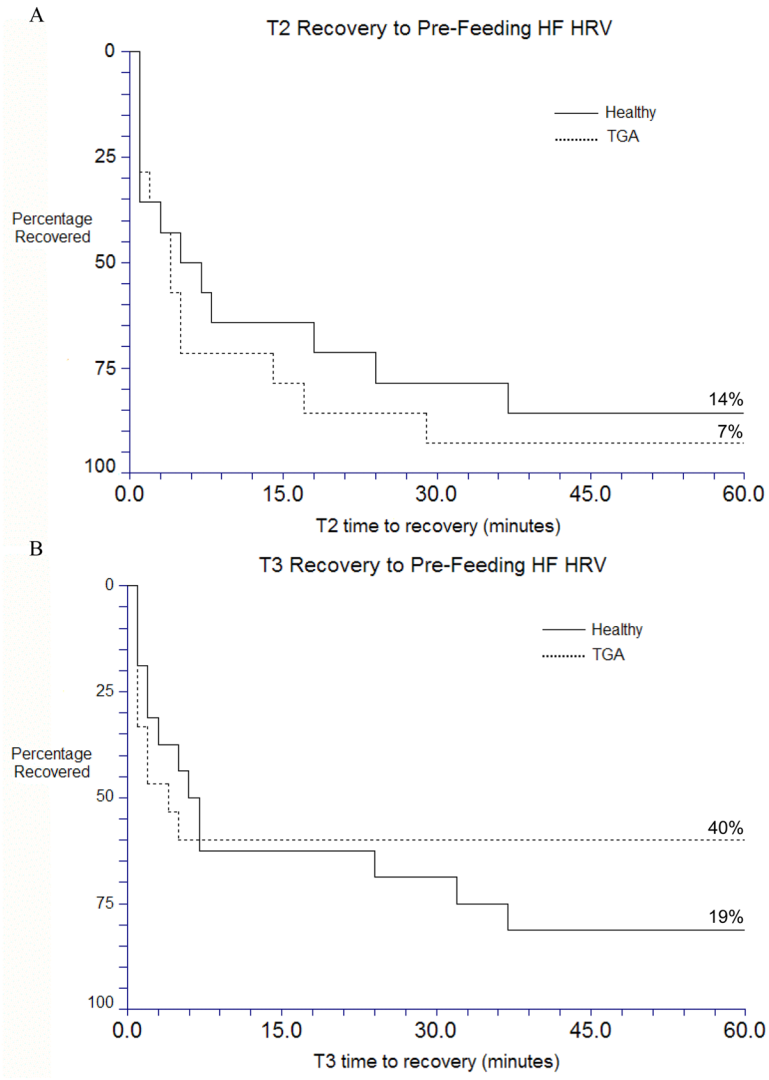

Figure 5.

Time 2 (A) and Time 3 (B) recovery to pre-feeding HF power by group. X axis indicates time in minutes since feeding was finished. Y-axis indicates percentage of infants who have recovered to pre-feeding mean HF power values. Solid lines indicate healthy infants; dashed lines TGA infants. At Time 2 (A), 14% of healthy infants and 7% of TGA infants had not recovered by the end of the 60 minutes post feeding observation. At Time 3 (B), 19% of the healthy infants and 40% of the TGA infants had not recovered.

Table 1

Pearson's Correlation: Mean N-N interval v. SDNN

	Time 1	Time 2	Time 3
TGA	0.329	0.267	0.224
Healthy	0.643	0.283	0.474

Note: N-N = Normal to Normal heart beat intervals, SDNN = Standard deviation of N-N intervals, a measure of total power.

Table 2

Heart Rate Variability Indices with Mann-Whitney Comparisons Between Groups[a]

	Healthy				TGA					
	Mean	**Median**	**SD**	**Range**	**Mean**	**Median**	**SD**	**Range**	***U***	***p***
High Frequency										
T1 Baseline	4.18	4.12	0.97	2.55 – 6.41	2.39	2.51	1.05	0.01 – 4.51	218	<0.001
T2 Pre-Feed	3.51	3.55	0.59	2.26 – 4.25	2.84	2.50	0.91	1.55 – 4.20	149	0.06
T2 During-Feed	2.99	3.26	1.05	0.54 – 4.58	2.76	2.76	1.04	1.35 – 4.68	133	0.38
T2 Post-Feed	3.55	3.51	0.78	1.89 – 5.51	2.80	2.51	0.97	1.42 – 4.18	155	0.08
T3 Pre-Feed	3.70	3.74	0.65	2.31 – 4.61	3.65	4.03	0.94	1.49 – 4.93	117	0.91
T3 During-Feed	3.39	3.53	0.73	2.04 – 4.83	3.26	3.13	0.88	1.27 – 4.41	118	0.81
T3 Post-Feed	3.64	3.69	0.47	2.79 – 4.48	3.45	3.37	0.81	1.36 – 4.57	133	0.63
Low Frequency										
T1 Baseline	5.27	5.17	0.67	4.45 – 6.63	1.72	1.93	1.29	.00 – 4.04	240	<.001
T2 Pre-Feed	4.34	4.22	0.61	3.31 – 5.59	2.81	2.75	1.26	.82 – 4.75	167	<.001
T2 During-Feed	3.98	4.30	1.01	1.84 – 5.31	2.79	3.13	1.59	.12 – 5.39	167	.02
T2 Post-Feed	4.65	4.67	0.56	3.62 – 5.58	2.72	2.96	1.36	.47 – 4.51	210	<.001
T3 Pre-Feed	4.76	5.06	0.90	2.66 – 5.85	4.95	5.12	0.97	2.62 – 6.36	111	.74
T3 During-Feed	4.68	4.76	0.87	3.20 – 6.00	4.65	4.82	1.06	2.74 – 6.29	111	.98
T3 Post-Feed	4.55	4.66	0.56	2.72 – 5.19	4.70	4.66	0.83	2.83 – 6.03	105	.57
LF/HF Ratio										
T1 Baseline[b]	1.29	1.27	0.18	1.03 – 1.81	0.85	0.55	0.84	.00 – 2.96	159	.05
T2 Pre-Feed	1.26	1.23	0.24	.96 – 1.97	1.08	1.14	0.42	.33 – 1.78	119	.35
T2 During-Feed	1.46	1.32	0.52	.89 – 3.15	1.04	1.10	0.54	.10 – 1.93	156	.07
T2 Post-Feed	1.35	1.31	0.29	.29 – 2.29	1.02	1.20	0.51	.04 – 1.82	149	.13
T3 Pre-Feed	1.30	1.32	0.21	.85 – 1.81	1.39	1.38	0.21	1.03 – 1.85	93	.30
T3 During-Feed	1.40	1.38	0.18	1.12 – 1.82	1.49	1.48	0.27	1.04 – 2.10	87	.31
T3 Post-Feed	1.26	1.25	0.13	1.01 – 1.48	1.37	1.30	0.20	1.12 – 1.94	80	.12

Note. T1 = pre-surgery; T2 = postsurgery; T3 = 6 weeks after T2. TGA = transposition of the great arteries.

[a] Values reported as ln (ms^2).

[b] One outlying TGA LF/HF ratio value removed from analysis (0.78/0.01=78).

Table 3

Parameter Estimates (Standard Error) HF Power Change Model

	Intercept	Group
T2PreDurCh	.396 (.532)	−1.678 (.838)*
T2DurPostCh	.788 (.539)	−1.041 (.761)
T3PreDurCh	.511 (.516)	−.258 (.745)
T3DurPostCh	.251 (.504)	.316 (.750)

Note. T2PreDurCh = Time 2 Pre-Feeding to During-Feeding Change in HF Power, T2DurPostCh = Time 2 During-Feeding to Post-Feeding Change in HF Power, T3PreDurCh = Time 3 Pre-Feeding to During-Feeding Change in HF Power, T3DurPostCh = Time 3 During-Feeding to Post-Feeding Change in HF Power.

*$p < .05$.