

**Quantification of the Burst Phase during Non-Nutritive Suck Production in
Preterm Infants**

BY

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Brief Overview

Premature birth places infants at increased risk for learning disabilities, delayed development of speech, language and motor skills, and mortality. The premature infant often has difficulties with respiration and feeding and therefore may remain in the hospital for prolonged periods of time. The non-nutritive suck (NNS) is a motor behavior which can be observed and used to make inference about brain development and organization in this young population. The purpose of this study was to quantify the frequency modulation of the NNS burst in two groups of preterm infants, including those with and those without respiratory distress syndrome (RDS). Thirty-two (32) preterm infants were consented and distributed into one of the following groups: Control (N=17) and RDS (N=15). Digitized samples of NNS compression pressure waveforms were collected 15 minutes prior to scheduled feedings on a weekly basis. Quadratic regression analysis revealed that healthy preterm infants produced longer NNS bursts and the mean burst initiation cycle periods were shorter when compared to the RDS group. Moreover, NNS burst initiation shows a prominent frequency modulated (FM) segment upon initiation which appears to be a significant feature of the suck central pattern generator (sCPG) and is markedly different for RDS preterm infants as compared to their healthy preterm counterparts. Identification of such characteristics provides specific criteria and description of the NNS CPG which may offer a new diagnostic criterion which can be used to gauge the developmental status of oromotor control systems among these fragile infants.

Chapter 1: Introduction

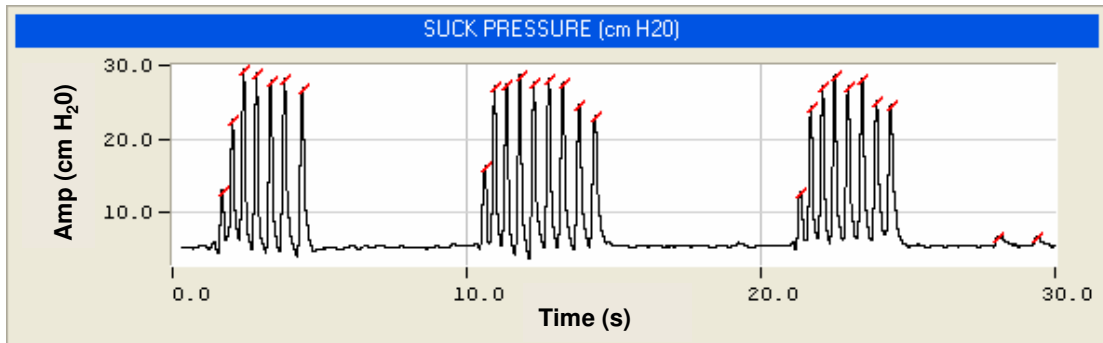
Prematurity has become increasingly more prevalent with an incidence rate of 12.8% in 2006. This is up from 9.4% in 1981 (Hoyert, Mathews, Menacker, Strobino, & Guyer, 2006). Infants that are born prematurely are at higher risk for developmental disabilities, learning disabilities, and delayed motor, speech, and language development than infants born at full term. Additionally, prematurity carries a higher morbidity and mortality rate than full term birth (Hoyert et al., 2006). Premature birth disrupts brain development and often introduces the infant to unfamiliar and often unpleasant stimuli. Infants born prematurely are at high risk for respiratory disease and feeding difficulties which contributes to prolonged stays in the neonatal intensive care unit (NICU). The third trimester of gestation (28 weeks gestation to birth) is dedicated to brain organization including the establishment of brain circuitry and preparation for the completion of development (Adams-Chapman, 2006). During the final months of gestation, Le Winn (1969) described the direct relation between brain circuitry and environmental interactions in the statement, "In large part the success or failure of the individual in relating to his environment depends on his neurological organization" (LeWinn, 1969). An interruption in neural organization can result in dyscoordination of motor behaviors including sucking and feeding.

Development of suck in infants

The sequence of oral motor movements *in utero* has been observed as early as 14 weeks postmenstrual age (PMA), but sucking and swallowing do not show coordination until 32-34 weeks PMA (Pinelli & Sympington, 2000). Hack,

Estabrook, and Robertson (1985) observed rhythmic bursts of oromotor activity between 28 and 33 weeks gestation. Non-nutritive suck (NNS) is defined as a repetitive mouthing activity on a pacifier or a nipple without expelling any liquid stimulus, is thought to be regulated by the suck central pattern generator (sCPG), and is presumed to provide the foundation for oral feeding (Goldson, 1987; Tanaka, Kogo, Chandler, & Matsuya, 1999; Wolff, 1968). The repetitive mouthing activity consists of two components, a burst component and a pause component. Figure 1 provides a graphical waveform plot visual tracing of the intraluminal pressure change during NNS.

Figure 1. 30-second sample of non-nutritive suck pressure amplitude measured in cmH₂O.



Advanced NNS activity is characterized by the classic ‘burst-pause’ compression pattern. As shown in Figure 1, the ‘burst’ consists of several cycles of compression behavior on the silicone nipple resulting from contraction of perioral, mandibular and lingual muscles around the cylinder of the Soothie pacifier. The time period of inactivity between bursts is known as the ‘pause’. Characteristics of the NNS can be described in terms of *coarse* and *fine* structure. The coarse structure of the NNS refers to a simple tally of the number of bursts and pauses, the duration of each, and

the number of sucks within each burst. The fine structure of the NNS defines within-burst characteristics such as the period and amplitude of each burst cycle (Lau & Schanler, 1996) or spatiotemporal stability (Poore, Zimmerman, Barlow, Wang, & Gu, 2008). Exploration into the coarse and fine structure of the NNS provides information on the modulation of the suck as a result of development, medical diagnoses, and sensory experience and can be used to assess the infant's neurological organization (Mizuno & Ueda, 2005; Stumm, Barlow, Estep, Lee, Cannon, Carlson, & Finan, 2008; Estep, Barlow, Vantipalli, Finan, & Lee, 2008; Poore et al., 2008; Barlow & Estep, 2006; Barlow, Finan, Chu, & Lee, 2008). The aim of this paper is to quantify and model the fine structure of the NNS burst by using regression to model the non-nutritive suck cycle periods, expressed as frequency, across the duration of the burst. Such a model would allow for comparison across groups varying in the degree of sensory deprivation/motor restriction and can be used to monitor change due to maturation and intervention.

Animal models suggest that the NNS pattern is driven by a CPG which is sensitive to sensory input, modified by experience, and modulated by descending inputs from somatosensory cortex and cerebellum. Löwel and Singer (1992) identified a key characteristic underlying the assembly and development of neural circuits, “neurons that fire together will wire together.” Herein lays the significance of experience. Genetics has a significant role in the development of such circuits, but these systems are also experience-dependent.

Prematurity not only disrupts the natural experiences obtained *in utero*, but also introduces the infant to an environment potentially filled with sensory deprivation, movement restriction and maladaptive stimuli. Preterm infants are at risk for respiratory and feeding difficulties and subsequently need medical intervention which may include insertion of a tube into the throat, placement of an oxygen mask over the nasal/oral cavity, and taping of poly tubes onto the face. There are three medical interventions commonly used in the treatment of respiratory insufficiency. Oxygen is introduced directly into the lungs using a ventilator and indirectly through continuous positive airway pressure (CPAP) and nasal cannula. Ventilation is accomplished through placement of oral tubes that descend through the trachea and terminate at the level of bifurcation of the trachea into the bronchi. CPAP incorporates a mask that can be placed over the nose (nasal CPAP), or over the mouth and nose, simply referred to as CPAP. Though less invasive than endotracheal intubation, this method limits the infant's access to the perioral region and presents an unexpected set of unpleasant sensory consequences. Nasal cannulation is the third method of oxygen therapy commonly utilized in NICUs. This approach introduces oxygen to the nasal cavity through an external tube secured to the infant's face using medical tape. Endotracheal tubes used for intubation can be metal or plastic and vary in size to provide the best fit for the patient. Tube sizes vary from 2.5 to 3.5 mm internal diameter and 5.5 to 11 cm in length (Table 1). The size of the endotracheal tube is determined by the infant's age and weight (American Heart Association, 2000).

Table 1. Oral and nasal tube internal diameters and length according to baby age in weeks.

Baby Age (weeks)	Baby Weight (weeks)	Baby Age (weeks)	Oral Tube Length at Lip (cm)	Nasal Tube Length at Nose (cm)
<32	<1.0	2.5	5.5	7.0
<32	1.0	2.5-3.0	6.0	7.5
32-38	2.0	3.0	7.0	9.0
>38	3.0	3.0	8.5	10.5
>38	3.5	3.0-3.5	9.0	11.0
>38	4.0	3.5	9.0	11.0

Oral feeding can also be difficult for the premature infant and thus require nutrition through alternative means. Tube and intravenous (IV) feedings are the primary alternative methods to meet the nutritional needs of the infant. There are two prominent modes of tube feeding both involving a poly tube extending from the face to the stomach. The nasogastric tube (NG) is inserted through the nose and terminates in the stomach. The NG is typically soft, flexible, and small in outside diameter (approximately 1.7 mm). The orogastric tube (OG) also terminates in the stomach by way of the oral cavity. The OG is typically larger in diameter (2.7 mm) than the NG and its position tends to drift and is difficult to secure to the face. Intravenous feedings usually take the form of total parenteral nutrition (TPN). This feeding mode provides the infant with all the necessary protein, lipids, carbohydrates, vitamins and minerals needed, but bypasses the digestive system and directly introduces these substances to the blood stream.

The respiratory and nutritional problems that arise as a result of prematurity are overcome through methods that unfortunately restrict oral movement and alter the

sensory environment for the baby. For example, the effect of limited accessibility to the perioral region or exposure to unpleasant stimuli may result in varying output of the sCPG or a disorganized NNS pattern. Stumm et al. (2008) found a significant difference in the number of NNS bursts and the peak amplitude of suck compression cycles among RDS infants in restrictive environments. These movement-restricted and sensory deprived infants demonstrated higher, less efficient burst frequencies and lower peak amplitudes as compared with their matched controls (Estep et al., 2008).

Effects of the Environment: Stimulation and Deprivation

The presence of salient sensory stimulation during the early postnatal period is critical to the development of the structure and function of the motor cortex and cerebellum (Pascual, Fernandes, Ruiz, & Kuljis, 1993; Pascual, Hervias, Toha, Valero, & Figueroa, 1998). Neuronal circuits are shaped by experience during critical periods of early postnatal life and may remain in a waiting state until appropriate sensory input is provided (Hensch, 2004). Several studies have been performed to explore the correlation between environmental factors and brain growth and development. Some studies explored the effects of deprived or stimulating environments. These studies demonstrated that dendrogenesis in the Purkinje cell is significantly influenced by movement restriction in the early post-weaning period of a rat. Specifically, the dendritic length and density was reduced in deprived environments as compared to the control environment (Pascual et al., 1993; Pascual et al., 1998). Additionally, environmental stimulation is a significant factor in the development of the pyramidal neurons present in the motor cortex during the early postnatal period. Manipulation

of the sensory system during the early postnatal period has profound effects on the development of the structure and function of the motor cortex. In fact, dendritic length and arborization is increased as a result of exposure to stimulating environments. Behavioral responses were improved when the subjects performed tasks such as exploration, balancing, climbing, and postural control (Pascual & Figueroa, 1996). The effects observed in each environment, deprived and stimulating, are irreversible.

Critical Periods

Critical periods are described as windows in development in which systems or processes are particularly vulnerable. The most rapidly growing tissues are most sensitive to the change in conditions (Stockard, 1921). Systems that demonstrate irreversible structural modification beyond a certain age may be said to have critical periods. Age is not the sole influence on critical periods. In fact, experience is said to play a role in the onset and duration of a critical period such that a critical period can be prolonged if the appropriate stimulus is not encountered. Classical studies have shown that the effects of sensory deprivation and alterations in sensory input are evident only when the manipulation of the sensory input is made during the critical period; similar deprivations and alterations in mature animals have little or no effect. During the critical period, some sensory functions reach maturity: for example, the end of the critical period for monocular deprivation roughly coincides with the completion of visual acuity development in a number of species. Experience-dependent plasticity during the critical period is closely related to the maturation of

sensory functions so that experience is required during the critical period in order that sensory functions fully mature. Some aspects of cortical organization are also modifiable, by experience, even in the adult. Hensch (2004) stated that a “Critical period is not just a simple, age-dependent maturational process but is rather a series of events itself controlled in a use-dependent manner.” Experience strongly determines the duration of critical periods. A total lack of experience usually prolongs critical periods and delays sensory development (Berardi, Pizzorusso, & Maffei, 2000).

Hensch (2004) described the main purpose of a critical period as tailoring the neuronal circuits so that they are “custom fit” for each individual. Critical periods greatly influence experience-dependent plasticity in visual, auditory and somatosensory systems (Berardi et al., 2000). Imprinting, ocular dominance, human language, and sound localization are examples of systems that have known critical periods (Hensch, 2004). Given the rate limiting processes present in the NICU, it appears that the emergence and stabilization of the sCPG may also have a critical period. Stumm et al. (2008) described a population of infants with respiratory distress syndrome (RDS) warranting extensive oxygen therapy as having lower average NNS amplitude pressures and high frequency, less efficient suck patterns.

Neural development during a critical period is required for proper motor control and coordinated movement later in life. Neuronal circuits are shaped by experience during critical periods of early postnatal life. If appropriate neural activation is not

provided at all, then developing circuits may remain in a waiting state until such input is available (Hensch, 2004; Bosma, 1973). However, such a delay may result in failure to fully develop the skills resulting in uncoordinated or absent behavior.

Central pattern generators

Central pattern generators (CPGs) can be thought of as neural circuits located in the cerebral cortex, brainstem, and spinal cord that drive rhythmic motor behavior such as sucking, breathing, mastication and locomotion and can be modulated by a variety of external inputs (Barlow et al., 2008; Ingersoll & Thoman, 1994; Sammon & Darnall, 1994; Barlow & Estep, 2006; Zimmerman & Barlow, 2008).

Westberg, Clavelou, Sandstrom, and Lund (1998) suggested three basic categories of neural circuits, dedicated, reorganizing and distributed. *Dedicated* circuits are hard-wired to perform a specific task, such as respiration. *Reorganizing* circuits are circuits that reconfigure or recombine with other circuits to modify or change their output. *Distributed* circuits link distinct locations of the central nervous system. Sucking is an example of a distributed circuit as the behavior links cortical sucking area in motor cortex with the reticular formation of the pons.

The relative inaccessibility of CPGs has limited its study to less complex animals such as insects and invertebrates. Research in *Drosophila* demonstrated embryonic peristaltic movement in mutant flies with impaired peripheral sensory function or almost no peripheral sensory neurons (Marder, 2002). Another characteristic of many CPGs is that different behaviors can be evoked through the coupling or coordination

of individual CPGs. This occurs within a large circuit by swinging interneurons from one circuit to another depending on the load dynamics and the desired output. For example, breathing and gasping are two behaviors which incorporate similar musculature but different components of a large circuit (Marder & Bucher, 2001). CPGs can also reconfigure in response to injury so that similar behaviors can be performed by way of differing pathways/circuits.

Ororhythmic and respiratory CPGs have been studied extensively. Lund and Kolta (2006) described the ororhythmic CPG as a complex interplay between cortex, pattern generators in the brainstem, reflex interneurons and lower motoneurons. Smith, Ellenberger, Ballanyi, Richter, and Feldman (1991) identified the location for the respiratory CPG in the Pre-Bötzinger complex located within the brainstem. Descending inputs play a role in modulating this CPG. Transections of the brainstem in rats were completed to localize neural circuits that drive ororhythmic movement (Tanaka et al., 1999). Ororhythmic patterns appear to be coordinated by bilateral neural circuits capable of functioning independently of one another in the presence of a hemisection. The minimal circuitry required to observe ororhythmic activity is found between the caudal trigeminal motor nucleus and rostrally within 1 mm of the trigeminal motor nucleus.

CPGs are dynamic and can be affected by external factors (Frigon & Rossignol, 2006). They can be modulated through pharmacological means, adjusting the work that is required, or manipulating external sensory input. Serotonin (5-HT) for

example, has been explored in many studies as a neuromodulatory chemical that has a direct influence on CPGs (Straub & Benjamin, 2001; Yeoman, Brierley, & Benjamin, 1996). Zimmerman and Barlow (2008) examined the effect of load dynamics on the sCPG. As dynamics changed by increasing or decreasing the stiffness of a pacifier, infants were observed to significantly modify their burst structure and output levels of the sCPG. Sammon and Darnall (1994) performed a study which examined the ability of a preterm infant to synchronize his/her respiration to the vestibular input experience through rocking. Infants not only demonstrated coherence, but they also found that the respiratory CPG had a maturational component such that younger infants demonstrated greater coherence than older infants. Ingersoll and Thoman (1994) explored the effects of the respiration rate of preterm infants when introduced to a rhythmic auditory stimulus. More regular breathing was observed in infants that were exposed to the stimulus thus supporting the ability of the respiratory CPG to modify in the presence of a patterned sensory input. These principles can also be applied to the ororhythmic CPG. Finan and Barlow (1998) explored the modulatory capabilities of the NNS by introducing rhythmic mechanical stimulation of the lips and tongue. Such stimulation activated cutaneous receptors. This study found that temporal aspects of the sCPG could be altered supporting previous research that sensory feedback has an important role in influencing the output of CPGs.

The present report is concerned with the patterning of the sCPG burst in RDS infants who have endured extended periods of sensory deprivation and motor restriction due to oxygen supplementation therapy. Particular attention is given to the NNS burst

initiation and frequency modulation of suck compression cycles among RDS and healthy control preterm populations. We expect to find a relation between the NNS trajectory and RDS severity which will lead to the formulation of a mathematical model of NNS burst cycle dynamics.

Chapter 2: Research Study

Methods

Subjects

The participants for this study were preterm infants admitted to and receiving care in the NICUs of Stormont-Vail Regional Health Center and the University of Kansas Medical Center. Infants were consented with the following inclusion criteria: head circumference within 10-90th percentile of mean for PMA, neurological examination showing no anomalies for PMA (response to light, sound, and spontaneous movements of all extremities), and with stable vital signs (heart rate, blood pressure, age appropriate respiratory rate, and oxygen saturation >92 SpO₂) to allow for NNS. Exclusion criteria: intracranial hemorrhage, hypoxia-ischemia encephalopathy, periventricular leukomalacia (PVL), neonatal seizures and culture positive sepsis or meningitis at time of testing, chromosomal anomalies or craniofacial malformation.

Thirty-two (32) infants were included in this study, 16 female and 16 male. The mean gestational age (GA) was 30.61 weeks and the mean birth weight was 1424.15 grams. These infants were distributed among two groups, Control and RDS, according to their oxygen and percent daily oral feeding histories. At 34.11 weeks

PMA, the Control infants (n=17) averaged less than a day and a half of oxygen therapy, no ventilation was required, and feeding 22.46% orally. Infants in the RDS group (n=15) had an average of 34.2 days of oxygen therapy and demonstrated marked deficits in oral feeding, 3.87% per Os (PO, i.e., by mouth) (Table 2).

Table 2. Clinical Characteristics of Infants.

VARIABLE		CONTROL (n=17)	RDS (n=15)
Gender (male: female)		8:9	8:7
Birth GA (wks)		31.5 (1.4)	29.6
Birth Weight (gms)		1518.7 (318.6)	1317.0 (480.8)
PMA (weeks)	Session 1	33.56 (1.7)	34.69 (1.9)
	Session 2	34.66 (1.6)	35.41 (1.8)
	Mean	34.11 (1.7)	35.05 (1.9)
% Oral Feed	Session 1	13.2 (4.0)	1.73 (6.4)
	Session 2	34.47 (9.5)	6.00 (10.1)
	Mean	22.46 (6.8)	3.87 (8.6)
O₂ History (days)	VENT	0.00 (0.0)	5.73 (8.1)
	CPAP	0.71 (1.1)	8.4 (8.6)
	Cannula	0.65 (1.3)	20.07 (18.9)
	Total	1.35 (1.7)	34.2 (28.6)

Data collection

Infants were consented by the study NICU nurse and neonatologist at Stormont-Vail Healthcare (Topeka, Kansas) and the University of Kansas Medical Center (Kansas City, Kansas). All infants had been extubated for at least 5 days at the time of testing. Recording of NNS was initiated after 32 weeks PMA and continued on a weekly

basis until the infant was discharged or transferred from the hospital. Infants were tested for NNS dynamics over two consecutive sessions at crib-side approximately 15 minutes prior to scheduled feedings.

Infants remained connected to pulse-oximetry monitors (respiration, EKG, and SpO₂) at all times prior to and during testing. A brief examination of the infant's physiological state including checking temperature, heartbeat, and lungs, was completed by the attending nurse prior to testing. The infant was placed in a developmentally supportive position, including head support, arms and hands swaddled at midline. The infant's pacifier was placed on a pressure instrumented receiver which allowed real time analysis of the NNS using NeoSuck RT[®], a software program developed in the Communication Neuroscience Laboratories at the University of Kansas.

Instrumentation

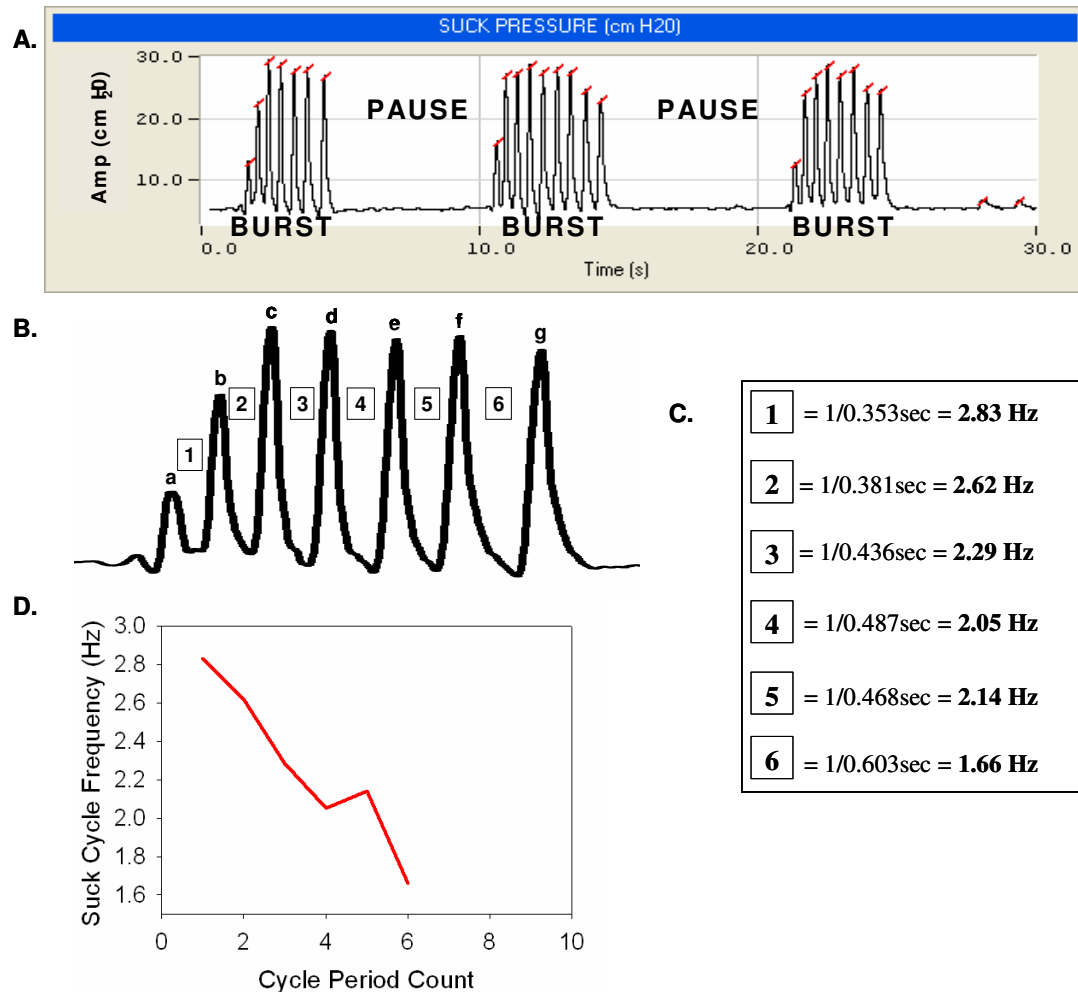
The Actifier II is a specialized device which enables detection of intraluminal pressure changes within a pacifier. The infant's Soothie[™] pacifier (Children's Medical Ventures, Inc.) was placed at the end of a specially designed lubricated Delrin receiver. A Luer pressure line attached the Delrin receiver to a pressure transducer. The analog signal detected by the pressure sensor was converted to a digital signal using a 16-bit analog-to-digital converter (3 Ksamples/sec).

Analysis

The numeric data consisted of time segments referred to as suck cycle periods. These suck cycle periods were obtained from the digitized NNS pressure waveform record

obtained using the Neosuck RT[®] software program and converted to frequency using the formula $F=1/T$; where F equals frequency (Hertz or Hz). This measure represents the instantaneous cycle rate between two consecutive pacifier nipple compression pressure peaks, and T is the time period (seconds) between two consecutive compression pressure peaks (Figure 2).

Figure 2. (A) Characteristic burst-pause pattern of NNS. (B) Outset window of the first burst in the 30-second sample. This burst has 7 cycles, identified by letters a-g, and 6 suck cycle periods, identified by numbers 1-6. (C) Each cycle period consists of a time segment describing the amount of time taken to accomplish 1 cycle. The time is recorded in milliseconds and converted to Hertz (Hz), as demonstrated. (D) Plot of cycle period count versus suck cycle frequency (Hz) for the frequencies derived in part (C).



Outliers, defined as burst length beyond 13 cycle periods for Control infants, and 9 cycle periods for RDS infants, were excluded from the analysis. The resultant data were graphed as suck cycle frequency (Hz) as a function of suck cycle period index. An exponential decay regression function was used to characterize the relation between these two variables.

Chapter 3: Results, Discussion and Concluding Comments

Results

T-tests were used to compare the mean burst length of the respective groups. There was a significant difference ($p < .05$) in the mean burst length between the groups with the longest mean burst length (5.67 cycles/burst) belonging to the healthy preterm controls and the shortest mean burst length (3.87 cycles/burst) associated with the RDS infants (Figure 3).

Figure 3. Mean burst length and standard error by group.

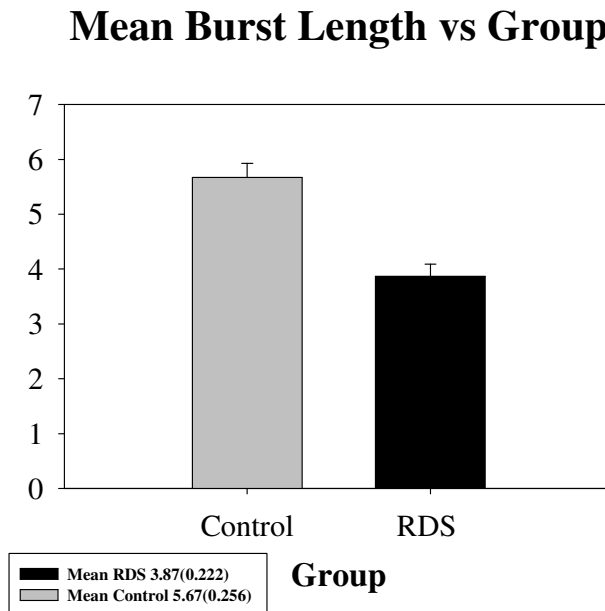
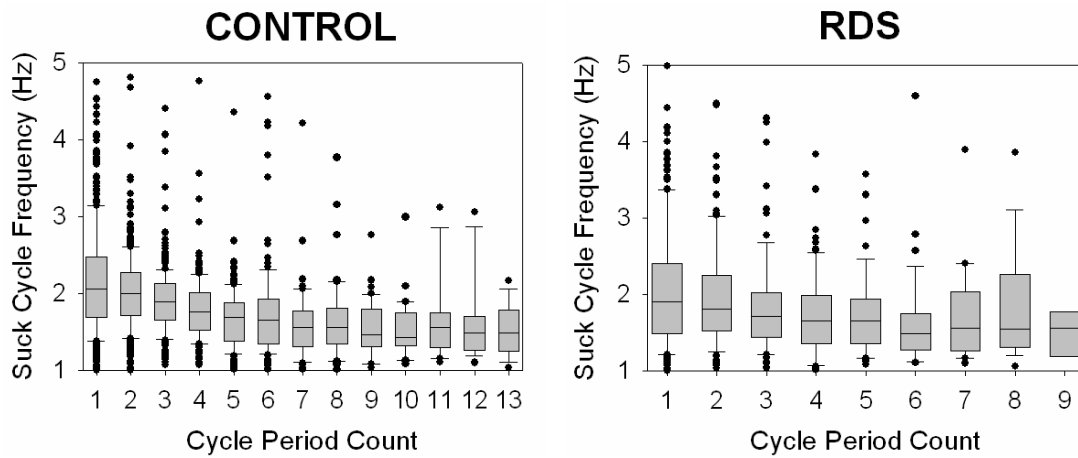
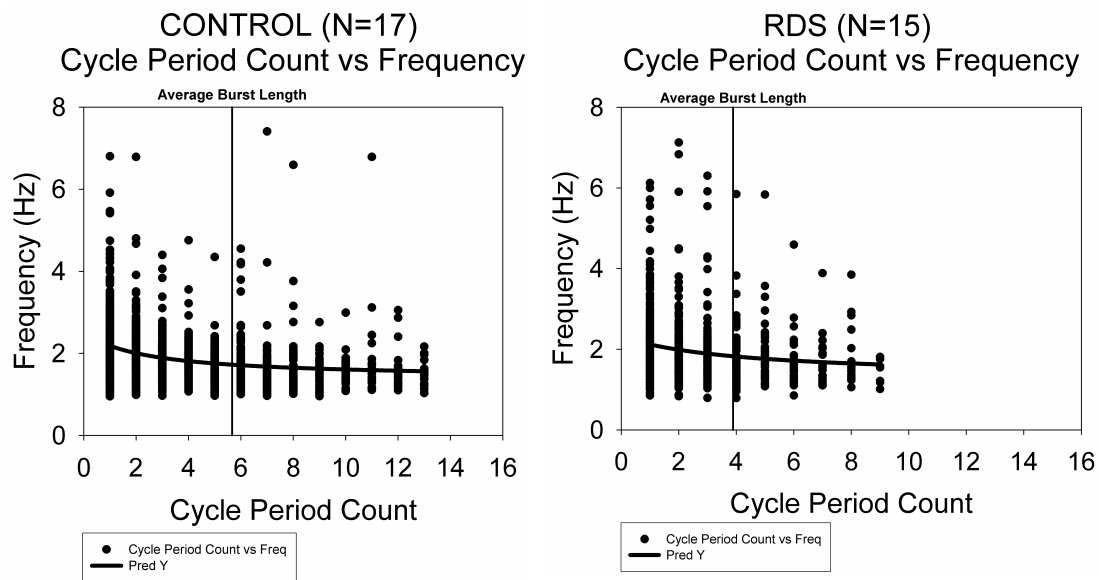


Figure 4. Control and RDS box plots.



An analysis of the data using box plots demonstrated the trajectory of the frequency modulated component providing further support of the use of exponential decay regression to describe the relation between suck cycle frequency and cycle period count (Figure 4).

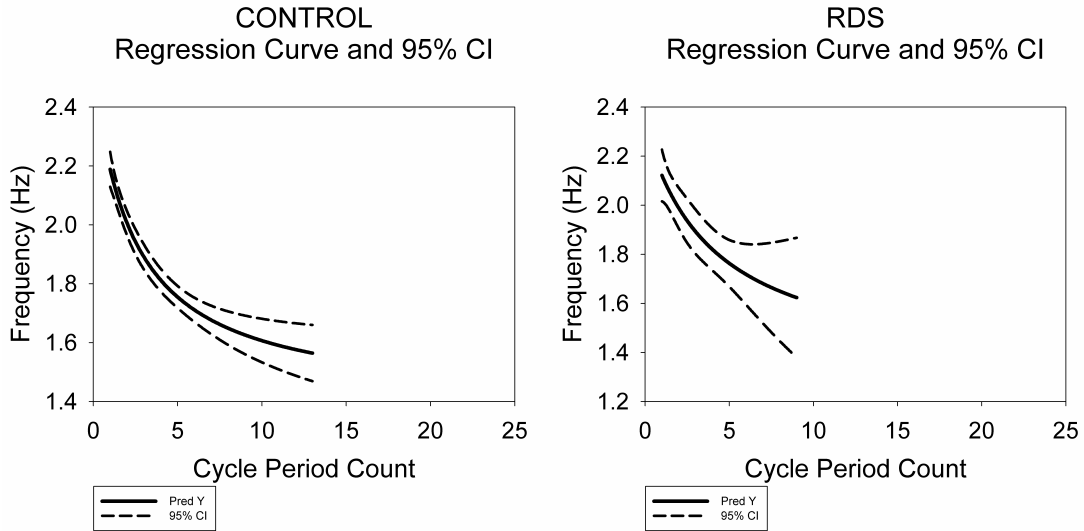
Figure 5. Control and RDS scatterplots with regression curve and average burst length superimposed.



Exponential decay regression revealed the mean suck rate of infants with respiratory distress as faster than the healthy control infants, 1.944 Hz and 1.905 Hz respectively (Figure 5).

A comparison between Control infants and infants with RDS demonstrated a significant difference in the frequency variability of the regression curve between groups. Relative to RDS infants, healthy preterm Control infants had much less variability in the trajectory and course of the regression curve across bursts, as observed in the narrower 95% confidence intervals. In contrast, the RDS infants had greater variability across bursts and subjects in the trajectory and course of the regression curve (Figure 6). The initiation and slope of the trajectory for each group was distinctly different though both lines demonstrate a decrease in frequency with progression through the burst (Figure 6). The Control regression line and RDS regression line were described by $y=1.3902^{1.9166/x+3.2240}$ and $y=1.3082^{3.1253/x+5.4661}$ respectively. The F-values for Control and RDS infants were 86.06 ($p<.0001$) and 11.80 ($p<0.0001$) respectively.

Figure 6. Control and RDS regression curve and 95% confidence interval.



Discussion

According to previous studies of the NNS, there are certain parameters expected to be present at various stages in gestation. For example, a well-organized suck consisting of approximately 7 cycles per burst, average frequency of 2 Hz, and average peak amplitude of 17 cm H₂O is expected by 32 weeks gestation (Pinelli & Sympington, 2000; Stumm et al., 2008; Estep et al., 2008; Wolff, 1968). While these are important global variables to consider when describing NNS behavior, they do not characterize the recruitment and evolution of the sCPG burst pattern.

The central nervous system, including central pattern generators can be modified by environmental factors (Pascual et al., 1993; Pascual et al., 1998; Zimmerman & Barlow, 2008; Estep et al., 2008; Stumm et al., 2008). In this study, the output of the

sCPG was presumably modified by the environmental factors associated with the treatment of RDS and not the structure or physiology of the disease state.

Specifically, the output of the sCPG for the RDS infants was decreased in burst length, burst initiation frequency, and frequency modulation relative to the healthy control infants. The results from this study are consistent with effects on systems that experience critical periods. A key feature of systems that have critical periods is the ability of that system to respond to perturbations during set times in development. A system that is able to be perturbed and return to typical output would not be considered to have a critical period. A system that is irreversibly influenced by environmental factors would be said to have a critical period. The NNS in infants with RDS demonstrated a pattern that was aberrant from the pattern of Control infants suggesting the vulnerability of the NNS during a specific time in development.

Frequency Modulation

Modulation of biological rhythms in the amplitude and frequency domain is an inherent property of many different systems, motor as well as sensory, voluntary as well as autonomic. Studies of locomotion including swimming in the lamprey and walking in the cat have identified this motor system with the ability to modulate in the frequency domain. The auditory and visual systems have also demonstrated frequency modulation in the decoding of sensory signals. Heart rate and interactions between sympathetic and parasympathetic nerves have demonstrated a degree of modulation as the heart rate changes in accordance with environmental factors. Typically this system provides a constant output, but has the capability to modify and

change when necessary. The respiratory system also modulates the rate, or frequency of chest wall movements, in response to changes in metabolic demands resulting from increased activity or emotive effects such as fear, anxiety, or excitement. Some systems have what could be considered an innate frequency modulation component. This component is considered innate because it does not fluctuate in response to environmental factors or physiological changes but is integral to a healthy system.

Wolff (1968) described the NNS as changing across segments such that the first and second segments were faster than the third. This observation is described in more detail through the work done in the current study. The frequency modulation (FM) segment of the suck describes the first five cycles of the burst in which the infant's frequency is rapidly decreasing. Figure 6 shows a sample burst in which the first five cycles are decreasing in frequency leveling off as the curve approaches the asymptote. The cycle period trajectories from burst initiation through the first 5 compression cycles revealed significant differences between healthy preterm control and RDS infants. For example, Control and RDS infant groups demonstrated distinctly different sCPG initiation patterns over the first 5 compression cycles. Healthy control infants manifest a robust initiation phase dominated by FM of NNS period with the first cycle period initiated at an average of 2.19 Hz and decreasing to an average of 1.75 Hz by the 5th cycle period whereas RDS infants showed a significantly compressed FM transition, initiated at a slower suck rate corresponding to an average of 2.12 Hz and then slowing at a steady rate through the succeeding

cycles to an average of 1.76 Hz by the 5th cycle period. The slope of the FM segment was -0.44 Hz and -0.36 Hz for Control and RDS infants, respectively. Thus, healthy preterm infants demonstrate a higher initiation frequency and a steeper FM function when compared to the RDS group.

Underlying Mechanism(s) for Frequency Modulation of a Biologic Rhythm

Frequency modulation can result for a number of reasons including metabolic demands, cellular mechanisms, or recruitment of cells. Metabolic demands can force a change in frequency. For example, in heart or respiratory rate, modulation in frequency results when metabolic demands change. An increase in the metabolic demands of the body during exercise results in an increase in the heart and respiratory rates.

Grillner (1991) identified the underlying cellular mechanisms involved in neural circuits to include reciprocal inhibition, mutual excitation, plateau properties or spike frequency adaptation (Ca^{2+} -dependent K^{+} channels). Frequency modulation could be the result of interplay between these cellular mechanisms resulting in a fine tuned and consistent output so that each burst starts with higher frequency cycles and then decreases as the burst progresses.

Perhaps the frequency modulation is a result of the components involved in the sCPG or the recruitment of cells involved in rhythmic behavior. Such as was studied by Armstrong and Drew (1984) who explored the involvement of pyramidal tract and

non-pyramidal tract neurons in locomotion. Understanding that the peripheral fields are innervated by various locations in the cortex, they determined which cells were involved by observing the locomotor behavior and correlating peripheral receptive field activity. This study only allowed for probable relationships between cell involvement (locomotor discharge) and receptive fields to be determined, but in later work, Drew (1993) discovered that there were transient increases and decreases in extensor and flexor muscles that were phase-dependent. Different cells were involved in different parts of the motor sequence. Such work supports the concept that different cells are involved in different components or aspects of the cycle. By way of extension, certain cells may be involved in regulating or participating in the NNS and perhaps even in the frequency modulation component.

Animal studies have explored the effects of lesions in different locations of the central nervous system (CNS). Motor behaviors produced by decerebrate and decorticate cats highlighted the ability to produce rhythmic behavior in both models, but the inability to modulate in response to the environment or to specific needs of the animal when the lesion eliminated input from the basal ganglia (Grillner, 1985). Understanding more about the components of the sCPG could expose a CNS location that is responsible for this temporal feature of the NNS.

Along with the above concept, frequency modulation occurs as part of a feedback loop specifically involving sensory feedback providing the CPG with information

about the phase of the motor behavior. In animal studies of gait the change in frequency was the result of peripheral afferent feedback during both ordinary gait and in tasks that required modulation of the gait (Drew, 1993). Grillner and Zangger (1984) also discovered that a motor pattern could break down in the absence of sensory input.

The present literature does not identify a specific mechanism responsible for frequency modulation and thus we hypothesize the mechanism that underlies frequency modulation of the NNS. Are there metabolic demands that force a change in frequency or could it be a synergistic relationship between cellular mechanisms? Perhaps there is a location in the CNS devoted to regulation of the frequency or maybe there are other sCPG components responsible for this aspect of the fine structure of the NNS. Further research must be done in order to determine the neural mechanism(s) that drives the intraburst characteristic that has been described by the present study.

Significance of Frequency Modulation in a Biological System

Physiological systems that typically demonstrate modulation are considered disordered when modulation is diminished or absent (Bar, Boettger, Koschke, Schultz, Chokka, Yeragani, & Voss, 2007). This understanding provides a basis for determining the degree of average modulation in NNS and the extent to which the modulation is influenced by environmental factors, genetic defects, or damage to the

CNS. Exploration of knowledge in this area would then provide insight into deficits and potential diagnostic and intervention methods.

Neural adaptation

Neural adaptation is a measure of the brain's ability to respond to changes in the environment. Neural adaptation which is regarded by some as a form of neural plasticity, occurs in two time frames; short- and long-term (Pearson, 2000). Short-term adaptation results in relatively rapid modification of system output. For example, a shift in task dynamics such as changing from walking forward to walking backward results in short-term adaptation of the neural and muscular systems involved in gait. In contrast, long-term adaptation results when a system is exposed to a stimulus over a longer period of time. A hallmark of long-term adaptation is long lasting or permanent effects and can be observed as a result of training, altered conditions, and/or response to injury (Pearson, 2000).

The frequency modulation of the NNS burst described in the current study may suggest short-term adaptation as an underlying mechanism. Although no external changes were made in task dynamics throughout the course of this experiment, a previous study has demonstrated modulation of NNS burst structure in response to changes in pacifier stiffness (environmental factor) (Zimmerman & Barlow, 2008). The implication of short-term adaptation in the NNS is significant as this ororhythmic behavior is regarded as a precursor to nutritive sucking (NS). NS is a complex behavior that requires dynamic and rapid changes to be made in musculature and components of the NNS, respiratory and swallowing neural circuits in response to

environmental factors. Successful feeding occurs when the timing and coordination of respiration, swallowing and suck work synergistically in response to environmental factors such as the rate of flow, viscosity, taste, odor, and temperature of the milk. When perturbations occur during NS, the infant responds by adjusting suck rate, often transitioning to the increased rate of NNS. The transition in motor output is indicative of the close relation between NS and NNS, and suggests that certain features apparent in the NNS burst structure, including the FM component described in the present report, may be used to help the infant modulate ororhythmic patterning (neural adaptation) to meet the challenging dynamics of NS.

Afferent information plays a critical role in adaptation. Such information enables a system to fine-tune or modify output in response to the environment, thus proper functioning of a system involves a synergistic relationship between efferent and afferent signals. Although afferent information is important in providing feedback to the system, long-term adaptation can occur in the absence or loss of such information, as with denervation, to enable the system to compensate.

One question that arises is to what extent day-to-day maintenance prepares a system for proper functioning when conditions are altered. In the case of NNS, how does the frequency modulation facilitate or at the minimum prepare the system for changes in musculature and task dynamics? Specifically, how does the NNS adapt to changes in the orofacial body plan due to growth of the facial skeleton and associated

musculature? How do these adaptations help to facilitate or prepare an infant for more complex tasks requiring coordination with other systems, such as in the case of NS? Finally, what is the result if an infant does not demonstrate frequency modulation? How will that infant respond to altered conditions or the demands of more complex behaviors?

Conclusion

In summary, healthy preterm infants manifest a significantly longer NNS burst structure when compared to infants with RDS. Second, there is an FM segment that is distinctly different for healthy Control and RDS infants. Third, healthy preterm infants suck at a higher frequency at the onset of the suck burst when compared with the RDS infants. Finally, for both infant groups, the suck cycle periods increase in duration from burst onset to completion. The ability to quantify the NNS allows assessment and subsequent intervention to be provided in a more efficient and successful manner.

This study enabled a more detailed look into the differences in the fine structure of the NNS for healthy as compared to infants with RDS. The differences that were observed present a qualitative means by which an organized or disordered NNS could be described. Future studies could explore the modulation of the NNS as a result of external stimulation. Such stimulation might include presentation of a pacifier that emulates the NNS in its burst-pause characteristics. The NTrainer is one such

stimulus. Introduction of that type of stimulus could reveal the extent to which the sCPG can be modulated as a result of external experiences (Barlow et al., 2008). The coupling of a study including the sensory deprived infants and infants receiving stimulation could expose a better understanding of the fine structure of the NNS as it is controlled by the sCPG. Additional information could then be used to tailor the output of a device, such as the NTrainer, so that infants would be presented with stimulation that matches their age and experience. Finally, such information may be used as a diagnostic tool for identifying aberrant NNS patterns and subsequently inform of underlying central nervous system organization in population that have experienced insults such as intraventricular hemorrhage (IVH), PVL, bronchopulmonary dysplasia (BPD) or genetic anomalies such as Down's syndrome.

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