Respiratory-swallowing interactions during sleep in premature infants at term

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Abstract

Non-nutritive swallowing occurs frequently during sleep in infants and is vital for fluid clearance and airway protection. Swallowing has also been shown to be associated with prolonged apnea in some clinical populations. What is not known is whether swallowing contributes to apnea or may instead help resolve these clinically significant events. We studied the temporal relationships between swallowing, respiratory pauses and arousal in six preterm infants at term using multi-channel polysomnography and a pharyngeal pressure transducer. Results revealed that swallows occurred more frequently during respiratory pauses and arousal than during control periods. They did not trigger the respiratory pause, however, as most swallows (66%) occurred after respiratory pause onset and were often tightly linked to arousal from sleep. Swallows not associated with respiratory pauses (other than the respiratory inhibition to accommodate swallowing) and arousal occurred consistently during the expiratory phase of the breathing cycle. Results suggest that swallowing and associated arousal serve an airway protective role during sleep and medically stable preterm infants exhibit the mature pattern of respiratory-swallowing coordination by the time they reach term.

Keywords: Control of breathing; Development; Swallow; Sleep; Apnea; Arousal; Infant

1. Introduction

Swallowing functions to transport food and liquids and to protect the airway (Jean et al., 1997; Jean, 2001; Sawczuk and Mosier, 2001). Multiple neural control elements regulate this complex behavior, including central pattern generating circuitry, sensory feedback and cortical control processes (McFarland and Lund, 1995; Jean, 2001; Larson et al., 1994; Oku et al., 1994; Gestreau et al., 1996; Bianchi and Pasaro, 1997; Sumi, 1963; Sawczuk and Mosier, 2001; Martin et al., 2002).

To prevent aspiration, breathing must be briefly inhibited and the laryngeal valve closed before, during and after swallowing (Kawasaki et al., 1964; Shaker et al., 1992; McFarland and Lund, 1993; Klahn and Perlman, 1999; Perlman et al., 2000). In adult humans, non-nutritive swallowing occurs consistently in the expiratory phase giving rise to the so-called “exhale-swell-exhale” or “ee” pattern (e.g., Clark, 1920; Nishino et al., 1989; Smith et al., 1989; Martin et al., 1994; Palmer and Hiemae, 2003). Somewhat different and less consistent respiratory-swallowing coordination has been observed for liquid swallowing in adult humans, although most swallows still involve the “ee” pattern (e.g., Martin et al., 1994; Klahn and Perlman, 1999; Martin-Harris et al., 2005). Swallowing in the expiratory phase may provide important airway protective and mechanical advantages such as facilitating laryngeal elevation (McConnel et al., 1986, 1988; Cook et al., 1989; Jacob et al., 1989; McFarland et al., 1994) and cricopharyngeal sphincter dilation (Miller, 1982; McConnel et al., 1986; Cook et al., 1989; Conklin and Christensen, 1994; Charbonneau et al., 2005).

Respiratory-swallowing coordination during sleep in infants is less studied. In premature infants Wilson et al. (1981) found that swallows occurred during all phases of the respiratory cycle and that the swallows consistently interrupted respiratory flow for about 1 s. Thach (2005) has stated that “infants . . . do not appear to coordinate timing of breathing and swallowing at all.” However, Wilson et al. excluded from analysis the many swallows that were initiated during respiratory pauses. In contrast to these studies in human infants, there is a highly stable
respiratory-swallowing relationship in newborn premature and full-term lambs (Feroah et al., 2002; Reix et al., 2003, 2004) with most swallows interrupting the inspiratory phase of the breathing cycle, a pattern similar to that observed in other adult non-human animals (Doty and Bosma, 1956; Kawasaki et al., 1964; McFarland and Lund, 1993). Understanding the stability of respiratory-swallowing patterning and the effect of maturation has significant clinical implications, as swallowing occurring at some phase relationships such as those at respiratory phase transitions (i.e., inspiratory to expiratory, expiratory to inspiratory) may be particularly perturbing to respiratory control and stability (Eldridge, 1972; Wilson et al., 1981; Paydarfar et al., 1986; Lewis et al., 1990).

Most studies of spontaneous swallowing during sleep in infants have focused on the potential role of swallowing in apnea of prematurity. Swallows occur more frequently during apnea than during normal breathing and repetitive swallows are often associated with prolonged apneas (Menon et al., 1984; Pickens et al., 1988, 1989). Although these data might suggest that swallowing causes apnea, swallows in these studies occurred more often during than before apnea and tended to precede recovery by 5 or 6 s (Menon et al., 1984), suggesting a potential protective role. Spontaneous non-nutritive swallowing in premature lambs also occurs after apnea onset, suggesting that stimulation of chemoreceptors or laryngeal mecanoreceptors during obstruction may trigger swallowing and contribute to airway protection (Reix et al., 2004). These data motivate continuing investigation of the functional role of swallowing in apnea in human infants.

By term, preterm babies are usually safely feeding orally and apnea of prematurity has typically resolved. The present investigation, therefore, was designed to test two key hypotheses in healthy preterm infants close to term gestational age. First, we hypothesized that given the vital nature of airway protection and the potential disruptive effects of unstable coordinative relationships, infants would exhibit highly consistent swallowing-breathing phase relationships with most swallows occurring in the expiratory phase of the breathing cycle as in adult humans. Second, we hypothesized that swallowing may serve an additional airway protective role during respiratory pauses and therefore that most swallows would occur during, as opposed to immediately before, respiratory pauses.

2. Methods

2.1. Subjects

Infants were recruited from the Preterm Nursery at the Royal Victoria Hospital, Montréal. Subjects were born preterm and studied as close to full term as possible. Infants were medically stable and close to discharge from hospital. They did not require oxygen or other respiratory support, and were not receiving intravenous medication or medication affecting the control of breathing (e.g., caffeine). All were receiving at least partial oral feeding at the time of the study, and feeding tubes if needed were removed during the study. Infants were excluded if there was clinical or radiological evidence of any neurological abnormality. The study was approved by the Institutional Review Boards of the Montreal Children’s Hospital, and the Royal Victoria Hospital and parents gave informed consent.

2.2. Study conditions

Infants were studied in a quiet room adjacent to the nursery. They were placed supine on an open incubator for the duration of the study, dressed in their usual clothing and covered with their usual bedding, with no external heat source. Each study was recorded using a VHS video recorder, trained on the infant with the face in full view, to assist with sleep staging.

Infants were monitored for a usual sleep period after a daytime feeding, using computerized polysomnography and audiovisual recording procedures. Electroencephalograms (EEG), electro-oculograms (EOG), electromyograms (EMG, submental), calibrated respiratory inductance plethysmography of the rib cage and abdomen (Respiritrace®, thoracic and abdominal bands and sum signal), EKG, oxygen saturation (SaO₂, Masimo Quartz®, set to 2-s averaging time) and nasal pressure (as a measure of air flow) were recorded. Pharyngeal pressure was also recorded using a Gaeltec® 6F/2 mm diameter solid-state pressure transducer introduced into the nasopharynx. All data were monitored on-line and stored digitally using a Nicolet Ultrasom polysomnography system for later analyses.

Polysomnographic and video recordings of each infant were staged in 30-s epochs to determine periods of wakefulness and sleep. Sleep was classified into Quiet, Active and Indeterminate. Epochs of wakefulness were further characterized as being quiet (termed Wake) or containing at least 15 s of movement (termed Movement).

Two-related analyses were performed. The first focused on the temporal and potential causal relationship between swallowing, respiratory pauses and associated arousal. The second focused on characterizing the coordinative relationship between spontaneously occurring swallows (not associated with respiratory pauses and arousal) and co-occurring respiration.

2.3. Respiratory pauses and arousals

Respiratory pauses (RP) were defined as a reduction in the respiratory inductance plethysmography sum signal and/or the nasal pressure signal to less than 20% of baseline, lasting at least 3 s. These respiratory pauses were greater in duration than those associated with respiratory inhibition to accommodate swallowing (see Fig. 4). We have decided to use the term respiratory pause as contrasted to apnea to avoid confusion with clinically significant apneas (American Thoracic Society, 1996). RPs were further categorized as central when no respiratory effort occurred, obstructive when there was ongoing respiratory effort, and mixed when there was a combination of the two. Changes in SpO₂ and/or the presence or absence of a fall in heart rate to below 80 beats/min was noted for each RP.

Arousals were defined as a change in at least two of the following signals, lasting at least 3 s: EEG frequency shifts to alpha, theta, or frequencies faster than 16 Hz; increases in chin EMG activity; increases in heart rate; changes in the shape of the pulse...
waveform (representing movement artifact); and movement artifact on the respiratory channels (ASDA, 1992; Mograss et al., 1994).

2.4. Swallowing detection

Swallows were identified by the highly characteristic increases in pharyngeal pressure that signal the pharyngeal phase of bolus transport during swallowing and by observation of other recorded signals including video records to assure that movement artifact did not lead to potential false indications of swallowing activity. A cluster of swallows was defined as a group of two or more swallows (with a maximum of four) where the first and last swallows were separated by less than 5 s.

2.5. Association between RPs, arousals and swallows

The temporal relationship between swallowing and RP or arousal was analyzed using a 10 s window centred over each swallow, with the presence and timing of RPs or arousals in relationship to the swallow being noted. This time frame was chosen because the American Sleep Disorders Association (ASDA) criteria for arousals requires 10 s of sleep between two arousals (ASDA, 1992), and therefore this seems a reasonable time frame to determine if swallows are temporally linked to arousals. Where swallows occurred in clusters, the window included 5 s before the first swallow and 5 s after the last swallow of the cluster. When an arousal was identified in association with a swallow, it was determined if the arousal occurred at the same time (within 1 s) or preceded or followed the swallow. When a RP was identified in association with a swallow, it was determined whether the swallow occurred within the 3 s before the RP; in the first, second or last third of the RP; or within 3 s after the end of the RP.

Swallowing, RPs and arousals occur frequently in infants (Menon et al., 1984; McNamara et al., 2002; Sanchez et al., 2006) and it was important to assure that any temporal correspondence between these behaviors was not due to chance co-occurrence. For this, a control period analysis was employed, similar to previous investigations (Menon et al., 1984). The RP control period was defined as the first 10 s of the 60 s preceding each RP, and was examined for the presence of a swallow. The swallow control period was defined as the first 10 s of the 60 s preceding each swallow, and was examined for the presence of an arousal. The control period was only considered valid if the sleep state in the control period was the same as that of the RP or swallow period, the control period occurred in the same sleep cycle as the RP or swallow period, the infant did not change position, and any arousal that occurred was spontaneous (i.e., not induced by the environment). If the control period as defined above was not valid, then the same procedure was applied (the first 10 s of the preceding 60 s) until a valid control period was found.

2.5.1. Swallowing-respiratory phase relationships

The second stage of data analysis involved the measurement of the coordinative relationship between spontaneously occurring swallows not associated with RP and the co-occurring respiratory cycles. RP significantly perturbs the respiratory cycle and consequently, swallows were chosen for these analyses that were not associated with RP. Analyses were further restricted to non-repetitive swallows preceded and followed by at least two unperturbed respiratory cycles as the perturbing effects of swallowing on respiratory control and stability can be cumulative. Details of our analysis methods used determine the respiratory phase in which swallows occur have been previously published (McFarland and Lund, 1993, 1995; McFarland et al., 1994; Charbonneau et al., 2005). In brief, the swallowing onset time (as detected from the pharyngeal pressure catheter) during the co-occurring respiratory cycle (Swallow) is measured and expressed as a percentage of the immediately proceeding cycle duration (Control). In this way, phase is normalized to control cycle durations. Swallows occurring during a prolongation of the cycle beyond control values and during an expiratory pause (a common occurrence in the adult human) are classified as 100% and consequently, respiratory phase values may potentially vary between 0% and 100% with 0% being the beginning of the inspiratory phase of the control cycle and 100% being values beyond control cycle expiratory duration. To further characterize the potential perturbing effects of swallowing on the respiratory rhythm, we measured the duration of the Control, Swallow and following two cycles (Swallow + 1 and Swallow + 2).

2.6. Statistical analysis

The proportion of the swallow and control periods containing RPs and arousals were compared using the chi-squared test or Fisher’s exact test where any group contained five or fewer observations. The timing of the swallow in relation to a RP was compared using the chi-square test, as were arousals occurring before, during and after a swallow. Analyses of variance were used to test for sleep/wake differences in the respiratory phase in which swallowing occurred and the perturbing effects of swallowing on post-swallow-respiratory cycle duration between the two groups. Values were judged significant if $p < 0.05$.

3. Results

3.1. Subjects

Six infants (four males) with a median gestation at birth of 31.6 weeks (IQR, 27.5–36.25 weeks), and median gestational age at the time of study of 40.5 weeks (range 39–41 weeks) were studied. Median birth weight was 1528 g (range 720–3110). The median total duration of the study recordings was 218 min (3.6 h, range 3.0–4.3 h). Median total sleep time was 82.5 min, with a median of 27.5% spent in active sleep, 23.3% in quiet sleep and 12.7% in indeterminate sleep.

3.2. Swallowing

A total of 552 spontaneously occurring swallows were identified in the six infants. The majority of swallows were single (370, 67%); there were 64 pairs (128 swallows, 23%), 14 triplets
(42 swallows, 7%), and three clusters of four swallows (12 swallows, 2%). Overall, 316 (57%) of the swallows occurred during wakefulness.

Swallowing frequency was not significantly different between quiet wakefulness (WAKE, 47 swallows/h), movement (42 h⁻¹) and active sleep (AS, 25 h⁻¹). Swallowing occurred significantly less frequently in quiet sleep (QS, 8 h⁻¹) compared to WAKE (p = 0.05). Swallows were more likely to occur in clusters of more than one when the infants were asleep than when they were awake (Fisher’s exact test, p < 0.001), but no difference was seen between sleep states.

3.3. Swallowing and RP

A total of 206 RPs were recorded, 89 central (43%), 98 mixed (48%) and 19 obstructive (9%). Most of these RPs were too short to be of clinical importance; only eight RPs were longer than 10 s, and none were longer than 20 s. Fourteen RPs (7%) led to desaturation below 93%; three desaturations were below 90%, the lowest being a SpO2 of 84%. Bradycardia occurred on only one occasion, to a lowest heart rate of 59 bpm. RP was less common in QS (10 h⁻¹) than in either AS (32 h⁻¹) or IS (27 h⁻¹), occurring in 30%, 25% and 12% of epochs of AS, IS and QS, respectively (p ≤ 0.05 for the difference between AS and QS and between IS and QS, Wilcoxon signed rank test).

Of the 180 swallows occurring during sleep, 61 (34%) were associated with a RP. Conversely, of 206 RPs recorded, swallowing occurred in association with a RP on 71 (34%) occasions. In comparison, swallows were significantly less frequent in the RP control periods (9.6%, p < 0.01, χ²-test). Mixed and obstructive RPs were more likely to be associated with swallowing (43% and 58%, respectively) than were central RPs (20%, p < 0.01, χ²-test).

Swallows most often occurred after the onset of RP: in the first third of the RP in 37%, the middle third in 13%, the last third in 33%, and in the 3 s after the end of the RP in 9%. In only 8.6% of swallow/RP pairs did the swallow precede the RP. An illustration of a swallow occurring in the last third of the RP is presented in Fig. 1. RPs longer than 10 s were more likely to coincide with at least one swallow (75% compared with 33% of shorter RPs, Fisher’s exact test, p = 0.02), and the number of swallows occurring within the RP was weakly correlated with the duration of the RP (r = 0.136, p = 0.05, Spearman). Bradycardia occurred in one subject and on only one occasion, following a mixed RP of 15 s. Four swallows occurred during this RP, which was followed by decreases in SpO2 to 90% and heart rate to 59 bpm.

3.4. Swallowing and arousals from sleep

Spontaneous arousals from sleep were common. The median arousal index was 17 h⁻¹ in QS and 33 h⁻¹ in AS (p ≤ 0.05, Wilcoxon signed rank test). Of 180 swallows that occurred during sleep, 68 (38%) were associated with an arousal from sleep. A valid control period was available for 153 swallows (85%). Arousal was more frequently associated with a swallow than in the control periods (27/153 (18%), p < 0.001, χ²-test). Swallowing was associated with a change in sleep stage in 60/180 (33%) swallows, 54 of which were from a sleep stage into movement or wakefulness. Of the 68 swallows associated with arousal, the arousal occurred before the swallow on only three occasions (4%); the arousal occurred in the same second as the swallow on 43/69 (63%) occasions, and after the swallow on 22 (32%) occasions. An arousal tightly linked and occurring after a swallow is illustrated in Fig. 1.

3.5. Respiratory-swallowing phase relationships

A total of 370 single and spontaneously occurring swallows not associated with RP longer than 3 s were analyzed. As summarized in Fig. 2, swallows occurred most frequently in the expiratory phase of the breathing cycle in both the Sleep and Wake conditions.

Mean respiratory phase in which swallowing occurred expressed as a percentage of control cycle duration and calculated across infants was 85% (S.D. = 18.67) for wakefulness and 85% (S.D. = 14.66) for sleep. In fact, 52% of the swallows during sleep and 53% of the swallows during wake occurred during a pause in the expiratory phase that extended beyond control cycle values (operationally defined as 100% of control cycle duration, see Section 2). An illustration of a swallow occurring during a pause in the expiratory phase is presented in Fig. 3.

As summarized in Fig. 4, the perturbing effects of swallowing on respiratory cycle duration were comparable between the Sleep and Wake conditions (ANOVA for repeated measures F(1, 4) = 2.002, p = 0.23). Swallowing prolonged the co-occurring respiratory cycle duration in both Sleep and Wake (F(3, 12) = 23.412, p < 0.001) but subsequent cycles were not affected. Post hoc comparisons revealed significant differences between Swallow and the preceding (Control) and following two cycles (Swallow + 1, Swallow + 2) only.
Fig. 2. Event histograms showing the respiratory phase in which swallows occurred during sleep (A) and wakefulness (B). Phase is expressed as a percentage of control cycle duration. Data are collapsed across infants in 10% bins. Also shown is the start of the expiratory phase (mean ± S.D.) calculated for control respiratory cycles. Swallows occurring in the 100% bin are those that occurred in a prolongation of the respiratory cycle in the expiratory phase beyond control cycle values.

Fig. 3. This figure illustrates a swallow (Sw) occurring during a brief prolongation of the expiratory phase of breathing. Inspiration (In↑) is indicated by upward deflection on the Nasal Pressure and respiratory inductive plethysmography Sum channels.

4. Discussion

The current study examined the co-ordination of spontaneous non-nutritive swallowing and respiration in preterm infants at term. While the infants in our study were born preterm, they were medically stable, feeding orally, and on no medication affecting respiratory control. The remarkably consistent results allow comparisons to previous studies of premature and term infants, adult humans and other animal species.

Consistent with previous studies of preterm and term infants, we showed that swallowing was more common during respiratory pauses (RP) than during uninterrupted breathing (Menon et al., 1984; Pickens et al., 1988, 1989; Don and Waters, 2003). These short RPs were not usually associated with desaturation or bradycardia and thus not clinically significant. Co-occurrence of RPs and swallowing has been demonstrated in studies of spontaneous swallowing and those using fluid infusion paradigms, although the study of naturally occurring swallows is important because bolus infusion may increase or otherwise modify the normal swallowing response.

Several potential explanations have been given to the co-occurrence and potential function of swallowing with RP (Don and Waters, 2003; Miller and DiFiore, 1995; Praud and Reix, 2005). Most data are consistent with Thach’s proposal that swallowing serves a protective role in preventing aspiration of upper airway secretions or gastric reflux that stimulate an apnea (Thach, 1992). Further, the swallowing synchrony, which involves patterned activity in a variety of oral–pharyngeal and laryngeal muscles, may actually assist in overcoming airway obstruction. The finding that swallowing tends to occur after a RP has already begun suggests that swallowing is not the cause of the RP but rather a protective response. Swallowing
occurring after the beginning of the apnea, and more frequently during mixed and obstructive (as contrasted to central apnea), argues for the potential role of chemo- or mechanoreceptor activation and associated swallowing responses (Reix et al., 2004; Praud and Reix, 2005). That is, laryngeal and/or oral/pharyngeal mechanoreceptors are likely to be activated during airway obstruction and potential fluid accumulation associated with mixed and obstructive apneas. Interestingly, nasal CPAP which is used to treat apnea in preterm newborns inhibits non-nutritive swallowing frequency in newborn lambs (Samson et al., 2005).

Unlike Don and Waters (2003), we found that arousal from sleep was commonly associated with swallowing, a result consistent with a protective function. However, Don and Waters studied a clinical population of infants aged 1–34-week-old infants, referred for investigation of a personal or family history of apnea or life-threatening event, some of whom might be expected to have an abnormal arousal response. Our current findings suggest that swallowing and associated arousal may be complementary protective mechanisms related to mixed and obstructive apneas.

We found a highly consistent coordination between breathing and swallowing in the study population. Swallows occurred most frequently during expiration independent of sleep state. In fact, swallows occurring during respiratory pauses and swallows occurring at or beyond 100% of control cycle duration were similar in that they both occurred at a time of zero airflow. Expiratory timing of spontaneously occurring swallowing is consistent with previous studies of adult humans (Clark, 1920; Nishino et al., 1989; Smith et al., 1989; McFarland and Lund, 1995; Charbonneau et al., 2005) and may provide the same airway protective and mechanical advantages for the infant (e.g., facilitating laryngeal elevation and cricopharyngeal sphincter opening) as in the adult (Charbonneau et al., 2005). This pattern is different from the only other study of non-nutritive swallowing–breathing phase relationships in infancy by Wilson et al. (1981) who found highly variable phase relationships. However, Wilson et al. (1981) excluded swallowings occurring during respiratory pauses and studied infants that were still premature (31–37 weeks) and may not have developed the mature pattern of co-ordination.

Previous investigations of respiratory-swallowing coordination during bottle feeding have also shown more variable phase relationships than we observed for non-nutritive swallowing during sleep (e.g., Bamford et al., 1992; Gewolb and Vice, 2006; Koenig et al., 1990; Lau et al., 2003). For example, Bamford et al. (1992) studied full-term infants during the first 14–48 h after birth during bottle feeding and found that swallowing occurred in all phases of the respiratory cycle and many interrupted the end-inspiratory phase (Bamford et al., 1992). This suggests that feeding may place additional demands on the coordinative relationship between breathing and swallowing and/or normal coordinative mechanisms may be disrupted in very young newborns (Sumi, 1975). Further study of non-nutritive swallowing in term infants shortly after birth would further elucidate the developmental time course of respiratory-swallowing coordination.

In summary, in this group of infants born preterm and studied at or near term during natural sleep, onset of a respiratory pause preceded both swallowing and arousal, suggesting that the latter events are part of a coordinated response for airway protection during sleep. Spontaneously occurring swallows not associated with RPs occurred consistently in the expiratory phase of the breathing cycle and prolonged that cycle, the mature pattern seen in adults. Additional experiments are needed to further elucidate the developmental sequence of respiratory-swallowing coordination during sleep in very young infants and how this might differ in infants with clinical disorders.

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