A Comparison of Swallowing During Apnea and Periodic Breathing in Premature Infants

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ABSTRACT

Periodic breathing and apnea are two forms of ventilatory instability which are commonly observed in premature infants. This study was undertaken to characterize the pattern of swallowing during apnea and compare this pattern to that present during periodic breathing. We assessed the frequency and distribution of swallows during the respiratory pauses of apnea and periodic breathing in 22 premature infants birth weight 1.2 ± 0.2 kg, postconceptional age 34 ± 2 wk. Twelve infants had apnea and 10 exhibited periodic breathing. During sleep the pharyngeal phase of swallowing was detected by a catheter in the pharynx and esophageal peristalsis by an

esophageal pressure catheter. Nasal airflow was monitored by a pneumotachometer. During apnea, the frequency of swallows was significantly greater than during the respiratory pauses of periodic breathing (15.9 ± 8.2 versus 0.72 ± 0.73 swallows/min, respectively, $p < 0.0001$) and also much higher than the rate of spontaneous swallows during sleep in either group (0.66 ± 0.66 and 0.58 ± 1.08 swallows/min, respectively). We conclude that an increased rate of swallowing is characteristic of apnea in premature infants, and distinguishes apnea from the respiratory pauses of periodic breathing. (*Pediatr Res* 37: 796-799, 1995)

Premature infants may exhibit respiratory pauses of varying duration and pattern. Prolonged respiratory pauses of 10 s or more associated with bradycardia (<100 beats/min) are generally referred to as apneic episodes, although the definition has varied (1-5). A clear-cut distinction cannot always be made between what is described as an apnea and other patterns of respiratory interruption which may occur in premature infants. Periodic breathing is a common abnormality of respiration in premature infants, which is characterized by regular bursts of ventilation, alternating with brief respiratory pauses (6). This has usually been considered to be a benign phenomenon because the respiratory pauses which occur are not associated with severe hypoxia or bradycardia. However, in some circumstances periodic breathing may indicate a pathologic state, for an increase in the frequency of periodic breathing has been identified as a risk factor in sudden infant death syndrome (7).

The exact relationship between apnea and periodic breathing is unclear: specifically, it is not known whether both types of respiratory pauses are produced by similar loci of inhibition within neuronal pathways to the muscles serving respiration. Previously, we have reported a striking similarity in the changes in pulmonary and upper airway resistance, respiratory drive, and duration of inspiration and expiration, which occur

preceding and after the respiratory pauses of apnea and periodic breathing (6, 8). Although these similarities do exist, they do not prove that an identical disturbance in respiratory drive underlies both disorders.

Recently, Menon *et al.* (9) described an unusual characteristic of apnea in infancy. It was observed that repetitive swallows occurred during apnea at a higher frequency than during uninterrupted sleep. Theoretically, such swallows could prolong apnea through reflex inhibition of respiration. Therefore, the current study was undertaken to characterize and compare the pattern of spontaneous swallows during periods of apnea and periodic breathing in two groups of infants, one primarily exhibiting apnea at the time of study, and a second group with only periodic breathing. We speculated that, if apnea and periodic breathing share a similar etiology, spontaneous swallows should occur with the same distribution during both types of respiratory rhythm disturbance.

METHODS

The study population consisted of 22 premature infants: mean birth weight 1.2 ± 0.2 kg, mean postconceptional age at study 34.1 ± 1.6 wk, mean postnatal age at study 4.9 ± 2.0 wk. All infants had completely recovered from any respiratory distress; none required supplemental oxygen therapy at the time of study. Twelve infants had a history of apnea of prematurity and had continuing apnea at the time of study, but

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no periodic breathing. Ten out of 12 of these infants were receiving oral theophylline therapy (mean serum level $5.6 \pm 2.1 \mu\text{g/mL}$). Ten infants exhibited periodic breathing on routine cardiopulmonary monitoring; of these, five of this group were also receiving theophylline as therapy for previous episodes of idiopathic apnea but did not exhibit apnea at the time of study. Pulmonary and upper airway mechanics in the apneic infants have been previously reported (7). The investigation was approved by the institutional human research committee, and informed consent was obtained from the parents before study.

Experiments were performed in the neonatal physiology laboratory over a 60–90-min period after each infant had been fed. During the study, nasal airflow was measured with a mask pneumotachometer and integrated to give tidal volume. Heart rate and O_2 saturation were continuously recorded from a Nellcor N-100 pulse oximeter (Nellcor, Hayward, CA). Esophageal pressure was measured with a 5 French saline-filled catheter connected to a Statham PD 23 pressure transducer (Gould, Cleveland, Ohio). Oropharyngeal pressure was measured with a 5 French Millar pressure sensitive catheter, passed transnasally to 5.5–6 cm from the anterior nares (Millar Instruments, Houston, TX). The frequency response of all pressure catheters was evaluated with a square wave pressure change and was satisfactory to 12 Hz. All experimental data were continuously recorded at a paper speed of 2 mm/s on a Gould 8-channel recorder and stored on magnetic tape.

For the purpose of this study, an apneic event was defined as a respiratory pause ≥ 10 s in duration, associated with at least a 20-beat/min decrease in heart rate. Each apnea was classified as mixed, obstructive, or central according to the criteria previously used in studies from this laboratory (10). Mixed apnea was characterized by obstructed inspiratory efforts as well as a central pause greater than or equal to 2 s in duration. In central apnea, inspiratory efforts ceased entirely and obstructed breaths were not observed. During obstructive apnea, obstructed respiratory efforts continued throughout the apnea, but no nasal airflow occurred. Periodic breathing was defined as repeated ventilatory cycles of ≥ 4 breaths/cycle, separated by discrete respiratory pauses of ≥ 2 -s duration (6). At least two consecutive minutes of repeated ventilatory cycles and respiratory pauses were analyzed in each infant with periodic breathing.

The pharyngeal phase of swallowing was characterized by a large positive wave on the pharyngeal pressure tracing with an amplitude > 5 times the normal respiratory fluctuation in pharyngeal pressure (11). Esophageal peristalsis also could be identified by a positive pressure wave on the esophageal catheter tracing. The pattern of swallowing and accompanying esophageal peristalsis was characterized during a total of 38 apneic events in 12 infants and during a total of 59 min of periodic breathing in 10 infants.

For the comparison of the characteristics of two infant study groups, results were analyzed by unpaired *t* test or Fisher exact test. For analysis of the swallowing pattern during apnea, analysis of variance, and the Newman-Keuls procedure for repeated measures were used. Data are expressed as mean $\pm$ SD.

RESULTS

The characteristics of the two groups of infants are shown in Table 1. No significant differences were found between the two groups of infants studied, in terms of birth weight, gestational age at study, days on supplemental oxygen therapy, or number of infants on theophylline at the time of study. Infants with periodic breathing exhibited 16.6 ± 8.3 min of periodic breathing per study. The group of infants which exhibited apnea but no period breathing had a mean of three apneas per study, range one to nine, mean duration 18 ± 9 s. The distribution of types of apnea was 72% mixed, 23% central, and 5% obstructive.

The characteristics of spontaneous swallows were compared during periodic breathing and apnea in the two groups of infants. Spontaneous pharyngeal pressure waves resembling swallows occurred during the ventilatory pauses in 37 out of 38 apneas (97%) (Fig. 1). The frequency of swallows was significantly higher at the beginning of an apnea ($p < 0.05$, Fig. 2); however, all apneas did not begin with a swallow. In fact, a swallow occurred within 3 s of the beginning of apnea (cessation of nasal airflow) in only 58% of apneas. Swallows were observed during all three types of apnea; mixed, obstructive, and central. The pharyngeal phase of swallows was followed by waves of esophageal peristalsis, which occurred at a mean frequency of three (range zero to three) swallows per esophageal peristalsis during apnea. In contrast, swallows were significantly less common (0.72 ± 0.73 swallow/min) during the respiratory pauses of periodic breathing ($p < 0.0001$ compared with swallow frequency during apnea 15.9 ± 8 swallows/min) (Fig. 3). Swallow frequency during periodic breathing was essentially the same as the incidence of spontaneous swallowing during uninterrupted sleep in these infants (0.66 ± 0.66 and 0.57 ± 1.0 swallow/min in infants with apnea and periodic breathing, respectively).

DISCUSSION

This study has shown that swallows occurred with greatly increased frequency during apnea of prematurity, whether the type of apnea was mixed, obstructive, or central. These data are consistent with the results of Menon *et al.* (9) who previously described this phenomenon in premature infants with apnea. The current study extends these authors' previous observations to include a comparison of the phenomenon of swallowing during apnea and periodic breathing. We observed that, unlike

Table 1. Comparison of premature infants with apnea and periodic breathing

	Infants with Apnea	Infants with Periodic Breathing	<i>p</i> *
<i>N</i>	10	12	
Birthweight (g)	1156 ± 346	1342 ± 242	0.15
Gestational age at birth (wk)	28.6 ± 2.5	29.9 ± 1.8	0.21
Gestational age at study (wk)	34 ± 1.5	34 ± 1.6	0.63
Days on oxygen therapy	15 ± 20	3.2 ± 2.8	0.07
Number of infants on theophylline	10/12	5/10	0.098

All data are expressed as mean $\pm$ SD.

* Statistical comparison by unpaired *t* test or Fishers exact test.

Figure 1. Characteristic pattern of spontaneous swallows during a mixed apnea. When the apnea continued beyond 15 s, tactile stimulation of the infant ($\uparrow$ stim) was applied in an attempt to terminate the apnea.

Figure 2. The frequency of pharyngeal pressure waves representing swallows was greatest at the onset of the apnea. * $p < 0.05$, analysis of variance. Data expressed as mean $\pm$ SD. Frequency = number of swallows per 10% of apnea duration.

apnea, respiratory pauses of periodic breathing are not associated with an increased frequency of swallowing. Thus, this characteristic distinguishes apnea from periodic breathing. Fur-

Figure 3. During the respiratory pauses of periodic breathing, swallowing, characterized by large positive pressure waves in the pharynx, did not occur.

thermore, swallowing must be initiated by a stimulus unique to the pathophysiology of apnea in infants, for an increased frequency of spontaneous swallows has not been reported during sleep apnea episodes in adults (12-15).

The origin of the swallows during apnea is not known. The coordinated muscular contractions of swallowing may be elicited by stimulation of sensory receptors in the pharynx and larynx (16-18). These receptors can respond to pressure and to the chemical stimulus provided by fluids of differing composition such as water or milk. Menon *et al.* (9) have speculated that accumulation of pharyngeal secretions may trigger the swallows during apnea, possibly through activation of pharyngeal or laryngeal receptors. Alternatively, undetected gastroesophageal reflux may be present, before apnea, and acidic stomach contents could trigger swallows when regurgitated to the level of the larynx. In support of this theory, gastroesophageal reflux has been found to be associated with approximately 22% of apneas in premature infants (9). These postulated etiologies for swallowing infer that the swallows occur because of stimuli within the oropharynx. However, other etiologies must also be considered. Neuronal networks for swallowing and respiration exhibit reciprocal inhibition (19-21). It is possible that inhibition of respiration during apnea is associated with activation (disinhibition) of motor neurons within the swallowing center, resulting in a brief burst of swallows. These etiologies for swallowing during apnea must remain speculative, until more detailed information is available on the mechanisms by which neuronal groups which serve respiration are inhibited during apnea.

The swallows which occur during apnea could contribute to the inhibition of respiration which occurs. Wilson *et al.* (11) first demonstrated in infants that spontaneous swallows during sleep were associated with a 0.5-1.9-s interruption of ventilation. Furthermore, Koenig *et al.* (22) have shown in infants that minute ventilation is inversely related to swallowing frequency during feeding. Inhibition of respiration during swallowing has also been elicited in animal models using direct recording of respiratory neural output from the medulla. In the anesthetized cat, Sumi (23)

observed that swallowing elicited by water boluses in the pharynx directly inhibited firing of inspiratory neurons in the medulla. Takagi *et al.* (24) demonstrated in the anesthetized, adult cat that reflexes from the upper and lower pharynx interact with and modulate respiration. Thus, there is evidence from a variety of human and animal studies to support the concept of direct inhibition of respiration during swallowing. While swallows could theoretically prolong the respiratory inhibition of an apnea, they cannot be the initiating event for all apneas, because a swallow occurred within 3 s of cessation of airflow in only 58% of apneas.

Insertion of a catheter into the oropharynx, as used in this investigation for pressure measurement, could have triggered spontaneous swallows during sleep. This stimulus could not account for the difference in swallow frequency during apnea and period breathing, for instrumentation technique was identical in both groups of infants. Furthermore, Menon *et al.* (9) have previously found that insertion of a catheter into the pharynx did not alter the frequency of spontaneous swallows during apnea.

Apnea and periodic breathing share a number of characteristics: both are observed in the newborn period and exhibit a higher incidence in premature infants. Both forms of respiratory instability have been observed to decline in frequency after birth over a 5–10-wk period, depending on the degree of the baby's prematurity (25–27). The respiratory pause in both apnea and periodic breathing is preceded by a decline in tidal volume and a prolongation of respiratory time, and both may be accompanied by obstructed breaths before the onset of cycles of respiration (6, 8). Apnea and periodic breathing differ, however, in the following respects: the respiratory pauses of apnea are not limited in duration, and, as this study confirms, apnea in premature infants is accompanied by frequent swallows. These comparisons do not, however, allow us to deduce the nature of the neurologic events which initiate either disorder. Indeed, it is possible that different forms of inhibitory input may evoke the respiratory patterns of apnea or periodic breathing through a final common pathway to the phrenic motoneurons. Further understanding of the etiology of these disorders must await a description of their neuroanatomic substrate, and will have to take into consideration the complex interactions between respiratory drive and deglutition.

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