Apnea-Associated Reduction in Lower Esophageal Sphincter Tone in Premature Infants

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Objective To characterize esophageal motility during episodes of prolonged apnea in premature infants.

Study design We retrospectively reviewed combined manometric and physiological monitoring studies performed in tube-fed premature infants from 1994 to 2002. Apnea was defined as a respiratory pause of >20 seconds. For each apneic event, pharyngeal swallowing, esophageal motility, and lower esophageal sphincter (LES) pressure were assessed before, during, and after apneic episodes.

Results Twelve episodes of apnea (duration, 20 to 120 seconds) were identified in 7 infants (34 to 37 weeks postmenstrual age (PMA); study weight, 1950 to 2380 g). During the apneic epsisodes, swallowing increased (median[interquartile range], 0[0,0], 5[4,7], and 1[0,2] swallows/minute before, during, and after apnea, respectively; $P < .05$), esophageal pressure wave sequences (PWS) increased (1[0,2], 5[3,6], and 2[1,3] PWS/minute before, during, and after apnea, respectively; $P < .05$) and LES pressure decreased (16[12,21], 6[5,8], and 27[12,32] mmHg before, during, and after apnea, respectively; $P < .05$).

Conclusion In premature infants, apnea is associated with reduced LES tone, potentially increasing the likelihood of reflux occurring after the onset of apnea. *(J Pediatr 2009;154:374-8)*

Apnea is a major problem in infants, with the incidence of apneic episodes being inversely proportional to gestational age.[1] Gastroesophageal reflux (GER) is commonly considered a cause of apnea, particularly if apnea occurs during feeding and/or is resistant to methylxanthine therapy. The widely proposed mechanism(s) for reflux-induced apnea are laryngeal afferent reflexes, whereby chemical or mechanical stimulation of superior laryngeal nerve afferents cause reflex inhibition of respiration for the duration of stimulation. The laryngeal chemoreceptor reflex (LCR) in response to laryngeal infusion of water and saline has been widely demonstrated in human neonates as well as in neonatal animal models.[2-10] Numerous clinical studies have produced variable findings in terms of demonstrating a direct causal link between GER and apnea, however,[12-28] and it seems that this relationship is more difficult to demonstrate than would be expected given the presence of an easily demonstrable LCR in infants with apnea and evidence that in infants, 80% of reflux episodes extend to the pharynx.[11]

To date, the likely gastrointestinal effects of stimulation of laryngeal afferent reflexes have been ignored in the context of the link between apnea and reflux. It is well known that the primary afferent neural pathway governing triggering of laryngeal afferent reflexes is the superior laryngeal nerve (SLN), and SLN stimulation also is known to trigger complete swallowing sequences. In separate physiological studies in adult animal models, SLN stimulation initiated a primary peristaltic swallow sequence complete with a propagated peristaltic wave and lower esophageal sphincter (LES) relaxation.[29] Unlike swallowing, which has been widely reported in relation to apnea, esophageal motility and LES pressure changes during apnea have not been described previously.

We undertook a retrospective review of all of our manometric studies in premature infants that were combined with simultaneous physiological monitoring.[30-33] Our aim was to identify prolonged apneic events of >20 seconds duration and to characterize esophageal motility patterns associated with these events.

GER	Gastroesophageal reflux	PWS	Pressure wave sequence
LCR	Laryngeal chemoreceptor reflex	SLN	Superior laryngeal nerve
LES	Lower esophageal sphincter	TLESR	Transient lower esophageal sphincter relaxation
PMA	Postmenstrual age		

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METHODS

A retrospective review was undertaken of all combined manometric and physiological monitoring studies performed in 156 tube-fed premature infants born at Women and Children's Hospital between 1994 and 2002. These patients were originally studied for the purpose of characterizing the development of esophageal motility and mechanisms of triggering of GER. Infants were not studied because they had apnea per se, and the patient cohort included infants with chronic lung disease, GER disease, and "healthy" infants with no significant morbidity other than prematurity.

Patterns of esophageal motility were recorded with a micromanometric feeding assembly (2 mm outer diameter) that incorporated a sleeve sensor for LES pressure measurement. The assembly was positioned with the midpoint of the sleeve straddling the LES. Manometric sensors located in the pharynx and esophagus recorded swallowing and esophageal pressure wave sequences (PWSs).

Physiological monitoring (oxygen saturation, heart rate, respiratory rate) was simultaneously performed using pulse oximetry (Novametrix Medical Systems, Wallingford, Connecticut) and neonatal cardiorespiratory monitoring (Hewlett Packard, Germany). Airflow at the nares was monitored using a pressure transducer. Analogue signals from pressure transducers and monitors were digitized and recorded simultaneously at 10 Hz using a Macintosh Quadra 700 with software based on National Instruments' Labview (MAD software; Royal Adelaide Hospital, C. Malbert).

The onset of apnea was defined by the timing of cessation of airflow through the nares, and the offset of apnea was defined by the recommencement of airflow through the nares. For the purposes of analysis, "prolonged" apnea was defined as a respiratory pause of >20 seconds. This duration was chosen because such prolonged apneic events were more likely to be laryngeal afferent reflex–related events, and they were less likely to overlap with more frequent and shorter durations of (< 10 seconds) apnea/periodic breathing, which is caused by immaturity of central mechanisms governing respiratory drive rather than by the triggering of laryngeal afferent reflexes.

Motility analysis involved measurement of pharyngeal, esophageal, and LES pressure to quantify the number of pharyngeal swallows, number of esophageal PWSs, and LES pressure, as described previously.[30-33] Motility patterns were analyzed for the period concurrent with the apneic episode and equivalent periods immediately before and after the apneic episode.

Statistical Analysis

Normally distributed data are presented as mean (± standard error of the mean). Nonparametric data are presented as median[25th percentile, 75th percentile]. Variables before, during, and after apnea were compared using Kruskal-Wallis 1-way analysis of variance on ranks ($P < .05$) and pairwise multiple-comparison procedures (Tukey's test) ($P < .05$).

RESULTS

Prolonged apneic episodes were observed in 7 of the manometric studies. The infants had a gestational age at birth of 24 to 34 weeks, a PMA of 34 to 37 weeks, a birth weight of 690 to 2360 g, and a study weight of 1950 to 2380 g. Three infants were receiving caffeine at the time of the study, and 6 were formula-fed. Twelve apneic episodes (all mixed apnea) fulfilled our selection criteria for prolonged apnea. All were associated with hypoxia and bradycardia (Figure 1A), with the latter occurring 5 to 33 seconds after the onset of apnea (average, 12.5[2.1] seconds). Cough was observed during 1 apneic episode (Figure 1B). All infants were sleeping quietly at the time of apnea; arousal was not monitored or noted. The characteristics of each apneic episode are summarized in the Table.

The changes in manometric patterns in association with apnea were remarkably consistent. Example tracings are shown in Figure 1, and all data are detailed in the Table. Swallowing and PWS increased from 0[0,0] and 1[0,2] per minute, respectively, before apnea to 5[4,7] and 5[3,6] per minute during apnea ($P < .05$), and then decreased to 1[0,2] and 2[1,3] per minute after apnea ($P < .05$). LES pressure before apnea was 16[12,21] mmHg; it decreased to 6[5,8] mmHg during apnea, then increased to 27[12,32] mmHg after apnea. The first swallow occurred between 2 seconds before apnea to 6 seconds after onset of apnea (average, 1.3[0.7] seconds after), and the nadir LES pressure during apnea was achieved between 2 and 11 seconds after onset of apnea (average, 5.8[0.8] seconds). The median LES pressure recorded for all apneic episodes over the period from 20 seconds before onset of apnea to 20 seconds after onset of apnea is shown in Figure 2.

Swallowing appeared to be a prerequisite for sphincter relaxation during apnea. Shorter-duration apneic episodes (<20 seconds) without swallowing were not associated with LES relaxation (Figure 1A). Recovery of LES pressure usually preceded the end of the apneic episode, and the average LES pressure at the time of apnea offset was 10.7(5.1) mmHg.

DISCUSSION

We present unique findings on pharyngoesophageal motility in association with spontaneous, clinically relevant apnea of >20 seconds duration. Prolonged apneic episodes were consistently associated with swallowing and LES relaxation to levels that may allow reflux to occur in association with straining events, such as coughing and airway obstruction.

We believe that the apneic episodes that we analyzed are laryngeal afferent reflex–mediated. In support of this proposition, we report swallowing at the onset of and during apnea. Swallowing is a universally reported manifestation of the LCR, initiated by pharyngeal/laryngeal fluid stimulation.[2-10] Other reported manifestations of the LCR include coughing (commonly occurring after arousal) and reflex bradycardia.[4-8] Of these other manifestations, coughing was observed in only 1 case. Although it was documented that infants were all sleeping quietly, sleep staging and the occurrence of arousal were not marked on the tracings or recorded