Respiratory Events in Infants Presenting with Apparent Life Threatening Events: Is There an Explanation from Esophageal Motility?

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Objective To test the hypothesis that proximal aerodigestive clearance mechanisms mediated by pharyngoesophageal motility during spontaneous respiratory events (SREs) are distinct in infants with apparent life threatening events (ALTEs).

Study design Twenty infants (10 with proven ALTE, 10 healthy controls) had pharyngoesophageal manometry to investigate motility changes concurrent with respiratory events detected by respiratory inductance plethysmography and nasal thermistor methods. We measured changes in resting upper esophageal and lower esophageal sphincter pressures, esophageal peristalsis characteristics, and gastroesophageal reflux. Statistical analysis included mixed models; data presented as mean ± SD, median (range), or percentage.

Results Infants with ALTE (vs controls) had: (1) delays in restoring aerodigestive normalcy as indicated by more frequent ($P = .03$) and prolonged SREs ($P < .01$); (2) a lower magnitude of protective upper esophageal sphincter contractile reflexes ($P = .01$); (3) swallowing as the most frequent esophageal event associated with SREs (84%), with primary peristalsis as the most prominent aerodigestive clearance mechanism (64% vs 38%, $P < .01$); (4) a higher proportion of failed esophageal propagation (10% vs 0%, $P = .02$); and (5) more frequent mixed apneic mechanisms ($P < .01$) and more gasping breaths ($P = .04$).

Conclusions In infants with ALTE, prolonged SREs are associated with ineffective esophageal motility characterized by frequent primary peristalsis and significant propagation failure, thus suggestive of dysfunctional regulation of swallow-respiratory junction interactions. Hence, treatment should not target gastroesophageal reflux, but rather the proximal aerodigestive tract. *(J Pediatr 2014;165:250-5)*.

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Apparent life threatening events (ALTEs) in infants are characterized by apnea, changes in color or muscle tone, and/or choking/gagging episodes.[1] The incidence of ALTEs varies from 0.5% to 6% and accounts for about 1% of emergency visits.[2-4] Apnea, hypoxia, and significant cardiorespiratory events may result in neurologic impairment.[5,6] Infants with ALTE most likely have a failure of regulation of central esophageal motility and/or airway mechanics that under the appropriate circumstances may be the cause of the life-threatening event. Thus, such infants may have extensive investigations for lower respiratory tract infections, gastroesophageal reflux (GER), or sleep disturbances. They also commonly receive empirical treatment for acid-GER.[2,3,7] Frequent and prolonged ALTE occurrences may result in multiple hospital readmissions, emergency visits, numerous parental work absences, and increased economic burden. In a study of 12 067 patients with ALTE, the average length of hospital stay was 4.4 days with an average cost of $15 567.[8] In a study from our institution, 113 ALTE-related admissions had hospital stays ranging from 0.4-17.1 days, costing an average of $9268 (range $1260-$68 756).[3]

Although GER and poor aerodigestive adaptation is commonly implicated during ALTEs,[9] the underlying mechanisms causing the pharyngeal-esophageal and respiratory rhythms remain unclear. Normally in adults, swallowing occurs during the expiratory phase of respiration,[10,11] whereas in neonates, swallowing can occur during inspiratory-, expiratory-, and inter-phases.[12-14] During normal swallowing, a brief pause in breathing with cessation of air flow is evident. This represents central deglutition-apnea, which is a normal protective mechanism to prevent aspiration during swallowing while facilitating safe oropharyngeal bolus transit. This phenomenon may be associated with prolonged respiratory inhibition and/or delayed swallowing. If deglutition-apnea does not occur, there is a possibility for choking and aspiration either before, during, or after deglutition. Furthermore, inappropriate swallowing and respiratory junction interactions, as a consequence of GER, increase the risk of retrograde aspiration.[12,13] Although lower esophageal sphincter tone can be decreased in some infants with pathologic apnea,[15] the physiological mechanisms leading to ALTEs are difficult to study formally as such events cannot be captured during routine investigations. There may be physiological overlap of ALTEs with

ALTE	Apparent life threatening event
GER	Gastroesophageal reflux
SRE	Spontaneous respiratory event

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more frequently occurring spontaneous respiratory events (SREs).[12,13,16] The objective of the study was to characterize and compare pharyngoesophageal motility mechanisms during SREs in infants with proven ALTE versus healthy control infants, with the hypothesis that proximal aerodigestive mechanisms are abnormal in infants with ALTE.

Methods

Ten infants with ALTE, referred to our Neonatal and Infant Feeding Disorders Program between October 2009 and January 2013, were compared with 10 healthy control infants who did not have this diagnosis and were part of ongoing research studies. To ensure subject safety, all studies were done at the crib-side and closely monitored by a registered nurse and physician. The protocol was approved by the ethics committee at Nationwide Children's Research Institute/Nationwide Children's Hospital Institutional Review Board; signed informed parental consent was obtained and complied with the Health Insurance Portability and Accountability Act authorization were obtained.

Tidal ventilation and respiratory function was assessed by thoracic and abdominal respiratory inductance plethysmography (Respitrace; Viasys, Conshohocken, Pennsylvania) utilizing infant respibands (Carefusion, Minneapolis, Minnesota) to record inhalation (upstroke) and exhalation (down stroke). Nasal airflow was assessed with a nasal thermistor (Integra Life Sciences, Plainsboro, New Jersey).

To measure esophageal motility, a specially designed manometry catheter (Dentsleeve International, Mui Scientific, Mississauga, Ontario, Canada) with 5 ports (pharynx, proximal-, middle-, distal- esophagus, and stomach) and 2 sleeves (upper- and lower- esophageal sphincter) was attached to a micromanometric water perfusion system (Dentsleeve International) via resistors, pressure transducers (Ohmeda TNF-R disposable transducers; Medical Measurement Systems, Dover, New Hampshire), and amplifiers (Solar-2; Medical Measurement Systems, Dover, New Hampshire) to record pharyngoesophageal pressure changes.[17-19] The catheter was placed nasally in a supine unsedated neonate with adequate time given for infant adaptation. Manometry signals were recorded concurrently with respiratory inductance plethysmography and nasal thermistor. Subject safety was also monitored by observing and recording vital signs. Data analyses were performed using Medical Measurement Systems software v. 8.21.

A Priori Respiratory Definitions

Because infants with ALTE cannot be studied during a true ALTE, the characteristics of swallowing-respiratory junction interactions were examined in controls and infants with ALTE during the more frequently occurring SREs. SRE was defined as an apneic event lasting greater than 2 seconds with at least 2 missed breaths determined by respiratory and air flow waveforms (**Figure 1**) based on the following published normal physiologic principles: (1) during spontaneous swallowing in neonates deglutition-apnea, or laryngeal adduction, is present as indicated by cessation of airflow with a duration of 2 seconds[12,13]; and (2) the American Academy of Sleep Medicine considers apnea during polysomnography studies as an interruption of airflow lasting the equivalent of 2 breaths in children.[16]

The duration of a SRE was defined as the period from first abnormal breath preceding the apneic event to restoration of normal breath. The type of apnea was based on respiratory and air flow waveforms and classified as central, obstructive, or mixed.[20] A gasp breath was defined as a single increased rapid inspiration relative to baseline respiration, and verified manometrically by a simultaneous decrease in esophageal body pressures.

A Priori Pharyngoesophageal Manometry Definitions

Esophageal motility changes occurring during SREs were investigated by evaluating upper and lower esophageal sphincter pressures, esophageal body characteristics, peristalsis, and GER events.[17-19]

Upper esophageal sphincter characteristics were as follows: (1) basal pressures before the SRE were measured during esophageal and respiratory quiescence; and (2) sphincteric response during the SRE was defined as contraction, relaxation, or none. Contraction was determined by a change of 4 mm Hg above baseline, and maximum contractile pressures were also measured. Generally, relaxation occurs during swallowing events; therefore, nadir pressures were measured. Following such events, postdeglutitive rise in pressure was also determined.[18] Lower esophageal sphincter characteristics were observed for the following measurements. Basal pressures before the SRE were measured during esophageal and respiratory quiescence; and (2) sphincteric response during the SRE event was defined as contraction, relaxation (change of 5 mm Hg below baseline), or none. During swallowing, nadir lower esophageal pressure was measured if relaxation was present. Esophageal body characteristics were observed for the presence of polymorphic waveforms during swallowing defined manometrically as multiple peaks in the proximal-, middle-, or distal-, esophagus.[21]

During SRE, peristalsis characteristics that restored respiratory normalcy were evaluated, giving specific attention to potential esophageal clearance mechanisms including primary peristalsis or secondary peristalsis, and their propagation mechanism classified as complete, incomplete, or failed. GER events were manometrically defined as previously published,[22-24] and distinguished by the presence of a transient lower esophageal sphincter relaxation lasting longer than 10 seconds along with the occurrence of esophageal common cavity pressure changes and retrograde waveforms.

SREs were correlated with esophageal events and categorized as deglutition-related, GER-related, or independent (**Figure 2**; available at www.jpeds.com). Correlation of SRE with deglutition was considered to be present if deglutition occurred 5 seconds before, during, or within 5 seconds after the SRE and in the absence of GER. Correlation of SRE with GER was considered to be present if GER