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

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Abstract

Objectives—To test the hypothesis that proximal aero-digestive clearance mechanisms mediated by pharyngo-esophageal motility during spontaneous respiratory events (SREs) are distinct in infants with apparent life threatening events (ALTE).

Study design—Twenty infants (10 with proven ALTE, 10 healthy controls) had pharyngo-esophageal 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 gastro-esophageal reflux (GER). Statistical analysis included mixed models; data presented as mean $\pm$ SD, median (range), or percentage.

Results—Infants with ALTE (vs. controls) had: (1) delays in restoring aero-digestive normalcy as indicated by more frequent ($P=0.03$) and prolonged SREs ($P<0.01$); (2) a lower magnitude of protective upper esophageal sphincter contractile reflexes ($P=0.01$); (3) swallowing as the most frequent esophageal event associated with SREs (84%), with primary peristalsis as the most prominent aero-digestive clearance mechanism (64% vs 38%, $P<0.01$); (4) a higher proportion of failed esophageal propagation (10% vs. 0%, $P=0.02$); and (5) more frequent mixed apneic mechanisms ($P<0.01$) and more gasping breaths ($P=0.04$).

Conclusions—In infants with ALTE, prolonged SREs are associated with ineffective esophageal motility characterized by frequent primary peristalsis and significant propagation

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failure, thus suggestive of dysfunctional regulation of swallow-respiratory junction interactions. Hence, treatment should not target GER, but rather the proximal aero-digestive tract.

Keywords

Respiratory events; ALTE; Esophageal motility

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 neurological 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 to 17.1 days, costing an average of \$9268 (range \$1,260 to \$68,756).³

Although GER and poor aero-digestive 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 oro-pharyngeal 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 pathological 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 more frequently occurring spontaneous respiratory events (SREs),^{12,13,16} The objective of the study was to characterize and compare pharyngo-esophageal motility mechanisms during SREs in infants with proven ALTE vs. healthy control infants, with the hypothesis that proximal aero-digestive mechanisms are abnormal in infants with ALTE.

METHODS

Ten infants with ALTE, referred to our Neonatal and Infant Feeding Disorders Program between October 2009 to 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 with 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 and HIPAA authorization were obtained.

Respiratory function was assessed by thoracic and abdominal respiratory inductance plethysmography (Respirace; Viasys, Conshohocken, PA) utilizing infant respibands (Carefusion, Minneapolis, MN) to record inhalation (upstroke) and exhalation (down stroke). Tidal ventilation was assessed with a nasal thermistor (Integra Life Sciences, Plainsboro, NJ).

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 two sleeves (upper-, and lower-esophageal sphincter) was attached to a micromanometric water perfusion system (Dentsleeve) via resistors, pressure transducers (Ohmeda TNF-R disposable transducers), and amplifiers (Solar-2; Medical Measurement Systems, Dover, NH) to record pharyngo-esophageal 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.

Apriori respiratory definitions

Because infants with ALTE cannot be studied during a true ALTE, the characteristics of swallowing-respiratory junction interactions were examined in control and infants with ALTE during the more frequently occurring spontaneous respiratory events (SREs). SRE was defined as an apneic event lasting greater than 2 seconds with at least two 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.

Apriori pharyngo-esophageal manometry definitions

Esophageal motility changes occurring during SREs were investigated by evaluating upper and lower esophageal sphincter pressures, esophageal body characteristics, peristalsis, and GER events¹⁷⁻¹⁹.

Upper esophageal sphincter characteristics were as follows: (1) basal pressures before the SRE were measured during esophageal and respiratory quiescence; (2) sphincteric response during the SRE was defined as contraction, relaxation, or none; and (3) contraction was determined by a change of 4 mmHg above baseline, and maximum contractile pressures were also measured. Generally, relaxation occurs during swallowing events; therefore, nadir pressures were measured. Following such events, post-deglutitive 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. Sphincteric response during the SRE event was defined as contraction, relaxation (change of 5 mmHg 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 sec along with the occurrence of esophageal common cavity pressure change 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 occurred within 30 seconds prior to the SRE. An independent SRE was defined as an absence of any esophageal event (deglutition or GER) along with quiescence. To determine temporal relationships between SRE and deglutition, subgroup analysis was performed to determine if deglutition happened prior to, during, or after the SRE event defined respectively as pre-, intra-, or post-deglutition.

Statistical Analyses

Data from ALTE and control groups were compared using SAS version 9.3 (SAS Institute, Cary, NC). Categorical variables were compared using χ^2 or Fisher exact tests. Continuous variables were compared using 2-sample t-tests. Nonparametric and Wilcoxon rank-sum tests were also used for of non-normal data comparisons. Linear mixed effects models were applied for the comparisons when reporting upper or lower esophageal sphincters, esophageal body, peristalsis, and GER characteristics. Log transformation was performed to achieve normality for the statistical analyses (mixed model). Data are presented as mean $\pm$ SD, or as median (IQR). A P-value <0.05 was considered significant.

RESULTS

Demographic and outcomes were similar except for APGAR scores (Table).

Spontaneous respiratory events

A total of 151 SREs (98 in ALTE and 53 in controls) were identified from 31.7 hours of cumulative manometric data analyzed in 30 second epochs from 20 subjects (10 ALTE and 10 controls). In one control patient there were no SREs. Infants with ALTE had more frequent SREs, 6(2–11) events/hr vs. controls 4(0–7) events/hr (6.2 ± 2.7 ALTE vs. 5.3 ± 3.5 control events/hr, $P=0.03$). In infants with ALTE, SRE duration (15.0 ± 1.8 sec, ranging from 2.6 – 97.3 sec) vs. controls (6.1 ± 2.2 sec, ranging from 2.1 – 23.7 sec) was prolonged ($P<0.01$). Central mechanisms for SREs were more frequent in controls (32% ALTE vs. 74% control, $P<0.01$), contrasting with more frequent mixed apneic mechanisms in infants with ALTE (68% ALTE vs. 26% control, $P<0.01$). The frequency of gasping breaths was also increased in infants with ALTE (47% ALTE vs. 28% control, $P=0.04$) (Figure 2, C).

Pharyngo-esophageal manometry characteristics

Upper esophageal sphincter and lower esophageal sphincter characteristics, esophageal events during SRE, and esophageal mechanisms restoring respiratory normalcy are shown in Figure 3. At SRE onset, there was no change in upper esophageal sphincter pressure in both groups (61% ALTE vs. 57% control, $P=0.5$). Swallow-associated nadir upper esophageal sphincter relaxation pressures were similar (6.0 ± 2.8 ALTE mmHg vs. 10.2 ± 3.3 mmHg control, $P=0.4$). However, the post deglutitive rise in upper esophageal sphincter contractile pressure occurred more frequently in infants with ALTE (54% ALTE vs. 36% control, $P=0.04$). During SREs, the presence of polymorphic esophageal body waveforms were similar (40% ALTE vs. 43% control, $P=0.8$). The frequencies of peristaltic propagation (complete: incomplete: failed, %) infants with ALTE vs. controls were 83:7:10 vs. 76:24:0 ($P=0.02$) respectively.

The temporal relationships between the SRE and swallow were also examined. Deglutition occurred most frequently during the SRE in both groups (92% ALTE vs. 95% control, $P=0.7$). Further analysis revealed that pharyngeal swallowing inhibited respiration most frequently at the onset of the SRE in both groups (74% ALTE vs. 73% control, $P=1.0$).

DISCUSSION

The characteristics of swallowing and respiratory junction interactions in infants with ALTE or during spontaneous respiratory events (SREs) have not been addressed before. The salient findings among infants with ALTE were that: (1) they have delays in restoring aero-digestive normalcy as indicated by more frequent and prolonged SREs associated with deglutition; (2) mixed mechanisms for SREs and gasping breaths were more frequent; (3) pre- and post- deglutitive rise in upper esophageal contractile pressure was of lesser magnitude; (4) lower esophageal sphincteric functions were similar and concern for GER disease should not be increased; (5) deglutition remains the most potent clearance mechanism during SREs than secondary peristaltic reflex; (6) APGAR scores were lower in the ALTE group; and (7) Infants with ALTE have dysfunctional proximal aero-digestive rhythms.

Although demographic characteristics were similar in most respects, the significantly lower APGAR scores in infants with ALTE draws attention. The mechanisms of aberrant aero-digestive reflexes in infants with lower APGAR scores are not fully understood, although we have proposed brain-stem dysregulation in infants with hypoxic ischemic encephalopathy as a plausible explanation for pharyngo-esophageal dysmotility.²¹ Not knowing the mechanism for ALTEs, multiple etiologies are investigated and empiric therapies are frequent.^{2,3,7,25} A common assumption of ALTE is the association with GER; however, the attributable aero-digestive mechanisms remain unclear. Hence, we evaluated the reciprocal relationships between swallow-integrated esophageal motility and respiratory waveform patterns. Swallow-dependent SREs were actually physiological deglutition-apneas masquerading as central apneas. In the absence of recording esophageal motility (Figure 1), these sequences appear like pathological apneas, as is commonly defined during polysomnography studies.¹⁶ Such occurrences can be physiological during swallowing events, and are not due to GER.

In infants with ALTE, prolonged SREs were linked with multiple deglutition attempts and multiple gasping events; all signaling proximal aero-digestive incoordination, laryngeal chemo reflex,^{15,26,27} pharyngo-glottal closure reflex,¹² or esophago-glottal closure reflex.¹³ Cumulatively, the occurrence of these reflexes suggests brainstem dysregulation controlling the superior laryngeal, vagal, glossopharyngeal, superior pharyngeal, and recurrent laryngeal nerves.^{28–30}

Exaggeration of respiratory inhibition during pharyngeal events may explain some of the functional disturbances related to ALTE. The delays in restoration of regulated spontaneous breathing are guided by aero-digestive clearance and primary peristalsis. Higher frequencies of primary peristalsis and incomplete/failed propagation in infants with ALTE indicate ineffective esophageal clearance. In controls, this was not the case, as secondary peristalsis was a major means for esophageal clearance. We speculate that proximal aero-digestive hypersensitivity and cortical hyper vigilance states may be factors that trigger multiple and mass reflexes that delay restoration of aero-digestive normalcy in infants with ALTE.^{17,31} Although there were similarities in basal esophageal motility characteristics, dysfunctional proximal aero-digestive protective mechanisms were detected, as demonstrated by a reduced magnitude of pre- and post- deglutitive rise in upper esophageal sphincter pressure and more frequent respiratory changes. These findings suggest possible deficits in central pattern generation of aero-digestive rhythms and regulation. This implies that infants with ALTE most likely have abnormal swallowing-respiratory junction interactions, identified as esophageal dysmotility and/or mechanical airway abnormalities, and in some circumstances may be a mechanism for the life-threatening event. Other possible etiologies and related mechanisms may also exist. Further work is needed to define the sensory-motor aspects of specific adaptive pharyngeal, esophageal, and airway reflex responses in order to determine definite areas of dysfunction within these domains. These can include mechanisms within the upper aero-digestive tract, lower aero-digestive tract, or esophageal peristaltic dysmotility.

Potential diagnostic markers and therapeutic targets should focus on the upper aero-digestive tract. Lower esophageal sphincter characteristics were similar with regards to basal tone,

relaxation response, and adequate nadir pressure in both groups, all suggestive of appropriate basal integrity of gastro-esophageal junction. Although GER related SREs were present, they were succeeded by the clearance of the aero-digestive tract with restoration of normal respiration. Indeed, deglutition is the most frequent esophageal event associated with SREs, not GER. Therefore, acid suppressive therapies are unwarranted (unless proven by pH/Impedance testing) particularly when proximal aerodigestive tract maladaptation is the reason for symptoms. Exaggeration of the swallowing and respiratory junction interactions occurs in infants presenting with ALTE. We speculate that this abnormality may improve with maturation, because several sensory-motor aspects of aero-digestive reflexes do improve with maturation over a 2–4 week period.^{9,11} Pharyngeal contractile waveform signals occurred most frequently at the onset and also during the SRE event, indicating efforts to swallow before resumption of breathing. Gasping was frequent in infants with ALTE, as has been noted in sudden infant death syndrome^{32,33} and can be a mechanism for auto-resuscitation.^{34–36} Gasp is often construed as a problem but in reality is an effort made for adequate airway protection when associated with deglutition. Potential therapeutic targets that may offer benefit are modification of upper esophageal sphincter tone, oropharyngeal swallowing therapies, pacing exercises during feeding, and modification of posture and position during feeding.

In conclusion, prolonged SREs in infants with ALTE are suggestive of dysfunctional central coordination and dysregulation. Greater frequency of primary peristalsis with propagation failure is suggestive of ineffective pharyngo-esophageal motility. Dysfunctional proximal aero-digestive mechanisms suggest deficits in central pattern generation and adaptive regulation of aero-digestive rhythms. Therapies should not be directed to treat GER without objective evidence; but rather target afferent and efferent pathways related to the proximal aero-digestive tract with an emphasis on coordination of the airway and swallowing functions.

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ABBREVIATIONS

ALTE	apparent life threatening event
SRE	spontaneous respiratory event
GER	gastro-esophageal reflux

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Figure 1.

Respiratory waveform patterns in control and ALTE. Notice normal breathing followed by a spontaneous respiratory event (shaded area) lasting longer than 2 seconds and two missed breaths succeeded by normal breathing.

Figure 2. Representative examples of pharyngo-esophageal and respiratory rhythm interactions in control (upper) and ALTE (lower)
 Shaded areas denote the SRE. A) Swallow associated SRE characterized by deglutition. B) Gastro-esophageal reflux (GER) associated SRE characterized by transient lower esophageal sphincter relaxation (TLESR), retrograde movement, upper esophageal sphincter contractile reflexes, and peristalsis. C) Independent SRE characterized by absence of esophageal motility changes. Observe evidence of gasping on manometry and respiratory waveforms. Note the respiratory perturbations seen in Fig 1 are exactly the same, but in Fig 2 are synchronized with pharyngo-esophageal motility changes.

Figure 3. Esophageal characteristics during SRE

A) Upper esophageal sphincter characteristics – Note similar basal pressure; however, response magnitude of protective contractile reflex (CR) during pre- and post-deglutition is lesser in infants with ALTE. B) Lower esophageal sphincter characteristics – Note basal and relaxation nadir pressures are similar. C) Esophageal event associated with SRE- Deglutition is most frequent in both groups. D) Esophageal clearance mechanism- Primary peristalsis is more frequent in infants with ALTE with a low occurrence of secondary peristalsis; thus, respiratory perturbations can be frequent.

Table 1

Subject demographics

Characteristic	ALTE population (n=10)	Control population (n=10)	P-value
Sex (male), n	7	7	1.0
Gestational age, wks	28.0 ± 4.3	29.8 ± 3.4	0.3
Birth weight, kg	0.86 (0.71 – 1.3)	1.2 (0.91 – 1.7)	0.4
Birth length, cm	34.2 (30.8 – 38.5)	38.0 (35.0 – 38.0)	0.4
Birth head circumference, cm	26.6 ± 5.1	26.7 ± 3.7	1.0
APGAR at 1 minute	3 (0 – 7)	7 (3 – 8)	< 0.01
APGAR at 5 minutes	7 (3 – 8)	8 (7 – 9)	< 0.01
PMA at evaluation, wks	40.4 ± 4.6	40.2 ± 3.2	0.9
Weight at evaluation, kg	3.1 ± 0.8	3.2 ± 0.8	0.8
Length at evaluation, cm	47.8 ± 4.0	47.7 ± 3.9	0.9
Head circumference at evaluation, cm	34.2 ± 2.8	34.4 ± 2.2	0.9

* Values shown as mean ± SD, median(range), or n