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Upstream Effect of Esophageal Distention: Effect on Airway

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Abstract

The pharyngoesophageal segment of the foregut has an important function in steering clear of luminal contents from the airway, across the age spectrum from a premature neonate to an aging adult. This complex neuromuscular interaction between the esophagus and the airway is maintained by a variety of mechanisms mediated by the parasympathetic and sympathetic afferent and efferent outflows involving the myenteric plexus, glossopharyngeal and vagus cranial nerves, phrenic nerve, and brainstem nuclei. The esophageal provocation during gastroesophageal reflux events results in esophageal distention, followed by responses in the esophagus, the airway, or both. Studies involving esophageal provocation in human adults and animal models are beginning to illuminate the pathogenetic mechanisms associated with aerodigestive tract disease. However, studies pertinent to this topic in infants or children have been lacking. In this paper, we review recent advances concerning the motor responses of the esophagus and the airway ensuing upon esophageal distention. Recent advances in methods to evaluate aerodigestive responses in infants that have been validated are discussed.

Introduction

The prevalence and severity of gastroesophageal reflux and airway problems are high in humans, regardless of age. Pulmonary symptoms can result from an absence or an exaggeration of airway responses. Information in infants or children regarding gastroesophageal reflux–associated aerodigestive tract protective mechanisms has been lacking. We focus the discussion on the following recent advances:

1. Epidemiology of aerodigestive problems
2. Embryology of the aerodigestive apparatus
3. Pathophysiology of esophageal airway interactions in infants compared with adults
4. Methodologies to evaluate esophagus airway interactions
5. Effects of esophageal distention on the esophagus and airway
6. Clinical correlates of esophageal airway interactions

Epidemiology and Significance of Aerodigestive Problems Across the Age Range: Infancy to Aging

Neonates receive many high-technology therapies to continue their survival. Consequently, there is a shift in morbidity with an alarming increase in the number of premature infants with special feeding and respiratory needs in which the pathophysiology is unclear [1]. The American Thoracic Society documents that 30% of preterm infants with low birth weight develop chronic lung disease of infancy [2]. A large survey of patients with gastroesophageal reflux disease (GERD) ($n=1980$ children, aged 2–18 years) showed that these patients were more commonly diagnosed with sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis than were control children ($n=7920$) [3]. Recently the incidence rate for esophageal adenocarcinoma in adulthood was found to be increased more than sevenfold in a large cohort ($n=3364$, prematurity at birth), and an 11-fold risk was found if the birth weight was less than 2000 g [4].

In contrast, in adults, a frequent causal association between GERD and supraesophageal conditions, such as asthma, chronic bronchitis, laryngitis, and laryngeal cancer, has been implicated [5]. In this review, encompassing several studies, it was consistently found that symptomatic GERD was present in 30% to 90% of adults with asthma. In another study involving US military veterans, a number of pulmonary diseases (asthma, pulmonary fibrosis, atelectasis, bronchitis, bronchiectasis, chronic obstructive disease, and pneumonia) were associated with esophagitis ($n=101,366$ patients with GERD), the strongest association being with bronchial asthma (odds ratio [OR] 1.5; 95% confidence interval, 1.43–1.59) [6]. However, the risk of antegrade and retrograde aspiration was found to be significantly high in the critically ill adults undergoing intensive care [7].

Embryologic Origins of Esophageal Airway Interactions

The relationship between the esophagus, stomach, and airways begins in embryonic life [8–10]. The laryngotracheo-bronchial diverticulum originates from the primitive foregut at 4 weeks of embryonic life. These organs share a similar nervous system regulation, with innervation by visceral afferents and efferents of the vagus nerve. These organs are richly supplied with autonomic fibers from parasympathetic fibers and sympathetic chains. Evidence suggests that nonadrenergic and noncholinergic systems are present in each organ, and nitric oxide and vasoactive intestinal polypeptide are possible mediators. The pathophysiology of this neuromotor relationship during later periods, that is, from postnatal life to aging, is not well understood.

Esophageal Airway–related Problems in Infants and Children

Infants are obligate nasal breathers with a relatively large tongue and small aerodigestive tract [11,12]. Infants breathe faster, and their feeding habits are different compared with those of older children or adults. In infants, sucking and swallowing of liquids precedes solid intake at weaning. Oromotor skills may not develop or may have regressed in infants with intracranial problems or respiratory disease, as opposed to adults, in whom a learned feeding behavior may disappear with neurologic insults. In the human infant esophagus, the

presence of rapid growth and maturation, different neuromotor responses, developmentally vulnerable brain and lungs, predominantly supine posture, smaller aerodigestive tract, and increased frequency of gastroesophageal reflux events and apparent life-threatening events causing airway compromise needs to be recognized.

Methodologies to Evaluate Esophageal Airway Interactions

Esophageal manometry and infusion protocols concurrent with other testing modalities

Studies in human adult or animal models have clarified the sensory and motor pathways pertinent to the esophagus and airway interactions [13–16,17•,18•,19]. Pharyngo-esophageal manometry studies and esophageal provocation either alone or in concert with endoscopic evaluation of the airway or functional magnetic resonance imaging of the brain have been performed to evaluate the sensory motor aspects of dysphagia and esophageal motility in human adults [20,21,22,23•,24,25]. In these studies, upon esophageal distention, the reflex characteristics of primary peristalsis, secondary peristalsis, upper esophageal sphincter (UES) responses, gastroesophageal reflux-specific responses, glottal closure responses, and cerebral cortical responses have been described. Airway reactivity and glottal closure upon esophageal distention and acid perfusion have also been elucidated using concurrent respiratory function tests or endoscopic evaluation of glottis [26•,27•]. Gastroesophageal reflux was noted to be a risk factor for bronchial asthma. Heightened bronchial reactivity, vagally mediated reflexes, or micro-aspiration were also considered as potential causes. Any of these methods can be fraught with difficulty in infant evaluations, particularly because of the noncompliance of subjects, invasive methods, dynamic growth parameters, and parental anxiety.

To investigate the afferent and efferent limbs of the vago-vagal reflex arc in human infants, we recently developed and validated methods to record luminal pressure changes using a special multi-lumen infant size-specific manometry catheter assembly connected to a pneumohydraulic water perfusion system, concurrent with respiratory inductance plethysmography and vital signs (Figs. 1 and 2) [28•,29,30•]. Aerodigestive reflexes triggered upon esophageal stimulation were identified and analyzed. Neuromotor indices, including stimulation threshold (the lowest volume of the stimulus to evoke 50% responses), frequency stimulation (the proportion of responses to a particular stimulus mode), response acuity (time to respond to the stimulus), magnitude of the peristaltic motor responses to graded stimulus mode, and change in UES pressure can be measured.

Ultrasonography to evaluate glottal adduction

Recently, we developed methods to evaluate glottal motion using a noninvasive approach [31•]. This method has been validated using concurrent nasolaryngoscopy and ultrasonography. Simultaneous ultrasonography of the glottis was performed in 10 subjects (aged 4.5 mo to 7.1 y) who underwent diagnostic flexible outpatient nasolaryngoscopy. The ultrasonography transducer was placed on the anterior neck at the level of the vocal cords. The video signals from nasolaryngoscopy and ultrasonography were integrated and synchronized into real-time cine loops. Frame-by-frame evaluation identifying glottal opening and closure time was compared between the two modalities by observers blinded to

nasolaryngoscopy images; this evaluation identified ultrasonographically determined glottal closure with 99% and 100% accuracy. This study showed that temporal characteristics of glottal motion can be quantified by ultrasonography with perfect reliability and safety. This method can be useful in measuring the presence and duration of laryngeal adduction.

Characterization of esophageal glottal closure reflex using concurrent ultrasonography of glottis and esophageal provocation during manometry

We performed concurrent esophageal manometric provocation and visualized glottal motion using ultrasonography [32•]. Manometry signals and ultrasonography images were transformed onto the video-integrated MMS motility system (Medical Measurement Systems, Dover, NH). As with other video endoscopy studies performed concurrently with manometry, the occurrence of esophago-glottal closure reflex from the onset of esophageal stimulus was identified.

Effects of Esophageal Distention on Esophagus and the Airway in Infants

Mechanoreceptor and chemoreceptor stimulation was performed using graded volumes of air, water, and apple juice (pH=3.7), respectively. The frequency and magnitude of the resulting esophago-deglutition response, secondary peristalsis, and esophago–UES contractile reflex were quantified. Mechanosensitive and chemosensitive stimuli evoked volume-dependent specific peristaltic and UES reflexes at both 33- and 36-week corrected gestational ages. The recruitment and magnitude of these reflexes are dependent on the physicochemical properties of the stimuli. These responses ensure the safety of the aerodigestive tract in the healthy premature infants who were studied.

In a pilot study in infants, esophago-glottal closure reflex was detected with a frequency of 94% of mechanostimulation (air-induced esophageal distention). Response latency and glottal closure duration were 0.4 ± 0.2 seconds and 0.3 ± 0.2 seconds, respectively (mean $\pm$ SD).

Clinical Correlates of Esophageal Airway Interactions

Figures 1 and 2 depict the clinical correlates of esophageal airway interactions. The pathophysiology of chronic lung disease of infancy is not well understood and may include a myriad causes including prenatal or postnatal inflammation, oxygen toxicity, and ventilation-associated lung injury; the role of esophageal provocation on airway interactions is not known in this patient population. Whatever the mechanism of action that incites lung injury, the final common symptom-complex includes hypoxemia, hypercarbia, coughing, choking and bronchospasm spells, apparent life-threatening events, recurrent pneumonias, and atelectasis [2,33]. Aggravating factors include dysphagia, GERD, nutritional failure, and airway compromise. The investigation of medical or surgical management strategies is at an early stage [2,33]. Chronic lung disease of infancy is recognized to be a multisystem disease; the pathophysiology of the interaction among various organ interactions is unclear. Many infants have life-threatening apneas and bradycardias during their hospital stay.

Conclusions

A relationship between the upstream effect of esophageal distention and airway responses exists in healthy individuals and in those with disease, from infancy to adulthood. Aerodigestive interactions differ between children and adults. It is likely that the majority of these afferent-efferent interactions accentuate airway protection against anterograde or retrograde aspiration. However, the airway-related symptoms may arise from an exaggeration of these reflexes. Characterization of the pathophysiology of these reflexes in the pediatric age groups is in process.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Stevenson DK, Wright LL, Lemons JA, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network. *Am J Obstet Gynecol.* 1998; 179:1632–1639. [PubMed: 9855609]
2. American Thoracic Society. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med.* 2003; 168:356–396. [PubMed: 12888611]
3. El-Serag HB, Gilger M, Kuebel M, Rabeneck L. Extraesophageal association of gastroesophageal reflux disease in children without neurologic defects. *Gastroenterology.* 2001; 21:1294–1299. [PubMed: 11729108]
4. Kaijser M, Akre O, Cnattingius S, et al. Preterm birth, low birth weight, and risk for esophageal adenocarcinoma. *Gastroenterology.* 2005; 128:607–609. [PubMed: 15765396]
5. Johanson JF. Epidemiology of esophageal and supraesophageal reflux injuries. *Am J Med.* 2000; 108(4A):99S–103S. [PubMed: 10718460]
6. El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology.* 1997; 113:755–760. [PubMed: 9287965]
7. McClave SA, DeMeo MT, DeLegge MH, et al. North American summit on aspiration in the critically ill patient: Consensus Statement. *J Parenter Enter Nutr.* 2002; 26:S80–S85.
8. Sadler, TW. Special embryology, respiratory system. In: Sadler, TW.; Langman, J., editors. *Langman's Medical Embryology, Part II, edn 7.* Philadelphia: Williams & Wilkins; 1995. p. 232–241.
9. Sadler, TW. Special embryology, digestive system. In: Sadler, TW.; Langman, J., editors. *Langman's Medical Embryology, part II, edn 7.* Philadelphia: Williams & Wilkins; 1995. p. 241–271.
10. Mansfield LE. Embryonic origins of the relation of gastroesophageal reflux disease and airway disease. *Am J Med.* 2001; 111(8A):3S–7S. [PubMed: 11749916]
11. Arvedson J, Rogers B, Buck G, et al. Silent aspiration prominent in children with dysphagia. *Int J Pediatr Otorhinolaryngol.* 1994; 28:173–181. [PubMed: 8157416]
12. Jolley SG, McClelland KK, Mosesso-Ronssaeau M. Pharyngeal and swallowing disorders in infants. *Semin Pediatr Surg.* 1995; 4:157–165. [PubMed: 7582886]
13. Thach B, Menon A. Pulmonary protective mechanisms in human infants. *Am Rev Respir Dis.* 1985; 131:S55–S58. [PubMed: 4003911]
14. Thach B. Reflux associated apnea in infants: evidence for a laryngeal chemoreflex. *Am J Med.* 1997; 103:120S–124S. [PubMed: 9422636]
15. Menon A, Schefft G, Thach B. Apnea associated with regurgitation in infants. *J Pediatr.* 1985; 106:625–629. [PubMed: 3981319]

16. Sengupta JN, Saha JK, Goyal RK. Stimulus-response function studies of esophageal mechanosensitive nociceptors in sympathetic afferents of opossum. *J Neurophysiol.* 1990; 64:796–812. [PubMed: 2230925]
17. Suwanprathes P, Ngu M, Ing A, et al. c-Fos immunoreactivity in the brain after esophageal acid stimulation. *Am J Med.* 2003; 115:31S–38S. [PubMed: 12928072] These authors provide an excellent review of literature and methods concerning identification of neural pathways in animal models.
18. Broussard DL, Altschuler SM. Central integration of swallow and airway protective reflexes. *Am J Med.* 2000; 108:62S–67S. [PubMed: 10718454] The authors provide an excellent review of the literature and methods of identification of neural pathways in animal models.
19. Sengupta JN. An overview of esophageal sensory receptors. *Am J Med.* 2000; 108:87S–89S. [PubMed: 10718458]
20. Fass R, Naliboff B, Higa L, et al. Differential effect of long-term esophageal acid exposure on mechanosensitivity and chemosensitivity in humans. *Gastroenterology.* 1998; 115:1363–1373. [PubMed: 9834263]
21. Torrico S, Kern M, Aslam M, et al. Upper esophageal sphincter function during gastroesophageal reflux events revisited. *Am J Physiol. Gastrointest Liver Physiol.* 2000; 279:G262–G267. [PubMed: 10915633]
22. Kahrilas PJ, Dodds WJ, Dent J, et al. UES function during deglutition. *Gastroenterology.* 1988; 96:52–62. [PubMed: 3371625]
23. Kern MK, Birn RM, Jaradeh S, et al. Identification and characterization of cerebral cortical response to esophageal mucosal acid exposure and distention. *Gastroenterology.* 1998; 115:1353–1362. [PubMed: 9834262] The authors validate the methods of eliciting cortical responses upon esophageal stimulation in human adults.
24. Schoeman MN, Holloway RH. Stimulation and characteristics of secondary esophageal peristalsis in normal subjects. *Gut.* 1994; 35:152–158. [PubMed: 8307463]
25. Shaker R, Lang IM. Reflex mediated airway protective mechanisms against retrograde aspiration. *Am J Med.* 1997; 103:64S–73S. [PubMed: 9422627]
26. Harding SM. Gastroesophageal reflux: a potential asthma trigger. *Immunol Allergy Clin North Am.* 2005; 25:131–148. [PubMed: 15579368] An excellent review of the mechanisms of links between asthma and gastroesophageal reflux.
27. Shaker R, Dodds WJ, Ren J, et al. Esophagoglottal closure reflex: a mechanism of airway protection. *Gastroenterology.* 1992; 102:857–861. [PubMed: 1537523] The authors characterize the esophago-glottal closure reflex in human adults using endoscopy and manometry performed concurrently.
28. Jadcherla SR, Duong HQ, Hoffmann RG, et al. Esophageal body and upper esophageal sphincter motor responses to esophageal provocation during maturation in preterm newborns. *J Pediatr.* 2003; 143:31–38. [PubMed: 12915821] These authors validate the techniques of esophageal micromanometry and esophageal infusion protocols. They characterize the sensory motor parameters of the deglutition response, secondary peristalsis, and UES contractile reflex in response to mechano- and chemostimulation of the mid-esophagus.
29. Jadcherla SR. Manometric evaluation of esophageal protective reflexes in infants and children. *Am J Med.* 2003; 115:157–160. [PubMed: 12893406]
30. Jadcherla SR, Duong HQ, Hofmann C, et al. Characteristics of upper esophageal sphincter and esophageal body during maturation in healthy human neonates compared with adults. *Neurogastroenterol Motil.* 2005; 17:663–670. [PubMed: 16185304] Cardinal differences between the pharyngo-esophageal motility parameters during spontaneous swallows in premature infants were studied longitudinally, and full-term infants and adults were compared.
31. Jadcherla SR, Gupta A, Stoner E, et al. Correlation of glottal closure using concurrent ultrasonography and nasolaryngoscopy in children: A novel approach to evaluate glottal status. *Dysphagia.* 2006; 21:1–7. [PubMed: 16544092] The authors validate the visualization by ultrasonography of the glottis performed concurrently with nasolaryngoscopy.
32. Jadcherla SR, Gupta A, Stoner E, et al. Characterization of esophago-glottal closure-reflex (EGCR) using concurrent ultrasonography of glottis and esophageal provocation during manometry in

infants. *Gastroenterology*. 2005; 128(S-2) A-410. In this abstract, the authors characterize glottal adduction upon esophageal mechanostimulation in human neonates. Noninvasive evaluation of the glottis with ultrasonography was performed.

33. American Academy of Pediatrics. Committee on fetus and newborn. apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003; 111:914–917. [PubMed: 12671135]

Figure 1.

This schematic diagram depicts the effects of esophageal distention-associated reflexes. Upon esophageal distention, motor responses originating in the pharynx, esophagus, upper esophageal sphincter (UES), and lower esophageal sphincter (LES) are shown on the *right*. These phenomena prevent the entry of stimulus upstream, thus favoring clearance. Shown on the *left* are the airway reflexes evoked upon pharyngo-esophageal stimulation. Consequences on airways can result in obstructive apnea, glottal closure, stridor, bronchospasm, atelectasis, and cough.

Figure 2.

The effect of mid-esophageal (M-Eso-Inf) stimulation with sterile water on esophageal and respiratory recordings is shown. Results of a manometry recording describing pharyngeal, upper esophageal sphincter (UES), proximal-, middle-, distal-esophageal body, lower esophageal sphincter (LES), and stomach waveforms in a premature infant with bronchopulmonary dysplasia (chronic lung disease of infancy) are shown. Results of concurrent thoracic and abdominal respiratory inductance plethysmography and nasal air flow (to monitor breathing), submental electromyography (to confirm swallow), and electrocardiography (to monitor heart rate) are also recorded. The esophageal distention is seen as a common cavity pressure increase. Note the presence of hypotonic UES and the occurrence of LES relaxation with infusion. The infusion was followed by the occurrence of apnea, cough, and deglutition responses. Finally, a stable respiratory pattern resumed after peristaltic activity was noted in the esophagus. D-Eso—distal esophageal; P-Eso—proximal esophageal.