Published in final edited form as:

Semin Respir Crit Care Med. 2010 October ; 31(5): 554–560. doi:10.1055/s-0030-1265896.

Physiology and Pathophysiology of Glottic Reflexes and Pulmonary Aspiration: From Neonates to Adults

Sudarshan R. Jadcherla, M.D.^{1,2}, Walter J. Hogan, M.D.³, and Reza Shaker, M.D.³

¹Department of Pediatrics, Sections of Neonatology, Pediatric Gastroenterology, and Nutrition, The Ohio State University College of Medicine, Columbus, Ohio

²Nationwide Children's Hospital, Columbus, Ohio

³Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract

Pulmonary aspiration is the consequence of abnormal entry of fluid, particulate material, or endogenous secretions into the airway. The two main types of aspiration scenarios include anterograde aspiration, which occurs during swallowing, and retrograde aspiration, which can occur during gastroesophageal reflux (GER) events. The important structures that protect against aspiration include the aerodigestive apparatus: pharynx, upper esophageal sphincter, esophageal body, glottis and vocal cords, and airway. In this article we review the neuroanatomy, physiology, and pathophysiology pertinent to glottic reflexes and airway aspiration across the age spectrum from neonates to adults. We also discuss recent advances in our understanding of glottal reflexes and the relationship of these reflexes to developmental anatomy and physiology, the pathophysiology of aspiration, and aerodigestive interactions.

Keywords

Pharyngoglottal closure reflex; esophagoglottal closure reflex; laryngeal adductor reflex; upper esophageal sphincter; gastroesophageal reflux

Pulmonary aspiration is the consequence of abnormal entry of fluid, particulate material, or endogenous secretions into the airway. The two main types of aspiration scenarios include anterograde aspiration, which occurs during swallowing, and retrograde aspiration, which can occur during gastroesophageal reflux (GER) events. The important structures that protect against aspiration include the aerodigestive apparatus: pharynx, upper esophageal sphincter (UES), esophageal body, glottis and vocal cords, and airway. There are several stimulatory reflexes involving the pharynx, esophagus, and larynx that prevent pulmonary aspiration. This includes the most important function, which is the laryngeal adductor reflex (LAR) mechanism. Other significant reflexes include the esophagoglottal closure reflex (EGCR) and the pharyngoglottal closure reflex (PGCR).

The UES is the most proximal gastrointestinal sphincter. It lies adjacent to the larynx and affords protection against oral escape of gastric contents. The UES response to esophageal distention and acidification is also reviewed. A close functional relationship exists between the airway and digestive tract defenses, which provide protection against pulmonary

aspiration. Technological advances and intensive care approaches have led to increased survival from stays in intensive care units for patients of all ages. Airway safety, swallowing problems, and aspiration syndromes constitute a significant challenge across the age range from neonates to nonagenarians. Inadequate airway protection during swallowing, GER, or emesis is an important contributory factor to aerodigestive morbidity. Appropriate glottal closure reflex mechanisms can ensure safe swallowing and enhance protection against aspiration, as recognized in studies from neonates and adult subjects.

In this article we review the neuroanatomy, physiology, and pathophysiology pertinent to glottic reflexes and airway aspiration across the age spectrum from neonates to adults. We also discuss recent advances in our understanding of glottal reflexes and the relationship of these reflexes to developmental anatomy and physiology, the pathophysiology of aspiration, and aerodigestive interactions.

EMBRYOLOGY, ANATOMY, AND SENSORIMOTOR NEURAL INNERVATIONS OF GLOTTIS AND ESOPHAGUS

The close relationship between the airway and foregut begins in embryonic life, and excellent monographs pertinent to this section are referenced.^{1–6} Embryological origins and the neuroanatomical connections of the upper gastrointestinal tract and airway are reviewed in this section.

The aerodigestive organs are developed from adjacent segments of the primitive foregut.^{1–4} The true vocal cords begin as glottal folds. By the sixth or seventh week of gestation, a structure superior to the true vocal cords evolves to protect the vocal cords and lower airway. This superior structure consists of the epiglottis, aryepiglottic folds, false vocal cords, and laryngeal ventricles. The epiglottis originates as a hypobranchial eminence behind the future tongue, and it becomes separated from the tongue by 7 weeks. Simultaneously, two lateral folds connect to the base of the epiglottis; the arytenoid cartilages develop at the distal end of this structure. The larynx originates as a groove in the primitive foregut, which folds upon itself to become the laryngotracheal bud, which subsequently divides and forms the bronchopulmonary segments.

Structurally, the esophagus is a hollow tubular organ consisting of an inner circular and outer longitudinal muscle layers with the myenteric plexus between the two layers. The distal esophagus has smooth muscle, whereas the proximal esophagus has striated muscle. The UES, a constriction between the pharynx and the proximal esophagus, is characterized by a high pressure zone generated by the cricopharyngeus (the principal muscle), proximal cervical esophagus, and inferior pharyngeal constrictor (Fig. 1).⁵ The UES is innervated by (1) the vagus nerve via the pharyngoesophageal, superior laryngeal, and recurrent laryngeal branches; (2) the glossopharyngeal nerve; and (3) the sympathetics via the cranial cervical ganglion. The distal end of the esophagus consists of specialized smooth muscle that is identified as the lower esophageal sphincter (LES), an autonomous contractile apparatus that is tonically active and relaxes periodically to facilitate bolus transit into the stomach. Although the LES is considered as an important functional segment in preventing GER, other neighboring structures, including the oblique sling fibers of the stomach, the musculofascial diaphragmatic sling, and the intraabdominal esophagus also contribute to this antireflux function.⁶

The musculature of the larynx is derived from the mesenchyme of the fourth and sixth pharyngeal arches, and all laryngeal muscles are innervated by branches of cranial nerve X. The superior laryngeal nerve innervates derivatives of the fourth pharyngeal arch

(cricothyroid, levator palatini, and constrictors of pharynx), and the recurrent laryngeal nerve innervates derivatives of the sixth pharyngeal arch (intrinsic muscles of the larynx).

The airways and esophagus share common innervations.⁵⁻⁷ Foregut afferents are derived from both the vagal and dorsal root ganglions with cell bodies in the nodose ganglion. This afferent apparatus conveys signals to the neurons in the nucleus tractus solitarius, located in the dorsomedial medulla oblongata. These signals are integrated in a specific terminal site of the nucleus tractus solitarius, known as the subnucleus centralis, which is the sole point of termination of esophageal afferents. Following sensory integration in the nucleus tractus solitarius, neural signals can in turn activate airway motor neurons in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve, thereby producing an efferent parasympathetic response and/or nonadrenergic, noncholinergic response.

In summary, the aerodigestive tract is innervated by (1) supraglottal mucosal areas from cranial nerves IX and X plus muscular areas from cranial nerve X, (2) infraglottal mucosal and muscular areas from cranial nerve X, and (3) pharynx and esophagus from cranial nerves IX and X.

FUNCTIONAL PHYSIOLOGY OF GLOTTIS AND ESOPHAGUS, FROM FETUS TO ADULT

The three most important and highly relevant functions of the glottis are to facilitate ventilation, facilitate phonation, and provide airway protection. Similarly, the three most important and highly relevant functions of the pharyngoesophageal segment are to facilitate safe deglutition and esophageal transport of enteric nutrients, to provide volume clearance with swallowing or emesis, and to protect the airway. Glottal and esophageal functions vary depending on the stage of life.^{4,8,9} During fetal development, for example, lung fluid is transported out of the primitive airway to the amniotic fluid pool, which is swallowed via the fetal pharynx by 11 weeks of embryonic life. Primitive swallowing ability develops by 11 weeks, and by 18 to 20 weeks sucking movements appear. When full-term gestation (37 completed weeks) is reached, the fetus can swallow and circulate nearly 500 mL of amniotic fluid per day. Thus swallow-induced peristaltic activity begins in fetal life, and glottal airway and pharyngoesophageal functions are arranged in series. Aspiration of amniotic fluid (combination of fetal lung fluid, fetal urine, debris from skin cells, and particulate matter) rarely occurs in utero, usually under conditions of fetal distress or asphyxia. Therefore, it is conceivable that the fetal larynx prevents aspiration under normal conditions.

With the first breath at birth, the glottal airway and pharyngoesophageal functions are arranged in parallel fashion but assume different roles. Immediately after birth, pharyngoesophageal functions continue as swallowing, whereas glottal opening and closure regulate the entry of air into and out of the lungs. Complete glottal adduction can occur as in the complex laryngeal chemoreflex, during which variable components of laryngeal adduction, apnea, repetitive swallowing, startle, hypertension and bradycardia, and hypoxia can be noted.⁸ In fetal and neonatal life, the laryngeal chemoreflex and glottal closure protect the airway from the potential hazard of aspiration, and repetitive swallowing clears the pharyngeal airway of any material. Apnea contributes in part to the important airway protective mechanisms in premature and full-term neonates, although the consequences of prolonged apnea and sustained laryngospasm can be deleterious by preventing air flow and interrupting lung ventilation, thereby causing hypoxia. Subsequently, during infancy and through adulthood, prolonged exhalations against a partially closed glottis occur in the form of the cough reflex, which functions to expel and clear irritants from the airway.

Conditions that point toward malfunction or maladaptation of glottal reflexes across the age spectrum include choking, anterograde and retrograde aspiration, life-threatening events or sudden deaths, dysphagia syndromes, gastroesophageal reflux disease, intractable chronic lung disease, ventilator-associated pneumonias, and vocal cord paralysis. The mechanisms of these conditions are not completely understood.

GLOTTAL AIRWAY PROTECTIVE MECHANISMS

Pulmonary aspiration is a leading cause of mortality and or morbidity in neurologically vulnerable patients of all ages. This includes premature infants, infants born with perinatal asphyxia, patients with cerebral palsy, patients with congenital airway and foregut anomalies, patients with dysphagia, and patients with chronic lung disease. Aspiration is also a serious issue for the elderly population.¹⁰

A series of coordinated neuromuscular events located within the laryngopharyngeal compartment normally protect the airway from aspiration. However, material passing through the aerodigestive axis can spill into the lungs when these safeguards are impaired. The larynx contains the vocal cords, which are two mobile membranous bands. The glottis is the space that encompassing the vocal cords, and the UES is adjacent to this airway complex and provides protection against gastroesophageal reflux or regurgitation. The larynx is a major effector organ that is responsive to stimulatory reflexes that prevent pulmonary aspiration.

The protective function of the larynx involves several antiaspiration reflexes attributed to the glottic zone. The three important glottal closure mechanisms consist of (1) vocal cord closure or laryngeal adductor reflex, (2) the esophagoglottal closure reflex, and (3) the pharyngoglottal closure reflex.^{11,12} These reflexes are discussed in more detail below.

Vocal Cord Closure (Laryngeal Adductor Reflex)

Studies of vocal cord closure have been accomplished using laryngoscopy studies; however, such studies cannot be performed in tiny infants. Recently, we have developed and validated methods to interrogate glottal motion using ultrasonography to characterize laryngeal adduction and abduction (Fig. 2).¹³ These noninvasive approaches are now feasible across the age range.

The duration and pressure of vocal cord closure are dependent upon the sequence of activity (e.g., coughing, straining, or eructation) (Fig. 3).¹⁴ The ensuing pressure provides a barrier against aspiration of swallowed contents during their transit through the pharynx. Two additional “closure mechanisms” that enhance vocal cord contractions, aryepiglottic adduction and epiglottic descent, have also been identified.

Primary vocal cord closure involves the most distal aspect of the cords and provides the most sustained barrier to aspiration. The closure of the vocal cords is induced by the contraction of the adductor and tensor muscles of the larynx, and the adductor muscles include the lateral cricoarytenoid and interarytenoid muscles. Contraction of the cricoarytenoid muscle causes median rotation of the arytenoid cartilages; thus adducting the anterior segment of the cords closes the anterior portion of the tracheal inlet. Interarytenoid muscle contraction prompts median adduction of the arytenoids, and this leads to adduction of the posterior segment of the vocal cords with closure of the posterior region of the tracheal inlet. The laryngeal tensor muscles include the vocalis and thyroarytenoid muscles. The contractions of these muscles and perhaps the cricothyroid muscle contribute to the enhancement of vocal cord closure pressure during various physical activities.

In summary, glottic dynamics encompass three tiers of laryngeal closure during the act of swallowing. Closure of the vocal cords is the initial action and anatomically the most caudal portion of the tiers, and the duration of vocal cords closure has been reported to be ~1.7 second.¹⁵ Laryngeal elevation follows in the majority of instances with an upward and forward movement; the vocal cords start to close during this time in a minority of instances. The third tier consists of the sphincteric function of the glottis, which occurs via results from laryngeal muscle activation and completes laryngeal closure.

Esophagoglottal Closure Reflex (EGCR)

Aspiration of gastric contents during regurgitation or vomiting imposes severe constraints on anti-aspiration reflexes. Large-volume esophageal refluxate propelled from the stomach causes abrupt intraluminal pressure increases that can overwhelm pressure in the UES with escape into the pharyngolaryngeal compartment. This situation presents a threat of aspiration of gastric contents. An esophagoglottal closure reflex has been identified in humans¹¹ and feline models.¹⁶ Abrupt esophageal distention involving the entire esophagus or various regions of the esophagus stimulates the EGCR reflex, thereby causing adduction of the vocal cords and preventing access to the trachea.

The sensory signal for the EGCR reflex consists of stretch receptors located within the esophageal body. Because it can be ablated by vagotomy, these afferents apparently run through the vagus nerve.¹⁶ Animal investigations suggest that the control mechanism for this reflex resides in the brain stem, and efferent nerves traverse the recurrent laryngeal nerve and stimulate the adductor muscles of the glottis.

The EGCR represents the close relationship that exists between the digestive and respiratory tracts during retrograde transit within the esophagus. The EGCR is most likely the primary airway protective mechanism during retrograde transit of gastric contents associated with belching, regurgitation, vomiting, and acid reflux events. This reflex is activated during spontaneous acid reflux episodes,¹⁷ and it is absent in approximately half of the patients over 70 years of age.¹⁸ Interestingly experimental esophagitis in the feline model either abolishes this reflex or significantly reduces its activation frequency.¹⁹ Studies in humans have found that a direct relationship exists between the duration of vocal cord closure and the degree of balloon distention of the esophagus (Fig. 4). Additionally the EGCR is more frequently stimulated by proximal versus distal balloon distention of the esophagus. A supportive explanation for this may be that the proximal esophagus receives innervations from both the cervical vagus nerve and the recurrent laryngeal nerves to augment the EGCR.²⁰

The EGCR has been recently defined in human premature infants using concurrent manometry and noninvasive glottal ultrasonography.²¹ Glottal responses were related to the type of esophageal peristaltic response, stimulus volume, and respiratory phase (inspiratory or expiratory). The frequency occurrence of EGCR was 83% when midesophageal infusions of air were given but considerably lower with the deglutition response (44%) and secondary peristalsis (34%), or when esophageal responses were absent (22%). The response time for esophageal reflexes was 3.8 ± 1.8 second and for EGCR was 0.4 ± 0.3 second. Volume-response relationships were significantly different (1 mL vs 2 mL, $p < 0.05$), and EGCR was noted in both respiratory inspiratory and expiratory phases; however, EGCR response time was faster during expiration ($p < 0.05$).

Pharyngoglottal Closure Reflex (PGCR)

Injection of small amounts of water into the pharynx induces brief vocal cord closure. Slow introduction of graded amounts of fluid into the pharynx causes partial adduction of the

vocal cords, whereas rapid injection results in complete closure of the cords.^{12,22} The threshold volume to stimulate the PGCR reflex appears to be smaller than that required to provoke an irrepressible pharyngeal swallow but similar to that required to induce an increase in resting tone in the UES. Significantly larger fluid volumes are required to trigger the pharyngoglottal closure reflex in elderly versus younger subjects as well as in smokers versus nonsmokers.²³

Using concurrent pharyngeal manometry and ultrasonography of the glottis, temporal changes in glottal closure kinetics (frequency, response latency, and duration) with spontaneous and adaptive pharyngeal swallows were defined in human premature infants.²⁴ Frequency, response latency, and duration of glottal closure with spontaneous swallows were 100%, 0.27 ± 0.1 second, and 1 ± 0.22 second, respectively. The glottis adducted earlier ($p < 0.0001$ vs UES relaxation) within the same respiratory phase as swallow ($p = 0.03$). With pharyngeal provocations, PGCR was noted first and then again with pharyngeal reflexive swallow. The frequency, response latency, and duration of glottal closure with PGCR were 100%, 0.56 ± 0.13 second, and 0.52 ± 0.1 second, respectively. Response latency to pharyngeal reflexive swallow was 3.24 ± 0.33 second. The glottis adducted 97% within 0.36 ± 0.08 second in the same respiratory phase ($p = 0.03$) and remained adducted for 3.08 ± 0.71 second. Glottal adduction was the quickest with spontaneous swallow ($p = 0.04$ vs PGCR), and the duration was the longest during pharyngeal reflexive swallow ($p < 0.005$ vs PGCR or spontaneous swallow). Glottal adduction during basal or adaptive swallowing reflexes occurs in either respiratory phase, thus ensuring airway protection against predeglutitive or deglutitive aspiration.

Upper Esophageal Sphincter (UES)

The major component of the UES is the cricopharyngeal muscle, which is attached in a C-shaped configuration to the cricoid cartilage. Fibers from the inferior pharyngeal constrictor muscle and the proximal esophagus itself help produce a basal (resting) UES tone. Laboratory studies have shown that the UES relaxes its tone in the majority of instances following abrupt, generalized distention of the esophageal body.²⁵ However, segmental esophageal distention does not always provoke UES relaxation,²⁶ which may be explained by differences in sensitivity and concentration of recruited stretch receptors stimulated by air or balloon inflation during investigations with human subjects. The effect of aging (70 years) on the resting UES pressure and its response to intraesophageal stimuli has shown that resting tone is significantly reduced, whereas the response to distention is preserved.²⁵ Interestingly the UES response to esophageal acidification has produced conflicting results in regard to altering basal tone. The UES pressure, like other sphincters, has a variable pressure range. Resting UES tone, for example, decreases significantly during sleep.²⁷ Forceful GER could overpower the UES barrier if it coincided with a hypotensive sphincter pressure.

Using micromanometry methods, pharyngeal and UES functions have been characterized in neonates and adults.²⁸ Remarkably, the resting UES tone increases with maturation and is dependent on the state of alertness and activity. The average resting UES pressure in preterm neonates at 33 weeks postmenstrual age was 17 ± 7 mm Hg, in full-term neonates it was 26 ± 14 mm Hg, whereas in adults it was 53 ± 23 mm Hg. With growth and maturation, the muscle mass and therefore the tone and activity of the UES improve. In neonates, esophageal provocation results in UES contractile reflex,^{29,30} and pharyngeal provocation results in pharyngeal reflexive swallow and PGCR.³¹

No increase in UES pressure has been recorded during acid reflux events studied in patients during awake³² or sleeping states.³³ However, the most critical period for UES protective function during a reflux event occurs at the onset of refluxate entry into the esophagus and

its clearance from the esophagus. Because of this finding, UES pressure was monitored at the onset of reflux events in a group of patients and control subjects.³⁴ The average percentage of maximum UES pressure increase over pre-reflux values ranged between 66% and 96% in control subjects and 34% and 122% in the patient group. The pressure increases lasted up to 5 to 25 seconds. There appears to be a significant relationship between UES pressure and intraesophageal pressure increases prompted by GER events, particularly when the intraluminal pH is below 4.0. Apparently, the UES is not a fail-safe sphincter.

Nonetheless, pharyngeal acid reflux events appear to occur in healthy subjects. Pharyngeal pH recording studies have primarily focused on the hypopharyngeal region, which is an area adjacent to the tracheal inlet and ~2 cm above the UES. During ambulatory 24-hour pH studies, ~20% of healthy subjects experienced one to three pharyngeal reflux events.³⁵ The prevalence of acid reflux in this pharyngeal region appears to be significantly higher in patients with reflux-attributed laryngeal and sinus disorders.³⁶

SUMMARY

Glottic reflexes provide the primary defense against airway aspiration across the entire age spectrum. Glottal relationships during swallowing and GER events are central to the etiology and investigative approach to dysphagia and aspiration syndromes, from neonates to nonagenarians. A close functional relationship exists between the airway and the upper gastrointestinal tract, which provides protection against pulmonary aspiration of material passing through the pharyngoesophageal compartments. Investigations of pharyngoesophageal–glottal relationships suggest that a hypervigilant state of the glottis is necessary to ensure airway protection. The UES further complements protection by preventing oral escape of gastric contents into the supraesophageal space. Coordination of these defensive mechanisms prevents unwarranted spillage of materials into the airway during routine daily and strenuous activities.

Acknowledgments

Supported in part by the NIH (NIDDK) grant funds RO1 DK 068158 (Jadcherla) and PO1 DK 068051 (Jadcherla and Shaker). The authors are grateful to Mr. Ken Cieszykowski and Ms. Vanessa Parks for their assistance with this manuscript.

REFERENCES

1. Sadler, TW. Special embryology, respiratory system. In: Sadler, TW., editor. Langman's Medical Embryology. 7th ed.. Baltimore: Williams and Wilkins; 1995. p. 232-241.
2. Sadler, TW. Special embryology, digestive system. In: Sadler, TW., editor. Langman's Medical Embryology. 7th ed.. Baltimore: Williams and Wilkins; 1995. p. 241-271.
3. Mansfield LE. Embryonic origins of the relation of gastro-esophageal reflux disease and airway disease. *Am J Med.* 2001; 111(Suppl 8A):3S–7S. [PubMed: 11749916]
4. Miller JL, Sonies BC, Macedonia C. Emergence of oropharyngeal, laryngeal and swallowing activity in the developing fetal upper aerodigestive tract: an ultrasound evaluation. *Early Hum Dev.* 2003; 71:61–87. [PubMed: 12614951]
5. Lang IM, Shaker R. Anatomy and physiology of the upper esophageal sphincter. *Am J Med.* 1997; 103(5A):50S–55S. [PubMed: 9422624]
6. Goyal, RK.; Sivarao, DV. Functional anatomy and physiology of swallowing and oesophageal motility. In: Castell, DO.; Richter, JE., editors. The Esophagus. 3rd ed.. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 1-31.
7. Goyal RK, Padmanabhan R, Sang Q. Neural circuits in swallowing and abdominal vagal afferent-mediated lower esophageal sphincter relaxation. *Am J Med.* 2001; 111(Suppl 8A):95S–105S. [PubMed: 11749933]

8. Thach BT. Maturation and transformation of reflexes that protect the laryngeal airway from liquid aspiration from fetal to adult life. *Am J Med.* 2001; 111(Suppl 8A):69S–77S. [PubMed: 11749929]
9. Allen J, Zwerdling R, Ehrenkranz R, et al. 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]
10. Reza Shariatzadeh M, Huang JQ, Marrie TJ. Differences in the features of aspiration pneumonia according to site of acquisition: community or continuing care facility. *J Am Geriatr Soc.* 2006; 54:296–302. [PubMed: 16460382]
11. Shaker R, Dodds WJ, Ren J, Hogan WJ, Arndorfer RC. Esophagoglottal closure reflex: a mechanism of airway protection. *Gastroenterology.* 1992; 102:857–861. [PubMed: 1537523]
12. Shaker R, Ren J, Bardan E, et al. Pharyngoglottal closure reflex: characterization in healthy young, elderly and dysphagic patients with predeglutitive aspiration. *Gerontology.* 2003; 49:12–20. [PubMed: 12457045]
13. Jadcherla SR, Gupta A, Stoner E, Coley BD, Wiet GJ, Shaker R. Correlation of glottal closure using concurrent ultrasonography and nasolaryngoscopy in children: a novel approach to evaluate glottal status. *Dysphagia.* 2006; 21:75–81. [PubMed: 16786412]
14. Shaker R, Dua KS, Ren J, Xie P, Funahashi A, Schapira RM. Vocal cord closure pressure during volitional swallow and other voluntary tasks. *Dysphagia.* 2002; 17:13–18. [PubMed: 11820382]
15. Zamir Z, Ren J, Hogan WJ, Shaker R. Coordination of deglutitive vocal cord closure and oral-pharyngeal swallowing events in the elderly. *Eur J Gastroenterol Hepatol.* 1996; 8:425–429. [PubMed: 8804869]
16. Shaker R, Ren J, Medda B, Lang I, Cowles V, Jaradeh S. Identification and characterization of the esophagoglottal closure reflex in a feline model. *Am J Physiol.* 1994; 266(1 Pt 1):G147–G153. [PubMed: 8304454]
17. Shaker R, Ren J, Hogan WJ, Lui J, Podursan B, Sui Z. Glottal function during post-prandial gastroesophageal reflux [abstract]. *Gastroenterology.* 1993; 104:A581.
18. Ren J, Shaker R, Dodds WJ, Hogan WJ, Hentz J. Effect of aging on the esophagoglottal closure reflex [abstract]. *Gastroenterology.* 1991; 100:A545.
19. Ren J, Shaker R, Medda B, Bonnevier J, Kern M, Dunn B. Effect of acute esophagitis on the esophagoglottal closure reflex in a feline model [abstract]. *Gastroenterology.* 1995; 108:A677.
20. Kobler JB, Datta S, Goyal RK, Benecchi EJ. Innervation of the larynx, pharynx, and upper esophageal sphincter of the rat. *J Comp Neurol.* 1994; 349:129–147. [PubMed: 7852622]
21. Jadcherla SR, Gupta A, Coley BD, Fernandez S, Shaker R. Esophago-glottal closure reflex in human infants: a novel reflex elicited with concurrent manometry and ultrasonography. *Am J Gastroenterol.* 2007; 102:2286–2293. [PubMed: 17617206]
22. Ren J, Shaker R, Dua K, Trifan A, Podursan B, Sui Z. Glottal adduction response to pharyngeal water stimulation: evidence for a pharyngoglottal closure reflex. *Gastroenterology.* 1994; 106:A558.
23. Dua K, Bardan E, Ren J, Sui Z, Shaker R. Effect of chronic and acute cigarette smoking on the pharyngoglottal closure reflex. *Gut.* 2002; 51:771–775. [PubMed: 12427774]
24. Jadcherla SR, Gupta A, Wang M, Coley BD, Fernandez S, Shaker R. Definition and implications of novel pharyngoglottal reflex in human infants using concurrent manometry ultrasonography. *Am J Gastroenterol.* 2009; 104:2572–2582. [PubMed: 19603008]
25. Shaker R, Ren J, Podvrsan B, et al. Effect of aging and bolus variables on pharyngeal and upper esophageal sphincter motor function. *Am J Physiol.* 1993; 264(3 Pt 1):G427–G432. [PubMed: 8460698]
26. Kahrilas PJ, Dent J, Dodds WJ, Hogan WJ, Arndorfer RC. A method for continuous monitoring of upper esophageal sphincter pressure. *Dig Dis Sci.* 1987; 32:121–128. [PubMed: 3803142]
27. Kern M, Bardan E, Arndorfer R, Hofmann C, Ren J, Shaker R. Comparison of upper esophageal sphincter opening in healthy asymptomatic young and elderly volunteers. *Ann Otol Rhinol Laryngol.* 1999; 108:982–989. [PubMed: 10526854]
28. Jadcherla SR, Duong HQ, Hofmann C, Hoffmann R, Shaker R. Characteristics of upper oesophageal sphincter and oesophageal body during maturation in healthy human neonates compared with adults. *Neurogastroenterol Motil.* 2005; 17:663–670. [PubMed: 16185304]

29. Jadcherla SR, Duong HQ, Hoffmann RG, Shaker R. Esophageal body and upper esophageal sphincter motor responses to esophageal provocation during maturation in preterm newborns. *J Pediatr.* 2003; 143:31–38. [PubMed: 12915821]
30. Jadcherla SR, Hoffmann RG, Shaker R. Effect of maturation of the magnitude of mechanosensitive and chemosensitive reflexes in the premature human esophagus. *J Pediatr.* 2006; 149:77–82. [PubMed: 16860132]
31. Jadcherla SR, Gupta A, Stoner E, Fernandez S, Shaker R. Pharyngeal swallowing: defining pharyngeal and upper esophageal sphincter relationships in human neonates. *J Pediatr.* 2007; 151:597–603. [PubMed: 18035137]
32. Vakil NB, Kahrilas PJ, Dodds WJ, Vanagunas A. Absence of an upper esophageal sphincter response to acid reflux. *Am J Gastroenterol.* 1989; 84:606–610. [PubMed: 2729231]
33. Kahrilas PJ, Dodds WJ, Dent J, Haerle B, Hogan WJ, Arndorfer RC. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. *Gastroenterology.* 1987; 92:466–471. [PubMed: 3792782]
34. 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]
35. Ulualp SO, Toohill RJ, Shaker R. Pharyngeal acid reflux in patients with single and multiple otolaryngologic disorders. *Otolaryngol Head Neck Surg.* 1999; 121:725–730. [PubMed: 10580227]
36. Ulualp SO, Toohill RJ, Hoffmann R, Shaker R. Possible relationship of gastroesophagopharyngeal acid reflux with pathogenesis of chronic sinusitis. *Am J Rhinol.* 1999; 13:197–202. [PubMed: 10392238]

Figure 1.
Aerodigestive anatomy. Midline sagittal view of aerodigestive anatomy showing (1) pharynx, (2) epiglottis, (3) larynx with vocal cords, and (4) the UES.

Figure 2.

Anatomy of glottis. Based on laryngoscopy and ultrasonography methods, the structures of the glottis are defined. Note the schematic diagram in the center for comparison with each modality. Modified from Jadcherla et al.¹³

Figure 3.

Comparison of vocal cord and intratracheal pressure during straining, swallowing, coughing, and phonation. Note the vocal cord pressure during straining, coughing, and swallowing was significantly higher than that of phonation ($p < 0.05$; top graph). Straining produced pressures significantly higher than coughing. Intratracheal pressure during straining (bottom graph) was significantly higher those for phonation and swallowing. For all studied events vocal cord pressures were significantly higher than the intratracheal pressures. Reprinted with permission from Goyal RK, GI motility online.

Figure 4.

Duration of vocal cord closure in relationship to magnitude of esophageal balloon distention. Vocal cord adduction and abduction duration was significantly longer for a 2.5 cm balloon compared with a 1.5 cm balloon. This increase was caused by prolongation in duration of maximal adduction. Abo-Abm: time interval between onset of post-adduction vocal cord to maximal resting position of the cords; Adm-Abo: time interval between maximal vocal cord adduction and onset of the opening of the cords; Ado-Adm: time interval between onset of vocal cord adduction to maximal adduction. Reprinted with permission from Goyal RK, GI motility online.