Review Article

The upper esophageal sphincter in gastroesophageal reflux disease

Michelle Lippincott, Vic Velanovich^

Department of Surgery, The University of South Florida Morsani College of Medicine, Tampa, FL, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Vic Velanovich, MD. Division of Gastrointestinal and Hernia Surgery, 5 Tampa General Circle, Suite 740, Tampa, FL 33606, USA. Email: vvelanov@usf.edu.

Abstract: The relationship of the upper esophageal sphincter (UES) and gastroesophageal reflux is not well established. The phenomenon of refluxate violation of the UES has been well documented. Laryngopharyngeal reflux (LPR) which occurs when the refluxate has breached the UES has been linked to various atypical reflux symptoms, including laryngitis, hoarseness, chronic cough, asthma, aspiration pneumonia, and globus. This paper aims to review existing research on both physiologic and pathological UES functions related to reflux. The vagally mediated esophago-upper sphincter contraction reflex prevents oropharyngeal reflux while the esophago-upper sphincter relaxation reflex (EURR) allows gas venting. The UES responds to liquid refluxate with a contractile response in healthy, supine subjects. This mechanism serves to protect the respiratory tract and is distinct from the UES belch relaxation reflex. This response is innate and likely diminishes with age. Deficient esophago-upper sphincter contraction reflex and hyper-attenuated EURR have been linked with symptoms of supra-esophageal reflux disease (SERD). When this type of reflux leads to symptoms and other pharyngeal, laryngeal or airway pathology, it is considered SERD. Artificial augmentation of UES pressure has been proposed as a therapeutic option for the prevention of SERD. These findings have been reproduced in subsequent studies and correlate with a reduction in regurgitation and extraesophageal symptoms.

Keywords: Upper esophageal sphincter (UES); gastroesophageal reflux disease (GERD); supra-esophageal reflux disease (SERD)

Received: 07 January 2021; Accepted: 11 March 2021; Published: 25 September 2022.
doi: 10.21037/aoe-21-3
View this article at: http://dx.doi.org/10.21037/aoe-21-3

Introduction

The upper esophageal sphincter (UES) is a high-pressure zone that separates the pharyngeal lumen and the esophageal lumen. It consists of the proximal cervical esophagus, cricopharyngeus, and inferior pharyngeal constrictors (1). Unlike the lower esophageal sphincter (LES), UES function in gastroesophageal reflux disease (GERD) is not as well understood, although one can presume that protection of the airway may be at least one of the goals. The review aims to assess the current state of knowledge of the responses of the UES to GERD.

The phenomenon of refluxate violation of the UES has been well documented. Laryngopharyngeal reflux (LPR), which occurs when the refluxate has breached the UES, has

^ ORCID: 0000-0003-0133-948X.

been linked to various atypical reflux symptoms, including laryngitis, hoarseness, chronic cough, asthma, aspiration pneumonia, and globus sensation (2-4). Furthermore, these symptoms may not necessarily correlate with the typical GERD symptoms of heartburn and regurgitation (5).

This review discusses the role of the esophago-pharyngeal reflexes in healthy and gastroesophageal reflux patients, how changes in these reflexes occur with chronic GERD, and how they contribute to extraesophageal symptoms of GERD.

UES contraction as a protective mechanism

In 1957 Creamer and Schlegel (6) were one of the first to study the UES response to esophageal distension in humans. They found that the UES contracts in response to both balloon and water-mediated esophageal distention. This contraction is followed by secondary peristalsis and is more pronounced as stimuli become more proximal to the UES (6). Subsequent studies on the subject were contradictory, with this theory being supported by some (7-11) and contradicted by others (12,13). These early discrepancies were likely due to differences in subject position, refluxate constituent, and limitations in early pressure measurement techniques.

Later, the distinction between the esophago-upper sphincter contraction reflex (EUCR) and esophago-upper sphincter relaxation reflex (EURR) became apparent (14,15). Pandolfino *et al.* (16) used high-resolution manometry (HRM) to delineate UES response as a function of the underlying reflux mechanism. They found that when reflux occurred due to transient LES relaxation (tLOSR), the dominant UES response was to relax, serving as a gas venting mechanism. When reflux occurred independently of tLOSRs, the UES did not change or contracted (16). Lang *et al.* (17) used animal models to determine that the EUSR was temporally correlated with esophageal air stimulation after a tLOSR rather than gastric distention or the tLOSR. This temporal correlation between air reflux and EUSR has further been observed in human models (18).

The UES contraction reflex in the supine position is present in premature infants suggesting that this reflex is of great physiological importance (19). It is also noted to diminish with age, offering a potential explanation for GERD complications in older individuals (20,21).

Babaei *et al.* (18,22) studied how differences in positioning might contribute to UES response. They found that UES relaxation was the predominant response to air distension in upright patients. In contrast, UES contraction was the response to liquid distention in supine patients. This response was volume-dependent for both reflexes and both types of stimuli (18,22).

Kim *et al.* (23) studied these reflexes in both GERD patients and healthy controls. They found that patients with GERD were more likely to demonstrate UES contraction during tLOSRs than controls, who more frequently displayed UES relaxation. This phenomenon is hypothesized to be due to the more acidic refluxate in patients with GERD (23).

Studies regarding the role of the pH of the infusate in producing these reflexes have been contradictory. Several showing no difference in EUS pressure response between acidic and nonacidic infusate (12,22,24). On the other hand, more recent studies in animal models suggest that pH plays a role in mediating response thresholds of these reflexes. Most notably, Lang *et al.* (15) found that short-term acute exposure of the thoracic esophagus to acid sensitized the EURR and desensitized the EUCR in decerebrate cats. A similar effect was seen after chronic acid exposure in awake, unanesthetized cats. Specifically, compared to day 1, day 4 of acid exposure resulted in a more attenuated EURR in response to air injection and dampened EUCR response (15).

In summary, the UES responds to liquid refluxate with a contractile response in healthy, supine subjects. This mechanism serves to protect the respiratory tract and is distinct from the UES belch relaxation reflex. This response is innate and likely diminishes with age. It is essential to note the limitations of the above studies. They all had small sample sizes, and most were performed on animal models or healthy patients with non-physiologic simulations of reflux.

Mechanism of UES-contractile and relaxation reflexes

What is currently known about the physiological mechanisms of the EUCR and EURR is primarily based on animal models. We know that these reflexes at least partially originate from the brainstem, as evidenced by their presence in decerebrate cats.

The EUCR reflex is likely mediated by slow adapting mechanoreceptors in the muscular layer of the esophagus (1,14,25,26). This would account for why this reflex is stimulated by slow distention with liquid rather than rapid distention with air. Conversely, the relaxation reflex is mediated by rapidly adapting receptors in the mucosa only (14,25). This is supported by studies showing an absence of UES relaxation in response to rapid distention with mucosal

anesthesia (25,26).

The afferent nerves of both reflexes consist of the thoracic vagus, the cervical branch of the recurrent laryngeal nerve (RLN), and the superior laryngeal nerve (14,25,27). Efferent nerves of these reflexes likely are the RLN and the cervical vagus, though this has not been definitively studied in humans (28). The EUCR is mediated by subnuclei of the nucleus tractus solitarii (NTS), dorsal motor nucleus, and the nucleus ambiguous in the medulla. The EURR is mediated by the NTS, nucleus ambiguous, area postrema, and dorsal motor nucleus (29).

Chronic EUS changes in response to GERD

Studies evaluating the effects of chronic GERD on the UES are limited and contradictory, with some showing an increase in basal cricopharyngeal basal pressures (7) or mean UES contractile integral in patients with GERD (30). On the other hand, an extensive retrospective review of patients who underwent HRM found that patients with GERD had lower resting UES pressures than healthy subjects (31). This is supported by Nadaleto *et al.* (32), who demonstrated a pattern of short and hypotonic UES pressures in patients with GERD. However, the proportion of patients with short, hypotonic UES pressure was notably higher in patients with extraesophageal symptoms than those with isolated esophageal symptoms (32). The above studies demonstrate inconsistencies in findings regarding chronic changes to the UES in GERD and emphasize the need for further research on this topic.

UES and esophagopharyngeal reflux

If the normal UES response to liquid reflux exists to prevent esophagopharyngeal reflux, one can conjecture that this response is abnormal in patients who experience supra-esophageal reflux. When this type of reflux leads to symptoms and other pharyngeal, laryngeal, or airway pathology, it is considered supra-esophageal reflux disease (SERD).

Derangements in both EUCR and EURR may contribute to SERD. Babaei *et al.* (33) compared the UES response in SERD patients to both healthy controls and patients with isolated GERD. They found deterioration of the EUCR reflex in SERD patients during rapid saline infusions and slow acid infusions compared to healthy controls and GERD patients. The authors further noted occasional aberrant UES relaxation during infusion of rapid saline in SERD patients (33). This would suggest that impairment of the protective UES reflex contributes to laryngeal symptoms. This idea is further supported by studies in which, during direct visualization of the UES via laryngoscopy, SERD patients demonstrate an inability to prevent pharyngeal violation of esophageal contents (34). Nadaleto *et al.* (32) found that GERD patients had a generally short and hypotonic basal UES, which was more pronounced in those with extraesophageal symptoms. These findings further add credence to the hypothesis that aberrant UES function is a potential factor in SERD.

Esophageal air distention may also play a role. Szczesniak *et al.* (35) found that patients with laryngitis symptoms had a lower threshold to trigger UES relaxation in response to rapid esophageal air distention. The authors suggest this as a mechanism for a hypersensitive belch reflex contributing to regurgitation; however, they recognize the need to consider chronic inflammation from suprapharyngeal reflex as the cause of this impaired reflex (35). However, prior animal studies would suggest that attenuated EUS relaxation is the cause of SERD symptoms rather than sequelae of inflammation (15).

While few studies exist looking at the function of the EUS in SERD, the above studies would suggest that alterations in normal EUS contraction and relaxation responses play a role in LPR.

UES augmentation as a solution to supra-esophageal reflux

Several researchers have taken the above observation a step further to create treatments, such as using external devices to augment UES pressure to reduce symptoms of SERD. In 2014 Shaker *et al.* (34) documented, via laryngoscopy, successful prevention of pharyngeal reflux in SERD patients with an artificial increase in EUS pressure by 20–30 mmHg. They augmented EUS pressure with a handmade UES assist device (UESAD) consisting of a cushion and elastic band which applied steady cricoid pressure (34). These findings have been reproduced in subsequent studies and correlate with a reduction in regurgitation and extraesophageal symptoms (36,37). This offers the UES as a potential therapeutic target for patients suffering from reflux-associated laryngeal symptoms. The Reflux Band™ by Somna therapeutics is the only FDA-approved, commercially available form of UESAD (38). It is currently undergoing clinical trials looking at its potential role in reducing SERD symptoms in lung transplant patients (39).

Discussion

These studies suggest the UES contracts in response to liquid refluxate to prevent oropharyngeal regurgitation in healthy subjects; this is more pronounced in patients lying supine. There has been no consistent evidence to suggest if the pH level of refluxate plays a role in UES contraction. This reflex is likely mediated by slow adapting mechanoreceptors in the muscular layer of the esophagus. In contrast, rapidly adapting receptors in the mucosa mediate UES relaxation in response to rapid air distention, serving as a "belch" reflex. Pathogenesis of SERD may be related to UES hypotonia, deterioration of the UES contraction reflux, or hyper-attenuation of UES relaxation in response to refluxate stimulus. A handful of trials have shown an improvement in SERD symptoms with artificial UES pressure augmentation. Overall, there is a paucity of quality studies on the topic, and further research is warranted.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Fernando A. M. Herbella) for the series "Upper Esophageal Sphincter" published in *Annals of Esophagus*. The article has undergone external peer review.

Peer Review File: Available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-3/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-3/coif). The series "Upper Esophageal Sphincter" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Lang IM, Shaker R. Anatomy and Physiology of the Upper Esophageal Sphincter. Am J Med 1997;103:50S-55S.
2. Bain WM, Harrington JW, Thomas LE, et al. Head and neck manifestations of gastroesophageal reflux. Laryngoscope 1983;93:175-9.
3. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101:1-78.
4. Koufman JA, Wiener GJ, Wu WC, et al. Reflux laryngitis and its sequelae: The diagnostic role of ambulatory 24-hour pH monitoring. J Voice 1988;2:78-89.
5. Shaker R, Milbrath M, Ren J, et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. Gastroenterology 1995;109:1575-82.
6. Creamer B, Schlegel J. Motor Responses of the Esophagus to Distention. J Appl Physiol 1957;10:498-504.
7. Hunt PS, Connell AM, Smiley TB. The cricopharyngeal sphincter in gastric reflux. Gut 1970;11:303.
8. Enzmann DR, Harell GS, Zboralske FF. Upper Esophageal Responses to Intraluminal Distention in Man. Gastroenterology 1977;72:1292-8.
9. Andreollo NA, Thompson DG, Kendall GP, et al. Functional relationships between cricopharyngeal sphincter and oesophageal body in response to graded intraluminal distension. Gut 1988;29:161.
10. Gerhardt DC, Shuck TJ, Bordeaux RA, et al. Human upper esophageal sphincter. Response to volume, osmotic, and acid stimuli. Gastroenterology 1978;75:268-74.
11. 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:G262-7.
12. Vakil NB, Kahrilas PJ, Dodds WJ, et al. Absence of an upper esophageal sphincter response to acid reflux. Am J Gastroenterol 1989;84:606-10.

13. Corso MJ, Pursnani KG, Mohiuddin MA, et al. Globus Sensation Is Associated with Hypertensive Upper Esophageal Sphincter but Not with Gastroesophageal Reflux. Digest Dis Sci 1998;43:1513-7.
14. Lang IM, Medda BK, Shaker R. Mechanisms of reflexes induced by esophageal distension. Am J Physiol Gastrointest Liver Physiol 2001;281:G1246-63.
15. Lang IM, Medda BK, Shaker R. Effects of esophageal acidification on esophageal reflexes controlling the upper esophageal sphincter. Am J Physiol Gastrointest Liver Physiol 2019;316:G45-54.
16. Pandolfino JE, Ghosh SK, Zhang Q, et al. Upper sphincter function during transient lower oesophageal sphincter relaxation (tLOSR); it is mainly about microburps. Neurogastroenterol Motil 2007;19:203-10.
17. Lang IM, Medda BK, Shaker R. Mechanism of UES relaxation initiated by gastric air distension. Am J Physiol Gastrointest Liver Physiol 2014;307:G452-8.
18. Babaei A, Bhargava V, Mittal RK. Upper esophageal sphincter during transient lower esophageal sphincter relaxation: effects of reflux content and posture. Am J Physiol Gastrointest Liver Physiol 2010;298:G601-7.
19. Jadcherla SR. Manometric evaluation of esophageal-protective reflexes in infants and children. Am J Med 2003;115 Suppl 3A:157S-160S.
20. Mei L, Dua A, Kern M, et al. Older Age Reduces Upper Esophageal Sphincter and Esophageal Body Responses to Simulated Slow and Ultraslow Reflux Events and Post-reflux Residue. Gastroenterology 2018;155:760-770.e1.
21. Kawamura O, Easterling C, Aslam M, et al. Laryngo-upper esophageal sphincter contractile reflex in humans deteriorates with age. Gastroenterology 2004;127:57-64.
22. Babaei A, Dua K, Naini SR, et al. Response of the Upper Esophageal Sphincter to Esophageal Distension Is Affected by Posture, Velocity, Volume, and Composition of the Infusate. Gastroenterology 2012;142:734-743.e7.
23. Kim HI, Hong SJ, Han JP, et al. Specific Movement of Esophagus During Transient Lower Esophageal Sphincter Relaxation in Gastroesophageal Reflux Disease. J Neurogastroenterol Motil 2013;19:332-7.
24. Andreollo NA, Thompson DG, Kendall GP, et al. Motor responses of the upper esophageal sphincter and body to intraluminal acid. Braz J Med Biol Res 1989;22:51-60.
25. Szczesniak MM, Fuentealba SE, Burnett A, et al. Differential relaxation and contractile responses of the human upper esophageal sphincter mediated by interplay of mucosal and deep mechanoreceptor activation. Am J Physiol Gastrointest Liver Physiol 2008;294:G982-8.
26. Medda BK, Lang IM, Layman R, et al. Characterization and quantification of a pharyngo-UES contractile reflex in cats. Am J Physiol 1994;267:G972-83.
27. Lang IM, Medda BK, Jadcherla S, et al. The role of the superior laryngeal nerve in esophageal reflexes. Am J Physiol Gastrointest Liver Physiol 2012;302:G1445-57.
28. Lang IM. The Physiology of Esophageal Reflexes. OBM Hepatology and Gastroenterology 2020;4:35.
29. Lang IM, Medda BK, Shaker R. Differential activation of medullary vagal nuclei caused by stimulation of different esophageal mechanoreceptors. Brain Res 2011;1368:119-33.
30. Marabotto E, Demarzo MG, Tolone S, et al. The Measurement of Upper Esophageal Sphincter Contractile Integral Reveals a Potential Protective Mechanism Against Pulmonary Aspiration in Patients with Achalasia and GERD. Neurogastroenterol Motil 2019;31:e13627.
31. Alani MA, AL-Jashaami L, Ahmed S, et al. Tu1281 - Upper Esophageal Sphincter is Hypotensive in Gastroesophageal Reflux Disease (GERD) and Has Impaired Relaxation in Achalasia. Gastroenterology 2019;156:S-1016.
32. Nadaleto BF, Herbella FAM, Pinna BR, et al. Upper esophageal sphincter motility in gastroesophageal reflux disease in the light of the high-resolution manometry. Dis Esophagus 2017;30:1-5.
33. Babaei A, Venu M, Naini SR, et al. Impaired Upper Esophageal Sphincter Reflexes in Patients With Supraesophageal Reflux Disease. Gastroenterology 2015;149:1381-91.
34. Shaker R, Babaei A, Naini SR. Prevention of esophagopharyngeal reflux by augmenting the upper esophageal sphincter pressure barrier. Laryngoscope 2014;124:2268-74.
35. Szczesniak MM, Williams RBH, Brake HM, et al. Upregulation of the esophago-UES relaxation response: a possible pathophysiological mechanism in suspected reflux laryngitis. Neurogastroenterol Motil 2010;22:381-6, e89.
36. Yadlapati R, Craft J, Adkins CJ, et al. The Upper Esophageal Sphincter Assist Device Is Associated With Symptom Response in Reflux-Associated Laryngeal Symptoms. Clin Gastroenterol Hepatol 2018;16:1670-2.
37. Jiao H, Mei L, Liang C, et al. Upper esophageal sphincter augmentation reduces pharyngeal reflux in nasogastric tube-fed patients. Laryngoscope 2018;128:1310-5.
38. K173934 510k Summary [Internet]. undefined. [cited 2021

Feb 20]. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173934.pdf
39. The Effect of the Reflux BandTM Upper Esophageal Sphincter (UES) Assist Device on Reflux for Lung Transplant Recipients - Full Text View - ClinicalTrials.gov [Internet]. undefined. [cited 2021 Feb 20]. Available online: https://clinicaltrials.gov/ct2/show/NCT03886961

doi: 10.21037/aoe-21-3
Cite this article as: Lippincott M, Velanovich V. The upper esophageal sphincter in gastroesophageal reflux disease. Ann Esophagus 2022;5:26.