

# The upper esophageal sphincter in gastroesophageal reflux disease

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**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)

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## 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

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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 (tLOSRR), the dominant UES response was to relax, serving as a gas venting mechanism. When reflux occurred independently of tLOSRRs, 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 tLOSRR rather than gastric distention or the tLOSRR. 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 tLOSRRs 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-contraction 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 solitarius (NTS), dorsal motor nucleus, and the nucleus ambiguus in the medulla. The EURR is mediated by the NTS, nucleus ambiguus, 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 Nadaletto *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). Nadaletto *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 reflex, 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.

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