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Physiology of the upper segment, body, and lower segment of the esophagus

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Abstract

The following discussion on the physiology of the esophagus includes commentaries on the function of the muscularis mucosa and submucosa as a mechanical antireflux barrier in the esophagus; the different mechanisms of neurological control in the esophageal striated and smooth muscle; new insights from animal models into the neurotransmitters mediating lower esophageal sphincter (LES) relaxation, peristalsis in the esophageal body (EB), and motility of esophageal smooth muscle; differentiation between *in vitro* properties of the lower esophageal circular muscle, clasp muscle, and sling fibers; alterations in the relationship between pharyngeal contraction and relaxation of the upper esophageal sphincter (UES) in patients with dysphagia; the mechanical relationships between anterior hyoid movement, the extent of upper esophageal opening, and aspiration; the application of fluoroscopy and manometry with biomechanics to define the stages of UES opening; and nonpharmacological approaches to alter the gastroesophageal junction (GEJ).

Keywords

muscularis mucosa; esophagus; smooth muscle; submucosa; GERD; upper esophageal segment; lower esophageal segment

MillerLarry

1. What is the function of the muscularis mucosa in the esophagus?

The mucosa of the esophagus plays a major role in protecting the underlying muscle layer. It is the first line of defense for the lower esophagus against the acid from the stomach. The major mucosal defenses against acid of the squamous mucosa of the esophagus are luminal acid clearance and tissue resistance. Tissue resistance has three protective components, which are designated as preepithelial, epithelial, and postepithelial defenses. The

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Conflicts of interest

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preepithelial defense consists of a surface mucus and unstirred water layer within which bicarbonate ions are trapped, providing an alkaline microenvironment. The epithelial defense consists of the apical cell membranes and junctional complexes, which act to limit the diffusion of H^+ from lumen to cell and intercellular space, respectively. The postepithelial defense is provided by the acid-buffering effects of HCO_3^- in cells and within the intracellular space. Blood supply is essential for the delivery of HCO_3^- .¹

A great deal is known about the anatomy and physiology of the muscular components of the gastroesophageal junction high-pressure zone (GEJHPZ) and their roles in preventing GERD. There is also a fair amount of literature with respect to the anatomy and physiology of the muscularis mucosa. The muscularis mucosa is a thin layer of smooth muscle located beneath luminal mucosa throughout the digestive tract. The longitudinal muscularis mucosa is innervated by postganglionic excitatory cholinergic nerves via the myenteric and submucous plexus from the vagal nerve in all animal species. Cholinomimetic drugs can evoke a sustained contraction of the esophageal muscularis mucosa through the activation of muscarinic M3 receptors in all animal species.

However, very little is known about the functional purpose of the muscularis mucosa. In previous *in vivo* studies in human subjects, we observed some very interesting and unique phenomena regarding the esophagus during deglutition. During deglutition, the mucosa in the distal esophagus shortened coincident with the relaxation of the GEJHPZ and the gastric mucosa was pulled up into the distal portion of the esophagus during swallowing.² We also observed that the mucosa of the distal esophagus shortened well before the rest of the esophagus shortened. By shortening proximally and pulling up the gastric mucosa, a narrow channel in the distal esophageal lumen was formed.³

Using both simultaneous endoluminal ultrasound and manometry and transabdominal ultrasound to investigate the distal esophagus and proximal stomach in normal control subjects, we observed an increase in cross-sectional surface area (CSA) of the mucosa/submucosa along with an increase in the thickness of the muscularis mucosa during swallowing (Fig. 1). This occurs independently and before the increase in the CSA of the circular smooth muscle (CSM) and longitudinal smooth muscle (LSM). Because the sonographic layer containing the muscularis mucosa is significantly thicker in the cardia than in the distal esophagus, this implies that the mucosa/submucosa of the proximal stomach is pulled into the distal tubular esophagus independent of shortening of the muscularis propria. What is remarkable is that the gastric mucosa/submucosa is pulled up into the distal esophagus at exactly the same time that the GEJHPZ relaxes during swallowing.

These observations strongly suggest that the mucosa/submucosa, along with the muscularis mucosa, may have other important physiologic functions in addition to their direct role as an epithelial protective barrier. It is our hypothesis that the contraction of the muscularis mucosa in the distal esophagus and proximal stomach acts as a protective mechanism during swallowing, by forming a mucosal plug or one-way valve, which occludes the lumen to gastric reflux. We further hypothesize that the absence of this muscularis mucosal protective mechanism may play a role in the development of GERD.

The new observations supporting this hypothesis are (1) at the level of the GEJHPZ during deglutition, the gastric mucosa/submucosa in the cardia of stomach is pulled up into the distal esophagus and coincides with the relaxation of the high-pressure zone; (2) the mucosa/submucosa of the distal esophagus contracts before the rest of the esophagus shortens and the initial movement of the mucosa/submucosa is independent of the movement of the muscularis propria; and (3) the combination of the gastric mucosa/submucosa being pulled

up into the distal esophagus leads to the formation of a narrow channel in the distal esophageal lumen starting at the initiation of deglutition and ending after the bolus leaves the esophagus, when all of the other muscular components within the GEJHPZ of the distal esophagus and proximal stomach are relaxed.

Preliminary studies demonstrate that, in patients with GERD, the mucosa does not shorten during swallowing. There are two possible explanations for this. First, due to chronic reflux of gastric contents, there may be an inflammatory reaction within the mucosa/submucosa which may release substances which secondarily inhibit contraction of the muscularis mucosa or cause direct damage to the muscularis mucosa.⁴⁻⁶ However, another possible explanation is that the lack of contraction of the muscularis mucosa may be a primary defective mechanism and the fact that the gastric mucosa/submucosa is not pulled up into the distal esophagus may be one of the pathophysiologic mechanism leading to GERD. We favor the later explanation, as all of the GERD patients studied were well controlled on either proton pump inhibitors (PPIs) or on H₂ blockers and had no endoscopic evidence of inflammation.

In an earlier study, our group described the lack of a distal muscarinic smooth muscle pressure component (gastric sling/clasp muscle fiber component) in GERD patients as opposed to normal control subjects.^{7,8} In these current studies we found that mucosal movement is also altered in patients with GERD. In normal subjects, the gastric mucosa/submucosa acts as a mechanical antireflux barrier by being pulled up into the distal tubular esophagus and forming a narrow channel or one-way valve during deglutition. This is brought about initially by contraction of the muscularis mucosa independently of the muscularis propria. This narrowing in the distal esophagus protects the distal esophagus from reflux of gastric contents at a time when the GEJHPZ relaxes, at the initiation of swallowing, until the bolus reaches the distal esophagus. This mechanism appears to be defective in patients with GERD.

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2. Excitatory and inhibitory neurotransmitters regulating the human esophageal smooth muscle esophagus

The main mechanisms of neurological control of human esophageal motility differ in the striated part of the esophagus (striated muscle), and in the smooth muscle esophagus. Esophageal peristalsis in the cervical esophagus is mediated by vagal fibers that make direct contact on striated muscle through the motor endplate, and the main excitatory neurotransmitter at this level is acetylcholine acting on nicotinic cholinergic receptors. This summary is focused on the smooth muscle part of the human esophagus, and in particular on the myenteric mechanisms and neurotransmitters controlling EB peristalsis and LES relaxation, and covers (1) the inhibitory neurotransmitters mediating human LES relaxation; (2) the functional asymmetry of human LES and the differences between clasp versus sling neurotransmission; (3) the neurotransmitters controlling peristalsis in the EB; (4) the mechanisms of selective stimulation of excitatory and inhibitory motor neurons (MNs) in the human esophagus; and (5) the impaired mechanisms of neurotransmission in patients with achalasia.

Our background is a parallel group of animal studies in pigs and rats. We found that porcine LES relaxation after stimulation of intrinsic inhibitory MNs is mediated by two main neuromuscular pathways: nitric oxide through guanylate cyclase signaling and apamin-insensitive mechanisms, and nonnitrgic apamin-sensitive neurotransmission mainly mediated by P2Y₁ receptors with a minor contribution of purinergic P2X₁₋₃ receptors and PACAP. Nitrgic and purinergic cotransmitters show parallel effects of similar magnitude

without major interplay. Our study shows no role for calcitonin gene-related peptide (CGRP) and only a minor one for vasoactive intestinal peptide (VIP) and carbon monoxide in porcine LES relaxation.⁹ Clasp and sling fibers of the porcine LES show marked intrinsic functional differences. Porcine LES showed a strong transverse functional asymmetry in the intrinsic mechanisms that control resting tone and the relaxing and contractile responses following stimulation of myenteric excitatory MNs. Tone developed by sling fibers was greater, less dependent on extracellular calcium sources, and more dependent on tonic input of excitatory MNs than that developed by clasp fibers. Neural stimulation induced stronger nitrergic responses and weaker cholinergic responses in clasp fibers, and in contrast, weaker nitrergic responses and stronger cholinergic responses in sling regions. This transverse functional asymmetry can be attributed to a specialization at the myenteric plexus level.¹⁰ Third, our results also suggest selective mechanisms for stimulation of intrinsic excitatory and inhibitory motor pathways in porcine LES. Inhibitory MNs are strongly stimulated by nAChRs and do not respond to stimulation of 5-HT₃ and P2X receptors. By contrast, excitatory MNs are stimulated through 5-HT₃ and P2X receptors, stimulation through nAChRs being difficult and causing a weak response.¹¹ In the rat LES, relaxation is mediated by nitric oxide (NO) and an apamin-sensitive mediator, and contraction primarily by acetylcholine. Despite the absence of c-Kit-positive immunocytochemistry in our model, nerve-muscle interaction can be accomplished likely by diffusion of neurotransmitters to the smooth muscle cells.¹² In the EB, our results suggest that timing (latency) and amplitude of esophageal contractions are determined by a balance of complex interactions between excitatory and inhibitory MNs. Latency depends on the activation of inhibitory MNs releasing NO and a minor purinergic contribution through P2Y₁ receptors, and excitatory MNs releasing ACh. Amplitude depends on a major contribution of excitatory MNs releasing ACh and tachykinins, and also on inhibitory MNs releasing NO, ATP or related purines, and peptidergic neurotransmitters acting as strong modulators of the excitatory neuroeffector transmission.¹³

We have also studied human esophageal specimens and we cut transmural strips, including the myenteric plexus, parallel to the circular muscle fibers from the clasp and the sling regions of the LES and the EB 5 cm above the transitional line. We transferred these human strips to organ baths and we performed experiments during stimulation of MNs by electrical fields and by using specific antagonists for each neurotransmitter.^{14,15} The human LES is not a muscular ring. The fibers are circular in the EB but not in the LES, as we found semicircular clasp fibers on the right side, and semicircular oblique sling fibers on the left at the angle of His. We explored the direct effect of the proposed inhibitory neurotransmitters in LES strips and found that the NO donor sodium nitroprusside (SNP), VIP, and the P2Y₁ receptor agonists induced muscular LES relaxation, and the P2X agonists induced a sustained contraction. At basal conditions, clasp strips responded with an intense *on* relaxation during the electrical stimulus and a weak *off* contraction, nitroarginine (LNNA) blocked relaxation, but a strong nonnitrergic off relaxation persisted in clasp strips, and also at basal conditions, sling strips responded with a less intense *on* relaxation that was strongly inhibited following LNNA.

We also explored the neurotransmitters involved in the nonnitrergic relaxation in LES strips: (1) the purinergic P2Y₁ antagonist inhibited the nonnitrergic relaxation by 60%, and (2) the VIP antagonist by 40%.¹⁴ Following stimulation of enteric MNs by electrical field stimulation (EFS) (Fig. 2), we found stronger inhibitory responses in clasp LES compared to sling and stronger excitatory responses in the EB, and similar direct effect of neurotransmitters in both LES sides, suggesting a mechanism of regional functional specialization at the level of the myenteric plexus. In addition, strips from the EB responded to electrical stimulation with an *on* contraction at the beginning of the stimulus and an *off* contraction following a latency period that controls the velocity of peristalsis. Both

amplitude and latency of off contractions increased with frequency of electrical stimulation, blockade of P2Y₁ receptors decreased amplitude of both on and off contractions, and LNNA fully abolished latency of off contractions. We also compared the electrical contractions induced in the EB with those in clasp and sling fibers in the LES. Amplitude of off contractions and those of on contractions following LNNA decreased abnormally, and as this on contraction following LNNA is blocked by atropine; these results suggest a decreasing effect of cholinergic neurons from the EB to both LES sides.

Finally, this experiment shows inhibitory MNs are efficiently stimulated both by electrical fields and nicotinic receptors, and in contrast, although esophageal excitatory MNs are efficiently stimulated by electrical fields, their stimulation through nicotinic receptors is very difficult, suggesting the participation of nonnicotinic mechanisms in neurotransmission to excitatory MNs in the human esophagus.¹⁵ We also had the opportunity to study some strips from patients with achalasia and found absence of EFS relaxation in the LES and EFS induced only on contractions without latency in the EB.

RuggieriMichael R.

3. What are the differences in esophageal muscle *in vitro* properties between the lower esophageal circular muscle, the clasp muscle, and the sling fibers?

The integrity of the antireflux barrier depends on proper functioning of the neuromuscular control mechanisms of the GEJHPZ. It has been well established for over 50 years that in human subjects, administration of the muscarinic receptor antagonist drug atropine reduces the intraluminal pressure of the GEJHPZ.^{16–19} Therefore, neuronal release of acetylcholine acting on smooth muscle muscarinic receptors maintains the *in vivo* tonic muscle tone of the sphincteric mechanisms in the human GEJHPZ. Anatomic structures of the GEJHPZ that are responsible for preventing reflux include the lower esophageal CSM (LEC, often referred to as the LES), the crural diaphragm skeletal muscle, the clasp and sling smooth muscle fibers of the proximal stomach (which some also refer to as the LES but which we refer to as the upper gastric sphincter (UGS)) and very likely, the muscularis mucosa smooth muscle. Our previous investigations demonstrated that in patients with GERD, the UGS does not contribute to intraluminal pressure of the GEJHPZ as it does in normal volunteers,⁷ suggesting that the underlying etiology of GERD may be a pathophysiologic defect within the gastric clasp/sling smooth muscle fiber complex. In order to understand the pathophysiologic neuromuscular mechanisms in GERD, it is first necessary to understand these mechanisms in normal tissue.

Detailed pharmacologic studies of *in vitro* contractile responses are not feasible using the minute muscle tissue obtained from an endoscopic biopsy, but are feasible using whole organs obtained from organ transplant donors. The following findings are from stomach and esophagus specimens obtained from human organ transplant donors without any history of GERD and no histologic evidence of Barrett's esophagus. Because atropine reduces intraluminal GEJHPZ pressure *in vivo*, relaxation of muscarinic receptor–precontracted clasp and sling muscle can serve as an *in vitro* physiologic equivalent of *in vivo* transient lower esophageal sphincteric relaxations involved in reflux. In clasp, sling, and LEC fibers, increasing concentrations of the mixed muscarinic and nicotinic receptor agonist carbachol induce a contractile response at lower concentrations and then abrupt relaxations at concentrations of 100 μ M and higher. The contractions at low carbachol concentrations are due to muscarinic receptor stimulation, whereas the relaxations at higher concentrations are due to nicotinic receptors. One of the major differences between these three different smooth

muscle fibers is that the contractions are greater in sling and LEC fibers than clasp fibers and the relaxations are greater in clasp fibers than sling or LEC fibers.²⁰

Alternatively, smooth muscle strips can be precontracted with the muscarinic receptor-specific agonist bethanechol then induced to relax with nicotine. Nicotine causes relaxation of bethanechol-precontracted clasp, sling, and LEC muscle strips indirectly, by activation of nicotinic receptors on enteric nerves that induces release of multiple relaxing substances. These relaxing substances include NO in clasp, sling, and LEC fibers, norepinephrine acting on β -adrenoceptors in clasp fibers, and GABA acting on GABA_A receptors in sling fibers. In sling fibers, activation of both β -adrenoceptors and GABA_A receptors is required to relax bethanechol-precontracted muscle whereas in clasp fibers, activation of β -adrenoceptors alone causes relaxation but activation of GABA_A receptors alone does not.²¹ Therefore it appears that GABA_A receptors are not present or not functional in clasp fibers, but increased intracellular cAMP with β -adrenoceptor activation does cause relaxation. Sling fibers are different in that either β -adrenoceptor-induced increased cAMP or increased intracellular chloride with GABA_A receptor activation are each individually insufficient to induce relaxation which requires increases in both cAMP and chloride.

Preventing action potentials by blocking sodium channels with tetrodotoxin (TTX) prevents nicotine-induced relaxations in bethanechol-precontracted clasp but not sling or LEC fibers.²² Thus the location of the nicotinic receptors on the enteric nerves mediating the relaxations in sling and LEC fibers is likely at or near the neuromuscular junction such that local depolarization induced by nicotinic receptor-induced sodium influx can induce release of inhibitory substances without the need to trigger action potentials. In clasp fiber enteric nerves, the nicotinic receptors must be located on the soma or along the axons but not near the neuromuscular junction because TTX sensitive, sodium channel-mediated action potentials are required for relaxation.

In muscle fibers not precontracted with bethanechol, nicotine relaxes clasp and LEC fibers but contracts sling fibers,²² indicating that nicotine either induces the release of contractile substances or acts directly on sling smooth muscle cells to induce contraction. It appears that sling fibers have a greater propensity to contract in response to cholinergic stimulation mediated by muscarinic receptors. Conversely, clasp fibers have a greater propensity to relax upon cholinergic stimulation mediated by nicotinic receptors. Although the neuronal nicotinic receptor-blocking agent hexamethonium does prevent the nicotine-induced relaxation in bethanechol-precontracted clasp and sling fibers and the relaxation to higher concentrations of carbachol in sling fibers, hexamethonium is ineffective in preventing the relaxations induced by higher carbachol concentrations in clasp fibers.²³ Thus, the nicotinic receptors mediating relaxations may be slightly different between the clasp and sling fibers of the UGS. Figure 3 illustrates the major differences between clasp and sling fibers in enteric nerve-mediated contraction and relaxation.

OuyangAnn

4. What is the relationship between pharyngeal contraction, relaxation of the upper esophageal sphincter muscle, and function in the normal swallow and in dysphagia?

Pharyngeal contraction and relaxation of the UES are critical components in normal swallowing. Methods used to assess pharyngeal contraction and UES relaxation include pressure transducers, electromyography (EMG), and ultrasound, while bolus movement is documented using fluoroscopy, impedance, or ultrasound. Relaxation of the UES requires both cessation of the tonic activity of the CP and opening of the UES by contraction of the

suprahyoid muscles, resulting in anterior and superior movement of the hyoid and larynx. Elevation of the larynx also enlarges the pharynx to receive the bolus and protects the larynx against aspiration.²⁴ Upper esophageal relaxation precedes the onset of increase in pharyngeal pressure.²⁵

Viscosity and volume of boluses have different effects on bolus transit in the oropharynx. High viscosity of the bolus delays oral and pharyngeal bolus transit, increases the duration of the pharyngeal peristaltic waves, and prolongs and increases UES opening. Bolus volume has less effect on the transit time but leads to prolonged UES opening, longer laryngeal closure duration, and longer swallowing apnea.

The maximum diameter of the UES is often used as a marker of UES relaxation, although it is probably more related to the movement of the larynx and the viscosity and size of the bolus. In a study using impedance to assess flow, the residual pressure in the UES was determined using high-resolution manometry (HRM). This study determined that the average UES impedance nadir is a good correlate of UES maximum diameter. In 40 patients with dysphagia, the average bolus residue score, flow interval, and swallow risk index were significantly greater in patients with a narrower UES diameter, suggesting that the UES relaxation was an important contributor to the presence or absence of dysphagia.²⁶

The correlation between several manometric and videofluoroscopic measures or observations were examined in 11 patients with oropharyngeal dysphagia and 7 normal controls. Multiple correlations were noted, but in general, increase in pressure-wave amplitude in the pharynx was associated with increased duration of the tongue base–pharyngeal wall contact and reduced bolus transit times and residues. Longer duration of pressure waves was associated with a longer bolus transit time and higher pharyngeal residue. Which event is the cause and which the effect cannot be determined. These findings suggest that the tongue base activity plays an important role in effective bolus clearance.²⁷

The effort of swallowing offers another variable that affects transit and risk of aspiration. Effortful swallow is used in treating patients with dysphagia. Effortful swallow of saliva in normals delays onset of pharyngeal pressure and UES relaxation compared to normal swallows but also elicits a longer pharyngeal pressure and longer UES relaxation, which may be helpful in avoiding aspiration.²⁵

Oropharyngeal dysphagia is common following central nervous system disorders, head and neck cancer (as a result of the tumor or treatment), dementia, progressive neurologic conditions such as amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy, Parkinson's, muscular dystrophy, multiple sclerosis, myasthenia gravis, and oculopharyngeal dystrophy. Structural conditions such as cervical osteophytes, or a cricopharyngeal bar after surgery can also cause oropharyngeal dysphagia.

Parkinson's patients exhibit greater durations of UES opening, oral transit, stage transition, pharyngeal transit and total swallow than young controls but not compared to older controls. Of all the parameters measured, only duration of UES opening was longer in patients with Parkinson's and aspiration than in both young and elderly controls. These data suggest that other parameters may also be important in contributing to aspiration/dysphagia.²⁸

Stroke patients that appear to swallow normally may have a longer pharyngeal swallow delay time than controls. Increasing volume and viscosity of swallowed boluses decreases (improves) the pharyngeal delay times (PDT) in both mildly and more severely neurologically impaired subjects. Faster pharyngeal response time (onset of laryngeal elevation to time of cricopharyngeal closure following passage of bolus) and shorter duration of laryngeal elevation, laryngeal closure, and cricopharyngeal opening time were

seen in stroke patients with mild swallowing difficulty compared to normals. The faster pharyngeal response time and shorter duration of laryngeal elevation, laryngeal closure, and cricopharyngeal opening than normal may result from a reduced range of laryngeal and pharyngeal movements in stroke patients. Normals exhibit increased duration of airway closure as bolus volumes increased, but this was not seen in stroke patients.²⁹

Dysphagia and aspiration are terms often used interchangeably when managing and evaluating patients with oropharyngeal bolus transit symptoms. When food is not cleared from the back of the throat into the esophagus, the main clinical concern is the risk of aspiration. In addition to the complex motor events that allow food to be masticated to a viscous bolus that is transferred into the esophagus, there are a number of events that prevent aspiration. There are muscle movements that contribute to this—namely the events that result in glottis closure. In addition, there are protective reflexes that detect a risk situation and result in initiating a swallowing response or cough to clear the pharynx.³⁰

For protective reflexes to be initiated, laryngopharyngeal sensitivity is important. The important contributions of both the motor and sensory components of airway protection have been demonstrated. An impaired laryngoadductor reflex (LAR) results in significant risk of aspiration of thin liquids even in patients with normal pharyngeal musculature. The risk of penetration and aspiration increased markedly with impaired pharyngeal musculature even with normal LAR; the presence of both impaired LAR and pharyngeal musculature was associated with a 100% risk of aspiration and penetration of thin liquids and a very high risk of penetration and aspiration of pureed food (Table 1).³¹

In summary, while there is a clear association of alteration in the relationship between pharyngeal contraction and relaxation of the UES muscle in swallowing in normals compared to patients with dysphagia, these relationships are not so tight that these alterations can confidently predict the presence of aspiration. There are multiple variables that can contribute to symptoms of dysphagia and presence of aspiration that also include the sensory protective mechanisms.

OuyangAnn

5. Is there a mechanical relationship between anterior hyoid movement, extent of upper esophageal opening, and aspiration?

The pharyngeal phase of swallowing is highly complex. A food bolus is propelled to the pharynx by tongue motion. Pharyngeal peristalsis develops that follows the tail of the bolus as it is cleared relatively slowly from the pharynx.³² The larynx is moved upward and anteriorly by contraction of the geniohyoid, mylohyoid, stylohyoid, thyrohyoid, digastric, stylopharyngeus, and palatopharyngeus muscles and contraction of the aryepiglottic, thyroarytenoid (TA), and oblique arytenoid muscles resulting in closure of the laryngeal inlet (glottal closure). The anterior movement of the hyoid results in a sudden drop in UES pressure³³ and coincides with the opening of the UES. This opening is more than a mechanical event, as EMG of this muscle reveals tonic activity that is decreased or silenced when the UES relaxes.³⁴ This relaxation occurs approximately 0.3 s after the onset of contraction of the mylohyoid muscle group and before arrival of the bolus head.

A literature review examining the physiologic variability of hyoid and laryngeal kinematics underscores the variety of methodologies in studies. A wide variability in the degree of anterior and superior hyoid excursion has been described, with means of anterior excursion varying between 7.4 and 18 mm and superior excursion varying between 5.5 and 25 mm. Potentially important factors contributing to this variability include age, height, gender, and

craniofacial morphology.³⁴ Most studies indicate that the greater the volume of the bolus, the greater the anterior and superior excursion that occurs.^{34–36}

The high-pressure zone of the UES has been shown by ultrasound to have a pharyngeal component, a CP component, and an upper esophageal component.³⁷ The tone in this high-pressure zone is due to tonic MN discharges in the MNs of the nucleus ambiguus, and cessation of this tonic discharge during swallowing results in cessation of EMG activity in the CP and thyropharyngeal muscles, while contraction of the suprahyoid muscles results in anterior lift of the hyoid, cricoid, and UES. Both volume and intrabolus pressure affect the extent of UES opening.³⁶

The resting UES pressure, the duration of UES relaxation, and the force of pharyngeal contraction are affected by age and gender. Increasing age is associated with decreased UES resting pressure, a shorter UES relaxation interval and duration, and higher pharyngeal contraction amplitude, and women have a modestly greater UES resting pressure and longer UES relaxation interval with water swallows than men.³⁸

When examining the relationship between glottic closure and CP opening, several coordination patterns have been described (Fig. 4). By measuring EMG directly from the TA and the CP in normals, the authors describe (A) a delay in the onset of TA after the EMG relaxation occurs, and (B) overlap of activity of TA and relaxation of CP.³⁶ The third pattern (C) of increased activity in the TA before the pause in CP electrical activity is theorized to increase the risk of aspiration. As the swallowed bolus increases in size, there is a tendency for the TA contraction time to move earlier in relation to the relaxation of the CP until a type C relationship is seen. Whether this translates into actual aspiration in normals is unknown. No similar study has been conducted in patients.

In normals, a number of protective reflexes are in place. These include the pharyngoglottal closure reflex, the pharyngo-UES contractile reflex, and the reflexive pharyngeal closure reflex. These reflexes are initiated even before there is actual spillage of fluid into the larynx, elegantly illustrated in a study where the larynx was visualized as fluid was introduced into the pharynx and the volume that could be instilled before initiating the three reflexes was compared to the volume that could be infused before spillage into the larynx when the pharynx was anesthetized with a topical anesthetic. Thus in normals, the protective mechanism also includes a sensory component that may be lost in patients with a number of neurologic conditions.³¹

Does impaired movement of the hyoid and larynx correlate with aspiration in patients? A prospective single-blind study of penetration/aspiration and pharyngeal residue was performed with objective frame-by-frame measures of hyoid and laryngeal excursions in 28 patients referred for videofluoroscopy (VFS).³⁹ This study corrected hyoid and larynx movement for height and calculated movement based on the distance between the second and fourth cervical spines. These investigators determined that there was a higher occurrence of penetration/aspiration when the anterior movement of the hyoid fell below the first-quartile boundary, and reduced anterior arytenoid displacement was significantly associated with postswallow residuals. Despite this statistical association, several swallows exhibited reduced displacement of the hyoid and arytenoids with no evidence of penetration/aspiration or residue, suggesting that there are other protective mechanisms in play.

The relationship of laryngeal elevation, UES opening, and bolus viscosity in patients with dysphagia has been studied. Of 70 subjects referred for VFS for dysphagia, studies showed thick fluid aspiration in 23 and thin fluid aspiration in 20, while 27 patients exhibited no aspiration. Risk factors for thin fluid aspiration were an increased latency of the timing of all the components of the swallowing reflex, pharyngeal transit time, and the interval between

arrival of the bolus at the vallecula and laryngeal elevation. Delays in the timing of these events were also delayed to a lesser extent in patients with thick fluid aspiration.⁴⁰

The complex nature of swallowed food, with a mixture of solids and liquids and viscosity and volume, makes study of normal physiologic function difficult. The field is complicated further by a lack of standardization in reported studies.

Overall, the literature suggests that there is a mechanical relationship between anterior hyoid movement and extent of UES opening and aspiration, but that this is not a simple relationship due to the complex effect of bolus consistency and the presence of redundant reflexes to protect the airway.

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6. To what extent can fluoroscopy and manometry with biomechanics define the various stages of UES opening?

During swallowing, the UES needs to open promptly and adequately to allow material to pass safely and efficiently from the pharynx into the esophagus. This is especially critical due to the close proximity between the UES and the airway entrance. In clinical practice, accurate evaluation of the different phases of UES opening during swallowing is critical to determine candidacy for and efficacy of safe and beneficial dysphagia treatment. VFS is the most available and frequently employed instrumental swallow assessment.⁴¹ This dynamic radiographic imaging assessment provides real-time direct visualization of bolus flow and structural movement as the UES opens during swallowing. On the other hand, manometry (traditional solid state or high-resolution) provides quantitative information regarding the timing, extent, and sequence of pressure events occurring during pharyngeal swallowing. Separately, neither of these techniques can capture each phase of UES opening. However, when combined (i.e., manofluorography), five distinct stages of UES opening can be captured. Cook *et al.* originally described these five distinct phases of UES opening based on a concurrent manofluorographic analysis in a cohort of 15 healthy young adult male volunteers.⁴² These stages are outlined below.

In the initial *relaxation* phase, vagal inhibition of the tonic contraction of the CP muscle cannot be seen on VFS but it can be observed manometrically. A drop in CP pressure occurs 200 ms before radiographic evidence of UES opening and lasts 300–600 ms.⁴²

In the second phase, passive UES *opening* occurs via the biomechanics of hyolaryngeal excursion (Fig. 5). This phase can be directly observed on VFS. Suprahyoid (geniohyoid, mylohyoid, stylohyoid, hyoglossus, and the anterior belly of digastric muscle) and infrahyoid (thyrohyoid) muscles contract to pull the hyoid bone and laryngeal complex in an anterior and superior direction during swallowing. The geniohyoid muscle has the greatest influence on the anterior movement of the hyoid bone during swallowing, which is said to pull the UES open.⁴³ The UES assumes an oval cross-section and is raised 2–2.5 cm in an orad direction. Notably, the UES can open with hyolaryngeal excursion alone, but CP relaxation in isolation has not been observed to open the UES. This suggests that traction forces applied by hyolaryngeal excursion have a bigger influence on UES opening than CP muscle relaxation. The terms UES relaxation and UES opening are therefore not synonymous.

In the third phase, the weight and volume of the onrushing bolus *distends* the lumen of the UES further. During this phase, the bolus is propelled by lingual and pharyngeal peristalsis through the hypopharynx and the stretched-open UES and into the cervical esophagus. Pharyngeal contraction can be evaluated manometrically during swallowing and the extent

(mm) and duration (seconds) of UES opening can be evaluated, albeit subjectively, from videofluoroscopic images. This distension *collapses* in the fourth phase as the bolus passes through the sphincter. Finally, in the fifth phase the UES *closes* as the CP actively contracts.⁴²

Manofluorography captures each of the above phases and hence can localize the nature of disordered UES opening during swallowing. This information is pivotal as, for example, those with weak pharyngeal propulsion or impaired hyolaryngeal excursion typically do not benefit from pharmaceutical (e.g., botulinum toxin A injections) or surgical (e.g., CP myotomy) intervention and are better suited to dysphagia rehabilitation. Those without pharyngeal involvement, on the other hand, tend to respond better to invasive procedures. Nevertheless, combined manofluorography, as with many diagnostic tools, presents with numerous limitations, which prevent it from being a gold standard assessment of UES opening. While CP relaxation can be viewed manometrically before UES opening is observed on VFS, several factors influence pressure measures including age, gender, anxiety, sensor location within the asymmetrical UES lumen, and catheter types.⁴⁴ Needle EMG is therefore considered to be a more accurate measure of CP relaxation. Second, videofluoroscopic measurement of hyolaryngeal excursion during swallowing is time consuming based on frame-by-frame analysis, and it is subjective, with varying normal ranges and poor interrater reliability.^{35,45,46} Finally, combined manofluorography is not readily available in the majority of clinical settings.⁴¹

In conclusion, combining videofluoroscopy and manometry provides good biomechanical data on UES opening and bolus pressure. The ability to identify impairment at each phase of UES opening is of paramount importance to clinicians working with dysphagia. Despite this, manofluorography is not often used in routine practice because of limited access to equipment.⁴¹ In clinical practice, where access to instrumental evaluations and in particular to manofluorography and needle EMG is limited, identification of each phase of UES opening is a major challenge for dysphagia clinicians. This has significant implications in terms of the selection and provision of appropriate and safe dysphagia management. In the future, developments in instrumental UES evaluation (e.g., HRM, impedance, functional lumen imaging probe) may advance our understanding of the nature of UES opening further.

OuyangAnn

7. What nonpharmacological approaches are available that can alter the gastroesophageal junction?

The GEJHPZ includes several components: the intrinsic LES muscle, the upper part of which overlaps the crural sphincter and the gastric sling fiber/clasp fiber complex, and the extrinsic muscle of the crural diaphragm.⁴⁷

There are no studies of nonpharmacologic approaches to control LES contraction and relaxation that meet criteria for any randomized controlled studies to be considered for meta-analysis studies. This discussion therefore addresses the nonpharmacologic approaches that have been tried in small studies and approaches that could theoretically influence these control mechanisms and affect GEJ function. Many approaches have been directed at treatment of reflux symptoms with limited or no study of their effects on gastroesophageal sphincter function.

Gastroesophageal junction pressure is controlled by LES tone and by crural diaphragmatic activity. LES tone is controlled by neurotransmitters released from the myenteric plexus, vagal tone and firing, and diaphragmatic activity by activation of the phrenic nerve

including reflexes such as splinting of the diaphragm during maneuvers that increase intra-abdominal pressure such as coughing and straining.

The crural diaphragm is an important component of the gastroesophageal reflux region. Voluntary diaphragmatic control has been used to control regurgitation in the rumination syndrome by preventing the abrupt increase in abdominal pressure when the crural diaphragm is relaxed. Voluntary control of the crural diaphragm as an approach to treatment of reflux has not been well studied. In a study in a single motivated patient, investigators demonstrated that by biofeedback, the LES pressure (LESP) could be increased by 100% with resolution of macroscopic esophagitis that had been recalcitrant to medical therapy.⁴⁸ The report dates prior to use of PPIs and is unclear if this change in LESP involved primarily crural diaphragm activity or the intrinsic LES. In a more recent study, abdominal breathing exercise aimed to strengthen the crural diaphragm used with on-demand PPI resulted in significant decrease in PPI usage and improved quality of life.⁴⁹ Interestingly, there was no significant change in LESP, but less esophageal acid exposure. The mechanism by which this therapeutic improvement was achieved is therefore unclear.

Transient lower esophageal sphincter relaxations (TLESRs) have been proposed to play an important role in gastroesophageal reflux in patients with normal LESP. TLESRs involve simultaneous relaxation of the LES and decreased activity of the crural diaphragm. The LES smooth muscle tone is vagally mediated. Activation of TLESRs appears to be via a vagal pathway, with gastric distention activating vagal afferents that simulate the dorsal motor nucleus of the vagus (DMV) and efferent vagal nerve activation. L-glutamate injection into the intermediate DMV in ferrets results in decreased EMG activity of the crural diaphragm and a decrease in LESP. Injection into the rostral area increases EMG activity of crural diaphragm and LES.⁵⁰ Can vagal activity be controlled nonpharmacologically? In animals, stimulation of acupuncture points can affect vagal activity.⁵¹ Electrical acupoint stimulation in healthy volunteers has demonstrated a decrease in the rate of TLESRs without an effect on basal LESP, residual LES pressure, or gastrointestinal symptoms. This was not mediated through μ -opioid receptors.⁵² One randomized controlled study has shown that acupuncture is as efficacious as a PPI as a primary treatment for gastroesophageal reflux⁵³ and there is one report of greater improvement of reflux symptoms with acupuncture treatment than with an increase in PPI dose.⁵⁴ The mechanism by which acupuncture was effective was not determined in these studies.

Other nonpharmacologic treatments have been studied. Melatonin has been postulated to affect the release of nitric oxide and prostaglandin E2 in the esophageal mucosa and to inhibit gastric acid secretion, which in turn may increase gastrin release, stimulating LES contraction. Studies of a small number of subjects suggest that a combination of melatonin and omeprazole 20 mg daily is more effective than either alone.⁵⁵

Several botanicals have been tried in the treatment of GERD symptoms.⁵⁵ While spearmint has been reported to be useful in the treatment of heartburn, a study in normal volunteers demonstrated no effect on LES or acid reflux. Iberogast (a combination of nine botanicals) was studied in a randomized trial with a primary indication of dyspepsia. A secondary observation that symptomatic GERD was improved with iberogast compared to placebo was noted, but no studies of physiologic function were performed.

The discussion of approaches to physically change the anatomic relationship between the LES, gastric fundus, and crural diaphragm will be limited to endoscopic approaches. The success of antireflux fundoplication surgery has led to attempts at endoluminal approaches to achieve a similar change in the anatomic relationship between the esophagus and stomach. A review of the literature between 1966 and 2007 determined that while a high

short-term success rate was reported for many of the endoscopic approaches, in the four randomized sham-controlled clinical trials, the response to placebo was as high as 50%.⁵⁶ It was felt that there were insufficient data on safety, efficacy, and durability of response to recommend the use of endoscopic endoluminal approaches at that time. Other endoscopic approaches have included the application of thermal injury to the GEJ or injection of a polymer into this region. The mechanism and effect on physiology of these approaches was not well investigated, but were proposed to be based on altering the anatomy of the cardia and possibly altering the compliance of the GEJ and its ability to relax. Neither approach is currently available due to lack of efficacy as judged by a decrease in PPI use and significant side effects.

In summary, there are multiple potential targets in the control of the GEJ for nonpharmacologic intervention, but only small studies of effectiveness of current approaches are available. The efficacy of nonpharmacologic treatments on heartburn symptoms does not appear to be always through an alteration of the function of the GEJ.

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Concise summaries

- There is a fair amount of literature with respect to the anatomy and functional purpose of the muscularis mucosa. Both simultaneous endoluminal ultrasound and manometry with transabdominal ultrasound to investigate the distal esophagus and proximal stomach strongly suggest that the mucosa/submucosa, along with the muscularis mucosa, may have other important physiologic functions in addition to their direct role as an epithelial protective barrier. In normal subjects, the gastric mucosa/submucosa acts as a mechanical antireflux barrier by being pulled up into the distal tubular esophagus and forming a narrow channel or one-way valve during deglutition.
- The mechanisms of neurological control of human esophageal motility differ in the striated part of the esophagus and in the smooth muscle esophagus. Esophageal peristalsis in the cervical esophagus is mediated by vagal fibers that make direct contact with striated muscle, and the main excitatory neurotransmitter at this level is acetylcholine acting on nicotinic cholinergic receptors.
- A parallel group of animal studies in pigs and rats allowed study of the inhibitory neurotransmitters mediating human lower esophageal sphincter (LES) relaxation, the functional asymmetry of human LES, the neurotransmitters controlling peristalsis in the esophageal body (EB), and the excitatory/inhibitory neurotransmitters regulating the human esophageal smooth muscle.
- Detailed pharmacologic studies of *in vitro* contractile responses are not feasible using the minute muscle tissue obtained from an endoscopic biopsy but are feasible using whole organs obtained from organ transplant donors. The differences in esophageal muscle *in vitro* properties between the lower esophageal circular muscle, the clasp muscle, and the sling fibers have been studied from stomach and esophagus specimens obtained from human organ transplant donors without any history of gastroesophageal reflux disease (GERD). GABA_A receptors are not present or not functional in clasp fibers, but increased intracellular cAMP with β -adrenoceptor activation does cause relaxation. Sling fibers are different in that either β -adrenoceptor-induced increased cAMP or increased intracellular chloride with GABA_A receptor activation are each individually insufficient to induce relaxation, which requires increases in both cAMP and chloride. The nicotinic receptors mediating relaxations may be slightly different between the clasp and sling fibers of the proximal stomach.
- There is a clear association of alterations in the relationship between pharyngeal contraction and relaxation of the upper esophageal sphincter (UES) muscle in swallowing in normal patients compared to patients with dysphagia, but these alterations cannot confidently predict the presence of aspiration.
- The physiologic variability of hyoid and laryngeal kinematics underscores the variety of methodologies in studies examining the pharyngeal phase of swallowing. The high-pressure zone of the UES has been shown by ultrasound to have a pharyngeal component, a cricopharyngeus (CP) component, and an upper esophageal component. Several coordination patterns have been described when examining the relationship between glottic closure and CP opening, with a number of protective reflexes including the pharyngoglottal closure reflex, the pharyngo-UES contractile reflex, and the reflexive pharyngeal closure reflex. The mechanical relationship between anterior hyoid movement and extent of

UES opening and aspiration is complex, due to the effect of bolus consistency and the presence of redundant reflexes to protect the airway.

- Overall, the literature suggests that there is a mechanical relationship between anterior hyoid movement and the extent of UES opening and aspiration but that this is not a simple relationship because of the complex effect of bolus consistency and the presence of redundant reflexes to protect the airway.
- Combining videofluoroscopy and manometry provides good biomechanical data on UES opening and bolus pressure, but is not often used in routine practice because of limited access to equipment.
- Manofluorography is, however, pivotal to localize the nature of disordered UES opening during swallowing as, for example, in patients with weak pharyngeal propulsion or impaired hyolaryngeal excursion who do not benefit from pharmaceutical or surgical intervention and are better suited to dysphagia rehabilitation.
- At the level of the gastroesophageal junction (GEJ), there are multiple potential targets in the control for nonpharmacologic intervention, but their efficacy on heartburn symptoms does not appear to be always through an alteration of the function of the components of the high-pressure zone.

Figure 1. Endoluminal ultrasound and manometry and transabdominal ultrasound of the distal esophagus and proximal stomach in normal control subjects.

Figure 2.

EFS-induced responses on human esophagus. (A) Electrical field stimulation-induced responses at different frequencies in both clasp and sling regions of the lower esophageal sphincter (LES) and the esophageal body (EB). (## $P < 0.01$ clasp vs. sling fibers; Ø $P < 0.05$ EB vs. clasp LES; † $P < 0.05$ EB vs. sling LES). Agonist-induced responses on human esophagus. (B) Concentration-response curves for carbachol (CCh, middle graph) and sodium nitroprusside (SNP, right graph) in the clasp and sling muscles of human LES and EB. (Ø $P < 0.05$ EB vs. clasp LES; † $P < 0.05$ EB vs. sling LES).

- Tetrodotoxin blocks nicotine induced relaxation of bethanechol pre-contracted clasp but not sling fibers
- Propranolol (β adrenergic antagonist) blocks nicotine induced relaxation clasp and sling fibers
- SR95531 (GABA_A antagonist) blocks nicotine induced relaxations of sling but not clasp fibers.
- Muscamol (GABA_A agonist) does not relax either clasp or sling fibers.
- Isoproterenol (β adrenergic agonist) relaxes clasp but not sling fibers.
- Combination of isoproterenol and muscamol relaxes sling fibers.

Figure 3.

Diagrams illustrating the major differences in the neuromuscular control of contraction and relaxation between clasp and sling fibers of the human upper gastric sphincter.

Figure 4.

Patterns of coordination between thyroarytenoid contraction and cricopharyngeal relaxation during swallowing that may affect risk of aspiration. (A) a delay in the onset of thyroarytenoid activity after the cricopharyngeus relaxation occurs; (B) overlap of activity of thyroarytenoid and relaxation of cricopharyngeus; and (C) increased activity in the thyroarytenoid before the pause in cricopharyngeus electrical activity. Adapted from Ref. 37.

Figure 5.

Six lateral videofluoroscopy images over a 2-s period in a 54-year-old male with oropharyngeal dysphagia poststroke swallowing a liquid bolus. Note timer display in hours: minutes: seconds: frames (25 frames per second). (A) Liquid barium bolus passes to the level of the pyriform sinuses before the pharyngeal swallow has been initiated. Note (i) UES remains closed; (ii) hyoid bone and larynx are in resting position; and (iii) airspace is evident between tongue base and posterior pharyngeal wall. (B) Pharyngeal swallow is initiated. Hyoid bone is being pulled anteriorly and superiorly toward mandible due to suprahyoid and thyrohyoid muscle contraction. Tongue base begins to retract toward posterior pharyngeal wall to propel bolus through UES. UES has not yet opened. (C) UES opens (49.21) and bolus begins to pass into the esophagus. (D) Material continues to pass through the UES. (E) UES closes (50.06). UES opened for 10 frames (0.40 s). (F) Residue in valleculae and pyriform sinuses observed postswallow. Penetration of barium is visible to the level of the vocal cords.

Table 1

Effects of pharyngeal musculature and laryngoadductor reflex on penetration and aspiration risk in patients

	Bolus	Normal pharyngeal musculature	Impaired pharyngeal musculature
Normal LAR	Thin liquid	P 15.3% A 0% <i>N</i> = 76	P 100% A 76.5% <i>N</i> = 17
	Puree	P 0% A 0% <i>N</i> = 59	P 35.3% A 17.6% <i>N</i> = 17
Absent LAR	Thin Liquid	P 100% A 40% <i>N</i> = 5	P 100% A 100% <i>N</i> = 41
	Puree	P 0% A 0% <i>N</i> = 5	P 95.1% A 78% <i>N</i> = 41

Note: Adapted from Ref. 31.

LAR, laryngoadductor reflex; P, penetration; A, aspiration; *N*, number of patients.