Regulation and dysregulation of esophageal peristalsis by the integrated function of circular and longitudinal muscle layers in health and disease

Ravinder K. Mittal

Department of Medicine, Division of Gastroenterology, San Diego VA Health Care System, San Diego, California and University of California, San Diego, California

Submitted 4 May 2016; accepted in final form 17 July 2016

Mittal RK. Regulation and dysregulation of esophageal peristalsis by the integrated function of circular and longitudinal muscle layers in health and disease. Am J Physiol Gastrointest Liver Physiol 311: G431–G443, 2016.—Muscularis propria throughout the entire gastrointestinal tract including the esophagus is comprised of circular and longitudinal muscle layers. Based on the studies conducted in the colon and the small intestine, for more than a century, it has been debated whether the two muscle layers contract synchronously or reciprocally during the ascending contraction and descending relaxation of the peristaltic reflex. Recent studies in the esophagus and colon prove that the two muscle layers indeed contract and relax together in almost perfect synchrony during ascending contraction and descending relaxation of the peristaltic reflex, respectively. Studies in patients with various types of esophageal motor disorders reveal temporal disassociation between the circular and longitudinal muscle layers. We suggest that the discoordination between the two muscle layers plays a role in the genesis of esophageal symptoms, i.e., dysphagia and esophageal pain. Certain pathologies may selectively target one and not the other muscle layer, e.g., in eosinophilic esophagitis there is a selective dysfunction of the longitudinal muscle layer. In achalasia esophagus, swallows are accompanied by the strong contraction of the longitudinal muscle without circular muscle contraction. The possibility that the discoordination between two muscle layers plays a role in the genesis of esophageal symptoms, i.e., dysphagia and esophageal pain are discussed. The purpose of this review is to summarize the regulation and dysregulation of peristalsis by the coordinated and dis coordinated function of circular and longitudinal muscle layers in health and diseased states.

esophagus; longitudinal muscle; peristalsis; transient relaxation; vagus nerve

Bayless and Starling at the turn of the 19th century described peristalsis or the “law of intestine” as it is known today, as the contraction on the proximal side and relaxation on the distal side of a bolus within the lumen of the small intestine or colon (6, 7). Their experiments indicated that the circular and longitudinal muscle layers of the intestine (the small intestine and colon) contract and relax together during peristalsis. In fact, they discussed the available literature at that time, which argued the above issue back and forth. The topic got renewed attention in the 1960s and 70s (47, 93), when the concept of reciprocal innervation of the two layers emerged, according to which the circular and longitudinal muscles contract and relax in an opposite phase in both the contracted and relaxed segments of the intestine. Even though reciprocal innervation never gained ground in the esophagus (25), studies suggested that the two layers are not perfectly synchronized, i.e., at any given site, contraction in the longitudinal muscle starts earlier and lasts longer than that of the circular muscle (63, 72, 87). Studies conducted during the last two decades, in both the esophagus (59) and colon (82, 83), convincingly prove that in fact the two layers contract and relax together during the ascending contraction and descending relaxation of the peristaltic reflex, respectively. The synchrony and asynchrony between the two layers is of fundamental importance to bolus propulsion in the antegrade and retrograde directions, respectively.

Coordination Between the Two Muscle Layers: Why Studies Yielded Conflicting Results?

The conflicting data on the coordination between the two muscle layers in the literature is most likely related to the different recording techniques used by the investigators. First, a large number of in vitro and in vivo studies used measurements at a focal point/location (e.g., intraluminal pressure recording) to record circular muscle contraction. On the other hand, global shortening of the esophagus, or a length of the small intestine/colon was often used to record longitudinal muscle contraction. Endoscopically (28, 72) or surgically placed radiopaque markers (24) and monitoring their motion fluoroscopically in animals and humans provides information on the global/segmental shortening rather than the local longitudinal muscle contraction at a point location. Second, as per

Address for reprint requests and other correspondence: R. K. Mittal, Mail Code 0061, Gilman Dr., Bldg. UC 303, La Jolla, CA 92093, San Diego, CA 92161 (e-mail: rmittal@ucsd.edu).

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G431
the law of mass conservation, shortening of any muscle in one direction leads to lengthening in the other direction, which can be falsely interpreted as muscle relaxation. In the in vivo studies of the esophagus, e.g., if only the circular muscles were to contract it would result in lengthening of the esophagus, and vice versa. Several studies used the strain gauge technique, usually 10 mm in length, and sutured them in the circular and longitudinal orientation to record circular and longitudinal muscle contraction, respectively (87). Third, circular and longitudinal muscle fibers are not necessarily oriented in the axis of the organ, e.g., circular muscles in the esophagus are actually oriented in a spiral/helical orientation (32, 90). Contraction of a spiral circular muscle actually causes axial shortening of the esophagus, which may be easily misinterpreted as longitudinal muscle contraction. Fourth, intraluminal pressure recordings techniques (manometry) record circular muscle contraction, when the lumen is fully collapsed on the recording probe. The circular muscle contraction actually begins at a moment when a fully distended lumen starts to collapse (which is not recorded by manometry). Depending on the size of the bolus and resultant luminal distension, there can be a delay of more than 1 s between the times of the onset to the time of full luminal collapse. At the cessation of contraction, manometry also misses a portion of circular muscle contraction because of the change in the shape of the esophagus (59). From my understanding there are only few techniques that can record the precise temporal relationship between circular and longitudinal muscle contraction in an ex vivo piece of intestine or in the in vivo setting. Intraluminal ultrasound (US) imaging that utilizes the law of mass conservation to record contraction in each muscle layer in the in vivo setting is one such technique (63). Intraluminal ultrasound (US) imaging that utilizes the law of mass conservation to record contraction in each muscle layer in the in vivo setting is one such technique (63). Intraluminal ultrasound (US) imaging that utilizes the law of mass conservation to record contraction in each muscle layer in the in vivo setting is one such technique (63). Intraluminal ultrasound (US) imaging that utilizes the law of mass conservation to record contraction in each muscle layer in the in vivo setting is one such technique (63).

**Patterns of Contraction of the Two Muscle Layers During Peristalsis and Transient LES Relaxation**

The esophagus is basically a conduit for the transfer of oral contents into the stomach, and in the reverse direction during gastroesophageal reflux (GER), belching, and vomiting. There are distinct patterns of contraction in the two muscle layers during antegrade (peristalsis) and retrograde [transient lower esophageal sphincter (LES) relaxation] transport. Studies in humans that utilized manometry and high-frequency US imaging show that at any given location in the esophagus the two muscle layers are perfectly coordinated/synchronized during peristalsis, with regards to the onset, the peak, as well as the duration of contraction (59). The two muscle layers contract in a relatively perfect synchrony during balloon distension-induced esophageal contraction as well (96). Another important aspect of peristaltic contraction is that at any given time a segment of the esophagus is contracted (in the long axis of the esophagus), the length of the contracted segment can be several centimeters and variable, e.g., it increases as the contraction traverses from the oral to the aboral end (17). The amplitude of circular and longitudinal muscle contractions are distributed in a bell-shaped manner (1), with the peak at the center of the curve, as shown in Fig. 1. The peak circular muscle contraction is located at the site of peak pressure and peak longitudinal muscle contraction at the site of greatest muscle thickness. In normal peristaltic contraction, peak pressure (circular muscle contraction) and peak thickness (longitudinal muscle contraction) move together from the oral to the aboral direction.

Recording the descending relaxation of peristaltic reflex in the esophagus is a bigger challenge than recording contraction because intraluminal pressure recordings do not show continuous/tonic contractile activity in the esophagus. One needs a barostat to record esophageal tone (54), a scenario similar to the fundus of the stomach. In animal studies, there are distinct changes in the resting membrane potential with relaxation (inhibition) and contraction (excitation) (20, 86). A reduction in the resting membrane potential or hyperpolarization represents relaxation, and a depolarization with spike bursts represents contraction. With swallows there is an initial hyperpolarization, the duration of which increases from proximal to distal esophagus. Sifrim and coworkers (79, 81) used an artificial high-pressure zone in the esophagus, created by distending a small balloon, to study swallow-induced esophageal relaxation in humans. They found that, at a given location, swallow induces relaxation first, which is followed by contraction. The duration of relaxation is greater in the distal compared with proximal esophagus. The implication of Sifrim’s and other studies was that, whereas the contraction in the esophagus travels in a sequential fashion, the relaxation occurs simultaneously throughout the esophagus. Pattern of esophageal luminal distension during peristalsis is another possible indicator of the relaxation with the understanding that a greater relaxation will result in a greater distension. Abrahao et al. (1) observed that during peristalsis the esophagus does not distend in the shape of a cylinder (or a sausage) as one would expect if the entire esophagus was relaxed at the same time. Rather, the distension is shaped like an “American football” with maximal distension at the center with tapering at the two ends. The bolus moves in the shape of an American football, from proximal to the distal end, which implies that 1) the maximal inhibition, similar to maximal contraction, is located at a point location (site of peak distension), and 2) similar to contraction, inhibition also travels the esophagus in a sequential or peristaltic fashion. It is not that there is not some degree of inhibition in the entire esophagus following a swallow but what it implies is that, similar to gradient of contractions, there also exist gradients of inhibition during peristalsis, and the two move sequentially, tightly coupled to one another. US imaging studies show that, during descending relaxation induced by a swallow or distension, there is thinning of the two muscle layers, which may be interpreted as synchronous relaxation in the two muscle layers (95).

Transient LES relaxation is a distinct motor pattern that was first described in connection with GER (21). It turns out that it is a motor pattern designed for retrograde transport of material through the esophagus (belching and vomiting) and is also the major mechanism of GER in normal subjects and patients with reflux disease. Since the original description of transient LES relaxation (TLESR), it has become clear that, in addition to LES relaxation, there is also inhibition of crural diaphragm, unique pattern of longitudinal muscle contraction in the distal esophagus, circular muscle contractions at the onset and at the
end of TLESR, and frequent mylohyoid muscle contraction at the beginning of TLESR (57). It was observed that swallows often fail to induce esophageal contraction during TLESR, which implied that the esophagus is inhibited during TLESR. Using a small balloon to record esophageal pressure, Sifrim et al. (80) observed contraction of the distal esophagus during TLESR that was diminished in patients with reflux esophagitis. Pandolfino et al. (66) observed axial shortening of the esophagus during TLESR is much stronger than the one observed with a swallow, a finding that has been confirmed by others (4, 49). It turns out that during TLESR there is selective contraction of the longitudinal muscle of the distal esophagus, which starts in the distal esophagus, before the onset of TLESR, and spreads in the oral direction (almost like reverse peristalsis, but only in the longitudinal muscle layer) (Fig. 1). Longitudinal muscle contraction lasts for the entire duration of TLESR, while the circular muscle remains relaxed (Fig. 2). Axial shortening of one layer and not the other implies that the two layers are not completely tethered together and must slide in relationship to each other (Fig. 2B). We found that during peristalsis there is greater axial shortening of the circular muscle layer than the longitudinal muscle in the distal esophagus, and the reverse happens during TLESR (67). Circular muscle contraction causes axial shortening of the esophagus because of its spiral orientation along the axis of the esophagus. At the end of TLESR, there is a sudden shift of the contraction pattern in the two layers to a peristaltic pattern, i.e., synchronous contraction of the two layers (Fig. 2A). Stimulation of the pharynx induces primary peristalsis in the esophagus and relaxation of LES. On the other hand, a subthreshold pharyngeal stimulus induces isolated LES relaxation in the absence of esophageal peristalsis (56, 70). A subthreshold pharyngeal stimulus also induces axial shortening in the proximal esophagus, just distal to the upper esophageal sphincter, or in other words contraction of the longitudinal muscle layer of the proximal esophagus (50). The relevance of axial esophageal shortening and sliding between the two muscle layers is discussed later.

Neural Control of Peristalsis and Transient LES Relaxation

Extrinsic (Vagus Nerve) and Intrinsic (Myenteric Plexus)

In general, the entire gastrointestinal (GI) tract has dual neural control through extrinsic (vagus and sympathetic) and intrinsic nerves (myenteric plexus). Nowhere else in the GI tract the role of cortical, brain stem, and vagal control (extrinsic) is as evident as it is in the esophagus, the reason for which is that swallow, which is a voluntary act, requires integration with the involuntary acts of esophageal peristalsis and LES relaxation. Stimulation of brain stem nuclei, e.g., nucleus tractus solitarius, can evoke peristaltic contraction in the esophagus (14). Studies show that there is topographical representation of different regions of gastrointestinal tract in the dorsomotor nucleus of vagus (DMV) nerve (12). Furthermore, contraction and relaxation of the LES is induced by the activation of rostral and caudal region neurons in the DMV, respectively (74). It is generally suggested that the end organs or the smooth muscle of the GI tract are not directly innervated by vagus nerve, the later only innervates the myenteric neurons, which in turn innervates the two muscle layers. Vagus nerve is thought to contain parallel excitatory and inhibitory efferent fibers that synapse with the excitatory and inhibitory...
motor neurons of the myenteric plexus (14). However, stimulation of entire trunk of the vagus nerve only induces relaxation of the circular muscles of esophagus and LES. It is felt that when stimulated simultaneously the inhibitory efferents predominate over the excitatory. Blockade of vagal efferent traffic abolishes primary peristalsis (16) and TLESR (53). Nerve suture studies in which the central end of the vagus nerve was sutured to the peripheral end of the accessory spinal nerve show that swallow evoked sequential discharges in the vagal efferent fibers (13). Single fiber recordings from the vagus efferents reveal swallow activated short- and long-latency fibers that may mediate relaxation and contraction of the esophagus, respectively (31). Whether short- and long-latency fibers discharge in a sequential manner along the length of the esophagus has never been proven. The problem with the single-fiber studies is that one can’t be sure of the destination of recorded efferents, e.g., do they go to skeletal or smooth muscles esophagus, or do they go to circular or longitudinal muscles? Sequential and coordinated activation of circular and longitudinal muscle layers through a central mechanism has never been assessed.

Simultaneous activation of the entire vagal trunk (all vagal efferents) induces simultaneous contraction in the skeleton muscle esophagus. Hence, peristalsis in the skeleton muscle esophagus can only be explained by sequential activation of motor neurons located in the nucleus ambiguous of vagus nerve that excite skeletal muscles along the length of the esophagus in a sequential fashion. One must keep in mind, though, that, similar to smooth muscles esophagus, enteric/myenteric neurons (inhibitory as well as excitatory) are present in the skeleton muscle esophagus and these enteric neurons innervate the neuromuscular junction of skeletal muscle esophagus, along with the vagus nerve (43, 94). It is speculated that these inhibitory, nitric oxide synthase-containing neurons modulate skeletal muscle contraction at the neuromuscular junction. However, the physiological studies do not clearly support the above claim (85).

Peristalsis in the smooth muscle esophagus is more complicated than in the skeleton muscle esophagus. Opossum esophagus has been studied extensively for physiological studies because similar to humans: the distal two-thirds of the opossum esophagus is also comprised of smooth muscles. Christensen and Lund (15) found that distension and electrical field stimulation of the ex vivo esophagus induced longitudinal muscle contraction during the entire period of stimulation and circular muscle contraction following the onset (“on” contraction) and a short period after the cessation of stimulus (“off” contraction). The off contraction traversed the esophagus in a peristaltic fashion toward the aboral end. Weisbrodt and Christensen (91) found that the circular muscle strips from the proximal esophagus had short latency compared with the distal esophagus. The latency gradient along the length of the esophagus is considered to be the basis of peristalsis in the circular smooth muscle. Since these muscle strips were connected neither to each other nor to the extrinsic nerves, the only conclusion one can arrive is that the latency gradients are
hardwired locally in the muscle. With advances in the manometry technique it became possible to record esophageal pressure and therefore the circular muscle contraction in vivo in the whole animals (22). Gidda et al. (30) observed that the latency as well as the amplitude of “on” and “off” contractions of circular muscles with vagal stimulation was dependent on the frequency of electrical stimulus; high-frequency stimulus reduces the speed of peristalsis and increases the amplitude and duration of contractions. Further studies found that the proximal and distal esophagus are under the influence of greater cholinergic and greater nitrergic nerves, respectively (19). Nitric oxide antagonist reduces latency of distal esophageal circular muscle contraction, suggesting a neural mechanism of peristalsis. Others found that even when all neural activity was blocked by TTX, direct stimulation of muscle by electrical stimulation induced peristaltic contraction in the esophagus, suggesting myogenic mechanism of peristalsis (73, 76).

With regards to the longitudinal muscle, stimulation of the entire cervical vagus nerve in an intact animal induces longitudinal muscle contraction during the entire period of stimulation (duration response). On the other hand, a swallow or stimulation of the superior laryngeal nerve (an experimental technique to induce swallow in an anesthetized animal) induces sequential/peristaltic response in the longitudinal muscle layer (88). Muscle strip experiments reveal that, similar to circular muscles, the longitudinal muscle contraction characteristics are also dependent on the electrical stimulus frequency: low-frequency stimulus induces an off response only; however, high-frequency stimulus results in duration response and post-stimulus response, the duration of which increases from proximal to distal location in the esophagus (18).

The conclusions one can draw from the above studies are as follows: 1) The fact that the vagus nerve stimulation induces duration response in the longitudinal muscle and an on and off response in the circular muscle suggests that the neural control for these two layers is different. 2) The fact that peristalsis can be induced by stimulation of the entire vagus nerve suggest that control of peristalsis at least in the smooth muscle esophagus resides in the esophageal wall (consisting of two muscle layers and myenteric neurons). 3) The stimulation of the entire vagal trunk causes simultaneous contraction in the skeletal muscle and peristaltic contraction off contraction in the smooth muscle implies that the control of peristalsis switches from a central to a peripheral control along the length of the esophagus. Alternatively, the mechanism of peristalsis in the in vivo situation is more complex than revealed by experimental studies.

Acetylcholine is the neurotransmitter of all preganglionic vagal efferent. On the other hand, acetylcholine and substance P are the neurotransmitters of postganglionic neurons of the longitudinal muscle. With regards to postganglionic circular muscle contraction, acetylcholine and withdrawal of nitrergic inhibition are the two chemical mediators. In the in vivo human (23) and animal studies (9), atropine abolishes the circular muscle contraction. Detailed studies in cat (9) show that the cholinergic mechanism of peristalsis involves both preganglionic and postganglionic sites. In the in vivo esophagus and in vitro muscle strips, blockers of nitric oxide reduce the latency of contraction of the circular muscle in the distal esophagus, thus converting a peristaltic contraction into a simultaneous contraction (62, 97). Nitric oxide antagonist also inhibits circular muscle esophageal contraction, suggesting that withdrawal of nitrergic inhibition is an important mechanism of peristaltic contraction in the circular muscle layer. Nitric oxide induces a biphasic response in the longitudinal muscle strips, initial relaxation followed by contraction that are mediated by cyclic GMP and prostaglandins, respectively (75).

Role of Stretch in the Peristaltic Reflex

Esophageal distension in smooth muscle esophagus, in bilateral vagotomized animals and in an ex vivo preparation of the esophagus, induces peristalsis in the circular muscle layer and LES relaxation. Using a three-partition chamber preparation, Paterson and colleagues (61) observed that distension of the proximal esophagus evokes nerve-mediated inhibitory and excitatory responses in the circular muscle of the distal esophagus that were blocked by nitric oxide antagonist but not by a synaptic blocker. They came to the conclusion that muscle stretch in the proximal esophagus activates inhibitory motor neurons in the distal esophagus to cause NANC (noncholinergic nonadrenergic)-mediated inhibition, and withdrawal of NANC inhibition induced esophageal contraction. Paterson used a balloon to distend the esophagus and therefore could not distinguish the effects of longitudinal vs. circumferential stretch on the peristaltic reflex. Using an in vivo whole animal preparation, we observed that an esophageal stretch in the axial and circumferential direction causes nerve-mediated LES relaxation and contraction, respectively (37), findings very similar to those of Spencer and Smith (82, 83), who used an in vitro preparation of the guinea pig colon to study peristaltic reflex. Our observation that axial stretch-induced LES relaxation has been confirmed in three animal species: opossum (26), rat (39), and mice (37). Similar to Paterson, we also observed that there is no synapse involved in the axial stretch-activated LES relaxation, suggesting that mechanical stretch activates motor neurons directly. In further studies, we developed a primary culture of esophageal myenteric neurons from the rat esophagus and using the intracellular calcium imaging technique observed that the inhibitory motor neurons are activated by mechanical stretch and release nitric oxide in response to mechanical stretch (Fig. 3). In other words, the motor neurons possess mechanosensitive properties (27). Our observations suggest a novel function of longitudinal muscle in peristalsis, i.e., that it may mediate descending relaxation of the peristaltic reflex. How? Contraction of longitudinal muscle in the contracted segment exerts an axial stretch in the receiving segments that causes mechanical distortion of myenteric neurons in the receiving segment. Furthermore, as discussed earlier, the longitudinal and circular muscle layers slide in relationship to each other during peristalsis and TLESR, which is likely to result in distortion of myenteric neurons located between the two muscle layers. It is proposed that the mechanical distortion of inhibitory motor neurons causes their activation and resultant nitric oxide release to induce descending relaxation of the peristaltic reflex. Why should axial and circumferential stretch activate inhibitory and excitatory motor neurons, respectively? Studies by Brookes, Costa, and colleagues (11, 99) reveal that the inhibitory and excitatory motor neurons project in the distal and proximal direction, respectively. Whether the polarity of stretch-activated reflexes is related to the polarity of anatomical projection of inhibitory and excitatory neurons requires investigation. If found to be...
true, such a mechanism would explain the tight coupling between ascending contractions and descending relaxation of the peristaltic reflex. It can also explain why contraction of longitudinal muscle in the distal esophagus induces relaxation of circular muscles of the esophagus and LES during TLESR. The LES relaxation during TLESR occurs faster and is usually more complete compared with a swallow-related LES relaxation (33). The above finding can be explained by the stronger longitudinal muscle contraction of the distal esophagus observed during a TLESR than a swallow. The latter will result in greater distortion of inhibitory motor neurons located between the two muscle layers and thus a stronger LES relaxation.

Relaxation of the crural diaphragm is an integral component of TLESR. Studies show that contraction of the longitudinal muscle is tightly linked to the crural diaphragm relaxation during distension of the esophagus by a balloon as well as during TLESR (51). It was thought that the inhibition of inspiratory neurons in the brain stem and cervical spinal cord that mediate crural diaphragm contraction is the mechanism of crural diaphragm relaxation during TLESR; however, that was not found to be the case (2, 3). We observed that the mechanism of crural diaphragm relaxation resides in the periphery (52) and is tightly linked to axial stretch exerted by the longitudinal muscle contraction on the crural diaphragm muscle (transmitted through the phrenoesophageal ligament) (51). Even though the crural diaphragm is innervated by the vagus nerve (98) it does not seem to contain any myenteric neurons. Therefore, how axial stretch induces crural diaphragm relaxation remains unclear.

Deglutitive Inhibition in the Esophagus

A swallow induces LES relaxation that begins quickly (within less than a second) and lasts for 6–8 s. Each swallow also induces inhibition in the esophagus that is best seen with repeated swallows at short intervals, a phenomenon referred to as deglutitive inhibition (89). During repeated swallows at short intervals, esophageal peristaltic contraction is only seen at the end of last swallow (Fig. 4). During the entire period of repeated swallowing the LES remains relaxed, and there are no contractions in the esophagus. Deglutitive inhibition is currently explained on the basis that each swallow elicits short-latency vagal inhibitory discharge to cause relaxation in the esophagus and LES. The long-latency vagal efferent fibers along with the withdrawal of nitric inhibition mediate peristaltic contraction (14). Pandolfino and colleagues (78) observed that the deglutitive inhibition involves circular as well as longitudinal muscles of the esophagus. Based on the observation that axial stretch on the esophagus activates inhibitory neurons of the myenteric plexus, there can be an alternative explanation for the deglutitive inhibition. With each swallow there is a superior and anterior elevation of the hyoid and cricoid bones because of the contraction of mylohyoid and other strap muscles of the chin (42, 77). Elevation of hyoid and cricoid bones lifts the upper esophageal sphincter and esophagus in the cranial direction, thus pulling the esophagus and LES in a cranial direction. A study by Muinuddin and Paterson (61) suggested that inhibitory motor neurons in the esophagus have long processes that project in the aboral direction toward the LES. It may be that the axial stretch on the esophagus, related to mylohyoid muscle contraction, activates inhibitory motor neurons of the esophagus and LES. Since mylohyoid muscle is the first recordable event of a swallow it will be expected to exert axial stretch on the esophageal wall with the onset of swallow to induce early LES relaxation and esophageal inhibition. With repeated swallows at short intervals, hyoid bone remains lifted, thus inducing sustained activation of inhibitory motor neurons of the esophagus and LES, similar to what happens during deglutitive inhibition. Withdrawal of nitric inhibition at the end of the last swallows results in an esophageal contraction following a sustained period of inhibition.
Mechanical Advantages to Bolus Propulsion by Simultaneous Contraction and Relaxation of the Two Muscle Layers During Peristalsis

If luminal obliteration caused by circular muscle contraction is the driving force for bolus propulsion in the esophagus, then what is the mechanical significance of longitudinal muscle contraction during peristalsis? One function described in previous paragraphs is stretch-activated descending relaxation. The other is providing unique mechanical advantages in the contracted segment. Longitudinal muscle contraction results in thickening of two muscle layers in the contracted segment (Fig. 2). By increasing muscle wall thickness in the contracted segment it reduces wall stress (48, 58, 64) and compliance of the esophageal wall that is needed for luminal occlusion required for bolus propulsion. Local longitudinal muscle contraction also brings the rings of circular muscle contraction together, resulting in greater intraluminal pressure at the site of greatest circular muscle density (10). On the other hand, in the receiving segment there is thinning of the esophageal wall that increases esophageal wall compliance, needed for bolus accommodation. What may happen if there were no longitudinal muscle contractions? The muscle thickness at the site of contraction would be low, resulting in high wall stress in the contracted segment that may interfere with luminal occlusion. Imagine a balloon with a focal area of a thinner wall; inflation of such a balloon will result in asymmetric bulging of the balloon during distension, more in the region of the thin wall compared with the thick wall that will appear as a “diverticulum” (bulging of the wall). Is diverticular formation in the GI tract related to a lack of longitudinal muscle? Interestingly, colon is the most frequent site of diverticular formation. Unlike other regions of the GI tract, where the longitudinal muscle layer surrounds the entire circumference of the organ, it is organized into three tenia in the colon, thus resulting in different wall stresses around the circumference of colon, which may be the reason for high incidence of diverticular formation in the colon. In the esophagus, esophageal diverticula occur in association with high-amplitude esophageal contraction. It may be that discoordination between the contractions of two muscle layers along with high-amplitude contraction plays a role in the formation of esophageal diverticula.

Mechanical Advantage of Longitudinal Muscle Contraction During Transient LES Relaxation

The motor pattern of TLESR is designed for retrograde transport of gastric contents into the esophagus as happens during gastroesophageal reflux, regurgitation, and vomiting. Longitudinal muscle contraction provides a distinct mechanical advantage for the retrograde transport: The bolus can move in the retrograde direction through a rigid tube more efficiently compared with a flaccid and large-diameter tube. The mechanical effects of longitudinal muscle contraction during TLESR are precisely the same; i.e., longitudinal muscle contraction decreases esophageal wall compliance and increases rigidity of the esophagus. Might it be that retrograde esophageal contraction observed with fluoroscopy during induced vomiting in the experimental setting is actually the longitudinal muscle contraction that starts in the distal esophagus and proceeds in the oral direction (60), similar to the pattern of contraction seen during TLESR (4). Using a small balloon to record pressure, Sifrim et al. (80) observed contraction of the distal esophagus during TLESR. In fact, longitudinal muscle contraction may increase balloon pressure through its mechanical effect of reducing wall compliance and decreasing luminal cross-sectional area.

Discoordination Between Circular and Longitudinal Muscle Contraction During Peristalsis in Esophageal Motor Disorders

Does discoordination between circular and longitudinal muscle layers occur during peristalsis, and does it lead to symptoms? The answer to the first question is indeed yes; however, whether it leads to symptoms can only be speculated at this time. Identification of discoordination between the two muscle layers requires simultaneous manometry and US imaging, which can be done relatively easily, but the challenge is US image analysis that is laborious. It is likely that the temporal disassociation between the two layers is more common than currently recognized and likely plays an important role in functional dysphagia and esophageal pain. We have described several patient groups that have discoordination between the two muscle layers, e.g., in patients with nutcracker esophagus the two layers do not contract in a perfectly synchronized fashion, the peak of contraction of the two muscle layers are separated by several seconds (40) (Fig. 5). The peak
of longitudinal muscle contraction mostly precedes circular muscle contraction. Further studies show that administration of cholinesterase inhibitor (edrophonium hydrochloride) induces discoordination between the two muscle layers in normal subjects (45) and atropine reverses naturally occurring discoordination between the two muscle layers seen in patients with nutcracker esophagus (46) (high-amplitude contraction). In patients with eosinophilic esophagitis, an allergic disorder characterized by infiltration of esophageal mucosa with eosinophils, there is selective reduction in the longitudinal muscle contraction amplitude (44); the circular muscle contraction is relatively well preserved in these patients (Fig. 6). In patients with achalasia esophagus, characterized by the loss of peristalsis and impaired LES relaxation, the longitudinal muscle contraction seems to be present even when there is marked reduction in circular muscle contraction and loss of peristalsis (35) (Fig. 7). Based on the manometry patterns, achalasia can be categorized into three different categories: type 1, type 2 and type 3; the difference is based on the swallow-induced esophageal pressure pattern (65). In all types of achalasia, swallows induce common cavity pressure waves instead of peristaltic contraction. The amplitude of pressure patterns is low (<30 mmHg) in type 1, >30 mmHg in type 2, and high in type 3 achalasia esophagus. It turns out that the longitudinal muscle contraction patterns are also quite different in three achalasia subtypes: type 1 patients have complete loss of longitudinal muscle contraction, and in type 2 it is present even though, unlike normal subjects, it does not show a peristaltic (sequential) pattern. In type 3 patients longitudinal muscle contraction is peristaltic, but there is temporal disassociation between the two muscle layers (34). Another distinct pattern of longitudinal muscle contraction is seen in association with esophageal pain (5) (Fig. 8) and heartburn (71), long-duration contractions not unlike what is seen during TLESR. The difference though is that the longitudinal muscle contraction associated with pain/heartburn is much longer in duration than with the TLESR (70/35 vs. 22 s).

How Does Discoordination Between Two Layers Cause Esophageal Symptoms?

The definitive evidence whether the discoordination between the two layers can lead to dysphagia and esophageal chest pain requires more work but one can speculate the following:

**Functional dysphagia.** Difficulty swallowing, i.e., dysphagia in the setting of a normal endoscopic examination, normal barium swallow study, and normal esophageal motility study is referred to as functional dysphagia (29). Discoordination between the two muscle layers is a possible mechanism of impaired bolus propulsion for two reasons because it will lead to 1) impaired inhibition of peristaltic reflex and 2) change in esophageal wall compliance in the receiving segment. All muscles when contracted are less compliant compared with when they are relaxed. Figure 9 shows the schematic of the effect of temporal discoordination on the luminal cross-sectional area of the esophagus in the receiving segment. Under normal physiological conditions, the two layers contract and relax together during peristalsis in the contracted and relaxed segments of the esophagus, respectively. A longitudinal muscle contraction traversing ahead of circular muscle contraction will make the receiving segment less compliant and therefore reduce the luminal cross-sectional area. A poorly distending receiving segment will result in the contracting segment pushing the bolus through a narrow path, resulting in resistance to

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![Fig. 6. Discoordination of 2 muscle layers in a patients with eosinophilic esophagitis: note the peak pressure and peak muscle thickness occur at the same time in the normal subjects (left). Right: selective dysfunction of longitudinal muscle with marked reduction in the amplitude of contraction of longitudinal muscle in a patient with eosinophilic esophagitis. Middle: extreme discoordination between the 2 muscle layers in eosinophilic esophagitis patient. E2–E22, E stands for esophagus and number represents centimeter above lower esophageal sphincter.](image-url)
Fig. 7. Longitudinal muscle contraction in a patient with achalasia esophagus: note simultaneous pressure waves (esophageal pressurization or common cavity pressure) in response to swallow. Also note the pattern of longitudinal muscle contraction in association with simultaneous pressure wave, as measured by changes in muscle thickness on ultrasound images. MCSA, muscle cross-sectional area.

Fig. 8. Sustained esophageal contraction in association with esophageal chest pain: note a sustained increase in the muscle thickness (longitudinal muscle contraction) prior to the pain event.
bolus flow, which is possibly a mechanism of dysphagia sensation.

Esophageal chest pain. Why should a long-duration longitudinal muscle contraction result in esophageal pain? Recent studies show that, similar to the myocardium, where blood flows into the myocardium during diastole and not systole, blood flow to the esophageal wall ceases during each esophageal contraction (36, 55) (Fig. 10). The most likely reason for the above is that blood vessels are mechanically constricted by the contracted muscles. Esophageal wall blood perfusion drops during each peristaltic contraction, when there is simultaneous contraction of the circular and the longitudinal muscle, as well as during TLESR, when there is selective contraction of the longitudinal muscle. It may be that a long-duration contraction of the longitudinal muscle results in a long-duration reduction in the esophageal wall blood perfusion that renders esophageal wall ischemic (38). The latter is a well-known mechanism of myocardial and intestinal pain, and it may indeed turn out to be the cause of esophageal pain.

Acid-Induced Longitudinal Muscle Contraction and Its Neural Pathway

Longitudinal muscle contraction of the esophagus leads to TLESR, which in turn is the major mechanism of GER or acid reflux. Studies also show that acid in the esophagus induces contraction of the longitudinal muscles of the esophagus. Animal (68, 92) as well as human studies (8) show that repeated exposure to acid sensitizes longitudinal muscle contraction and induces sustained esophageal shortening, which may be relevant to the pathogenesis of sliding hiatus hernia and heartburn. Repeated acid infusion in the human esophagus also induces stronger symptoms of heartburn that occur with a shorter latency compared with the first acid infusion. Interestingly, symptom sensitivity is associated with increased contractility of the longitudinal muscles of the esophagus (8). A series of studies by Paterson et al. (69) show that acid-induced contraction of the longitudinal muscle is mediated through the mast cells located in the mucosa of the esophagus. Mediators released by mast cells act at the capsaicin-sensitive nerve endings to activate a local reflex that mediates longitudinal...
muscle contraction through substance P and neurokinin. Whether acid-induced heartburn and pain are actually mediated through the longitudinal muscle contraction requires further investigation.

Unanswered Questions

The focus of work on the esophageal peristalsis has been mainly on the circular muscle layer for a long time, and a clinical esophageal motility study even in the year 2016 only assesses circular muscle function. Studies conducted during the last 20 years have shed some light on the role of longitudinal muscle but have raised many questions.

Does vagus nerve innervate the circular and longitudinal muscles differently? Does it only innervate the myenteric plexus and not the smooth muscle layers directly? Do the DMV neurons and vagus nerve have only excitatory efferents and the inhibitory effect is related to the longitudinal muscle contraction-related axial stretch and activation of inhibitory motor neurons of the myenteric plexus?

Is peristalsis in the distal esophagus-circular muscle really cholinergic, or is it because of the rebound excitation following nitrergic inhibition? Can nitrergic neurons be activated by contraction of the longitudinal muscle?

It is generally felt that in achalasia esophagus there is degeneration and loss of inhibitory and not the excitatory neurons of myenteric plexus (41). If longitudinal muscle contraction of the esophagus is still present in achalasia esophagus, does it mean that there is loss of excitatory nerves of the circular and not the longitudinal muscle layer? It may be that the circular muscle contraction in the distal esophagus under normal conditions is entirely rebound excitation following nitrergic inhibition and the degeneration of inhibitory neurons causes impairment of LES relaxation along with the loss of circular muscle contraction of the esophagus?

What is the mechanism of discoordination between the two muscle layers and how important is it in causing dysphagia and chest pain? Is this discoordination related to central or peripheral pathology?

The answer to the above questions will require detailed physiological experiments in animals and humans and may not be answered for a long time because these studies are difficult and not popular. The high-resolution manometry has reinvigorated interest in clinical esophageal manometry; however, in the current format it does not record half of the muscle mass of the esophagus (i.e., longitudinal muscles), and I suspect that the secret to advancing our understanding of esophageal symptoms and pathophysiology lies in the longitudinal muscle function and dysfunction. I am optimistic that this article will inspire interest in esophageal physiology, especially among young investigators.

GRANTS

This work was supported by an NIH Grant DK060733 and VA MERIT Grant.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

R.K.M. conception and design of research; performed experiments; analyzed data; interpreted results of experiments; prepared figures; drafted manuscript; edited and revised manuscript; approved final version of manuscript.

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49. G442 REGULATION OF ESOPHAGEAL PERISTALSIS


