Physiology and Motility of the Normal and Replaced Esophagus

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The Structure of the Esophagus

Gross Anatomy

The esophagus is a hollow, muscular tube that allows for passage of food from the pharynx to the stomach. It sits posterior to and runs alongside of its cartilaginous counterpart, the trachea, until the carina at level T4-T5. The esophagus begins with the UES and ends with the LES. There are three functional regions involved with no specific landmarks including (1) UES, (2) esophageal body, and (3) LES.

The UES is a physiologic intraluminal high-pressure zone between the pharynx and the esophageal body, which is a musculocartilaginous structure that offers both elastic and tonic benefits. The anterior aspect of the UES is formed by the cricoid cartilage as well as the arytenoid and interarytenoid muscles, both of which are controlled by the recurrent laryngeal nerve [1]. The posterior side of the UES is formed by the thyroglossus muscle, which makes up the upper two third, as well as the cricopharyngeus muscle, which accounts for the lower third. The vagus nerve provides motor innervation to these two muscles, whereas sensory fibers come from

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A. Pimpalwar (ed.), *Esophageal Preservation and Replacement in Children*,
https://doi.org/10.1007/978-3-030-77098-3_2

the vagus, glossopharyngeal, and maxillary division of the trigeminal nerve [2]. It is 0.5–1 cm at birth and increases to 3 cm in adulthood [3].

The LES is another high-pressure zone with specialized thickened circular smooth muscle. It is innervated by vagus (parasympathetic or inhibitory) and spinal (sympathetic or excitatory) nerves and neurons of the myenteric plexus (excitatory and inhibitory) [4]. Like the UES, the LES is about 1 cm at birth and increases to 2–4 cm during adulthood [3]. The LES, in coordination with the crural diaphragm, which is made up of skeletal muscle and innervated by phrenic nerve, forms the esophagogastric junction (EGJ). These two structures are anatomically superimposed and are anchored to each other by the phrenoesophageal ligament.

The esophageal body has four separate cellular layers. The muscularis propria layer consist of inner circular and outer longitudinal muscle layer. The predominant type of muscle fiber depends on the location, with striated muscle proximally and smooth muscle distally. The middle of the esophagus has both striated and smooth muscle. Neural control of the skeletal and smooth muscle of the esophagus occurs through the nucleus ambiguous (NA) and dorsomotor nucleus of the vagus nerve, respectively. Myenteric plexus (Auerbach's plexus), located in the muscularis propria, provides local control with both excitatory (Ach and substance P) and inhibitory neurons (NO and vasoactive intestinal polypeptide) [5]. It is 8–10 cm at birth and increases to 18–22 cm in adulthood [3].

The Enteric Nervous System (ENS)

The nervous system of the gastrointestinal tract is known as the enteric nervous system. Meissner's plexus, also known as the submucosal plexus, lies within the submucosa and helps direct gastrointestinal secretion, absorption, and local blood flow. Auerbach's plexus, also known as the myenteric plexus, lies between the circular and longitudinal muscle layers and plays a role in gastrointestinal motility [6]. Figure 2.1 demonstrates the interconnections between Meissner's plexus, Auerbach's plexus, and the autonomic nervous system. Sensory fibers from the gastrointestinal epithelium send afferent fibers to the enteric nervous system, the prevertebral ganglia of the sympathetic nervous system, spinal cord, and the vagus nerve leading to the brain stem.

The Physiology of the Esophagus

The wall of the gastrointestinal tract is circumferentially lined by smooth muscle, and the contractions of these the smooth muscles help propel the bolus of food along allowing proper digestion and absorption to occur. The electrical activity of these muscles dictates the location, time, and intensity of the contraction. The GI tract is excited by nearly continuous slow intrinsic electrical activity and two separate electrical waves known as "slow waves" and "spikes," which both play a major role in gastrointestinal motility. The resting membrane potential of the smooth

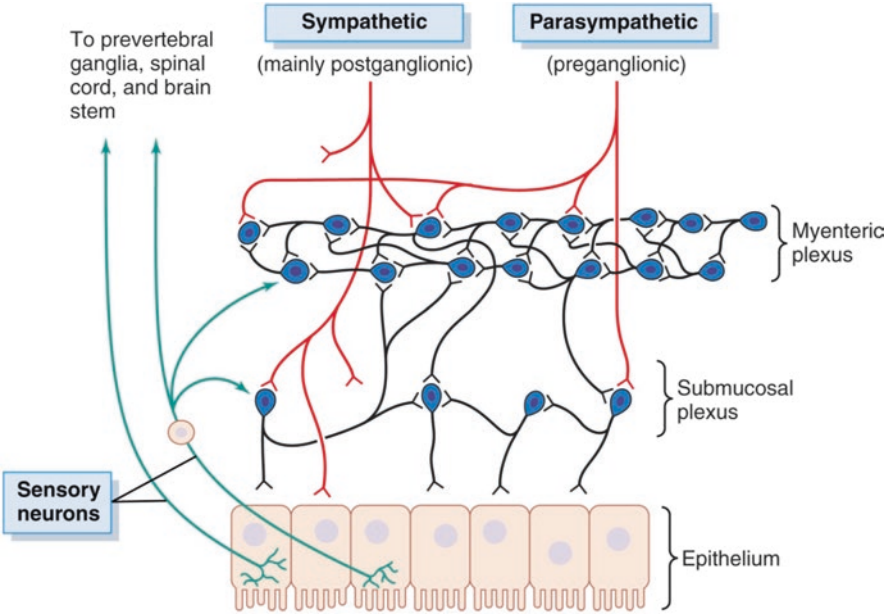

Fig. 2.1 Neural control of the gastrointestinal wall. The submucosal and myenteric plexuses communicate with each other. Both plexuses receive innervation from the sympathetic and parasympathetic nervous system. Sensory neurons receive information from the luminal epithelium and send that information to the enteric nervous system plexuses, the prevertebral ganglia, spinal cord, and brain stem [7]

muscle plays a large role in determining if the additional electrical activity is enough to depolarize the muscle and thus allow for a contraction. The resting membrane potential of the GI tract's smooth muscle generally stays between −50 and −60 millivolts [7].

The resting membrane potential can become less negative, referred to as "depolarized," which means the muscle fibers are more excitable. As seen in Fig. 2.2, physical stretching of the muscle, stimulation of muscle fibers from parasympathetic nerves releasing acetylcholine, and specific hormones can all depolarize the membrane. On the contrary, the muscle fibers can become less excitable if the membrane potential becomes more negative, known as "hyperpolarized." Catecholamines such as norepinephrine and epinephrine as well as stimulation from the sympathetic nervous system can both hyperpolarize the membrane.

Slow waves primarily direct the rhythmic nature of the smooth muscle contractions (Fig. 2.2). These slow waves are not action potentials, but are instead slow, rolling changes in resting membrane potential. The intensity of these slow waves ranges from 5 to 15 millivolts and the frequency ranges from 3 to 12 per minute, depending on the location in the GI tract. The specific etiology of slow waves is not completely understood, but it is believed to be a result of interactions between the smooth muscle cells and the interstitial cells of Cajal, which behave similarly to

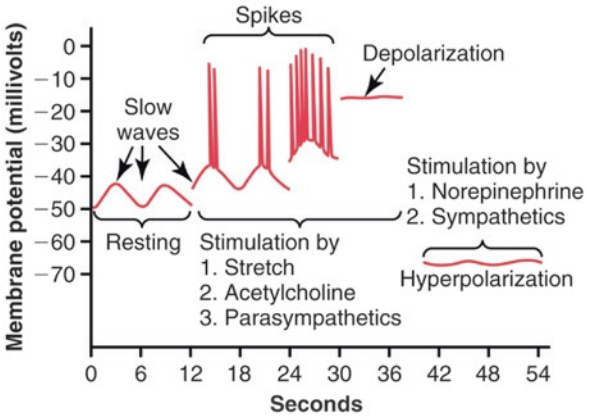

Fig. 2.2 Electrical activity of the esophagus [7]

electrical pacemakers for smooth muscle cells. The interstitial cells of Cajal possess ion channels that intermittently open, resulting in inward current flow that is believed to cause cyclic changes in membrane potential, also known as slow wave activity [7]. In the esophagus, these slow waves are incapable of producing muscle contractions by themselves.

The spikes represent action potentials and occur automatically when the resting membrane potential of the GI tract reaches a specific voltage. As you can see from Fig. 2.2, when the slow wave's peak reaches above −40 millivolts, spike potentials occur. The higher the peak of the slow wave, the more frequent the spike potentials occur. Each gastrointestinal spike potential lasts up to 10–20 milliseconds [7]. Unlike nerve fibers whose action potentials are elicited almost entirely by rapid shifts of sodium ions though channels, the smooth muscle of the GI tract responds to a slightly different stimulus. The GI tract channels responsible for action potentials primarily allow for transfer of calcium ions and, to a much lesser extent, sodium ions, therefore being known as calcium-sodium channels. These GI tract channels open and close much slower than the channels of nerve fibers, thus accounting for the long duration of the action potentials [8].

The Esophageal Function and Motility

The primary function of the esophagus is to act as a conduit between the pharynx and the stomach. The coordination of the GI motility is regulated by multiple control systems including CNS, ANS, ENS, ICC, and myogenic mechanisms [9–11].

At baseline, the UES functions to provide the most proximal physical barrier of the GI tract against pharyngeal and laryngeal reflux during esophageal peristalsis. It also prevents the entry of air into the digestive tract during negative intrathoracic pressure events. The LES has a baseline myogenic tone that is modulated by the myenteric plexus and neurohumoral factors which prevent retrograde movements of gastric content into the esophagus. Both UES and LES relax during swallowing, belching, and vomiting.

When the relaxation of LES is unrelated to either swallowing or secondary peristalsis, it is called transient LES relaxation (TLESR). TLESR is a reflex triggered by gastric distension that enables venting of gas from the stomach to prevent excess gas accumulation. It is accompanied by longitudinal muscle contraction of the distal esophagus and inhibition of the crural diaphragm. It is believed to be the predominant mechanism for gastroesophageal reflux disease [12–14].

Peristalsis is a sequence of coordinating relaxation and contractions. There are two types of peristalsis:

1. Primary (bolus-induced) peristalsis: This is triggered by the swallowing center. Starting from the pharyngeal phase, the UES relaxes in conjunction with a contraction of the hyoid muscle, which then allows the passage of the food bolus into the esophagus. Simultaneously, inhibition of the esophagus smooth muscle called "deglutitive inhibition" is initiated first, followed by the peristaltic contraction. Repetitive swallowing at short intervals would induce sustained inhibition and one peristaltic contraction at the end of the last swallow. The peristaltic wave travels at a speed of 2 cm/s. During peristalsis, the longitudinal muscle is responsible for shortening the esophagus, while the circular muscle forms lumen-occluding contractions. An active relaxation of LES starts 2 s after the initiation of the proximal esophagus peristaltic contraction and lasts 5–10 s until the peristaltic wave arrives. During the relaxation, the LES pressure drops to the level of gastric pressure. An axial shortening of the esophagus during peristalsis and lifting of the LES also contribute to the relaxation. Then the LES is passively opened by the bolus. Last, the relaxation is followed by an after-contraction of the upper part of the LES [15, 16].
2. Secondary (distention-induced) peristalsis: This is induced by esophageal distension from the retained bolus, refluxed material, or swallowed air. It also results in an increased pressure in UES called esophago-UES contractile response (EUCR). The primary role is to clear the esophagus of retained food or any gastroesophageal reflux.

Tertiary contractions, which are more often observed in elderly people, are non-peristaltic, simultaneous, isolated, and dysfunctional contractions that have no known physiologic role.

The peristalsis of the esophageal body is further divided into three pressure segments separated by two lower pressure troughs on the topography (Fig. 2.3), one in the striated muscle region and two in the smooth muscle region [17].

While various modalities are available for evaluating esophageal dysfunction such as barium esophagography, upper endoscopy, or esophageal intraluminal impedance, esophageal manometry is the test of choice to assess esophageal motility and is considered the gold standard test. Recent advancements in the field of motility have led to a better design of manometry catheters called HRIM (high-resolution impedance manometry) which combines conventional high-resolution manometry and impedance sensors integrated in the same catheter to better delineate details on bolus movements and chemical clearance. With the aid of advanced techniques, Chicago Classification was developed to characterize motor

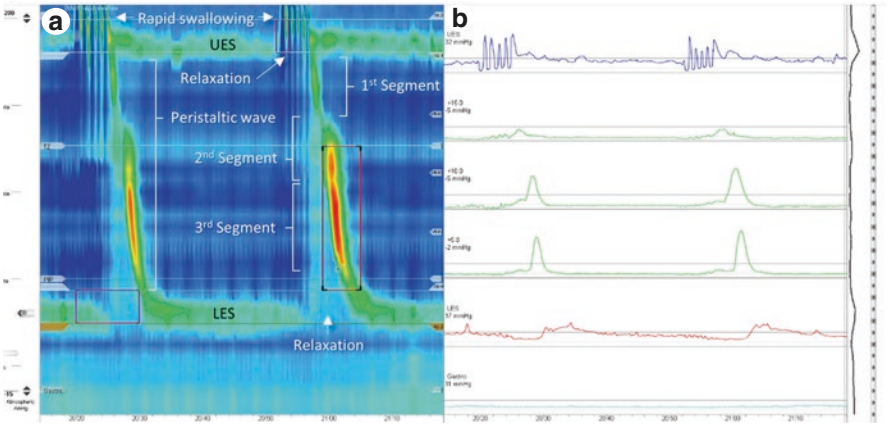

Fig. 2.3 Normal esophageal manometry. (**a**) Colored graphic (**b**) Conventional tracing. During multiple rapid swallowing, deglutitive inhibition of the esophagus with UES relaxation can be observed, followed by one peristaltic wave after the last swallow. Three high-pressure segments can be identified. LES relaxation starts 2 s after swallowing followed by an after contraction when the peristalsis arrives.

abnormalities of the esophagus [18]. Although it has been applied for the pediatric population and studies have shown the interpretation of HRM is reproducible, the diagnostic criteria should be used cautiously to avoid incorrect diagnoses [19]. Normal manometry pattern is showed in Fig. 2.3.

Common Surgical Esophageal Motility Disorders

Common indications in children who may require esophageal replacement include long-gap esophageal atresia, severe peptic/caustic strictures, anastomotic strictures, and some rare esophageal disorders such as achalasia [20].

Many of these postsurgical disorders have very nonspecific motility findings. In our anecdotal experience, we have seen a combination of normal, partially normal, and abnormal swallows. The Chicago Classification has specified a term "ineffective esophageal motility (IEM)" to encompass these abnormalities under a group of minor disorders of peristalsis where LES pressures are normal but esophageal contraction vigor is abnormal in over half of the wet swallows [21].

Common dysmotility findings in selected surgical conditions pertaining to this chapter are discussed as below.

Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia (EA) is the most common esophageal malformation with an incidence of 1 in 3500 live births [22]. As the mortality has improved, the focus of

this issue has evolved to morbidities and quality of life [23]. The esophageal dysmotility often leads to gastroesophageal reflux (GER), dysphagia, aspiration, and feeding disorders. This lead to a publication of an international guideline for the evaluation and management of gastrointestinal and nutritional complications in children with EA [24].

The etiologies of the esophageal dysmotility remain unknown. Several studies have suggested a congenital abnormality in the development of innervation and musculature [25–27], which was supported by the histologic findings such as Auerbach plexus hypoplasia, inadequate and abnormal neuronal innervation, or reduced density and immaturity of interstitial cells of Cajal [28–30]. Secondary postsurgical damage and complications (including leaks, anastomotic stenosis, and subsequent esophageal dilations) may contribute to local trauma and inflammation resulting in neuronal and muscular damage, which ultimately leads to dysmotility [22, 24, 31].

The esophageal motility has been characterized by various modalities in both children and adults with details as below:

1. Most of the studies reported patients had normal UES relaxation when evaluated by manometry except for two newborns with incomplete relaxation [26, 32].
2. Almost all patients with EA had abnormal esophageal peristalsis. A recent retrospective review conducted by *Lemoine* et al., focusing on 40 postsurgical pediatric patients who had either type A or type C EA, has identified three peristaltic patterns: (1) complete aperistalsis (no peristaltic wave identified on all 10 swallows), (2) pressurization (a simultaneous contraction of the entire body length following deglutition associated with EGJ relaxation), and (3) distal contraction (with middle or distal thirds of the esophagus as the only contracting segments) (Fig. 2.4) [32].
3. Impaired LES function with low resting pressure was found in several studies, while others are normal [26, 32–37].

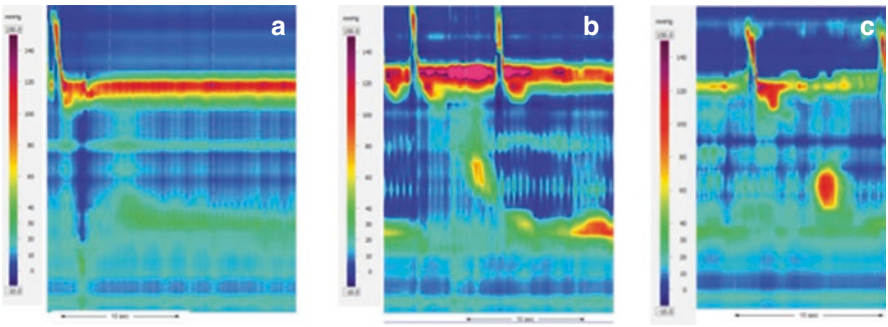

Fig. 2.4 Abnormal peristalsis pattern seen on patient with EA. (**a**) Aperistalsis pattern. (**b**, **c**) Various types of distal contraction pattern [42]

Long-gap EA, with no universal definition, remains a challenge for pre- and postsurgical care. Statistically, almost all of them developed postsurgical complications (such as anastomotic stricture or leaks) [38, 39]. Regardless of possible congenital dysmotility, the above post a higher risk for secondary injury from our perspective. Motility analysis for this specific group is limited. The study from Lemoine et al. reports that patients with type A EA, long-gap defect, and postoperative anastomotic leak seem to have a worse motor function (predominantly have aperistalsis) [32].

Currently, the motility patterns are not predictive of symptoms or outcomes, and there is no correlation between esophageal dysmotility and dysphagia [32, 37, 40]. This part may be due to the fact that children with EA have never experienced "normal" peristalsis, hence unable to recognize "abnormal" symptoms. GER-related signs mainly occurred in aperistalsis group compared to the distal-contraction group, which has a better bolus clearance and less duration of acid exposure [32, 37, 41].

The esophageal dysmotility will cause inadequate swallowing coordination and abnormal esophageal clearance. This will impair normal bolus transit causing dysphagia, increase the duration of mucosal exposure to gastric acid that leads to GERD, and contribute to food or secretions retention that puts the patient at a higher risk for aspiration and feeding disorders.

Caustic Ingestion

Caustic-induced injuries in children remain a serious public health concern worldwide, which can ultimately lead to life-threatening acute complications causing respiratory compromise, gastrointestinal perforation, and bleeding. Dysphagia with or without stricture can develop anywhere from 2 to 6 weeks after the ingestion. Some strictures progress to carcinoma after decades [43].

Motor dysfunction has been reported, possibly from penetrating muscular injury, fibrosis, or myenteric plexus insult. The motility of the esophagus has been studied with conventional manometry for children who had injury greater than 2B or 3A noted endoscopically according to Zargar's classification. The function of UES and LES is typically normal. Dysmotility can be found as early as day 5 after ingestion. Patients with alkali ingestions are generally associated with abnormalities such as aperistalsis. They can also experience later stricture development and persistent dysmotility even after full resolution of their initial injuries. Patients with persevered peristalsis but decreased low-velocity peristaltic waves in acute phase often normalize and may develop only partial or nonobstructive stricture. Hence, esophageal manometry may be useful as a prognostic indicator [44].

Motor Function of the Replaced Esophagus

Various replacement strategies have been discussed, which commonly include gastric transposition (also referred to as gastric pull-up), gastric tube interposition,

colon interposition, and Ileal/jejunal interposition [20]. Motility studies are available but limited as most studies are completed with esophagram or conventional manometry. Current findings for each method are briefly discussed below. However, the motility findings are not always correlated to the clinical outcome. The pros and cons of each procedure are vast and out of the scope of this chapter.

Gastric Interposition

The motor behavior of the gastric substitute has been evolving. A denervated stomach, once considered to have no contractility, recently was hypothesized that the motor function may recover over time and even generate complete migrating motor complexes [45]. Electrical impedance tomography and surface electrography also reported that instead of behaving like an inert conduit, the transposed stomach retains its reservoir function with an extremely irregular emptying pattern [46].

Several motility studies utilizing manometry have been done. Gupta et al. conducted a prospective study using a conventional manometry on 18 patients who underwent gastric transposition (pull-up). Postprandial mass contractions were seen in 12 of the 18 patients [47]. Similarly, a retrospective/prospective review study was performed on 16 patients who received reversed (antiperistaltic) gastric tube replacement, and 11 of them demonstrated postprandial mass contraction on the conventional manometry [48]. Recently, Kekre et al. lead an observational study using high-resolution manometry on ten patients (four gastric pull-ups, four isoperistaltic, and two reverse gastric tubes), and all of them showed postprandial simultaneous mass contraction [49]. No propagating peristalsis was found in any of above studies.

Colonic Interposition

Lately, studies have characterized two colonic activities on the general population by high-resolution manometry including (1) high-amplitude propagated contraction (HAPC) and (2) low-amplitude propagated contraction (LAPC) [50]. HAPC is a meaningful peristaltic activity that can transfer colonic contents over a long distance. The propagation velocity averages 1–2 cm/second in the right colon but increases as the waves migrate caudally. It could occur spontaneously, in response to pharmacological agents or colonic distention. It also increases upon awakening, is much more common during the day, and increases after meals [51]. During fasting, the colon demonstrates low amplitude, mostly non-propulsive, segmental contractions with rare peristaltic movements [50].

The motility of the interposed colon has been considerably controversial. Some considered the graft has no contractility [52–56], while others demonstrated either simultaneous or peristaltic contraction with various simulations [57–60], such as (1) intraluminal acid, (2) distension secondary to the intraluminal fluid stimulus or wet swallows, and (3) bisacodyl. The conflicting results are likely multifactorial, including different catheter usage, postsurgical complications, inconsistent poststimulation observation time, or interobserver variabilities.

The control of the colon is complicated, involving ENS, CNS, and myogenic response. In the authors' opinion, the transposed colon should at least persevere its

intrinsic motor activity. The pressurization, lower-amplitude contractions, or contractions noted far from the stimulus may represent LAPCs. Lack of HAPCs may be due to insufficient stimulation or a short observation period. Regardless, most studies reported that patients were not able to swallow "normally" when laying down. The above indirectly suggests that gravity still plays a major role. The peristaltic contraction, if not occurring in a timely manner, may have limited contribution. Whether bisacodyl or other stimulants can assist the esophagus clearance remains unclear.

Jejunal and Ileal Interposition

Finally, the jejunal interposition (for both free and pedicle grafts) has persevered segmental peristaltic activity, which is one of its major advantages [61–63]. Retainment of peristaltic activity has been demonstrated after ileocecal and ileal interposition [64].

The application of above findings to the clinical setting remains unclear and debatable. Further studies such as HRIM on different interpositions may help clarify if the emptying is facilitated by the contraction or solely by gravity.

Summary

The esophagus, besides serving as a conduit, has a unique motor pattern. The need for surgery of the esophagus secondary to a variety of indications is not uncommon in children. The surgical interventions may have serious implications on the subsequent motility that adversely affect long-term outcomes and quality of life. Motility studies are available with major limitations. This includes limited number of patients to date, technical differences in measurements performed, use of different manufacturers and equipment, and lack of correlation to symptoms with dysmotility finings. Further studies are needed to fill this gap. With advanced motility equipment, diagnostic techniques, and a better understanding of normal findings, we believe that a multicentered prospective outcome study including both motility and histologic outcomes would provide more insight to fulfill these knowledge gaps.

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