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Esophageal Function Testing: Beyond Manometry and Impedance

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Introduction

Endoscopy, Barium swallow, high resolution manometry (HRM), pH measurement (either catheter based or using Bravo system) and impedance monitoring of the esophagus are major esophageal function testing techniques that are available in most academic centers and centers of excellence for esophageal function testing. These recording techniques provide key information on the sensory and motor function of the esophagus that allows one to treat patients based on the physiologic understanding of the patient's symptoms. Another esophageal function testing technique that, even though has not gained wide popularity and acceptance, is ultrasound (US) imaging of the esophagus using either catheter based intravascular US imaging probe or US endoscope. The latter is suited for anatomical/ morphological information of the esophageal muscle and identification of lesions that affect esophageal function by compression of the esophagus. On the other hand, catheter based US imaging provides information on anatomy/morphology as well as functional aspects of esophageal muscle function. In order for US imaging, especially dynamic US imaging, to gain popularity it will have to be user friendly and less expensive. To date, dynamic US imaging has only been used in research laboratories. There is no question though that the static and dynamic US imaging, using either US endoscopes or catheter based US probes provides key information of esophageal functions that is unparallel to any other technique.

Laser Doppler blood perfusion measurement of the esophageal wall is another important modality, especially if future testing confirms that “non-cardiac” chest pain and proton pump inhibition (PPI) resistant heartburn are related to a low blood perfusion or relative ischemia of the esophageal wall. The goal of this writing is to provide the principles underlying these techniques and to update the status of information that these techniques have yielded.

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Ultrasound Imaging of Esophagus

The esophagus is no exception - like the rest of the gastrointestinal tract, its outer muscular coat or muscularis propria is organized into an outer longitudinal and an inner circular muscle layer. Recent studies prove that the longitudinal muscles of the esophagus play an important role in the physiology and pathophysiology of the sensory and motor function of the esophagus and one can study longitudinal muscle function using dynamic US imaging. The esophageal longitudinal muscle starts proximally as 3 bundles: 1) a main longitudinal muscle bundle that originates from the posterior surface of the cricoid cartilage, 2) an accessory muscle bundle from the postero-lateral surface of cricoid cartilage and 3) an accessory muscle bundle from the contralateral surface of the cricopharyngeus muscle. Muscle bundles from the two sides quickly fan out to surround the entire circumference of the esophagus, leaving only a triangular space, the area of Laimer that is not surrounded by the longitudinal muscle at the most cranial end of the esophagus. At the caudal end, longitudinal muscle fibers continue into the stomach and some may be inserted in the circular muscle bundles of the lower esophageal sphincter (LES). Contraction of the longitudinal muscles causes axial shortening of esophagus. Circular muscles of the esophagus do not travel in a perfectly circular fashion along the length of the esophagus, instead they are oriented in the helical fashion, especially in the distal part of the esophagus[1-3]. The angle of these helices increases as one goes towards the distal direction. Because of the helical morphology of circular muscle[3] part of the axial esophageal shortening during peristalsis is the result of circular muscle contraction. Unlike circular muscle contraction and relaxations, which can be easily recorded by intraluminal pressure probes/manometry, it is difficult to measure contraction and relaxation of the longitudinal muscle. Dynamic US imaging provides information on the local longitudinal muscle contraction and axial shortening of the esophagus[4].

In the animal experiments, longitudinal muscle contraction can be recorded by surgically implanted strain gauges in the long axis of the esophagus[5]. Longitudinal muscle contraction can also be recorded by radio-opaque markers implanted in the long axis of esophagus (in humans[6, 7] and animals[8]) in combination with X ray fluoroscopy, which records motion of the radio-opaque markers as a proxy of longitudinal muscle contraction. Clearly, these studies have provided important information, however they are of limited use for the human experimentation for several obvious reasons; 1) strain gauze implantation is not practical and 2) radiation exposure for prolonged recordings limits its use. More recently, a sensor that utilizes magnet and electromagnetic field (Hall's effect) has been used to study axial motions of the squamo-columnar junction/esophagogastric junction, as an indirect marker of longitudinal muscle contraction of the esophagus[9]. One of the limitations of all of the above methods is that they do not record longitudinal muscle contraction at one site (local contraction) in the esophagus, like manometry does for circular muscle.

Ultrasound (US) imaging, performed using thin (1-2mm diameter) intravascular catheters can record longitudinal muscle contraction at a focal point in the esophagus over extended time periods[10, 11]. US imaging also provides other important information; i.e., esophageal muscle hypertrophy and luminal distension during peristalsis and gastroesophageal reflux, other key esophageal functions that can't be measured by the other modalities. For recording

longitudinal muscle contraction, US imaging relies on the “law of mass conservation”, i.e. when esophagus shortens in length (axial shortening) it causes a proportional increase in the esophageal muscle cross sectional area and muscle thickness, which can be visualized and quantitated by US image analysis. The strength of these recordings technique is that they can be done in humans for extended time periods. The major limitations of US imaging is that the equipment is expensive and data analysis are time consuming. The methodology to record US imaging and data analysis have been described in detail in an earlier publications[11].

Static US Imaging

Muscle Hypertrophy in Esophageal Motor Disorders and its Significance—US imaging, endoscope based or catheter based, provides important information of the esophageal muscle thickness in the resting or baseline condition. In normal subjects, both circular and longitudinal muscles are relatively thin (0.75mm each)[10, 12]. Muscle thickness is greater in the distal esophagus and it decreases in the proximal direction[13]. Atropine decreases baseline muscle thickness[14] which suggests presence of baseline tone in the circular and longitudinal muscles of the esophagus and confirm early studies that utilized esophageal barostat to measure esophageal tone. Using echo endoscopes, several investigators reported case reports of marked muscle hypertrophy in patients with non-specific motor disorders and nutcracker esophagus. Systematic assessment of patients with various types of esophageal motor disorders revealed interesting differences in muscle thickness between normal subjects and patients, as well as among patients with various types of motility disorders. Patients with primary or idiopathic motor disorders in general have increase in the thickness of both circular and longitudinal muscle layers; even though the circular muscle thickness is greater than the longitudinal muscle[11]. The increase in muscle thickness is seen primarily in the distal esophagus and it decreases gradually from distal to the proximal end. Another important finding is that the degree of muscle thickness increase or in other words muscle hypertrophy differs in different motor disorders; generally it follows (not always) the following pattern, muscle thickness in achalasia esophagus > diffuse esophageal spasm > nutcracker esophagus > non-specific motor disorders (Figure 1). In the case of a distended esophagus, like in achalasia esophagus, muscle thickness decreases as esophagus becomes dilated; however the cross sectional area of muscle which represents the muscle mass is significantly larger in achalasia esophagus than other motor disorders. In a study of 98 consecutive patients referred to the motility lab for various symptoms, simultaneous manometry and US imaging was performed to determine the relationship between various motility disorders and muscle hypertrophy[15]. Nearly all patients with primary motility disorders, based on manometry, were found to have an increased thickness of muscularis propria. Interestingly, 25% of patients with normal esophageal manometry also had thicker esophageal muscle than normal subject, albeit of smaller magnitude than seen in patients with typical motility disorders. Keep in mind that even though manometry may have been normal in these patient patients they had esophageal symptoms of dysphagia, chest pain and heartburn. One interpretation of these findings is that normal manometry does not guarantee normal esophageal function and US imaging could be more sensitive technique than manometry to detect esophageal motor dysfunction.

What does an increase in muscle thickness signifies and what is its relevance? Major cause of increase in muscle thickness/muscle hypertrophy in all muscles is over activity or contraction of the muscle against resistance (afterload). For examples, systemic hypertension and aortic stenosis cause hypertrophy of the left ventricle. Animal studies show that outflow obstruction to the esophagus induces hypertrophy/increase in esophageal muscle thickness and alteration in esophageal motor function that is not dissimilar to the one seen in association with primary/idiopathic spastic motor disorders. It may be that the fundamental abnormality in primary/idiopathic motor disorders lies in the lower esophageal sphincter (LES) function, which either does not either relax or opens up normally and changes in the esophageal motor function are secondary to the LES dysfunction. The degree of LES dysfunction may determine the severity of esophageal motor dysfunction and muscle hypertrophy. For example the LES dysfunction is most severe in achalasia esophagus and so is the esophageal body dysfunction and so on. Another pathologic process that causes muscle hypertrophy is inflammation, e.g., patients with crohn's disease have hypertrophy of muscles of small intestine. Transforming growth factor-β1 (TGF-β1) and related growth factors are key players in the inflammation induced muscle hypertrophy[16]. It is unlikely though that inflammation plays important role in esophageal muscle hypertrophy because types of inflammation that afflicts the esophagus, i.e., reflux induced esophagitis and eosinophilic esophagits are not associated with an increase in the muscle thickness. To the contrary, muscle thickness is reduced in patients with reflux esophagitis and it is not altered significantly in eosinophilic esophagitis[17]. Systemic sclerosis or scleroderma esophagus is associated with loss of muscle mass and decease in the esophageal muscle thickness[18].

Dynamic US Imaging

Patterns of longitudinal muscle contraction in health and their significance to normal esophageal function—Dynamic US imaging of the esophagus is performed using catheter based, intravascular US probes that are 1-2mm in diameter. They were designed initially to study coronary arteries. These catheters can be easily placed via nose into the esophagus. Using these probes, US imaging of the esophagus can be performed continuously for hours; we have recorded US images for up to 24 hours[19]. Images are usually recorded on a videotape, digitized and then analyzed, even though one can record images in the digital format directly without using videotape. US images recorded by current systems are cross sectional/tomographic/B-mode images that can be converted into M-mode US images to display changes in muscle thickness over time[20]. These M-mode US images then can be superimposed on the manometry or other types of recordings to determine the relationship between changes in pressure or other parameters of interest and changes in the muscle thickness. Manometry studies show that during esophageal peristalsis, certain length or a segment of the esophagus, rather than a point location, contracts in a peristaltic or sequential fashion. This segment of circular muscle contraction progresses sequentially from oral to aboral direction. The length of the contracted segment increases as it moves in the caudal direction[21]. Pressure in the contracted segment is distributed in the form of a bell shaped curve with peak pressure in its middle. US images show that the longitudinal muscle contracts in harmony with the circular muscle; the two are precisely coordinated in location and timing[20]. The peak of contraction in the circular and longitudinal layer occurs within one second of each other (Figure 2 & 3). Distension of a balloon in the esophagus also

induces contraction and relaxation of the two muscle layers, cranial and caudal to the site of distension respectively[22]. However, that does not mean that the two layers can't contract independent of each other, e.g., during transient LES relaxation, a key motor event that allows retrograde transport of gastric contents into the esophagus (vomiting, belching and reflux) pattern of contraction in the two muscle layers is different from peristalsis[23, 24]. Just before the onset of TLESR, longitudinal muscle contracts independent of circular muscle, starting at the caudal end of the esophagus and it marches in the oral direction. Longitudinal muscle contraction during TLESR is significantly greater in amplitude and longer in duration than during peristalsis. Another distinct pattern of longitudinal muscle contraction is seen in association with sub-threshold stimulation of pharynx during which there is also relaxation of the LES[25]. Longitudinal muscle contracts only at the cranial end of the esophagus, i.e. just caudal to the upper esophageal sphincter with subthreshold pharyngeal stimulus. These findings prove that the two layers can contract together during peristalsis and independent of each other during transient LES relaxation. Recent studies also prove that the two muscle layers are not anchored/cemented to each other; rather they slide against each other during peristalsis and transient LES relaxation[26]. Interestingly, they slide in the opposite direction during these two motor events, i.e., there is greater axial shortening of the circular muscle than the longitudinal muscle during peristalsis and reverse is the case during transient LES relaxation.

Occlusion of the lumen caused by circular muscle contraction and its sequential aboral or oral progression (peristalsis or reverse peristalsis) causes bolus propulsion and retropulsion, respectively. Then what does longitudinal muscle layer, which comprise 50% of the muscle mass of the muscularis propria do? Longitudinal muscle contraction and relaxation results in thickening and thinning of the two muscle layers respectively[11, 22], which provide distinct mechanical advantages. Increase in muscle thickness reduces esophageal wall stress[27] and compliance in the contracted segment, both of which are important for esophageal lumen occlusion, which is an essential element for the bolus propulsion. On the other hand, decrease in esophageal wall thickness in the relaxed segment increases esophageal wall compliance that is also an essential requirement for the bolus propulsion. Another important function of longitudinal muscle contraction is that it causes lengthening of the esophageal segment distal to the site of contraction[6] and axial pull on the LES in the oral direction. Recent studies prove that a pull of the LES in the oral direction induces neurally-mediated relaxation of the LES[28, 29]. Along the same lines, it is likely that elongation of esophageal segment distal to contraction site induces its active relaxation (descending relaxation)[30]. Relaxation of esophagus and LES distal to the site of contraction allows contracted segment to propel bolus with minimal resistance (Figure 3). Relaxation of the esophagus distal to the site of the contraction and resulting increase in esophageal wall compliance allow distension of the esophagus. The degree of distension of the esophagus during peristalsis is an indirect marker of active relaxation of esophagus. US imaging allows quantitation of luminal distension. Studies show that similar to contraction, active relaxation of esophagus occurs in a peristaltic fashion thus allowing bolus to move efficiently during peristalsis.

Patterns of longitudinal muscle contraction in the diseased states

As pointed earlier, during normal peristalsis longitudinal and circular muscles contract in a synchronous fashion, with peak contraction of the two muscle layers occurring within one second of each other. An increase in cholinergic activity, i.e, administration of acetylcholinestrase inhibitor (edrophonium) induces disassociation between the two muscle layers so that the peak longitudinal muscle contraction occurs prior to the peak circular muscle contraction[31]. In patients with nutcracker esophagus, which appears to be a hypercholinergic state, there is spontaneous disassociation between contractions of the two muscle layers. Peak contraction of the two muscle layers is separated by several seconds[32] in nutcracker esophagus (Figure 4). Interestingly, the disassociation between the two muscle layers is abolished by atropine (an anticholinergic agent) in patients with nutcracker esophagus[33]. Above suggests that nutcracker esophagus represents a hypercholinergic state that on one hand induces high amplitude contraction and on the other it causes a disassociation between the two muscles layers. An immunohistochemistry study found an increase in the expression of muscarinic receptors on the esophageal muscles in patients with nutcracker esophagus[34]. How does discoordination in the two layers cause esophageal symptoms? Although this is not entirely clear, it may be that discoordination between the two layers interferes with descending relaxation or distension of esophagus, thus causing relative narrowing of esophagus which impedes with the bolus propulsion. Dysphagia, an important symptom in patients with nutcracker esophagus may be related to discoordination between the two layers.

Another example of the discoordination between longitudinal and circular muscle layers is seen in achalasia esophagus, a disorder in which LES relaxation is impaired and there is no peristalsis in the circular muscle[35]. In achalasia esophagus, swallows induces simultaneous pressure increase throughout the length of the esophagus, which is also termed as common cavity pressure or esophageal pressurization (figure 5). Concurrent high resolution manometry (HRM) and ultrasound imaging reveal that pressurization of the esophagus is actually the results of another unique longitudinal muscle contraction pattern, in which longitudinal muscle contracts in the distal esophagus (similar to transient LES relaxation). Latter causes axial shortening of the esophagus and decrease in esophageal luminal cross sectional area, both of which reduce esophageal volume. Since esophagus is closed at the two ends (by upper and lower esophageal sphincters), reduction in esophageal volume leads to a proportional increase in the pressure (Boyles law of physics) which manifests as common cavity or pressurization of the esophagus. It is clear that esophageal pressurization caused by longitudinal muscle contraction is a crucial factor in whatever little swallow-induced esophageal emptying occurs in patients with achalasia esophagus.

Based on the swallow-induced esophageal pressure patterns seen with high resolution manometry, achalasia has been divided into 3 types: Type 1, with minimal pressurization of esophagus, type 2 in which esophageal pressurization exceeds 30mm Hg, and type 3 with a spastic type of esophageal contraction[36]. Several studies show that among different types of achalasia, type 2 respond best to treatment (botox injection, pneumatic dilation or surgery)[36-38]. It turns out that the longitudinal muscle contraction patterns are also quite different in three types of achalasia[35]. Type 1 achalasia shows minimal or no longitudinal

muscle contraction, in type 2 achalasia, strong longitudinal muscle contractions occur with swallows and in type 3 there is severe discoordination between the two muscle layers. It may be that robust longitudinal muscle contraction in type 2 achalasia, which is largely responsible for esophageal pressurization and emptying is a reason for the good response to medical/surgical therapy in type 2 achalasia in contrast to type 1 and type 3 achalasia patterns.

Eosinophilic esophagitis, a disease entity that is being diagnosed with increasing frequency since 1990's is caused by allergy to various food constituents[39]. Increase in numbers of eosinophils (>20/high power field) in the esophageal mucosa is a hallmark histologic feature of eosinophilic esophagitis[40]. Dysphagia, the major symptom of eosinophilic esophagitis, is thought to result from narrowing of the esophagus due to eosinophil-induced submucosal fibrosis. Studies show that there is a decrease in esophageal compliance in patients with eosinophilic esophagitis[41]. Esophageal manometry, which measures circular muscle contraction, is relatively normal in most patients with eosinophilic esophagitis. On the other hand, ultrasound imaging study shows that the longitudinal muscle function is severely impaired in these patients[17]. Latter manifests as reduced amplitude of longitudinal muscle contraction, discoordination between the two muscle layers and reduced response to cholinergic agents. It is very possible that longitudinal muscle dysfunction leads to impaired descending relaxation, which manifests as relative narrowing on the radiologic studies and reduced esophageal wall compliance on the functional (FLIP) studies.

Etiology of esophageal “angina like” pain (pressure, squeeze and tightness) and heartburn (burning sensation in the retrosternal region) resistant to acid suppression therapy remains elusive. In the era of over the counter proton pump inhibitors (PPIs), physicians, especial specialists, seldom see patients with heartburn and esophageal pain in their clinics that is responsive to PPI therapy. Prolonged manometry studies in the 1980's and early 1990's excluded esophageal spasm as the cause of “angina like” pain. Current thinking is that “non-cardiac” pain and PPI-resistant heartburn are related to hypersensitivity of the esophagus (hypersensitivity to acid, esophageal distension and other physiological stimuli)[42]. Prolonged ultrasound imaging recordings reveal a close temporal correlation between sustained (prolonged) contraction of longitudinal muscle and esophageal pain[19] as well as heartburn[43] (Figure 6). The mean duration of contraction was 70 seconds in the case of chest pain and 33 seconds in the case of heartburn in these studies. It may be that longitudinal muscle spasm is actually the cause of esophageal pain and PPI-resistant heartburn. Since prolonged ultrasound imaging studies are not practical (equipment is expensive and data analysis is cumbersome), alternative strategies are needed to demonstrate the cause and effect relationship between longitudinal muscle spasm and esophageal pain. One such possibility is prolonged ambulatory high resolution manometry that can detect cranial lift of the LES as a marker of longitudinal muscle contraction. The feasibility of this approach has recently been demonstrated[44]. How does prolonged contraction of the longitudinal muscle causes esophageal pain/heartburn is not known but it clearly reduces esophageal wall blood perfusion as discussed in the section of laser Doppler flow monitoring of the esophageal wall.

Luminal Distension Measurement by US imaging and Impedance Recordings

Distension of esophagus during passage of bolus is an important parameter that is somewhat difficult to measure. It is important because the flow through a tube is directly related to its cross sectional area and therefore it is not difficult to imagine that if the esophagus did not distend well it would lead to difficulty swallowing or dysphagia. Barium swallow study provides information on the luminal diameter during passage of bolus in the esophagus, however, it is surprising that even in year 2014, it is not clear as to the normal luminal diameter or the cross sectional area of the esophagus for the passage of swallowed contents through the esophagus. Luminal distension depends upon the biomechanical properties of the esophageal wall and relaxation of the muscle in association with peristalsis also known as descending relaxation. US images provides important information on the luminal contents (air, liquid) as well as distension of the esophagus during antegrade and retrograde flow in the esophagus. US imaging studies show that luminal distension is directly related to the volume of swallowed bolus[45]. Distension of the esophagus is also an important marker of relaxation or descending inhibition of the peristaltic reflex. Studies show that similar to contraction, relaxation of the esophagus also travels in a peristaltic fashion. Multiple intraluminal impedance (MII) measurements that has been extensively used for last 20 years to record non-acidic reflux, weakly acidic reflux and air reflux into the esophagus is another possible way to record luminal distension of the esophagus during peristalsis. Impedance value during passage of conductive bolus in the esophagus is inversely related to the esophageal cross sectional area. A recent study[46] that used simultaneous US imaging and impedance recording found that arrival of the bolus on the impedance electrodes causes a major drop in esophageal impedance (approximately 70-80% of the total baseline value). Subsequent distension of the esophagus causes a further but small drop in impedance (Figure 7). The amplitude of small drop in impedance corresponds to the luminal cross sectional area or the degree of luminal distension. Following swallow of a conductive solution, nadir impedance occurs with peak luminal distension. MII recordings show that nadir impedance on the MII recordings travels in a peristaltic fashion, from oral to aboral end during peristalsis[47], which confirms that with swallow-induced peristalsis, similar to contraction, inhibition of the esophagus also travels in a peristaltic fashion. One can also measure luminal distension associated with reflux (GER) during transient LES relaxation with US imaging and one such study found that some of chest pain episodes related to GER occur in association with large volume reflex and marked esophageal distension[48]. Future studies need to assess if poor luminal distension, whether related to biomechanical properties of the esophageal wall or poor descending relaxation is the cause of functional dysphagia, also referred to as non-obstructive dysphagia.

Laser Doppler Flowmetry to Measure Esophageal Wall Blood Perfusion

The blood flows into the myocardium during diastolic phase of cardiac cycle because during systolic phase myocardial contraction constricts/occludes blood vessels and prevents blood from entering into the myocardium. A similar phenomenon was found in the stomach[49]. Along the same lines, recent studies show that during swallow-induced esophageal contractions (primary peristalsis) there is almost complete cessation of the esophageal wall perfusion[50, 51] (figure 8 and figure 9). Remember, during peristalsis circular and longitudinal muscle contract simultaneously. Transient LES relaxation that is associated

with esophageal longitudinal muscle contraction is also associated with significant reduction in the esophageal wall perfusion. These observations raise possibility that prolonged contractions of longitudinal muscles of the esophagus (sustained esophageal wall contraction) could lead to ischemia of esophageal wall and, similar to myocardial pain, “angina-like” esophageal pain may result from esophageal wall ischemia. Laser Doppler recording require that the laser Doppler probe is anchored to the esophageal wall so that the laser beam stay directed towards the esophageal wall. We used Bravo probe delivery system to anchor the laser Doppler probe to the esophageal wall and using such a system we recorded esophageal wall perfusion for extended time periods (Figure 9). Interestingly, the recordings appear similar to pH recordings and therefore are amenable to relatively easy data analysis. Future studies will be able to answer question whether esophageal wall ischemia is an important cause of esophageal pain and PPI resistant heartburn/chest pain.

Summary & Conclusions

Esophagus is a simple organ, relative straight tube with relatively simple function, i.e., to transfer the swallowed contents into the stomach or in the other opposite direction during reflux, belching and vomiting. Diversity of the techniques available to test esophageal function described in this edition of “Clinics of North America” is a testament that may be it is not that simple of an organ and may be our understanding of its functioning is not yet complete. Etiology of dysphagia remains obscure in large number of patients. Dysphagia in the setting of normal endoscopy, barium swallow study and manometry is labeled as functional dysphagia. From a mechanical point of view, for transfer of material through a tube only two things are important, the diameter/cross sectional area of a tube and driving pressure or pressure gradients along the length of the tube. High resolution manometry (HRM) is almost a perfect tool to measure driving pressures and pressure gradients across the tube. On the other hand, I believe none of the available technique provides accurate measurement of the cross sectional area of the esophagus during bolus transport. FLIP (functional luminal imaging) can measure the relationship between esophageal pressure and cross sectional of the esophagus during induced- distension of the esophagus but not during bolus transport. Dynamic US imaging of the esophagus can measure luminal dimensions during bolus transport but there are limitations, i.e., equipment is expensive, swallowed air causes disruption of esophageal imaging, image analysis is time consuming and one can only obtain information at one level in the esophagus at a given time unless one use multiple US probes. Barium swallow or esophagram provides approximation of esophageal diameter during bolus transport but there are limitations. MII has been mostly used to detect weakly acidic and non-acidic reflux but work of Omari and colleagues show that MII can detect luminal dimension during bolus transport. Our recent study shows that there is an inverse but statistically significant linear relationship between the esophageal cross sectional area and impedance value. If MII technique can be further developed along these lines, it could add significantly to our diagnostic armamentarium because HRM Z (manometry + impedance) are easy to record and number of recording systems are already available.

“Angina like” esophageal pain and heartburn, non responsive to proton pump inhibition therapy are major health care issues and consume tremendous amount of health care resources. The precise pathogenesis of these symptoms is highly debated. We have excellent

methodologies to diagnose acid and non acid reflux but it is clear that reflux is not the cause of the symptoms in majority of these patients. Current thinking is that “esophageal hypersensitivity” is the cause of these symptoms, which implies that normal stimuli such as, low levels of esophageal distension, normal amount of acid reflux and even normal esophageal contractions are felt as pain by these patients. One possibility is that the commonly used esophageal function testing does not record the actual culprit or the offending stimulus. May be it is the longitudinal muscle spasm that is the cause of esophageal pain but and as pointed out earlier it is not easy to record. Since esophageal pain and heartburn occurs intermittently and infrequently one requires prolonged, ambulatory monitoring technique, such as ambulatory HRM to detect LES lift/esophageal shortening as a marker of longitudinal muscle spasm. Our recent work indicates that longitudinal muscle contraction can cause low esophageal wall blood perfusion. If future studies prove that ischemia of the esophageal wall is an important cause of esophageal pain, laser Doppler flowmetry could become an important tool in the esophageal function testing laboratories across the country very quickly.

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Key points

1. Manometry and impedance provide only surrogate information regarding longitudinal wall function and are focused on contractile amplitude and lumen cointent.
2. Ultrasound imaging provides a unique perspective of esophageal function by providing important information regarding longitudinal muscle contraction.
3. Laser Doppler assessment of perfusion may be an important complemenatry tool to assess abnormal wall blood perfusion as a possible mechanism of pain

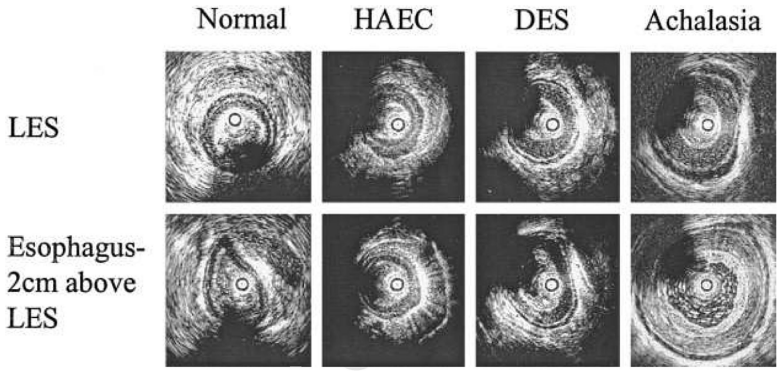

Figure 1. Muscle Hypetrophy in Esophageal Motor Disorders

Ultrasound images of the lower esophageal sphincter (LES) and esophageal body in healthy subjects and patients with high-amplitude esophageal contractions (HAEC), diffuse esophageal spasm (DES), and achalasia of the esophagus. The LES image is from the center of the LES. The esophageal images are from a time when there was no esophageal contractile activity, which was observed through manometry. Note the differences in the muscle thickness in 4 subjects, with the thickest muscle in patients with achalasia of the esophagus.

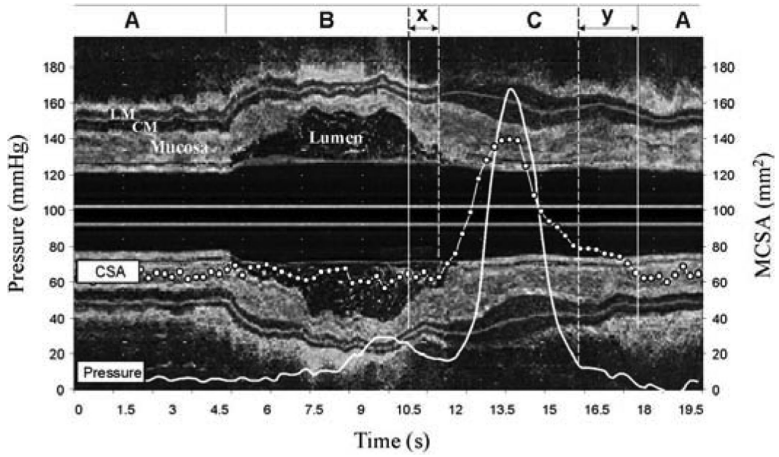

Figure 2. Coordination of Esophageal Circular and Longitudinal Muscle during Peristalsis

M-mode echo-esophagraph with superimposed, intraesophageal pressure and muscle cross sectional area (MCSA) during 5 ml water swallow; ultrasound transducer positioned 2 cm above the lower esophageal sphincter. A: baseline esophagus, prior to swallow; B: bolus induced distension- bolus pressure, thinning of mucosa and muscle layers; C: esophageal contraction. Note the dissociation between increase in MCSA and increase in intraluminal pressure. The increase in MCSA (—O—) begins before and outlasts the intraluminal pressure wave (▬▬▬). The difference between the onset of CSA and pressure is due to the delay in recording circular muscle contraction by manometry. LM: longitudinal muscle, CM: circular muscle . (Source – Mittal et al. Am J Physiol Gastrointest Liver Physiol 2006;290:G431-8)

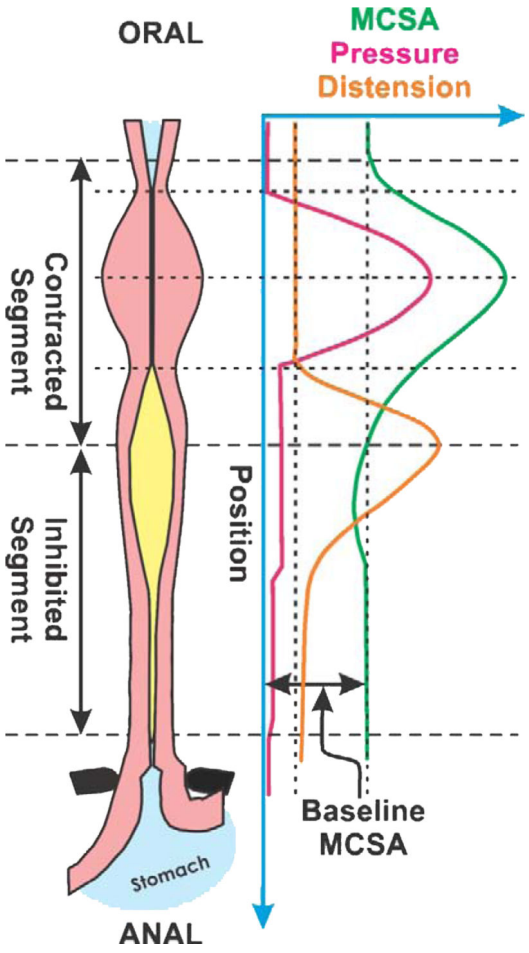

Figure 3. Schematic of Contraction and Distension during Swallow Induced Peristalsis

Note that the pressure and muscle cross sectional area (MCSA), surrogate markers of circular and longitudinal muscle contractions respectively, precede distension. The latter marches distally in front of the onset of contraction wave in a peristaltic fashion. (From- Abrahao Jr. L, et al. Neurogastroenterol Motil. 2011 :23(3):201-7

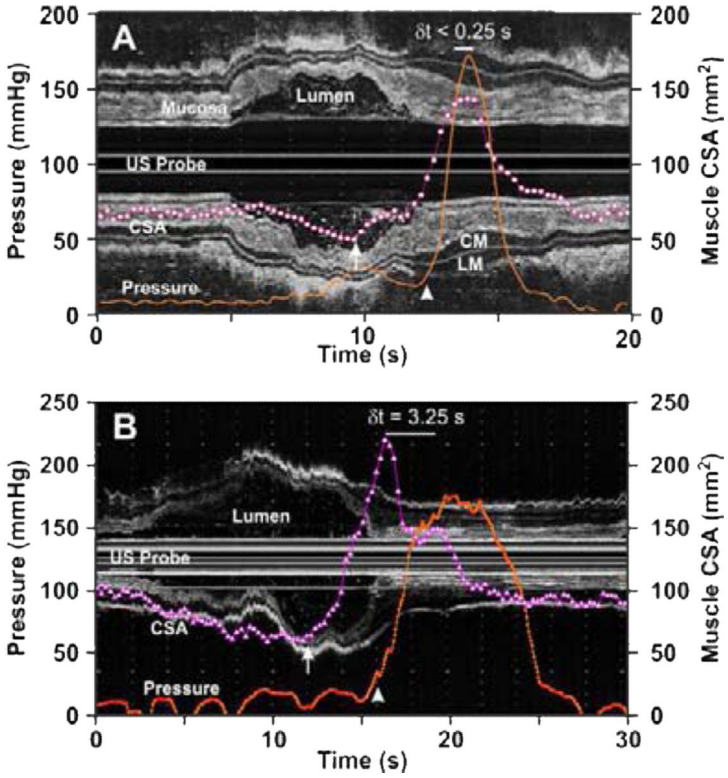

Figure 4. Discoordination between Circular and Longitudinal Muscle Layers in Nutcracker Esophagus

A: Relationship between M-mode ultrasound (US) images, Muscle CSA and the pressure wave in a normal subject. Note the onset of lumen collapse occurs at the same time as the onset of the increase in muscle CSA. Pressure wave occurs at the same time as the first complete collapse of the lumen on the manometric probe. Peak of manometric contraction and peak CSA occurred with a delta-t ≤ 0.5 s during all 28 swallows at the 2 cm and all 28 swallows at the 10 cm level. **B:** An example of dissociation between circular (CM) and longitudinal (LM) muscle contraction in a patient with Nutcracker esophagus. These recordings were obtained at 2 cm above the lower esophageal sphincter. Note the disassociation between the peak pressure and peak muscle CSA. (From Jung et al, Gastroenterology 2005;128:1179-86).

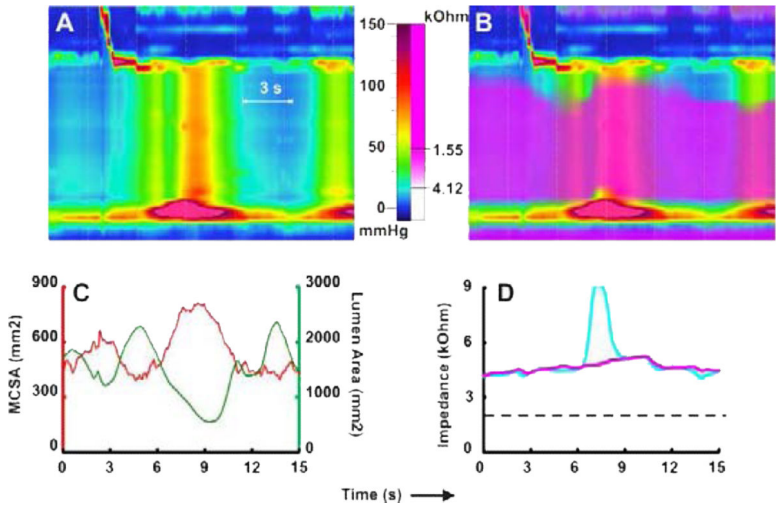

Figure 5. Longitudinal muscle contraction in Type 2 Achalasia Esophagus

Simultaneous HRM, impedance, and US image-recorded changes in esophageal lumen and muscle CSA (MCSA) in a patient with type 2 achalasia: (*A*) HRM alone, (*B*) HRM and impedance, (*C*) changes in MCSA and lumen (derived from US images), and (*D*) impedance recording from a pair of electrodes above and below the EGJ. Following swallow, there is a simultaneous pressure wave throughout the length of the esophagus (common cavity wave; pan-esophageal pressurization). EGJ record shows minimal relaxation to contraction following swallow. Impedance recording shows no flow across the EGJ. US image-derived data show a decrease in luminal CSA and increase in MCSA during the period of common cavity pressure wave (pan-esophageal pressurization). The increase in muscle CSA suggests contraction of the longitudinal muscle of the esophagus.

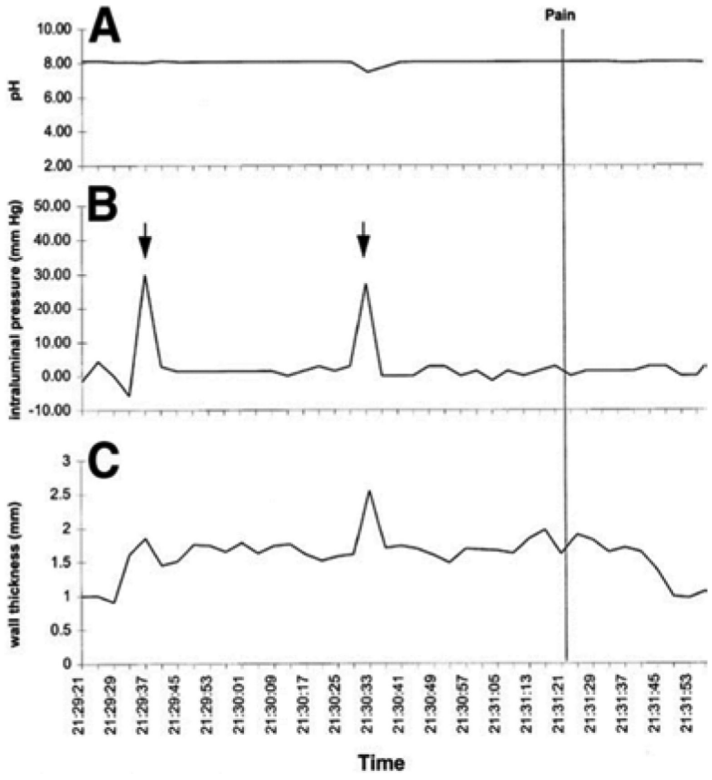

Figure 6.

Sustained esophageal contraction associated with chest pain. Esophageal pH (*top*), distal esophageal pressure (*middle*), and esophageal smooth muscle thickness (*bottom*) are shown during a 2.5-minute recorded interval. The onset of chest pain is depicted by the vertical line (time = 0). The onset of sustained esophageal contraction (SEC) occurs approximately 120 seconds before the onset of pain. The pressure record shows two small contractions (*arrows*) that are accompanied by brief increases in esophageal muscle thickness during the SEC. (From Balaban et al, Gastroenterology 1999;116:29-37)

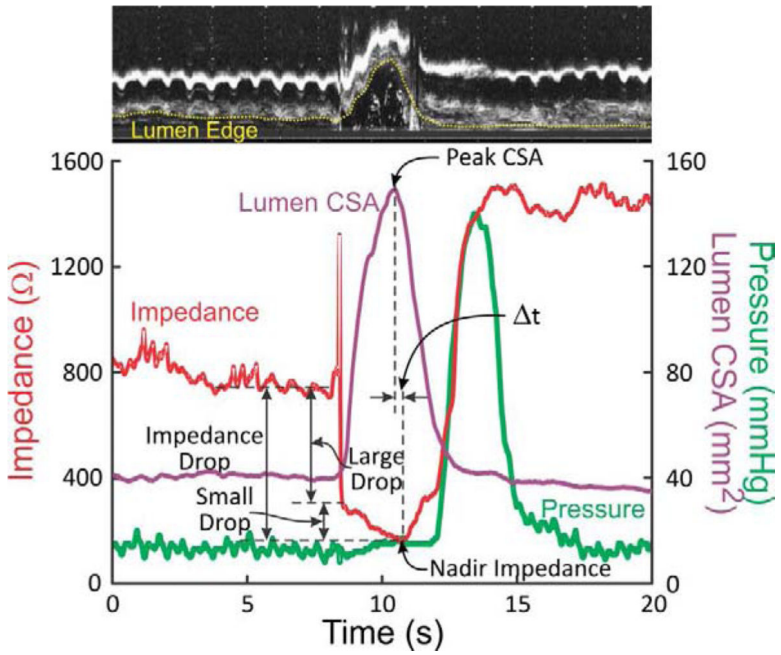

Figure 7.

Temporal correlation between changes in luminal CSA and changes in impedance values. A B-mode US image is shown on the top of the graph and it shows changes in luminal CSA over time on one side of the US probe. Note an increase in impedance coincides with the passage of air through the esophagus, followed by a large drop in impedance with the onset of increase in luminal CSA, which was followed by a slow fall in impedance associated with the increase in the luminal CSA. Peak cross sectional area coincides approximately with the nadir impedance.

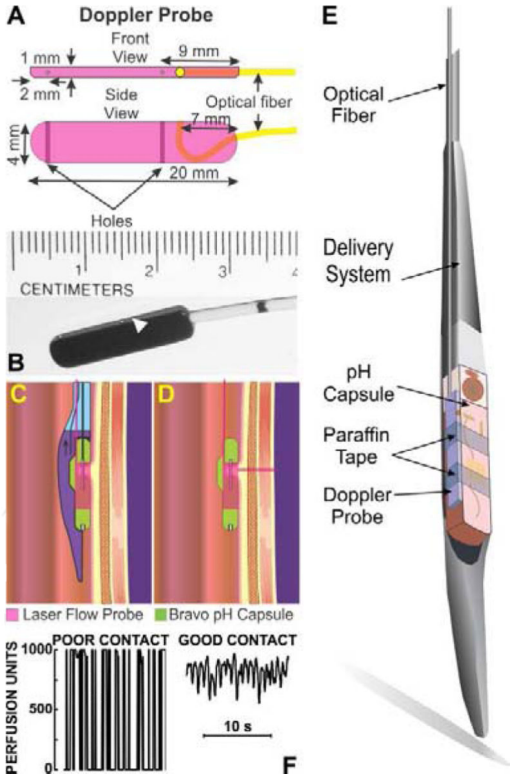

Figure 8. Laser Doppler Technique to record Blood Perfusion of the Esophageal Wall

A: Schematic of laser Doppler probe and B: Photograph of the Doppler probe with scale in background; C & D: Schematic of Bravo and laser Doppler probe anchored to the esophageal wall – Laser Doppler probe was taped to the Bravo pH capsule. Using the Bravo pH delivery system (C) the capsule was anchored to the esophageal wall and delivery system was removed (D); (E): Laser Doppler perfusion recordings when capsule was inadequately fixed to the esophageal wall (poor contact) and (F) when properly anchored. When poor contract the recordings yield artifact but with good contact a stable recording can be obtained continuously for hours.

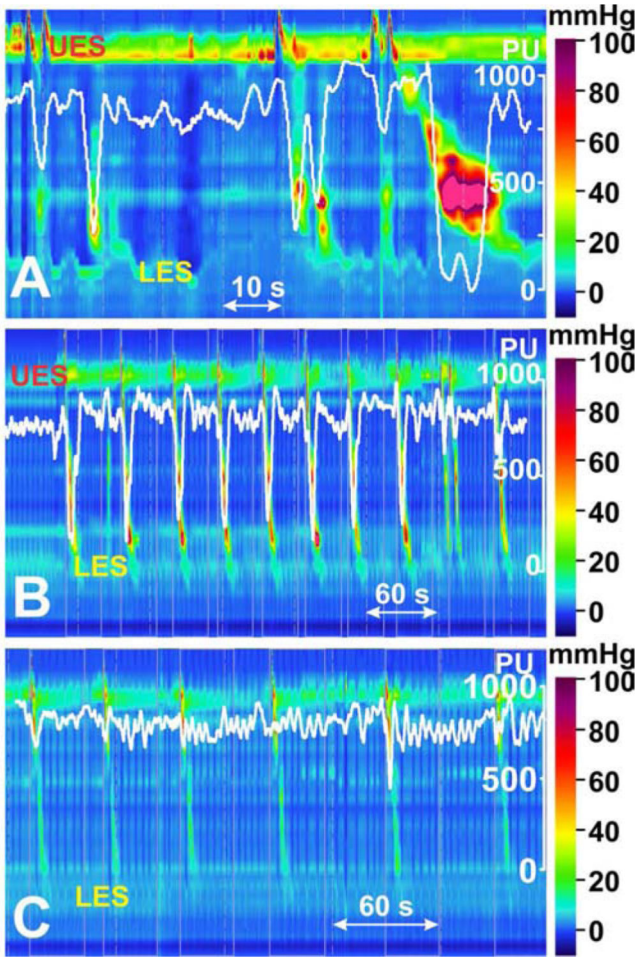

Figure 9. Esophageal Wall Perfusion during Swallow Induced Esophageal Contractions

Doppler perfusion tracings are superimposed white line on the high resolution manometry tracings. Doppler transducer was taped to the Bravo pH capsule which was anchored 4 to 6 cm above the lower esophageal sphincter. In panel A, note the fall in laser Doppler perfusion with each swallow induced esophageal contraction. Amplitude and duration of perfusion record is related to the amplitude and duration of esophageal contraction. In panel B, note the effect of wet swallows induced esophageal wall contraction on the reduction in esophageal wall perfusion. Panel C shows the effect of atropine on the laser Doppler perfusion during wet swallow. Note, atropine reduced the esophageal contraction amplitude and reduction in blood perfusion with esophageal contractions. (From Mittal et al Am J Physiol Gastrointest Liver Physiol 2011;301:G1093-8)