Why so Many Patients With Dysphagia Have Normal Esophageal Function Testing

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Abstract

Esophageal peristalsis involves a sequential process of initial inhibition (relaxation) and excitation (contraction), both occurring from the cranial to caudal direction. The bolus induces luminal distension during initial inhibition (receptive relaxation) that facilitates smooth propulsion by contraction travelling behind the bolus. Luminal distension during peristalsis in normal subjects exhibits unique characteristics that are influenced by bolus volume, bolus viscosity, and posture, suggesting a potential interaction between distension and contraction. Examining distension-contraction plots in dysphagia patients with normal bolus clearance, ie, high-amplitude esophageal peristaltic contractions, esophagogastric junction outflow obstruction, and functional dysphagia, reveal 2 important findings. Firstly, patients with type 3 achalasia and nonobstructive dysphagia show luminal occlusion distal to the bolus during peristalsis. Secondly, patients with high-amplitude esophageal peristaltic contractions, esophagogastric junction outflow obstruction, and functional dysphagia exhibit a narrow esophageal lumen through which the bolus travels during peristalsis. These findings indicate a relative dynamic obstruction to bolus flow and reduced distensibility of the esophageal wall in patients with several primary esophageal motility disorders. We speculate that the dysphagia sensation experienced by many patients may result from a normal or supernormal contraction wave pushing the bolus against resistance. Integrating representations of distension and contraction, along with objective assessments of flow timing and distensibility, complements the current classification of esophageal motility disorders that are based on the contraction characteristics only. A deeper understanding of the distensibility of the bolus-containing esophageal segment during peristalsis holds promise for the development of

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innovative medical and surgical therapies to effectively address dysphagia in a substantial number of patients.

Keywords

Dysphagia; Distension Contration Plot; Esophageal Peristalsis; Functional Dysphagia

Epidemiology of Dysphagia Symptom

A cross-sectional study of the US population found a dysphagia prevalence of 16% in the general population, with 92% experiencing symptoms in the previous week.[1] Sixteen percent of the respondents described their symptom to be either "quite a bit" or "very severe". Drinking liquids to help with dysphagia was reported by 86% and taking longer time to finish eating by 77%. Dysphagia prevalence increases with age and other comorbidities such as gastroesophageal reflux disease (30.9%), eosinophilic esophagitis (EOE) (8.0%), and esophageal stricture (4.5%). Interestingly, only half of individuals with dysphagia sought medical care for their difficulty swallowing. An earlier study found the dysphagia incidence to be 7.8% in the US.[2] A similar study in Australia and Argentina reported prevalence rates of 16%[3] and 13%,[4] respectively. Therefore, similar to the heartburn and reflux disease, dysphagia is highly prevalent in the western world. On the other hand, dysphagia rate was reported to be lower in the Asian population,[5] only 1.7% in China.

Etiology of Dysphagia

Dysphagia generally can be categorized into oropharyngeal and esophageal. The focus of this article is on esophageal dysphagia, which can be due to structures extrinsic and/or intrinsic to the esophagus. Mediastinal structures such as blood vessels, heart, and mediastinal tumors may compress the esophagus resulting in obstruction to the passage of swallowed contents. Dysphagia, due to the pathology intrinsic to the esophagus, may be further divided into mucosal and neuromuscular. Rings and web in the esophagus, e.g., Schatzki ring is a common cause of dysphagia and one can diagnose it with a well-done barium swallow and endoscopy exam. Inflammation of the esophageal mucosa related to viral (herpes) and fungal (candida) infection may cause dysphagia and odynophagia, and these are easily diagnosed with endoscopy and biopsy, and treated with antiviral and antifungal agents, respectively. Reflux disease and esophagitis resulting in mucosal inflammation and strictures is a common cause of dysphagia and reflux disease; it can also be easily diagnosed with endoscopy and pH/impedance monitoring of the esophagus. Scleroderma esophagus may lead to recalcitrant reflux disease and esophageal stricture. During the last 3 decades, EOE has attracted significant interest.[6] Endoscopy with biopsy showing an eosinophil count of 15 HPF allows one to make a definitive diagnosis of EOE.[7] A normal endoscopy and biopsy in patients with dysphagia should be followed by high-resolution manometry impedance high resolution manometry impedance (HRMZ) study to assess the esophageal motor and lower esophageal sphincter function.[8] The Chicago Classification of esophageal motility disorders has allowed specific criteria to diagnose esophageal motility disorders into major (achalasia, nutcracker/jackhammer esophagus,

esophagogastric junction outflow obstruction (EGJOO), and absent peristalsis) and minor ones (ineffective peristalsis, fragmented peristalsis).[9] These criteria are based on the contraction phase of peristalsis. Except for patients with achalasia esophagus and EGJOO, the reason for dysphagia in patients with major and minor motility disorders remains unclear because minor motor disorders are seen not infrequently in asymptomatic individuals.[10] Also, it is not clear why patients with supernormal contraction phase of peristalsis, ie, nutcracker esophagus and jackhammer esophagus should have dysphagia.[11,12] Furthermore, 30%–50% of patients referred for HRMZ study with dysphagia turn out to have a normal study and can be classified into functional dysphagia (FD)[13,14] (Figure 1). According to the ROME criteria, FD is characterized by sensation of abnormal esophageal bolus transit with no evidence of structural lesions, i.e., gastroesophageal reflux disease, EOE, and histopathology-based esophageal motor disorders.[8] FD is a diagnosis of exclusion; and its prevalence in the general population is not clear. Seven percent and 8% of the respondents from a house holder survey reported dysphagia that was unexplained by the questionnaire ascertained disorders, with less than 1% reporting frequent dysphagia.[15,16] Zero point six percent of patients with functional gastrointestinal disease complain of frequent dysphagia.[17] Since the majority of patients referred for HRMZ studies have normal barium swallow, normal endoscopy, and normal esophageal mucosal biopsy, one can argue that patients with normal HRMZ studies would likely fit into the category of FD. Above suggests that the etiology of dysphagia in many patients remains unknown and is the subject of discussion in this review. The majority of the patients seen in my clinical practice (Mittal) fall into this category. A brief review of physiology of peristalsis is presented before its discussion in the context of dysphagia and why these patients may have normal esophageal function testing.

Physiology of Esophageal Peristalsis

The neuromuscular apparatus of the smooth muscle distal esophagus is endowed with an integrated system that has the capacity to alternate from relaxation that reduces resistance to bolus flow (relaxation), to contraction that actively drives the bolus flow. Bayliss and Starling, at the turn of the 19th century studied peristalsis in the small and large intestines of dogs and observed that peristalsis consists of initial inhibition, followed by contraction ("the law of intestine").[18,19] Along those lines, esophageal peristalsis also consists of initial inhibition followed by excitation. Each swallow initiates an esophageal contraction (primary peristalsis) following a latency period in the proximal skeletal and distal smooth muscle esophagus. The latency in the skeletal muscle esophagus is due to the sequential activation of neurons in the nucleus ambiguous of the vagus nerve nucleus. On the other hand, in the case of smooth muscle esophagus, the latency is related to either a central (sequential activation of neurons in the dorsal motor nucleus of vagus) or a peripheral mechanism.[20] The latter can be either neurogenic (myenteric plexus and inhibitory motor neurons), or myogenic[21] (syncytium formed by the muscles through which depolarization spreads sequentially). Nitric oxide containing nerves in the myenteric plexus play an important role in the inhibitory phase of peristalsis and the latency period.[22] One can measure the latency period in-vivo (distal latency) from the high-resolution manometry (HRM) -recording; it is the time interval from the onset of swallow (onset of upper esophageal sphincter (UES)

relaxation) to the onset of contraction in the most distal part of the esophagus.[23] A shorter distal latency (<4.5 sec) is a hallmark of diffuse esophageal spasm, and it is due to the impaired inhibitory, nitric oxide containing nerves of the myenteric plexus.[22,24] Indirect evidence of inhibition during peristalsis can also be observed in human recordings with repetitive swallowing (deglutitive inhibition).[25] If one swallows twice, less than 2 seconds apart, the 2nd swallow inhibits the contraction from the first swallow. Multiple swallows at short intervals result in only 1 contraction, which follows the last swallow. Electro-physiologic recordings provide direct proof of inhibition and contraction during esophageal peristalsis.[26] Both, primary peristalsis[27] (swallow-induced) and secondary peristalsis[28] (esophageal distension-induced) result in hyperpolarization and depolarization of the resting membrane potential of the smooth muscle, which are equivalent of inhibition and excitation, respectively. The inhibition results in receptive relaxation, which allows distension of the esophagus before contraction so that the latter can propel the bolus with minimal resistance.

Unlike the lower esophageal sphincter, manometry recordings do not reveal a resting tone in the esophagus and therefore relaxation of the esophagus can't be recorded by manometry.[29] To demonstrate relaxation of the esophagus, Sifrim created artificial high-pressure zones in the esophagus by distending small balloons and observed its relaxation in normal subjects but not in patients with diffuse esophageal spasm.[30,31] Ultrasound imaging studies reveal that during swallow-induced peristalsis, the esophagus distends in the shape of an "American Football", as the bolus travels through the esophagus.[32] Above implies that the degree of inhibition in the distended segment varies and the maximal inhibition during peristalsis in the esophagus is located at the point of peak distension, which moves sequentially through the esophagus. In other words, similar to contraction, the inhibition/distension wave also travels sequentially through the esophagus during peristalsis (Figure 2). Thus, as timing and amplitude of the contraction are the markers of the excitatory phase, the timing and amplitude of distension is a marker of the inhibitory phase of peristalsis. In healthy subjects, the 2 phases of peristalsis are spatiotemporally linked, and breakage of this linkage can be a marker of the peristaltic dysfunction. Measuring luminal distension during peristalsis is challenging and not done routinely in the current clinical practice.

Measuring Luminal Cross-sectional Area/esophageal Distension During Peristalsis

Barium esophagogram is a simple method to assess the esophageal diameter during peristalsis. Schatzki reported maximal esophageal diameter of 40 mm in the context of Schatzki ring.[33] Others found maximal diameter of distal esophagus, ranging from 20 to 33 mm (median 25 mm).[34–37] The reason for this large range is likely is related to number of factors; 1) barium esophagograms are not done in a standardized manner, and thus are highly operator dependent, 2) bolus volume, viscosity and subject posture (supine, prone, or upright) are important determinants of the luminal dimensions during peristalsis, 3) single vs multiple swallows during bolus passage may make a difference in the esophageal distension (luminal dimensions) and, 4) definition of distal esophagus may vary because the phrenic ampulla, widest portion of the esophagus, is likely a part of the stomach because axial shortening of the esophagus results in a physiological sliding hiatus hernia with each

peristaltic contraction, 5) abdominal compression during swallow study if done, increases resistance to outflow and may increases the luminal diameter. A single-plane, 2D X Ray imaging allows one to measure the width of the esophagus, which is called its diameter. Bear in mind that the transit of bolus through a tube is dependent on its luminal cross-sectional area (CSA). If the esophagus were to distend in a circular fashion during peristalsis, the luminal CSA calculation from the esophageal width seen on barium swallow study would be valid. However, such is not the case, as revealed by intraluminal ultrasound imaging and computerized tomography (CT) scan imaging. Based on the CT scan imaging, esophagus expands 33% more in the lateral than in anterior-posterior direction during distension.[38] Also bear in mind that small changes in the diameter can make large difference in the luminal CSA, (CSA $=\pi r^2$, r being the radius). The CSA for diameters of 13 mm, 15 mm, 17 mm and 20 mm would be, 133 mm^2, 177 mm^2, 227 mm^2, and 314 mm^2, respectively.

Our laboratory has used high-frequency intraluminal ultrasound catheters for almost 30 years to study luminal distension during reflux events and peristalsis.[39,40] Using 2 high-frequency intraluminal ultrasound catheters located at 2 cm and 10 cm above the lower esophageal sphincter (LES), it was observed that similar to contraction, the esophagus also distends sequentially along the length of the esophagus during peristalsis.[32] Furthermore, the esophagus distends in the shape of an "American Football" (not in a cylindrical fashion) at each location in the esophagus during peristalsis. The "American Football" shape of the bolus during esophageal transit is also observed during barium swallow if one records transit following a single swallow, especially in the supine position. Endoflip studies that record distension-induced esophageal peristalsis also reveal above phenomenon during repetitive antegrade contraction (Figure 2). Mean CSA at 12 cm and 2 cm above the LES were 120 mm^2 and 275 mm^2 as recorded by ultrasound (US) images in one study (10 ml bolus and subject in supine position).[32] The CT scan images show CSA values of approximately 160, 180 and 395 mm^2 at the level of carina, left atrium, and phrenic ampulla, respectively (10 ml bolus in the supine position). The difference in CSA in the distal esophagus is likely related to the location, it might be distal esophagus or phrenic ampulla.[38]

The impedance methodology is another possible technique to measure the luminal CSA, it has been used in many organ systems, ie, heart, stomach, and esophagus. One can record left ventricular volume, cardiac ejection fraction,[41] gastric volume and gastric emptying[42,43] using impedance methodology. Since 1980's, impedance technique has been in use to measure the CSA of a distended balloon in the esophagus, in-vivo.[44] Functional luminal imaging probe, currently used in clinical practice, is also based on the Ohm's law of electricity and impedance principles.[45] It actually measures luminal CSA, which is then converted mathematically to diameter, based on the assumption of a circular geometry of the esophagus. The HRMZ catheters currently used for routine clinical manometry studies have intraluminal impedance electrodes located every 2 cm along the length of the esophagus. These impedance recordings are currently used to detect whether bolus clearance during peristalsis is complete or incomplete. Kim found a significant linear correlation between the luminal CSA measured by intraluminal US imaging and inverse of impedance (also called admittance).[46] The difficulty though is that subjects may swallow air residing in the oropharynx, along with the swallowed saline bolus,[38] which confounds the impedance values recorded in the esophagus and hence confounds the accurate measurement

of esophageal luminal CSA.[47] One can mitigate above situation by swallowing in the Trendelenburg position, air being lighter than liquid gets separated during transit through the esophagus.[47] Nguyen[48,49] and Omari[50,51] found that following swallow of saline bolus, the nadir impedance (a marker of maximal luminal CSA/distension) travels sequentially through the esophagus. Luminal CSA measured by impedance technique recordings performed with the subject in the Trendelenburg position, is similar to the one measured by intraluminal US images, (median value of 125 mm^2, at 7 cm above LES).[47] Therefore, it is possible to record luminal CSA/distension during peristalsis from the HRMZ recordings, thus opening the door for recording distension-contraction plots of peristalsis during routine clinical manometry studies. Omari has championed the use of automated impedance manometry in patients with oropharyngeal swallowing disorders[52] and nonobstructive dysphagia,[50] which in principle is similar to the concept of distension-contraction plots.

Characteristics of Distension Contraction Waveforms in Normal Subjects

In normal subjects, using concurrent MII, manometry and X-Ray fluoroscopy, 4 phases of liquid bolus flow tied to pressure topography landmarks can be identified.[53] The phase I (accommodation phase) represents the time between the opening and closing of the UES during which bolus is propelled by the pharyngeal pump into the esophagus. Phase II (compartmentalization phase) represents the time period between the UES closure, to the arrival of the contraction wave in the transition zone. No bolus leaves the esophagus during phase I and II. Phase III (esophageal emptying phase) is the time during which peristaltic contraction propels bolus to the contraction deacceleration point (CDP).[54] Phase IV (ampulla emptying phase) is the time from the CDP to the completion of bolus transit into the stomach. Distension-contraction plots reveal that esophageal distension during passage of bolus during peristalsis varies along the length of the esophagus. The distension values increase from proximal to the distal location in the esophagus.[55,56] Based on barium swallow studies and CT imaging, the phrenic ampulla is the location of maximally luminal distension. The computer software program (Distension Plots) allows one to visualize distension (measured from the impedance part of HRMZ recordings) and contraction (measured by pressure sensors) in several formats, ie, waveforms, color topographical plots and videos of esophageal distension during peristalsis. These recordings show the amplitude and location of distension and temporal correlation between contraction and distension during bolus transit through the esophagus at close intervals (every 1–2 cm). For the numerical analysis, instead of quantifying distension at one specific location in the esophagus, DPlot provides the average distension value in 4 equal segments of the esophagus, starting from the lower edge of UES to the CDP of peristaltic contraction. The CDP is located above phrenic ampulla, and thus values reported in our publications do not include the phrenic ampullary region. We are not certain whether the impedance technique can measure phrenic ampullary distension values accurately; the reason is that the stomach and esophagus are lined by columnar and squamous epitheliums that have low and high impedance values, respectively. Axial shortening of the esophagus during peristalsis results in relative movement between the sensors on the manometry catheter and esophagus, eg, a sensor locate in the lower esophageal sphincter before swallow may moves into the stomach during peristalsis. Before peristalsis, the recording electrode located in the

esophagus may move into the phrenic ampulla with peristalsis and can confound the luminal CSA calculation.

Several studies show the effect of bolus volume and viscosity, and posture on the characteristics of esophageal contraction waveforms.[57–59] Distension-contraction plots shows a similar effect of the above variables on the amplitude of distension waveforms during primary peristalsis[60,61] (Figure 3). In addition, these studies also show alterations in the temporal correlation between distension and contraction waveforms during esophageal transit. Ten milliliters of 0.5 N saline, swallowed in the Trendelenburg position has been used for our studies because we reasoned that a 5 ml bolus used during clinical studies is not enough volume to study esophageal distension and it is less likely to distinguish patients from normal. The important characteristics of distension waveform during peristalsis are 1) the lumen distends in the shape of an "American Football" at each location, along the entire length of the esophagus, 2) the peak of distension moves sequentially along the esophagus, 3) amplitude of distension increases from the proximal to distal location along the length of esophagus, and 4) peak distension velocity and bolus flow rate decrease from proximal to distal location in the esophagus.[62] With regards to the temporal correlation between distension and contraction waveform, the important features are; the pharyngeal pump propels swallowed bolus into the mid esophagus quickly (without any assistance from esophageal contraction) resulting in a significant time interval between the distension and contraction waves in the proximal, mid, and at times in the distal esophagus. On the other hand, there is a closer temporal correlation between the contraction and distension wave in the distal esophagus. Trendelenburg position and increase in bolus viscosity increases the amplitude of distension, decreases velocity of bolus movement, and distance traveled by bolus due to pharyngeal pump.[62] Distension-contraction waveforms are more closely aligned with each other throughout the length of esophagus with a viscous bolus.

The luminal distension may affect contraction and vice versa via several mechanisms. Larger distension resulting in an increase in the muscle fiber length will generate greater contraction based on the length-tension principle described in the context of cardia muscles (Starling principle). Luminal distension by a moving bolus can influence contractions and vice versa, also through the activation of peripheral and central neural reflex pathways.[63] Greater distension results in greater esophageal wall tension, an important stimulus for the activation of vagal and spinal sensory pathways associated with the conscious perception of swallowing and esophageal symptoms.[64–66]

Bolus Flow and Distension Contraction Patterns in Patients With Dysphagia

Ineffective esophageal contractions (low amplitude, fragmented, or failed) following a swallow result in either no clearance or incomplete bolus clearance from the esophagus.[67] The latter is also observed in patients with achalasia esophagus. However, the patterns of esophageal emptying are different in the 3 types of achalasia. In patients with achalasia type 1, characterized by low amplitude or absent esophageal contraction and impaired LES relaxation, the entire swallowed bolus remains in the esophagus when there is no assistance from gravity (supine position).[68] In patients with type 2 achalasia, a unique pattern of longitudinal muscle contraction leads to reduction in the esophageal luminal volume that

results in esophageal pan-pressurization, and if and when esophageal pressure exceeds LES pressure there is partial/incomplete esophageal emptying.[68] In patients with type 3 achalasia (same entity as diffuse esophageal spasm in prior literature), impedance recordings reveal that distal esophagus empties completely, however, ultrasound imaging reveals that distal to the bolus, there is luminal occlusion and thinning of the muscle layers 6[69,70] (Figure 4). As a consequence, bolus is compressed between the contraction proximal to bolus and luminal occlusion distal to bolus. Latter results in high bolus pressure and bolus travelling closer to the contraction peak. Abnormality in the phrenic ampulla phase of emptying can been seen in patients with the obstructive crus of the diaphragm (hiatus).[71] The esophagus empties completely in these patients, but the bolus is trapped in the phrenic ampulla may reflux back into the esophagus at the termination of peristaltic contraction, especially if the LES pressure were to be low.

With the ability to measure luminal CSA, and temporal correlation between the peak distension and contraction from HRMZ recordings, studies show abnormal patterns of luminal distension and temporal correlation between distension and contraction in patients with nutcracker esophagus, EGJOO and function dysphagia (Figures 5 and 6). The 3 parameters that distinguish patients from normal are 1) rapid bolus flow through the proximal and midesophagus resulting in a shorter time interval (T1) between the onset of swallow and peak luminal distension in the distal esophagus, 2) lower amplitude of luminal distension or CSA, and 3) a shorter time interval between the peak luminal distension and peak contraction and a smaller duration of distension wave during peristalsis.[72] The first 2 parameters are related, they are the due to a narrow lumen esophagus during the distension phase of peristalsis. As expected by the Poiseuille law of physics, swallowed bolus propelled by the pharyngeal pump will travels faster through a narrow as compared to wide lumen esophagus, and thus arrives in the distal esophagus faster. An analogy of the above may be seen in daily life, eg, constricting the opening of a garden hose results in an increase in the velocity of ejected water stream which gets further into the lawn. A shorter time interval between the distension and contraction wave is due to dynamic obstruction to flow cause by luminal collapse distal the bolus that compresses bolus between the contraction and luminal closure distal to bolus.[48,69,70]

A solid food challenge test during manometry, championed by Sweiss, Fox and others over many years show that a greater number of patients with dysphagia have abnormal esophageal motility and reproduction of dysphagia symptom during manometry studies with a solid food than with saline bolus swallows.[73–75] In one of their reports, only 35% of patients with dysphagia were found to have major motility disorders with saline swallows as compared to 67% with solid bolus (cheese and onion pasties or soft-cooked long grain rice).[73] More impressive was the reproduction of symptoms during manometry study, which is extremely rare with saline swallows (1%), as compared to 61% with the solid food. A likely explanation for the above is that that a solid bolus requires a wider lumen than the liquid bolus to get through the esophagus. The differences in contractions between the liquid and solid bolus swallows is likely due to relative obstruction to the passage of solid bolus through the esophagus. There are many challenges, however, with using solid food during routine manometry studies: 1) studies take longer time, 2) standardized meal must vary according to the ethnicity and liking of the individual, and 3) one can't assume that

normality of motor patterns is identical with different types of solid foods. We suspect, that the above challenges have prevented wide acceptance of solid food challenge during routine clinical HRMZ studies.

Genesis of Esophageal Symptoms Based on the Alteration in Bolus Flow Pattern

Dysphagia is an important symptom of all patients with motility disorders. However, in general, there is a poor correlation between the severity of symptoms and severity of manometric abnormalities.[76,77] Patients with achalasia esophagus have greater symptom severity (dysphagia associated with weight loss) as compared to other motility disorders.[78] However, many patients with minor motility disorders may present with significant dysphagia and weight loss. A recent study found that the anxiety score is a better predictor of symptom severity than the manometric abnormalities.[78] It is difficult to know though whether greater anxiety is because of greater dysphagia severity or vice versa. Dysphagia is often associated with incomplete emptying of the esophagus during peristalsis, eg in achalasia esophagus, the column of liquid barium in the upright position of > 5 cm, at 1 minutes after swallowing of 100–200 ml of barium is a marker of symptom relief.[79] During manometry investigations, however, it is rare for patients to complain of dysphagia with incomplete bolus clearance.[80] Wall tension and strain are important stimuli for the activation of physiological and nociceptive afferents located in the spinal and vagus nerves.[65,66] Balloon distension in the esophagus generates circumferential passive tension in the esophageal wall. Heathy subjects perceive balloon distension at all levels in the esophagus; however, the proximal esophagus appears most sensitive to this stimulus which most likely relates to regional differences in the wall tension, sensory afferent innervation and/or mechanoreceptor density.[29,81,82] In healthy subjects who perceive dysphagia with solid boluses, dysphagia sensation is associated with bolus hold-up within the lumen of the proximal esophagus in the transition zone. Hold-up of a noncompressible solid bolus causes a sustained luminal distension. Might be that the circular muscle contracting and moving over the static bolus produces dysphagia sensation, and conscious awareness.[83] The mechanisms of symptom generation in the setting of complete bolus clearance is likely different. In patients with type 3 achalasia/diffuse esophageal spasm, we found luminal occlusion and thinning of the muscle layers distal to the bolus during peristalsis, which results in a contraction wave pushing bolus against resistance,[70] (Figure 4). Similarly, in patients with high-amplitude esophageal contractions, EGJOO and FD, contraction wave propels liquids through a narrow esophagus that results in larger luminal pressure and greater wall tension during the distension wave of peristalsis.[84] Patients generally do not report dysphagia during manometry studies, when swallowing saline bolus. Majority of the patients have symptoms when swallowing solid rather than the liquid bolus.[85] It is likely that the wall stress and strain values achieved during liquid bolus transit are not high enough to produce symptoms, and not representative of what happens during solid bolus swallow. We believe that dysphagia related to the bolus flowing through a narrow lumen esophagus is analogous to the dyspnea sensation experienced by patients with bronchospasm (air flowing through a narrow trachea-bronchial tree). It may be that higher than normal tension value

observed in patients during manometry studies is a marker of abnormality, which become clinically significant with solid bolus swallows result in dysphagia sensation.

Pathogenesis of Low Distensibility of Esophageal Wall in Patients With Motility Disorders

A recent study found that patients with FD have stiffer or less compliant esophageal wall as compared to normal subjects. Hill (1938)[86] proposed that the compliance function (volume change relative to pressure change) of a muscular tube is related to 3 factors: 1) viscoelastic elements or the connective tissue within the muscle, 2) viscoelastic properties of the muscle itself, and 3) active muscle contraction. Proximal and distal esophagus are made of skeletal and smooth muscles, respectively, and these have different compliances as revealed by supraphysiological levels of distending pressure.[29,81,82] The majority of the described esophageal motility disorders affect the distal/ smooth muscles esophagus which has tone that reduces its compliance thus making the lumen less distensible at the time of initial opening until such time as neural inhibitory mechanisms are activated to cause muscle relaxation. Lack of descending inhibition or impaired relaxation of the circular and longitudinal muscle layers during peristalsis would be an example of the active element of esophageal wall reducing luminal distensibility. Studies show that patients with nutcracker esophagus[87] and EOE[88] have discoordination between the circular and longitudinal muscle layers of the esophagus, which can cause low distensibility.[89] An increase in muscle thickness (muscle hypertrophy in nutcracker esophagus and other motility disorders[90]) and mucosal fibrosis in patients with EOE are examples of passive elements that may reduce esophageal distensibility. On the other hand, FD patients whilst exhibiting dysregulated bolus flow and distensibility patterns do not generally have an increase in the muscle layer thickness at baseline or at peak distension.[91] We have observed that unlike normal subjects, patients with achalasia esophagus show lack of sliding between the LES and crural diaphragm,[92] which we believe might be another factor causing low distensibility in the bolus domain segment of the esophagus during peristalsis. It is likely that more than one factor is responsible for the low esophageal wall compliance in the motility disorders of esophagus.

Conclusion

High-resolution manometry (HRM) and Chicago classification[9] have been a huge step forward in the diagnosis of esophageal motility disorders. However, majority of patients seen in the current clinical practice of the first author of this paper fall into the category of FD, which raises the question, why so many patients with dysphagia have normal esophageal function testing? The simple answer may be that the current techniques used to measure esophageal distension during peristalsis are not adequate. The HRM and current scheme of classifying esophageal motor disorders in the current format emphasize only half of the story of peristalsis, probably the less important of the 2 halves, ie, the contraction phase of peristalsis. Esophagus in the resting state is a collapsed tube with no lumen. For the bolus to reach its destination, ie, stomach, the esophageal lumen must first distend to a size larger than the swallowed bolus, irrespective of the driving force, or the push of the

peristaltic contraction. A simple analogy is that of a car, it cannot get through a roadway that is smaller than its own width, irrespective of the horsepower of its engine. Studies show that a contraction amplitude of 20–30 mm Hg, which may be considered as the horsepower of peristaltic engine, is enough to propel the barium bolus efficiently,[93] provided that the esophageal lumen is wide open (Figure 7). Patients with scleroderma esophagus, with complete absence of the contraction phase of peristalsis,[94] do not develop dysphagia until they develop reflux stricture. The majority of patients with EOE have normal contraction phase of peristalsis; dysphagia in these patients is due to the lack of esophageal distension, thought to be related to submucosal fibrosis[95–97] or possibly due to impaired inhibition of the peristaltic reflex.[88] Patients with achalasia esophagus do extremely well once obstruction at the LES is reduced, even in the absence of esophageal contractions and peristalsis. Since humans eat in an upright posture, pharyngeal pump and gravity can be enough for the bolus to reach to the stomach. Barium swallow, is not an ideal test to measure the luminal dimension of the esophagus, even if done methodically, it is likely to overestimate the luminal CSA. Ultrafast CT scanning and US imaging to measure luminal CSA are impractical.[38] The intraluminal impedance recordings, which are already part of the HRMZ recording, and distension-contraction plots, which can measure luminal CSA, velocity of bolus flow, temporal correlation between distension and contraction, and esophageal distensibility during peristalsis can provide a better picture of esophageal motor function. Future studies are needed to determine the cause of non-compliant esophagus which we contend is prevalent in large number of patients with dysphagia, who have normal motility and normal bolus transit based on the current diagnostic criteria. A better understanding of the distension function of esophagus during peristalsis and direct correlation of bolus perception and distension-contraction properties will likely lead to improvements in the diagnosis of dysphagia. The question though remains regarding the optimal treatment for the impaired distension function of the esophagus and whether improvement in the distension function will lead to improvement in dysphagia symptom.

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Abbreviations used in this paper:

CSA	cross-sectional area
EGJOO	esophagogastric junction outflow obstruction
EOE	eosinophilic esophagitis
FD	functional dysphagia
HRMZ	high resolution manometry impedance
LES	lower esophageal sphincter

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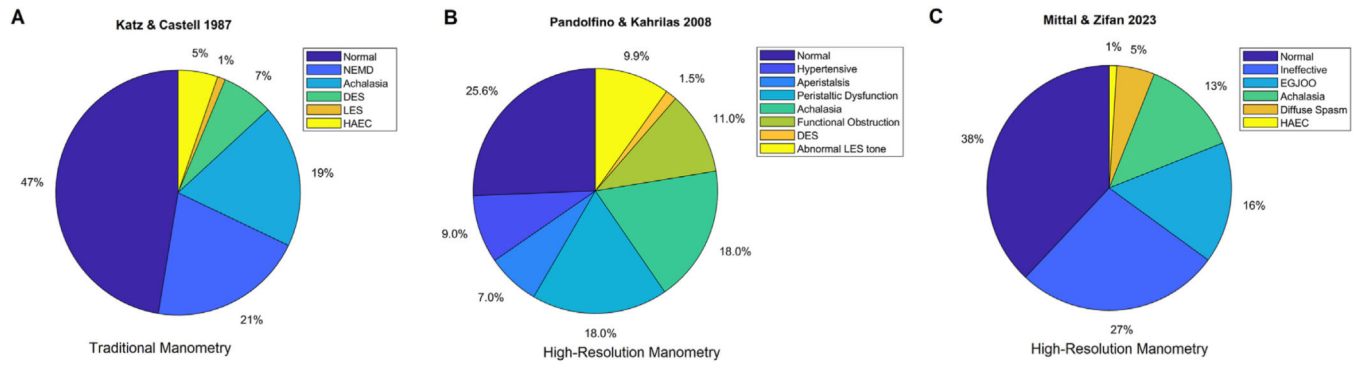
Figure 1.

(A–C) Prevalence of esophageal motor disorders in patients with dysphagia referred for esophageal manometry from 3 tertiary care centers.
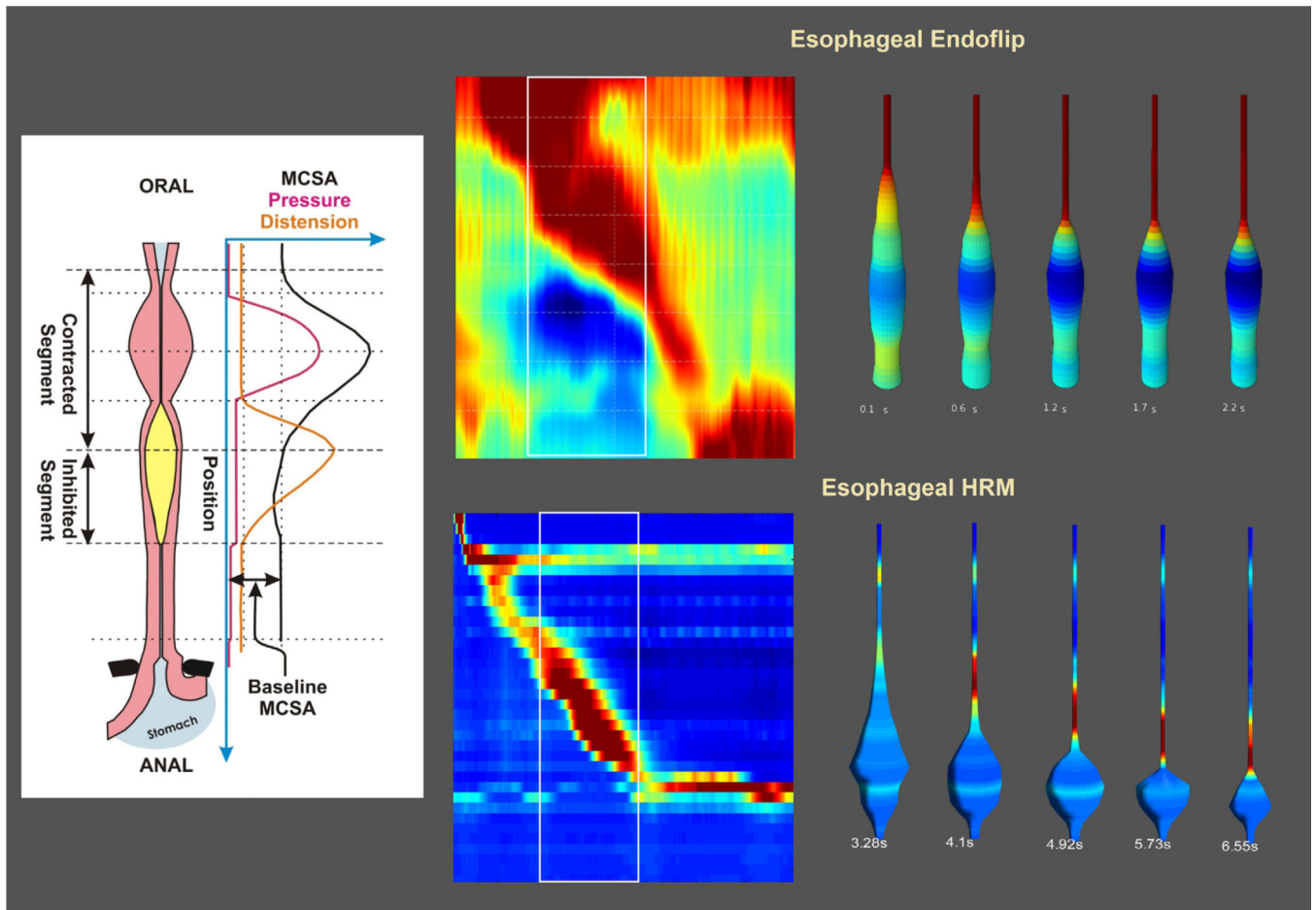
Figure 2.
Bolus moves through the esophagus in the shape of an "American Football" during peristaltic transport during primary and secondary peristalsis, recorded by 3 different methods: 1) ultrasound image derived data, 2) Antegrade contraction recorded by Endoflip technique, and 3) impedance derived luminal cross-sectional area of the esophagus.
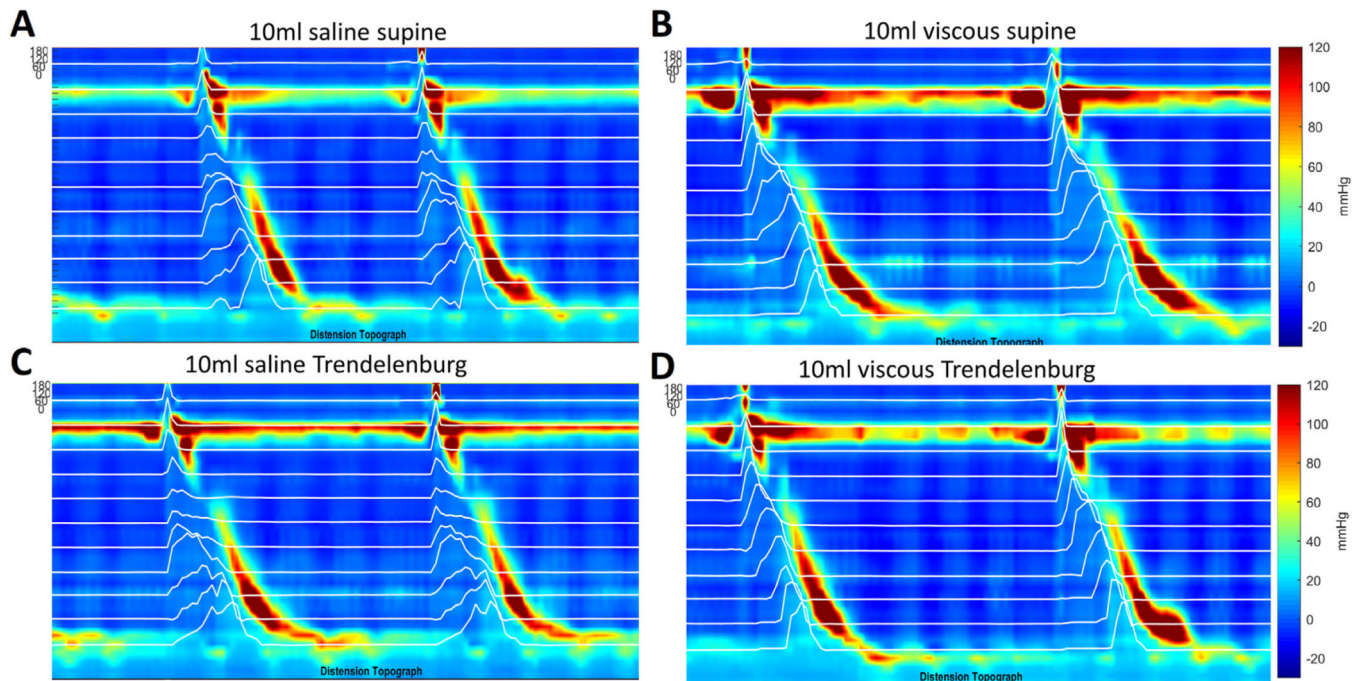
Figure 3.

Effect of posture and bolus viscosity on the distension-contraction waveforms. Esophageal distension shown as waveform and contraction as color heat map. Saline bolus in the supine position arrives much faster in the mid and distal esophagus as compared to the Trendelenburg position (A and C). The latter position slows the speed of bolus and bolus travels closer to the contraction wave along the length of the esophagus. Viscous bolus moves slowly through the esophagus in close relationship with the onset of contraction. Supine (B) vs Trendelenburg (D) position with viscous bolus did not influence the temporal relationship between contraction and dissension waveform. Reproduced with permission from Mittal RK, Muta K, Ledgerwood-Lee M, et al. Relaionship between distension-contraction waveforms during esophageal peristalsis: effect of bolus volume, viscocity and posture:In Press. Am J Physiol 2020; 319(4):G454–G467.
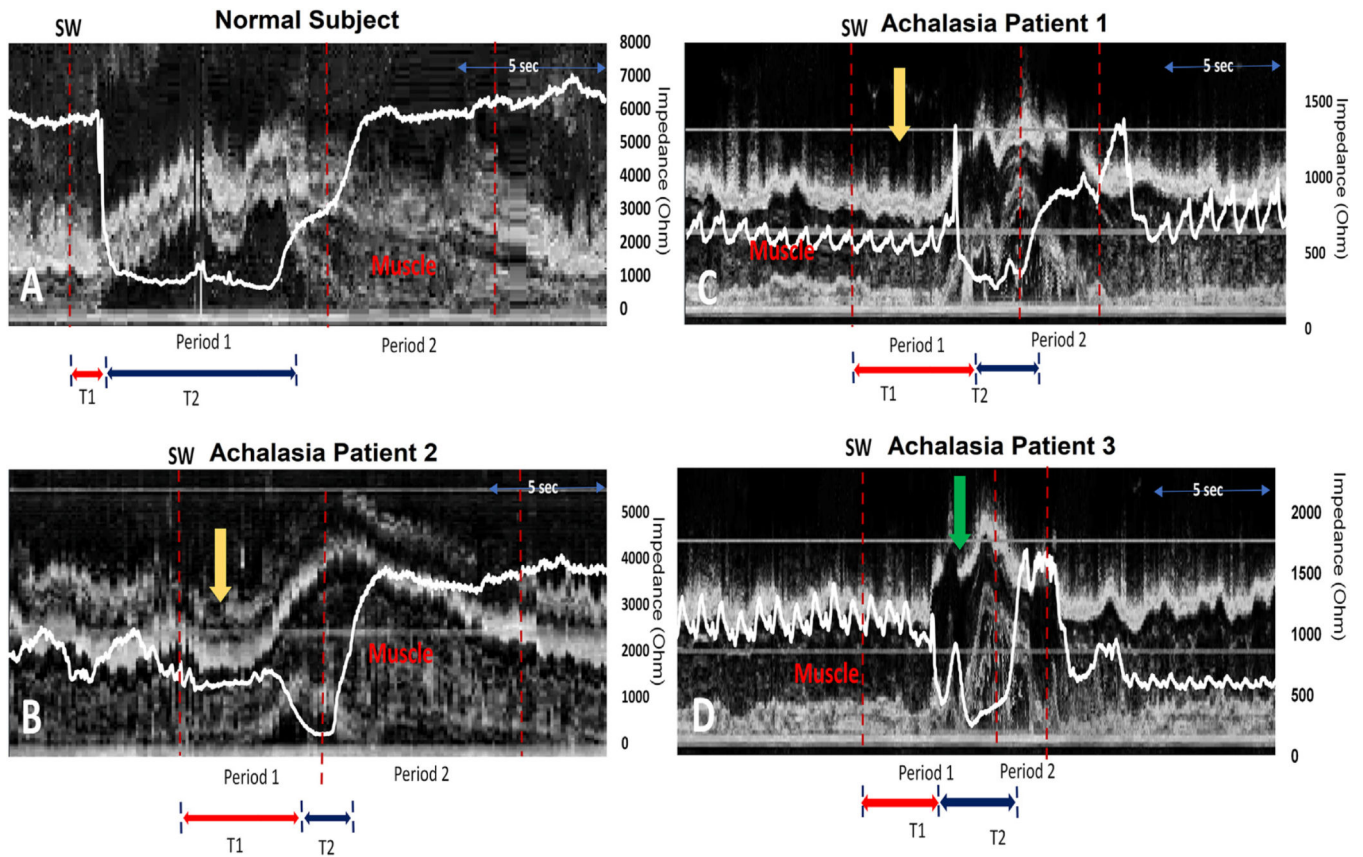
Figure 4.
m-Mode US image at 5 cm above the LES along with impedance line tracing to show the relationship between bolus arrival, bolus clearance, luminal distension, and muscle thickness with swallows in normal subject (A), and 3 patients with achalasia esophagus type 3 (B–D). X axis is time in these recordings. Yellow arrows show that unlike normal subject, there is luminal closure before arrival of bolus in achalasia 3 esophagus which results in delayed arrival of bolus in the distal esophagus and bolus travelling closer to the contraction wave. D shows luminal opening, followed by collapse (green arrow) and then opening again in this swallow. Time 1 = time between the onset of swallow and bolus arrival, Time 2 = time between bolus arrival and bolus clearance. Reproduced with permission from Park S, Zifan A, Kumar D, et al. Genesis of esophageal pressurization and bolus flow patterns in patients with achalasia esophagus. Gastroenterology 2018;155:327–336.
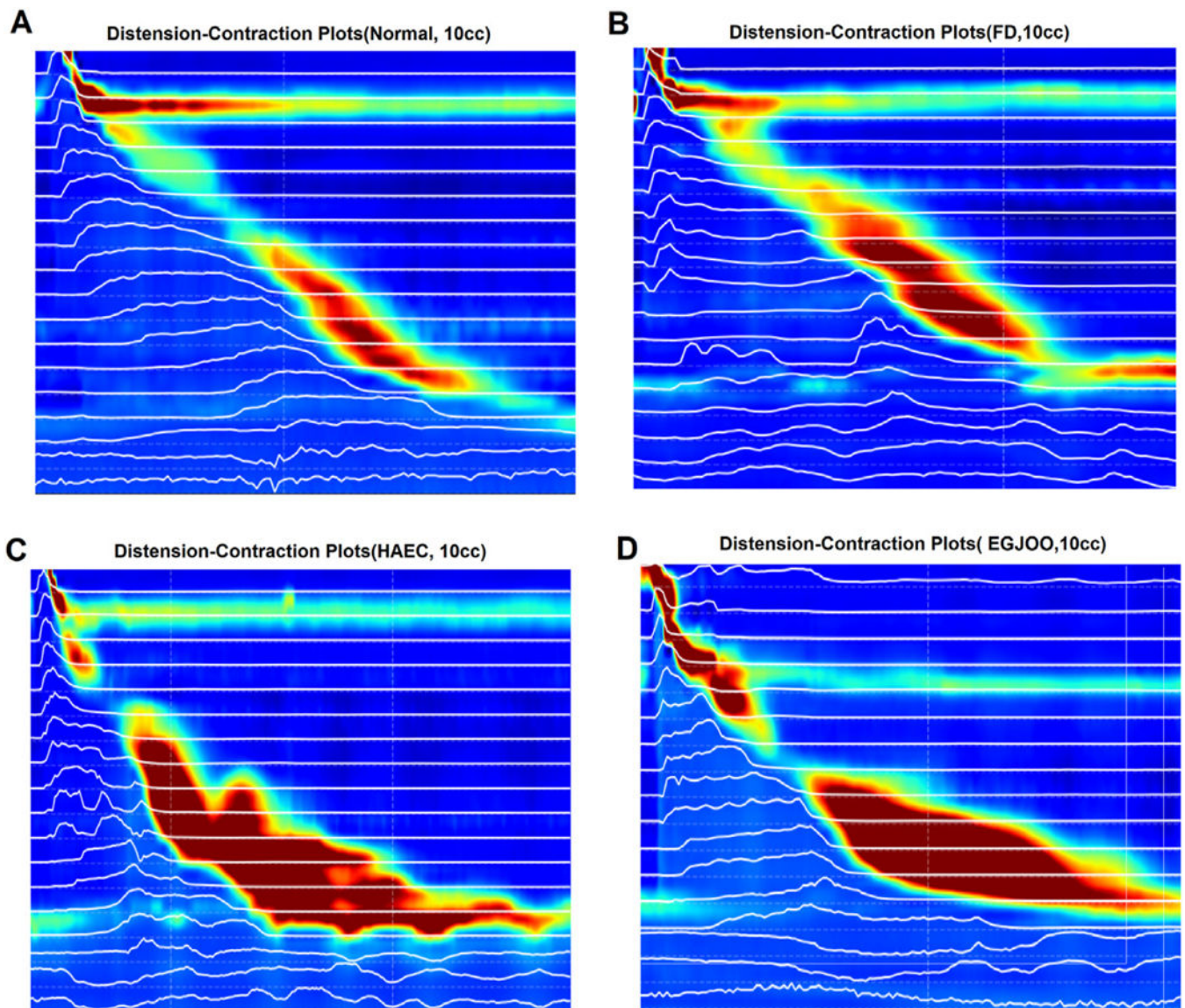
Figure 5.
Distension-contraction plots in a normal subject (A), a patient with nutcracker esophagus (C), function dysphagia (B) and esophagogastric junction outflow obstruction (D). Distension is seen as waveform and contraction as a color topograph. Note that the bolus arrives in the distal esophagus much ahead of the contraction. Also note that the amplitude of distension is smaller in patients. Finally, note the difference in the distension waveform between normal and patients.
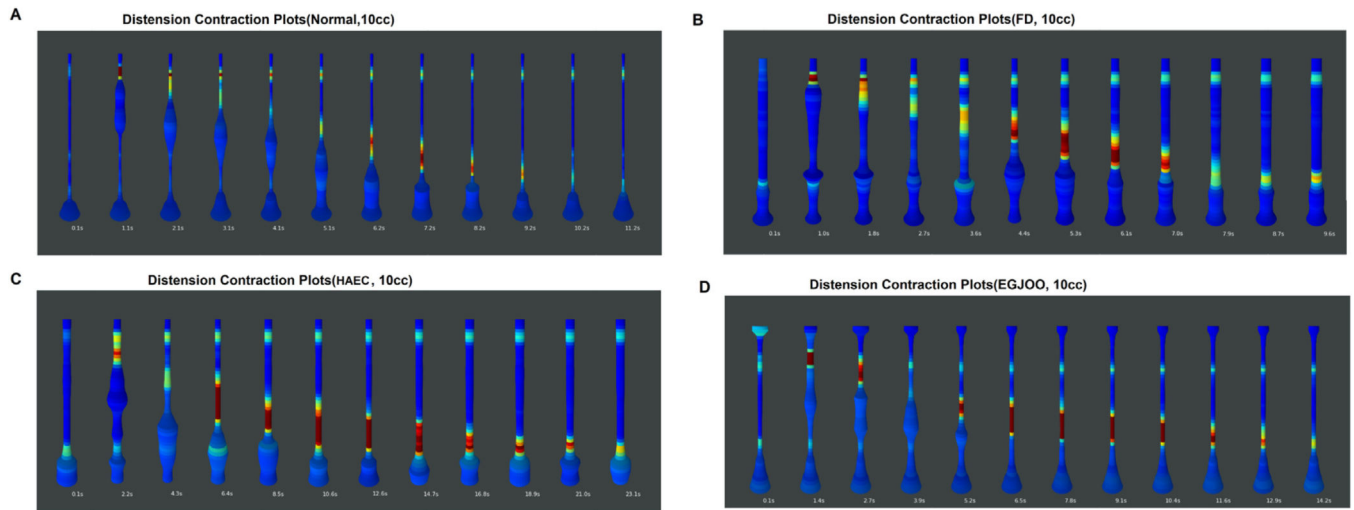
Figure 6.
Distension-contraction plots in a normal subject (A), a patient with nutcracker esophagus (C), function dysphagia (B) and esophagogastric junction outflow obstruction (D). Serial images during one swallow in each subject. These 4 subjects are same as in Figure 5. Note the differences in the temporal relationship between distension and contraction in normal subject vs patients. Also the amplitude of distension is smaller in patients with dysphagia but different diagnosis based on the manometry study.
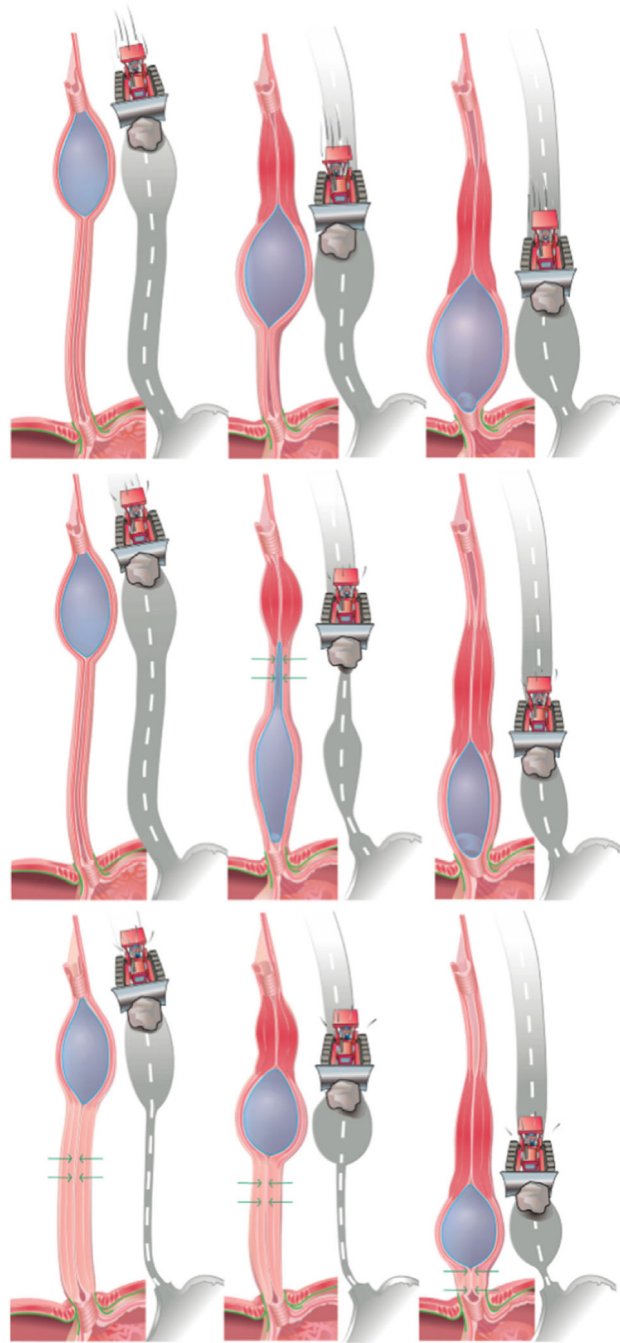
Figure 7.
The schematic show relationship between contraction and distension in normal subject (top row), patient with functional dysphagia (middle row) and patient with achalasia 3 esophagus (bottom row) Top row: The esophagus distends in the shape of an "American Football" ahead of the contraction. Middle row: Note a narrow lumen esophagus distal to the contraction wave that results in rapid transit of bolus to the distal esophagus. Bottom row: Note, luminal occlusion distal the distension that impedes the bolus flow.