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Genesis of Esophageal Pressurization and Bolus Flow Patterns in Patients with Achalasia Esophagus

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Abstract

Background & Aims: In patients with achalasia esophagus, swallows induce simultaneous pressure waves known as esophageal pressurization. We studied the mechanism of esophageal pressurization and bolus flow patterns in patients with type 2 or type 3 achalasia.

Methods: We recorded high-resolution manometry with impedance and intraluminal ultrasound images concurrently in patients with type 2 achalasia (n=6) or type 3 achalasia (n=8) and in 10 healthy subjects (controls) during swallows of 5 ml, 0.5 N saline. For each swallow, the ultrasound image was aligned with the pressure and impedance tracings to determine cavity and contact pressure, bolus arrival, bolus dwell time, and changes in muscle thickness at 5 cm and 10 cm above the lower esophageal sphincter.

Results: In patients with type 2 achalasia, esophageal pressurization was associated with an increase in the muscle thickness and luminal narrowing but not complete luminal closure (therefore, cavity pressure). Bolus arrival time in the distal esophagus, after the onset of a swallow, was delayed in patients with type 3 achalasia compared with controls due to early luminal closure. The early luminal closure was associated with a decrease in the muscle thickness. The bolus dwell time was shorter in patients with type 3 achalasia compared with controls. In patients with type 3 achalasia, the onset of simultaneous pressure wave was always a cavity pressure, but during contraction there were different periods of cavity and contact pressures, in association with increases in muscle thickness that resulted in bolus segmentation.

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Author Contributions:

RKM- Conceived the project, designed experiments, data acquisition, data analysis, and wrote the manuscript, SP-Data acquisition, analysis, figures preparation and writing paper, DK-data collection, intellectual input, and manuscript revision, AZ – data analysis/ interpretation, and manuscript writing and revision.

COI: None of the authors have any conflict of interest

Conclusions: We observed distinct mechanisms of esophageal pressurization and bolus flow patterns in patients with type 2 or type 3 achalasia esophagus compared with controls. These findings will increase our understanding of mechanisms of dysphagia.

Keywords

Esophageal peristalsis; LES; Corkscrew Esophagus; Simultaneous Esophageal Contraction

Introduction

Achalasia esophagus, a major motility disorder, is characterized by failure or incomplete relaxation of the lower esophageal sphincter (LES), and absence of esophageal peristalsis or sequential contraction in the distal esophagus[1]. In achalasia esophagus, swallows induce simultaneous pressure waves in the esophagus, also referred to esophageal pressurization. Based on the amplitude of esophageal pressurization, achalasia esophagus has been divided into 3 types, type 1- minimal pressurization, type 2-esophageal pressurization of > 30mm Hg and type 3 – with spastic type of esophageal contractions, (high amplitude contractions)[2]. We recently found differences in the onset and end of pressurization pattern between type 2 and type 3 achalasia esophagus; in type 2 achalasia, the onset as well as the end of esophageal pressurization waves are simultaneous. On the other hand, in patients with type 3 achalasia, the onset of pressurization wave is simultaneous, but the end is peristaltic[3]. Bolus clears only partly as a result of pressurization in type 2 achalasia esophagus, but it clears almost completely from the distal esophagus of patients with type 3 achalasia[4]. These differences suggest that the genesis of pressurization in type 2 and type 3 achalasia esophagus are different. If bolus clearance in type 3 achalasia is relatively normal then what is the mechanism of dysphagia in these patients?

Manometry techniques record intraluminal esophageal pressure, and the increase in pressure with each swallow can be categorized as cavity or contact pressure[5]. The contact pressure implies that the wall of the esophagus is in contact with the manometry probe, and it is generally due to luminal occlusion caused by circular muscle contraction of the esophagus. On the other hand, the cavity pressure implies presence of bolus between the esophageal wall and manometry probe. There can be many mechanisms of the cavity pressure, e.g., bolus entrapment between a progressive peristaltic contractions trying to propel the bolus against a closed LES[6, 7] and possibly others. Manometry can't distinguish between the cavity and contact pressure. It is not clear whether the simultaneous onset of pressure waves in the distal esophagus of type 3 achalasia esophagus is a cavity or a contact pressure. Intraluminal ultrasound image recordings of the esophagus can distinguish between cavity vs contact[8]. Furthermore, the intraluminal impedance recordings can also distinguish cavity vs contract; low impedance generally implies the presence of bolus and high impedance, the presence of contact with the esophageal wall[9, 10].

We observed that following a swallow, bolus arrives late in the distal esophagus of patients with type 3 achalasia, as compared to normal subjects, a pattern described by Omari et al. in patients with non-obstructed dysphagia[11–13]. Using high resolution manometry, intraluminal impedance and intraluminal high frequency catheter based US imaging (HFIUS), the goal of

our study was to determine the genesis of esophageal pressurization in type 2 and type 3 achalasia esophagus. Our hypothesis is that the motor events that lead to pressurization and bolus flow in the distal esophagus of patients with achalasia 2 and achalasia 3 are different. Our data show that the simultaneous onset of the pressure wave in the distal esophagus is a cavity pressure. We also identified a distinct closure of the esophagus between the onset of swallow, and onset of "simultaneous pressure wave" that resulted in delayed arrival, and compartmentalization of bolus in the distal esophagus of patients with type 3 achalasia.

Materials and Methods

The Institutional Review Board of the University of California, San Diego approved the protocol for the studies, and all participants gave a written informed consent before participating in the research study.

Criteria for Inclusion in the Study

Studies were performed in 10 healthy asymptomatic normal subjects, and 14 patients with achalasia esophagus, 6 type 2 achalasia, and 8 type 3 achalasia. The diagnosis of achalasia was made based on the HRM study done for clinical diagnostic purpose, prior to their participation in the research protocol. The clinical diagnostic HRM recordings were analyzed to determine the type of achalasia esophagus. Briefly, the HRM criteria for diagnosing achalasia are: absent peristalsis in the esophagus and incomplete EGJ relaxation (integrated relaxation pressure, IRP, > 15 mmHg/sec). The distinction between types of achalasia esophagus was based on the characteristics of swallow-induced esophageal pressure waveforms. Type 2 achalasia was diagnosed when the swallow-induced pressurization was > 30mmHg with ≥ 80% of the swallows. For type 3 achalasia, the criteria for "simultaneous pressure" waveform in the distal 10 cm of the esophagus were based on; 1) simultaneous onset of isocontour of 30mmHg (velocity of peristalsis of>8cm/sec) in the distal esophagus and distal contractile integral of > 450mmHg of ≥ 20% contractions. In addition, the distal latency was required to be < 4.5 seconds for > 20% of swallows in achalasia 3 esophagus. The onset as well as the end of the 30mm isocontour were simultaneous in type 2 achalasia. On the other hand, in patients with type 3 achalasia the onset of contractions (isocontour of 30mmHg) were simultaneous but the end of esophageal contraction were sequential or in other word peristaltic.

Simultaneous HRMZ and HFIUS Image Recordings

All subjects were studied using a catheter assembly that consisted of an HRMZ catheter (4.2-mm diameter; Medtronics Inc., Los Angeles, CA), equipped with 36 pressure transducers, spaced 1 cm apart and 18 impedance electrodes spaced 2 cm apart, taped to a 6F, HFIUS catheter, (Boston Scientific Instruments, Boston, MA). The US catheter was interfaced to the HP Sonos100 ultrasound machine (Hewlett Packard Sonos Intravascular, Andover, MA). The US images were acquired on the Manoscan computer and program, along with the HRMZ recording using Manoscan V (Model A-400), as well as on a DVD recorder (for back up). The ultrasound (US) transducer was positioned to acquire images at 5 cm above the LES. Liquid lidocaine spray (2 % lidocaine topical solution, USP) and viscous lidocaine (1% lidocaine hydrochloride topical solution, USP) were administered orally and

nasally for local anesthesia, followed by placement of the HRMZ-US catheter assembly through the nose. Eight to 10 swallows with 5ml, 0.5N saline were performed with the US transducer located at 5cm above the LES. The catheter was then pulled back until the US transducer was located 10 cm above the LES and additional 8–10 swallows were performed.

Data Analysis

Pressure Waveform Analysis: The HRM recordings were analyzed to determine the pressure pattern with each swallow as described earlier. As per Chicago classification > 20% of swallows are required to have distal latency of < 4.5 seconds which allows for heterogeneity from swallow to swallow in the diagnosis of achalasia esophagus. Furthermore, identification of contractile deceleration point (CDP) which is required for the calculation of distal latency can be challenging in patients with esophageal motor disorders[14]. In our analysis, we assessed whether the onset and end of isocontour of 30mmHg were simultaneous or sequential. While patients with type 2 achalasia showed homogeneity in pressure pattern from swallow to swallow, achalasia 3 patient revealed heterogeneity, as shown in Figure 1 with subtle differences in appearance, but meeting the criteria of simultaneous onset of isocontour of 30mmHg, except for pattern 6 that appeared to be peristaltic (sequential onset of isocontour of 30mmHg). The latter was observed in one patient who met criteria for type 3 achalasia on the diagnostic HRM study, but was found to have peristaltic onset of contraction on the research study. In one patient all the waveforms were pattern 2, in another patient all pattern 3. In the remaining 5 patients, different waveforms as shown in Figure 1 were found in the same subject.

Ultrasound Image Analysis

For each swallow, a composite image of the HRM, M-mode US image and line impedance recording at the location of the US transducer was generated. The M-mode US image was generated from the B-mode US images and converted into 16 equally spaced M-mode US images (every 22.5° apart) using a custom built software, as described previously[15, 16]. A M-mode US image, orthogonal to the esophageal wall, in which both circular and longitudinal muscle layers were clearly visualized was selected for the data analysis. To isolate impedance waveform at the level of US transducer, the impedance data were exported in excel sheets and converted into a line drawing. The M-mode ultrasound images and impedance recordings at the location of the US were aligned with the HRMZ recording for each swallow. Five to 8 swallows were analyzed in each subject at 5 cm and another 5–7 swallows at 10 cm above the LES.

Cavity vs Contact Pressure

Each HRM-impedance-M-mode US image, at 5cm and 10cm above the LES was analyzed to determine whether the recorded pressure was a contact or a cavity pressure. Events following each swallow were divided into two periods. The period between the onset of pharyngeal contraction and the onset of an isocontour of 30mmHg was defined as period 1, and between the onset and end of isocontour of 30mmHg was period 2, (Figure 2). In normal subjects, period 1 is the time when bolus travels through the esophagus and generally implies cavity pressure, as the wall of the esophagus is not in contact with the manometry

probe; in other words, there is either liquid or air present between the manometry probe and the lining/ mucosa of the esophagus. On the other hand, period 2, between isocontour of 30mmHg is generally thought of as the contact pressure and implies circular muscle contraction related occlusion of the esophageal lumen/manometry probe. The HFIUS images and impedance recordings of each swallow were assessed for the presence of cavity and contact, during period 1 and period 2. Our determination of cavity and contact pressure was based upon, **1)** the review of M-mode and B-mode US images, which show the presence of liquid/air between the manometry probe and mucosa for the cavity pressure, and close opposition of the manometry probe and mucosa all around the circumference for the contact pressure. **2)** In addition to the above, impedance line tracing was also reviewed during period 1 and period 2 to determine cavity versus contact pressure; low impedance values (<500 Ohms) for cavity, and high impedance values (>500 Ohms) for the contact pressures[9]. The mean and range of pressure during the entire period 1 was determined for normal subjects and patients with achalasia 3 esophagus.

Bolus Arrival and Bolus Dwell time

Impedance recordings can be used to determine the bolus arrival (fall of impedance to 50% of the baseline), and bolus clearance (return of impedance to the same value as bolus arrival impedance) at a given site in the esophagus[10]. The bolus arrival time at 5cm and 10cm above the LES is the time difference between pharyngeal contraction (swallow), and drop in esophageal impedance to 50% of the baseline value (T1). The bolus dwell time was the time period between bolus arrival and bolus clearance times (T2), as shown in Figure 2.

Statistical Analysis

Data are presented as mean ± standard deviation (S.D.). Unpaired Student's t-test with unequal variance was used to estimate the statistical significance between the groups. P-value less than 0.05 were considered statistically significant.

Results

Normal subjects

Figure 2, shows an HRM recording, with a superimposed M-mode US image and impedance line tracing at 5 cm above the LES in a normal subject. Following pharyngeal contraction and upper esophageal sphincter relaxation, the bolus arrives faster than the pressure wave (contraction) at 5cm above the LES. At the onset of esophageal contraction (or the pressure wave) there is a rapid return of impedance to the baseline value. The bolus arrival time at 10 cm and 5 cm levels were 0.61 ± 0.2 seconds and 0.9 ± 0.4 seconds respectively. Bolus dwell times at 10 cm and 5 cm levels were 4.9 ± 1.1 sec and 6.3 ± 1.3 seconds respectively. Ultrasound images show distension of the esophagus with liquid during period 1. Compared to baseline, the muscle gets thinner during the entire distension period. With the onset of pressure wave (contraction) there is complete occlusion of the esophageal lumen with increase in the muscle thickness. The peak of pressure wave is temporally aligned with the peak muscle thickness.

Achalasia Type 2

Figure 3A shows changes in impedance, luminal dimension and muscle thickness during swallow-induced esophageal pressurizations in a patient with type 2 achalasia esophagus. Following swallows, the changes in pressure amplitude throughout the length of the esophagus was approximately the same, (difference of < 10mmHg). The M-mode US images revealed a distended esophagus prior to swallow, and with each pressurization there is a decrease in the luminal dimension along with an increase in the muscle thickness. Greater the increase in pressure amplitude, greater was the increase in muscle thickness and greater the reduction in esophageal lumen. The impedance value generally increased during pressurizations. Forty five swallows were analyzed at 5cm, and 41 swallows at 10 cm level in six patients with achalasia 2 esophagus (6–7 swallow per subject at each of the two sites). Impedance value increased during the majority of swallows at 5 cm above the LES (Figure 3B). On the other hand, the change in the impedance value at 10 cm above LES was variable. The muscle thickness increased (Figure 3C) and lumen size decreased (Figure 3D) during the majority of swallows at both, 5cm and 10cm above the LES. All swallows, at 5cm and 10cm levels were determined to be cavity pressures with increase in muscle thickness.

Achalasia Type 3

The esophageal pressurization pattern in response to swallows in patients with type 3 achalasia esophagus revealed heterogeneity of pressurization, as shown in (Figure 1). As per definition, the onset of pressure wave with all swallows was simultaneous at isocontour pressure of 30mmHg. On the other hand, the end of the pressure waves were peristaltic in all patients during all swallows. In one patient who met the criteria for achalasia 3 esophagus on the diagnostic HRM study, showed peristaltic esophageal contraction on the research study (Figure 1F).

We compared periods 1 in normal or type 3 achalasia patients with respect to various parameters. In patients with type 3 achalasia, the mean “bolus” pressure during period 1, (12.7 ± 4.8 mm Hg) was higher than the normal subjects (3.6 ±2.3 mmHg), ($P < .001$). Unlike normal subjects in whom the lumen was distended during the entire period 1, we identified periods of luminal closure (contact pressure) during period 1 in patients with achalasia 3 esophagus (Figure 4). The lumen either opened late after the onset of swallow (23/76 swallows) (Figure 4B and C), or after initially opening for a brief period, it closed and then opened again (22/76 swallows), (Figure 4D). Both of the above abnormalities were found during period 1 in 7/76 swallows. Thus 78% of the swallows demonstrated abnormal luminal opening patterns during period 1. The above described abnormal pattern was found during 30% −100% (median 60%) of swallows in each of the studied subjects. These periods of luminal closure were generally associated with thinning of the muscle. These patterns of luminal closure and opening during period 1 resulted in either delayed arrival or compartmentalization of bolus at 5cm above the LES, as determined by the impedance recordings and US image analysis. The bolus arrival time was longer and bolus dwell time shorter at both, 5cm and 10cm level in achalasia 3, as compared to normal subjects (Figure 2).

At 5 cm above the LES, the pressure at the instance of 30mm Hg was always a cavity pressure, as determined from the US images (presence of liquid between the US probe and mucosa) and impedance values (decrease in impedance compared to baseline), (Figure 5, 6A). On the other hand, at 10cm above the LES, at the instance of 30mmHg it was always a contact pressure with increase in impedance and increase in muscle thickness (data not shown). The presence of cavity vs contact among six different patterns of achalasia 3 contraction waves was not different (Figure 6B).

The entire period 2 (between isobaric contours of 30mmHg) is a contact pressure in normal subjects. In contrast, patients with type 3 achalasia show the presence of cavity, contact or mix of the two during period 2, (Figure 5). During some swallows, almost the entire period 2, except for the last 1–2 seconds, was a cavity pressure, (figure 5B). The muscle thickness was higher than baseline during majority of the period 2, both during cavity as well as contact pressure.

Figure 7 shows the schematic of bolus flow and muscular contraction in the esophagus of normal subjects and patients with type 2 and type 3 achalasia esophagus. In normal subjects, soon after the onset of swallow, and until the arrival of esophageal contraction wave, the esophageal lumen is open and allows free passage of bolus through the esophagus. In patients with type 2 achalasia bolus flows into the stomach occurs intermittently due to esophageal muscle contraction that starts in the distal esophagus and proceeds proximally. The above contraction results in a decrease of the luminal dimensions and thus pressurization of the entire esophagus, which forces the esophageal contents into the stomach against a closed (non-relaxed) lower esophageal sphincter. On the other hand, in patients with achalasia 3 esophagus the distal esophageal lumen is closed prior to the arrival of contraction wave that is associated with thinning of the muscle layers. Pressures during period 2 are mix of cavity and contact pressure with increase in muscle thickness. The above patterns of luminal opening and closing results in the compartmentalization of bolus and obstruction to the bolus passage through the esophagus.

Discussion

The major finding of our study are, **1)** swallow induced esophageal pressurization in achalasia 2 esophagus is a cavity pressure. This pan-esophageal pressurization results from reduction in the luminal dimension/esophageal volume as a result of muscle contractions of the distal esophagus, **2)** in patients with achalasia 3 esophagus, during period 1 (between the onset of swallow and onset of isocontours of 30mmHg) there is delayed opening or intermittent closure of the lumen resulting in either delayed arrival and or compartmentalization of bolus in the distal esophagus, **3)** in achalasia 3 patients, the pressure at the onset of period 2 is a cavity pressure and during period 2, various time periods of cavity and contact pressures were found. We observed thicker muscle as compared to baseline during the entire period 2, indicative of active muscle contraction.

Esophageal peristalsis has been studied extensively in humans using various types of manometry techniques. The HRM that displays topographical color plots of pressure waveform during peristalsis, at every one cm along the length of esophagus, is currently

used routinely in the clinical settings to evaluate motility disorders of the esophagus. The purpose of all types of manometry methods is to record esophageal muscle contractions. However, in reality intraluminal manometry techniques record intraluminal pressures which may or may not be related to muscle contractions. Investigators have attempted to separate pressure increases in the esophagus due to either contact or a cavity pressure. Generally, in normal subjects, most of the contact pressure is related to contraction of the circular muscle of esophagus. On the other hand, in patients with esophageal motility disorders one can observe large increase in esophageal pressure with the cavity present. There are several possibilities with regards to the genesis of cavity pressure, it may be due to, 1) bolus trapped between an aborally progressing peristalsis and a closed distal esophagus related to poor sphincter relaxation or mechanical obstruction, 2) due to reduction in the esophageal volume, either axial shortening or circumferential constriction of the esophagus, and 3) a combination of the above two. One can differentiate between the above patterns by looking at the changes in muscle thickness; esophageal muscle generally get thinner with pattern 1 and thicker with pattern 2. Our findings show that in type 2 achalasia esophagus, the esophageal pressurization is related to muscle contraction that results in reduction of the lumen size/esophageal volume and is in accordance with the Boyles law of physics (also described as “pump gun” mechanism by Tutian et al[17]). One can argue whether the muscle contraction in achalasia type 2 is related to longitudinal muscle or non-lumen obliterating circular muscle contraction. Irrespective, the pattern of muscular contraction in type 2 achalasia is different from the normal subjects in whom there is sequential increased in muscle thickness along the length of the esophagus. On the other hand in patients with achalasia type 2 esophagus there is no sequential contraction. Instead, there is a distinct pattern of contraction that begins soon after the onset of swallow in the distal esophagus, it is stronger at 5cm level as compared to 10cm level above the LES, a pattern similar to what is seen in association with the transient LES relaxation[18].

In normal subjects, following a swallow, the esophageal lumen distends with bolus and remains distended until the arrival or the onset of esophageal contraction, what we defined as period 1[19]. The pressure in the esophagus, also known as bolus pressure is generally low during period 1, and the distension travels in a sequential or a peristaltic fashion along the length of the esophagus[20]. The onset of collapse of the esophageal lumen at the end of distension is associated with contraction of the circular and longitudinal muscles, as measured by changes in the esophageal muscle cross section area over time[21]. In patients with nutcracker esophagus there is a delay between the onset of lumen collapse and peak pressure recorded by manometry, which we suggested to be related to lack of synchrony between circular and longitudinal muscle contraction[22]. In this study we observed an increase in muscle thickness (muscle contraction), while the esophageal lumen was still not fully collapsed for variable periods of time during period 2, and sometimes during period 1, in achalasia 3 patients. The baseline esophageal muscle in achalasia 3 esophagus is 2–3 times thicker than normal subject, and gets even thicker with contraction, yet it is not able to fully collapse the lumen. The latter suggests resistance to luminal collapse, which is likely related to high bolus pressures in the esophagus due to an outflow obstruction, the bolus trapped between an aborally progressing peristaltic contraction and a poorly relaxing LES.

A novel finding of our study is the luminal closure during period 1 that results in delayed arrival of bolus in the distal esophagus in patients with type 3 achalasia esophagus. First question is why does the lumen close during period 1 and second, what does it mean? We observed that unlike normal subjects where the lumen is wide open during period 1, in patients with achalasia 3 esophagus the lumen is closed ahead of an oncoming peristaltic contraction. Sifrim used an ingenious method of recording esophageal inhibition, using a small balloon in the esophagus to create an artificial high pressure zone and observed inhibition of the artificial high pressure zone with swallows in normal subjects[23], but not in patients with spastic esophageal motility disorders[24]. More recently, Carlson et al, using another novel methodology, functional luminal imaging probe (FLIP), studied responses to esophageal distension in normal subjects and patients with achalasia 3 esophagus. They observed antegrade contractions in normal subjects but retrograde contractions in patients with achalasia 3 esophagus[25, 26]. Techniques used by Sifrim and Carlson detect changes in luminal dimensions and not necessarily muscular contraction. We suspect that the luminal closure during period 1 that we observed with US imaging is the same phenomenon as described by Sifrim and Carlson. This luminal closure occurs in response to swallow and is associated with thinning rather than thickening of the muscle and is unlikely to be muscle contraction. In normal subjects there is also thinning of the muscle during period 1, but unlike achalasia 3 patients it is associated with the luminal opening or distension[21, 27]. The precise reason for luminal closure associated with the thinning of muscle in patients with achalasia 3 esophagus is likely related to loss of inhibitory innervation. Alternatively, it may be a purely mechanical issue related to swallow-induced proximal pull on the distal esophageal muscle, which is markedly thicker than normal subjects and thus has lower compliance that resists luminal distension.

What is the relevance of luminal closure ahead of peristaltic contraction and delayed arrival of bolus in the distal esophagus? Using impedance methodology, Omari and colleagues observed delayed arrival of bolus in the distal esophagus of patients with functional dysphagia and patients who developed dysphagia after fundoplication[12]. They measured 3 parameters from the concurrent manometry impedance recordings to calculate a “dysphagia risk index”[12]. These 3 parameters were, 1) high pressure at the instance of nadir impedance, “bolus pressure” 2) steeper slope of the intrabolus pressure and, 3) a short time interval between nadir impedance and peak of contraction wave. The third parameter in their “dysphagia risk index” implies delayed arrival of bolus in the distal esophagus, and is similar to what we observed in type 3 achalasia esophagus. Similar to their findings[11], we also found that the bolus pressures are high and bolus travels much closer to the contraction wave in the distal esophagus of patients with type 3 achalasia esophagus. The real relevance of luminal closure ahead of peristaltic contraction is that it introduces functional obstruction or in other words resistance to the bolus flow driven by the contraction wave. Generally, dysphagia is thought to be associated with either ineffective peristalsis or delayed clearance of bolus in the esophagus, even though, there is poor correlation between these parameters[10]. May be it is the resistance to bolus propulsion and not the actual bolus retention that is experienced by the patients as dysphagia sensation[13, 28], which would explain why patients with achalasia 3 esophagus have a relatively normal bolus clearance yet complain of dysphagia.

Classical description of diffuse esophageal spasm on barium swallow study is what is described as “corkscrew esophagus or rosary bead esophagus”. One of the hallmark of these descriptions is segmentation or compartmentalization of bolus along the length of the esophagus. To the best of our knowledge, manometric counterpart of the corkscrew esophagus has never been described. Our finding of luminal closure during the middle of period 1 results in the compartmentalization of bolus. Also, muscular contractions during period 2 with bolus present in the lumen can give an appearance of segmented bolus on the esophagogram. We speculated in an earlier publication that the so called “diffuse esophageal spasm” in the older literature may be the same entity as achalasia 3 esophagus[3], as per Chicago classification[14]. It is interesting that the published barium swallow images of achalasia 3, and not achalasia type 2 esophagus show a corkscrew pattern[29]. Patients with achalasia type 2 esophagus generally do not have a dilated esophagus. Our findings that with swallowing the esophageal volumes/lumen actually become smaller in achalasia 2 patients provides rationale for the lack of significant esophageal dilation in these patients. On the other hand, lack of pressurization and absence of muscular contractions in response to swallow, we propose is a reason for the dilated esophagus observed in type 1 achalasia patients.

Some of the topographical patterns in achalasia 3 esophagus that we show in Figure 1 may appear akin to what one might see in patients that are classified as esophagogastric junction outflow obstruction (EGJOO), based on the Chicago Classification. Our study inclusion criteria were stringent as stated in the method section. We did not find differences in the cavity and contact pressure frequency between isocontours of 30mmHg among 6 topographical patterns (figures 1 and 6). More important is that we found luminal closure during period 1 in all of our achalasia 3 patients and not in normal subjects, which is the major finding our study and we believe is the cause of dysphagia sensation in these patients. Studies are in progress in our laboratory to determine if luminal closure or inadequate opening during period 1 is present in patients classified as EGJOO (defined by Chicago Classification) and functional dysphagia (defined by Rome Criteria).

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References

1. Kahrilas PJ, Katzka D, Richter JE. Clinical Practice Update: The Use of Per-Oral Endoscopic Myotomy in Achalasia: Expert Review and Best Practice Advice From the AGA Institute. Gastroenterology 2017;153:1205–1211. [PubMed: 28989059]
2. Pandolfino JE, Kwiatek MA, Nealis T, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008;135:1526–33. [PubMed: 18722376]
3. Kim TH, Patel N, Ledgerwood-Lee M, et al. Esophageal contractions in type 3 achalasia esophagus: simultaneous or peristaltic? Am J Physiol Gastrointest Liver Physiol 2016;310:G689–95. [PubMed: 26950858]
4. Hong SJ, Bhargava V, Jiang Y, et al. A unique esophageal motor pattern that involves longitudinal muscles is responsible for emptying in achalasia esophagus. Gastroenterology 2010;139:102–11. [PubMed: 20381493]

5. Brasseur JG, Dodds WJ. Interpretation of intraluminal manometric measurements in terms of swallowing mechanics. Dysphagia 1991;6:100–19. [PubMed: 1935258]
6. Mittal RK, Ren J, McCallum RW, et al. Modulation of feline esophageal contractions by bolus volume and outflow obstruction. Am J Physiol 1990;258:G208–15. [PubMed: 2305886]
7. Massey BT, Dodds WJ, Hogan WJ, et al. Abnormal esophageal motility. An analysis of concurrent radiographic and manometric findings. Gastroenterology 1991;101:344–54. [PubMed: 2065909]
8. Mittal RK, Liu J, Puckett JL, et al. Sensory and motor function of the esophagus: lessons from ultrasound imaging. Gastroenterology 2005;128:487–97. [PubMed: 15685559]
9. Kim JH, Mittal RK, Patel N, et al. Esophageal distension during bolus transport: can it be detected by intraluminal impedance recordings? Neurogastroenterol Motil 2014;26:1122–30. [PubMed: 24861157]
10. Sifrim D, Blondeau K. New techniques to evaluate esophageal function. Dig Dis 2006;24:243–51. [PubMed: 16849851]
11. Nguyen NQ, Holloway RH, Smout AJ, et al. Automated impedance-manometry analysis detects esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry. Neurogastroenterol Motil 2013;25:238–45, e164. [PubMed: 23113942]
12. Myers JC, Nguyen NQ, Jamieson GG, et al. Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. Neurogastroenterol Motil 2012;24:812–e393. [PubMed: 22616652]
13. Chen CL, Yi CH, Liu TT, et al. Characterization of esophageal pressure-flow abnormalities in patients with non-obstructive dysphagia and normal manometry findings. J Gastroenterol Hepatol 2013;28:946–53. [PubMed: 23432518]
14. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160–74. [PubMed: 25469569]
15. Abrahao L Jr, Bhargava V, Babaei A, et al. Swallow induces a peristaltic wave of distension that marches in front of the peristaltic wave of contraction. Neurogastroenterol Motil.
16. Zifan A, Mittal RK. Ultrasoundx: Advanced Interactive Graphical user Interface for the Calculation of Cross-Sectional Area and Thickness from Ultrasound Video Sequences of the Esophagus. Gastroenterology 2017;152:S1034–S1035.
17. Tutuian R, Pohl D, Castell DO, et al. Clearance mechanisms of the aperistaltic oesophagus: the “pump gun” hypothesis. Gut 2006;55:584–5. [PubMed: 16354796]
18. Babaei A, Bhargava V, Korsapati H, et al. A unique longitudinal muscle contraction pattern associated with transient lower esophageal sphincter relaxation. Gastroenterology 2008;134:1322–31. [PubMed: 18384786]
19. Mittal RK, Padda B, Bhalla V, et al. Synchrony between circular and longitudinal muscle contractions during peristalsis in normal subjects. Am J Physiol Gastrointest Liver Physiol 2006;290:G431–8. [PubMed: 16210472]
20. Abrahao L Jr., Bhargava V, Babaei A, et al. Swallow induces a peristaltic wave of distension that marches in front of the peristaltic wave of contraction. Neurogastroenterol Motil 2011;23:201–7, e110. [PubMed: 21083789]
21. Nicosia MA, Brasseur JG, Liu JB, et al. Local longitudinal muscle shortening of the human esophagus from high-frequency ultrasonography. Am J Physiol Gastrointest Liver Physiol 2001;281:G1022–33. [PubMed: 11557523]
22. Jung HY, Puckett JL, Bhalla V, et al. Asynchrony between the circular and the longitudinal muscle contraction in patients with nutcracker esophagus. Gastroenterology 2005;128:1179–86. [PubMed: 15887102]
23. Sifrim D, Janssens J, Vantrappen G. A wave of inhibition precedes primary peristaltic contractions in the human esophagus. Gastroenterology 1992;103:876–82. [PubMed: 1499938]
24. Sifrim D, Janssens J, Vantrappen G. Failing deglutitive inhibition in primary esophageal motility disorders. Gastroenterology 1994;106:875–82. [PubMed: 8143993]
25. Carlson DA, Lin Z, Kahrilas PJ, et al. The Functional Lumen Imaging Probe Detects Esophageal Contractility Not Observed With Manometry in Patients With Achalasia. Gastroenterology 2015;149:1742–51. [PubMed: 26278501]

26. Carlson DA, Hirano I. Application of the Functional Lumen Imaging Probe to Esophageal Disorders. Curr Treat Options Gastroenterol 2017;15:10–25. [PubMed: 28265971]

27. Yamamoto Y, Liu J, Smith TK, et al. Distension-related responses in circular and longitudinal muscle of the human esophagus: an ultrasonographic study. Am J Physiol 1998;275:G805–11. [PubMed: 9756512]

28. Mittal RK, Shaffer HA, Parollisi S, et al. Influence of breathing pattern on the esophagogastric junction pressure and esophageal transit. Am J Physiol 1995;269:G577–83. [PubMed: 7485510]

29. Pandolfino JE, Kahrilas PJ. Presentation, diagnosis, and management of achalasia. Clin Gastroenterol Hepatol 2013;11:887–97. [PubMed: 23395699]

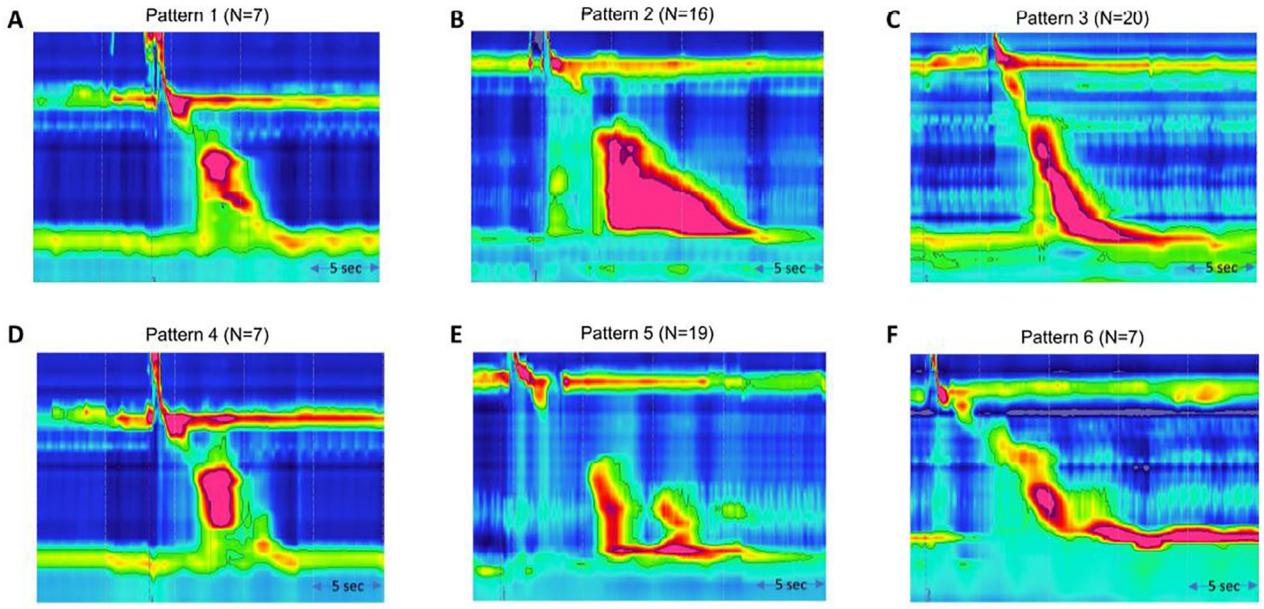

Figure 1:

(A-F) Esophageal pressure topograph patterns in patients with achalasia 3 esophagus. Note, the heterogeneity. The onset of 30 Hg isobaric pressure in the distal esophagus is simultaneous but the end is peristaltic.

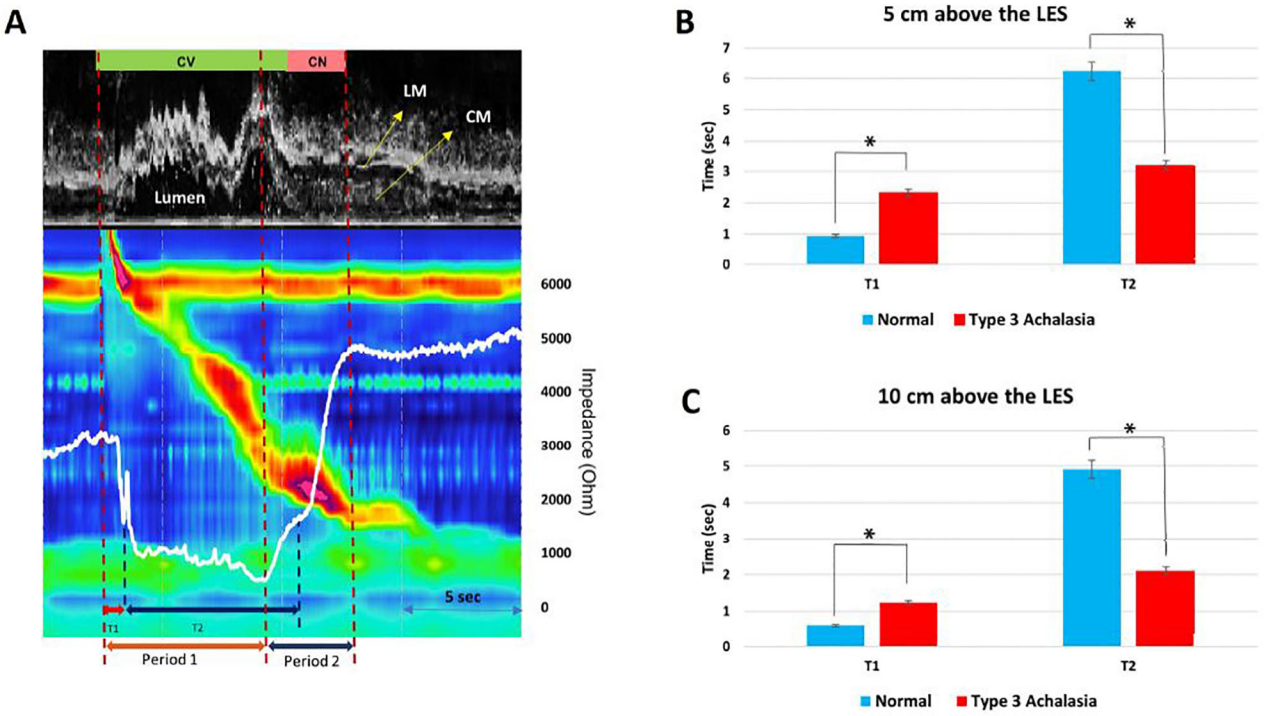

Figure 2:

(A) HRM, impedance line tracing and m-Mode US image at 5 cm above the LES in a normal subject. Note, the arrival of bolus soon after the onset of swallow in the distal esophagus (by impedance and US image) and clearance by the contraction wave. Period 1 = the time between the onset of swallow and onset of contraction at 5 cm above the LES (30mm Hg isocontour). Period 2 = is the time between the isocontours of 30mm, at the beginning and end of contraction wave). T1 (bolus arrival time) = time between the onset of swallow and arrival of bolus at 5 cm above the LES, T2 (bolus dwell time) = time between the bolus arrival and bolus clearance time. Bolus arrival and bolus dwell times in the distal esophagus in normal subjects and patients with achalasia 3 esophagus at **(B)** 5cm and **(C)** 10cm above the LES. The bolus arrival time is longer and bolus dwell time shorter in achalasia 3 esophagus patients as compared to normal subjects.

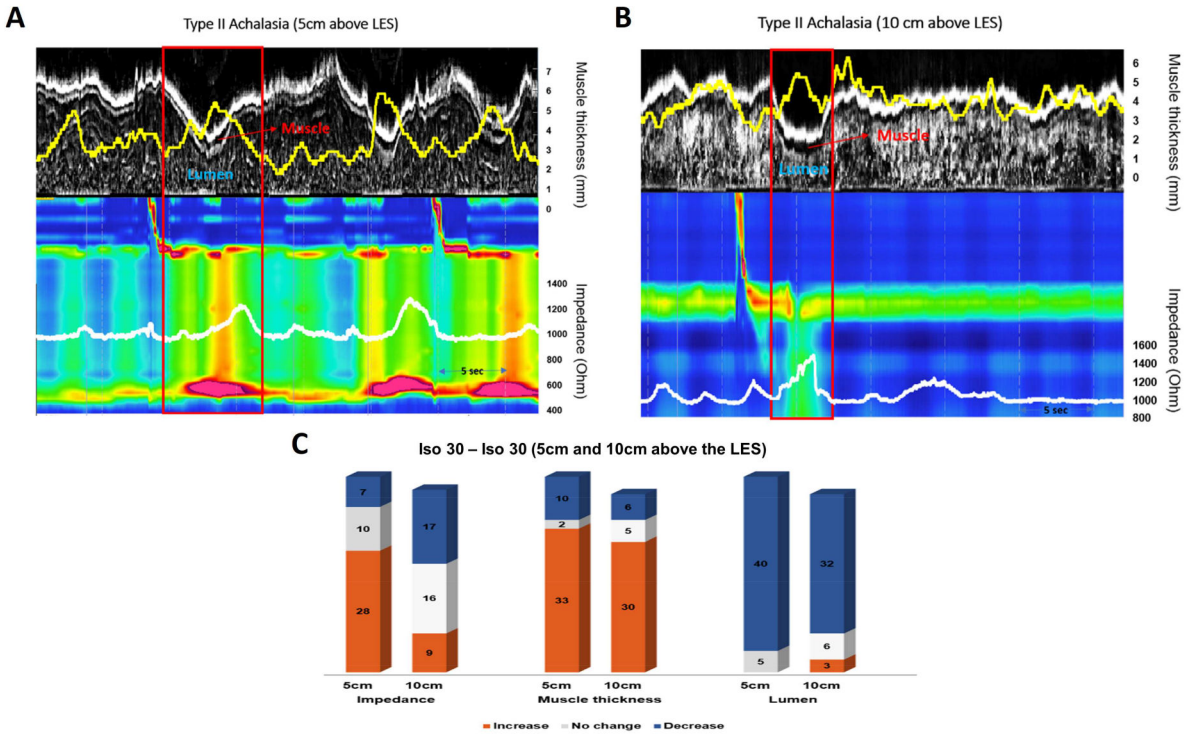

Figure 3:

HRM, impedance line tracing, and m-Mode US image at 5 cm **(A)** and 10 cm **(B)** above the LES in a patient with achalasia esophagus, type 2. Note, that esophageal pressurization (red box) is associated with an increase in the muscle thickness, decrease in the esophageal lumen and an increase in esophageal impedance, (**C)** Frequency of increase, decrease or no change in the impedance, muscle thickness, and luminal size in achalasia 2 esophagus.

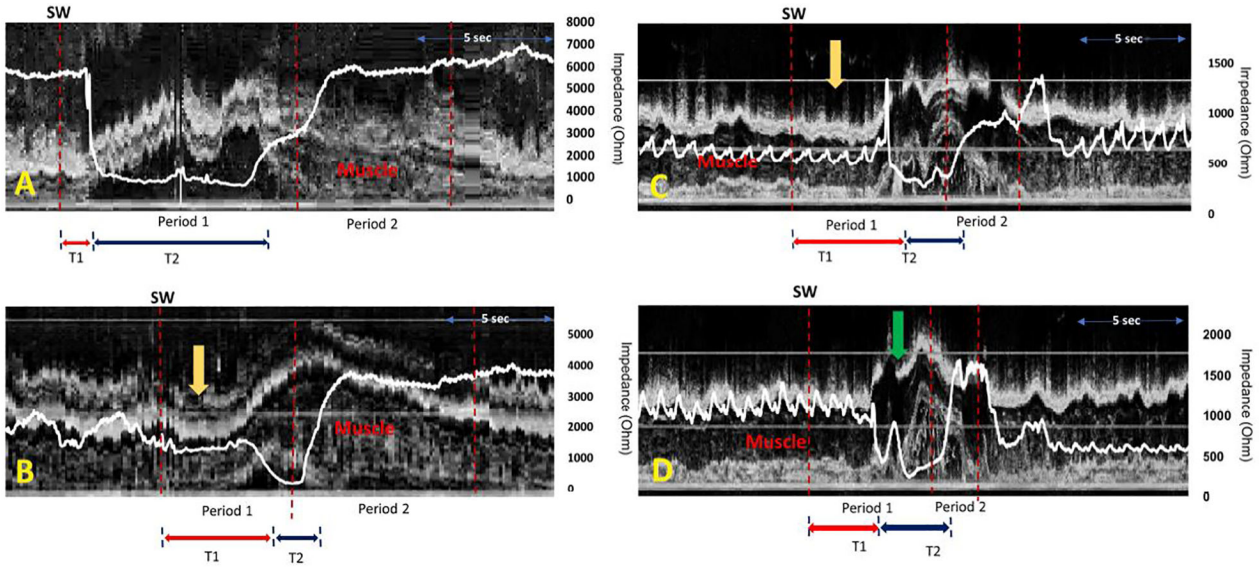

Figure 4:

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 3 esophagus **(B, C, D)**. Yellow arrows shows luminal closure during period 1 in achalasia 3 esophagus which results in delayed arrival of bolus. **(D)** shows luminal opening, collapse (green arrow) and opening during period in this swallow. Time 1 = time between the onset of swallow and bolus arrival, Time 2 = time between bolus arrival and bolus clearance.

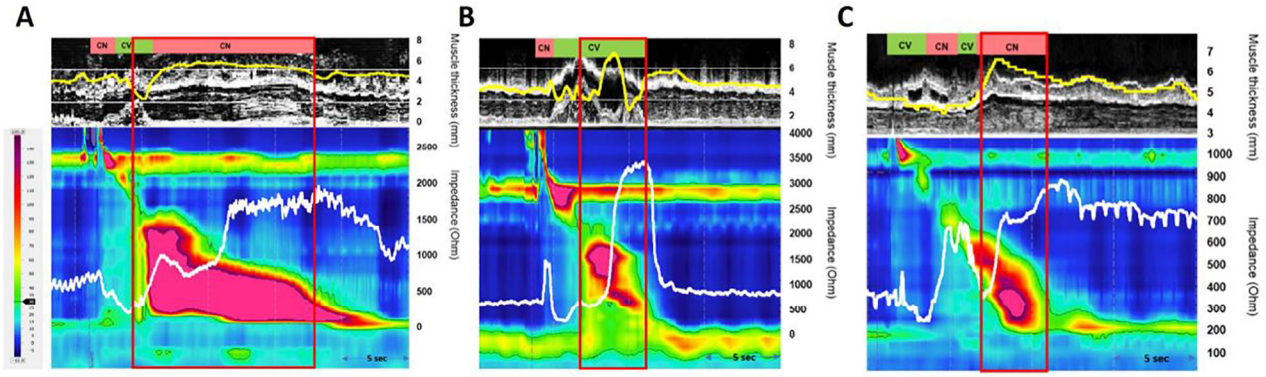

Figure 5:

HRM, impedance line tracing (white line) and m-Mode US image at 5 cm above the LES during 3 swallows in 3 different patients with achalasia 3 esophagus. Note, the relationship between bolus arrival, luminal distension and changes in muscle thickness. Red boxes denote time between isocontour of 30mmHg. The periods of contact (CN) and cavity (CV) are shown on the top of the m-mode US images. Yellow line on the US images represents muscle thickness.

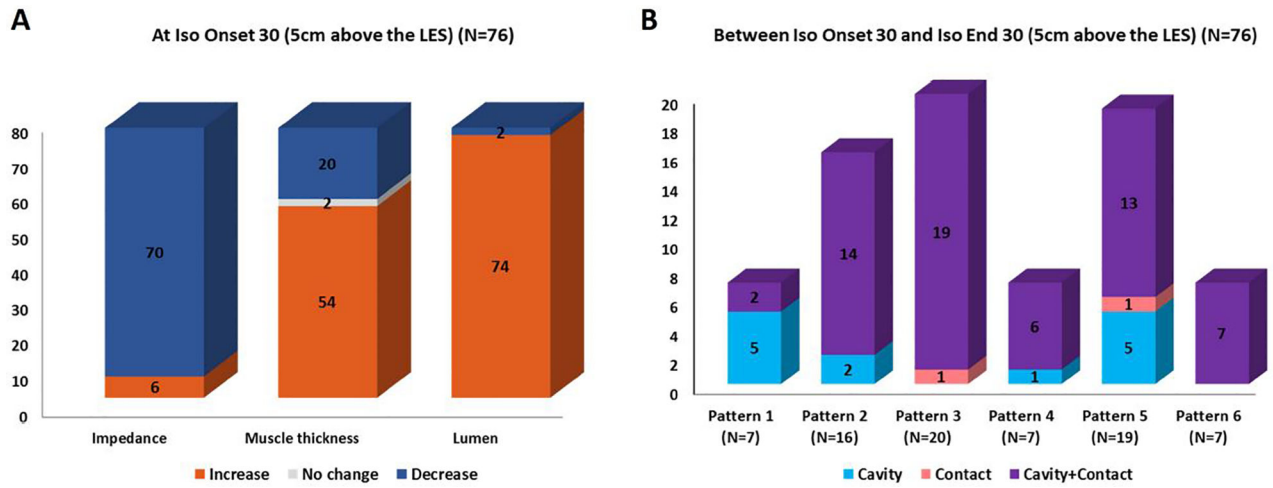

Figure 6:

(A) The number of swallows associated with an increase, decrease or no change in impedance, muscle thickness and luminal dimension at the onset of isocontour of 30mm Hg, at 5 cm above the LES. In majority of swallow these parameters were suggestive of cavity pressure at the isocontour of 30mmHg. **(B)** The cavity vs contact pressure was not different with different waveforms described in figure 1 in achalasia 3 esophagus patients.

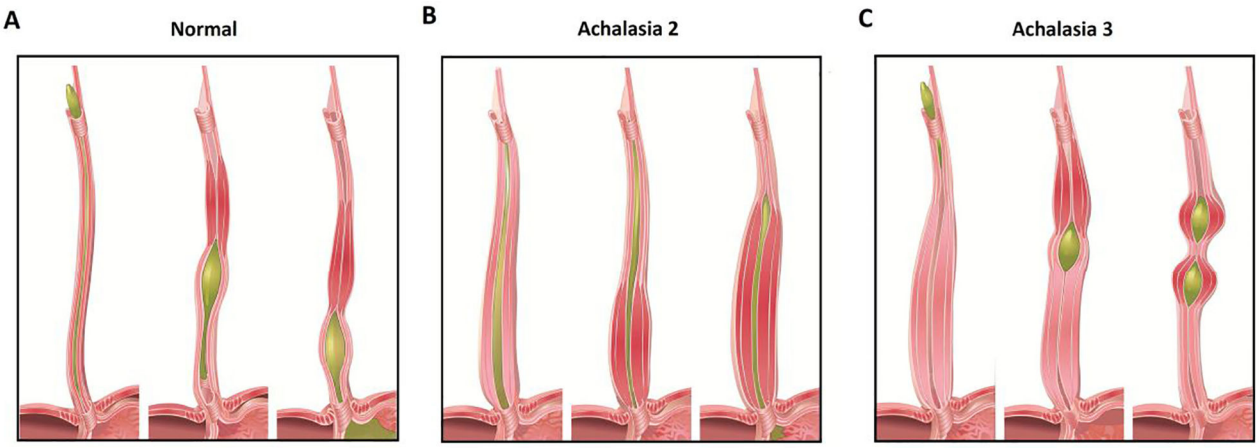

Figure 7:

Schematics of esophageal muscle contraction and bolus flow patterns in normal subjects and patients with achalasia 2, and achalasia 3 esophagus. Note, in normal subject, peristaltic contraction and sequential bolus induced distension of the esophagus. In patient with achalasia 2 esophagus, esophageal pressurization is related to contraction of the muscles of distal esophagus that results in reduction in the luminal size. In achalasia 3 esophagus, there is closure of the esophagus in front of the bolus and compartmentalization of bolus related to muscle contractions.