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

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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 of 0.5N 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 (ie, 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 control individuals because of 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 control individuals. 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. **CONCLUSIONS:** We observed distinct mechanisms of esophageal pressurization and bolus flow patterns in patients with type 2 or type 3 achalasia esophagus compared with control individuals. These findings will increase our understanding of the mechanisms of dysphagia.

Keywords: Esophageal Peristalsis; LES; Corkscrew Esophagus; Simultaneous Esophageal Contraction.

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 greater than 30 mm Hg; and type 3, 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 and 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 geneses 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, for example, bolus entrapment between progressive peristaltic contractions trying to propel the bolus against a closed LES[6,7] and possibly others. Manometry cannot distinguish between 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 after a swallow, bolus arrives late in the distal esophagus of patients with type 3 achalasia compared with healthy subjects, a pattern described by

Abbreviations used in this paper: HRIUS, high-frequency catheter-based ultrasonography; HRM, high resolution manometry; HRMZ, high resolution manometry impedance; LES, lower esophageal sphincter; US, ultrasonography.

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CLINICAL AT

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

In patients with achalasia esophagus, swallows induce simultaneous pressure waves known as esophageal pressurization.

NEW FINDINGS

Esophageal pressurization in type 2 achalasia is due to a distinct muscle contraction that results in luminal narrowing. In patients with type 3 achalasia esophagus, a motor pattern in the distal esophagus results in luminal closure and resistance to the passage of bolus flow.

LIMITATIONS

Understanding of the genesis of pressurization and bolus flow pattern in the esophagus will improve our understanding of the mechanism of dysphagia in esophageal motility disorders.

IMPACT

The authors studied the genesis of esophageal pressurization and bolus flow patterns in achalasia esophagus. These findings improve our understanding of the mechanism of dysphagia in esophageal motility disorders.

Omari et al in patients with non-obstructed dysphagia.[11–13] Using high-resolution manometry, intraluminal impedance, and intraluminal high-frequency catheter-based ultrasonography (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 types 2 and 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 written informed consent before participating in the research study.

Criteria for Inclusion in the Study

Studies were performed in 10 healthy asymptomatic subjects and 14 patients with achalasia esophagus, 6 with type 2 achalasia and 8 with type 3 achalasia. The diagnosis of achalasia was made based on the high resolution manometry (HRM) study done for clinical diagnostic purposes before 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 esophagogastric junction relaxation (integrated relaxation pressure, $>$15 mm Hg/s). 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 greater than 30 mmHg with 80% or more 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 30 mmHg (velocity of peristalsis of $>$8 cm/s) in the distal esophagus and (2) distal contractile integral of greater than 450 mm Hg of 20% or more of contractions. In addition, the distal latency was required to be less than 4.5 seconds for more than 20% of swallows in achalasia 3 esophagus. The onset and end of the 30-mm isocontour were simultaneous in type 2 achalasia. On the other hand, in patients with type 3 achalasia, the onsets of contractions (isocontour of 30 mm Hg) were simultaneous, but the ends of esophageal contractions were sequential or, in other words, peristaltic.

Simultaneous HRMZ and HFIUS Image Recordings

All subjects were studied using a catheter assembly that consisted of a high resolution manometry impedance (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; Medtronics, Minneapolis, MN) and on a DVD recorder (for backup). The US transducer was positioned to acquire images at 5 cm above the LES. Liquid lidocaine spray (2% lidocaine topical solution; USP, Rockville, MD) 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 5-mL of 0.5N saline were performed with the US transducer located at 5 cm above the LES. The catheter was then pulled back until the US transducer was located 10 cm above the LES, and an 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. As per Chicago classification, more than 20% of swallows are required to have distal latency of less than 4.5 seconds, which allows for heterogeneity from swallow to swallow in the diagnosis of achalasia esophagus. Furthermore, identification of contractile deceleration point, 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 30 mm Hg were simultaneous or sequential. Although patients with type 2 achalasia showed homogeneity in pressure pattern from swallow to swallow, achalasia 3 patients showed heterogeneity (Figure 1) with subtle differences in appearance but meeting the criteria of simultaneous onset of isocontour of 30 mm Hg, except for pattern 6, which appeared to be peristaltic (sequential onset of isocontour of 30 mm Hg). The latter was observed in 1 patient who met criteria for type 3 achalasia on

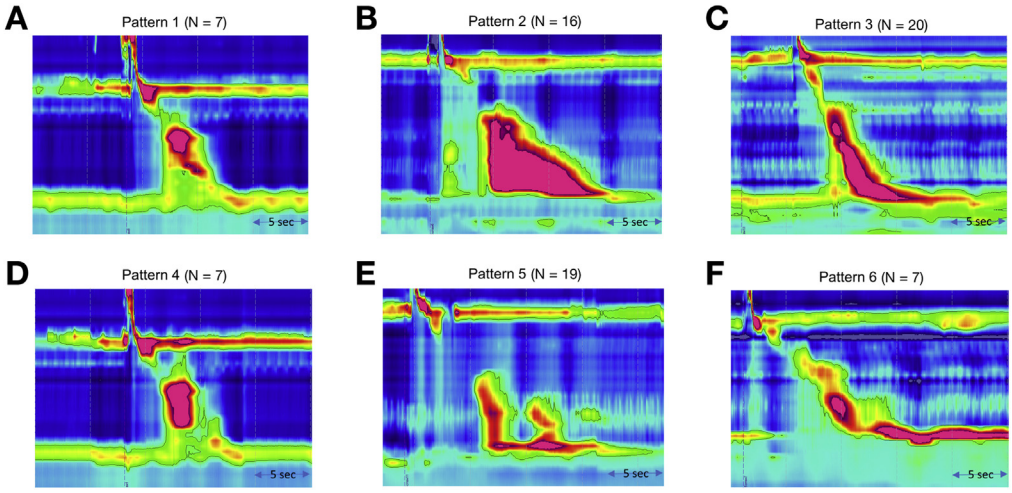

Figure 1. (*A–F*) Esophageal pressure topographic patterns in patients with achalasia 3 esophagus. Note the heterogeneity. The onset of 30 Hg mm isobaric pressure in the distal esophagus is simultaneous, but the end is peristaltic.

the diagnostic HRM study but was found to have peristaltic onset of contraction on the research study. In 1 patient, all the waveforms were pattern 2, in another patient, all were pattern 3. In the remaining 5 patients, different waveforms (Figure 1) were found in the same subject.

US 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) with a custom software, as described previously.[15,16] An 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 the US transducer, the impedance data were exported in Excel spreadsheets (Microsoft, Redmond, WA) 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 were analyzed at 10 cm above the LES.

Cavity vs Contact Pressure

Each HRM-impedance M-mode US image, at 5 cm and 10 cm above the LES, was analyzed to determine whether the recorded pressure was a contact or a cavity pressure. Events after each swallow were divided into 2 periods. The period between the onset of pharyngeal contraction and the onset of an isocontour of 30 mm Hg was defined as period 1, and the period between the onset and end of isocontour of 30 mm Hg was defined as period 2 (Figure 2). In healthy subjects, period 1 was the time when bolus travels through the esophagus and generally implies cavity pressure, because 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 and/or mucosa of the esophagus. On the other hand, period 2, between isocontour of 30 mm Hg, is generally thought of as the contact pressure and implies circular muscle contraction–related occlusion of the esophageal lumen and/or 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 on the following. First, the review of M-mode and B-mode US images, which show the presence of liquid and/or 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. Second, impedance line tracing was also reviewed during period 1 and period 2 to determine cavity vs contact pressure; low impedance values ($<500\ \Omega$) for cavity and high impedance values ($>500\ \Omega$) for the contact pressures.[9] The mean and range of pressure during the entire period 1 was determined for healthy 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 5 cm and 10 cm 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) (Figure 2).

Statistical Analysis

Data are presented as mean ± standard deviation. Unpaired Student *t* test with unequal variance was used to estimate the statistical significance between the groups. *P* values less than .05 were considered statistically significant.

Results

Healthy 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 healthy subject. After pharyngeal contraction and upper esophageal sphincter relaxation, the bolus arrives faster than the pressure wave (contraction) at 5 cm above the LES. At the onset of esophageal contraction (or the pressure wave), there is a rapid return of impedance to the

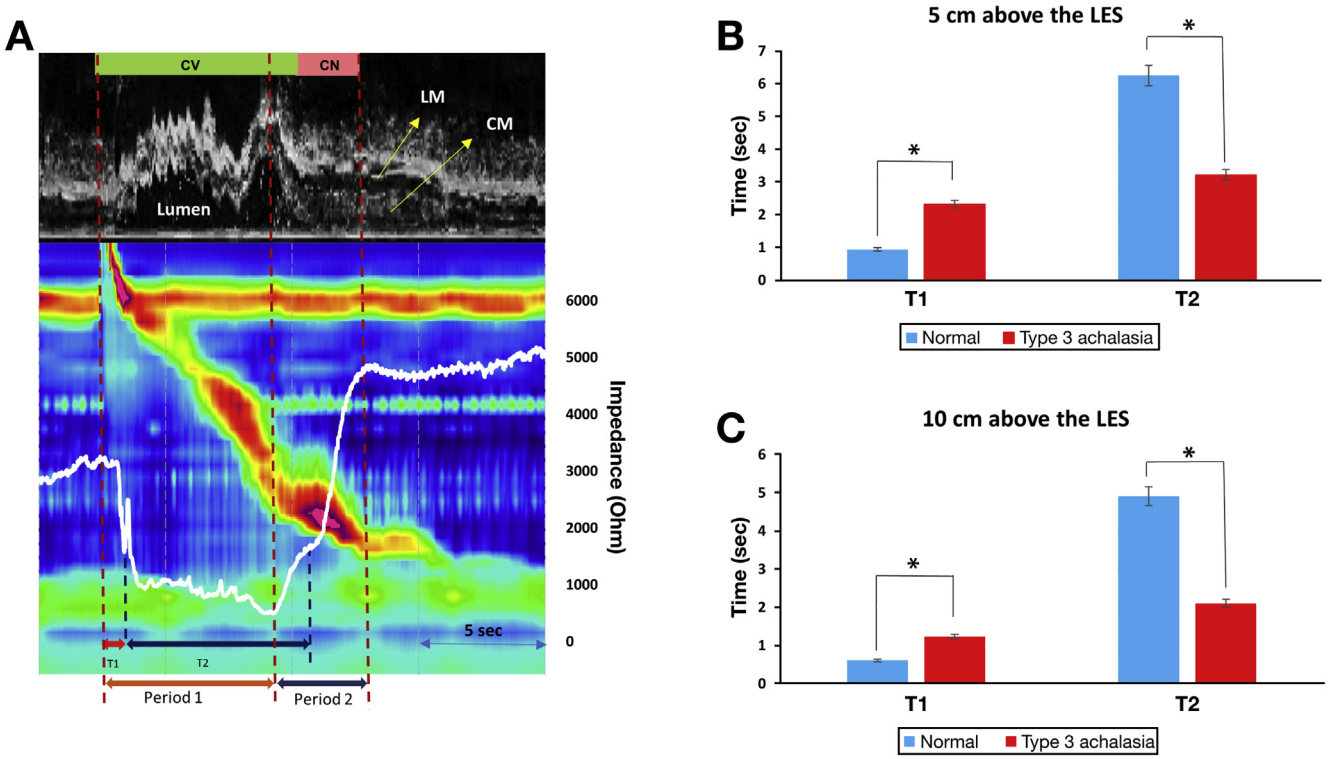

Figure 2. (*A*) HRM, impedance line tracing, and m-Mode US image at 5 cm above the LES in a healthy subject. Note the arrival of bolus soon after the onset of swallow in the distal esophagus (by impedance and US image) and clearance by the contraction wave. Period 1 is the time between the onset of swallow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

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 seconds and 6.3 ± 1.3 seconds, respectively. US images show distension of the esophagus with liquid during period 1. Compared with 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 the pressure wave is temporally aligned with the peak muscle thickness.

Achalasia Type 2

Figure 3*A* shows changes in impedance, luminal dimension, and muscle thickness during swallow-induced esophageal pressurizations in a patient with type 2 achalasia esophagus. After swallows, the changes in pressure amplitude throughout the length of the esophagus were approximately the same (difference of <10 mm Hg). The M-mode US images showed a distended esophagus before swallow, and with each pressurization there was a decrease in the luminal dimension, along with an increase in muscle thickness. The greater the increase in pressure amplitude, the greater was the increase in muscle thickness, and greater was the reduction in esophageal lumen. The impedance value generally increased during pressurizations. Forty-five swallows were analyzed at the 5-cm level and 41 swallows at the 10-cm level in 6 patients with achalasia 2 esophagus (6–7 swallows per subject at each of the 2 sites). Impedance value increased during the majority of swallows at 5 cm above the LES (Figure 3*B*). On the other hand, the change in the impedance value at 10 cm above LES was variable. The muscle thickness increased (Figure 3*C*) and lumen size decreased (Figure 3*D*) during most swallows at both 5 cm and 10 cm above the LES. All swallows, at the 5-cm and 10-cm 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 showed heterogeneity of pressurization, as shown in Figure 1. As per the definition, the onset of pressure wave with all swallows was simultaneous at isocontour pressure of 30 mm Hg. On the other hand, the ends of the pressure waves were peristaltic in all patients during all swallows. One patient who met the criteria for achalasia 3 esophagus on the diagnostic HRM study showed peristaltic esophageal contraction on the research study (Figure 1*F*).

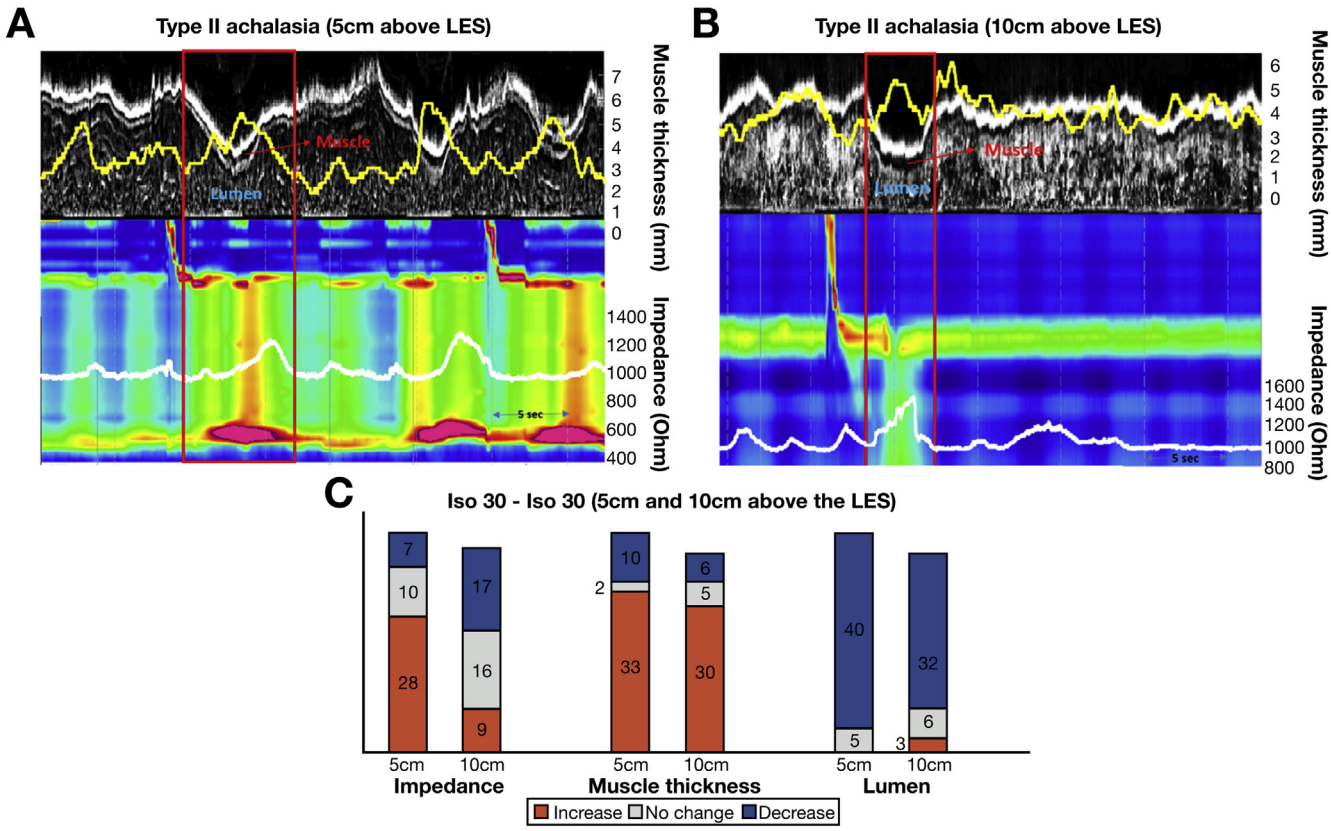

Figure 3. HRM, impedance line tracing, and M-mode US image at (*A*) 5 cm and (*B*) 10 cm above the LES in a patient with achalasia esophagus, type 2. Esophageal pressurization (red box) is associated with an increase in the muscle thickness, decrease in the esophageal lumen, and increase in esophageal impedance, (*C*) Frequency of increase, decrease, or no change in the impedance, muscle thickness, and luminal size in achalasia 2 esophagus.

We compared period 1 in healthy 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 healthy subjects (3.6 ± 2.3 mmHg) ($P < .001$). Unlike healthy 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 4*B* and *C*), or after initially opening for a brief period, it closed and then opened again (22/76 swallows) (Figure 4*D*). Both of these abnormalities were found during period 1 in 7 out of 76 swallows. Thus, 78% of the swallows showed abnormal luminal opening patterns during period 1. The 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 5 cm 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 the 5-cm and 10-cm levels in achalasia 3 compared with healthy subjects (Figure 2).

At 5 cm above the LES, the pressure at the instance of 30 mm 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) (Figures 5 and 6*A*). On the other hand, at 10 cm above the LES, at the instance of 30 mm Hg 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 6 different patterns of achalasia 3 contraction waves was not different (Figure 6*B*).

The entire period 2 (between isobaric contours of 30 mm Hg) is a contact pressure in healthy subjects. In contrast, patients with type 3 achalasia show the presence of cavity pressure, contact pressure, or mix of the 2 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 5*B*). The muscle thickness was higher than baseline during most of the period 2 during both cavity and contact pressures.

Figure 7 shows the schematic of bolus flow and muscular contraction in the esophagus of healthy subjects and patients with type 2 and type 3 achalasia esophagus. In healthy subjects, soon after the onset of swallow and until the arrival of the esophageal contraction wave, the esophageal lumen is open and allows free passage of bolus through the esophagus. In patients with type 2 achalasia,

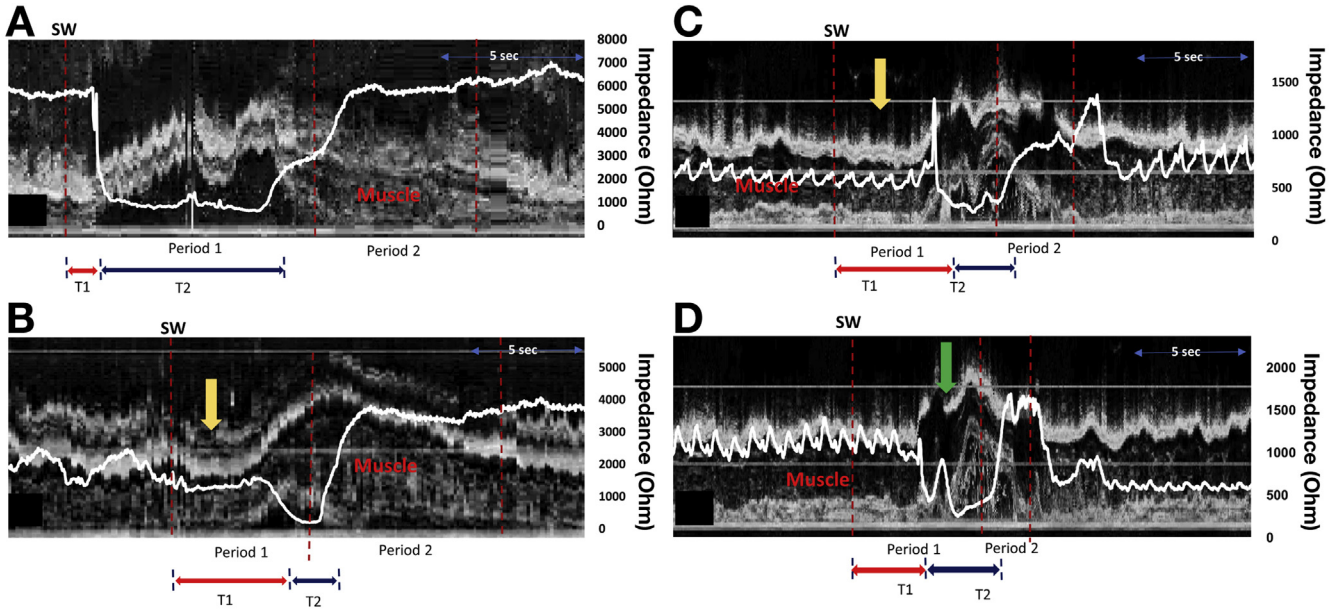

Figure 4. M-mode US image at 5 cm above the LES along with impedance line tracing to show the relationship between bolus arrival, bolus clearance, luminal distension, and muscle thickness with swallows in (*A*) a healthy subject and (*B–D*) 3 patients with achalasia 3 esophagus. Yellow arrows show luminal closure during period 1 in achalasia 3 esophagus, which results in delayed arrival of bolus. (*D*) Luminal opening, collapse (green arrow), and opening during the period of this swallow. T1 = time between the onset of swallow and bolus arrival. T2 = time between bolus arrival and bolus clearance. SW, swallow.

bolus flows into the stomach occurs intermittently because of esophageal muscle contraction that starts in the distal esophagus and proceeds proximally. This 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 (nonrelaxed) lower esophageal sphincter. On the other hand, in patients with achalasia 3 esophagus, the distal esophageal lumen is closed before the arrival of the contraction wave that is associated with thinning of the muscle layers. Pressures during period 2 are a mix of cavity and contact pressure with increase in muscle thickness. These patterns of luminal opening and closing result in the compartmentalization of bolus and obstruction to the bolus passage through the esophagus.

Discussion

The major finding of our study are as follows. (1) Swallow-induced esophageal pressurization in achalasia 2 esophagus is a cavity pressure. This pan-esophageal pressurization results from reduction in the luminal dimension and/or 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 30 mm Hg), there is delayed

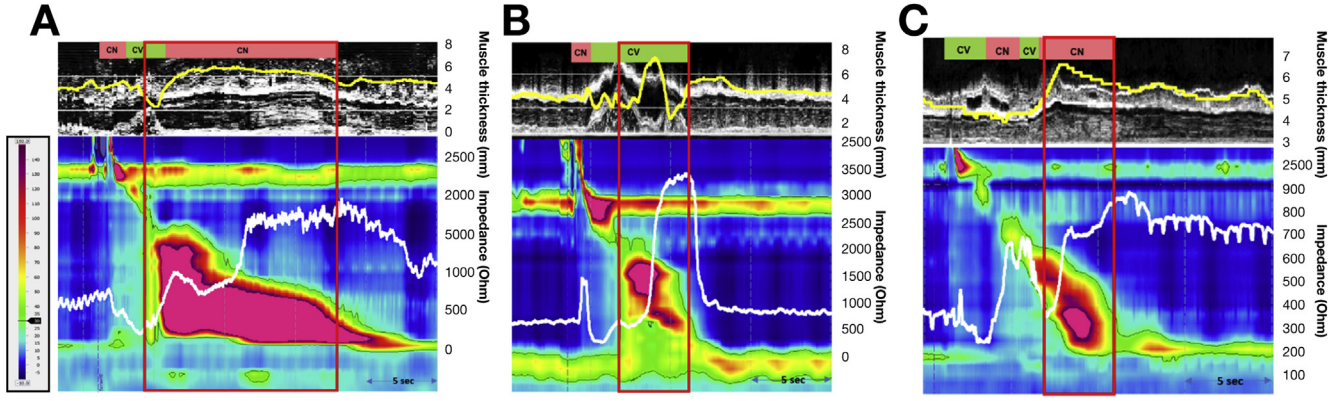

Figure 5. HRM, impedance line tracing (white line) and M-mode US image at 5 cm above the LES during 3 swallows in 3 different patients with achalasia 3 esophagus. Note the relationship between bolus arrival, luminal distension, and changes in muscle thickness. Red boxes denote time between isocontour of 30 mm Hg. 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.

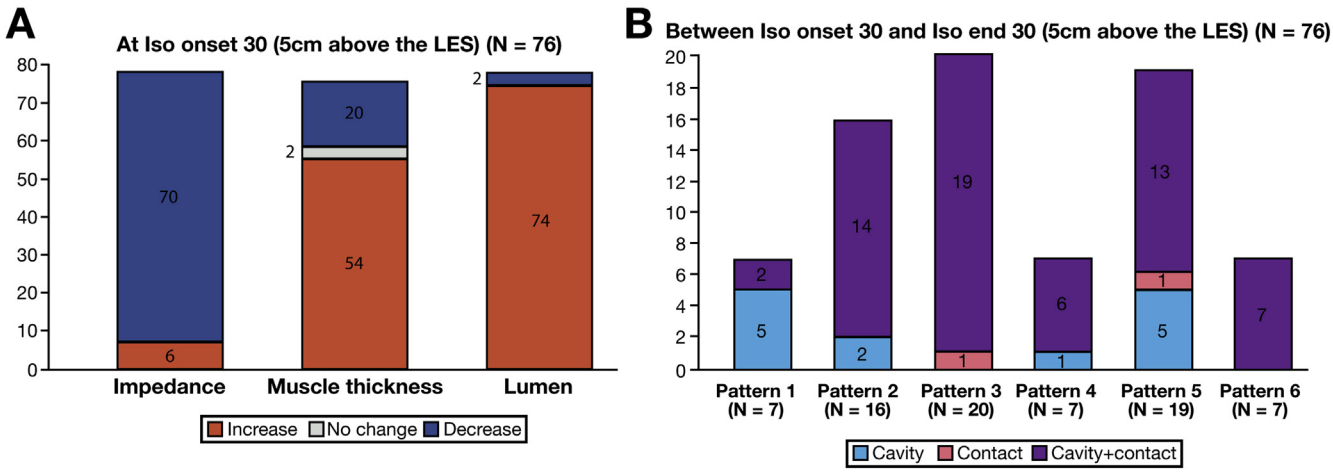

Figure 6. (*A*) The number of swallows associated with an increase, decrease, or no change in impedance, muscle thickness, and luminal dimension at the onset of isocontour of 30 mm Hg, at 5 cm above the LES. In most swallows, these parameters were suggestive of cavity pressure at the isocontour of 30 mm Hg. (*B*) The cavity vs contact pressure was not different with different waveforms described in Figure 1 in achalasia 3 esophagus patients.

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 compared with 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 topographic color plots of pressure waveform during peristalsis, at every 1 cm along the length of esophagus, is currently used routinely in 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 that are due to either contact or cavity pressure. Generally, in healthy subjects, most of the contact pressure is related to contraction of the circular muscle of the esophagus. On the other hand, in patients with esophageal motility disorders, one can observe a large increase in esophageal pressure with the cavity present. There are several possibilities with regard 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) reduction in the esophageal volume, either axial shortening or circumferential constriction of the esophagus; or (3) a combination of these. One can differentiate between these patterns by looking at changes in muscle thickness; esophageal muscle

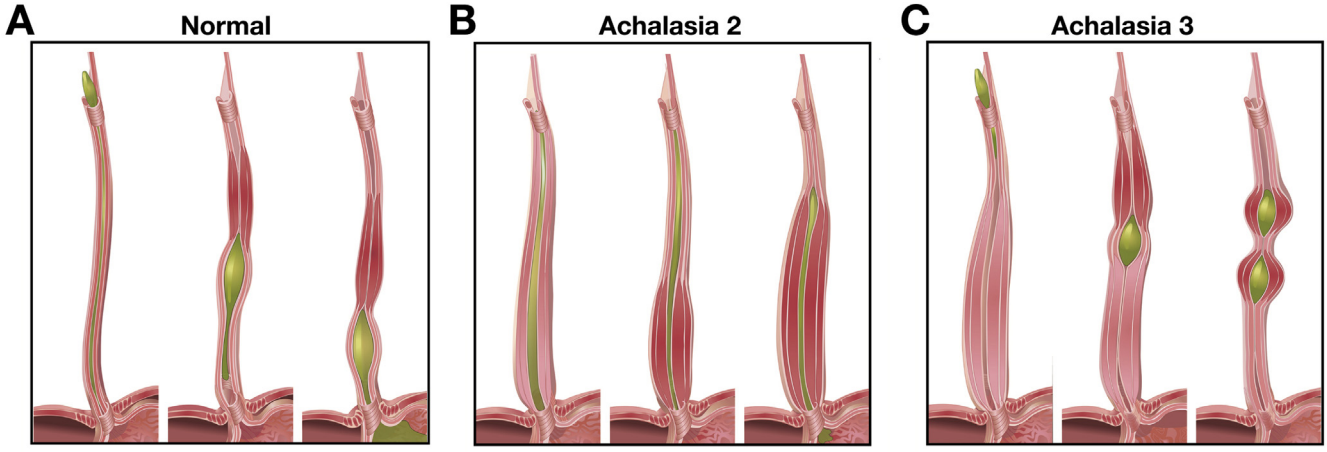

Figure 7. Schematics of esophageal muscle contraction and bolus flow patterns in (*A*) healthy subjects and patients with (*B*) achalasia 2 and (*C*) achalasia 3 esophagus. Note in the healthy subject the peristaltic contraction and sequential bolus-induced distension of the esophagus. In achalasia 2 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.

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 and/or esophageal volume and is in accordance with the Boyles law of physics (also described as the "pump gun" mechanism by Tutuian 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. Regardless, the pattern of muscular contraction in type 2 achalasia is different from that in healthy subjects, in whom there is sequential increase 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 the 5-cm level compared with the 10-cm level above the LES, a pattern similar to what is seen in association with transient LES relaxation.[18]

In healthy subjects, after 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.[15] 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-sectional area over time.[20] In patients with nutcracker esophagus, there is a delay between the onset of lumen collapse and peak pressure recorded by manometry, which we suggest to be related to lack of synchrony between circular and longitudinal muscle contraction.[21] In this study, we observed an increase in muscle thickness (muscle contraction), and 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 in healthy subjects, and it gets even thicker with contraction, yet it is not able to fully collapse the lumen. The latter point suggests resistance to luminal collapse, which is likely related to high bolus pressures in the esophagus due to an outflow obstruction, with the bolus trapped between an aborally progressing peristaltic contraction and a poorly relaxing LES.

To our knowledge, 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. Why does the lumen close during period 1, and what does this mean? We observed that, unlike in healthy 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 et al 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 healthy subjects[22] but not in patients with spastic esophageal motility disorders.[23] More recently, Carlson et al, using another novel methodology, functional luminal imaging probe (FLIP), studied responses to esophageal distension in healthy subjects and patients with achalasia 3 esophagus. They observed antegrade contractions in healthy subjects but retrograde contractions in patients with achalasia 3 esophagus.[24,25] 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 healthy subjects there is also thinning of the muscle during period 1, but unlike in achalasia 3 patients, it is associated with the luminal opening or distension.[21,26] 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 in healthy 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 et al 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 that 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] Maybe it is the resistance to bolus propulsion and not the actual bolus retention that is experienced by the patients as dysphagia sensation,[13,27] which would explain why patients with achalasia 3 esophagus have a relatively normal bolus clearance yet complain of dysphagia.

The 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.[28] Patients with achalasia type 2 esophagus generally do not have a dilated esophagus. Our finding that with swallowing the esophageal volumes and/or lumen actually become smaller in achalasia 2 patients provides rationale for the lack of significant esophageal dilation in these patients. On the other hand, we propose that lack of pressurization and absence of muscular contractions in response to swallow is a reason for the dilated esophagus observed in type 1 achalasia patients.

Some of the topographic patterns in achalasia 3 esophagus that we show in Figure 1 may appear akin to what one might see in patients who are classified as having esophagogastric junction outflow obstruction (EGJOO), based on the Chicago Classification. Our study inclusion criteria were stringent, as stated in the Materials and Methods section. We did not find differences in the cavity and contact pressure frequency between isocontours of 30 mm Hg among 6 topographic 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 healthy subjects, which is the major finding our study and which 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 having esophagogastric junction outflow obstruction (defined by Chicago Classification) and functional dysphagia (defined by Rome Criteria).

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Conflicts of interest
The authors disclose no conflicts.

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