Esophageal contractions in type 3 achalasia esophagus: simultaneous or peristaltic?

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1Department of Medicine, Division of Gastroenterology, San Diego VA Health Care System & University of California, San Diego, California; and 2Department of Internal Medicine, Division of Gastroenterology, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Kim TH, Patel N, Ledgerwood-Lee M, Mittal RK. Esophageal contractions in type 3 achalasia esophagus: simultaneous or peristaltic? Am J Physiol Gastrointest Liver Physiol 310: G689–G695, 2016. First published February 25, 2016; doi:10.1152/ajpgi.00459.2015.—Absence of peristalsis and impaired relaxation of lower esophageal sphincter are the hallmarks of achalasia esophagus. Based on the pressurization patterns, achalasia has been subdivided into three subtypes. The goal of our study was to evaluate the esophageal contraction pattern and bolus clearance in type 3 achalasia esophagus. High-resolution manometry (HRM) recordings of all patients diagnosed with achalasia esophagus in our center between the years 2011 and 2013 were reviewed. Recordings of 36 patients with type 3 achalasia were analyzed for the characteristics of swallow-induced “simultaneous esophageal contraction.” The HRM impedance recordings of 14 additional patients with type 3 achalasia were analyzed for bolus clearance from the impedance recording. Finally, the HRM impedance along with intraluminal ultrasound imaging was conducted in six patients to further characterize the simultaneous esophageal contractions. Among 187 achalasia patients, 30 were type 1, 121 type 2, and 36 type 3. A total of 434 swallows evaluated in type 3 achalasia patients revealed that 95% of the swallow-induced contractions met criteria for simultaneous esophageal contraction, based on the onset of the pressure wave being simultaneous (velocity of peristalsis >8–9 cm/s and latency of distal esophageal contraction of <4.5 s) (25). Richter and colleagues (7, 10) found that simultaneous contractions were associated with tertiary contraction and segmental contraction, with impaired bolus transit on the barium swallow X-ray fluoroscopy study. Identification of the onset of true circular muscle contraction wave on manometry may be difficult because intraluminal manometry can’t distinguish between contact pressure and bolus or common cavity pressure (16, 19).

The goal of our study was to reassess the nature of “simultaneous esophageal contractions” in type 3 achalasia esophagus. One of the reasons for this ongoing effort in our laboratory is to understand why patients with type 3 achalasia don’t respond well to medical and surgical therapies (5, 23, 30).

METHODS AND EXPERIMENTAL DESIGN

Record review. Protocol for the studies was approved by the University of California San Diego Institutional Review Board for the Protection of Humans, and patients who underwent simultaneous HRM impedance (HRMZ) and ultrasound measurements signed an informed consent prior to participation in the study. The GI function laboratory at the UCSD Medical Center is a referral center for the greater San Diego area; patients are referred for assessment of suspected “esophageal symptoms.” The clinical reports of all esophageal HRM studies conducted during January 2011 through December 2013 were reviewed for manometric diagnosis. The HRM studies with manometric diagnosis of achalasia esophagus were examined to determine three achalasia subtypes, according to the published criteria (23). The manoscan software 3.01 was used for the HRM waveform analysis. Briefly, the criteria for diagnosis were that, for all types of achalasia, the patient was required to have impaired LES relaxation (integrated relaxation LES pressure of >15 mmHg) and complete loss of peristalsis. The distinction between three types of achalasia esophagus was based on the characteristics of swallow-induced esophageal pressure waveforms. For type 1 achalasia, esophageal pressurization of ≥80% swallows was <20 mmHg. The type 2 achalasia was diagnosed when the swallow-induced esophageal pressurization was ≥20 mmHg with ≥80% of the swallows. For type 3 achalasia, the criteria for “simultaneous pressure” waveform in the distal 10 cm of the esophagus were 1) simultaneous onset of isocountour of 30 mmHg (velocity of peristalsis of >8 cm/s), 2) mean latency of contraction in

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the distal esophagus of <4.5 s, and 3) distal contractile integral of >450 mmHg of ≥20% contractions. In patients with type 3 achalasia, in addition to the onset of pressure waveform, the peak and the end of esophageal contractions were analyzed to determine whether they were sequential. For the peak of pressure wave, the line tracing was evaluated between 3 and 11 cm above the LES and the first peak was evaluated (in case of multipeaked contraction) by criteria similar to the onset of pressure waveform, i.e., velocity of peristalsis of <8 cm/s for peristaltic contraction and >8 cm/s for simultaneous contraction. The termination of contraction was identified by using isocontour of 30 mmHg and was marked as simultaneous or peristaltic by criteria similar to the one for the onset of contraction.

HRMZ recordings of another 14 patients diagnosed with type 3 achalasia esophagus (different from those described in the previous paragraph) were analyzed to determine the progression of bolus with simultaneous contractions in the distal 10 cm of the esophagus. Progression of bolus was defined as orderly, i.e., “in the aboral direction,” based on the analysis of impedance waveform. For the bolus movement to be defined orderly, the impedance waveform had to meet the following two criteria: 1) the nadir of impedance waves in the distal esophagus had to be sequential, and 2) the bolus clearance, defined as return of esophageal impedance to 50% of its baseline value, had to be sequential and progressing in the aboral direction. Six patients from this group of 14 patients with HRMZ recordings were invited to participate in a simultaneous HRMZ and ultrasound (US) imaging study. The 36-channel pressure and 18-channel impedance (HRMZ) catheter (GIVEN, Duluth, GA) was taped to a high-frequency intraluminal ultrasound imaging (HFiUS) catheter (3.5 F, 30 MHz; CVIS, Sunnyvale, CA). The US catheter was interfaced to the HP Sonos 100 ultrasound machine (Hewlett Packard Sonos Intravascular, Andover, MA). The US images were acquired on a DVD recorder.

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 and US catheter assembly through nose. Swallows were performed using 5 ml of 0.5 N saline, at least 30 s apart. Eight to 10 swallows were recorded with the US transducer located at 5 cm and then at 10 cm above the LES.

Ultrasound image analysis. US images were captured from the DVD files with Adobe Premier 6.0 (Adobe Systems, Mountain View, CA) and then converted to BMP tomographic or B-mode US image. The latter was converted to 16, equally spaced, M-mode US images (every 22.5° apart) by use of custom-built software, as described previously (1). An M-mode US image, orthogonal to the esophageal wall, in which both circular and longitudinal muscle layers were clearly visualized was selected for data analysis. Borders representing the inner edge of circular muscle, the outer edge of longitudinal muscle layer and intermuscular septum between the two layers were manually drawn with Sigma Scan Pro 5 (Jandel Scientific, San Rafael, CA). Distance between the outer longitudinal muscle edge and septum represents the longitudinal muscle thickness and between the septum and the inner circular muscle edge the circular muscle thickness. Muscle thicknesses were corrected by the magnification factor to estimate the thickness in millimeters. The thickness of circular muscle layer was considered as the radius of the circle, and, by using the equation $\pi r^2$, the circular muscle cross-sectional area (CSA) was calculated. The CSA based on the total muscle thickness of circular and longitudinal muscle thickness was subtracted from the circular muscle CSA to determine the longitudinal muscle CSA. Temporal plots of pressure, impedance wave at the location of the US transducer, circular muscle CSA, and longitudinal muscle CSA were constructed for five to seven swallows in each subject. From these temporal plots the CSA and muscle thickness measurements were selected, before and at the peak of swallow-induced contractions.

Statistical analysis. Data are presented as means ± SE except where stated otherwise. Mean values for each subject were calculated and used to estimate the overall mean. Unpaired Student’s $t$-test with unequal variance was used to estimate statistical significance between the groups. $P$ values less than 0.05 were considered statistically significant.

RESULTS

During the 2-yr period, 187 patients were diagnosed with achalasia esophagus; 30 met criteria for type 1 achalasia, 121 for type 2, and 36 for type 3 achalasia (Fig. 1A). Of the 36 type 3 achalasia patients, 20 were male (mean age = 61) and 16 female (mean age = 58). Dysphagia was the predominant symptom ($n = 31$) in these patients; some also had regurgitation ($n = 6$), chest pain ($n = 5$), food impaction ($n = 5$), epigastric pain ($n = 3$), and heartburn ($n = 3$).

Patients with type 3 achalasia were assessed for the characteristics of pressure waveform in the distal esophagus (the onset, the peak, and the end of contraction) by using the line tracing (Fig. 2 and Table 1). The onset of pressure wave was simultaneous by the criteria described in METHODS AND EXPERIMENTAL DESIGN, with almost all contractions (420/434).

![Fig. 1. Three types of achalasia: type 1, type 2, and type 3. Pressure line tracings at multiple locations in the esophagus are superimposed on the high-resolution manometry (HRM) plot with a 30-mm isocontour plot.](http://ajpgi.physiology.org/)
tion was sequential with 70% of the 434 contraction. In the remainder 30%, peaks were either simultaneous or retrograde. Twenty-nine of the 36 subjects had more than two types of peak contraction (sequential, simultaneous, and retrograde). Median number of contractions with sequential peaks per subjects was 73% (range 28 –100%), simultaneous 13% (range 0 –67%), and retrograde 0% (range 0 –45%). The termination or end of contraction wave was also sequential with 80% of the 434 swallow-induced contractions. In the remainder 20%, it was either simultaneous or retrograde, and 25 of 36 patients had a mix of peristaltic, simultaneous, and retrograde end of contraction [median for sequential 80% (range 33–100%), simultaneous 13% (range 0 –53%), and retrograde 0% (range 0 –20%)].

Impedance HRM analysis. Fourteen patients with type 3 achalasia esophagus, different from the group of 36 described in the previous paragraphs, were studied for bolus clearance with esophageal contraction. In total 136 swallows were analyzed. One hundred nineteen (88%) of the 136 contractions met the criteria for type 3 contractions; the remainder were either type 2 or type 1 contractions. There was either incomplete or no bolus clearance with type 1 and type 2 achalasia contractions. On the other hand, the bolus clearance was complete with 94% of type 3 achalasia contractions. In 112 type 3 achalasia contractions that resulted in complete bolus clearance, sequential peak and sequential termination of contraction were seen in 92% (103/112) and 97% of instances, respectively. In seven type 3 achalasia contractions that met criteria for incomplete bolus clearance, sequential peaks and sequential ends were seen in four of seven and four of seven instances, respectively. Definition of complete clearance included sequential nadir impedance and sequential return of impedance to 50% of the baseline value and both traveling in the aboral direction in the last 10 cm of the esophagus (Fig. 3).

Ultrasound and HRM analysis. US data from six patients in this study were compared with data from 16 normal subjects reported in a recently published study (26) (Figs. 4 and 5). The baseline muscle thicknesses in these normal subjects is identical to those reported in our earlier studies (9, 27, 35) and by Miller and colleagues (17, 22). The baseline muscle thickness in patients was significantly larger at 5 cm as well as at 10 cm above the LES compared with normal subjects, which was true for both circular and longitudinal muscle. The baseline muscle thickness in patients was significantly greater at 5 cm compared with the 10-cm level (P < 0.05). With esophageal contraction there is an increase in the thickness of circular and longitudinal muscle in normal subjects as well as patients. Axial shortening of the circular muscle during contraction (ratio of peak CSA to baseline CSA) was much greater at 5 cm compared with 10 cm above the LES in normal subjects as well as in patients (P < 0.05). Axial shortening of the two layers was significantly smaller in patients compared with normal at 5 cm above the LES (Table 2).

Table 1. Analysis of achalasia type 3 contractions: analysis of pressure waveforms

<table>
<thead>
<tr>
<th>Peristaltic</th>
<th>Onset of Peristalsis</th>
<th>Peak of Peristalsis</th>
<th>End of Peristalsis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simultaneous</td>
<td>Retrograde</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>Peristaltic</td>
<td></td>
<td></td>
<td>Peristaltic</td>
</tr>
<tr>
<td>14 (3%)</td>
<td>420 (97%)</td>
<td>0 (0%)</td>
<td>304 (70%)</td>
</tr>
<tr>
<td>70 (16%)</td>
<td>18 (4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = 36 subjects, number of contractions analyzed = 434.
DISCUSSION

The criteria for defining simultaneous contraction have varied over the years. Prior to manometry, tertiary contractions and segmentation seen on X-ray fluoroscopy were used to define diffuse esophageal spasm. Manometric definition of simultaneous contraction is based on the onset of contraction (pressure wave) in the distal esophagus. Velocity of peristalsis of greater than 8–9 cm/s in the distal esophagus is currently considered simultaneous contraction. Behar and Biancani (4) found that the latency of swallow-induced distal esophageal contraction was shorter in patients with simultaneous esophageal contractions compared with normal subjects. The shorter latency is consistent with impaired deglutitive inhibition in patients. The authors suggested that the short latency in the distal esophagus represents defective nitrinergic innervations of the esophagus because nitric oxide antagonism causes decrease in the latency of distal esophageal contraction and increase in the velocity of peristalsis (20, 33, 36). Using a novel distal esophageal landmark, the contraction deceleration point (CDP) in the HRM recording (15, 24), Pandolfino et al. (25) found that short distal esophageal latency (<4.5 cm) was a better criterion to diagnose simultaneous esophageal contraction than the velocity of peristalsis.

Many investigators have struggled to define what actually represents simultaneous esophageal contraction on manometry (2). The difficulty stems from the fact that identifying the onset of esophageal contraction on manometry recordings is challenging for several reasons: 1) presence of bolus in the esophagus, distal to the contraction contributes to the esophagus pressure, the so-called bolus/common cavity pressure (28). For the above reason Behar and Biancani (4) assessed dry swallow—rather than the wet swallow—induced esophageal contractions.
However, dry swallows may not completely eliminate bolus pressure because infusion manometry was used to study esophageal motor activity. The common cavity pressure resulting from a trapped bolus between peristaltic esophageal contraction and partially closed/relaxed LES can contribute significantly to the intraluminal esophageal pressure. The pressure waveform at any location in the esophagus is a blend of bolus pressure and contact pressure. Some investigators have arbitrarily assumed that the esophageal pressure due to bolus has a slow rate of pressure increase and argued that the rapid onset of pressure wave reflects the true contact pressure (10, 29), which may be true in normal subjects and under some circumstances. Others have argued for using isobaric pressure of 30 mmHg to recognize the onset of contact pressure. It is also suggested that cavity pressure can’t be greater than the residual LES pressure with swallow-induced LES relaxation (25), which may not be necessarily true, as one can see in Figs. 2 and 3.  

Table 2. Analysis of achalasia type 3 contractions: circular and longitudinal muscle thickness in normal subjects and patients with type 3 achalasia esophagus at baseline and peak of swallow-induced contractions

<table>
<thead>
<tr>
<th>Muscle Thickness</th>
<th>Normal Healthy Person (N = 16)</th>
<th>Achalasia Type 3 Patient (N = 6)</th>
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<tbody>
<tr>
<td></td>
<td>CM (mm)</td>
<td>LM (mm)</td>
</tr>
<tr>
<td>10 cm Baseline</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Peak/Baseline ratio</td>
<td>2.19</td>
</tr>
<tr>
<td>5 cm Baseline</td>
<td>0.68</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Peak/Baseline ratio</td>
<td>2.94†</td>
</tr>
</tbody>
</table>

*P < 0.05 baseline muscle thickness between normal subjects and patients; †P < 0.05, peak-to-baseline thickness (marker of axial shortening) is bigger at 5 cm compared with 10 cm in normal subjects; ‡P < 0.05 peak-to-baseline thickness (axial shortening of circular and longitudinal muscle) is significantly smaller in patients compared with normal subjects at 5-cm level. CM, circular muscle; LM, longitudinal muscle.

Fig. 5. A and B: relationship between changes in US images, pressure, impedance, and CSA of the circular and longitudinal muscle of the esophagus at 5 cm above the LES in 2 patients with type 3 achalasia esophagus. Note, the onset of luminal distension is associated with drop in impedance, and luminal closure is associated with increase in thickness of circular and longitudinal muscle thickness (CSA). Also note that the muscle thickness is significantly greater in patients compared with normal subjects (Fig. 4, A and B).
Muscle thickness in achalasia esophagus type 3 (even more), a finding also observed by Krishnan et al. (14). Normal subjects is not subtle, it is severalfold (2 to 3 times or more) in patients with achalasia type 3. Interestingly, Tutuian et al. (34) found marked heterogeneity in muscle thickness in patients with DES and recognized difficulty in identifying the simultaneous esophageal contraction. They also felt difficulty in distinguishing bolus pressure from the contact pressure in esophageal pressure waveform.

We do not imply that true simultaneous contractions do not exist but our contention is that majority of the so-called simultaneous contractions in type 3 achalasia are not truly simultaneous. Type 3 achalasia esophagus is an intriguing entity for several reasons: 1) Some investigators believe that these patients were previously classified as either DES or vigorous achalasia. 2) If peristalsis is indeed intact in patients with achalasia esophagus type 3 then why do these patients have dysphagia to begin with? 3) Several studies show that patients with achalasia type 3 do not respond as well to medical and surgical treatments as patients with type 2 and type 1 achalasia. We did not measure muscle thickness of normal subjects and achalasia patients in a blinded fashion, which could be considered as the weakness of our study. However, the difference in thickness values between type 3 achalasia and normal subjects is not subtle, it is severalfold (2 to 3 times or even more), a finding also observed by Krishnan et al. (14). Muscle thickness in achalasia esophagus type 3 > type 2 achalasia > type 1 achalasia (18). We speculate that the thicker muscle in type 3 achalasia esophagus leads to poor distensibility of the esophagus, which may allow liquid bolus to pass through but not a solid bolus. The functional luminal imaging probe (FLIP) can easily measure distensibility of the esophagus. Future studies may investigate whether reduced distensibility of the esophagus is the reason for poor response to treatment in patients with type 3 achalasia esophagus.

In summary, our findings show that majority of esophageal contractions in type 3 achalasia esophagus are sequential and are associated with adequate clearance of liquid bolus. Type 3 achalasia contractions, similar to normal subjects, are associated with an increase in the circular and longitudinal muscle thickness as well as axial shortening of the esophagus. We propose that the mechanism of dysphagia in achalasia type 3 is not the lack of peristalsis; rather it is related to hypertrophy of the muscularis propria, which results in poor distensibility of the esophagus. The latter may also be the reason for poor response to medical and surgical therapy because pneumatic dilation of the LES and surgical myotomy may not address poor distensibility of the esophagus.

**REFERENCES**


