Relationship between esophageal muscle thickness and intraluminal pressure in patients with esophageal spasm

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Pehlivanov, Nonko, Jianmin Liu, Ghassan S. Kassab, Cheryl Beaumont, and Ravinder K. Mittal. Relationship between esophageal muscle thickness and intraluminal pressure in patients with esophageal spasm. Am J Physiol Gastrointest Liver Physiol 282: G1016–G1023, 2002; 10.1152/ajpgi.00365.2001.—We previously showed, in normal subjects, a positive correlation between the esophageal contraction amplitude and peak muscle thickness. The goal of this study was to determine the relationship between esophageal muscle thickness and contraction amplitude in patients with high-amplitude peristaltic and simultaneous contractions. Eleven patients with high-amplitude peristaltic contractions, 8 with diffuse esophageal spasm (DES), 7 with nonspecific (NS) motor disorder of the esophagus, and 10 normal subjects were studied using simultaneous pressure and ultrasound imaging. Pressure was recorded by manometry and ultrasound imaging with a high-frequency ultrasound probe catheter. Recordings were performed in the lower esophageal sphincter (LES) and at 2, 4, 6, 8, and 10 cm above the LES during resting state and swallow-induced contractions. Baseline esophageal muscle thickness was thicker in the distal, compared with the proximal esophagus both in normal subjects and patient groups. Patients with DES and nutcracker esophagus (NC) have a higher baseline muscle thickness compared with normal and NS patients. Correlation between the peak pressure and the peak muscle thickness was weaker in patients with NC and DES compared with normal subjects and patients with NS. Whereas normal subjects have good correlation between delta (difference between peak and baseline) muscle thickness and peak pressures, this relationship was absent in patients with NC and DES. Increase in contraction amplitude in patients with NC and DES was associated with an increase in baseline thickness of esophageal muscularis propria. Increase in baseline thickness was specific to patients with spastic motor disorders and was not seen in patients with NS.

diffuse esophageal spasm; nutcracker esophagus; high-amplitude contractions; ultrasound

A NUMBER OF INVESTIGATORS have reported the use of high-frequency intraluminal ultrasound (HFIUS) to measure esophageal contractility (10, 11, 15, 22, 25). Increase in the thickness of circular and longitudinal muscle during esophageal contraction is temporally related with the increase of intraluminal pressure. In a given individual, as well as among different subjects, there is a marked variability in the esophageal contraction amplitudes from one swallow to another. We found a significant correlation between peak pressure and peak muscle thickness during esophageal contractions in a given individual as well as among normal subjects (17). The Laplace's equation states that wall stress is directly proportional to the intraluminal pressure and inversely proportional to the vessel thickness-to-radius ratio (2, 7). We proposed that a positive correlation between esophageal thickness and intraluminal pressure serves to maintain a constant wall stress.

Nutcracker esophagus (NC) and diffuse esophageal spasm (DES) are characterized by greater-than-normal contraction amplitudes in the body of the esophagus (1, 18). The mechanism of this increase in contraction amplitude is thought to be due to an imbalance between excitatory and inhibitory neural innervation. It is hypothesized that patients with spastic motor disorders of the esophagus have an impaired inhibitory innervation (19, 20). An unopposed excitatory innervation, in the presence of reduced inhibitory innervation, allows for the increase in the contraction amplitudes. An alternative hypothesis that has never been explored is that the higher contraction amplitude in patients with NC and DES is due to differences in the thickness of the muscularis propria (either a higher baseline thickness or a bigger increase in thickness during contraction). Hence, the goal of this study was to determine the relationship between muscle thickness and contraction pressure in patients with high-amplitude contraction of the esophagus compared with normal subjects.

MATERIALS AND METHODS

Subjects

We studied four groups of subjects: 11 patients with NC, 8 patients with DES, 7 patients with nonspecific (NS) motor disorder of the esophagus, and 10 normal subjects. The Hu-
man Investigation Committee of the University of California, San Diego, CA, approved the protocol, and all subjects signed an informed consent before their participation in the study protocol. Data on the normal subjects have been published recently (17). Motility disorders were classified according to previously defined criteria (4). NC was diagnosed when the mean peristaltic amplitude of 8–10 swallows at any given level in the esophagus exceeded 180 mmHg. DES was diagnosed when >30% of the standardized wet swallows induced simultaneous contractions interspersed with normal peristaltic contractions. A number of these contractions were associated with repetitive contractions, prolonged duration contractions, high-amplitude contractions, frequent spontaneous contractions, and/or lower esophageal sphincter (LES) abnormalities such as a high baseline LES pressure or impaired LES relaxation. We did not include those patients with DES that had low-amplitude (<50 mmHg) simultaneous contractions. The diagnosis of NS esophageal motility disorder was made when the findings did not fit any of the above definitions, despite the presence of esophageal motor abnormalities, such as segmental simultaneous contractions, prolonged duration contractions (>6 s), triple-peaked contractions (4), and high resting LES pressure (>35 mmHg).

Study Protocol

Subjects fasted overnight, and the investigations were performed in the right recumbent position. Esophageal pressure and HFIUS images were recorded simultaneously using a catheter assembly consisting of a 4-mm-diameter water-perfused manometry catheter (Dentsleeve, Wayville, Australia) and a 2.3-mm ultrasound probe equipped with a 20-MHz transducer (model UM-3R; Olympus, Japan). The two catheters were attached so that the transducer of the HFIUS probe and one of the side holes of the manometry catheter were located at the same level.

The nasal cavity and the oropharynx were anesthetized with 1% lidocaine gel and 1% benzocaine spray, respectively. The catheter assembly was then positioned via the nose into the esophagus and stomach. A standard pull-through procedure with stations at every 0.5 cm was performed to estimate the length of LES. The catheter was then withdrawn at 2-cm increments until the ultrasound transducer was at 10 cm above the LES. Five wet swallows with 5 ml water at room temperature were performed with the HFIUS probe and the side hole located at each of the following levels: middle of the LES, and at 2, 4, 6, 8, and 10 cm above the upper edge of LES. Subjects were asked to refrain from swallowing 10 s before and 30 s after each wet swallow. Pressure tracings were recorded and saved onto a computer through PC Polygraph (Medtronic Synectics, Shoreview, MN), a commercially available program. Ultrasound images were recorded in real time on a videotape using an ultrasound system (model EU-M30; Olympus, Melville, NY) and a videocassette recorder. The pressure and ultrasound recordings were synchronized using a time code device (Thalane Electronics, Ann Arbor, MI).

Measurements

Esophageal muscle thickness was measured, from digitized ultrasound images, (Adobe Premiere 4.0; Adobe Systems, Mountain View, CA) during two different phases of the esophageal activity, 1) baseline or before contraction and 2) at the peak of contractions. Baseline pressure images were selected at the time of end expiration on the basis of the pressure tracings 30 s before the corresponding swallow-induced contraction, at each of the described levels in the esophagus. Ultrasound images during contraction were selected at the instance of peak pressures recorded during the corresponding swallow. Muscle thickness corresponding to the peak intraluminal pressure was called the peak thickness. Image analysis was performed using a commercially available computer program (SigmaScan Pro; Jandel Scientific, San Rafael, CA). Images were magnified ×12 to improve measurement accuracy. Thickness of the muscularis propria (circular + longitudinal muscle layers) originally measured in pixels was automatically converted into millimeters. Muscle thickness was measured at five different sites around the esophageal circumference, and final results represent the mean thickness. Delta thickness was the difference between the peak and the baseline muscle thickness. Additionally, shape of the esophagus and content of the lumen at rest and at the peak of contractions were recorded.

Statistical Analysis

Demographic data were analyzed using descriptive statistics and were represented as means ± SD. Pressure and thickness values are also expressed as means ± SD. The Pearson correlation test and multilinear regression were applied to estimate the relationship between pressure and thickness. Statistical differences between thickness values were estimated using Student’s t-test and the Mann-Whitney U-test.

RESULTS

Ten healthy subjects (8 men, 2 women; mean age 46.5 ± 13.8 yr) and 26 patients participated in the investigation protocol. Patients were selected on the basis of a clinical motility study done within 2 mo of the research study protocol. Eleven patients satisfied the criteria of NC, 8 of DES, and 7 of NS motor disorder of the esophagus. The demographic and medical history of each group is summarized in Table 1. Mean number of swallows analyzed from each patient and normal subject were 28.5 and 26.9, respectively (range 3–5 at each esophageal level). Some of the swallows were not selected according to previous definitions, such as segmental simultaneous contractions, prolonged duration contractions (>6 s), triple-peaked contractions (4), and high resting LES pressure (>35 mmHg). No motility disorder

Table 1. Demographic data of healthy controls and patient groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>M/F</th>
<th>Mean Age, yr</th>
<th>Reflux</th>
<th>Heartburn</th>
<th>Dysphagia</th>
<th>NCCP</th>
<th>Mean Duration of Symptoms, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>8:2</td>
<td>46.5 ± 13.8</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5.8 ± 4.6</td>
</tr>
<tr>
<td>NS</td>
<td>7</td>
<td>2:5</td>
<td>53.4 ± 9.5</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>5.4 ± 7.2</td>
</tr>
<tr>
<td>NE</td>
<td>11</td>
<td>6:5</td>
<td>51.6 ± 17.0</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>3.2 ± 2.1</td>
</tr>
<tr>
<td>DES</td>
<td>8</td>
<td>6:2</td>
<td>58.6 ± 11.9</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5.8 ± 4.6</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects; M/F, men/women; Control, healthy controls; NS, nonspecific motility disorder; NE, nutcracker esophagus; DES, diffuse esophageal spasm; NCCP, noncardiac chest pain.
analyzed because of poor image quality due to the presence of air in the esophagus.

**Healthy Controls**

The baseline LES muscle thickness (in the middle of LES) was 1.92 ± 0.43 mm. The LES muscle was significantly thicker compared with that of esophageal body at all levels \( (P < 0.0001) \). Mean baseline muscle thickness at 2-cm level was 1.25 ± 0.28 mm, and it decreased to 1.05 ± 0.18 mm at the 10-cm level (Fig. 1). Muscle at the 2-cm level was significantly thicker compared with other sites in the esophagus. After a swallow-induced LES relaxation, at the peak of aftercontraction, the LES muscle thickness was 2.54 ± 0.39 mm. In the body, the esophagus peak muscle thickness was largest at the 2-cm level (2.30 ± 0.53 mm) and smallest at the 10-cm level (2.03 ± 0.43 mm; \( P = 0.009 \)). Contraction amplitudes during induced swallows ranged from 19 to 267 mmHg (mean 120 ± 50 mmHg). There was a significant correlation between the swallow-induced contraction amplitudes and the peak muscle thickness in a given individual (mean \( r = 0.75 \), range 0.62–0.79), as well as among all swallow-induced contractions in 10 subjects \( (r = 0.55) \). Similar to the peak muscle thickness, there was good correlation between the delta muscle thickness and the peak contraction amplitudes (mean \( r = 0.72 \), range 0.62–0.82). There was no correlation between the baseline muscle thickness and the peak pressures.

**Patients with motility disorders of the esophagus.**

Esophageal contraction amplitudes on the two study days (routine manometry day and investigation study day), 1–140 days apart, median 21 days, are shown in Table 2. There was no significant difference in the contraction amplitudes on the two study days in these patients. Baseline muscle thickness in the middle of LES and at five different sites in the esophagus is shown in Fig. 1. Mean muscle thickness of LES and the body of the esophagus were significantly greater in patients with NC and DES compared with normal subjects and patients with NS motor disorder. This was true for both circular as well as longitudinal muscles of the esophagus (data not shown). There was some overlap in the muscle thickness between NC and normal subjects, but this overlap was only seen in patients with contraction amplitudes close to 200 mmHg. None of the patients with a contraction amplitude of >250 mmHg showed any overlap in muscle thickness with normal subjects. Similar to normal subjects, there was a gradient in the muscle thickness along the length of the esophagus.

![Fig. 1. Esophageal muscle thickness (circular and longitudinal muscle) at rest (baseline) in the 4 groups of subjects: healthy controls (Cntr), nonspecific motor disorders (NS), nutcracker esophagus (NC), and diffuse esophageal spasm (DES). Comparisons were made at the lower esophageal sphincter (LES) and 2, 4, 6, 8, and 10 cm above the LES. LES and the body of the esophagus were significantly thicker in the NC and DES groups compared with the NS and control groups. Muscles of the esophagus were thicker in DES compared with NC. \( +P < 0.05 \) vs. Cntr and NS subjects. \( +P < 0.05 \) vs. DES subjects.](image)
the esophagus, with muscle being thickest at 2 cm above LES compared with the other esophageal sites (Fig. 2). This gradient of muscle thickness from distal to proximal site was present in all three patient groups. Baseline muscle thickness was highest in DES patients compared with other groups. There was no significant difference in muscle thickness between normal subjects and patients with NS motor disorders. As seen during baseline measurements, peak muscle thickness was greater in distal compared with proximal esophagus. Change in muscle thickness during esophageal contractions (delta thickness) was not significantly different between patient groups and normal subjects (Fig. 3).

Relationship between peak pressure and muscle thickness. Contraction amplitude in patients with NC and DES were higher compared with the normal subjects and patients with NS (Fig. 3). There was no statistically significant difference in contraction amplitudes between DES and NC. Contraction amplitudes were higher in the distal (2-cm and 4-cm levels) compared with the proximal esophageal sites in all groups. Peak pressures correlated well with peak thickness at different levels of the esophagus in healthy controls ($r = 0.75$, range $0.62–0.79$ for different esophageal levels). Corresponding values for correlation coefficients in patient groups are as follows: NS, $r = 0.67$ (range $0.58–0.74$); NC, $r = 0.34$ (range $0.15–0.46$); and DES, $r = 0.22$ (range $0.13–0.57$). Correlation between peak thickness and peak pressure of cumulative data of all wet swallows at all five esophageal levels in healthy controls was $r = 0.55$. Corresponding values in patients with NS, NC, and DES were $0.74$, $0.45$, and $0.42$, respectively. In other words, correlation be-

Table 2. Comparison between the esophageal pressure measurements acquired on two different days: clinical esophageal motility test (day 1) and research study day combined with high-frequency intraluminal ultrasound (day 2)

<table>
<thead>
<tr>
<th>Esophageal Level of Measurement</th>
<th>NC, mmHg</th>
<th>DES, mmHg</th>
<th>NS, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm Day 1</td>
<td>196 ± 49</td>
<td>235 ± 71</td>
<td>73 ± 35</td>
</tr>
<tr>
<td>Day 2</td>
<td>200 ± 63*</td>
<td>201 ± 88</td>
<td>107 ± 66</td>
</tr>
<tr>
<td>6 cm Day 1</td>
<td>148 ± 47</td>
<td>257 ± 14</td>
<td>91 ± 58</td>
</tr>
<tr>
<td>Day 2</td>
<td>168 ± 48</td>
<td>174 ± 85</td>
<td>97 ± 57</td>
</tr>
<tr>
<td>8 cm Day 1</td>
<td>148 ± 59</td>
<td>224 ± 66</td>
<td>69 ± 38</td>
</tr>
<tr>
<td>Day 2</td>
<td>145 ± 28</td>
<td>147 ± 58</td>
<td>77 ± 45</td>
</tr>
<tr>
<td>10 cm Day 1</td>
<td>128 ± 59</td>
<td>145 ± 45</td>
<td>46 ± 22</td>
</tr>
<tr>
<td>Day 2</td>
<td>105 ± 29*</td>
<td>141 ± 76</td>
<td>53 ± 45</td>
</tr>
</tbody>
</table>

Values are means ± SD. *$P < 0.05$ vs. corresponding values at level during day 2.

Fig. 2. Gradient of the esophageal muscle thickness from the LES to 10 cm above the LES. Each bar represents baseline muscle thickness (closed bars) and peak muscle thickness during contraction (open bars).
between peak muscle thickness and peak pressures were weaker in patients with NC and DES compared with normal subjects and NS patients.

Baseline thickness correlates with peak pressure in patients with NC and DES only ($r$ values of 0.53 and 0.38, respectively). Increase in thickness of muscle layer of esophagus (delta thickness) in patients with DES and NC did not differ from normal subjects as shown in Fig. 3. Correlation between peak pressure and delta muscle thickness in controls and NS patients was similar to the correlation between peak pressure and peak thickness (0.72 and 0.69, respectively). Patients with NC and DES, however, showed no correlation between peak pressure and delta muscle thickness: NC, 0.20 (range 0.05–0.33) and DES, 0.19 (range −0.08–0.47) (Fig. 4).

**Esophageal wall shape and content of lumen.** Shape of resting esophagus in normal subjects was oval with no visible lumen (Fig. 5). Shortly after ingestion of a water bolus, esophageal shape became circular and the esophageal wall became thinner as a result of distension from the bolus. The lumen became wide open and filled, first with hyperechoic air bubbles followed by the hypoechoic water. During esophageal contraction, shape of the esophageal wall was nearly circular. In patients with motor disorders of the esophagus, baseline muscle thickness was higher and the esophagus was relatively more circular in the baseline period compared with normal subjects. Similar to normal subjects, the esophagus became circular in shape during contraction (Fig. 5).

**DISCUSSION**

The present study showed that patients with DES and NC have a higher baseline muscle thickness com-

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**Fig. 3. LES and esophageal baseline, peak muscle thickness, and corresponding peak pressure in LES and at 5 different sites in the esophagus. Each bar represents the total (peak) thickness and also shows two components, i.e., baseline thickness (closed bars) and increase in thickness during contraction (open bars). Mean peak pressures are shown as a line above the bars.**
Fig. 4. Correlation between delta (difference between peak and baseline) muscle thickness and peak pressures in normal controls and patients with NS, NC, and DES (cumulative data). Whereas patients with NS and healthy controls show a significant correlation between peak pressures and delta muscle thickness, this correlation was nonexistent in patients with NC and DES.

Fig. 5. An ultrasonographic picture of normal esophagus compared with a patient with NC and DES in the baseline (before contraction) and at the peak of esophageal contraction. Note that both circular (CM) and longitudinal muscle layers (LM) are markedly thicker in the patient with as well as DES.
pared with normal subjects and patients with NS. The esophageal muscle was thicker in the distal compared with the proximal esophagus in the normal subjects, and this gradient of thickness was also seen in patient groups. Correlation between peak pressure and peak muscle thickness was weak in patients with NC and DES compared with normal subjects and patients with NS motor disorders of the esophagus. Whereas normal subjects have a good correlation between the delta muscle thickness and the peak pressures, this relationship was almost nonexistent in patients with NC and DES. On the other hand, patients with NC and DES, but not normal subjects and NS patients, showed a significant correlation with the baseline muscle thickness and peak pressure.

Our findings in normal subjects are in agreement with Nicosia et al. (16), who reported a significant correlation between the esophageal muscle cross-sectional area and the contraction amplitudes in normal subjects. Autopsy studies in patients with DES clearly show an increase in the thickness of the muscularis propria (3, 5, 6). Stiennon (21) described an increase in the thickness of circular muscle in patients with achalasia of the esophagus and DES. His measurements, however, were made from the X-ray images, and the details of the number of patients studied and their pressure measurements are not reported. An increase in the esophageal muscle thickness using ultrasound technique has been described in patients with high-amplitude contraction (13, 14) and in one patient with prolonged-duration contractions (8). Limitations of these studies, however, are that the number of subjects studied was small and that the pressure was not concurrently measured with the ultrasound imaging (8, 13, 14). Furthermore, these studies did not distinguish between the baseline and the peak muscle thickness. Our data show a marked increase in the baseline thickness of the muscularis propria in DES and NC patients but not in patients with NS motor disorders of the esophagus.

Normal subjects show a marked variability of contraction amplitudes from one swallow to another. We found a similar variability in the peak and delta muscle thickness during swallow-induced contraction in normal subjects. In this study, we find that patients with high-amplitude contractions, peristaltic or simultaneous, have a higher peak muscle thickness. The difference between the patients and normal subjects, however, was that the higher peak muscle thickness was not the result of an increase in the delta muscle thickness during contraction; rather it was due to a higher baseline muscle thickness. These observations would indicate that the baseline and the delta muscle thickness increase are important determinants of the contraction amplitude. Ours is the first study that shows a gradient of muscle thickness in the esophagus from the proximal to distal direction in normal subjects as well as in different patient groups. It is interesting that, similar to the muscle thickness, pressures are also higher in the distal esophagus, both in normal subjects and different patient groups, again suggesting a relationship between the muscle thickness and pressures. Patients with NC and DES had a poor correlation between the contraction amplitude and the muscle thickness compared with normal subjects and patients with NS. For a given pressure, the muscle was thicker in the NC and DES patients compared with normal subjects. The latter suggested that contractile mechanism of the muscle in NC and DES was defective. The reason for a defective contractile mechanism in NC and DES was not clear, but we speculate that this situation may be analogous to the muscle in the hypertrophic cardiomyopathy.

DES is thought to be the result of an imbalance between excitatory and inhibitory innervation of the esophagus (9, 20). It is proposed that an impaired inhibitory innervation induces a state of an unopposed excitation, which results in an increase in the contraction amplitude. Although never reported, a similar mechanism may be proposed for the high amplitude peristaltic esophageal contractions (NC). We propose that the increase in the muscle thickness is the reason for high-amplitude peristaltic and simultaneous esophageal contractions. Our reasoning is based on Laplace’s law, according to which there is a direct relationship between the pressure and wall thickness. Hashimo et al. (12) found that nitric oxide knockout mice have a thicker stomach wall compared with wild-type mice, which may suggest that lack of inhibitory innervation may be the primary reason and that increase in thickness of muscularis propria is secondary to the loss of inhibitory innervation. Our study did not allow us to determine whether the primary problem in DES and NC patients was muscle hypertrophy (myogenic), impaired inhibitory innervation (neurogenic), or both. Furthermore, our study did not distinguish whether the increase in muscle thickness in DES and NC patients was related to an increase in muscle tone or hypertrophy of the muscle.

Pathogenesis of dysphagia in DES is thought to be due to the impaired peristalsis or simultaneous contractions in the esophagus. On the other hand, patients with NC have normal peristalsis and the reason for dysphagia in these patients, as reported by several investigators (1, 23, 24), is not clear. An increase in the muscle thickness in NC esophagus, as seen in this study, is likely to reduce esophageal compliance, which in turn may diminish the ability of the esophagus to accommodate a bolus. We speculate that the increase in muscle thickness could be an important reason for impaired bolus transit in NC patients and may explain dysphagia symptom in these patients.

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