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Defective mucosal movement at the gastroesophageal junction in patients with gastroesophageal reflux disease

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Abstract

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BACKGROUND—Little is known about the role of muscularis mucosa at gastroesophageal junction (GEJ).

AIM—To evaluate the movement of the mucosa/ muscularis-mucosa/submucosa (MMS) at the GEJ in normal subjects and in patients with gastroesophageal reflux disease (GERD).

METHODS—Gastroesophageal junctions of 20 non-GERD subjects and 10 patients with GERD were evaluated during 5mL swallows using two methods: 1) High-resolution endoluminal ultrasound and manometry-the change in the GEJ luminal pressures and cross-sectional area of esophageal wall layers were measured. 2) Abdominal ultrasound-the MMS movement at the GEJ was analyzed.

RESULTS

Endoluminal ultrasound: In the non-GERD subjects, the gastric MMS moved rostrally into the distal esophagus at 2.17 sec after the bolus first reached the GEJ. In GERD patients the gastric MMS did not move rostrally into the distal esophagus. The maximum change in cross-sectional area of gastroesophageal MMS in non-GERD subjects and in GERD patients were 289% and 183% respectively.

Abdominal ultrasound: In non-GERD subjects the gastric MMS starts to move rostrally significantly earlier and to a greater distance than muscularis propria (MP) after the initiation of the swallow (1.75sec vs. 3.00sec) and (13.97mm vs. 8.91mm). In GERD patients, there is no significant difference in the movement of gastric MMS compared to MP (6.74mm vs. 6.09mm). The independent movement of the gastric MMS in GERD subjects was significantly less than in non-GERD subjects.

CONCLUSION—In non-GERD subjects the gastric MMS moves rostrally into the distal esophagus during deglutitive inhibition and forms a barrier. This movement of the MMS is defective in patients with GERD.

Keywords

Gastroesophageal reflux disease; Muscularis Mucosa; Gastroesophageal Junction; Endoluminal Ultrasound; Endoscopic Ultrasound; Abdominal Ultrasound

Introduction

The muscularis mucosa is a thin layer of smooth muscle located beneath luminal mucosa throughout the digestive tract. The anatomy and histology of the smooth muscle within the muscularis mucosa differ between various regions of the gastrointestinal tract. Esophageal muscularis mucosa is composed of only longitudinal smooth muscle, while gastric and intestinal muscularis mucosa is composed of both outer longitudinal smooth muscles and inner circular smooth muscles [1].

Although there is an extensive literature describing contraction of the esophagus during swallowing and peristalsis, most of this literature evaluates the muscularis propria (MP) [2-9]. We hypothesize that mucosa/ muscularis mucosal / submucosa complex (MMS) at the gastro-esophageal junction (GEJ) may have a role in protecting the distal esophagus from

reflux of gastric contents in addition to its role in luminal acid clearance and tissue resistance. The aim of this study is to evaluate the movement of the MMS in the GEJ during swallowing in non-GERD subjects and in patients with GERD.

Methods

University Institutional Review Board approved the study and informed consent was given by all the participants in the study. This is a prospective study with 20 non-GERD subjects and 10 patients with GERD (Table 1). All non-GERD subjects were normal volunteers recruited just for the purpose of the study. The study was performed after an overnight fast for at least 12 hours. None of the subjects were taking any medications that could affect esophageal motility. None of the subjects had a hiatal hernia on upper endoscopy or a history of upper gastrointestinal surgery. Tobacco use was not permitted on the day of the study. There were two subjects with mild esophagitis on endoscopy in the GERD group. Three to four swallows were performed with 5 ml of water during breath holding and waiting at least 30 seconds between each swallow. None of the subjects were sedated in this study. All data is expressed as means $\pm$ standard error of mean. Comparisons were performed by unpaired t tests when appropriate. Significance was declared at $P < .05$.

Endoluminal ultrasound and simultaneous manometry

A high-resolution (20MHz) ultrasound transducer (Olympus UM-3R probe on Olympus EU-M30S ultrasound system, Olympus America, Center Valley, PA) was attached to a 3.0-F manometric catheter and placed at the GEJ high-pressure zone as previously described [10].

Ultrasound images of the esophagus demonstrate seven sonographic layers. The esophageal MMS can be distinguished from the gastric MMS by the thickness of the second hypo-echoic layer [10,11]. (Figure 1)

Data acquisition: Ultrasound images were collected from the start of the swallow to end of the swallow. The cross-sectional surface areas of the MMS, CSM and LSM were measured. All the pressure measurements reported were relative to the baseline gastric pressure. Longitudinal shortening of the CSM and LSM was calculated using the law of mass conservation (local increase in tissue cross-sectional area during muscle contraction is accompanied by a proportional decrease in length of the tissue, so that length during contraction multiplied by cross-sectional area during contraction = length at rest multiplied by cross-sectional area at rest) [7]. The cross-sectional area of the MMS, containing the muscularis mucosa was also measured. However the law of mass conservation does not apply to the MMS as it is compressible under physiologic pressures. Changes in MMS cross-sectional area during peristaltic contraction at the GEJ reflect the differences in the overall thickness of the squamous MMS of the esophagus compared to the columnar MMS of the cardia of stomach. The deep mucosa containing the muscularis mucosa is thin in the esophagus and thicker in the stomach. Therefore, an increase in the cross-sectional area of the MMS and an increase in the thickness of the deep mucosal layer was due to the gastric MMS moving up into the tubular esophagus during swallowing [11]. The changes were measured from the initiation of the swallow until the entire bolus passed through the GEJ.

Abdominal imaging

Abdominal ultrasound of the GEJ was performed using an Aloka SSD-5000 ultrasound machine (Wallingford, CT, U.S.A.) with a 3 MHz abdominal ultrasound transducer. All subjects were placed at 30-degrees right lateral decubitus position and the ultrasound transducer was positioned in the epigastric area just below the xiphoid process, so that the distal esophagus and proximal stomach were imaged. The layers of the esophageal and gastric wall were seen in sagittal/transverse view in a triangular shaped configuration with the distal portion of the esophagus to the left and the stomach to the right [12]. (Figure 2)

The subjects were given 5 mL of water to hold in his/her mouth and then asked to swallow when the GEJ was clearly visualized (initiation of the swallow was marked as zero time). The swallows were recorded at 30 frames/second. All the measurements were made off line on frames from the recorded video. The distance and velocity of gastroesophageal MMS and MP movement was measured on the lesser curvature side during bolus transit using Image J software (NIH, Bethesda, MD). The adventitia was used as a surrogate marker for the movement of the MP since it was difficult to measure movement of the MP directly due to its acoustic properties. Measurements were made on a series of images every 0.5 seconds during the swallow. Distance and time that the gastroesophageal MMS and MP moved per 0.5 second were measured for each subject for the duration of the bolus transit. Velocities for each subject were calculated by multiplying the distance moved by the time it took for that movement. Average velocities at every 0.5 seconds of gastroesophageal MMS and MP for all subjects within the groups (normal Controls and GERD subjects) were calculated.

Results

Results of endoluminal ultrasound during bolus transit

The maximal change in cross-sectional area of the MSM in non-GERD subjects is significantly greater than in GERD patients. There is no significant difference in the maximal change in cross-sectional area of the CSM and LSM between non-GERD subjects and GERD patients (Table 2). There is no significant difference in the time of maximal change in cross-sectional area of the CSM and LSM between non-GERD subjects and GERD patients ($p = 0.664$ and $p = 0.548$ respectively). In non-GERD subjects the gastric columnar MSM moved up into the tubular esophagus at 2.17 ± 0.55 sec after the bolus first reached the GEJ and remained in the distal tubular esophagus for an average of 5.62 ± 0.69 sec. The cross-sectional area of the CSM and LSM did not change significantly until the cross-sectional area of the MSM started to decrease. (Figure 3A) In GERD patients the gastric MMS did not move into the distal esophagus. (Figure 3B) There is no significant difference in intra-luminal pressures during maximal cross-sectional area of the gastroesophageal MMS, CSM and LSM between non-GERD subjects and GERD patients. (Video 1 and Video 2)

Results of abdominal ultrasound during bolus transit

The total distance that the gastroesophageal MMS moves and the distance that the gastroesophageal MMS moves independently of the MP movement in GERD patients is significantly less than in non-GERD subjects ($P = 0.014$ and $P = 0.049$). The distance that

the MP moves in GERD patients is not significantly different than in the non-GERD subjects ($P=0.173$). (Table 3) (Figure 4) (Video 3 and Video 4)

In Non-GERD subjects the rostral movement of the gastroesophageal MMS starts before that of the MP and both move together for 1.25 seconds. In GERD patients there is no significant difference in rostral movement (6.74 ± 1.22 mm. vs. 6.09 ± 1.13 mm, $P=0.709$) or caudal movement of MSM and MP (7.92 ± 1.81 mm. vs. 6.87 ± 0.57 , $P=0.601$) (Figure 4).

In non-GERD subjects the acceleration of the gastroesophageal MMS in the rostral direction differs significantly when compared to the acceleration of the MP in the rostral direction. The gastroesophageal MMS demonstrates two phases of acceleration. The initial acceleration of the gastroesophageal MMS is independent of the acceleration of the MP. The later phase of acceleration of the gastroesophageal MMS coincides with the acceleration of the MP. This indicates that at least part of the later phase of acceleration of the gastroesophageal MMS is due to movement of the MP pulling gastroesophageal MMS along with it. (Figure 5A) In GERD subjects the acceleration of the gastroesophageal MMS in the rostral direction is not significantly different than that of MP. This indicates that the gastroesophageal MMS does not move independently but is dragged by the MP. (Figure 5B)

Qualitative description of mucosal movement

In normal control subjects, the MMS movement starts before the arrival of the bolus in the distal esophagus, while movement of the MP starts just as the bolus is arriving in the distal esophagus. The gastric MMS moved rostrally into the distal tubular esophagus due to the initial contraction of the esophageal MMS, causing narrowing of the esophageal lumen in the area of GEJ high-pressure zone when there is decreased pressure within this area due to relaxation of MP. As the tail of the bolus reaches the narrowed channel, the gastric MMS and MP simultaneously start to move caudally to reach their original resting position. This mechanism appears to be defective in the patients with GERD.

Discussion

During peristalsis, the components of GEJ relax to allow passage of contents. A wave of muscle inhibition precedes peristaltic contraction waves and there is relaxation of GEJ immediately upon the initiation of swallowing or during secondary peristalsis which eliminates the active tone of the GEJ. The GEJ pressure also decreases during transient lower esophageal sphincter relaxations. Whenever gastric pressure is higher than the esophageal pressure, a pressure gradient exists between the abdominal and thoracic cavity that can drive the flow of gastric contents from the stomach into the esophagus [13-15]. This makes the lower esophagus vulnerable to reflux of gastric contents.

Very little is known about the functional purpose of the muscularis mucosa. Using simultaneous endoluminal ultrasound and manometry and abdominal ultrasound in non-GERD subjects, we observed an increase in cross-sectional area of the MSM during swallowing. This occurs at the same time that the GEJ relaxes during swallowing. This movement of the gastric MMS creates a narrowing in the distal esophagus which acts to

prevent gastric reflux while the pressure within the high-pressure zone is low. This movement of the gastroesophageal MMS was lacking in the GERD patients.

The new observations in this study, suggest that the gastroesophageal MMS may have other important physiologic functions in addition to their direct role as epithelial protective barriers. The new observations supporting our hypothesis are: 1) at the level of the GEJ during deglutition, the gastric MMS in the cardia of the stomach is pulled up into the distal esophagus and coincides with the relaxation of the GEJ high-pressure zone. 2) The MMS of the distal esophagus moves before the rest of the esophagus moves. The initial movement of the gastroesophageal MMS is independent of the movement of the MP. 3) The gastric MMS movement into the distal esophagus forms a narrow channel in the distal esophageal lumen while the pressure is low within the GEJ during swallowing.

We believe that in GERD patients the gastric mucosa was not pulled into the distal esophagus because of lack of contraction of the gastroesophageal MMS in GERD patients. The defect may be in either esophageal muscularis mucosa or gastric muscularis mucosa or both. We believe that the first peak in the velocity of the MMS is due to muscularis mucosa contraction-induced mucosal movement, followed by the second peak which is due to MP shortening, pulling the mucosa along with it. There are two possible explanations for this lack of movement of the gastroesophageal MMS in GERD patients. First, due to chronic reflux of gastric contents there may be an inflammatory reaction within the mucosa which may release substances which secondarily inhibit contraction of the muscularis mucosa or cause direct damage to it [16,17]. However, another possible explanation is that the lack of contraction of the muscularis mucosa may be a primary defective mechanism and the fact that the gastric MMS is not pulled up into the distal esophagus may be one of the pathophysiologic mechanisms in development of GERD.

The limitations of this study include the fact that overweight or obese participants (BMI>25) were excluded from the abdominal ultrasound portion of this study due to the inability to image the esophagus through the thick abdominal wall. We don't know if the defective movement of the gastroesophageal MMS in GERD patients is a cause or an effect of GERD. We were concerned that the observation of mucosal movement during the endoluminal ultrasound portion of the study might be due to displacement of the ultrasound probe into the cardia of stomach secondary to esophageal shortening. However, our previous studies and the abdominal ultrasound portion of this study demonstrated rostral movement of the muscularis mucosa starting before shortening of the muscularis propria.

In this study we looked at the gastroesophageal MMS of the distal esophagus and cardia of the stomach in non-GERD subjects and in GERD patients. In non-GERD subjects the gastric MSM acts as a mechanical anti-reflux barrier by moving up into the distal tubular esophagus and by forming a narrow channel during deglutitive inhibition of the GEJ. This is brought about initially by contraction of the muscularis mucosa independently of the MP. This narrowing in the distal esophagus protects the esophagus from reflux of gastric contents at a time when the GEJ relaxes, at the initiation of swallowing, until the bolus reaches the distal esophagus. This mechanism appears to be absent in GERD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Endoluminal Ultrasound of GEJ during Swallowing

Figure - 1. Endoluminal Ultrasound and manometry-cross-sectional images of Gastroesophageal junction

Cross-sectional ultrasound images of the gastroesophageal junction during 5 mL water swallow. A. GEJ during initiation of swallow. B. GEJ just before the water bolus enters the GEJ. C. GEJ during bolus transit. D. GEJ when the gastric mucosa is pulled up in to the esophagus. The second hypo-echoic layer, containing the muscularis mucosa, appears markedly thicker than in the previous or subsequent panels. This demonstrates that the gastric mucosa was pulled up into the tubular esophagus. E. GEJ at the end of bolus. The second hypo-echoic is much thinner than in the previous panel. This demonstrates that the gastric mucosa has left the tubular esophagus and the esophageal squamous mucosa has returned to the level of the ultrasound transducer.

Figure - 2. Abdominal ultrasound image of Gastroesophageal junction

This is an image of GEJ using abdominal ultrasound during 5 mL water swallow. The liver is seen in the top left of the image. The aorta is inferior to the esophagus. The esophagus is to the left and the stomach as to the right. The gastroesophageal junction appears as a triangular shape as outlined by the black lines. The mucosa/submucosa, muscular propria and adventitia are clearly visible. The crural diaphragm/phrenoesophageal ligament is seen between the aorta and esophagus.

Figure - 3. Graph of cross sectional area and pressure changes at gastroesophageal junction during swallowing using endoluminal ultrasound and manometry

This graph demonstrates the percent change in cross sectional surface area of the mucosa/muscularis mucosa/submucosa, circular smooth muscle of muscularis propria, and longitudinal smooth muscle of muscularis propria in non-GERD subjects (panel A) and in patients with GERD (panel B). X-axis shows time from the initiation of swallow, primary Y-axis shows percent change in cross sectional area and secondary Y-axis shows pressure in mm Hg. The times at which water is first seen on ultrasound and then completely disappears are marked with dotted line. The time at which the gastric mucosa/muscularis mucosa/submucosa is first seen and then disappears, as demonstrated by the appearance and disappearance of the thickened second hypoechoic layer, is marked with a broken line. A. In normal volunteers there is a slow decline in pressure as the gastric mucosa is pulled up into the tubular esophagus. B. In GERD subjects the gastric mucosa does not pull up into the tubular esophagus as demonstrated by no change in the thickness of the second hypoechoic layer.

Figure - 4. Graph of mucosal movement at Gastroesophageal junction during swallowing using abdominal ultrasound

This graph shows the total movement of mucosa/muscularis mucosa/submucosa and the muscularis propria during swallowing in GERD and non-GERD subjects. Y-axis is the total distance travelled in millimeters. Panel-A shows the movement in the rostral direction. Panel-B shows the movement in the caudal direction at the end of swallow.

Rostral Velocity of Mucosa and Muscularis Propria

Figure - 5. Graph of velocity of the mucosa/muscularis mucosa/submucosa and muscularis propria at the gastroesophageal junction during swallowing using abdominal ultrasound
 This is a graph of velocity versus time of the mucosa/submucosa (solid line) and the muscularis propria (Broken line) at gastroesophageal junction during swallowing. Velocity is on the Y axis in mm/sec and time is on the x axis in seconds. Panel A. In non-GERD subjects the acceleration of the mucosa/submucosa shows two peaks. While the acceleration of the muscularis propria shows only one peak. The first peak in the acceleration of the mucosa/submucosa is independent to the movement of muscularis propria. However, the second peak in the acceleration of the mucosa/submucosa coincides with the peak in the acceleration of the muscularis propria. Panel B. In GERD patients the acceleration of the

mucosa/submucosa shows only one peak, as opposed to two peaks in non-GERD subjects. The one peak in GERD subjects is coincident with movement of the muscularis propria.

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Table 1
Participant information

	Non-GERD subjects[#]	GERD patients^{##}
Endoluminal Ultrasound and manometry	n=7 (41.7 Yrs, 5M, 2F)	n=6 (44 Yrs, 4M, 2F)
Abdominal Ultrasound [*]	n=13 (25 Yrs, 7M, 6F)	n=4 (27 Yrs, 4M, 0F)

[#] non-GERD subjects were free of gastrointestinal symptoms.

^{##} GERD patients had a history of heartburn, a history of taking Proton pump inhibitors or H2 blocker with relief of the heartburn.

^{*} Overweight/Obese participants (BMI>25) were excluded from abdominal imaging part of the study, as it is extremely difficult to image the GEJ through abdominal wall in this group.

Table 2
Results of Endoluminal Ultrasound

		Non-GERD	GERD	P Value[¥]
GE-MSM	Maximal increase in CSA	289 ± 22%	183 ± 30%	<i>P</i> = .013
	Intaluminal Pressure	14.73 ± 9.21 mmHg	9.07 ± 5.12 mmHg	<i>P</i> = .619
	Time of event	4.26 ± 0.58 sec	(N/A)	
CSM	Maximal CSA	149 ± 16%	139 ± 12%	<i>P</i> = .635
	Intaluminal Pressure	53.36 ± 19.10 mmHg	32.51 ± 13.65 mmHg	<i>P</i> = .408
	Time of event	9.35 ± 0.73 sec	10.18 ± 1.83 sec	<i>P</i> = .664
LSM	Maximal CSA	147 ± 13%	132 ± 10%	<i>P</i> = .395
	Intaluminal Pressure	49.13 ± 19.90 mmHg	26.16 ± 15.02 mmHg	<i>P</i> = .390
	Time of event	8.88 ± 0.80 sec	9.97 ± 1.67 sec	<i>P</i> = .548

GE-MMS= Gastroesophageal Mucosa/ Muscularis-mucosa/ Submucosa.

CSM= Circular Smooth muscle of Muscularis Propria

LSM= Longitudinal Smooth muscle of Muscularis Propria.

Maximal increase in CSA = Maximal increase in cross sectional area from the baseline

Intaluminal Pressure = Intaluminal pressure during maximal CSA from baseline

Time of event = time of event during maximal CSA

[¥] P values were calculated by using an independent *t* test with equal variance. *P* < .05 was considered to indicate a significant difference.

Table 3
Results of Abdominal ultrasound in Non-GERD

	MSM	MP	P Value [¥]
Start of rostral movement	1.75 ± 0.26 sec	3.00 ± 0.37 sec	<i>P</i> = .012
The total rostral movement	13.97 ± 1.38 mm	8.91 ± 1.02 mm	<i>P</i> = .007
Average Velocity of rostral movement	5.10 ± 0.37 mm/sec	3.37 ± 0.31 mm	<i>P</i> = .001
Start of caudal movement	7.72 ± 0.36 sec	7.66 ± 0.33 sec	<i>P</i> = 0.915
The total caudal movement	13.37 ± 1.14 mm	6.86 ± 0.66 mm	<i>P</i> = .00008
Average Velocity of caudal movement	6.04 ± 0.9 mm/sec	4.20 ± 0.98 mm/sec	<i>P</i> = .183

MSM = Mucosa/Submucosa/Muscularis-mucosa

MP = Muscularis Propria

Start of rostral movement = Start of rostral movement after initiation of swallow.

[¥] P values were calculated by using an independent *t* test with equal variance. *P* < .05 was considered to indicate a significant difference.