Effect of lower esophageal sphincter tone and crural diaphragm contraction on distensibility of the gastroesophageal junction in humans

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Shaker, Reza, Eytan Bardan, Chengming Gu, Benson T. Massey, Thomas Sanders, Mark K. Kern, Raymond G. Hoffmann, and Walter J. Hogan. Effect of lower esophageal sphincter tone and crural diaphragm contraction on distensibility of the gastroesophageal junction in humans. Am J Physiol Gastrointest Liver Physiol 287: G815–G821, 2004; 10.1152/ajpgi.00120.2004.—Previous studies of distensibility of the gastroesophageal junction (GEJ) in humans have not tried to distinguish between the effects of muscle action and passive elastic tissue properties of the GEJ. We studied 15 healthy subjects (ages 23–67 yr, 11 men/4 women) by using a catheter with a highly compliant bag positioned manometrically at the GEJ. The bag was distended with air at a rate of 20 ml/min while intrabag pressure was recorded. Distensions were performed during normal breathing, with breath held at maximum inspiration (MI) to activate the diaphragmatic crura, and with midesophageal balloon distension (BD) to relax the lower esophageal sphincter. In 10 subjects, distensions were performed after atropine injection (12 μg/kg iv). Pressure-volume curves and incremental distensibility values were calculated and compared among the different conditions. Both MI and BD significantly altered the slopes of the pressure-volume curves, whereas no effect was seen with atropine. Maximum distensibility was seen at the volume increment of 5–10 ml and was reduced with larger volumes. Distensibility measurements for the various test conditions tended to converge at the largest volume increment, suggesting that distensibility at this degree of distension was more related to the passive elastic properties of the GEJ. On the basis of these findings, we conclude that there can be significant active muscular contributions to recordings of distensibility at the GEJ, variations that must be controlled for during different study conditions.

MATERIALS AND METHODS

Subject selection. We studied 15 healthy volunteers (11 men/4 women, ages 23–67 yr) without any symptoms attributable to the gastrointestinal tract. The study was approved by the Human Research Review Committee of the Medical College of Wisconsin, and the volunteers gave written informed consent before their studies. Subjects were compensated nominally for their participation in the study. Before their studies, each volunteer underwent transnasal unsedated upper gastrointestinal endoscopy (25) to ascertain the absence of hiatal hernia and asymptomatic reflux esophagitis (27).

Recording apparatus. Distensibility measurements of the GEJ were obtained with a specially designed catheter. This catheter consisted of an eight-lumen, 4.6-mm-diameter polyvinyl tube that was 100 cm long (Fig. 1). A 7-cm-long, thin polyethylene bag that was tapered at both ends was tied around the catheter shaft distally. When maximally distended, this bag assumed a roughly cylindrical shape in its midportion, with a maximum diameter of 2.5 cm and a total volume of 28 ml. The bag was designed so that it would be infinitely compliant up to its maximum distending volume, so that any pressure increase recorded within the bag at submaximal volumes would reflect the

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distensibility of the adjacent hollow viscus, rather than the distensibility of the bag. Ex vivo continuous infusion of air at the rate of 20 ml/min into the infinitely compliant bag resulted in near zero intrabag pressure up to 20 ml volume. Between 20 and 25 ml the intrabag pressure increased to 3 ± 3 mmHg. Beyond 25 ml the intrabag pressure increased exponentially. Therefore, distension volumes of 0–25 ml were used in this analysis. One lumen of the catheter located proximally underneath the bag was used to distend the bag with air using a Harvard Pump (compact infusion pump model 975; Harvard Apparatus, Millis, MA), whereas another lumen located distally underneath the bag was used to record the intrabag pressure and was connected to a pressure transducer.

A cylindrical 2.5-cm-long balloon made of thin latex tubing was tied around the catheter 8 cm proximal to the oral margin of the infinitely compliant bag with one of the catheter lumens being used to distend this balloon. During studies, this balloon was located in the midesophagus and was distended to a 2.5-cm diameter using 10 ml of air starting 10 s before ramp bag distensions, to induce relaxation of the LES (8, 17, 23).

The remaining lumens of the catheter were used as perfused sideholes to record intraluminal pressures. Sideholes were positioned at either end of the infinitely compliant bag and distending balloon, as well as at a midpoint between the bag and the balloon. These lumens were connected to a pneumohydraulic capillary infusion system and pressure transducers. The pressure transducers were connected to a computerized manometric recording system (Medical Measurement Systems, Enschede, Netherlands), which also had an event marker for recording the start and end of distensions.

Study protocol. Subjects were studied after an overnight or 6-h fast. Before catheter placement, the bag and balloon were distended to check for leaks. The subject’s nostril was lubricated with 2% lidocaine jelly, and the catheter assembly was passed transnasally so that the infinitely compliant bag was within the stomach. Studies were performed with the subjects supine. A station pullthrough of the LES was performed by using the manometric port just proximal to the bag to determine the basal LES pressure and location of the LES high-pressure zone. This information was used to position the infinitely compliant bag across the GEJ. This position was confirmed by observing the changes in pressure with deep inspiration at the pressure-recording sites at each end of the bag. At the end of the study, a repeat station pullthrough of the LES was performed to determine whether the baseline pressure characteristics of the LES had changed during the study.

Once the catheter was in the appropriate position, the bag was distended with 30 ml of air to unfold the bag, and then the bag was deflated. Subsequently, intrabag and intraluminal pressure recordings were made while the bag was distended with air at a constant rate of 20 ml/min until 30 ml of air was infused. During this distension, the intrabag and intraesophageal pressures were recorded. Bag distensions were performed in triplicate for the following conditions: 1) during normal breathing (NB), 2) while the subjects held their breath after a maximum inspiration (MI), and 3) during NB and MI while the midesophageal balloon was distended (BD) to 2.5 cm. To avoid the confounding effect of deglutitive LES relaxation and aftercontraction as well as esophageal peristalsis, volunteers were instructed to withhold swallowing during the bag distension period. Data from distensions during which deglutitive peristalsis was detected were discarded.

In 10 of the 15 volunteers, the distension protocol was also performed during NB on a separate day before and after intravenous infusion of 12 µg/kg atropine sulfate (5). They also had distensions performed with BD during NB after atropine. Furthermore, five male subjects were studied on a separate day using a single distension protocol during NB with concurrent videofluoroscopy to ascertain the shape and spacial relationship of the distended bag and the GEJ junction.

Data analysis. Pressure-volume curves for the different distension protocols were generated by taking the recorded intrabag pressure at 5-ml increments of bag distension, up to 25 ml. Pressure readings were taken independently by two different investigators and found not to be significantly different (P > 0.9). Differences in pressure for a given distension volume were compared for the different distension protocols. Distensibility was assessed by two different methods. First, the overall slope of the pressure-volume curve was taken as a measure of distensibility over the range of distension volume used, so that larger slopes indicated less distensibility. Incremental distensibility was defined as the relationship between incremental changes in volume relative to incremental changes in pressure and was calculated by dividing 5 ml by the observed pressure changes for the volume increments of 0–5 ml, 5–10 ml, 10–15 ml, 15–20 ml, and 20–25 ml (i.e., ΔV/ΔP).

Comparisons of the slopes of the pressure-volume response curves generated during the different distension protocols were performed by using a growth curve analysis approach. Growth curve analysis uses regression curves that are fit to the individual subject’s pressure-volume curve to estimate the common slope and the variability in the common slope across subjects. Because each condition (with and without balloon, etc.) was examined in the same subject, the random within-subjects variability in the slope was used for paired or repeated-measures comparisons between conditions. Testing for differences in pressure at the 5-ml increments of distending volumes for the different distension protocols was performed by using ANOVA. ANOVA was also used to compare changes in incremental distensibility of the GEJ among the different distension protocols. In the case of comparing the conditions (with and without balloon, etc.), an a priori hypothesis of the additional effect of the balloon on the pressure response curve, as well as physiologically based a priori effects of inspiration and atropine on the pressure-volume curves, do not require a multiple-comparisons correction. On the other hand, when examining the pressure-volume curves for differential distensibility by volume (deviations from linearity in the pressure-slope curve), there were no a priori hypotheses and the post hoc Tukey correction for multiple comparisons was used to ensure that the experiment-wise α-level was kept at 0.05. Data in the text are presented as means ± SE unless stated otherwise. Data on LES pressures before and after distension protocols were performed and were compared by using Student’s paired t-test. Statistical analyses were performed by using SigmaStat for Windows 2.03 software (SPSS, Chicago, IL).
RESULTS

All subjects tolerated the procedure well. There were no reports of pain or discomfort with distension of the bag used for determining the pressure-volume curve or the BD used for inducing LES relaxation. Distension of the infinitely compliant bag within the GEJ did not affect the resting LES pressure. The average resting LES pressure immediately before the studies (16 ± 2 mmHg) was similar to that following the studies (14 ± 3 mmHg, P = 0.59).

Effect of respiration on GEJ distensibility recording. The pressure-volume curve during NB and MI is shown in Fig. 2A. The relationship between pressure and distending volume appears roughly linear over the range of distension volumes tested. Comparisons of the pressure-volume response curves between the two conditions showed that the slope of the curve for MI is significantly greater than that of NB (1.46 ± 0.12 vs. 0.93 ± 0.13 mmHg/ml, P = 0.003). In addition, the intrabag pressures at all levels of intrabag volumes for MI were significantly higher than for NB. The calculated values for incremental distensibility showed a nonlinear relationship to the distending volume with the highest degree of distensibility occurring at the volume increment from 5 to 10 ml (P < 0.05) for both NB and MI (Fig. 2B). ANOVA showed that MI reduced overall distensibility (P = 0.046), although pairwise comparisons at different volumes were not significantly different between NB and MI.

Effect of esophageal distension-induced LES relaxation on GEJ distensibility recording. The pressure-volume curves showing the effects of BD on NB and MI are shown in Fig. 3A. BD significantly decreased the slope of pressure-volume curve for both NB (0.93 ± 0.13 vs. 0.73 ± 0.12 mmHg/ml, P = 0.004) and MI (1.46 ± 0.12 vs. 1.06 ± 0.10 mmHg/ml, P = 0.009). For both NB and MI during BD, the intrabag pressures generated at points where the intrabag volumes reached 5, 10, 15, 20, and 25 mmHg were significantly lower (P < 0.05) compared with the sequences during which there was no BD, except for a pressure at 25-ml volume during NB (P = 0.052). ANOVA showed that BD resulted in no significant change in the incremental values of distensibility for either NB or MI, although the study was underpowered to detect significant differences of the magnitude observed (Fig. 3B). Again, the highest values of incremental distensibility were seen for the volume increment of 5–10 ml, with a tendency for distensibility values to converge at the highest volume increment for all distension protocols.

Effect of atropine on the GEJ distensibility recording. The effect of atropine on GEJ distensibility during NB is shown in Fig. 4. Intravenous infusion of 12 μg/kg of atropine did not result in any appreciable change in the slope of the pressure-volume curve (0.93 ± 0.13 vs. 1.01 ± 0.12 mmHg/ml, P = 0.84). Atropine also had no effect on the incremental distensibility values (data not shown). However, subsequent BD after atropine did result in a significant decrease in the slope (0.78 ± 0.15 mmHg/ml, P = 0.024). BD after atropine injection also resulted in a significant decrease in intrabag pressure corresponding to volumes of 5, 10, 15, 20, and 25 ml compared with pressures before BD (ANOVA, P < 0.03).

Concurrent videofluoroscopic studies. Still frames of a videofluoroscopic recording of the GEJ during intrabag air infusion are shown in Fig. 5. As seen, the deflated bag is situated in three compartments: the esophagus, GEJ, and stomach. During air infusion, the portions of the bag that were in the stomach and esophagus distended more compared with the portion that was within the GEJ. Opening of the GEJ was minimal in the beginning, and at the maximum capacity, the bag develops a dumbbell shape, with the GEJ straddling the middle, narrow part. Bag distension did not result in displacement of the bag completely into the esophagus or the stomach. This pattern of bag filling was observed in all 5 subjects.

DISCUSSION

In this study, we determined the influence of LES tone and crural diaphragm contraction on the recorded distensibility of the GEJ in a group of healthy subjects. The results from this
study strongly support the conclusion that both contraction of the crural diaphragm and LES tone significantly reduce the distensibility of the GEJ, as evidenced by changes of the pressure-volume curves during NB compared with end-inspiration breath hold, as well as with concurrent esophageal body BD. Thus interpretation of the recordings of distensibility of the GEJ must take into account the dynamic state of these two structures. For instance, if a study protocol uses an intervention that decreases LES tone, but the side effects induce psychological distress that increase activity in the diaphragmatic crura, no change in distensibility may be observed. Distinquishing between the active muscular and passive tissue components that determine GEJ distensibility may have clinical relevance. For example, an achalasia patient undergoing a myotomy of the LES who develops fibrosis of the esophageal wall at the operative site might postoperatively have an increase in the total distensibility of the GEJ, but a decrease in the distensibility due to passive elastic elements, thus leading to persistent postoperative symptoms.

Previous studies (12, 15, 16) have shown that maneuvers that activate the diaphragmatic crura, such as leg raising, valsalva, and Mueller maneuvers, increase pressure at the GEJ. Thus a maneuver that activates the diaphragmatic crura, such as MI, would be expected to affect the pressure-volume curve during GEJ distension. Other factors can also affect the activity of the diaphragmatic crura, such as acute stress (19), which may be difficult to control from one study session to the next or among individuals within a study.

To eliminate the LES tone to determine its contribution to recorded GEJ distensibility, we used BD as a surrogate for deglutitive LES relaxation. LES relaxation induced by swallowing and BD are similar in terms of causing smooth muscle LES, but not striated muscle crural diaphragm relaxation (11, 17). However, unlike deglutitive LES relaxation, LES relaxation induced by BD is not accompanied by distal esophageal peristalsis during the period of distension (22), and the relaxation can persist throughout the period of BD. The fact that the effect of diaphragmatic crural activation on the pressure-volume curves persists after esophageal distension is consistent with the concept that nonpainful BD does not affect crural tone.

This study found that LES tone has a significant effect on the pressure-volume curves generated by GEJ distension. LES basal tone shows significant temporal variation (4) and is affected by various physiological states, such as the migrating motor complex (6). This variability must be taken into consideration in evaluating changes in distensibility between studies for individual subjects, if the LES tone is not otherwise inhibited during the studies.

![Fig. 3. A: effect of midesophageal balloon distension (BD) on the GEJ pressure-volume curve during NB and MI. As seen, for both test conditions, the slope of the curve was decreased significantly by midesophageal distension, indicating the effect of lower esophageal sphincter tone. The fact that the curve for maximum breath hold did not approximate that of NB during midesophageal BD suggests absence or negligible effect of esophageal BD on crural contraction. B: effect of midesophageal BD on distensibility of the GEJ during NB and MI. As seen, the pattern of highest distensibility at the volume increment of 5–10 ml distension is present both with as well as without esophageal distension (P < 0.05). Note convergence of distensibility values at the largest incremental volume.

Fig. 4. Effect of atropine on the GEJ pressure-volume curve during NB. As seen, atropine did not have any significant effect on this curve. On the other hand, subsequent BD significantly (P = 0.024) decreased the slope of the curve.
Our finding that atropine at the dose of 12 μg/kg did not affect the pressure-volume curve was unexpected, as the dose of atropine used in this study has previously been found in our laboratory (5) to have a significant inhibition of basal LES pressure that persisted for 30 min, a finding replicated in other studies (13) that have used similar doses. However, the LES does generate an active tone in response to distension (2). Although a prior study (1) suggested that the muscarinic antagonist propantheline inhibited the decreased basal LES pressure observed with increasing manometric probe size, the maximum diameter studied (1 cm) was small and only about twice the size of the resting diameter of the distensibility catheter used in our study. Whereas we saw a small decrease in observed intrabag pressure at lower distending volumes, this was not significant, although the study was underpowered to detect a change of this size.

Although the overall pressure-volume curves generated by the different distension protocols had a generally linear form, the values for incremental distensibility were decidedly nonlinear, with the highest distensibility observed at relatively low volume increments. A similar nonlinear relationship between distensibility and distending pressure was observed previously in the esophageal body of normal subjects and patients with systemic sclerosis (29). In general, distensibility was lowest at the highest volume increments, suggesting that at this degree of distension, the GEJ was reaching its intrinsic elastic limit. Inspection of the distensibility plots indicates that, whereas there was considerable variability in values among the different distension protocols for lower volume increments, distensibility values tended to converge at the highest volume increment. Thus dynamic contributions to the distensibility measurement appear negligible in this range, and the values obtained more closely reflect the intrinsic distensibility of the GEJ structures that results from its passive elastic properties.

There are other potential limitations to our study. The distensibility recording bag does not reside solely in the GEJ, but extends into the distal-most esophageal body and proximal stomach. Thus the measurements obtained may reflect, in part, the distensibility of these regions also. Given that there are no universally agreed-upon definitions of the boundaries of the GEJ, that the length of the GEJ varies among individuals, and that the location of the GEJ will vary with respiration, there is no available apparatus that will be capable of recording consistently just from the complete length of the GEJ. The design of our apparatus did avoid the potential problem of the distending bag being displaced from the GEJ, as observed fluo-

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Fig. 5. Representative still frames from videofluoroscopic recordings demonstrating the spatial relationship of the distensibility bag and the esophagus, GEJ, and stomach during NB. As seen in image 6 (03:00:58:42) the bag, seen just above the barium contrast swallowed before air infusion for better visualization, develops a shape resembling a “dumbbell” with the narrowed area representing the GEJ.
roscopically. It is also possible that the part of the bag residing within the esophageal lumen, once distending, could have resulted in some inhibition of the LES tone, although distal esophageal distensions are less effective in eliciting LES relaxations (8). Nevertheless, if any relaxation was produced, it was not maximal, given the changes seen after the distension of the more proximal balloon.

Although standard intraluminal manometry can identify certain dynamic abnormalities of LES motor function that could decrease distensibility, such as a hypertensive basal pressure or impaired deglutitive relaxation, manometric recording of sphincter pressure will not be able to assess intrinsic abnormalities of distensibility, as occur with stenoses at that level. In experimental models, extreme reductions in distensibility of the GEJ can result in an increase in the upstream intrabolus pressure (14), which can be identified on intraluminal manometry. Elevation of intrabolus pressure has been recognized in the setting of the reduced distensibility of the upper esophageal sphincter associated with cricopharyngeal bars (3) and has been described in patients with tight fundoplication wraps (26). However, elevation in intrabolus pressure cannot be a reliable measure of GEJ distensibility, because many other factors influence intrabolus pressure, including esophageal peristaltic function, LES relaxation, and intragastric pressure, as well as the physical properties (volume and viscosity) of the swallowed bolus (9, 24). Moreover, in the presence of outflow obstruction, the velocity of peristaltic transport in the esophageal body slows, which serves to limit increases in intrabolus pressure. These limitations make the intrabolus pressure an indirect and unreliable surrogate for evaluation of GEJ distensibility. A resistometer has also been employed to examine the resistance to flow of air across the GEJ in response to various physiological states and pathological conditions (10). Whereas this technique may be useful for assessing the mechanics of the GEJ at its opening, it appears that once the GEJ is open the recording system is quickly limited by its maximum flow rate. Thus a resistometer may be unable to detect a subtle limitation in the intrinsic distensibility of the GEJ at wider opening diameters, wherein swallowed liquid boluses within the physiological range may not be impeded, but extra force may be necessary to pass a larger solid bolus.

Given the limitations of the above recording modalities, measurements of distensibility of the GEJ may prove to be of clinical value. Because calculations of distensibility describe incremental properties of the hollow viscus, they often provide insight not readily observable from the typical pressure-volume curves generated to assess the compliance of the luminal wall. For example, a GEJ with a higher resting cross-sectional area may have a pressure-volume curve that is shifted upward compared with that of a GEJ with a lower resting cross-sectional area but identical intrinsic distensibility. Studies of distensibility of the esophageal wall have found a nonlinear relationship to the distending volume (29). Whereas increases in distensibility of the GEJ have been found to increase the propensity for gastroesophageal reflux in patients with reflux disease and hiatal hernia (20), reductions in the normal intrinsic distensibility of the GEJ structures would be expected to impair the factors that serve to open the GEJ and permit bolus transit, thus resulting in symptoms of obstructive dysphagia. Rings, tight strictures, and neoplasms at the GEJ are obvious causes of abnormal distensibility and are usually amenable to diagnosis by radiographic or endoscopic studies. However, more subtle abnormalities of intrinsic distensibility, such as could occur with muscular hypertrophy or fibrosis of the LES, an excessively narrow crural repair, or a fundoplication wrap created around too narrow a bougie, may be difficult to detect by the above modalities, because barium and the endoscope may be able to pass completely through the GEJ. For instance, undetected abnormalities in the intrinsic distensibility of the GEJ are a possible explanation for food bolus impactions in patients for whom no obvious stricture is identified (28).

In conclusion, the present study has shown the feasibility of using a relatively simple recording apparatus for recording the distensibility of the GEJ. With this system, we were able to determine that LES tone and activation of the diaphragmatic crura have significant effects on the recording of GEJ distensibility. Therefore, potential variations in these parameters must be considered and controlled for during studies of distensibility. Their presence may also complicate measurements of the contribution of passive tissue properties to GEJ distensibility, at least at lower distending volumes.

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