CLINICAL–ALIMENTARY TRACT

Esophagogastric Junction Opening During Relaxation Distinguishes Nonhernia Reflux Patients, Hernia Patients, and Normal Subjects

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See editorial on page 1258.

Background & Aims: Flow across the esophagogastric junction (EGJ) is strongly related to opening dimensions. This study aimed to determine whether opening of the relaxed EGJ was altered in patients with gastroesophageal reflux disease (GERD). *Methods:* Seven normal subjects (NL), 9 GERD patients without hiatus hernia (NHH), and 7 with hiatus hernia (HH) were studied. Cross-sectional area (CSA) of the relaxed EGJ was measured during low-pressure distention using a modified barostat technique that resulted in filling a compliant bag straddling the EGJ with renograffin to the set pressure. Swallows were imaged fluoroscopically at distensive pressures of 2–12 mm Hg. The diameter of the narrowest point of the EGJ in PA and lateral projections was measured from digitized images. CSA was determined as a function of intrabag pressure. *Results:* The minimal EGJ opening aperture occurred at the diaphragmatic hiatus in all subjects. At pressures ≤0 mm Hg, EGJ opening was observed only in HH patients, making it plausible for these patients to reflux during deglutitive relaxation. At pressures >0 mm Hg, there were significant increases in EGJ CSA both for HH and NHH compared with NL ($P < 0.001$) and for HH compared with NHH ($P < 0.005$). This difference may explain the diminished air/water discrimination seen during transient lower esophageal sphincter (LES) relaxation–associated reflux in GERD patients. *Conclusions:* Anatomic degradation of the EGJ distinguishes GERD patients from normal subjects, and these changes may impact on both the observed mechanisms of reflux and the constituents of reflux during transient LES relaxation. Therapy focused on EGJ compliance may benefit GERD patients.

The primary determinant of gastroesophageal reflux is esophagogastric junction (EGJ) incompetence permitting excessive reflux of gastric juice into the esophagus. Reflux events may occur in the context of transient lower esophageal sphincter relaxations (tLESRs), strain-induced reflux, or free reflux during periods of either lower esophageal sphincter (LES) pressure or deglutitive relaxation.[1–4] Several investigations have demonstrated that tLESRs account for up to 90% of reflux episodes in asymptomatic controls and in symptomatic gastroesophageal reflux disease (GERD) patients without hiatus hernia (NHH).[1,5,6] In contrast, GERD patients with hiatus hernia (HH) exhibit a more heterogeneous reflux pattern, with reflux episodes frequently occurring during periods of low LES pressure, straining, and even swallow-induced LES relaxation.[3,5]

To help explain the distinct reflux profile observed in HH patients, we hypothesized that there existed a mechanistically important difference in EGJ opening characteristics rather than of LES relaxation per se. Using a combined barostat/manometry/fluoroscopy protocol, we found that the EGJ opened at lower pressures and to greater diameter during LES relaxation in HH patients compared with asymptomatic normal subjects (NL).[7] Although these findings are of potential mechanistic significance, that preliminary investigation exposed important methodologic limitations in our experiment, most of which were a consequence of the measurement technique that utilized a 7-mm OD barostat/manometry assembly straddling the EGJ. That limitation forced us to explore the mechanical properties of the relaxed EGJ in an opening diameter range (>10 mm) and a distensive pressure range (10–30 mm Hg) greater than what we believe to be physiologically important in GERD. Specifically, tLESRs are elicited experimentally as a conse-

Abbreviations used in this paper: CSA, cross-sectional area; EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; HH, GERD patients with hiatus hernia; LES, lower esophageal sphincter; NHH, GERD patients without hiatus hernia; NL, normal subjects; tLESR, transient lower esophageal sphincter relaxation.

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quence of gastric distention, typically resulting in an average of only a 3-mm Hg increment of intragastric pressure.[8] Thus, the aim of this study was to explore the mechanical characteristics of EGJ opening in GERD patients and normal subjects at what we believe to be more physiologic apertures and intraluminal pressures.

Materials and Methods

Subjects

Seven NL (4 males, 23–33 years old) without reflux symptoms, 7 patients with GERD and HH (5 males, 28–53 years old), and 9 GERD patients without HH (NHH) (5 males, 24–48 years old) were studied. The patients were enrolled from the gastrointestinal diagnostic laboratory at Northwestern Memorial Hospital. Patients were classified as HH or NHH based on recent upper endoscopy results (performed by P.J.K. or J.E.P.). The endoscopic criterion for HH was that the position of the squamocolumnar junction was 2 cm proximal to the center of the hiatal impression after aspirating excess air from the stomach. Presence or absence of HH was confirmed with fluoroscopy using the criterion of persistent rugal folds proximal to the hiatus between dilute barium swallows. The HH subjects had axial displacement ranging from 2.0 to 4.4 cm based on fluoroscopic measurements. Nonhiatus hernia patients had <1 cm axial herniation during endoscopy and subsequent fluoroscopy. GERD was defined by the presence of ≥Los Angeles A esophagitis on current or recent endoscopy (HH, 5 of 7; NHH, 2 of 9) and/or abnormal 24-hour ambulatory pH monitoring using a cutoff value of 4.2% total time, pH < 4 (HH, 2 of 7; NHH, 9 of 9) (Table 1). At the time of the experimental study, all patients were in symptomatic remission as a result of maintenance treatment with a proton pump inhibitor (n = 12) or nonprescription therapy (n = 4), and none were taking any medication known to affect esophageal contractility. None of the subjects had a history of surgical manipulation of the EGJ. The protocol was approved by the Northwestern University Institutional Review Board, and informed consent was obtained from all participants.

Manometry

Subjects underwent baseline manometry before or shortly after the hydrostat protocol but never on the same day. Manometry was done using a water-perfused system (Dentsleeve Pty Ltd, Parkside, South Australia). The manometric catheter was an 8-lumen silicone rubber extrusion with a 6-cm sleeve sensor and 7 side-hole recording sites. Each side-hole channel was connected to an extracorporeal pressure transducer and perfused with sterile water at 0.15 mL/min using a low compliance perfusion pump (Dentsleeve Mark II, 16-channel model); the sleeve channel was perfused at 0.6 mL/min. Output of the pressure transducers was connected to a computer polygraph set at a sampling frequency of 40 Hz (Neomedix Systems Pty Ltd, Warriedwood, NSW, Australia) and processed using Gastromac software (Neomedix systems Pty Ltd). The transducers were calibrated at 0 and 70 mm Hg prior to recording using externally applied pressure. Response characteristics of each side-hole manometric channel exceeded 200 mm Hg/s. Basal LES pressure was measured at end expiration during a 5-minute baseline period. Relaxation pressure was defined as the mean LES pressure during maximal deglutitive relaxation.[9] All manometric pressure values were referenced to intragastric pressure.

The hydrostat was designed as a means of improving fluoroscopic imaging of the EGJ at minimal opening diameters (Figure 1). An electronic barostat (Distender Series II, Dual Drive Barostat, G and J Electronics) was connected to a large bore polyvinyl tube (OD, 4.0 mm; ID, 3.2 mm) that was in turn connected to a 250-cc bag. The barostat bag was made from polyethylene sandwich bags using a heating iron (Impulse Heat Sealer, Midwest Pacific, St. Louis, MO) and tied to the end of the tubing with nylon suture. The unique adaptation of the hydrostat was to place the barostat bag within a 500-mL glass container via a 2-holed rubber stopper. The glass container was partially filled with 50% renograffin. Barostat bag expansion then resulted in renograffin flow through a second piece of polyvinyl tubing traversing the second hole in the rubber stopper and connected to a second bag (hydrostat) that then filled with renograffin to the pressure setting of the barostat.

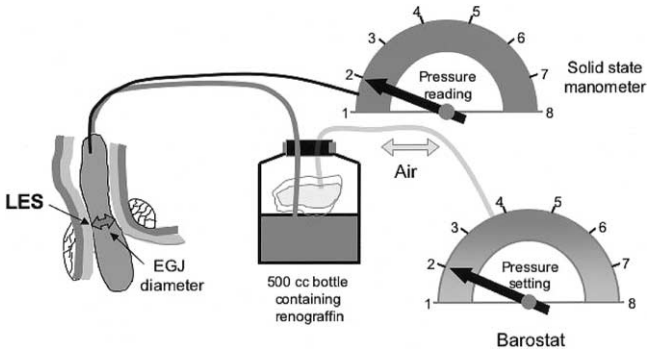

Figure 1. Diagram of the hydrostat. The barostat bag expands within a 500-cc glass container filled with 50% renograffin. Pressure applied by the barostat bag is thus transmitted to the contrast-filled bag straddling the EGJ through a noncompliant polyvinyl tube. A solid-state manometry catheter is also placed into the end of the hydrostat bag to monitor pressure and to ensure correlation between the barostat setting and the pressure within the contrast-filled bag.

Table 1. Study Subject Demographics

	Normal subjects	GERD without hiatus hernia	GERD with hiatus hernia
Male/total subjects	4/7	5/9	5/7
Age range (*yr*)	23–32	24–48	28–53
Esophagitis	0/7	2/9	5/7
Abnormal pH study[a]	0/7	9/9	7/7

[a]Total percentage time pH less than 4 greater than 4.2%.

Hydrostat Instrumentation

Hydrostat bags were designed so that, when fully distended, they had a cylindrical shape, 2 cm in diameter and 10 cm in length. The length of the bag ensured that position could be maintained across the EGJ during distention without need for repositioning (pilot experiments with 6-cm bags failed because of bag migration). Hydrostat bags were end-mounted on the polyvinyl tubing with nylon surgical suture over a plastic tie point. In addition, a single sensor solid-state manometric catheter (Medical Measurements Inc., Hackensack, NJ) was incorporated into the assembly positioned such that the sensor was within the hydrostat bag, 1 cm beyond the distal end of the polyvinyl tubing. Prior to use, the entire system was checked for leaks ex vivo by inflation to 40 mm Hg.

Experimental Protocol

After an overnight fast, the hydrostat catheter was passed orally with the patient in a sitting position such that the end of the catheter was at least 50 cm distal to the incisors. The subject was then placed in a supine position under a fluoroscope (Easy Diagnostics, Phillips Medical Systems, Shelton, CT) and shielded below the umbilicus with a lead apron. The assembly was positioned under fluoroscopy such that the bag was within the stomach. Pressure within the hydrostat bag was heavily dependent on hydrostatic considerations. Thus, prior to experimentation, the height of the hydrostat bottle was adjusted in relation to the patient such that there was no flow of contrast within the system. Intragastric pressure was then measured for a 1-minute period. Guided by fluoroscopy, the bag was then unfolded, positioned straddling the EGJ, and secured in position to the subject's cheek with tape.

EGJ Anatomy and Distensibility (Compliance)

EGJ opening dimensions were imaged in both posterior-anterior (PA) and lateral projections during deglutitive relaxation as a function of hydrostat distention pressure. Distention pressure was increased in 2-mm Hg increments up to 12 mm Hg (Figure 2). One swallow was recorded at each pressure with the potential for a repeat swallow if the first was technically inadequate. Fluoroscopic images were recorded using a videotape recorder (Panasonic VO 9800) and synchronized with manometric data from the single solid-state catheter in the proximal portion of the hydrostat bag and the pressure volume data from the barostat using a video timer (model VC 436, Thalner Electronics Laboratories, Ann Arbor, MI) that encoded time in hundredths of a second on each video frame and sent a 1 V 10-ms pulse to an instrumentation channel of the polygraph at whole second intervals.

Mechanical Simulation of Air and Water Flow Through the EGJ

To estimate the impact of observed EGJ opening apertures on flow of air and water across the EGJ, we set up the barostat and hydrostat to measure flow through 1-cm lengths of polyurethane tubing. Tubing sizes were selected to encompass the average opening apertures of the 3 subject groups observed during 4-mm Hg distention (the average pressure increment observed during tLESRs). The barostat was used to measure airflow rates, and the hydrostat was used to measure water flow rates. Airflow and water flow rates through the simulation tubing were measured for 20 seconds and mean flow rate reported. Of note, the maximal barostat inflation rate was measured to be 57 mL/s without any outflow restriction. Therefore, flow rates were extrapolated using a liquid:air viscosity ratio of 55:1 when maximal flow rate was exceeded.

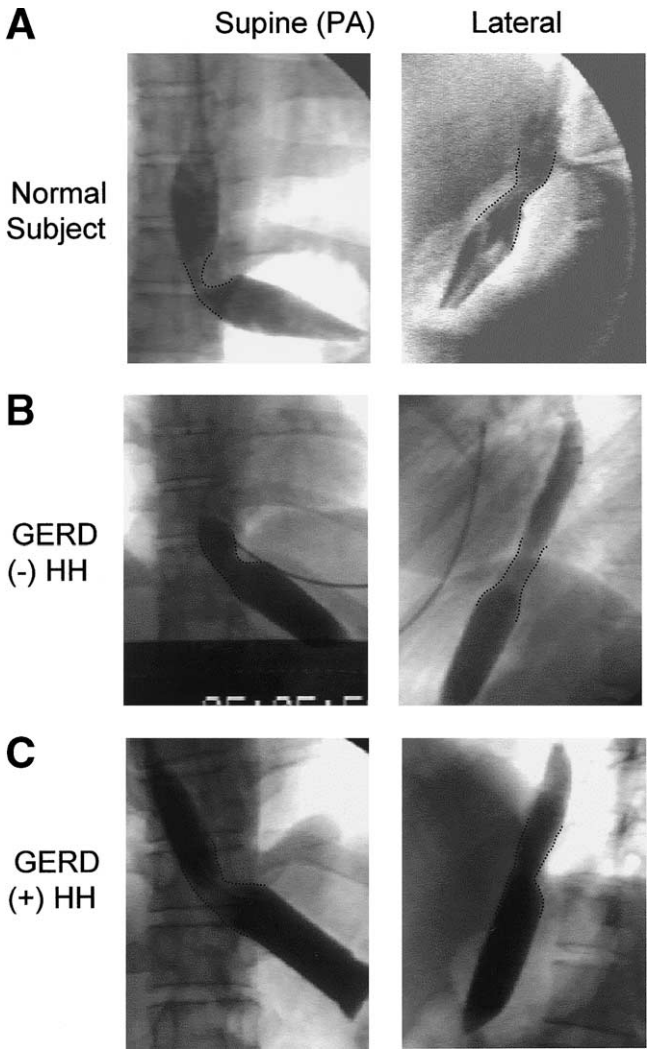

Figure 2. Representative hydrostat images from the 3 study groups at an intrabag pressure of 6 mm Hg relative to intragastric pressure. The assembly was passed orally and positioned fluoroscopically across the EGJ. The diameter of the narrowest point of the EGJ was measured from digitized images using National Institutes of Health image software. A vertebra was used as a spatial reference, and the 10-mm ring on the manometric catheter was used to correct for magnification. Note the rugal folds in the hiatal canal in the GERD HH (+) subject.

Table 2. Manometric Measures of EGJ Function Among Subject Groups

	Normal subjects	GERD without hiatus hernia	GERD with hiatus hernia
Basal LES pressure (*mean* ± *SE*)	15.6 ± 1.1 mm Hg	12.2 ± 2.0 mm Hg	9.7 ± 1.2 mm Hg[a]
LES relaxation pressure (*mean* ± *SE*)	1.6 ± 1.4 mm Hg	1.5 ± 1.8 mm Hg	0.6 ± 0.2 mm Hg
Intragastric pressure (*mean* ± *SE*)	3.3 ± 0.9 mm Hg	4.9 ± 1.9 mm Hg	5.1 ± 0.0 mm Hg

[a]$P < 0.005$ when compared with normal subjects.

Data Analysis

Maximal deglutitive opening diameter at the narrowest point within the EGJ was measured from digitized video fluorographic images using Macintosh video and NIH image software. A vertebra was used as a spatial reference, and the 10-mm length of the proximal tie ring on the hydrostat assembly was used to correct for magnification (Figure 2). Every measurement was made independently by 2 investigators. Hydrostat distention pressures were indexed to intragastric pressure. Cross-sectional surface area at the narrowest part of the EGJ was calculated using the formula for the area of an ellipse using the PA and lateral radii (area).

All results are summarized as mean ± SEM unless specified otherwise. One-way ANOVA was used to compare the manometric parameters among the 3 groups. Student paired *t* test was used to compare the manometric parameters between groups, with $P < 0.0253$ considered significant. ANOVA was used to compare differences in EGJ opening CSA among subject groups at each distensive pressure. Slope of the area pressure relationship was calculated using simple regression analysis. Least square regression analysis was used to determine the correlation between the slope of the area/pressure relationship and the basal LES pressure. A P value <0.05 was considered significant.

Results

Manometric Measures of EGJ Function

Manometric data for each group are shown in Table 2. Using ANOVA, no significant difference existed in mean basal LES pressure among the 3 groups. However, an unpaired *t* test revealed a significant difference in LES pressure between NL and HH patients ($P < 0.005$). Neither ANOVA nor an unpaired *t* test revealed any significant differences in LES relaxation pressure or intragastric pressure among the 3 subject groups.

EGJ Opening During Low-Pressure Distention

The smallest EGJ opening aperture during deglutitive relaxation occurred at the level of the diaphragmatic hiatus in all subjects. Radial asymmetry was noted in the NL during pressure distention, with the lateral diameter being greater than the PA (Figure 3). The GERD patients with and without HH appeared to have a more symmetrical EGJ opening, especially during greater distention pressure settings.

By ANOVA analysis, EGJ cross-sectional opening areas at pressures ≤0 mm Hg (intragastric pressure) were significantly greater in HH compared with both NL and NHH patients ($P < 0.05$) (Figure 4). At pressures >0 mm Hg, EGJ cross-sectional opening areas were significantly greater in the HH patients compared with the NHH patients ($P < 0.01$) and also in the NHH patients compared with NL ($P < 0.0001$) (Figure 4). As another indication of the altered compliance of the EGJ in both GERD groups, the slope of the EGJ CSA/distention pressure relationship in the HH and NHH patients was at least twice that of NL subjects (HH = 0.09 cm^2/mm Hg, NHH = 0.08 cm^2/mm Hg, NL = 0.03 cm^2/mm Hg) (Figure 4).

Correlation Between LES Pressure and EGJ Opening During Low-Pressure Distention

The slope of the CSA/distention pressure relationship was calculated for each subject so that the relationship between EGJ opening during low-pressure distention and basal LES pressure could be evaluated. This analysis revealed poor correlation between these variables ($r = -0.36$) (Figure 5).

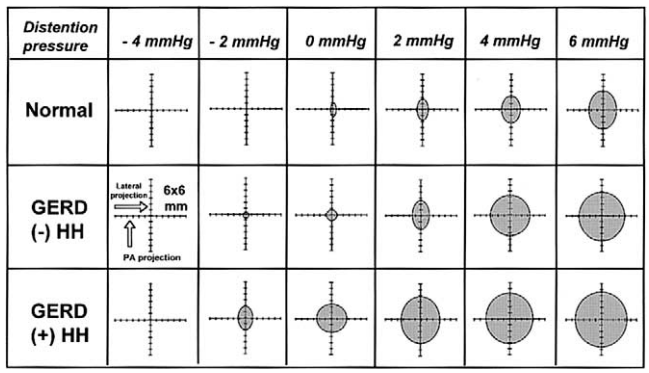

Figure 3. Dimensions and radial symmetry of the EGJ. Measurements of EGJ opening diameters were made from PA and lateral fluoroscopic projections and are plotted for each intrabag pressure relative to intragastric pressure distention pressure. Some degree of radial asymmetry of the hiatus was seen in all 3 groups; the lateral diameters were similar among the 3 groups, but the HH and NHH GERD patients had increased PA diameters compared with normal subjects.

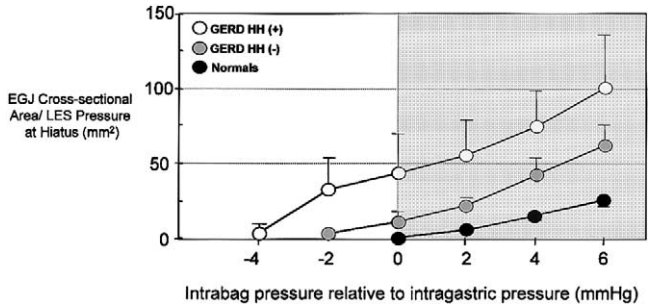

Figure 4. EGJ cross-sectional area as a function of distention pressure. Cross-sectional area at intrabag pressures >0 mm Hg was significantly increased in the NHH GERD patients compared with normal subjects ($P < 0.0001$) and in the HH patients compared with the NHH patients ($P < 0.005$). At pressures ≤0 mm Hg, the EGJ cross-sectional area of HH GERD patients was significantly greater than both the NHH GERD patients and NLs ($P < 0.05$). At pressures below 0 mm Hg, there was no significant difference between NHH GERD patients and NLs. Thus, NHH GERD patients exhibited similar distensile properties to HH patients at pressures greater than intragastric pressure and similar to normal subjects at pressures less than or equal to intragastric pressure.

Simulation of Airflow and Water Flow Through the EGJ

Extrapolating from Figure 4, the mean opening apertures of the NL, NHH, and HH patient groups at a 4-mm Hg distention pressure was approximately 13, 40, and 75 mm^2, respectively. These diameters are roughly equivalent to the CSA of 4-, 7-, and 10-mm ID tubing respectively (13, 38, and 79 mm^2, respectively). Simulated flow rates of air and water through tubing of sizes encompassing these cross-sectional dimensions and length of 1 cm are shown in Table 3. Evident in the Table, flow of air exceeds the technical specifications of the barostat through tubing sizes greater than 2 mm. Hydrostat estimates of water flow, however, are much more modest and reveal that flow is increased about 3-fold in GERD patients without hiatus hernia and twice again in GERD patients with hiatus hernia.

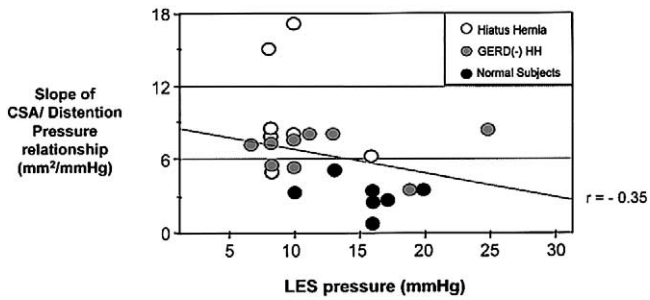

Figure 5. Correlation between basal LES pressure and slope of the EGJ CSA/distention pressure relationship. A weak relationship was observed with an r value of −0.36. Basal LES pressure likely plays only a small role in determining the cross-sectional area of opening of the relaxed EGJ during pressure distention.

Table 3. Simulated Flow Rates of Water and Air Across the EGJ Using a Hydrostat or Barostat and Short Lengths of Polyurethane Tubing

Tube size ID (*mm*)	Area mm^2	Water flow mL/s	Airflow mL/s
2	3	.7	40
3	7.1	1.5	83[b]
4, Normal subjects[a]	12.6	2.8	154[b]
6	28.3	5.5	303[b]
7, GERD without hiatus hernia[a]	38.5	8.5	468[b]
8	50	11.1	610[b]
10, GERD with hiatus hernia[a]	78.5	19.5	1073[b]

NOTE. The diameter of the tubing used to model each group simulates cross-sectional area observed with distention pressures of 4 mm Hg.
[a]Diameter of tubing simulating cross-sectional area of each study group with distention pressures of 4 mm Hg.
[b]Given the fact that 57 mL/s was the greatest flow rate attainable with the barostat, air flow rates were extrapolated from liquid flow rates using a liquid:air viscosity ratio of 55:1.

Discussion

The central hypothesis leading to this report was that mechanical alterations of the EGJ might underlie differences in both the volume and the constituents of reflux in GERD patients with or without hiatus hernia. The major findings of the paper were that (1), at distention pressures greater than intragastric pressure, the relaxed EGJ opened incrementally wider in HH patients compared with NHH patients and in NHH patients compared with NL subjects, and (2) at distention pressures greater than atmospheric pressure but less than intragastric pressure, opening of the relaxed EGJ was observed only in HH patients. These differences in EGJ opening characteristics may account for some of the observed differences in the air/fluid content of reflux in GERD patients compared with normal subjects and for the unique mechanistic profile of reflux observed in HH patients.

Recent investigations utilizing intraluminal impedance monitoring suggest that a qualitative difference exists in the air/liquid content of refluxate between NL and GERD patients.[10,11] Those investigations found that the difference between GERD patients and controls was not of an increased frequency of tLESRs but of an increased proportion of tLESRs associated with liquid (and acid) as opposed to uniquely gas reflux.[10–12] It was theorized that these differences may be attributable to differences in the distribution of gastric juice within the proximal stomach. We propose an alternative hypothesis that the anatomic degradation leading to wider opening of the relaxed EGJ observed in the present investigation may partly explain the difference in the quality of the refluxate between GERD patients and controls. Flow

through a tube, be it round or elliptical, is highly dependent on both the CSA of the tube and the viscosity of the fluid flowing through it.[13] Table 3 illustrates the simulated effect of the observed differences in EGJ opening diameter among our study populations on trans-EGJ flow with an intragastric-intraesophageal pressure gradient of 4 mm Hg. Evident from the Table 3, the observed differences in EJG opening dimensions among subject groups could lead to potentially important differences in the flow rate of gastric juice across the relaxed EGJ. On the other hand, flow rates for air are essentially "out of range" regardless of the tubing diameter. Thus, gas venting during tLESRs in NL is preserved, and reflux of gastric juice is restricted as a result of small opening CSA. In contrast, GERD patients have lost this discriminative resistance between air and liquid.

Although tLESRs are the dominant mechanism of reflux in normal controls and in reflux patients when evaluated as a heterogeneous group,[1,2] several more recent investigations have identified unique mechanistic considerations amongst GERD patients with HH.[4,5,8,14,15] GERD patients with HH exhibit a more heterogeneous mechanistic profile for individual reflux events, are subject to prolonged esophageal acid clearance because of superimposed reflux that occurs during swallowing while in a supine posture, and are more susceptible to distention-induced tLESRs. Some of these observations may be attributable to the observation made in the current investigation that, in GERD patients with HH, the EGJ opens at distention pressures equal to or even slightly less than intragastric pressure (Figure 4). Thus, swallow-induced LES relaxation results in EGJ opening and can be associated with reflux of gastric juice that has accumulated within a HH. With respect to the elicitation of tLESRs, recent data suggest that these are triggered by vagal stretch receptors (intraganglionic lamellar endings or IGLEs) anatomically localized to the gastric cardia.[16] Assuming no inherent abnormality of the IGLEs themselves and extrapolating the observed changes at the hiatus to the adjacent cardia, the markedly increased slope of the pressure-distention relationship evident amongst the HH patients in Figure 4 offers a potential physiologic explanation for the diminished threshold for eliciting tLESRs observed in response to distention amongst HH patients.[8]

Although the data reported herein reveal significantly increased EGJ opening diameter during low-pressure distention in GERD patients with or without HH compared with NL subjects, it does not identify the component of the EGJ responsible for this increased compliance. It does, however, suggest that axial hiatus hernia, although important, is not the only relevant defect with respect to EGJ incompetence. Other factors that may contribute to increased compliance of the EGJ are radial disruption of the crural diaphragm, integrity of the phrenoesophageal ligament, grade of gastroesophageal flap valve,[17] or thickness of the LES smooth muscle.[18] However, the data in Table 2 and Figure 5 revealing similar basal LES pressures among subject groups and a weak correlation between basal LES pressure and the slope of the CSA/LES pressure relationship make it unlikely that differences in opening characteristics are attributable to difference in basal LES pressure. Furthermore, CSA was measured during swallow-induced relaxation, further negating the potential influence of basal LES pressure. The increased opening dimensions found in GERD patients with hiatus hernia compared with GERD patients without hiatus hernia could be partially explained by differences in the mechanical properties of the distal esophagus and the gastric folds residing within the hiatal canal. It is possible that the gastric folds are more distensible than the LES.

In summary, these experiments used a novel combination of barostat, manometric, and fluoroscopic methods to study the opening characteristics of the relaxed EGJ during low-pressure distention. The EGJ opened wider in GERD patients than normal controls, and this difference could not be explained entirely by presence of axial hiatus hernia or by alterations in LES pressure. Thus, mechanical degradation of the EGJ other than HH distinguishes GERD patients from normal subjects. Other potentially important compromises of EGJ include competence of the crural diaphragm, integrity of the phrenoesophageal ligament, or even alterations in the muscular wall of the LES. This observation raises the possibility that EGJ compliance may be a viable target for antireflux therapy. Endoscopic therapies using implantable polymers or radiofrequency energy delivery at the EGJ may provide therapeutic efficacy by decreasing EGJ compliance. Verifying that speculation, however, will require further, appropriately controlled, investigation.

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