Distension during gastroesophageal reflux: effects of acid inhibition and correlation with symptoms

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Tipnis NA, Rhee P-L, Mittal RK. Distension during gastroesophageal reflux: effects of acid inhibition and correlation with symptoms. Am J Physiol Gastrointest Liver Physiol 293: G469–G474, 2007. First published June 7, 2007; doi:10.1152/ajpgi.00019.2007.—We studied spontaneous gastroesophageal reflux (GER)-induced esophageal distension using ultrasound imaging and its role in the genesis of esophageal symptoms before and during esomeprazole therapy. Ten controls and 10 GER disease (GERD) patients were studied by combined impedance, esophageal pH, manometry, and ultrasonography before and during esomeprazole therapy. Physiological data and symptoms were recorded for 2 h following a standardized meal. From ultrasound images, the esophageal cross-sectional area (CSA) at the peak of GER-induced distension was determined and compared between controls vs. patients, symptomatic vs. asymptomatic GER episodes, and before vs. during esomeprazole in GERD patients. The mean lumen CSA is greater in the patients than controls (271 ± 71 mm² vs. 163 ± 56 mm², P = 0.001) but not different among asymptomatic reflux episodes, and those associated with regurgitation (290 ± 110 mm²) or heartburn (271 ± 67 mm²). Eight chest pain episodes associated with reflux revealed a tendency toward larger mean esophageal distension (459 ± 40 mm²) compared with asymptomatic reflux (268 ± 70 mm², P = 0.058). Following esomeprazole treatment, most GER episodes were nonacidic and asymptomatic except in two patients in whom cyclical reflux was associated with large esophageal distensions. Esomeprazole did not alter the lumen CSA during GER. Esophageal distension is greater in the GERD subjects compared with controls; however, it is unlikely that the GER-induced distension of the esophagus plays a significant role in the genesis of heartburn sensation. Esomeprazole therapy does not alter the GER-induced distension of the esophagus.

Intraluminal impedance; ultrasound imaging of the esophagus

Reflex of gastric acid (HCl) into the esophagus is an important cause of heartburn and inhibition of acid with proton pump inhibitors (PPI) a potent therapy for heartburn relief (8, 27). However, prolonged pH monitoring studies indicate that there is a poor correlation between acid reflux into the esophagus and heartburn symptoms (24, 25). Furthermore, only 5–10% of acid reflux episodes are associated with heartburn symptoms (4). It is unclear why only a small percentage of acid reflux episodes result in gastroesophageal reflux (GER) symptoms. In addition, some patients continue to feel heartburn despite adequate acid suppression by PPI therapy. In these patients, symptoms may be related to nonacid reflux (28).

Several investigators have observed that distension of the esophagus with a balloon induces heartburn sensation (7, 26). It is possible that, in addition to esophageal acidification, GER-induced distension of the esophagus may cause heartburn sensation. It may be that the majority of reflux episodes are small in volume and do not cause significant distension of the esophagus whereas large volume reflux occurring at infrequent intervals induces significant distension of the esophagus and is responsible for the heartburn.

PPI therapy increases gastric pH, which is often used as a surrogate marker of the effectiveness of acid suppression (9, 16). The percent time that the gastric pH is >4 does correlate with the healing of esophagitis (1). Besides increasing gastric pH, PPI therapy suppresses the volume of acid secretion in the stomach (5, 13). Reduction of the volume of gastric acid secretion may reduce the volume of esophageal refluxate and associated esophageal distension. Therefore, it is possible that the beneficial effects of PPI therapy in reducing heartburn may be related to the reduction in the volume of reflux and associated esophageal distension.

Esophageal pH and impedance monitoring techniques do not measure the volume of reflux or esophageal distension during GER (18, 23). We recently described the ability of high-frequency intraluminal ultrasonography (HFIUS) technique to determine esophageal distension during GER. Combining HFIUS imaging with multiple intraluminal impedance (MII) and pH monitoring allows evaluation of esophageal distension during acid and nonacid reflux episodes. The goals of our study were 1) to compare esophageal distension during spontaneous GER episodes between healthy individuals and patients with GER disease (GERD), 2) to compare the degree of esophageal distension between symptomatic and nonsymptomatic GER episodes in patients with GERD, and 3) to determine the effects of potent acid suppression on the GER-induced distension of the esophagus.

METHODS

The Human Research Protection Program at the University of California San Diego approved the study protocol and each subject signed a consent form before enrollment and participation in the study. The study population consisted of 10 healthy individuals (7 men, ages 18–64 yr) with either no or minimal symptoms of GERD (no more than one time per month, no nocturnal symptoms, and no symptoms requiring H2 receptor antagonist or PPI) and 10 patients (6 men, age range 20–56 yr) with chronic heartburn symptoms and objective evidence of GERD by either pH criteria or esophagitis observed on endoscopy. Patients with GERD were asked to discontinue all acid suppression therapy and prokinetic agents for at least 7 days before the first study day.

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Catheter assembly. A custom-built catheter assembly consisting of a 2-mm-diameter, four-channel solid-state pressure transducer catheter (Gaeltec, Isle of Skye), 1.5-mm-diameter Comfertech MII-pH impedance-pH probe (Sandhill Scientific, Highlands Ranch, CO), and 1.2-mm, 30-MHz HFUS catheter (CVIS, Sunnyvale, CA) was used for these studies. The catheters were assembled and positioned in the esophagus in a fashion that one pressure transducer, pH sensor, and ultrasound transducer were located at one level in the esophagus, 5 cm above the lower esophageal sphincter (LES) (Fig. 1). All physiological measurements were recorded on a physiological recorder (Sandhill Scientific, Highlands Ranch, CO) and ultrasound images were recorded in real time on an S-VHS recorder using a Hewlett Packard System. The two recording equipments were synchronized by using a video timer (Thalaner Electronics, Ann Arbor, MI).

Study protocol. The catheter assembly was placed transnasally and the LES was identified by the station pull-through method. Subjects were studied for at least 2 h following the ingestion of a standardized, mixed liquid-solid meal (850 kcal, consisting of a 250-g egg salad sandwich, 8 oz. of tomato soup, 8 oz. of peas, and 16 oz. of lemon-lime soda). All recordings were obtained with the subjects in a semirecumbent, right decubitus position. Subjects were required to maintain quiet during the study and were not allowed to sleep. Symptoms of regurgitation, heartburn, chest pain, and any others reported by the subjects during the monitoring period were recorded onto the physiological recorder. Patients with GERD were treated with esomeprazole magnesium (Nexium, Astra-Zeneca, Wilmington, DE) 40 mg daily for at least 7 days, following which physiological monitoring was repeated.

Data analysis. GER episodes were identified from the pH and MII records in the postprandial period by the computer program (Bio-view Analysis Software, Sandhill Scientific). Confirmation of reflux episode (by pH and MII criteria) was performed manually. The MII criterion for reflux entry into the esophagus was a 50% reduction in the baseline impedance value at both 3 and 5 cm above the LES. GER criterion for reflux entry into the esophagus was a 50% reduction in sode (by pH and MII criteria) was performed manually. The MII Analysis Software, Sandhill Scientific). Confirmation of reflux episodes in the postprandial period by the computer program (Bio-view System. The two recording equipments were synchronized by using a video editing system (Pinnacle DV500 and Adobe Premiere 6.0, Adobe Systems, Mountain View, CA). The circumference of the esophageal lumen at baseline, and cross-sectional area (CSA) (reported as mean mm² ± SE) and circumference of the esophageal lumen at the peak esophageal distension was measured with graphing software (Sigma Scan Pro, Jandel Scientific, San Rafael, CA). To determine esophageal stretch caused by GER, Greene’s strain was calculated by the equation as described previously (26).

Statistical analysis. The number of GER episodes and frequency of liquid, gas, or mixture reflux (liquid-air) was noted for each GER episode. Impedance data revealed that 98% of GER episodes were acid, weakly acidic, and nonacid GER were evaluated between controls and GERD patients. These comparisons were made using χ² likelihood ratio or Fisher’s exact test. To minimize the effects of outliers and GER frequency on the analysis of esophageal distension, the mean esophageal lumen CSA at peak distension during GER episode was determined for each subject. By using ANOVA with correction for multiple comparisons where appropriate, the mean esophageal lumen CSA was compared between 1) normal subjects and patients with GERD and 2) GERD patients on the study day 0 and day 7 of esomprazole therapy. Pairwise t-test was used to compare the mean esophageal lumen CSA among the GER episodes categorized by acid composition and sensation.

RESULTS

Characteristics of GER in control subjects. A total of 109 GER episodes (by pH and impedance recording) were recorded in 10 control subjects, of which 92 could be adequately analyzed. Poor ultrasound images prevented analysis in the remainder (Fig. 2). Eighty-three (76%) GER episodes were acid, 10 (9%) weakly acidic, and 16 (15%) nonacid; 54% of weakly acidic and nonacid reflux episodes were detected during first half hour recording period following the ingestion of meal, with smaller numbers in the later hour of the study. Impedance data revealed that 98% of GER episodes were liquid reflux and only 2% were air or mixed (liquid-air) reflux. Ninety-two percent of GER episodes reached the proximal esophagus (impedance segments 15 or 17 cm above the LES). Esophageal lumen CSA at the peak of esophageal distension ranged from 132 to 356 mm². The mean lumen CSA at peak

Fig. 1. Schematic of combined high-frequency intraluminal ultrasound (HFUS), multiple intraluminal impedance (MII), pH and manometry catheter assembly. The catheter is assembled such that the ultrasound transducer and pH sensor are located at 5 cm above the lower esophageal sphincter (LES). Solid-state pressure transducers are located intragastrically and 5, 10, and 15 cm above the LES. Impedance electrodes are located to allow recording of impedance channels at 3, 5, 7, 9, 15, and 17 cm above the LES. This arrangement allows simultaneous recording of ultrasound, pH, pressure and impedance data at a level 5 cm above the LES and impedance and pressure data 15 cm above the LES.
distension was 224 ± 47 mm² for nonacidic, 190 ± 24 for weakly acidic, and 161 ± 54 mm² for acidic GER episodes. In subjects with both nonacidic and acidic GER (n = 6), the mean lumen CSA was greater for the nonacidic compared with acidic GER (P = 0.006). Similarly, in subjects with both weakly acidic and acidic GER (n = 6), the mean lumen CSA was greater for weakly acidic compared with acidic GER (P = 0.02). There was no statistical difference between the nonacid and weakly acidic GER in the control subjects (n = 5). None of the reflux episodes in normal subjects were associated with heartburn and chest pain but regurgitation was experienced during six GER episodes in four subjects.

Characteristics of GER in patients with reflux disease. A total of 120 GER episodes were recorded in 10 patients with the GERD. Ninety-two of these episodes were of good quality and allowed complete analysis. Eighty-eight percent (n = 106) of the GER episodes in the GERD subjects were acid reflux, 7% (8) were nonacid, and 5% (6) weakly acidic. Similar to the control subjects, 40% of the weakly acidic and nonacid reflux episodes were recorded in the first half-hour period after ingestion of the meal, with smaller percentages in the later hour of the study. Impedance data revealed that 81% of the GER episodes were of liquid and 18% were of air or mixed (air and liquid) variety. Ninety-four percent of the GER episodes reached the proximal esophagus. The luminal CSA at the peak of esophageal distension in patients ranged from 68 to 521 mm² (Fig. 3). There was no difference in the median CSA of the esophageal lumen at peak distension for nonacid (275 ± 78 mm²), weakly acidic (332 ± 107 mm²), and acid GER episodes (259 ± 66 mm²) in the GERD patients.

Comparison of esophageal distension between GERD and control subjects, and symptomatic GER. The median CSA of the esophageal lumen at the peak of distension was significantly greater in GERD subjects compared with controls (Fig. 4). The difference in the CSA is equivalent to a diameter of ~12 mm.

Nine patients reported heartburn during the recording period. The total number of GER-associated symptoms of regurgitation, heartburn, and chest pain was 15, 28, and 8, respectively. All nine subjects reporting symptoms had positive SI scores (8 were 100%, 1 was 60%). One subject had two episodes of heartburn that were not associated with MII or pH GER. Five subjects had >50% asymptomatic GER. Two subjects contributed 15 heartburn and 7 chest pain episodes to the total number of respective symptoms. These patients demonstrated a characteristic reflux pattern, i.e., recurring reflux episodes every 10–15 s, continuously for 60–90 min after the ingestion of the meal. There was no difference in the luminal CSA between asymptomatic GER episodes and those that were accompanied by regurgitation and heartburn. In the three individuals with chest pain, GER episodes associated with chest pain had a tendency for greater esophageal distension.
than asymptomatic episodes (Fig. 5). Similarly, esophageal strain was greater in episodes associated with chest pain (3.08 ± 0.34) but did not reach significance compared with episodes that were asymptomatic (2.29 ± 0.30, P = 0.098) or associated with regurgitation (2.51 ± 0.03, P = 0.090) or heartburn (2.51 ± 0.14, P = 0.173).

Effect of PPI therapy on characteristics of GER in patients. Two of the 10 patients did not return for a recording session following PPI therapy (one lost to follow-up and one did not want repeat testing). Subjectively, all patients reported significant improvement in symptoms during the PPI therapy. The frequency of GER episodes while on treatment with PPI therapy was not significantly different compared with pretreatment GER frequency (10.3 ± 3.7 and 8 ± 2, respectively, P > 0.05). Ninety percent (n = 58) of the GER episodes while on treatment with esomeprazole were nonacidic, and of the remainder 7% (4) were weakly acidic and 3% (2) were acidic. The esophageal lumen CSA was not different between the 2 study days (pretreatment 273 ± 80 mm² vs. on treatment 252 ± 77 mm², P > 0.05). Reflux episodes were less likely to be associated with symptoms following esomeprazole treatment (55 vs. 37%, P = 0.02). GERD symptoms reported after acid suppression included regurgitation (4), heartburn (10), and chest pain (2). Thirteen of the 16 (81%) symptoms occurred with nonacid reflux episodes. One episode each of regurgitation and chest pain were associated with weakly acidic reflux and one episode of regurgitation with acidic reflux. Two patients with frequent reflux episodes before the esomeprazole therapy continued to experience the same on treatment and accounted for all 10 heartburn episodes, and one of these patients accounted for both of the chest pain episodes. No symptoms were reported during the other 44 GER episodes.

DISCUSSION

Distension of the esophagus with a balloon is a reproducible stimulus to induce esophageal sensation of heartburn and chest pain. Our study is the first attempt to determine the role of GER-induced distension in the genesis of spontaneous heartburn. We recorded luminal CSA (as a surrogate marker of esophageal distension) during spontaneous GER in normal subjects and patients with reflux disease to determine the relationship between esophageal distension and symptoms. Our data shows that the luminal CSA is greater in GERD patients compared with normal subjects, which is consistent with findings of Pandolfino et al. (15), who found a more compliant gastroesophageal junction in GERD patients. A more compliant esophagus was also found in GERD subjects in esophageal balloon distension experiments (10, 11). The major new finding of our study is that there is no difference in the esophageal luminal CSA between GER episodes that elicited symptoms compared with the ones that did not produce heartburn and regurgitation. There were eight chest pain symptoms in three subjects that showed tendency toward larger esophageal distensions than the other reflux episodes, but one may argue that these numbers are relatively small for a meaningful comparison. The number of GER episodes and esophageal symptoms was reduced following PPI therapy; however, reflux-induced distension of esophagus was not affected, also suggesting that the GER-induced distension of the esophagus is unlikely to play a major role in the genesis of heartburn. It may be that physiological (GER-induced) esophageal distension is insufficient in diameter to serve as the major stimulus in the genesis of heartburn. Esophageal CSA during GER episodes is much smaller than the CSA of the balloon (35 mm diameter balloon = CSA 963 mm²) often used in the experimental studies to elicit heartburn and chest pain sensation.

One may question whether or not our recording technique is adequate to measure esophageal distension during GER. Increases in the volume of swallowed and injected water boluses into the esophagus do increase luminal CSA in a linear fashion, with volumes ranging between 5 and 15 ml (18). Therefore, we believe that the lumen CSA is a reasonable marker of reflux-induced distension of the esophagus.

Esomeprazole is a potent inhibitor of gastric acid secretion. More than 90% of GER episodes, following once-a-day therapy with 40 mg esomeprazole, were nonacidic and the remainder...
weakly acidic reflux, a finding similar to the one reported by Vela and others (5, 13, 28, 29). These findings demonstrate the potency of acid inhibition with esomeprazole and confirm the compliance for drug ingestion in our study subjects. Despite the increase in pH of reflux contents, esophageal distension during spontaneous GER episodes was not different between the 2 study days, which is surprising and contrary to our expectation. Vidon and others (29) show that treatment with lansoprazole decreased postprandial gastric acid secretion and the volume of gastric contents. Therefore, one would expect a significant decrease in the gastric volume following esomeprazole treatment and also a decrease in the volume of reflux content. However, such was not the case. It is possible that acid, being in the liquid phase of gastric contents, empties relatively quickly and does not contribute significantly to the postprandial gastric volume.

Although perfusion of acid in the esophagus, as during the Bernstein test, proves that acid can indeed cause heartburn (2), the question is why is there a poor correlation between acid reflux and spontaneous heartburn even in patients with well-documented reflux disease and why only 5–10% of acid reflux episodes cause heartburn. It is likely that other stimuli besides acid and distension induce heartburn. One such stimulus may be sustained esophageal or longitudinal muscle contraction (SEC) (17). We did not analyze our ultrasound image data for the SECs in this study. Another possible explanation is esophageal hypersensitivity. Closely spaced acid reflux episodes over a short interval are more likely to be associated with heartburn compared with isolated acid reflux episodes (21, 22). A second acid infusion in a patient with acid-sensitive esophagus induces stronger symptoms with a shorter latency compared with the first acid infusion (3). Infusion of acid in the distal esophagus decreases sensitivity to electrical stimulus in the distal as well as proximal esophagus (19, 20). Similarly, repeated esophageal distensions reduce the threshold of distension-induced sensation (14). Studies also show that acid in the esophagus reduces threshold for distension-induced sensation and maybe there is role for summation effect of multiple stimuli in producing heartburn (6, 12). We observed that two subjects with a cycling pattern of GER experienced more frequent and more severe symptoms (chest pain) compared with the other GERD subjects. Following esomeprazole therapy, all reflux episodes in these two subjects were nonacidic; however, they continued to experience a cyclic pattern of GER, heartburn, and chest pain whereas most others did not. We believe that repeated stimuli and induction of hypersensitivity and possible summation effect of different stimuli may be the reason for lack of correlation between symptom and a given noxious stimulus in the esophagus.

There are several limitations of our study. First, our data were collected with the subjects in the semirecumbent right decubitus position. Second, the ultrasound images were collected only at one location, 5 cm above the LES. Third, our data analysis could not assess the role of sensitization because repeated distension or summation effect of different stimuli on the genesis of symptoms. Fourth, we only studied patients with documented evidence of GERD by endoscopy and pH monitoring. Therefore, our findings may be applicable only to this select group of patients and not necessarily to the entire heartburn population. Withstanding those limitations, our data argue against GERD-induced esophageal distension as the sole and major stimulus in the genesis of spontaneous heartburn sensation.

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REFERENCES


