Effect of prolonged gastric distension on motor function of LES and of proximal stomach

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Allocca, M., M. Mangano, and R. Penagini. Effect of prolonged gastric distension on motor function of LES and of proximal stomach. Am J Physiol Gastrointest Liver Physiol 283: G677–G680, 2002. First published April 10, 2002; 10.1152/ajpgi.00526.2001.—Gastric distension is a potent stimulus of transient lower esophageal sphincter (LES) relaxation. To investigate the time effect of prolonged gastric distension on the rate of transient LES relaxations, LES pressure, and the motor and sensory functions of the proximal stomach, we performed a continuous isobaric distension of the proximal stomach at the 75% threshold pressure for discomfort for 2 h in seven healthy subjects. A multilumen assembly incorporating a sleeve and an electronic barostat was used. The rate of transient LES relaxations (n/30 min) was constant during the first hour [4.1 ± 1.2 (0–30 min) and 5.4 ± 1.1 (30–60 min)] but markedly decreased (P < 0.05) in the second hour [2.1 ± 0.5 (60–90 min) and 2.3 ± 0.9 (90–120 min)], whereas LES pressure, baseline volume and volume waves within the gastric bag, hunger, and fullness did not change throughout the experiment. It is concluded that the rate of transient LES relaxations decreases with time during prolonged gastric distension, thus suggesting that this type of stimulus should not be used in sequential experimental conditions.

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gastrointestinal tone; lower esophageal sphincter pressure; barostat

TRANSIENT LOWER ESOPHAGAL SPHINCTER (LES) relaxation is the mechanism that allows venting of gas during belching, and it is now established to represent an important motor event underlying gastroesophageal reflux (GER) in patients with GER disease (6, 16). There is ongoing interest in developing drugs that can decrease GER by interfering with transient LES relaxations (3, 9, 14, 15, 19). In addition to exploring possible new approaches to the treatment of GER disease, this research is valuable in gathering information concerning the neural pathways involved in the control of transient LES relaxations. To perform studies of an acceptable duration, the rate of transient LES relaxations needs to be stimulated. This has so far been done by means of various experimental models that have used proximal gastric distension as a stimulus (7, 10). The most physiological model is the ingestion of a meal, but because the rate of transient LES relaxations is not constant over the postprandial period (11, 18), presumably because of gastric emptying, it is difficult to assess more than one experimental condition per day. Furthermore, this model, as well as others using gas (24), liquid infusion in the fundus (12, 19), or balloon inflation without the use of a barostat (10), does not allow simultaneous monitoring of the effects of the study drug on the rate of transient LES relaxations and proximal gastric motor function. Understanding the relationship between these two variables is vital to increase our knowledge of the control of transient LES relaxations and for future drug development (23).

Distension of the proximal stomach by means of a bag connected to a barostat (3) is a valuable model, but to plan experiments, it would be useful to know if the rate of transient LES relaxations and gastric motor function are stable during prolonged distension. The aim of this study was to investigate the effect of prolonged isobaric gastric distension on the rate of transient LES relaxations, LES pressure, and motor function of the proximal stomach. Gastric sensory perception was also evaluated to gather information concerning the afferent neural pathways and to be able to better speculate on the possible mechanisms modulating the rate of transient LES relaxations during prolonged distension.

METHODS

Study Group

We studied seven healthy subjects (2 men) aged 23–32 yr with no symptoms or past history of gastrointestinal disease. The study was approved by the Human Research Review Committee of the Ospedale Maggiore of Milan.

Manometric and Barostat Measurements

Separate manometric and barostat assemblies were used. Esophageal manometry was performed using a multilumen assembly that incorporated a 6-cm-long sleeve sensor (19) for monitoring LES pressure. Side holes recorded pressure in the gastric fundus and 3, 8, and 13 cm above the LES, and a further side hole in the pharynx monitored swallowing. The assembly was perfused with degassed distilled water by
means of a low-compliance pneumohydraulic infusion pump. The gastric side hole and sleeve were perfused at 0.5 ml/min, whereas the side holes in the esophageal body and pharynx were perfused at 0.13 ml/min to minimize the fluid load to the subject. Proximal gastric motor function was measured using an electronic barostat (Synectics Medical, Stockholm, Sweden), which maintained a constant pressure in a 1,400-ml polyethylene bag by introducing or withdrawing air from the bag at a rate of 30 ml/s via a tube of 2.5-mm internal diameter (ID) and 650-mm length whenever the intrabag pressure differed from the set pressure by >0.4 mmHg. The pressure in the bag was sensed via a 0.97-mm ID tube incorporated into the barostat inflation assembly. Two further in-built manometric lumina had side holes positioned 25 and 50 mm proximal to the top of the barostat bag, which allowed reliable positioning of the bag within the stomach by detecting the characteristic patterns of pressure at the level of the diaphragm. These lumina were also perfused with degassed distilled water. The data from the pressure recording system (Synectics Medical) and barostat were digitized and recorded on computer for on-line display and subsequent analysis.

**Study Design**

All subjects fasted for at least 8 h before the experiment (Fig. 1). The barostat assembly, with the bag folded around it, was introduced via an anesthetized nostril and positioned in the stomach on the basis of the manometric recordings. The bag was then unfolded by inflation with 500 ml air while ensuring that the pressure inside the bag did not exceed 20 mmHg. The bag was then deflated and adjusted to its final position so that the point of respiratory reversal lay between the manometric sideholes, thereby positioning the proximal portion of the bag just below the diaphragm. The manometric assembly was introduced into the esophagus through the other anesthetized nostril, the sleeve sensor being positioned to straddle the LES. The two assemblies were then fixed in this position by taping them to the nose. The subjects sat upright on a comfortable stool in a standardized position so as not to compress the abdomen. After intubation and a 10-min adaptation period, the intragastric bag was inflated by 2-mmHg stepwise increases every 2 min until the discomfort threshold was reached. The bag was then deflated completely and reinflated at a pressure corresponding to 75% of the previously determined discomfort threshold pressure, which was maintained throughout the 2-h experiment. Hunger and fullness were evaluated before and every 15 min during distension using a validated (22) 100-mm visual analog scale.

![Fig. 1. Design of the study. (*) a measure of proximal gastric tone and phasic contractions, respectively.](http://ajpgi.physiology.org/)

**Data Analysis**

**Transient LES relaxation.** Transient LES relaxation was defined according to previously established criteria (12): 1) absence of swallowing from 4 s before to 2 s after the onset of LES relaxation; 2) relaxation rate of ≥1 mmHg/s; 3) time from the onset of relaxation to complete relaxation of ≤10 s; 4) nadir pressure of ≤2 mmHg. The rate of transient LES relaxations was expressed as number per 30 min.

**LES pressure.** LES pressure, referenced to intragastric pressure, was expressed as the mean end expiratory pressure during each 15-min interval, obtained using the mean pressures at 1, 6, and 11 min (21).

**Baseline intrabag volume and volume waves.** Baseline volume, as a measure of proximal gastric tone, was calculated as the mean value of each 5-min interval, excluding variations due to volume waves, and expressed as the mean value every 15 min. A volume wave, i.e., phasic contraction, was defined as a change in volume of >30 ml that reverted to a volume within 50% of the previous level in <2 min (2). The rate of volume waves was expressed as number per 30 min.

**Statistical Analysis**

Data are expressed as mean values ± SE. The statistical significance of differences during the various time periods was tested by ANOVA followed by Fisher’s protected least-significant difference test for multiple comparisons.

**RESULTS**

Intrabag pressure during the 2-h study was 10.7 ± 1.4 mmHg. The rate of transient LES relaxations remained constant during the first hour of gastric distension but decreased ($P < 0.05$) in the second hour (Fig. 2). LES pressure (Fig. 3) and baseline intrabag volume (Fig. 4) did not change over time. The rate of volume waves per 30 min showed a nonsignificant trend toward lower values in the last 30-min period (16.9 ± 3.8, 17.1 ± 3.9, 15.1 ± 3.8, and 11.4 ± 3.6 in periods 0–30, 30–60, 60–90, and 90–120, respectively). Hunger decreased, although not significantly ($P = 0.09$ by ANOVA), when the stomach was distended, whereas fullness increased ($P < 0.05$) and remained stable throughout the experiment (Fig. 5).

**DISCUSSION**

This is the first study looking at the time effect of prolonged gastric distension on the rate of transient LES relaxations, LES pressure, and the motor and sensory function of the proximal stomach. Results showed that the rate of transient LES relaxations decreased over time, whereas the other variables remained relatively stable. Data from a previous study (24) using ingestion of two solutions generating 1 liter of CO$_2$ have suggested a decrease in the rate of transient LES relaxations over 10-min periods in the sitting position; however, occurrence of belching is likely to have been a confounding variable and, at least in part, diminished the distending stimulus over time. Which is the possible mechanism underlying the decline in the rate of transient LES relaxations that we observed? There are no data in this respect; however, on the basis of current knowledge, a few hypotheses
can be suggested. Transient LES relaxation is a vagovagal reflex integrated at the level of the brain stem (16); therefore, modulation of its rate may occur at various sites. A change in stimulation of the gastric mechanoreceptors was presumably not involved in the decline we observed, because gastric tone was stable and volume waves did not show significant changes over time. However, a trend toward a decrease in the number of volume waves was recorded in the later part of the study; thus the hypothesis that proximal gastric contractions may influence triggering of transient LES relaxations cannot be excluded and should be formally addressed in a future study. Another possible reason for the decline in the rate of transient LES relaxations was adaptation of the gastric mechanoreceptors to the distending stimulus. Studies on mechanoreceptors in the fundus of the cat and ferret and in the stomach of the goat (1, 13, 17) have shown that discharge of the majority of them in response to gastric distension undergoes modest and slow (within minutes) adaptation or no adaptation over time. A minority of receptors, which were presumably sensitive to changes in stretch or tension, adapted to the stimulus, but this occurred within a few seconds. It is, therefore, unlikely that the decrease in the rate of transient LES relaxations was due to changes in electrical discharge of the gastric mechanoreceptors. In support of this contention, we did not observe any changes in the perception of hunger or fullness over time. A third possibility is neural modulation either at the periphery along the afferent pathways or at the level of the central nervous system, and in our view, this is the most likely.

Our results may have pathophysiological relevance for GER disease. Some data suggest that the physiological postprandial increase in transient LES relaxations is more marked and prolonged in patients with GER disease than in controls (11). Although this could be partly due to a delayed recovery of proximal gastric

Fig. 2. Rate of transient lower esophageal sphincter (LES) relaxations. Mean values ± SE. *P < 0.05 vs. periods 0–30 and 30–60 min.

Fig. 3. LES pressure. Mean values ± SE.

Fig. 4. Baseline intrabag volume. Mean values ± SE.

Fig. 5. Perception of hunger (open bars) and fullness (filled bars). Mean values ± SE. *P < 0.05 vs. before distension.
tone after a meal (20), it is possible to hypothesize impaired adaptation of the rate of transient LES relaxation to prolonged gastric distension, which may be secondary to the autonomic nerve dysfunction already described in patients with GER disease (4, 5).

Our data also have implications for the design of future studies of transient LES relaxations, suggesting that only one experimental condition should be tested per day when using continuous gastric distension as a stimulus. However, it would be useful to test whether a period of bag deflation after distension is capable of resetting the rate of transient LES relaxations, thus allowing repeated distensions under different experimental conditions on the same study day without a carry-over effect.

Finally, a brief comment on hunger and fullness. Our data confirm that proximal gastric distension, when not accompanied by food intake, has a weaker effect on hunger than on fullness (8), thus suggesting that the former is not simply the reciprocal of the latter.

In conclusion, prolonged gastric distension with a barostat is a valuable means of stimulating the rate of transient LES relaxations and making simultaneous measurements of LES pressure and gastric motor and sensory function. However, adaptation of the rate of transient LES relaxations occurs over time, thus suggesting caution in testing more than one experimental condition during studies evaluating new pharmacological strategies for the control of transient LES relaxation.

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REFERENCES