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Reflux Mechanisms in Gerd : Analysis of the role of transient lower esophageal sphincter relaxations

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Citation
Straathof, J. W. A. (2005, October 31). *Reflux Mechanisms in Gerd : Analysis of the role of transient lower esophageal sphincter relaxations*. Retrieved from https://hdl.handle.net/1887/11001

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
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Note: To cite this publication please use the final published version (if applicable).

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PROVOCATION OF TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS DURING CONTINUOUS GASTRIC DISTENSION

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Scand J Gastroenterol 2002;37:1140-1143.

ABSTRACT

Background: Transient lower esophageal sphincter relaxations (TLESRs) are triggered by gastric distension. Aim of the study was to investigate TLESRs during controlled prolonged gastric distensions using the barostat technique.

Methods: Twelve healthy volunteers (4M; 8F, age range 19-42 yr.) were studied under fasting conditions with combined esophageal manometry (Dentsleeve) and gastric barostat. Randomized isobaric distensions at 0 (control), 10, 12, 14mmHg, were performed each period for 30min with 30min recovery periods in between.

Results: The frequency of TLESR was significantly ($p<0.05$) higher during all distension periods compared to control periods (4.0±0.4 TLESR/30 min vs. 2.6±0.4 TLESR/30min). The frequency of TLESR in the first 15min period of distension was significantly ($p<0.001$) higher compared to the second 15min period pointing to adaptation (2.7±0.3 TLESR/15min vs. 1.3±0.2 TLESR/15min respectively). The frequency of TLESR correlated significantly with intragastric pressure ($r=0.47$; $p<0.01$) and wall tension ($r=0.48$; $p<0.01$), but not with intragastric volume. TLESR characteristics such as duration were not related to pressure or wall tension.

Conclusions: Acute gastric distension increases the frequency of TLESR but adaptation occurs rapidly. The frequency of TLESR during distension is related to pressure and wall tension rather than to intragastric volume.

INTRODUCTION

Transient lower esophageal sphincter relaxations (TLESRs) are triggered by gastric distension (1,2). Under fasting conditions the frequency of TLESR is low, about two relaxations per hour. Ingestion of a meal increases the frequency of TLESR to about 3-6 TLESR per hour in the first postprandial hour, thereafter diminishing in 2-3 hours to basal TLESR frequency depending on the rate of gastric emptying. The volume of meals used in studies for triggering TLESR varied from 150 to 800ml (3-7). Intragastric insufflation of air or carbon dioxide has been used to distend the proximal stomach. Volumes varied from 250 to 1000ml, compatible with small to very large volume meals (8-11). However, the effect of these stimuli diminished over time due to gastric emptying of the ingested meal or belching of the inflated air. Within 10 min after air insufflation most of the air has escaped from the stomach, resulting in gastric distension for only very short period. Intragastric balloon distension enables distensions of the proximal stomach standardized for volume and time (1).

In this study we have used an electronic barostat to stimulate TLESRs. The barostat maintains a constant pressure level by regulation of the volume of inflated air within the intragastric bag (12-14). Using a barostat technique continuous prolonged stimulation of the proximal stomach is performed with fixed intragastric pressures. Aim of the study was to explore the relation between gastric distension and TLESRs.

MATERIALS AND METHODS

Subjects

Twelve healthy volunteers (8 female; age range 19-42 years) participated in a single blind randomized placebo controlled study. Subjects were free of gastrointestinal symptoms and had no history of abdominal surgery. Informed consent was obtained from each individual and the protocol had been approved by the ethical committee of the Leiden University Medical Center.

Lower esophageal sphincter manometry

The manometry catheter consisted of a multilumen silicone rubber tube (outer diameter 5.0mm) with 7 side holes located at 29, 23, 18, 13, 8, 3 and -4cm from the mid-point of the 6cm long sleeve sensor (Dentsleeve Pty Ltd, Belair, South Australia). The catheter was continuously perfused with gas-free distilled water by a low compliance pneumohydraulic capillary infusion system (Arndorfer Med Specialties, Greendale, Wisconsin, U.S.A.) at a rate of 0.5ml/min.

Gastric Barostat

An electronic barostat (Visceral stimulator; Synectics Medical, Stockholm, Sweden) was used to distend the proximal stomach. A polyethylene bag (maximal capacity 1100ml) was tied to the end of a multilumen tube (outer diameter 4.7mm). This catheter was connected to the barostat. The barostat is able to maintain a constant pressure level by an electronic feedback regulation mechanism of the air volume within the intragastric bag. When the stomach contracts, the barostat aspirates air. When the stomach relaxes, the system injects air. The pressure (mmHg) and volume (ml) output of the manometric and barostat recordings were processed by a sixteen channel analogue/digital converter (PC Polygraph HR, Synectics Medical), continuously displayed on one monitor and stored on a personal computer system for later analysis (Polygram for Windows 1.11, Gastrosoft Inc., Synectics Medical).

Study design

The studies were started at 8:30 AM after an overnight fast. The manometry catheter was introduced through the nose into the esophagus and positioned so that the sleeve sensor straddled the LES. The proximal side hole was positioned in the pharynx and was used to record swallow signals. The distal side hole was used as reference point for intragastric pressure. Than the barostat catheter with bag was introduced through the mouth into the fundus. The correct position was checked by fluoroscopy. Subjects were seated in a comfortable chair in a semi-recumbent position with the lower extremities just below abdominal level and supported to prevent abdominal wall straining. LES motility was recorded during the entire study including distension and recovery periods. After a basal period with deflated bag (pressure: 0mmHg), three intermittent isobaric distension periods were performed. The intragastric bag was inflated in randomized order at pressure levels of 10, 12 and 14mmHg for 30min duration. These pressures were chosen because they corresponded with gastric volumes and satiety scores in the postprandial range(18). In between each distension period subjects had a recovery period of 30min. During these periods the bag was deflated (pressure: 0mmHg).

Data analysis

Lower esophageal sphincter tracings were analyzed for resting LES pressure and TLESR with previously described criteria (7,15). Gastric bag volume during distensions is calculated as average values over 5min periods. The first 15min period was compared to the second 15min period of the 30min distensions. Gastric wall tension was calculated by applying Laplace's law: T=P*R/2. Expressing barostat pressure P in mmHg and the length of the radius (R) in centimeters, with the assumption that the intragastric bag is spherical (16).

Statistical analysis

Results are expressed as mean ± SEM. LES pressure data were analyzed for statistical significance using MANOVA. When this indicated a probability of less than 0.05 for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which values between or within the experiments differed significantly. Frequencies of TLESR were analyzed for statistical significance using Mann-Whitney-U test for nonparametric data. A p value of <0.05 was considered significant for all analyses.

RESULTS

Intermittent isobaric distensions

Combined esophageal manometry and gastric barostat distensions were well tolerated by each subject. In each individual a higher intragastric pressure resulted in an increases of bag volume. The intragastric bag pressure was significantly correlated with bag volume ($r=0.86$; $p<0.01$). Bag volumes during 30-min distensions at 10mmHg, 12mmHg and 14mmHg were 376±71ml, 464±66ml and 487±65ml respectively. The bag volume of the first 15min period was not significantly different compared to the second 15min period. Wall tension during distension periods of 10mmHg, 12mmHg and 14mmHg was 43±4mmHg*cm, 56±3mmHg*cm and 67±3mmHg*cm respectively.

Lower esophageal sphincter pressure

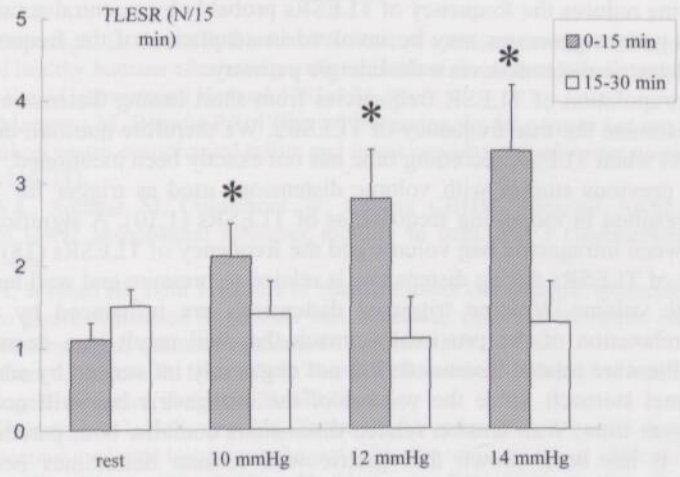
Basal LES pressure was 19±1mmHg. LES pressure increased during the gastric distensions. When the intragastric bag was deflated LES pressure decreased again to basal pressure. During gastric distensions the LES pressure was 23±2mmHg, which is significantly ($p=0.02$) higher than during the recovery period (19±2mmHg). At intragastric pressures of 12mmHg and 14mmHg, but not at 10mmHg, LES pressure was significantly ($p<0.05$) higher compared to the recovery period. LES pressure during gastric distension at 10, 12 and 14mmHg was respectively 20±2mmHg, 24±2mmHg and 25±3mmHg.

Transient lower esophageal sphincter relaxation

The frequency of TLESRs in the recovery periods was 2.6±0.4 TLESR/30min. Gastric distensions significantly ($p<0.05$) increased the frequency of TLESRs at 10 mmHg to 3.5±0.6 TLESR/30min, at 12mmHg to 3.8±0.7 TLESR/30min, at 14mmHg to 4.6±1.0 TLESR/30min. The frequency of TLESRs was significantly ($p<0.001$) higher in the first 15 min of the distension period compared to the second 15min period of distension (Figure 1). The frequency of TLESRs during 30min gastric distensions was significantly ($p<0.01$) correlated

with pressure (r=0.47) and wall tension (r=0.48), but not with volume. The duration of TLESRs was not significantly different between the control period and gastric distensions (control: 18±1sec; 10mmHg:17±2sec; 12mmHg: 17±2sec; 14mmHg: 18±1sec).

Figure 1. *Frequency of transient lower esophageal sphincter relaxations during intermittent isobaric distension periods - first 15min period versus second 15min period. Asterisks denote significant (p< 0,05) differences in TLESR frequency in the first 15min period compared to control period and compared to the second 15min period.*



DISCUSSION

The results of the present study support previous findings that in humans simultaneous assessment of proximal gastric pressure and lower esophageal sphincter pressure is well feasible and that gastric distension significantly increases the frequency of TLESRs (1,17-19).

During gastric distension periods the frequency of TLESRs doubled compared to rest periods. These findings correspond with the results found in previous studies in humans (1,17-19) and dogs (20). However, the frequency of TLESRs during gastric distension found by Boulant et al. (18) was considerably higher (9.1±4.0 TLESR/30min). These authors studied TLESRs at much higher intragastric pressures by reaching 75% of the pressure threshold for pain. Because of the higher pressure level the intragastric volumes were therefore larger compared to the present study: around 800ml versus at maximum 500ml in our study.

The frequency of TLESRs during distension diminished over time (second versus first 15min period). Identical patterns of a diminishing frequency of TLESRs over time are

observed after ingestion of a meal (4,5,7) and after insufflation of air (11). After meal ingestion the increase in TLESR frequency is most pronounced in the first and second postprandial hour. The TLESR frequency after intragastric air is highest in the first fifteen minutes after insufflation, thereafter it gradually returns to basal values. These observations can be explained by the fact that the stimulus diminishes over time, since the meal or air is emptied from the stomach. In the present study the stimulus used for triggering TLESR was a constant intragastric pressure. Therefore, the lower frequency of TLESRs during the second quarter suggests adaptation to the stimulus. The mechanism of triggering TLESR involves a neural pathway linking receptors in the esophagogastric region via the vagus nerve to nuclei of the brain stem. A central pattern generator in the brain stem is believed to mediate TLESR (2). Atropine reduces the frequency of TLESRs probably by a central action in the brain stem (19). This pattern generator may be involved in adaptation of the frequency of TLESRs to prolonged gastric distension via a cholinergic pathway.

Extrapolation of TLESR frequencies from short lasting distensions to 60min periods will overestimate the true frequency of TLESRs. We therefore question the results of studies on TLESRs when TLESR recording time has not exactly been mentioned.

In previous studies with volume distensions used as trigger for TLESR, increasing volumes resulted in increasing frequencies of TLESRs (1,10). A significant correlation was found between intragastric bag volume and the frequency of TLESRs (18). We found that the frequency of TLESRs during distensions is related to pressure and wall tension rather than to intragastric volume. Volume triggered distensions are influenced by the mechanism of adaptive relaxation of the proximal stomach that will result in a decrease in intragastric pressure. Pressure related distensions are not negatively influenced by adaptive relaxation of the proximal stomach, since the volume of the intragastric bag will not decrease but will increase over time. Wall tension related distensions combine both parameters: pressure and volume. It has been shown that gastric wall tension determines perception of gastric distension (16). Based on our results wall tension triggered gastric distensions (Tensostat) may be a more accurate trigger for TLESR than pressure or volume.

Distension of the proximal stomach caused a significant increase in LES pressure. The increase in LES pressure was a true increase in pressure and not an artifact caused by pressure of the intragastric bag on the sleeve pressure sensor because LES pressure is calculated relative to intragastric pressure. Other studies using either a barostat or a balloon, also observed an increase in LES pressure during gastric distension (1,18). This increase in LES pressure during gastric distension has formerly been referred to as reflex contraction and may prevent gastro-esophageal reflux. However, earlier studies have described a negative correlation between LES pressure and fundic pressure after air insufflation and have debated the reflex contraction (21).

In conclusion, acute standardized pressure driven gastric distension significantly increases the frequency of TLESRs but adaptation occurs already after 15min. The frequency of TLESR during distension is related to pressure and wall tension rather than to intragastric volume.

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