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

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## PROVOCATION OF TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS BY GASTRIC DISTENSION WITH AIR

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## ABSTRACT

**Background:** Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism permitting not only gastroesophageal reflux but also venting of air from the stomach. Triggering of TLESRs is provoked by gastric distension. Antireflux surgery is associated with impaired ability to belch. It is not known whether a reduced capacity to belch results from postoperative reduction in TLESRs.
**Methods:** We studied the occurrence of TLESRs, common cavities (indicator for gas gastroesophageal reflux) and belching after standardized acute gastric distension by air insufflation (750 ml). Control subjects (n = 10), patient with GERD (n = 22) and patients after fundoplication (n = 24) were studied. LES and esophageal motility were recorded with perfusion manometry (Dent-sleeve).
**Results:** Gastric distension with air significantly ($p<0.05$) increased TLESR frequency in controls ($1.6 \pm 0.3$ to $3.5 \pm 1.0$ per 20 min), GERD patients ($1.2 \pm 0.3$ to $3.1 \pm 0.5$ per 20 min) and post fundoplication ($0.5 \pm 0.1$ to $1.8 \pm 0.6$ per 20 min). Post fundoplication the number of TLESRs was significantly ($p<0.05$) reduced both under fasting conditions and after air insufflation. The number of common cavities and belches after gastric air distension also was significantly ($p<0.05$) reduced post fundoplication: $2.3 \pm 0.6$ versus $4.7 \pm 0.4$ in controls and $4.1 \pm 0.4$ in GERD patients. About half of the common cavities occurred during TLESRs, half during other mechanisms. An impaired ability to belch in daily life correlated with an impaired belching response during the test. An impaired ability to belch occurred only in patients with complete and not in patients with partial fundoplication and was associated with a reduced number of common cavities after gastric air insufflation.
**Conclusions:** short lasting gastric air distension 1) provokes TLESRs but does not differentiate GERD patients from controls; 2) reveals impaired belching capacity in patients after complete fundoplication; 3) shows that common cavities do not exclusively occur during TLESRs.


## INTRODUCTION

It has been well established that transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism permitting gastroesophageal reflux in man (1). Patients with gastroesophageal reflux disease (GERD) are believed to have a higher frequency of TLESRs compared to controls (2,3). Other investigators have pointed to an increased percentage of TLESRs associated with acid reflux in GERD patients (1,4). Reflux occurs especially in the postprandial periods (5). After meal ingestion the number of TLESRs increases depending on the size of the meal and meal composition. Gastric distension, especially of the fundus, is a trigger for TLESRs (6,7). To study TLESRs in patients with GERD, prolonged intraluminal recording of pressure and pH after meal ingestion is necessary. The aim of this study is to explore whether a short-duration provocation test with gastric distension by air insufflation is able to detect differences in TLESRs between GERD patients and controls.

TLESRs are also considered the physiological mechanism allowing venting of excess gas from the stomach (8,9). TLESRs underlie virtually all episodes of gas reflux during belching. After fundoplication the frequency of TLESRs decreases significantly (10).

Antireflux surgery is associated with impaired ability to belch, abdominal bloating, and increased flatulence. It is not known whether a reduced capacity to belch results from postoperative reduction in TLESRs. Gastric distension with air allows us to investigate both the presence of TLESRs, frequency of belching and their correlation in patients after fundoplication.

## METHODS

*Subjects*

Three groups were studied including in total 56 subjects:

1) Healthy volunteers (n=10; 6 females, 4 males; age 20 - 48 years). None of them had a history of gastro-intestinal disease, reflux symptoms or previously underwent surgery or was on chronic medication.

2) Patients with GERD (n=22; 8 females, 14 males; age 27 - 59 years). Gastroesophageal acid reflux in these patients was proven by endoscopy (esophagitis) or by 24 hour ambulatory pH metry. A hiatal hernia was present in 12 subjects with mean length 4.3 ± 0.4 cm. All patients underwent 24 hour pH metry and total time pH<4 ranged from 0.9 to 48.5 % (mean ± SEM: 10.5±2.6%; normal value <4.0%).

3) Patients after laparoscopic antireflux surgery (n=24; 11 females, 13 males; age 31 - 76 years). Fourteen patients underwent a complete (360o) Nissen fundoplication. Ten patients underwent a partial (180°-270°) fundoplication. Postoperatively the percentage of time esophageal pH<4 during 24 hour pH metry ranged from 0 to 11.7% (mean ± SEM: 3.7±0.8%).

Informed consent was obtained from each individual. The study had been approved by the Ethics Committee of the Leiden University Medical Center.

*Manometric and pH technique*

The manometry catheter consisted of a multilumen silicone tube (outer diameter 5.0 mm) with seven side holes located at 29, 23, 18, 13, 8, 3 and -4 cm from the mid of the 6 cm 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 Medical Specialties, Greendale, Wisconsin, U.S.A.) at a rate of 0.5 ml/min. The external pressures transducers (Medex Inc., Ohio, U.S.A.) were connected via an analogue/digital converter (PC Polygraph HR, Synectics Medical, Stockholm, Sweden) to a personal computer system. The data were displayed continuously on a monitor and stored on the personal computer system (Polygram Upper GI 6.30, Gastrosoft Inc., Synectics Medical, Stockholm, Sweden).

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 for identification of swallow signals. The middle side holes registered esophageal body motility. The distal side hole was used as reference point for intragastric pressure. A glass pH electrode (Ingold LOT 440 continue glassreference electrode; Ingold Messtechnik AG, Urdorf, Germany) was passed through the nose and positioned 5 cm above the upper margin of the LES. The pH electrode had been calibrated at pH 4.0 and pH 7.0.

*Study protocol*

The experiments were started at 9.00 a.m. after an overnight fast. The subjects were studied in the upright position, sitting in a comfortable chair. The manometry and pH catheter were introduced into the esophagus and positioned as described above. Esophageal pH and motility were registered simultaneously for one hour under basal, fasting conditions (time 0 to 60 min) and during two 20 min periods after air insufflation. Air was insufflated into the stomach at time 60 min and at time 80 min in 750 ml portions insufflated in 2 min through the distal intragastric side hole of the manometry assembly using a 60 ml syringe. The occurrence of TLESRs, common cavities and belches (definition see below) was scored in 20 min periods (basal, air insufflation). If the subject perceived gastropharyngeal reflux of air (belching) a mark was set on the computer tracing. If necessary, remaining air was removed from the stomach, at the end of the study protocol.

*Lower esophageal sphincter data analysis*

Lower esophageal sphincter tracings were analyzed for LES resting pressure (LESP) and LES relaxations (LESR). LESP was defined as mean end-expiratory LESP relative above intragastric pressure. LESR are divided in swallow induced LESR and spontaneous LESR. Swallow induced LESR are preceded by active swallows starting with a pharyngeal contraction. Spontaneous LESR, better known as transient LES relaxation (TLESR) are divided in non-swallow related TLESR, and swallow related TLESR. Spontaneous, non swallow related TLESR are defined as decreases in LESP of $\geq$ 5 mmHg with a rate of $\geq$ 1 mmHg/sec, within 10 sec reaching a pressure of $\leq$ 2 mmHg above intragastric pressure. No swallow signal occurs in the interval from 4 sec before to 2 sec after onset of LESR. Swallow related TLESR are defined as spontaneous TLESR, irrespective of the timing of LESR to swallowing when the duration of LESR is at least 10 sec (1).

*Gastroesophageal gas or acid reflux*

Common cavities were defined as abrupt simultaneous and sustained rises of basal esophageal pressure to intragastric pressure in at least the two lower esophageal body manometry recording sites (11). Common cavities are considered as markers of gas (or liquid) reflux from the stomach into the esophagus. Belching consists of gas gastroesophageal reflux (common cavity) followed by gas esophagopharyngeal reflux. We considered the occurrence of common cavities as indication for gas gastroesophageal reflux during the distension experiments. The belching response was considered impaired when $\leq$1 common cavity per 20 min air insufflation period was observed. The mechanisms of each gas or acid reflux episode was scored using previous described criteria (12).

*Symptom analysis*

Subjects were asked for symptoms of bloating and the ability to belch. These symptoms were scored on a scale from 0 to 3 (0 = no symptoms, able to belch; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms, not able to belch).

*Statistical analysis*

Data are expressed as mean ± SEM. Data were analyzed for statistical significance using (multiple) analysis of variance to compare results between the groups of patients and the controls. When this indicated a probability of less than 0.05 for the null hypothesis,

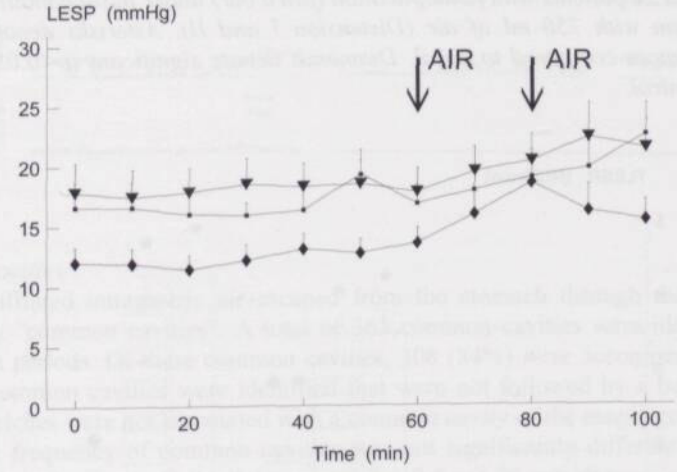
Student-Newman-Keuls analyses were performed to determine which values between or within the experiments differed significantly. A p value of $<0.05$ was considered significant for all analyses.

## RESULTS

*Lower esophageal sphincter pressure*

LES pressure was significantly ($p<0.05$) higher in patients after fundoplication ($18 \pm 2$ mmHg) compared to patients with GERD the ($11 \pm 1$ mmHg), but not compared to controls ($16 \pm 2$ mmHg). In patients with GERD the LES pressure was significantly lower ($p<0.05$) compared to controls. Intragastric insufflation of air resulted in small, non-significant increases in LES pressure (Figure 1).

**Figure 1.** *Lower esophageal sphincter pressure (mean ± SEM) in 10 healthy controls (small squares), 22 patients with gastroesophageal reflux disease (diamonds) and 24 patients after fundoplication (triangles) under basal fasting conditions and during gastric distension with air.*



*Transient lower esophageal sphincter relaxations*

The frequency of TLESRs in the basal state was not significantly different between patients with GERD and controls (1.2 ± 0.3 vs 1.6 ± 0.3 per 20 min). Patients after fundoplication had a significantly ($p<0.05$) lower frequency of TLESRs (0.6 ± 0.1 per 20 min) compared to controls (Figure 2). Gastric distension with 750 ml air significantly ($p<0.05$) increased the frequency of TLESRs in the control group (to 3.5 ± 1.0 per 20 min), in patients with GERD (to 3.1 ± 0.5 per 20 min) and in patients after fundoplication (to 1.8 ± 0.6 per 20 min). The number of TLESRs was not significantly different between the first and second distension procedure. Although the frequency of TLESRs in response to distension increased in patients with fundoplication it remained significantly ($p<0.05$) reduced compared to control subjects and patients with GERD. The frequency of TLESRs was not significantly different between patients with a complete fundoplication compared to patients with a partial fundoplication, neither basally (0.6±0.2 versus 0.5±0.2 per 20 min) nor after gastric distension (1.9±0.8 versus 1.4±0.5 per 20 min). The presence of a hiatal hernia in patients with GERD did not significantly influence the frequency of TLESR: 3.1±0.8 versus 3.1±0.7 per 20 min (hiatal hernia versus no hiatal hernia).

**Figure 2**. *Frequency of transient lower esophageal sphincter relaxations (N/20 min; mean ± SEM) in 10 healthy controls (open bar), 22 patients with gastroesophageal reflux disease (shaded bar) and 24 patients with fundoplication (filled bar) under basal conditions and after gastric distension with 750 ml of air (Distension I and II). Asterisks denote significant ($p<0.05$) differences compared to basal. Diamonds denote significant ($p<0.05$) differences compared to control.*

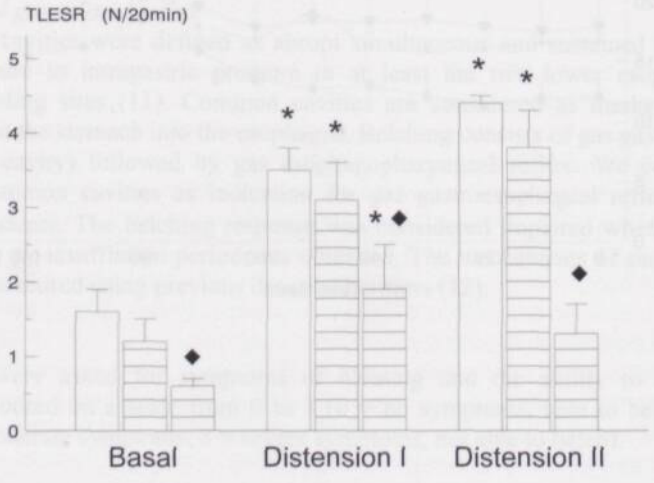
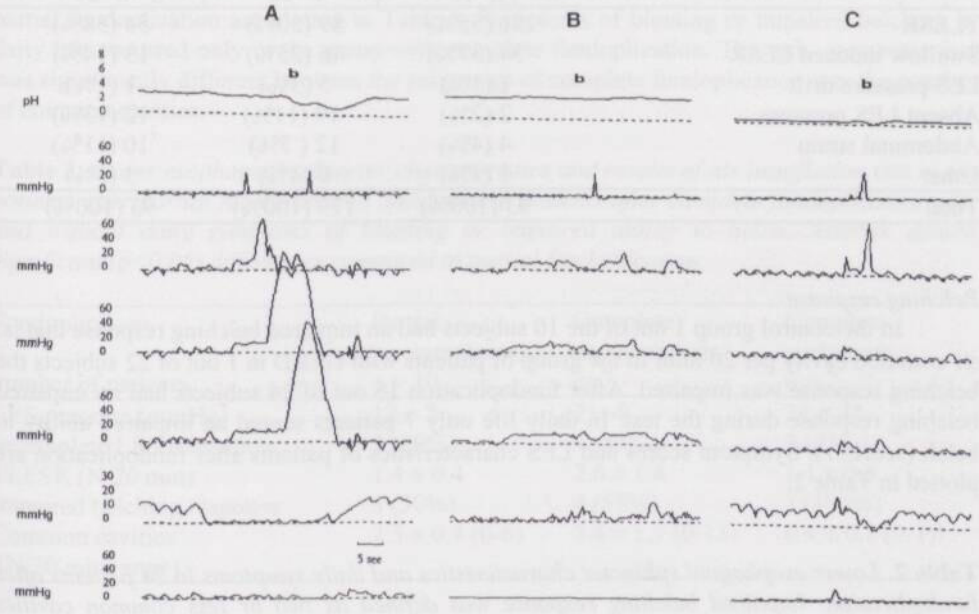


**Figure 3.** *Examples of common cavities during a transient LES relaxation (A); during low LES pressure (B) and after abdominal straining (C) (b = belch. Upper line: esophageal pH; 2nd line: pharynx; 3rd - 5th line: esophageal motility (5 cm intervals); 6th line: LES (sleeve); distal line: stomach.*




*Common cavities*

Insufflated intragastric air escaped from the stomach through the esophagogastric junction by "common cavities". A total of 365 common cavities were identified during all insufflation periods. Of these common cavities, 308 (84%) were accompanied with a belch. Thus, 57 common cavities were identified that were not followed by a belch. On the other hand, 37 belches were not associated with a common cavity of the esophageal body.

The frequency of common cavities was not significantly different between patients with GERD and controls (4.1 ± 0.4 versus 4.7 ± 0.4 per 20 min distension period). Patients after fundoplication had significantly ($p<0.05$) less common cavities (2.3 ± 0.6 per 20 min) compared to controls or patients with GERD. The frequency of common cavities was not significantly different between patients with complete or partial fundoplication (2.0 ± 1.0 versus 2.7 ± 0.7 per 20 min).

Common cavities occurred mainly during relaxations of the LES. The main mechanism "permitting" common cavities was a TLESR. However, common cavities also occurred during swallow induced LES relaxation, episodes of absent LES pressure or abdominal straining (Table 1). TLESRs accounted for 50 to 60% of the common cavities in all groups studied.

**Table 1.** *Mechanisms of common cavities (total number/40 min) in healthy controls, patients with gastroesophageal reflux disease and patients with fundoplication during two successive gastric distensions with 750 ml air.*

| | Control n=10 | GERD n=22 | Fundoplication n=24 |
|---|---|---|---|
| TLESR | 51 (55%) | 89 (50%) | 54 (58%) |
| Swallow induced LESR | 34 (37%) | 46 (25%) | 13 (14%) |
| LES pressure drift | 1 (1%) | 5 (3%) | 1 (1%) |
| Absent LES pressure | 2 (2%) | 19 (11%) | 12 (13%) |
| Abdominal strain | 4 (4%) | 12 ( 7%) | 10 (11%) |
| Other | 1 (1%) | 8 (4%) | 3 (3%) |
| Total | 93 (100%) | 179 (100%) | 93 (100%) |

*Belching response*

In the control group 1 out of the 10 subjects had an impaired belching response that is: ≤1 common cavity per 20 min. In the group of patients with GERD in 1 out of 22 subjects the belching response was impaired. After fundoplication 16 out of 24 subjects had an impaired belching response during the test. In daily life only 7 patients scored an impaired ability to belch (score≥1). Symptom scores and LES characteristics of patients after fundoplication are plotted in Table 2.

**Table 2.** *Lower esophageal sphincter characteristics and daily symptoms in 24 patients after fundoplication. Impaired belching response was defined as two or less common cavities during two successive intragastric insufflations of 750 ml of air in 40 min. Asterisks denote significant ($p<0.05$) differences compared to normal.*

| Belching response number of patients | Normal n = 8 | Impaired n = 16 |
|---|---|---|
| Complete fundoplication (Nissen) | 3 (37%) | 11 (69%) |
| Daily life symptoms: | | |
| bloating (score≥1) | 0 (0%) | 4 (25%) |
| impaired belching (score≥1) | 0 (0%) | 7 (44%)* |
| LES pressure (mmHg) | 11 ± 3 | 22 ± 2* |
| Incomplete LES relaxation (N) | 1 (13%) | 8 (50%)* |
| TLESR (N/20 min) | 3.5 ± 1.2 | 0.8 ± 0.3* |
| Common cavities (N/20 min;range) | 5.6 ± 1.1 (3-13) | 0.4 ± 0.1* (0-1) |

Compared to patients after fundoplication with a normal belching response in the test, in patients with an impaired belching response in the test the LES pressure was significantly higher, LES relaxation after wet swallows was frequently incomplete and the number of TLESR was significantly lower. Eleven patients (69%) with an impaired belching response in the test had a complete Nissen fundoplication in contrast to the group of patients with a normal belching response in the test (37%). LES characteristics of patients with a complete or partial fundoplication are plotted in Table 3. Symptoms of bloating or impaired belching in daily life occurred only in the group with complete fundoplication. The only parameter that was significantly different between the subgroups of complete fundoplication was the number of common cavities.

**Table 3.** *Lower esophageal sphincter characteristics and results of air insufflation test in ten patients after partial fundoplication and fourteen patients after complete fundoplication with and without daily symptoms of bloating or impaired ability to belch. Asterisk denote significant ($p<0.05$) differences compared to partial fundoplication.*

| Fundoplication | Partial | Complete | Complete |
|---|---|---|---|
| | no symptoms | no symptoms | symptoms |
| number of patients | n = 10 | n=7 | n = 7 |
| LES pressure (mmHg) | 12 ± 2 | 21±4 | 24 ± 3* |
| Incomplete LES relaxation | 2 (20%) | 4 (57%) | 3 (43%) |
| TLESR (N/20 min) | 1.4 ± 0.4 | 2.6 ± 1.4 | 1.1 ± 0.5 |
| Impaired belching response | 5 (50%) | 4 (57%) | 7 (100%) |
| Common cavities (N/20 min;range) | 2.5 ± 0.7 (0-6) | 3.4 ± 1.7 (0-13) | 0.4 ± 0.1 (0-1)* |

*Mechanisms of gastro-esophageal acid reflux*

Under fasting conditions and after gastric distension the number of reflux episodes and the amount of time pH < 4 were very low in the healthy volunteers (1.1 episodes per subject per hour; 0.33% time pH < 4), in patients with GERD (1.3 episodes per subject per hour; 0.97% time pH < 4) and patients after fundoplication (1.0 episodes per hour; 0.88% time pH <4).

## DISCUSSION

Acute gastric distension of the proximal stomach with air significantly increases the frequency of TLESRs. Patients with GERD were not different from healthy controls with respect to the frequency of TLESRs. However, in patients after antireflux surgery significantly less TLESRs occurred compared to patients with GERD and controls. A large subgroup of patients after fundoplication had an impaired belching response after gastric distension with air. These patients were characterized by regular symptoms of bloating and impaired belching, had significantly less TLESRs and were confined to the group with total fundoplication. The occurrence of TLESRs after fundoplication is therefore an important mechanism preventing bloating after antireflux surgery.

As expected, basal LES pressure in patients with GERD was lower than in the controls. In the patients after antireflux surgery LES pressure was significantly higher. During gastric distension with air LES pressure increased, although not significantly. This finding is in line with previous studies both in man and in animals reporting small increments in LESP in response to gastric distension (6,7,13,14).

Gastric distension with air resulted in increases in the frequency of TLESRs both in healthy subjects, patients with GERD and patients after antireflux surgery. However, in patients after fundoplication the frequency of TLESRs was significantly reduced compared to GERD and controls. Surprisingly, the number of TLESRs after air provocation was not higher in patients with GERD compared to controls. Several investigators (7,9,13,15,16) have shown that gastric distension with air increases the frequency of TLESRs. However, the effect of air insufflation is only short lasting because with the occurrence of TLESRs air escapes through belching and there after the distension of the stomach rapidly diminishes. It is not clear whether patients with GERD have an altered TLESR frequency after gastric distension. A previous study reported that patients with GERD have a significantly higher basal frequency of TLESRs compared to healthy subjects (7). However, gastric distension in that study was performed using an intragastric balloon and in contrast to air insufflation, the air could not escape from the balloon.

Numerous studies have shown that ingestion of meal increases the frequency of TLESRs (2,4,17-19). However, these studies have not clearly shown that patients with GERD truly have more TLESRs than controls. The percentage of TLESRs associated with acid reflux however, is increased in patients with GERD compared to controls. It remains to be elucidated why some TLESRs are accompanied with reflux and others are not. Intraluminal electrical impedance measurement has been shown to discriminate between liquid and gas gastroesophageal reflux and may prove a useful tool to answer these questions (20).

We have considered common cavities as markers of gas gastroesophageal reflux. The volume of belched air was not quantified, but is was a consistent finding that the insufflated air was released from the stomach during 3 to 4 common cavities. Half of the common cavities occurred during TLESRs. However a substantial number of common cavities occurred during swallow related LES relaxations or other mechanisms. Air can escape from the stomach through TLESRs but also by other mechanism. This is in line with the findings of studies on mechanism of acid reflux that although TLESRs are the predominant mechanism permitting acid reflux, that reflux of acidic gastric content occurs by other mechanism in 40 to 50%.

After antireflux surgery not only the number of TLESRs was diminished, but also the numbers of common cavities and belches were significantly less compared to GERD patients or controls. Smith et al have studied belching ability in patients after antireflux surgery and normal volunteers (21). After fundoplication patients had per belch lower volumes of expelled air compared to healthy subjects, but the belching frequency was similar. In the group of patients we studied different types of operation have been performed. With respect to TLESR frequency or numbers of common cavities patients with partial fundoplication were not significantly different from patients with complete fundoplication. However, a subgroup of patients with complete fundoplication had significantly less common cavities after air insufflation. These patients did have daily symptoms of bloating and an impaired ability to belch. A higher LES resting pressure, was the only parameter that was significantly different between the patients after complete fundoplication with impaired belching response in the test and impaired belching response in daily life versus those without an impaired belching response in daily life.

Based on the results of the air insufflation test we differentiated the groups of patients in those with a normal and those with an impaired belching response. Of the patients with an impaired response in the test 50% has troubles with belching in daily life. In the patients with impaired belching response esophageal manometry revealed LES insufficiency (i.e. incomplete LES relaxations and diminished number of TLESRs). Daily symptoms of impaired belching and bloating occurred only in patients with a complete fundoplication. Patients after (complete) fundoplication who did have symptoms had a lower number of common cavities. TLESR are probably neurally mediated since cooling of the vagus nerve and atropine inhibit the frequency of TLESR (9,16,18,22). Antireflux surgery may interfere with cholinergic nerve fibers at the esophagogastric junction. The diminished frequency of TLESR may result from local denervation. The fundic wrap covers the cardia which is a potent zone for triggering of TLESRs. It is therefore possible that the fundoplication prohibits gastric distension induced triggering of TLESRs.

Insufflation with air induces only a short lasting gastric distension because the insufflated air is usually vented by belching. Compared to this method an intragastric bag monitored by a barostat may be a more constant trigger for TLESRs. Prolonged gastric distension may discriminate between GERD and healthy subjects with respect to the triggering of TLESRs. After antireflux surgery we found that our test results and symptoms correlated, that is, all patients with postoperative bloating and an impaired ability to belch, had during the test procedure an impaired belching response. On the other hand, an impaired belching response during the test occurred frequently in postoperative patients while in daily life no symptoms of bloating or impaired belching are reported. The results of this study are in favor of partial fundoplication with respect to the postoperative symptoms of bloating and impaired ability to belch.

In conclusion: short lasting gastric distension with air is a potent trigger for TLESRs but does not discriminate between patients with GERD and healthy subjects. In patients after fundoplication the frequency of TLESRs and common cavities was significantly reduced. After antireflux surgery intragastric insufflation revealed impaired belching capacity in two-third of the patients while only half of them have symptoms in daily life. Common cavities occur not only during TLESRs but also by other mechanisms.

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