Reduced tLESR elicititation in response to gastric distension in fundoplication patients

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LAPAROSCOPIC NISSEN FUNDOPLICATION is increasingly advocated for the treatment of gastroesophageal reflux disease (GERD), and its efficacy for the control of acid reflux and reflux symptoms has been well established. Long-term success rates as high as 90% have been reported (2, 12). At present, the principal underlying mechanism of action of a successful antireflux operation is still incompletely understood (15, 19). Hypothesized mechanisms of efficacy include increased intraluminal pressure at the site of the esophagogastric junction (EGJ), incomplete EGJ relaxation, and a decreased transient lower esophageal sphincter relaxation (tLESR) frequency (9, 10, 13).

Although recent studies have established that tLESRs play a pivotal role in the pathogenesis of GERD, reports to date on the effect of a fundoplication on tLESR elicitation are limited (9, 10, 21). Animal data indicate that tLESRs are a vagally mediated reflex and can be abolished by experimentally cooling the cervical vagus (14). Distension of the proximal stomach, especially in the area of the gastric cardia, is a major stimulus for tLESRs to occur (7). With fundoplication, a fundic wrap of variable length is created surrounding this area and possibly limiting such distension. Therefore, it is reasonable to hypothesize that the anatomic alterations after fundoplication may increase the threshold for eliciting tLESRs. In line with this hypothesis, it has recently been reported that the frequency with which tLESRs occur after fundoplication was reduced following a meal (9) or short-lasting distension with air (5, 10, 21). In a recent study (29), it was also demonstrated that the tLESR increase during adaptive gastric relaxation to a meal is mainly due to the release of hormones, including CCK, after the arrival of nutrients in the duodenum. Furthermore, gastric adaptive relaxation was found to be reduced and gastric emptying to be accelerated after fundoplication (25). However, experiments using a purely mechanical stimulus are, up to now, lacking.

To obtain better insight into the effect of persistent mechanical distension applied in the proximal gastric area on tLESR elicitation and gastric accommodation postfundoplication, we employed an experimental technique using simultaneous EGJ manometry and distension by means of a barostat. The aims of this investigation were to determine the effect of a successful laparoscopic fundoplication on 1) tLESR frequency both at rest and during persistent gastric distension, 2) the efficacy of tLESRs in facilitating gastric venting after fundoplication compared with normal controls and GERD patients, and 3) the effect of fundoplication on another vagally mediated reflex, gastric accommodation to barostat distension.

MATERIAL AND METHODS

Esophageal manometry and isobaric distension of the stomach were performed simultaneously in healthy subjects, in patients with uncomplicated GERD, and in patients who...
had undergone a laparoscopic Nissen fundoplication. The study protocol was approved by the Northwestern University Institutional Review Board, and written, informed consent was obtained from all participants.

Subject groups. Subjects for this study were derived from a pool of normal volunteers, patients with symptomatic reflux disease, and patients who had undergone laparoscopic Nissen fundoplication to treat chronic reflux disease. They included nine healthy volunteers (5 men, 4 women), eight GERD patients (4 men, 4 women), and eight patients (3 men, 5 women) who had undergone fundoplication. All patients with reflux disease had a history of endoscopic esophagitis but were in endoscopic and symptomatic remission as a result of maintenance therapy with a proton pump inhibitor. On endoscopy, no hiatal hernia >3 cm in axial length was observed at endoscopy in any of these patients. The patients who had undergone fundoplication were at least 6 mo postoperative at the time of the study, were free of heartburn, had no significant dysphagia, and were using no antisecretory medications. The mean ages of the control subjects were 32 ± 7 yr; GERD patients, 44 ± 10 yr; and patients who had undergone fundoplication, 47 ± 9 yr. Before the study, administration of proton pump inhibitors was discontinued for at least 5 days, and drugs that could affect esophageal motility were discontinued for at least 24 h. Tobacco use was not permitted on the day of the study.

Laparoscopic fundoplication. All laparoscopic fundoplications were performed by the same surgeon (R. J. Joehl) using the same technique. The gastrocolic and gastroplenic omentum, including the short gastric vessels, were divided, and the proximal gastric fundus was mobilized. The right diaphragmatic crus was approximated with single 2-0 silk sutures. The proximal gastric fundus was mobilized. The right diaphragmatic crus was approximated with single 2-0 silk sutures. A loose wrap of Maloney bougie placed in the esophagus and traversing the esophagogastric junction was anchored to the esophageal musculature and was placed above the anatomic EGJ. At the time of the experiment, >6 mo after surgery, all patients were on an unrestricted diet.

Manometry assembly and barostat system. A 12-lumen silicone catheter (Dent Sleeve, Wayvill, South Australia) was used for manometry. The assembly incorporated three side-hole recording sites positioned 3, 6, and 9 cm proximal to the sleeve sensor, a 6-cm-long reversed perfused sleeve sensor, 7 side-hole recording sites on the opposite face of the sleeve positioned 1 cm apart, one side hole 1 cm distal to the sleeve to record intragastric pressure, and a large oval channel (1.9 × 2.4 mm inner diameter) lumen for air transit to and from the barostat bag (Fig. 1). Each catheter lumen was perfused with sterile water at 0.15 ml/min by using a low-compliance perfusion pump (Dentsleeve, Mark II, 16-channel model). Swallowing was monitored with a submental electromyography (EMG) recording obtained by using two disc electrodes positioned under the chin and a grounding patch attached to the side of a subject’s neck. Manometry and swallowing EMG channels were connected to a computer polygraph set at a sampling frequency of 40 Hz for manometry and 200 Hz for EMG (Neomedix Systems, Warriewood, New South Wales, Australia), and processed by using a Gastromac software (version 3.5; Neomedix, Warriewood, New South Wales, Australia). The barostat channel was connected to a polyethylene bag (maximal capacity 1,200 ml) at one end and an electronic barostat (Janssen, JSI, Beerse, Belgium) at the other. Pressure within the barostat bag was monitored from within the barostat cylinder, and air was injected or aspirated when that pressure differed from the preselected pressure by >0.2 mmHg. Intragastric bag volume data were stored in a digital data logger (MMS, Enschede, The Netherlands).

Pilot experiment. A pilot study was performed in 10 normal subjects to determine the optimal intragastric pressure associated with an adequate intragastric distension volume stimulus (~400 ml) for triggering TLESRs (7). Beginning at minimal distending pressure (MDP; see below), pressure was increased stepwise by 2 mmHg every 5 min until participants reported intolerable discomfort or the intragastric bag reached a volume of 650 ml. From that pressure level, pressure was decreased stepwise by 2 mmHg every 5 min until MDP was reached again. Mean pooled volume data during inflation and deflation are depicted in Fig. 2; 8 mmHg above MDP was chosen as the most suitable fixed-pressure stimulus.

Manometry and barostat recording. Subjects were studied after an overnight fast of at least 10 h. Participants were seated comfortably in an upright position and asked to use a saliva aspirator to minimize swallowing during recording. The manometry assembly, including the lubricated and folded barostat bag, was passed transorally. The bag was then inflated manually with 200 ml of air to unfold it and to assure that it was positioned correctly. The bag was then deflated and connected to the barostat. The catheter was then positioned so that the sleeve was straddling the EGJ high-pressure zone. With the catheter in this position, four to five side-hole recording sites were located in the esophageal body, six to seven side-hole recording sites were within the esophagogastric high-pressure zone, and one side-hole was measuring the intragastric pressure. The MDP was determined after insertion and positioning the catheter by increasing the intrabag pressure, in 1-mmHg steps from 0 mmHg (atmospheric pressure) to the pressure level that first provided an intragastric bag volume of >30 ml in accordance with the Aspiraz definition (1). After MDP determination, subjects were allowed to recover for 15 min. This was fol-
RESULTS

Effect of isobaric distension on proximal gastric volume and EGJ pressure. Minimal distending pressure was similar among the three subject groups: 5.5 ± 0.2 mmHg in the controls, 5.5 ± 0.4 mmHg in the GERD group, and 5.0 ± 0.2 mmHg in the fundoplication group. Gastric accommodation during distension (change in volume/change in pressure) was also not significantly different among subject groups: 52 ± 21 ml/mmHg among controls, 43 ± 13 ml/mmHg among the GERD patients and 46 ± 19 ml/mmHg among fundoplication patients. Gastric distension at 8 mmHg above MDP significantly increased intragastric volume in normal, GERD, and fundoplication patients as illustrated in Fig. 3. Intragastric volume changes were not significantly different among any of the subject groups (P > 0.5). EGJ pressure was significantly lower among the GERD patients (18 ± 4 mmHg) compared with either the control subjects (23 ± 3 mmHg) or the fundoplication patients (28 ± 4 mmHg), and this did not change during distension in any subject group: normal, 24 ± 4 mmHg; GERD, 17 ± 3 mmHg; fundoplication, 27 ± 3 mmHg.

Effect of barostat distension on tLESRs. The rate at which tLESRs occurred during each experimental condition for each subject group is illustrated in Fig. 4. Normal subjects and GERD patients exhibited similar tLESR rates in the basal state. Fundoplication patients, however, showed a significantly lower tLESR rate during baseline compared with normal controls (P < 0.01) and GERD patients (P < 0.01). During barostat distension, the tLESR rate increased signif-

![Fig. 2. Pilot experiment to determine optimal distension pressure. Mean pooled volume data during inflation and deflation during stepwise gastric distension in 10 healthy subjects. Data illustrated are means ± SE. A pressure of 8 mmHg above minimal distending pressure (MDP) was chosen as fixed-pressure stimulus.](image)

![Fig. 3. Intragastric volume during distension at a fixed pressure (8 mmHg above MDP) assessed in 10-min intervals in healthy controls, patients after Nissen fundoplication, and gastroesophageal reflux disease (GERD) patients. Intragastric volume during the 60-min distension episode was not significantly different between any of the subject groups (P > 0.5).](image)

![Fig. 4. The rate at which transient esophageal sphincter relaxations (tLESRs) occurred and the percentage of tLESRs associated with a common cavity during baseline recording and during the period of gastric distension among subject groups. *P < 0.01 baseline vs. distension. †P < 0.01 fundoplication (FP) vs. normal controls and GERD patients.](image)

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cantly in both normal (P < 0.01) and GERD patients (P < 0.01) but not in the fundoplication group. The percentage of tLESRs associated with a CC during the baseline recording was also similar among controls and GERD patients (63 and 65%, respectively) but significantly lower among the fundoplication patients (25%; P < 0.05). During barostat distension, the comparative figures were 68% in normal subjects, 66% in GERD patients, and 47% in fundoplication patients. Although the percentage of tLESRs associated with a CC among the fundoplication patients increased during distension, the increase was not significant compared with baseline, and the percentage remained significantly less than that observed in either of the other subject groups.

In addition to the observed quantitative differences in tLESR rate, significant qualitative differences were observed among the fundoplication subjects. Table 1 compares the nadir relaxation pressures observed during swallowing and during tLESRs among the subject groups. Note that in all cases, the relaxation pressure achieved during tLESRs was slightly lower than that achieved during swallowing but was significantly higher in both cases among the fundoplication patients. Only exceptionally was a complete tLESR (nadir pressure of <2 mmHg) observed in the fundoplication group. The elevated relaxation pressure during tLESRs is exemplified in the manometric tracings illustrated in Fig. 5; note that, as was often the case, no CC was observed in the example illustrated. The duration of tLESR was not altered by fundoplication but was similar among the three groups both during baseline and during distension.

DISCUSSION

Although tLESR has been identified as an important physiological mechanism underlying gastroesophageal reflux (16), data on tLESR elicitation and characteristics after a laparoscopic fundoplication are limited. The major finding of this study was that patients who had undergone a successful fundoplication exhibit a lower rate of tLESRs at rest and showed a marked attenuation of the tLESR increase during prolonged gastric distension compared with either healthy controls or GERD patients.

Table 1. Nadir pressure during swallowing and during tLESRs in normal subjects, patients with GERD and patients who had undergone fundoplication

<table>
<thead>
<tr>
<th></th>
<th>Nadir EGJ Pressure, mmHg During Swallows</th>
<th>tLESR Nadir Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Distension</td>
</tr>
<tr>
<td>Normal controls</td>
<td>3.8 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>GERD</td>
<td>3.6 ± 0.5</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Fundoplication</td>
<td>10.3 ± 1.0*</td>
<td>9.9 ± 2.4*</td>
</tr>
</tbody>
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Values are means ± SE. tLESRs, transient lower esophageal sphincter relaxations; GERD, gastroesophageal reflux disease; EGJ, esophagogastric junction. *P < 0.05 vs. normal subjects and GERD patients.

Fig. 5. Manometry tracing illustrating an example of a tLESR recorded during the baseline period in a normal control (A) and in a fundoplication patient (B). For clarity, not all manometric channels are depicted. The horizontal dashed line in the esophagogastric junction (EGJ) channel represents the corresponding intragastric pressure. Although the subject in B swallowed, as evident in the electromyographic recording, this event occurred after the onset of the tLESR. Note that in A, the EGJ relaxation is complete and accompanied by a common cavity, whereas in B, neither condition is achieved. Also note that, as was often the case, the respiratory effect on the manometric signal was less distinct after fundoplication.
GERD patients. Furthermore, most tLESRs in fundoplication patients were characterized by a higher residual pressure (incomplete relaxation) and associated with fewer common cavities. In contrast to tLESR elicitation after operation, the gastric accommodation response to prolonged distension was not impaired after fundoplication. These findings suggest that, in addition to a substantially higher EGJ pressure (13), reflux control after fundoplication is partly attributable to an increased threshold for eliciting the most frequent mechanism of reflux, a tLESR.

In the present experiment, prolonged gastric distension was applied and found to be an effective trigger for tLESRs in normal subjects and GERD patients. In both groups, the tLESR rate increased by about four per hour. However, no significant augmentation in tLESR rate was evident in the fundoplication patients. This observation corroborates earlier reports using 750 ml of intragastric carbon dioxide (10, 21, 24) or a meal (9, 22) to achieve gastric distension that also reported a reduced number of distension-induced tLESRs after fundoplication. However, with bolus gas infusion or with a meal, gastric distension diminishes over time due to gas escape or gastric emptying, respectively, making the stimulus intensity variable over time. In addition, Zerbib et al. (29) demonstrated that a duodenally administered meal resulted in a similar tLESR rate increase compared with an oral meal, suggesting the involvement of nutrient-induced hormonal factors, especially CCK (4). We elected to use long-lasting isobaric distension of the proximal stomach to circumvent these potential limitations. Another advantage of the barostat method is the ability to apply a sustained stimulus for a period of an hour, a major advantage in the study of a physiological event as infrequent and random as a tLESR. At face value, these results seem to contradict a previous study reporting a higher frequency of tLESR in response to gastric air distension in patients with a hiatus hernia (11). However, there are significant methodological differences between the studies that may explain the discrepancy. First, the definition of hiatus hernia was different. In the previous study, a clip technique was used and axial displacement of the SCJ relative to the hiatus was assessed fluoroscopically, whereas in the present study, endoscopy was used. In our experience, the size of hiatus hernia-estimated endoscopy is always larger than that measured with the clip technique, and several patients thought to have a hiatus hernia on endoscopic grounds will have no demonstrable hernia when the clipping method is used. Because no hiatal hernia ≥3 cm in axial length was observed endoscopically in any of the GERD patients investigated in this study, one would anticipate that they would have either no or small hernias if the clipping method was used, making them more comparable with the nonhernia group in our previous publication (11). The second significant methodological difference between the studies was in the method of gastric distension; in the previous study, continuous intragastric air infusion was used, whereas in this case a close intragastric bag was used.

A key finding in the present study was that gastric accommodation of the stomach to prolonged distension was not impaired with fundoplication. This finding is at variance with recent data (25, 27) demonstrating a reduced gastric accommodation response after a meal. Again, methodological differences may account for the discrepancy. Gastric wall elongation after a meal is due to nutrient-induced hormone release (including CCK) accompanied by minimal intragastric pressure variation (29). In contrast to this, the present experiment employed isolated and purely mechanical distension at fixed pressure in the proximal stomach. Accommodation to the latter stimulus may be partially dependent on viscoelastic properties of the smooth muscle cells and connective tissue in the gastric wall (27). Consistent with the findings of the present study, Vu et al. (25) found gastric compliance unchanged after fundoplication.

A major question raised by this and prior investigations is how fundoplication increases the threshold for triggering tLESRs. Present thinking is that tLESR is a vagal reflex elicited mainly by gastric distension. Although the receptive field for triggering tLESRs is not completely clear, mechanoreceptors in the region of the gastric cardia are commonly implicated (6, 16). On the basis of studies in ferrets (3), two types of mechanoreceptors have been proposed: receptors in series with smooth muscle fibers, responding to wall tension variation, and receptors in parallel with smooth muscle fibers, responding to elongation of the gastric wall. Both types of receptors are activated during gastric distension (18, 23). However the gastric cardia is situated, after fundoplication, within the fundic wrap, presumably with a reduced ability to stretch or elongate (27). Thus an identical and constant distension stimulus likely results in a diminished cardiac cross-sectional area compared with what would be observed if the same stimulus were applied in normal subjects or GERD patients. Reduced cross-sectional area would, in turn, result in decreased wall tension and elongation, thereby reducing the activation of both types of receptors potentially responsible for triggering tLESRs. Furthermore, because tLESR elicitation and gastric receptive relaxation are both mediated by the vagal nerve and gastric accommodation was not affected by fundoplication in either our experiment or an earlier experiment (25), it is tempting to speculate that the vagal afferent field for triggering tLESRs is either independent of or contained within a larger area responsible for elicitation of gastric receptive relaxation and that only the first is substantially reduced by fundoplication.

Another finding confirmed in the present study was of incomplete relaxation during tLESR, as first described by Ireland et al. (9). Despite the fact that tLESRs scored in the fundoplication patients (Fig. 4B) closely resembled the distinctive temporal profile of tLESRs observed in normal subjects (Fig. 4A), they technically do not meet the criteria established by Holloway et al. (8) because the nadir pressure was ≥2 mmHg in most instances. However, as was also dem-
onstrated by the Adelaide group, deglutitive lower esophageal sphincter relaxation was incomplete in these patients, justifying the use of the modified criteria defined by Ireland et al. (9). Postprandial epigastric fullness and bloating appear in 10–80% of patients after Nissen fundoplication (17, 20), and an inability to relieve this discomfort by belching is frequently reported (13). A tLESR associated with a common cavity is the most relevant manometrically identified mechanism of gastric gas venting (28). Apart from a fall in the mean number of tLESRs, a significant reduction of the percentage of tLESRs associated with a common cavity was also found in fundoplication patients. These data are in concordance with findings by the Adelaide group, who found a significant reduction in the number of common cavities during gaseous distension of the stomach (10 min) after fundoplication (10, 24). The observed pattern of incomplete relaxation during tLESRs provides a potential explanation for the frequently reported symptoms related to increased amounts of intestinal gas after fundoplication.

In summary, fundoplication patients exhibit a diminished rate of tLESRs both at rest and during isobaric gastric distension compared with both normal controls and GERD patients. Second, tLESRs in fundoplication patients were characterized by a higher residual pressure and a lower efficacy of facilitating gastric emptying than was seen in normal subjects or GERD patients. Finally, gastric accommodation was not impaired with fundoplication, suggesting that the vagal afferent field for triggering tLESRs is contained within a wider field for elicitation of gastric receptive relaxation and that only the first is affected by fundoplication.

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REFERENCES