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

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PATIENTS AND METHODS

ABSTRACT

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PROSPECTIVE STUDY ON THE EFFECT OF LAPAROSCOPIC NISSEN FUNDOPLICATION ON REFLUX MECHANISMS

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ABSTRACT

Background: Laparoscopic Nissen fundoplication effectively reduces acid reflux and reflux-symptoms. Little is known about the effect on reflux mechanisms especially on transient lower oesophageal sphincter relaxations (TLOSRS).

Methods: Twenty-seven patients were prospectively studied before and after laparoscopic Nissen fundoplication, by simultaneous recording of pH and lower oesophageal sphincter characteristics using sleeve manometry. In all of the twenty-seven patients the operation was judged successful, based on major improvement or resolution of reflux symptoms and acid reflux. Vagus nerve integrity was studied indirectly by the secretion of pancreatic polypeptide (PP) in response to insulin induced hypoglycaemia.

Results: After fundoplication basal LOS pressure significantly ($P<0.05$) increased from 13 ± 1 mmHg to 22 ± 1 mmHg. Laparoscopic Nissen fundoplication significantly ($P<0.05$) decreased the number of TLOSRS per hour in the fasting period from 2.5 ± 0.5 TLOSRS/h to 0.6 ± 0.2 TLOSRS/h and in postprandial period from 4.0 ± 0.4 TLOSRS/h to 1.3 ± 0.3 TLOSRS/h. The percentage of TLOSRS associated with reflux also decreased significantly ($P<0.05$), in the fasting period from $24\pm 10\%$ to $0\pm 0\%$ and postprandial period from $42\pm 6\%$ to $12\pm 6\%$, respectively before and after fundoplication. Postoperatively the PP response was abnormal in three patients, pointing to vagus nerve dysfunction. Postoperative TLOSRS frequency and LOS pressure were not different between patients with and without vagus nerve dysfunction.

Conclusions: Laparoscopic Nissen fundoplication significantly increases fasting and postprandial lower oesophageal sphincter pressure and significantly decreases the rate of TLOSRS. This results in a significant reduction of oesophageal acid exposure but postprandial LOS characteristics are preserved.

INTRODUCTION

Antireflux surgery is considered when patients with proven gastro-oesophageal reflux disease (GORD) are refractory to medical therapy (1). The Nissen fundoplication is the most commonly applied antireflux procedure. Since the introduction of laparoscopic techniques, antireflux surgery has received renewed attention. Minimally invasive antireflux procedures provide excellent symptom relief with rapid recovery and low postoperative morbidity, assuming sufficient surgical expertise (2).

Several studies have shown that the most prevalent mechanism of reflux in patients with GORD and in healthy subjects is the transient lower oesophageal sphincter relaxation (TLOSRS) (3-5). Despite the fact that antireflux procedures are frequently performed, the mechanism of action of antireflux surgery is poorly understood. Previous studies on 'open' procedures have shown that Nissen fundoplication and partial (Belsey Mark IV) fundoplication reduce the frequency of TLOSRS (6,7). Although much has been published about the outcome after laparoscopic Nissen fundoplication in terms of symptom relief (8) and reflux control (9), the effect of laparoscopic Nissen fundoplication on TLOSRS has not been studied.

In the present study, patients with GORD were investigated prospectively before and six months after laparoscopic Nissen fundoplication with emphasis on TLOSRS as the major mechanism of reflux. Oesophageal pH and sleeve manometry were performed under fasting conditions in response to a meal.

PATIENTS AND METHODS

Patients

Between January 1993 and December 1997 75 patients underwent laparoscopic Nissen fundoplication as primary antireflux procedure for GORD that was resistant to medical therapy. Twenty-seven of these patients agreed to participate in a prospective study evaluating the effect of the laparoscopic Nissen procedure on mechanisms of gastro-oesophageal reflux. All patients (11 male, 16 female; mean age 45 yr, range 21-72 yr) had symptoms of gastro-oesophageal reflux such as heartburn, regurgitation, retrosternal pain or dysphagia. GORD was documented in all patients by endoscopy and/or by ambulatory 24-hour pH monitoring. At this institution preoperative evaluation includes upper gastrointestinal endoscopy, oesophageal manometry, 24-h ambulatory pH monitoring and vagus nerve function test. Postoperative evaluation, including oesophageal manometry, 24-h ambulatory pH metry and vagus nerve function test was performed 6 months after the operation.

Indications for antireflux surgery were the presence of reflux symptoms not responding sufficiently to prolonged medical treatment (more than 6 months) including proton pump inhibitors. Objective signs of reflux disease had to be present (endoscopic esophagitis and/or abnormal 24-h oesophageal pH measurements). The surgical procedure, laparoscopic Nissen fundoplication, was performed by one surgeon (J.R.). The operative technique entailed initial oesophageal mobilization and posterior hiatal repair. The gastric fundus was not routinely mobilized. The fundus was wrapped around the oesophagus, which was calibrated with a 42-Fr bougie within the oesophageal lumen, to enable construction of a floppy 360° fundoplication.

Mechanisms of gastro-oesophageal reflux were investigated in 27 patients before and 6-12 months after the operation. All patients were studied after an overnight fast. Medication was stopped at least 72 h before the study. Informed consent was obtained from each individual and the protocol had been approved by the local ethical committee.

Endoscopy

The severity of esophagitis was graded endoscopically according to the criteria of Savary and Miller. Preoperative endoscopy showed esophagitis grade 0 in six patients, grade I in eight patients, grade II in ten patients, grade III in three patients.

24 hour pH metry

We performed 24 hour ambulatory intra-oesophageal pH monitoring as described previously (10). Gastro-oesophageal reflux was considered pathological when the oesophageal pH fell below 4 for 4.0 per cent or more of total recording time (10). Preoperative evaluation revealed abnormal 24 h pH measurements in 24 patients, in three patients reflux time was in the normal range but the patients had endoscopic signs of reflux disease (oesophageal pH below 4 for 0-4 per cent of the monitoring time).

Vagus nerve integrity

Vagus nerve integrity was measured indirectly by the secretion of plasma pancreatic polypeptide (PP) in response to insulin-induced hypoglycaemia (11,12). PP was measured by

a sensitive and specific radioimmunoassay (13). A peak increment in plasma PP below 47 pmol/l is considered to be compatible with vagus nerve dysfunction (11).

Manometric and pH technique

The manometry catheter consisted of a multilumen silicon tube (outer diameter 5.0 mm) incorporating a 6 cm long sleeve sensor (Dentsleeve Property, Belair, South Australia, Australia). The manometry catheter was introduced through the nose into the oesophagus and positioned so that the sleeve sensor straddled the LOS. A glass pH electrode (Ingold, Urdorf, Germany) positioned 5 cm above the upper margin of the LOS.

Study protocol

Experiments were started at 9 AM after an overnight fast. The subjects were studied in the upright position, sitting in a comfortable chair. They were not allowed to doze because of the effect of sleep on TLOSRS. Oesophageal manometry and pH were recorded simultaneously during a 30 min fasting period and for 180 min after a standard breakfast consisting of 400 ml Nutridrink (Nutricia, Zoetermeer, The Netherlands) containing 20 g protein, 26 g fat and 72 g carbohydrates (2520 kJ).

Lower oesophageal sphincter data and pH analysis

LOS tracings were analyzed for LOS resting pressure and LOS relaxations (LOSR) including TLOSR. TLOSRS were defined according to Mittal *et al.*(14) Gastro-oesophageal reflux episodes and the mechanisms of each reflux episode were scored using criteria described previously (7).

Statistical analysis

Data are expressed as mean \pm SEM. Statistical analyses of TLOSR and reflux were performed using Wilcoxon's signed rank test and the Mann-Whitney U test. Differences in LOS pressure before and after operation and in response to meal ingestion were analyzed for statistical significance using multiple analysis of variance. A $P < 0.05$ was considered significant for all analyses.

RESULTS

In all of the 27 patients who participated in the study the operation was judged successful, based on major improvement or absence of reflux symptoms and gastro-oesophageal acid reflux. One patient had severe dysphagia after operation. This patient is included in the data analysis. After the postoperative studies she underwent reoperation during which the wrap was dismantled.

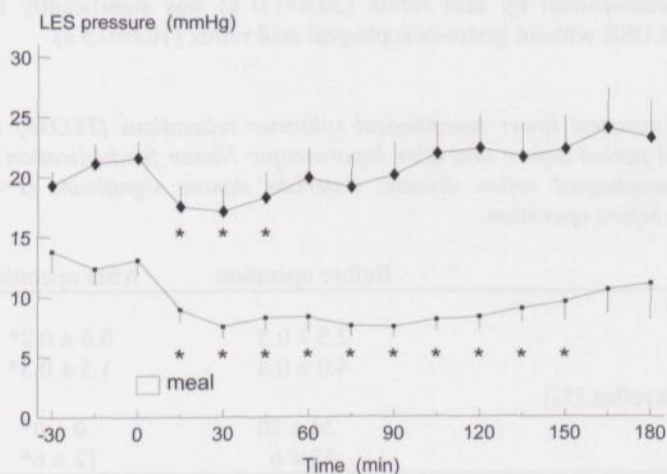
Vagus nerve integrity

Preoperatively, all patients had plasma PP peak increments in the normal range (above 47 pmol/l) before operation, with a mean value of 146 ± 11 pmol/l. After fundoplication, the PP response was normal in all but three patients who had PP peak values indicative for vagus nerve dysfunction (47 pmol/l or less). None the less, the LOS pressure and TLOS frequency of these three patients were not different from the other patients, who had no signs of vagus nerve dysfunction. The mean value of postoperative plasma PP peak increment of the patients with responses in the normal range was 121 ± 10 pmol/l.

24 hour oesophageal pH metry

Compared to preoperative values total reflux time during 24-h oesophageal pH measurements decreased significantly from 11.7 ± 2.3 (range 2.1-49.2) per cent to 0.8 ± 0.3 (range 0-6.0) per cent. ($P < 0.01$)

Figure 1. Mean (s.e.m.) basal and postprandial lower oesophageal sphincter (LES) pressure at the gastro-oesophageal junction before (squares) and after laparoscopic Nissen fundoplication (diamonds) in 27 patients with gastro-oesophageal reflux disease. * $P < 0.05$ versus basal value (before meal) (Manova test).



Lower oesophageal sphincter pressure

After fundoplication basal LOS pressure before a test meal increased significantly from 13 ± 1 mmHg to 22 ± 1 mmHg ($P < 0.001$) (Figure 1). Before operation, LOS pressure was significantly decreased ($P < 0.05$) between 15 to 150 min after the start of the meal, reaching a minimum of 7 ± 1 mmHg 30 min postprandially. After the operation, meal ingestion reduced LOS pressure between 15 to 45 min postprandially, reaching a minimum of 17 ± 2 mmHg at 30 min. Postprandial LOS pressures after operation were significantly higher compared to preoperative values ($P < 0.001$).

Transient lower oesophageal sphincter relaxations

TLOSRS were identified in all patients before operation. However, after laparoscopic Nissen fundoplication, TLOSRS were registered in only 21 of the 27 patients. In six subjects only spontaneous LOS relaxations with incomplete LOS relaxation were identified (Figure 2). All the postoperative TLOSRS had a residual LOS pressure of 2 mmHg or less, according to the definition of TLOSRS. A total of 76 spontaneous LOS relaxations which met all criteria for TLOSRS apart from reaching the intragastric nadir pressure, were observed after laparoscopic Nissen fundoplication. Residual pressures during these relaxations varied from 3 to 28 mmHg. According to the definition these relaxations were not scored as TLOSRS.

The total number of TLOSRS recorded in all subjects decreased after the operation from 47 to 11 in the fasting period and from 274 to 98 in the postprandial period. The number of TLOSRS per hour in the fasting period and after the meal decreased significantly ($P < 0.01$; Table 1) postoperatively. Fundoplication not only reduced the number of TLOSRS but also significantly ($P < 0.05$) decreased the percentage of TLOSRS associated with gastro-oesophageal acid reflux in the fasting and postprandial period from 24 ± 10 and 42 ± 6 per cent respectively before operation to 0 ± 0 and 12 ± 6 per cent respectively after operation.

The mean duration of TLOSRS was 18.4 ± 0.5 s before fundoplication and decreased significantly to 16.0 ± 1.1 s after fundoplication ($P < 0.05$). Preoperative and postoperative duration of TLOSRS accompanied by acid reflux (20.4 ± 1.0 s) was significantly longer ($P < 0.001$) than that of TLOSRS without gastro-oesophageal acid reflux (16.6 ± 0.5 s).

Table 1. Frequency of transient lower oesophageal sphincter relaxations (TLOSRS) in the fasting and postprandial period before and after laparoscopic Nissen fundoplication in 27 patients with gastro-oesophageal reflux disease. Asterisks denote significant ($P < 0.01$) differences compared to before operation.

	Before operation	After operation
TLOSRS (number/hour)		
basal	2.5 ± 0.5	$0.6 \pm 0.2^*$
postprandial	4.0 ± 0.4	$1.3 \pm 0.3^*$
TLOSRS associated with reflux (%)		
basal	24 ± 10	$0 \pm 0^*$
postprandial	42 ± 6	$12 \pm 6^*$

Mechanism of reflux

The total number of gastro-oesophageal reflux episodes was 284 before operation and 15 after operation (Table 2). The predominant mechanism of reflux was TLOSР: 43% before and 60% after fundoplication.

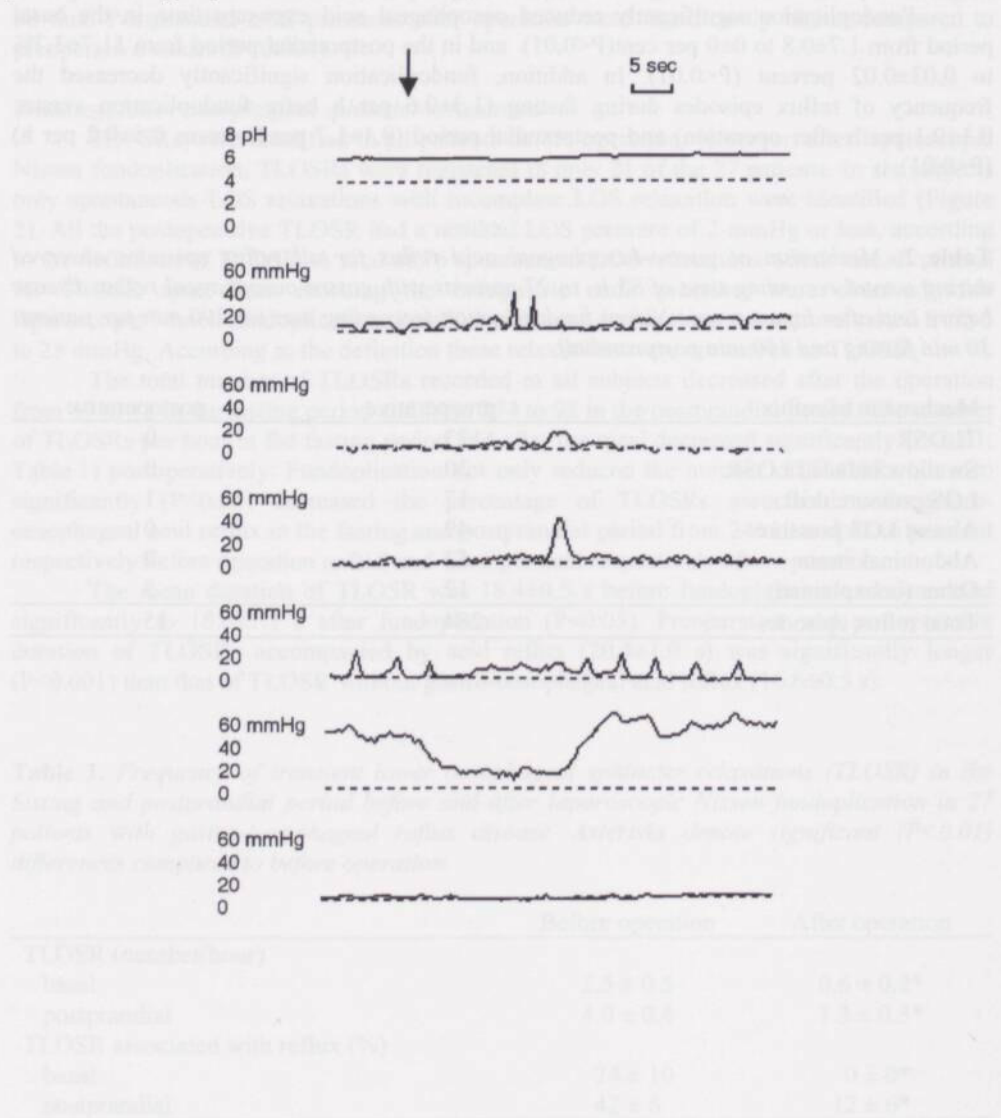
Gastro-oesophageal reflux

Fundoplication significantly reduced oesophageal acid exposure time in the basal period from 1.7 ± 0.8 to 0 ± 0 per cent ($P < 0.01$) and in the postprandial period from $11.7 \pm 3.7\%$ to 0.03 ± 0.02 percent ($P < 0.01$). In addition, fundoplication significantly decreased the frequency of reflux episodes during fasting (1.3 ± 0.6 per h before fundoplication versus 0.1 ± 0.1 per h after operation) and postprandial period (9.1 ± 1.7 per h versus 0.5 ± 0.2 per h) ($P < 0.01$).

Table 2. Mechanism of gastro-oesophageal acid reflux for all reflux episodes observed during a total recording time of 85 h in 27 patients with gastro-oesophageal reflux disease before and after laparoscopic Nissen fundoplication (recording was for 190 min per patient: 30 min fasting and 160 min postprandial).

Mechanism of reflux	preoperative	postoperative
TLOSР	123	9
Swallow induced LOSР	30	0
LOS pressure drift	17	1
Absent LOS pressure	49	0
Abdominal strain	53	0
Other (unexplained)	12	5
Total reflux episodes	284	15

Figure 2. Tracing of an 'incomplete' transient lower oesophageal sphincter relaxation (arrow) in a patient after laparoscopic Nissen fundoplication. The tracings show (from top to bottom) oesophageal pH, pharyngeal pressure, three oesophageal body pressure channels, lower oesophageal sphincter (LOS) pressure and intra gastric pressure. The dotted line denotes intragastric pressure or pH 4. The LOS pressure does not decrease to intragastric pressure during a spontaneous LOS relaxation.



DISCUSSION

Laparoscopic Nissen fundoplication effectively reduces gastro-oesophageal reflux (15,16). However the effect of laparoscopic surgery on reflux mechanisms had not been studied previously. This study has shown that the number of TLOSRS is decreased both in fasting and the postprandial state after the laparoscopic Nissen fundoplication. These results are consistent with findings in a previous study on the effect of open Nissen fundoplication on the rate of TLOSRS (6). A study on the effect of partial fundoplication (Belsey Mark IV) on TLOSRS also showed a postoperative reduction in the rate of TLOSRS and a decrease in the percentage of TLOSRS associated with gastro-oesophageal acid reflux (7).

The mechanism by which laparoscopic Nissen fundoplication decreases the number of TLOSRS is not understood. Several factors may be involved. Distension of the proximal stomach, either by air insufflation, by insufflation of barostat bag or by meal ingestion, is a potent trigger for TLOSRS. The frequency of TLOSRS is related to the volume of the proximal stomach and the degree of fundic distention (17). After Nissen fundoplication postprandial relaxation of the proximal stomach is impaired; i.e. after meal ingestion the maximum volume of the proximal stomach is significantly smaller in patients with Nissen fundoplication than in non-operated patients with GORD or healthy controls (18,19). Therefore the decreased frequency of TLOSRS after fundoplication may be related to impaired postprandial relaxation of the proximal stomach.

The vagus nerve is involved in the pathway through which TLOSRS are triggered. Vagotomy and atropine decrease the frequency of TLOSRS (20,21). After Nissen fundoplication vagus nerve dysfunction may occur in up to 30 per cent and lead to symptoms such as nausea, bloating or diarrhoea. Such symptoms were observed in the patients who participated in this study. There was evidence for postoperative vagus nerve dysfunction in only 3 of the 27 subjects. The reduction in frequency of TLOSRS after the operation does not therefore appear to result from vagus nerve dysfunction.

After fundoplication TLOSRS with complete LOS relaxation reaching intragastric pressure occurred in 21 patients. However, in six subjects only incomplete spontaneous LOS relaxations occurred. The incomplete TLOSRS have all the characteristics required for TLOSRS apart from residual LOS pressure. Fundoplication not only influences the frequency of TLOSRS but may also prohibit complete relaxation of the LOS during TLOSRS or during swallowing.

Dysphagia is common in the early postoperative period and may be related to LOS dysfunction especially incomplete LOS relaxation. In a recently published randomized clinical trial of open versus laparoscopic Nissen fundoplication the relative risk of postoperative dysphagia was in favour of open surgery, but LOS relaxation was not evaluated (22). Apart from acid reflux TLOSRS are also a mechanism for venting gas for the stomach, i.e. belching (23). An impaired ability to belch is common after antireflux surgery. Johnsson *et al* (24) noted that patients after 360° fundoplication with concomitant highly selective vagotomy did not exhibit TLOSRS or common cavities in response to gastric distension. An absence of TLOSRS may therefore be related to an inability to belch and may lead to gas bloat syndrome. The frequency of TLOSRS decreased after laparoscopic Nissen fundoplication in all of the present patients but TLOSRS, both complete and incomplete, still occurred; this may be relevant for the physiological venting of air from the stomach.

In conclusion, laparoscopic Nissen fundoplication significantly increased fasting and postprandial LOS pressure and significantly decreased the rate of TLOS. It significantly decreased oesophageal acid exposure and reduced mechanisms of reflux, however, with preservation of postprandial LOS characteristics.

The mechanism by which laparoscopic Nissen fundoplication decreases the incidence of TLOS is not understood. Several factors may be involved. Relaxation of the proximal stomach, either by distension or by inhibition of contractile peristalsis, is a common event during the LOS. The frequency of TLOS is related to the volume of the proximal stomach and the degree of gastric distension (17). After Nissen fundoplication postprandial relaxation of the proximal stomach is reduced, i.e. after each swallow the maximum volume of the proximal stomach is significantly smaller in patients with Nissen fundoplication than in non-operated patients with GORD or healthy controls (18,19). Therefore the decreased frequency of TLOS after fundoplication may be related to improved postprandial relaxation of the proximal stomach.

The other factor is involved in the pathway through which TLOS are triggered. Voluntary and involuntary relaxation of the LOS (20,21). After Nissen fundoplication vagus nerve dysfunction may occur in up to 50 patients and lead to symptoms such as gastric bloating or distension. Such symptoms were observed in the patients who participated in the study. There were no symptoms of vagus nerve dysfunction in only 1 of the 27 subjects. The reduction in frequency of TLOS after the operation does not therefore appear to result from vagus nerve dysfunction.

After fundoplication TLOS with complete LOS relaxation leading to regurgitation occurred in 24 patients. However, in the majority of these patients postoperative LOS relaxations occurred. The recognised TLOSs have all the characteristics required for TLOS apart from residual LOS pressure. Fundoplication may also influence the frequency of TLOS but may also involve complete relaxation of the LOS during TLOS or during swallowing.

Dysphagia is common in the early postoperative period and may be related to LOS dysfunction especially incomplete LOS relaxation in a recently published randomised clinical trial of open versus laparoscopic Nissen fundoplication. The relative risk of postoperative dysphagia was in favour of open surgery, but LOS relaxation was not evaluated (22). Apart from acid reflux TLOS are also a mechanism for vomiting gas for the stomach, i.e. belching (23). An increased ability to belch is common after antireflux surgery. Johnson *et al.* (24) noted that patients after 360° fundoplication with esophageal highly selective vagotomy did not exhibit TLOS or constant cavities in response to gastric distension. An absence of TLOS may therefore be related to an inability to belch and may lead to gas distension. The frequency of TLOS decreased after Nissen fundoplication. However, the frequency of TLOS decreased after Nissen fundoplication in all of the present patients but TLOSs both complete and incomplete still occurred; this may be relevant for the physiological setting of antral distension.

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SUM

SUMMARY

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