

GASTROESOPHAGEAL REFLUX DISEASE: TREATMENT, OUTCOME  
AND SPECIAL ASPECTS

Ph. D. Thesis

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## 1. Introduction

Gastroesophageal reflux disease (GERD) is probably the most frequently occurring functional foregut disorder and accounts for approximately 75% of esophageal pathology in the industrial countries. Beside its frequency it is also very expensive in both primary and secondary care. The annual direct cost for managing GERD in the USA is estimated to be more than \$ 9 billion dollars (1). Although GERD is very common, the definition of the disease is still not unitary. It can be best described as abnormal (time and/or quantity) reflux of gastric content into the esophagus leading to esophagitis and/or reflux symptoms sufficient to impair quality of life, or risk of long term complications. This definition emphasizes that gastroesophageal reflux becomes a disease when it either causes macroscopic damage to the esophageal mucosa or affects quality of life due to symptoms or complications. The disease can be manifested by typical and atypical symptoms and can lead to esophageal mucosal injury in approximately 50 % of affected patients (2). The precise prevalence of GERD is unknown, one systematic review (3) identified 31 articles that assessed the prevalence of heartburn in the community, reporting on a total of 77 671 patients. In western populations, 25% of people report having heartburn at least once a month, 12% at least once a week and 5% describe daily symptoms. In East Asia the prevalence of heartburn is lower with 11% reporting heartburn at least once a month, 4% weekly and 2 % daily (4). There is a lack of information about the prevalence of heartburn in other geographical regions, but symptoms of GERD are less common in non-western populations (5). Recent population-based studies revealed a 15-31% overall prevalence of GERD in Europe (6-8).

The basic pathophysiologic abnormality in this disease is the increased esophageal exposure to gastric juice, which may result from three major known causes. The first is a mechanically defective lower esophageal sphincter (LES), which is present in approximately 60% of patients with GERD (9). Incompetence of the LES can be caused by inadequate pressure, overall length, or abdominal length (i.e. the portion exposed to the positive pressure environment of the abdomen measured

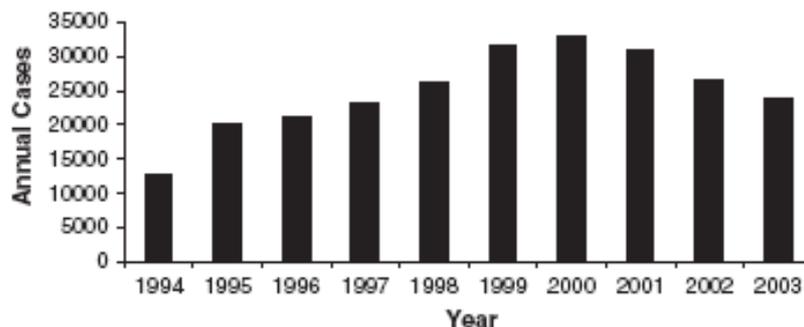
on manometry). The probability of abnormal acid reflux is 69-76% if one component of the sphincter is abnormal, 65-88% if two components are abnormal, and 92% if all three components are abnormal. The second cause of abnormal esophageal acid exposure is inefficient esophageal clearance of refluxed material (10). This can result in an abnormal gastroesophageal reflux in individuals who have a mechanically intact LES and normal gastric function by the failure to clear physiologic reflux. The four factors important in esophageal clearance are gravity, esophageal motor activity, salivation, and anchorage of the distal esophagus in the abdomen. Gastric abnormalities as the third cause, that increase esophageal exposure to gastric juice includes gastric dilatation, increased intragastric pressure, persistent gastric reservoir and increased gastric acid secretion. The effect of gastric dilatation is to shorten the overall length of the LES resulting a decrease in sphincter resistance to reflux. Increased intragastric pressure occurs in patients with outlet obstruction due to scarred pylorus or duodenum or after vagotomy. The persistence of gastric reservoir results from delayed gastric emptying secondary to myogenic abnormalities such as is seen in patients with advanced diabetes, diffuse neuromuscular disorders or post-viral infections. Gastric hypersecretion can increase esophageal exposure to gastric juice by physiologic reflux of large amounts of concentrated acid. The relative contributions of each of these components of the antireflux mechanism to increase esophageal exposure to gastric juice should be determined prior considering specific therapy for this disease. The identification of a defective LES as the cause of abnormal esophageal acid exposure is important because it is the only causative factor that antireflux surgery is designed to correct. The other two causes (i.e. inefficient esophageal clearance and abnormalities of gastric reservoir) cannot be corrected by an antireflux procedure.

The first ever antireflux operation was published by Rudolf Nissen in 1956 with the title: „a simple surgical technique to influence reflux esophagitis” (11). Before that in 1936 Rudolf Nissen performed an operation on a patient with esophageal ulcer. The ulcer was resected and the fundus was used to cover the esophageal suture. 15 years after the

operation Nissen had the opportunity to examine this patient once more and he observed that the esophageal ulcer was completely diminished. Therefore he performed two further cases of fundoplication, which was published in 1956. Later this so called Nissen fundoplication was performed on several hundred patients in Europe and in the USA for more than two decades. Unfortunately this relatively long and tight fundoplication often caused several side effects such as dysphagia, gas-bloat and dumping syndromes. In order to reduce these dramatic side effects several attempts were made. One was the use of a partial wrap such Toupet or Belsey published (12,13). The other concept was developed from surgeons from Chicago such as Bombeck, Donahue and DeMeester. In 1977 Donahue et al.(14) published the „short floppy Nissen” which offered an effective surgical treatment for GERD. Reflux symptoms were immediately improved with 70-90% good results reported at up to 20 years after surgery (15-19). Because of mortality rate up to 1,4% and morbidity of 12% for the open procedure, H2R antagonists or proton pump inhibitors remained the preferred treatment (20-22). In 1991 Dallemagne et al. (23) published their initial experience with laparoscopic Nissen fundoplication. The initial operative outcome of laparoscopic approach was similar to that open procedure, but mortality and morbidity were less than 0,2% and 5% respectively (24). Since its introduction in 1991 the number of performed laparoscopic Nissen fundoplication has risen significantly and become the most widely applied antireflux procedure. Data from the USA showed that in 1994, the annual rate of surgical fundoplication was 4.4/100,000 patients with less than 1% of operations performed by way of laparoscopy. By 1997, 12/100,000 patients underwent fundoplication, and 64% of these procedures were laparoscopic (25). In 1999, 87 of every 100,000 hospital discharges were due to laparoscopic antireflux operation (26). Bálint et al. showed that in a Hungarian university hospital the number of antireflux operation between 1990 and 1994 were 24. A nearly three times increased was observed in the number of antireflux operation during 1995 and 1999 (27). The best outcomes, with 5-year or longer follow-up after Nissen fundoplication report, patient satisfactions of 86% to

96%, making the laparoscopic Nissen fundoplication the gold standard for antireflux procedures (28-36).

Recently laparoscopic fundoplication has been called into question (37-39). The rate of failure following fundoplication for gastroesophageal reflux disease (GERD) varies from 2%–30%, depending on how “failure” is defined; for example, failure requiring resumption of medical therapy versus failure requiring reoperation. Approximately, 5% to 17% of patients will have objective evidence of failure with pathologic reflux with or without continued reflux symptoms (40-42), and nearly 5% to 10% of these patients will face revisional antireflux surgery (43,44). Beside these failure rates and a possible need for reoperation, several other factors may have dampened enthusiasm for antireflux surgery. These that may have reduced patient referrals to surgeons for antireflux surgery include the availability of over-the-counter proton pump inhibitors since 2003 and new endoscopic therapies for treating gastroesophageal reflux. A recent study from the USA showed a 30% decline of antireflux operation from 1999 to 2003 (Figure.1) (45).



**Figure 1.** Annual number of antireflux surgery procedures performed in the United States, based on data from the Nationwide Inpatient Sample, 1994 to 2003. (Finks JF, Wei Y, Birkmeyer JD. The rise and fall of antireflux surgery in the United States. *Surg Endosc.* 2006;20:1698-1701)

## **2. Results and outcome of laparoscopic antireflux surgery**

### **2.1. Patients and methods**

#### *Study population*

From January 1998 to December 2006, 241 patients with GERD underwent a laparoscopic Nissen fundoplication in the Department of Surgery Medical Faculty University of Pécs. There were 140 women and 101 men with a mean age of 48,7 years (range 18-80). Before the operation all patients underwent our routine functional foregut investigations, which contain barium X-ray esophagogram, endoscopy with biopsies from the distal esophagus, stationary water perfusion manometry and 24-hour esophageal pH monitoring. In selected cases 24-hour Bilitec (bilirubin monitoring) was also performed.

#### *Esophageal Manometry*

Medication that could affect esophageal motility was stopped at least 48 hours in advance. Manometry was performed using a water-perfused system (perfusion manometry and portable data recording system, Medtronic, Sweden) with a multiple-lumen catheter with 5 measurement points with 0,8 mm opening, located 5 cm apart. A pneumohydraulic pump was used for perfusion with distilled water at a rate of 0.5 mL/min. The catheter was introduced transnasally into the stomach. Then, the catheter was retracted to determine the distal and proximal margin of the lower esophageal sphincter. The mean end-expiratory LES pressure, length (overall, intraabdominal) of the LES, and LES relaxation were determined. Intraluminal esophageal pressures were recorded at 5, 10, and 15 cm above the upper margin of the LES. The manometric response to 10 standardized wet swallows (5-mL water bolus) was recorded. Mean amplitude and duration of the esophageal contractions in response to the wet swallows were determined.

#### *24-hour esophageal pH monitoring*

All medicaments which interfere with acid production were discontinued two weeks before the measurement. After an overnight fast

24-hour esophageal pH monitoring was performed (portable pH recording system, Medtronic, Sweden) by placing an antimony multi-use electrode 5 cm above the upper border of the manometrically determined LES. After 24 hours of measurement the probe was removed and data was downloaded into a computer and analyzed using a commercial software (Polygram, Medtronic, Sweden). DeMeester score was used to define the esophageal acid exposure.

#### *24-hour Bilitec monitoring*

In selected cases where duodenogastric or duodeno-gastroesophageal reflux was suspected long term bilirubin monitoring of the esophagus or stomach was performed. After an overnight fast 24-hour bilirubin monitoring was performed by placing the probe in the stomach 5 cm below the lower border or in the esophagus 5 cm above the upper border of the LES which was defined earlier by manometry. Calibration of the probes was performed before and after the measurement. Bilirubin monitoring (Bilitec 2000, Medtronic, Sweden) was performed and analyzed by a commercial software (Polygram NET, Medtronic, Sweden). Patients were asked to eat three meals and were provided with a diary for intake of food and drink to avoid artefacts and interference with bilirubin absorbance spectra.

#### *Surgical procedure*

In all patients a floppy Nissen-DeMeester fundoplication was performed. Patient is placed in the lithotomic position. Pneumoperitoneum of 13-15 mmHg is created inserting a Veres needle above the umbilicus at approximately one third of the line connecting the navel and the xyphoid cartilage. A 10 mm trocar is placed at this site for the 30° telescope. The other trocars are then inserted under direct visual control. A 10 mm trocar for the liver retractor is placed in the right anterior axillary line, a 5 mm trocar for an atraumatic grasper in the midclavicular line under the costal margin and two further 10 mm trocars under the left costal margin, one in the midclavicular line for dissection and one in the anterior axillary line for an additional atraumatic grasper or later, at the changed position, for the

camera. As soon as all instruments are in position, and the left liver lobe is retracted upwards the hiatal hernia can be visualized. After identifying the hernia the upper portion of the stomach is pulled back to the abdomen and the gastric fundus is mobilized by dissecting the short gastric vessels and the detachment of the retrofundic area. After complete dissection of the fundus, the left crus is identified. The right crus is visualized after dividing the hepatogastric ligament above the hepatic branch of the vagal nerve. The peritoneal layer between the right crus and the gastroesophageal (GE) junction is split and the division of the peritoneum continues anteriorly, along the phrenoesophageal ligament to the left crus. The dissection is then extended posteriorly behind the GE junction. Once the crura are dissected the distal esophagus is mobilized in the lower mediastinum. The hiatus is then closed using non-absorbable single stitches, starting at the preaortic membrane. Finally the fundus was pulled through behind the esophagus and a 360 degree floppy fundoplication was performed with three single stitches. One of the stitches was also sutured to the muscle of esophagus to anchor the fundoplication. During the hiatoplasty and the fundoplication a 60 Ch bougie was inserted through the esophagus to prevent dysphagia.

#### *Postoperative management*

All patients were started on regular doses of antiemetic for the first 24 hours. No postoperative nasogastric decompression was used. A Gastrografin swallow was performed on postoperative day 1 to check wrap integrity, rule out leakage, and assess esophageal clearance. Patients were then started on a liquid diet. If they tolerated the liquids, solid food was allowed and they were discharged home on the 3rd postoperative day. Instructions were given to slowly change their intake from pureed to normal food over the ensuing 3 weeks. They were allowed to resume full activity on discharge. Patients were routinely examined in our gastrointestinal surgery outpatient department 6 weeks postoperatively, then again at 6 months, and thereafter at 1-year intervals. All patients were asked to undergo repeat barium esophagogram if they were free of symptoms. If any symptoms of dysphagia or recurrent reflux appeared

functional testing, including endoscopy, 24-hour pH recording and esophageal manometry was performed.

## **2.2. Results**

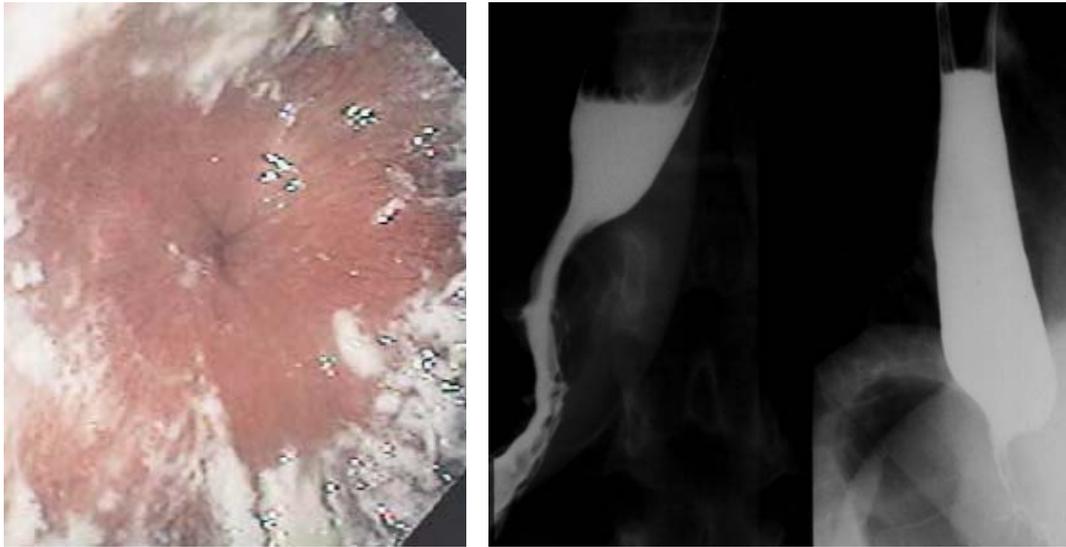
A total of 261 procedures were performed for 241 patients. Before the surgical intervention all patients had experienced symptoms of GERD and had tried a course of proton pump inhibitors (PPIs). These had been unsuccessful at curing symptoms, had not been tolerated, or had been discontinued when patients did not want to receive long-term medication. The principal presenting symptoms before the operation were heartburn (n = 180, 74,7%), regurgitation (n = 123, 51%), epigastric pain (n = 106, 43,9%), dysphagia (n = 31, 12,9%), and respiratory symptoms (n = 41, 17%). The mean duration of symptoms was 59,4 months (range, 1–396 months). Endoscopic findings showed that 58 (24,1%) of the 241 patients had no esophagitis, 65 (27%) had esophagitis Savary-Miller grade 1, 61 (25,3%) had grade 2, 30 (12,4%) had grade 3, and 27 (11,2%) had grade 4 esophagitis. Barrett's metaplasia was observed in 24 (9,9%) patients. The mean preoperative DeMeester score was 50,8 (range, 8,2–222,4), average LES pressure was 9,7 mmHg (range, 3,1-35 mmHg).

Major intraoperative complications occurred in 15 cases (6,2%). There were 6 bleeding, 1 injury of the spleen, 3 stomach and 5 esophageal perforations. 3 of the 5 esophageal perforation was identified only on the second, third and fifth postoperative day. (Table 1.) These complications were manifested by a rapid onset of tachycardia, pyrexia, and peritonism. Unfortunately Gastrografin swallows showed no sign of leakage. The patients were returned to the theater, and the perforation was repaired through a midline laparotomy. 2 of the 3 delayed reoperated patients died (0,82%). Conversion to laparotomy was performed in 13 (5,4%) of 241 patients. Indication for conversion was 6 bleeding, one splenectomy, 3 stomach and two esophageal perforation and one cardiopulmonary insufficiency due to pneumoperitoneum. Pneumothorax was observed in 11 patients, which was managed by a thoracic drainage. The average hospital stay was 6,4 days (range 3-16).

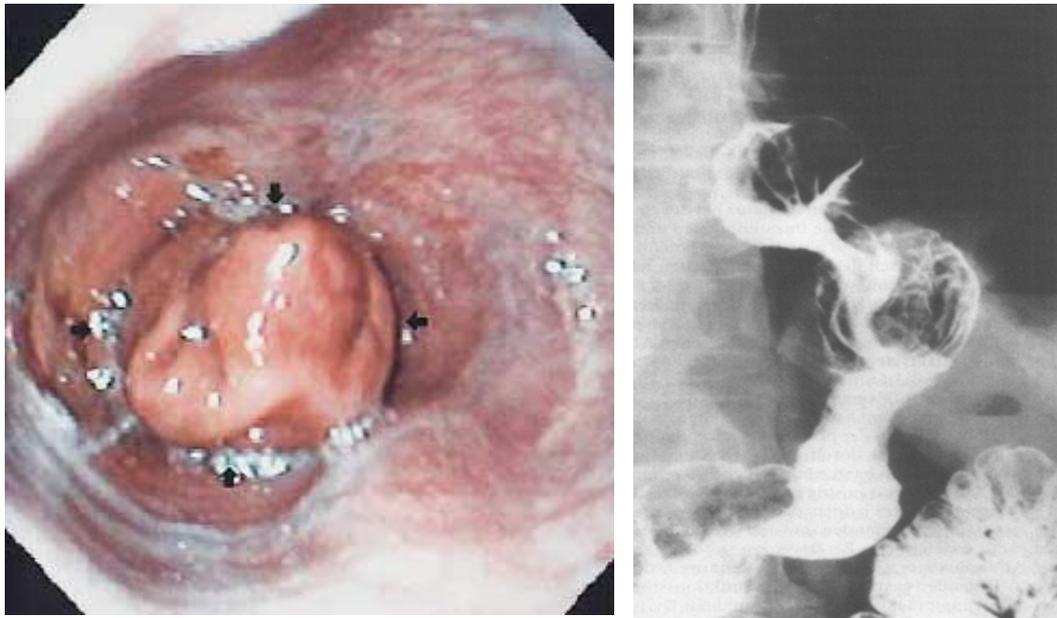
**Table.1.** Complications and conversions in the primary laparoscopic antireflux operation and the refundoplication group. \*In the redo group only 10 laparoscopic attempts were made from that 3 (30%) were converted to open procedure. All other reoperation was performed in n open fashion

|                        | Primary antireflux<br>(n=241) | Remedial antireflux<br>(n=30) |
|------------------------|-------------------------------|-------------------------------|
| Bleeding               | 6 (2,48%)                     | 0                             |
| Splenectomy            | 1 (0,41%)                     | 1 (3,3%)                      |
| Stomach perforation    | 3 (1,24%)                     | 3 (10%)                       |
| Esophageal perforation | 5 (2,07%)                     | 0                             |
| Overall complications  | 15 (6,2%)                     | 4 (13,3%)                     |
| Conversions            | 13 (5,4%)                     | 3*(30%)                       |

The mean postoperative follow-up was 48,5 months (range 2-107 months). From the 241 operated patients with GERD revisional surgery was necessary in 20 patient, which makes an overall failure rate of 8,3%. Indication for redo was therapy resistant dysphagia or recurrent reflux symptoms with objective evidence of failure with pathologic reflux on 24-hour esophageal pH monitoring. Reason for failure was dysphagia (Figure 2) in three (15%), slippage of the fundoplication on the stomach (“telescope phenomenon” Figure 3.) in three (15%), disruption of the wrap (Figure 4) in one (5%), paraesophageal hiatal hernia and disruption of the wrap in two (10%) and recurrent hiatal hernia (Figure 5) in 11 (55%) patients. In addition another 10 remedial operations were performed, in whom the primary fundoplication was performed by other hospitals. In all but one of these cases the cause for failure was a recurrent hiatal hernia. One patient had recurrent hiatal hernia with disruption of the wrap. This makes a 67% of overall failure rate due to recurrent hiatal hernia (Table 2).



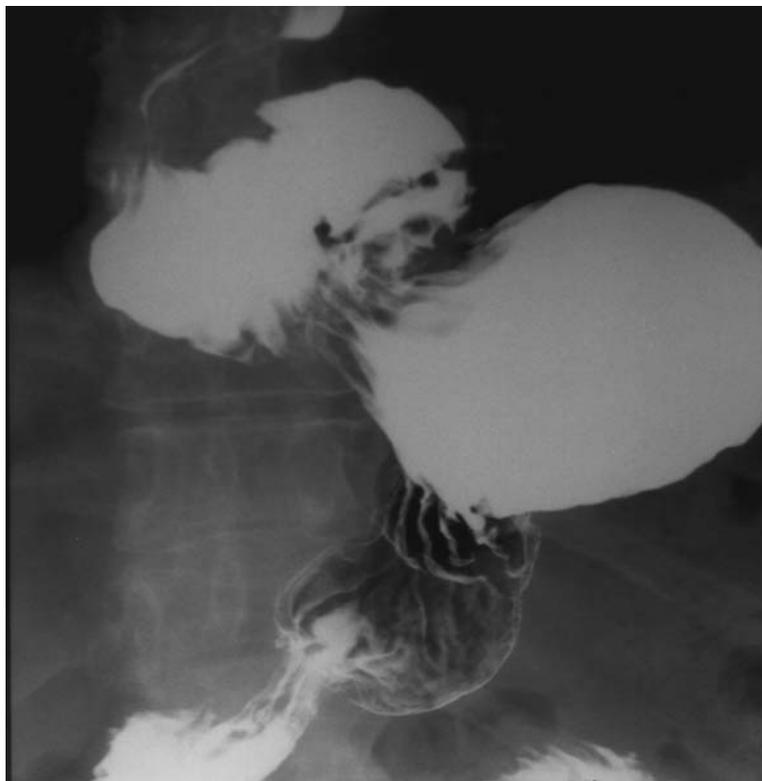
**Figure 2.** Dysphagia caused by a too tight wrap



**Figure 3.** Telescope phenomenon



**Figure 4.** Disruption of the wrap shown by esophagogram



**Figure 5.** Recurrent hiatal hernia after laparoscopic fundoplication.

**Table 2.** Reason for failure in patients who underwent remedial surgery

|   | Own patients | Patients operated elsewhere | All redo patients |
|---|--------------|-----------------------------|-------------------|
| Patients number                           | 20           | 10                          | 30                |
| Dysphagia                                 | 3 (15%)      | 0                           | 3 (10%)           |
| Fundoplication slippage into the stomach  | 3 (15%)      | 0                           | 3 (10%)           |
| Wrap dysruption                           | 1 (5%)       | 0                           | 1 (3,3%)          |
| Paraesophageal hernia and wrap disruption | 2 (10%)      | 1 (10%)                     | 3 (10%)           |
| Recurrent hiatal hernia                   | 11 (55%)     | 9 (90%)                     | 20 (66,7%)        |

In our series patients with revisional fundoplication were presented between 3 and 83 months (mean 23,4) after their initial operation. 7 redo fundoplications were completed laparoscopically, 3 were converted to laparotomy, 7 were open fundoplication and 3 were performed through a thoracotomy. Intraoperative complication occurred in 2 cases (10%) cases. There were 1 stomach perforation and one delayed splenectomy due to left subdiaphragmatic abscess. From all 30 patients with remedial surgery the complication rate was 13,3% with two additional gastric perforation. Both conversion rate and major intraoperative complications were significantly higher in the remedial surgery group, compared to primary laparoscopic antireflux patients (Table 1).

### **3. Factors predicting outcome of antireflux surgery**

#### **3.1. Introduction**

The surgical management of gastroesophageal reflux disease (GERD) has improved with a better understanding of the underlying pathophysiology of the disease and technical refinements of the antireflux repair (46). However, the failure rate of all antireflux procedures, both open and laparoscopic, is reported to be 10%, ranging from 3%–30% (46–51). The most common pattern of fundoplication failure is anatomical; this includes fundoplication disruption, crus closure failure, paraesophageal hernia formation, a slipped Nissen, and a too tight fundoplication (52,53). The purpose of this analysis was to objectively identify factors that predispose to antireflux surgical failure. In order to do so we investigated the correlation between various prognostic factors and failure of antireflux procedure. Failure was defined symptomatically and functional testing basis and requirement of remedial surgery. Those patients who required resumption of medical therapy without redo surgery were not identified as failed antireflux operation cases.

#### **3.2. Patients and methods**

A retrospective case-control study was completed to determine the influence of different factors on antireflux surgery failure by retrospectively analyzing the data accumulated prospectively before the primary antireflux procedure, regarding to our standard preoperative investigations. Twenty study cases that underwent reoperative antireflux surgery and 221 control group patients without clinical evidence of failure after primary antireflux surgery were compared. Our prospectively collected data was maintained on an Excel spreadsheet, and statistical analysis was performed using SpSS Version 13.0. All predictors, such as symptoms (regurgitation, heartburn, dysphagia, epigastric pain), presence of Barrett's metaplasia, supraesophageal symptoms, preoperative response to PPI, use of antidepressant medications and short esophagus on endoscopy were recorded as "Yes" or "No", except age, sex, onset of symptoms and the objective assessors of the disease severity, which included grade of

esophagitis, size of hernia, lower esophageal sphincter pressure and DeMeester score. The alpha level for the entire analysis was set at 0.05. The univariate analysis was performed using the Student *t* test and the chi-square test when appropriate.

### **3.3. Results**

#### *Baseline characteristics*

The two groups were comparable regarding to patients characteristics. In the study group the average age was 45,2 years (range 22-70) compared to a mean age of 49,4 years (range 18-80) in the control group ( $p=0,40$ ). There were 60% female in the case group, and 58% female in the control group ( $p=0,85$ ). The univariate analysis showed that age and gender have no role in the outcome of antireflux surgery.

#### *Symptoms*

Of the preoperative registered symptoms investigated none of them were found to be associated with failure of antireflux surgery. Although heartburn, regurgitation and epigastric pain were more frequent in the study group (90 % vs. 73%, 65% vs 49% and 45% vs. 43,9%) univariate analysis did not reached the level of significance ( $p=0,1$ ; 0,19; 0,92). Dysphagia were recorded only 5% of redo patients compared to 13,5% of the control group ( $p=0,27$ ). Respiratory symptoms were almost similar (15% vs. 17,2%) between the two groups. Analysis of the length of the symptoms also showed no significant difference ( $p=0,13$ ).

#### *Medications*

From medications, patients used before the operation, the daily usage of antipsychotic drugs (antidepressant or tranquillizer) and the response to PPI were investigated. We found that almost one quarter of the patients with GERD (24,5%) uses some kind of antipsychotic drug daily. In the study group this ratio was 40 % compared to 23 % in the control group, which was not a statistically significant difference ( $p=0,092$ ). Also the percentage of patients in the study group, who did not respond well to PPI, was higher (30%) compared to the control group (9%). This

difference was statistically significant ( $p=0,004$ ), which means that no response to PPI has influence on the outcome of antireflux surgery. Univariate analysis of baseline characteristics, symptoms and medications are shown in Table 3.

**Table 3.** Baseline characteristics, symptoms and medication in the two groups

| <b>Factors</b>                      |                    | <b>Study group</b>   | <b>Control group</b> | <b>P value</b> |
|-------------------------------------|--------------------|----------------------|----------------------|----------------|
|                                     |                    | <b>Redo<br/>n=20</b> | <b>N=221</b>         |                |
| <b>Patients characteristics</b>     | Age (years)        | 45,2                 | 49,4                 | 0,40           |
|                                     | Male               | 8 (40%)              | 93 (42%)             | 0,85           |
|                                     | Female             | 12 (60%)             | 128 (58%)            |                |
| <b>Symptoms</b>                     | Heartburn          | 18 (90%)             | 162 (73%)            | 0,10           |
|                                     | Regurgitation      | 13 (65%)             | 110 (49%)            | 0,19           |
|                                     | Epigastric pain    | 9 (45%)              | 97 (43,9%)           | 0,92           |
|                                     | Dysphagia          | 1 (5%)               | 30 (13,5%)           | 0,27           |
|                                     | Respiratory        | 3 (15%)              | 38 (17,2%)           | 0,13           |
| Length of the the symptoms (months) |                    | 53,4                 | 60,1                 | 0,36           |
| <b>Medications</b>                  | Antipsychotics     | 8 (40%)              | 51 (23%)             | 0,092          |
|                                     | No response to PPI | 6 (30%)              | 20 (9%)              | 0,004*         |

### *Disease severity*

Endoscopic severity of esophagitis showed no significant difference between the two groups by univariate analysis. Comparison of all grades of esophagitis is shown in Table 4. The only factor from the endoscopic parameters, which had prognostic value by univariate analysis on the success of the antireflux surgery, was the esophageal shortening. Short esophagus described by the endoscopist was present 60% of the patients who later had failed antireflux procedure compared to 6,8 % of the patients who have no signs of failure (p=0,0001).

**Table 4.** Endoscopic findings in the failed and in the control group

| <b>Factors</b>          |                    | <b>Study group</b> | <b>Control group</b> | <b>P value</b> |
|-------------------------|--------------------|--------------------|----------------------|----------------|
|                         |                    | <b>Redo n=20</b>   | <b>N=221</b>         |                |
| <b>Disease severity</b> | NERD               | 4 (20%)            | 54 (24,4%)           | 0,65           |
|                         | Esophagitis Gr.I   | 4 (20%)            | 61 (27,6%)           | 0,46           |
|                         | Esophagitis Gr.II  | 5 (25%)            | 56 (25,3%)           | 0,97           |
|                         | Esophagitis Gr.III | 4 (20%)            | 26 (11,7%)           | 0,28           |
|                         | Esophagitis Gr.IV  | 3 (15%)            | 24 (11%)             | 0,57           |
|                         | Barrett metaplasia | 2 (10%)            | 22 (9,9%)            | 0,99           |
|                         | Short esophagus    | 12 (60%)           | 15 (6,8%)            | 0,0001*        |

### *Functional tests*

From the routinely used esophageal functional tests, DeMeester score, LES pressure and motility disorders of the esophageal body were investigated. The latter was defined if any problem with the amplitude, velocity or propagation of a swallow wave was observed on manometry. Although more severe reflux on pH monitoring was recorded in the study

group (mean DeMeester score: 51,1 vs. 48,7) and the LES pressure was also lower (11,2 mmHg vs. 13,5), none of these factors reached the statistical significance ( $p=0,94$ ;  $p=0,60$  respectively) to be related to surgical failure. Esophageal body motility disturbances had no influence on outcome of laparoscopic antireflux surgery ( $p=0,67$ ).

### *Hiatal hernia*

Because we found that the most common reason for failure is a recurrent hiatal hernia this factor was examined in details. Regardless of hernia size, hiatal hernia is not a predictive factor on outcome of the antireflux surgery ( $p=0,83$ ). Although the percentage of patients with a hiatal hernia preoperatively was almost the same in the two groups (57,5 % vs. 55%), the percentage of patients with hernia of more than 3 cm in size was significantly higher in the study group ( $p=0,007$ ). We found that patients with preoperative hiatal hernias greater than 3 cm were significantly associated with failure after antireflux surgery. Assessment of functional tests and hiatal hernia is shown in Table 5.

**Table 5.** Manometrical and pH monitoring data and the effect of hiatal hernia size on outcome

| <b>Factors</b>          |                    | <b>Study group</b> | <b>Control group</b> | <b>P value</b> |
|-------------------------|--------------------|--------------------|----------------------|----------------|
|                         |                    | <b>Redo n=20</b>   | <b>N=221</b>         |                |
| <b>Functional tests</b> | LES pressure mmHg  | 11,2               | 13,5                 | 0,60           |
|                         | Motility disorders | 3 (15%)            | 26 (11,7%)           | 0,67           |
|                         | DeMeester score    | 51,1               | 48,7                 | 0,94           |
| <b>Hiatal hernia</b>    | Any size           | 11 (55%)           | 127 (57,5%)          | 0,83           |
|                         | Greater than 3 cm  | 10 (50 %)          | 50 (22,7%)           | 0,007*         |

### **3.4. Discussion**

Successful antireflux surgery is largely defined by two factors: achieving long-term relief of reflux symptoms and the absence of complications or complaints induced by the operation. In practice, achieving these two deceptively simple goals is difficult. Both are critically dependent on establishing that the symptoms for which the operation is performed are due to abnormal esophageal exposure to gastric juice, as well as the proper performance of the appropriate antireflux procedure. All of the patients in this study underwent an antireflux procedure which was performed in a standardized manner by two surgeons, from the same unit. As such, whether the technical performance of the procedure affects the outcome, was not part of the study. Rather clinical variables predicting failure of antireflux operation were determined. In order to do so we compared a study group (failed antireflux operation) to a group of control patients without any evidence of an unsuccessful antireflux operation. Failure was defined when patients had therapy resistant dysphagia or recurrent reflux symptoms with objective evidence of abnormal esophageal acid exposure on esophageal pH monitoring or recurrent hiatal hernia on esophagogram. We used this definition because the reflux symptoms after antireflux surgery or the usage of PPIs are poor indicators for failure (54-56). Furthermore a study from Szendrőnyi et al showed a significant correlation between hiatal hernia, abnormal acid reflux on pH monitoring and symptoms. They found no correlation regarding reflux symptoms, manometry and signs of esophagitis on endoscopy (57).

Regarding to the baseline characteristics of the patients (age and gender) we did not find significant differences between the two groups. Similar to our result most of the studies on predictive factors contributing to failure of laparoscopic antireflux operation showed no association of age and gender to failure (58-61). In contrast to that some publications (62,63) stated that younger male patients with typical symptoms had favorable outcome after antireflux operation.

From symptoms we were not able to draw any correlation between the symptoms (heartburn, regurgitation, epigastric pain, dysphagia and respiratory symptoms) and the failure rate following antireflux procedure. On the other hand symptoms responding to PPI therapy found to be a predictive factor. We found that those patients who did not respond to PPI had significantly more chance for failure. Although this finding is for a long supported by other publications (59,61,62), some stated that poor response to PPI is not a contraindication for laparoscopic antireflux operation (64).

Other medications which often used in GERD are the drugs for psychiatric problems. A relationship between psychological factors and GERD is widely accepted in anecdotal form but sparsely documented in the medical literature. Watson et al. (65) first showed that antireflux surgery is less satisfactory among patients with personality disorders. Since that several studies published data, that patients who daily use some kind of antidepressant had significantly poorer outcome after antireflux surgery than those without any psychologic disorders (61,66,67). In our study we did find that 40 % of the patients who later had failure were on antipsychotics therapy, compared to 23 % of the control group, but this difference was not statistically significant. But before patients with psychiatric disorders would be excluded from laparoscopic antireflux operations there is a study from Kamolz et al. (68) who showed that quality of life of these patients was improved after antireflux operation and even panic disorders was eliminated in one third of their patients.

Beside quality of life improvement it is known that laparoscopic antireflux surgery can achieve an excellent surgical outcome in patients with erosive gastroesophageal reflux disease. Less is known about the long-term surgical outcome in GERD patients who have no evidence of esophagitis (NERD) before surgery. It is also known that approximately 40-60 % of GERD patients have no signs of esophagitis on endoscopy (69-73). From our 241 patients 58 (24,1%) presented with NERD. Comparing the failed and successful groups of patients we found that NERD had no effect on the outcome of antireflux surgery. In accordance to our finding several other publications (74-77) showed that NERD is not

a predictive factor for failure. From these studies one can also see, that grade of the esophagitis has no role in the unsuccessful antireflux operation. Regarding to the disease severity on endoscopic finding, we also did not find any correlation between the endoscopic grading and the failure rate. In contrast one recent study from Thibault (78) showed the patients with NERD had poorer outcome after antireflux surgery compared to those with endoscopic esophagitis. It was interesting to see that not only the grade of esophagitis, but Barrett metaplasia has also no effect on outcome. This finding was confirmed by others as well (79-81). The only significant predictive factor for failure we found amongst the endoscopic signs was the shortening of the esophagus. The short esophagus is still a big debate between laparoscopic antireflux surgeons, because some believes that it does not exist (82-84), while on the other hand others think that the unrecognized short esophagus can be responsible for failure of the antireflux operation in some proportion of the patients (85,86). The term "short esophagus" itself can be confusing, because a concrete and consistent definition has not been set. Horvath et al. (87) categorize the short esophagus into three categories: (1) true, reducible; (2) true, nonreducible; and (3) apparent. An apparent short esophagus is one of normal length that has accorded within the chest and thus appears short before proper mobilization. A true, reducible short esophagus is shorter in length although reduction of the gastroesophageal junction to 2.5 cm below the hiatus is still possible. Only the true, nonreducible short esophagus requires a lengthening procedure. Acquired shortening of the esophagus is thought to arise from a cycle of repetitive esophagitis, and submucosal fibrosis, which leads to subsequent shortening (88). A study by Awad and colleagues (89) demonstrated that patients with reflux have an average esophageal length 5mm shorter than that in normal control patients, although the amount of shortening was not influenced significantly by the degree of esophagitis. According to the advocates of short esophagus, esophageal shortening occurs with advanced GERD and the increasingly severe endoscopic grades of esophagitis should be associated with a shorter esophageal length, but most studies, have not supported this (89,90). Our study showed that esophageal shortening was

almost 10 times more frequent in the failure group but on the other hand the same degree of association of the severity of the esophagitis and failure was not detectable. Whether patients in the failure group indeed had an unrecognized true short esophagus or the dissection was not sufficient enough remain unclear, but these results is a warning, that greater attention is necessary in patients with short esophagus. The short esophagus can be determined by barium X-ray, endoscopy, intraoperatively during laparoscopy or with manometry.

Although manometry as a part of the functional foregut investigations together with esophageal pH monitoring play an important role in the proper diagnosis of GERD it has little predictive value for failure. The preoperative LES pressure has no effect on outcome after laparoscopic antireflux surgery (91,92), which was also shown by our study. Regarding to esophageal body motility disorders one can think that by making a fundoplication, which causes somehow a kind of outlet obstruction, can worsen the already existing motility problems, causing a severe dysphagia for the patients. Therefore some authors tried to tailor the fundoplication to the manometric finding (93,94), but several study, including ours, showed that motility disorders has no effect on outcome after Nissen fundoplication (95-100). Whether the praeoperatively registered abnormal esophageal acid exposure has any impact on success rate after antireflux operation is still questionable. Some published that, patients with more severe gastroesophageal reflux on 24-hour pH monitoring has superior outcome compared to those without abnormal acid exposure (59,61,101), but one recent publication (102) showed that reflux variables is of no value in predicting outcome. Similar to the latter paper we also did not find any correlation between the esophageal pH monitoring data and the failure of our laparoscopic Nissen fundoplication.

From the failed antireflux operation we know that the most frequent reason for failure is the recurrent hiatal hernia. Hiatal hernia itself regardless of size was not a significant predictor of an unsuccessful antireflux operation. Indeed there were more patients with hiatal hernia in the control group than in the study group. But if we look carefully the size

of the hiatal hernia plays an important role on the outcome after laparoscopic antireflux procedures. If hernia size was taken into account, we found that hiatal hernia bigger than 3 cm is a significant prognostic factor on outcome. Similar to our result Power et al (61) also showed that if the hiatal hernia is larger than 3 cm it carries a significant risk for failure after laparoscopic Nissen fundoplication.

### **3.5. Conclusion**

From the several factors investigated only three had effect on the outcome of laparoscopic Nissen fundoplication by univariate analysis. We found that large hiatal hernia and short esophagus can predict a possible failure after laparoscopic fundoplication and patients who had no response to PPI are also at greater risk for failure. All other factors (i.e age, gender, symptoms, endoscopic severity of esophagitis, functional tests results) had no influence on the outcome of laparoscopic Nissen fundoplication.

## **4. Special aspects of gastroesophageal reflux disease**

### **4.1. Hypertensive conditions of the lower esophageal sphincter**

It is well known that one of the most important factors in the pathogenesis of gastroesophageal reflux disease is the insufficient pressure of lower esophageal sphincter (LES). This can be due to an inadequate overall or intraabdominal length of the sphincter and/or hypotension of LES. Although the association between GERD and hypertensive conditions of lower esophageal sphincter has always seemed paradoxical, several studies reported that such conditions (i.e Hypertensive lower esophageal sphincter, Achalasia) can be accompanied with GERD. Both achalasia and hypertensive lower esophageal sphincter (HLES) is characterized with elevated lower esophageal sphincter pressure. The difference between the two diseases is the capability of the LES to relax. In HLES there are no esophageal body motility disturbances and relaxation of the LES is normal, while in achalasia the loss of inhibitory neurons of the LES resulting in an incomplete relaxation of LES during swallow. The normal peristaltic activity of the esophageal body disappears, or simultaneous wave forms are generated by the initiation of a swallow. The exact cause of both achalasia and HLES is still unknown.

#### **4.1.1. Hypertensive lower esophageal sphincter**

HLES was first described by Code et al in 1960 (103). It is classified as a primary esophageal motility disorder and characterized by a high resting pressure of LES, which exceeds the upper limit of LES pressure measured in normal population. It is distinguished from diffuse esophageal spasm and achalasia, which also presented with elevated pressure of LES, by normal esophageal body motility and LES relaxation. The most common symptoms in patients with HLES are dysphagia and chest pain (104-106), and therefore, therapy was mostly focused on decreasing the pressure of LES by surgical or medical means. Recent reports showed that HLES can also be associated with symptoms of GERD and abnormal esophageal acid exposure, measured by 24-h pH monitoring (107,108). Therefore, therapy recommendation for reducing sphincter pressure raises

questions of worsening gastroesophageal acid reflux. On the other hand, therapy for abnormal acid exposure with a fundoplication carries a possible risk of more severe obstructive symptoms. Our very first patient with HLES had abnormal gastroesophageal acid reflux on pH monitoring with typical symptoms of GERD. We performed a laparoscopic cardiomyotomy with Dor fundoplication. One year later, reflux symptoms of the patient worsened, and abnormal esophageal acid exposure on pH monitoring remained. A revisional Nissen fundoplication then had to be performed. This experience led us to perform a prospective study on patients with HLES associated with GERD to evaluate the effect of laparoscopic fundoplication.

#### **4.1.1.1. Patients and methods**

##### *Overall Patients' Characteristics*

Between January 1999 and 2006, a total of 241 patients underwent laparoscopic fundoplication for GERD. Out of them, six patients had GERD associated with HLES. Inclusion criteria were HLES detected by stationary manometry and typical symptoms of GERD. Patients with achalasia or other esophageal motility disorders were excluded. All patients underwent endoscopy, 24-h esophageal pH monitoring, stationary esophageal manometry, and barium swallow as well. There was no disturbance in esophageal clearance on barium X-ray. Out of the six patients who entered the study, there were five women and one man with a mean age of 40.5 years (range 19–74). Four patients had endoscopic signs of esophagitis and 3 presented with a hiatal hernia. In all patients, laparoscopic floppy Nissen fundoplication was performed. No intra- and perioperative morbidity was observed. There was no mortality. Patients were first called back for manometry and 24-h pH monitoring 6 weeks after the operation. Then, they were yearly followed by symptom questionnaire and barium swallows. At later follow-ups, patients who agreed underwent 24-h esophageal pH monitoring and stationary esophageal manometry. The mean follow up time was 56 months (range 50–61). At late follow-up, only two patients agreed to undergo functional testing.

#### *Stationary esophageal manometry*

Esophageal manometry was performed with a water perfused catheter system (perfusion manometry and portable data recording system, Medtronic, Sweden). HLES was defined if the pressure of LES was above 35 mmHg (>95 th percentile of normal population), relaxation of LES was normal and no esophageal body motility disorder was present.

#### *24-h esophageal pH monitoring*

Esophageal pH monitoring was performed as described earlier.

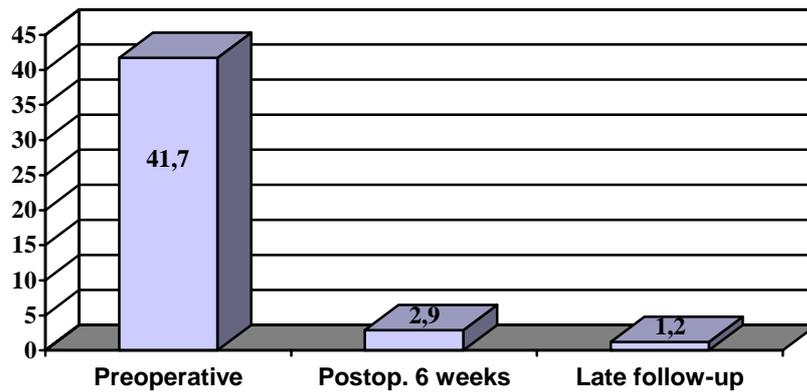
#### *Symptom assessment*

Symptoms were assessed by one of the surgeons. A structured questionnaire for foregut symptoms was performed. Patients with HLES were included only if three major symptoms of GERD (regurgitation, heartburn, epigastric pain) were present. Dysphagia as minor symptom was no reason for exclusion.

### **4.1.1.2. Results**

#### *24-hour esophageal pH monitoring*

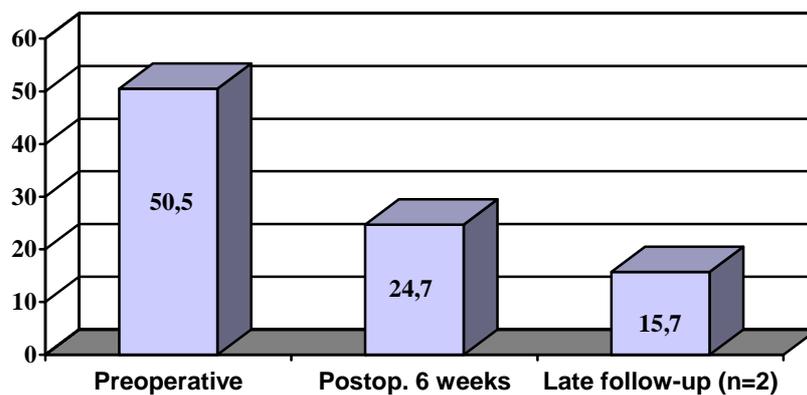
Before the operation the mean DeMeester score was 41,7 (range 16,7-86). Six weeks after surgery the score returned to a normal value of 2,9 (range 0,3-4,1). At late follow-up only two patients agreed to undergo 24-hour pH monitoring. The mean DeMeester score was 1,2 (Figure 6.).



**Figure 6.** Changes of the DeMeester score before and after laparoscopic fundoplication for patients with HLES

*Stationary esophageal manometry*

The mean pressure of LES was 50,55 mmHg (range 35,6 - 81,3) before surgery. After the operation the average LES pressure was 24,7 mmHg (range 23,2 - 26,6) at six weeks and 15,7 mmHg at late follow-up (Figure 7.).



**Figure 7.** Changes of the LES pressure (mmHg) before and after laparoscopic fundoplication for patients with HLES

## *Symptoms*

Besides major symptoms of reflux, two patients also had a slight dysphagia. Although the pressure of LES was higher in the two patients who had dysphagia besides their reflux symptoms, there was no significant difference regarding LES pressure (54.8 vs. 48.4) or DeMeester score (41.5 vs. 41.9) between the two patients with slight dysphagia and the other four without dysphagia. The only difference was that the two patients with dysphagia had the more severe esophagitis on endoscopy, and they both had a hiatal hernia. No chest pain was observed before the operation. Six weeks after the operation, all patients were symptom-free. No new onset dysphagia or chest pain developed in the first year of follow-up. The dysphagia, in the two patients who had minor dysphagia before the operation, was also resolved. One patient developed dysphagia 2 years after surgery. He needed a redo surgery. A laparoscopic exploration was performed. As a reason for dysphagia, a too tight posterior hiatoplasty was diagnosed, which was managed laparoscopically. No abnormality with the wrap was observed. After this remedial operation, the patient became symptom free. The annually performed symptom assessments revealed no recurrence of any of the three major reflux symptoms, and no further case of dysphagia was observed during the average of 56 months follow-up.

### **4.1.1.3. Discussion**

The etiology and pathophysiology of hypertensive lower esophageal sphincter are still unknown. It is thought to be a primary esophageal motility disorder characterized by elevated LES pressure and predominant symptoms of dysphagia and chest pain (109-111). A recent study from Gockel et al. (112) showed that typical reflux symptoms also frequently present in patients with HLES. They found a 75% of regurgitation and 71% of heartburn beside the 71% of dysphagia and 49% chest pain in HLES patients. Furthermore, 26% of the patients who also underwent 24-hour esophageal pH monitoring in this series presented with abnormal esophageal acid exposure. In our study, all patients had primary symptom of reflux and abnormal DeMeester score on 24-hour esophageal pH

monitoring, which is due to our patient selection. The reason for this selection was the hypothesis that abnormal esophageal acid reflux can cause an elevation in the pressure of LES to “protect” the esophagus mucosa from further acidic injury. This reaction of a sphincter muscle to acid is not an undescribed phenomenon. Reports on the association of GERD and Zenker diverticula with elevated upper esophageal sphincter pressure have been published (113,114). In some reports, even the connection between gastroesophageal reflux disease and achalasia was also suspected (115-117). Furthermore, Sullivan (118) reported that after small intravenous doses of pentagastrin increased the LES pressure in all of eight patients with epigastric pain, which was believed to be due to a HLES.

Unfortunately, surgical myotomy of these patients was unsuccessful. To investigate the hypothesis that GERD plays an important role of pathogenesis of HLES in a selected group of patients, a laparoscopic antireflux operation was performed. Criteria for selection were primary symptoms of GERD and HLES. Here, we have to mention that none of these six patients had severe dysphagia or chest pain. The treatment of HLES, whether it is associated with reflux symptoms or with dysphagia and chest pain, is still controversial. Because HLES believed to represent an outflow obstruction medical therapy has been limited to muscle relaxant such as calcium channel blockers or nitroglycerine with little clinical efficacy (119,120). Another possible treatment unfortunately with also similar disappointing result is the endoscopic management with dilatation or with botulinum toxin injection (121,122). Surgical therapy for outflow obstruction would be a cardiomyotomy. Before the study, we have performed a laparoscopic cardiomyotomy with a Dor fundoplication in a patient with GERD associated HLES. Reflux control was insufficient in this case, the patients had to be reoperated, and a total fundoplication had to be performed. On the other hand, Champion et al. (123) found that in 16 patients with HLES, esophagomyotomy with posterior partial fundoplication provides good result regarding to dysphagia or chest pain. During our study period, four classic hypertensive LES patients were also observed with dysphagia and chest pain. They are all on medical therapy,

and all underwent endoscopic pneumatic dilatations. One patient who did not respond to conservative therapy had laparoscopic myotomy and anterior fundoplication.

Accepting the possibility that HLES may have more than one etiology and HLES can be secondary to gastroesophageal reflux, antireflux therapy seems to be the choice of treatment. Katzka et al. (124) reported nine patients with HLES and GERD who were treated successfully with antireflux medication and further three with fundoplication. Similar to all of our GERD patients, all six patients with HLES were on PPI before the operation. They all had temporary or partial relief of their reflux symptoms, and therefore, we were not able to use the PPI test as a guide for which hypertensive LES patient might respond to fundoplication. We also found, similar to the study from Barreca (125), that after a laparoscopic fundoplication, patients were symptom-free, preoperative dysphagia resolved, and no new-onset dysphagia appeared. In accordance to our results, Tamhamkar et al. (126) showed that after a Nissen fundoplication in 12 patients with GERD-associated HLES, all patients had complete relief of their dysphagia and chest pain. In addition, in this series, four further patients with isolated HLES were successfully treated with myotomy and partial fundoplication. Unfortunately, results were based only on symptoms and patients satisfaction, and no functional testing was performed. In our series postoperative 24-hour esophageal pH monitoring and esophageal manometry was also performed. At a mean of 56 months follow-up, esophageal acid exposure and LES pressure were in a normal range, which is significantly different compared to the preoperative data. We found that by performing a 360° fundoplication, no new-onset dysphagia developed. Although a 60 Ch Bougie is inserted through the esophagus during the fundoplication, we do not believe that the bougie prevented early dysphagia in patients with HLES because we use the same technique for routine antireflux operations for GERD and still we observe approximately 10% of early temporary dysphagia 6 weeks after the operation. Instead, the originally high pressure of LES returned to a normal level. The latter finding seems to contradict the consideration that these HLES patients with GERD represent only GERD patients above the

95 percentile because normally, a fundoplication would elevate the pressure of LES as it was designed to do so.

A possible explanation of our findings is that some HLES is caused by acid reflux and this elevated pressure can be interpreted as a protective action of LES to hinder gastroesophageal reflux. By eliminating excessive esophageal acid exposure with a fundoplication, the protective reaction of LES is no longer needed, and the pressure of LES can return to a normal level.

#### **4.1.1.4. Conclusion**

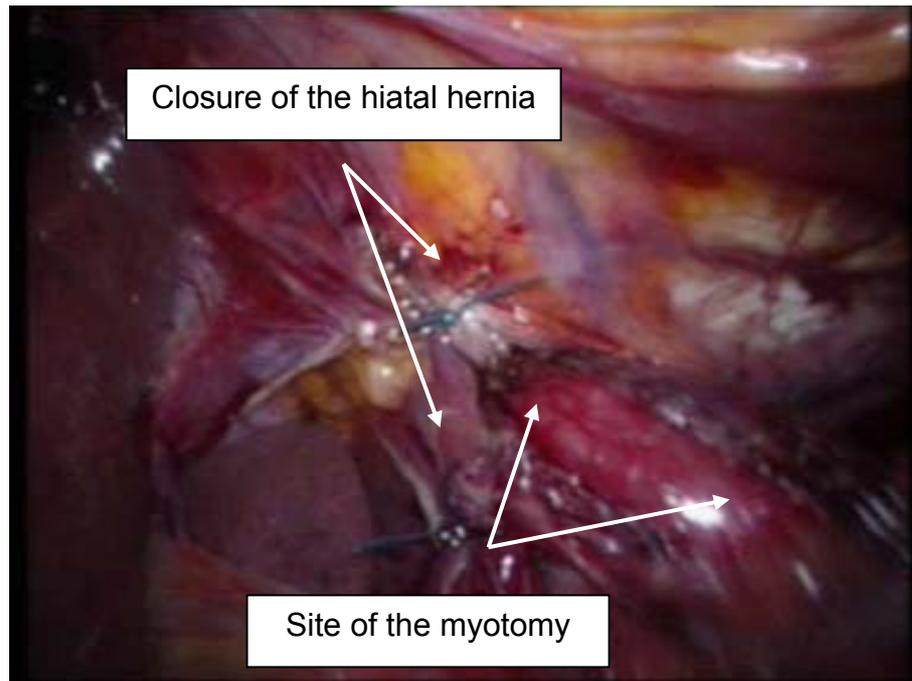
On the basis of our results, we must assume that there are two types of HLES. One is a primary esophageal motor disorder with symptoms of dysphagia and chest pain and with good response to myotomy. The other is the HLES, which is probably secondary to abnormal gastroesophageal acid exposure. In these patients, primary symptoms include typical symptoms of gastroesophageal reflux, and abnormal esophageal acid exposure can be observed on pH monitoring. Therefore, we suggest that in this subgroup of HLES patients, a 360° fundoplication should be performed instead of a cardiomyotomy, to control reflux and thereby eliminate the cause of HLES.

#### **4.1.2. Achalasia and gastroesophageal reflux disease**

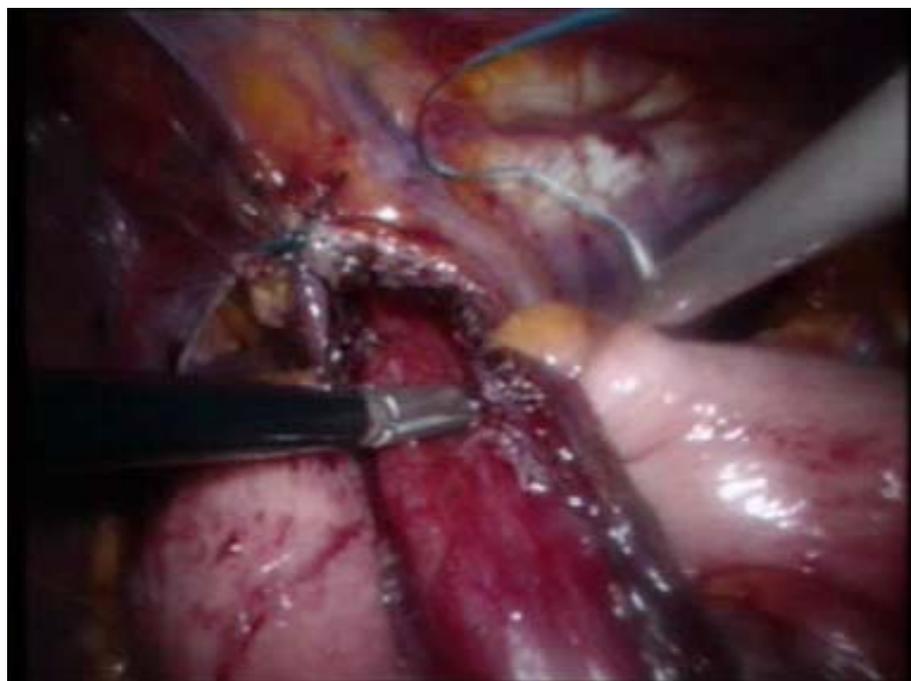
Achalasia is a primary motor disorder characterized by usually a hypertensive lower esophageal sphincter, which fails to relax completely after swallowing and by aperistalsis of the thoracic esophagus, (127-130) due to a loss of Auerbach's plexuses (129,130). Since the LES of achalasia patients is normo- or hypertensive and relaxation is absent or impaired, there is controversy whether gastroesophageal reflux can occur in these patients prior to treatment.

There are several prospective 24h pH studies which have shown, that untreated achalasia patients are capable of demonstrating true acid reflux (131-134). Heartburn was described in one third of patients with achalasia (132), furthermore esophagitis and Barrett's esophagus were also found in some patients (134,135) and some reports showed that the prevalence of hiatal hernia in achalasia patients varies between 4-10 % (136-139) which can be as high as 25 % in the elderly population (137). And not even axial but paraesophageal hiatal hernia is published with associated achalasia (140,141). It is still not clear whether two coincidental diseases (i.e. achalasia and GERD) are present or one disease can transform into the other.

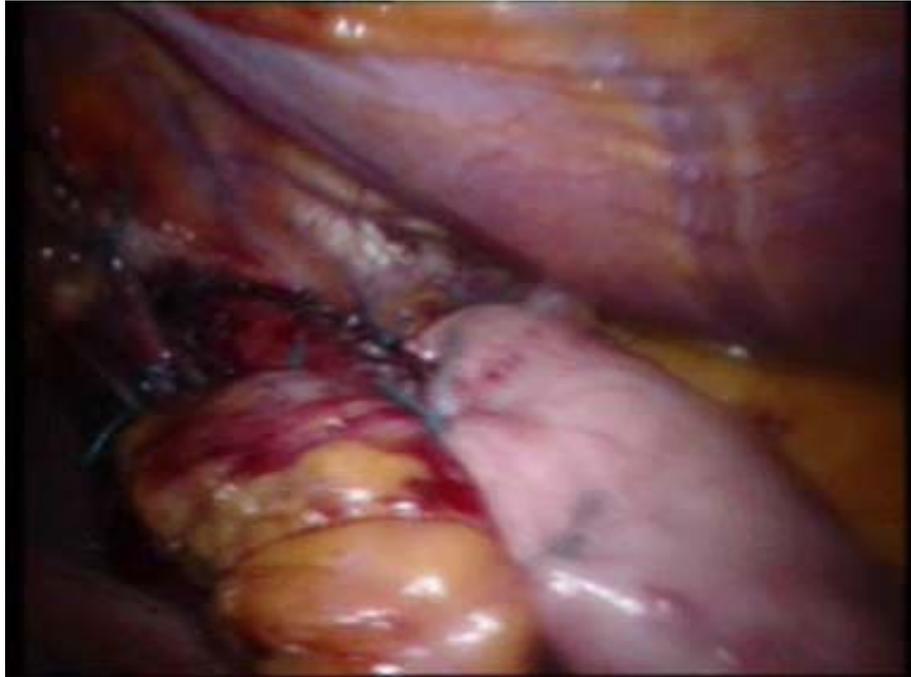
Since all treatment of achalasia is directed toward elimination of the outflow resistance to obtain a good esophageal emptying into the stomach one can assume that patients with GERD associated achalasia need different treatment because standard cardiomyotomy could worsen gastroesophageal reflux. In order to rule out this possibility we changed our therapeutic strategy in patients with GERD associated achalasia and instead of the routinely used laparoscopic Heller myotomy with anterior Dor fundoplication, we performed laparoscopic myotomy with 360 degree Nissen fundoplication. In the time interval 1998-2006 26 patients underwent laparoscopic surgery for achalasia. From them 3 patients had suspected gastroesophageal reflux associated achalasia and therefore they all underwent laparoscopic myotomy but instead of an anterior fundoplication, a 360 degree Nissen fundoplication was performed. Steps of the operation are shown in figure 8,9,10.



**Figure 8.** The hiatus is closed posteriorly and anteriorly. A cardiomyotomy is then performed



**Figure 9.** The mobilized fundus is pulled behind the esophagus and first sutured to the muscle of the esophagus



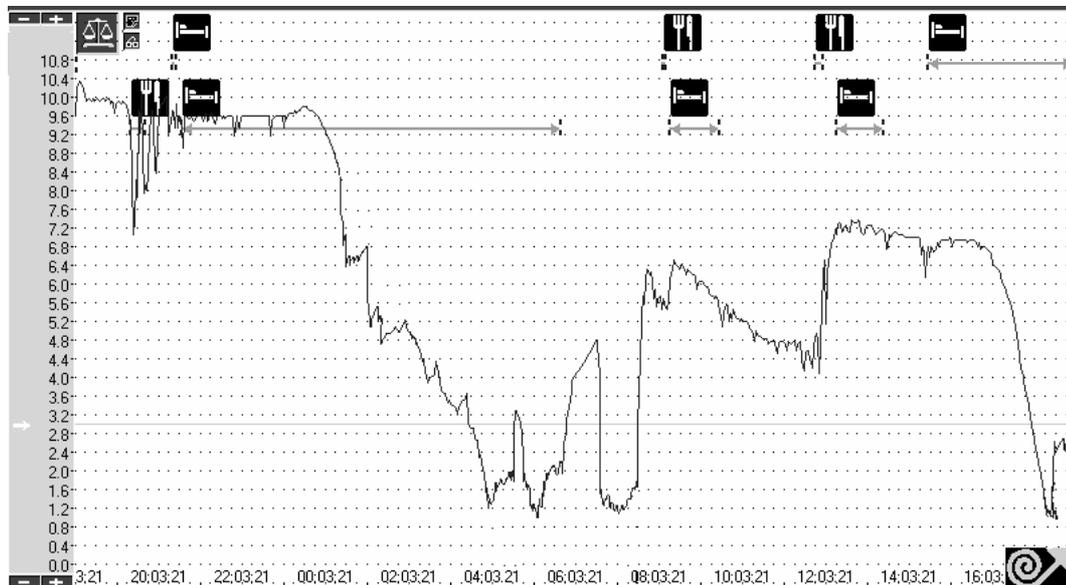
**Figure 10.** Finally a full fundoplication is performed, which covers the myotomy

#### **4.1.2.1. Case reports**

##### *Case 1.*

A 44-year-old male, with a two year history of classic heartburn and dysphagia, presented in February 1999. His heartburn and symptoms of gastroesophageal reflux started in 1997, heartburn was decreased after meal. These symptoms were transformed into dysphagia within a year. Symptoms were progressive over a 6-months period until dysphagia occurred with every meal when he stopped to eat and drank cold water. 15 kg-s weight loss was observed in this two year period. Esophagogastroscopy was performed in 1998, showing erosive esophagitis, inflammation was found in the squamocolumnar junction by histology as well. Patient was treated with lansoprazole 30 mg once a day and cisapride 10 mg three times daily resulting in improvement of the symptoms. Clinically, dysphagia progressed rapidly when reendoscopy was performed which revealed a dilated esophageal body with intact mucosa. Cardia was closed, but the endoscope could pass through the cardia

suspected to be fibrotic. Barium swallow showed dilated esophageal body with a short smoothly tapered segment at the esophagogastric junction, decreased peristalsis and retention of barium thought to be consistent with achalasia. Esophageal manometry demonstrated LES average resting pressure of 34.4 mm Hg. LES did not relax properly (relaxation < 90%). Deglutitory waves were of low amplitude and simultaneous, „mirror image” wave forms were generated by the initiation of a swallow. 24hr pH-metry showed acid reflux, with total DeMeester score of 94,9. Using pH 3 as a discriminant threshold for GERD the reflux score was: 62,3 (Figure 11).



**Figure 11.** pH recording of the patient with achalasia and GERD

Hypertrophy of the LES was found during operation, with the rigidity of the cardia. After a follow-up of 72 months the patient is symptom free. On esophagogram no signs of dysphagia or reflux were seen.

*Case 2.*

42-year-old man presented in September 2000 with the chief complaint of dysphagia. Symptoms were progressive over a four months period. He felt heartburn, regurgitation, gastroesophageal reflux was experienced the same time that was inhibited by on demand taking of H2 blocker, nizatidine (150 mg). Endoscopy revealed dilatation and atony of the esophageal body, closed cardia that did not open during the procedure. Mild inflammation was found in the distal portion of the esophagus, the instrument passed through the sphincter with an increased pressure. Barium swallow showed a slightly dilated esophageal body with nonpropulsive contractions, tight, nonrelaxing sphincter that allowed contrast material to escape in small quantities from the esophagus (Figure 12).



**Figure 12.** Esophagogram of the second patient.

Sequentially propagated waves transversing the distal esophageal body were absent, low amplitude simultaneous contraction waves were observed. Baseline pressure of the esophageal body was elevated. The resting pressure of the LES was not increased (24,4 mm Hg) however incomplete relaxation could be observed. 24 h pH-metry revealed nocturnal acid reflux that was not related to meal. Patient was last seen on follow-up 58 months after the operation. He had no dysphagia and a reflux symptom was also not recorded. Barium X-ray still showed some dilatated esophagus but no outflow obstruction was detected. Gastroesophageal reflux was not seen by esophagogram.

### Case 3.

A 65-year old woman was admitted to our clinic in 2003. She had a history of seven years of typical reflux symptoms with heartburn, regurgitation. No dysphagia was observed at that time. The first endoscopy was performed in 2001 where Savary-Miller II stage esophagitis was described with *Helicobacter pylori* infection from the stomach. Patient was put on PPI therapy and eradication of *H.pylori* was performed. Control endoscopy in 2002 showed no signs of esophagitis with normal cardia and stomach. Before the admittance the patient's reflux symptoms disappeared and dysphagia progressed. Endoscopy found esophageal dilatation, with esophagitis and the cardia was narrowed. Histology of biopsies from the distal esophagus showed chronic esophagitis and Barrett's metaplasia. Manometry and 24 hour pH monitoring was performed. The LES pressure was 34,3 mmHg with percent relaxation of 11,5. Esophageal motility showed that 25 % of the swallows was simultaneous and 75 % were uncoordinated with the mean pressure of 23,4 mmHg. At that time there was no abnormal acid reflux on pH monitoring. The first two follow-up of the patients was uneventful. No dysphagia or reflux was observed. At three years follow-up the patient was still symptom free, but esophagogram revealed a small amount of reflux in Trendelenburg position, without any signs of obstruction of the distal cardia. The patient was very satisfied with the result of the operation and

she did not agreed to undergo 24-hour pH monitoring, so she was advised to take PPI regularly.

#### **4.1.2.2. Discussion**

Achalasia is a rare primary motor disorder of unknown origin. The primary abnormality seems to be the degeneration of esophageal myenteric plexus causing the selective loss of inhibitory nitrinergic innervation of the LES (142). As myenteric neurones synthesizing nitric oxide are responsible for the inhibitory component of esophageal peristalsis and LES relaxation, it is considered likely that these neurons are involved in this disease. Data to support this come from histochemical, immunohistochemical, and biochemical studies (143,144). This degeneration is associated with an inflammatory infiltrate (predominantly T lymphocytes) of the myenteric plexus—providing evidence of an immune mediated destruction of the myenteric plexus (145,146). While potential etiologies proposed for achalasia include infection, genetic predisposition, spontaneous neurodegeneration, and others, autoimmune mediated ganglion destruction has gained support because serum from achalasia patients has been shown to contain antineuronal antibodies (147,148).

All of these changes cause a failure of the lower esophageal sphincter to completely relax upon swallowing, which results in a functional obstruction and pressurization of the esophageal body. Defective esophageal emptying progressively leads to dilatation of the esophagus with loss of the peristaltic waveform. Overall deterioration of esophageal function and structure with time, and the fact that peristalsis can return after surgical myotomy, suggest that the motor abnormalities secondary to esophageal outflow obstruction may be reversible and that early definitive treatment of achalasia is essential to preserve esophageal function (149). In about 40% of patients the diagnosis of achalasia is delayed by the reported symptoms of chest pain and heartburn simulating gastroesophageal reflux disease.

Because some studies reported that approximately 5-25% of untreated achalasia patients had abnormal esophageal acid exposure on pH monitoring (150-152) one can speculate that GERD could also be a

possible etiologic factor in the development of achalasia. This was first proposed by Smart et al. who (153) described five patients presenting with symptomatic gastroesophageal reflux, proven by radiologic studies or pH monitoring, who subsequently developed achalasia confirmed by radiology and manometry after an interval of 2 to 10 years. They concluded that gastroesophageal reflux do not protect against the subsequent development of achalasia and suggested that the autonomic nerve damage eventually leading to achalasia may in its initial phases cause gastroesophageal reflux. In order to investigate this possibility 3 patients with suspected GERD associated achalasia underwent a proper preoperative functional workup and laparoscopic Heller's myotomy followed by a Nissen fundoplication. An interesting observation from the two studies (132,152) on the issue of GERD and achalasia was that the pressure of LES was lower in patients with achalasia and GERD compared to pure achalasia patients. This is in accordance to our patients, while one patient had normal LES pressure and the other two had only a little elevated LES pressure with a value of approximately 35 mmHg. From these data one can speculate that there is a distinct population of achalasia patients presented with close to normal LES pressures, where GERD precedes the onset of achalasia. All of our three patients have had a longstanding gastroesophageal reflux before the development of achalasia. Interestingly pH studies of two of our patients showed prolonged reflux episodes appeared during night, when the patients were in recumbent position. Therefore we hypothesized that a transient complete relaxation of the LES caused acid regurgitation from the stomach, and poor clearance of the aperistaltic esophagus could be the origin of such prolonged acidification. This hypothesis is supported by the study of Hirano et al. (142) and Sifrim et al. (154) who demonstrated that transient lower esophageal sphincter relaxation can be observed in achalasia patients. Furthermore complete LES relaxation has been documented in a study from van Herwaarden et al. (155) postprandially during prolonged manometry, which may not have been detected in the short-term routine studies. Recently a paper from Savojardo et al. (156) also showed that multiple rapid swallows can induce complete LES relaxation in patients with achalasia.

On the other hand dysmotility (157,158) and esophageal distension can also cause heartburn (159,160), which can be indistinguishable from GERD. Pseudo-GER, caused by lactate accumulation from food fermented by *Lactobacillus* in the dilated esophagus (150) with or without esophagitis (161), may also cause heartburn. The pH of this fermented acid can be as low as 3,5 (162), and the onset of heartburn has been reported as occurring at pH 4. In our cases 2 patients had Sievert 2. stage of achalasia where no retained food can be observed in the esophagus. Neither esophagoscopy, nor barium X-ray found retained material in the esophagus of these two patients. Regarding to pH monitoring the use of pH 3 as a discriminant threshold was offered as a simple objective method to discriminate between acid reflux from food fermentation (150). Even if the lower threshold was used in those two patients (who had abnormal pH-metry), pH data were in the abnormal range.

The standard operation for achalasia is a cardiomyotomy with some kind of antireflux procedure, mostly anterior hemifundoplication. But even with an antireflux procedure reflux after Heller's myotomy can be observed approximately 10-30 % of the cases (163-165). The longest follow-up study from Csendes et al (166) with a mean follow-up of 190 months showed that final clinical results in 67 patients demonstrated excellent or good results in 73% of the cases, development of epidermoid carcinoma in 4.5%, and failures in 22.4% of the patients mainly due to reflux esophagitis. Furthermore 9 patients developed Barrett metaplasia. Question rises why some patients have reflux after Heller myotomy, while others haven't, if the same procedure was performed on them. So, one can speculate that reflux after Heller's myotomy is not a failure and does not happen as a random fate, because in the subgroup achalasia patients with associated GERD even more severe reflux may develop after Heller-Dor operation. In order to exclude this possibility we proposed to perform a 360 degree fundoplication instead of Dor fundoplication after Heller's myotomy in patients where GERD suspected to be a causative factor. At late follow-up no dysphagia was observed, so this procedure carries no additional risk of dysphagia. In accordance several studies showed that a 360 degrees fundoplication eliminates reflux without adding dysphagia in

the majority of patients treated for achalasia (167-169). Regarding to reflux symptoms no subjective signs of reflux were recorded at follow-ups, but still one patient had gastroesophageal reflux on esophagogram. The importance of this so called silent reflux in achalasia patients after myotomy, was also emphasized by Burpee et al. (164). They showed that 23% of their achalasia patients following laparoscopic Heller's myotomy had objective reflux without subjective heartburn. Other factors might support our hypothesis that GERD can cause some changes in the LES muscle, which can inchoate consecutive events similar to achalasia, include alterations of GERD patients similar to achalasia. For example Altorjay et al. (170) found LES muscle hypertrophy on biochemical examination taken from patients underwent laparoscopic antireflux operation for GERD. And a study from Moses et al. (171) showed that positive immunostaining of the myenteric plexus was detected in significantly more achalasia and GERD samples than control samples, and immunoreactivity was significantly more intense with achalasia and GERD serum samples than controls.

If preoperative examinations produce a strong suspicion of achalasia, which developed on the basis of GERD, we suppose that instead of an endoscopic dilatation a Heller's myotomy should be considered with a proper 360 degree fundoplication, as anterior hemifundoplication does not protect fully against reflux.

## **4.2. Large hiatal hernias**

### **4.2.1. Introduction**

A half century ago the concept of gastroesophageal reflux disease were characterized and the classical surgical correction initiated. Better understanding of the pathophysiology of GERD and technological advances of the last decade has made laparoscopic Nissen fundoplication the standard surgical procedure. Indications for laparoscopic fundoplication have expanded from GERD to more complicated conditions, such as large hiatal and paraesophageal hernia.

Once the diagnosis of type II or type III paraesophageal hiatal hernia is made, because they imply a greater risk for the patient such as hemorrhage, strangulation, volvulus and perforation (172-174), it is recommended to perform elective repair. Although laparoscopic repair of type I sliding hernia is well established with a proven record of efficacy and safety, results regarding laparoscopic paraesophageal hiatal hernia seems to be controversial. Short and intermediate results of feasibility and efficacy were promising (175), but recently several series showed a variable incidence of recurrence ranging between 0 and 40 % on midterm follow-up (176-178). Outcome results usually depend on how the recurrence is defined, anatomically or subjectively. Although the dissection and posterior closure of the crura, the so called posterior hiatoplasty is an essential step in any antireflux operation, the breakdown of this repair and the recurrent hiatal hernia is the one of the most common reason for failure of antireflux surgery (179-181). This is probably due to the constant movement of the diaphragm and the pressure gradient between the negative intrathoracic and positive intraabdominal pressures during coughing, sneezing or laughing. Another problem of hiatal repair is the lack of a strong fascia adjacent to the hiatal aperture for which the closing sutures encompass predominantly the muscle of the crura. In some cases, especially in large hiatal hernias, the hiatal closure can be performed only with tension between the cruras. So it seems that the hiatal closure is the weakest link in the otherwise well elaborated methods of antireflux surgery.

To overcome this problem several attempts were made to reinforce the closure. In order to avoid using any foreign material around the cardia the employment of the teres ligament, as described earlier for cardiopexy, seemed suitable. In 2003 a prospective study was introduced in our department which was design to evaluate the safety and efficacy of a new laparoscopic procedure (182). Midterm result of this study (183,184) leaded us to start another prospective study from 2006 with a modification of mesh hiatoplasty to prevent recurrence and mesh related complications. In order to compare the results and outcome of the different procedures for large hiatal hernia retrospective analysis of our prospectively collected

data was performed. A historical control group was set up, which contained patients without any reinforcement of the repair for large hiatal hernia. The further two groups included patients from the above mentioned two prospective studies.

#### **4.2.2. Patients and method**

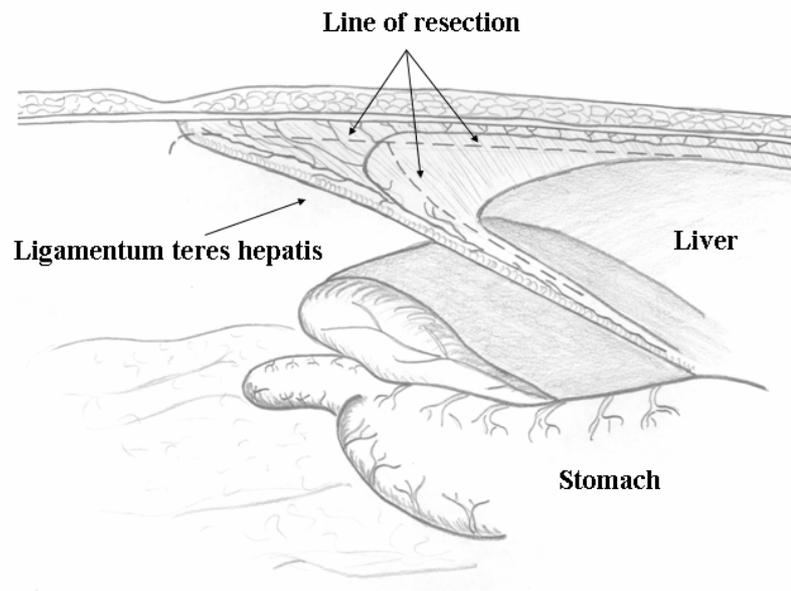
From the 241 patients in the time interval from 1998-2006 there were 60 patients presented with large hiatal hernia. Another 10 patients, who had large hiatal hernia secondary to a failed antireflux operation performed in other hospitals, were also enrolled in this study, which made a total of 70 patients with large hiatal hernia. 31 patients underwent laparoscopic Nissen-DeMeester fundoplication with posterior hiatoplasty between 1998-2002 (Group A). In 26 patients from 2003-2006 reinforcement of the hiatal closure was performed with ligament teres hepatitis (Group B) and in 2006 a further 13 patients underwent a modified mesh repair (Group C). The mean age was 57 years (range 33-74) in Group A, 62,8 (range 39-80) in Group B and 59 (range 43-72) in Group C respectively. Patients' characteristics are shown in table 6. Patients were followed with our standard follow-up procedure, to obtain objective data and to discover any possible anatomic recurrence. On a regular basis (3 months, 6 months, 1 year after the operation and then yearly) patients were called back for evaluation. All patients were questioned for symptoms including heartburn, regurgitation, dysphagia, chest pain. Barium swallow were also performed in all cases at all follow-up times. If any symptom of reflux was detectable functional foregut testing was performed. Anatomic recurrence was defined if a recurrent sliding hiatal hernia, without subjective symptoms was detected. Symptomatic recurrence was defined if large axial or paraesophageal hiatal hernia was observed with subjective symptoms confirmed with functional testing and if a remedial surgery was indicated.

**Table 6.** Basic characteristics of the different groups

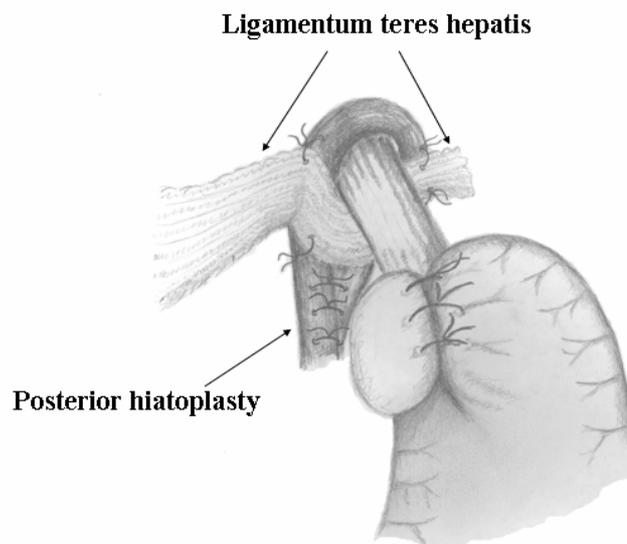
|             | Group A<br>N= 31 | Group B<br>N=26 | Group C<br>N=13 |
|-------------|------------------|-----------------|-----------------|
| Age         | 57 (33-74)       | 62,8 (39-80)    | 59 (43-72)      |
| Male/female | 16/15            | 7/19            | 2/11            |

### *Surgical procedure*

In Group A our standard antireflux procedure was performed as described earlier. In patients in Group B the surgical procedure was the same until the hiatal closure. After the hiatoplasty the position of the camera is changed to the left lateral port and the liver retractor is changed to a grasper. The teres ligament is stretched downward with a grasper and is dissected with ultrasonic dissector from the parietal peritoneum. Great care has to be taken to preserve the blood supply of the ligament and to avoid haematoma formation. In order to do so the dissection should proceed between the two vascular arcades (liver and peritoneal attachment), which supplies the ligament, and should stop at the hepatic branch, which feeds the hepatic vascular arcade (Figure 13). After mobilization of the ligament teres the initial position of the instruments are restored and the ligament is pulled through the GE window (between the closed crura and the posterior esophageal aspect). The stronger part of the ligament, which is covered by peritoneum, is sutured to the left crus with two non-absorbable stitches at the level of the esophagus. The right crus is then also sutured to the ligament at the same level creating a U-shaped reinforcement of the crura around the posterior aspect of the esophagus (Figure 14.). Finally a Nissen-DeMeester fundoplication is performed.

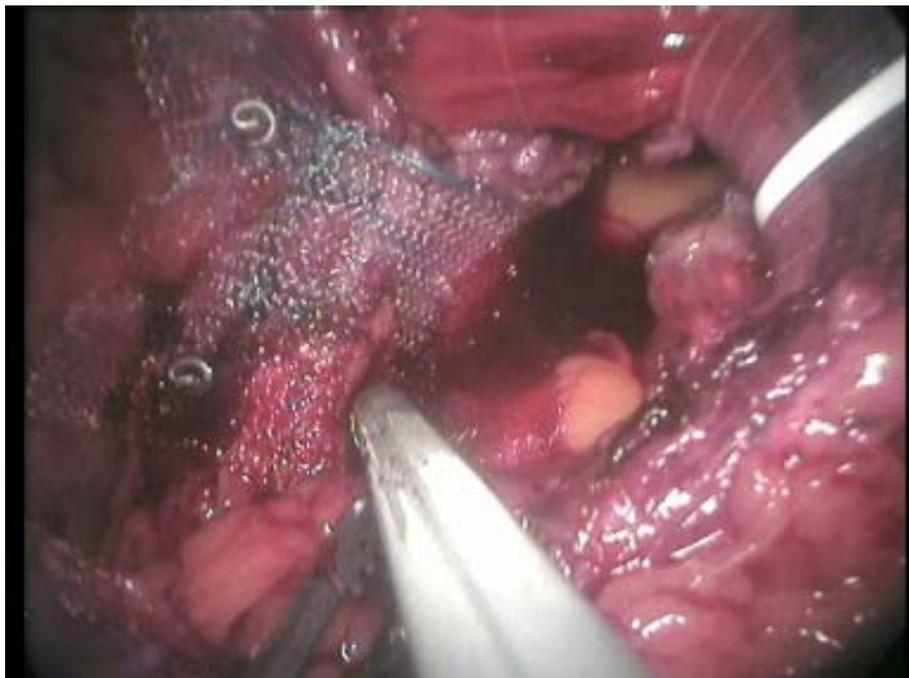


**Figure 13.** The dissection of the teres ligament from the parietal peritoneum with ultrasonic dissector

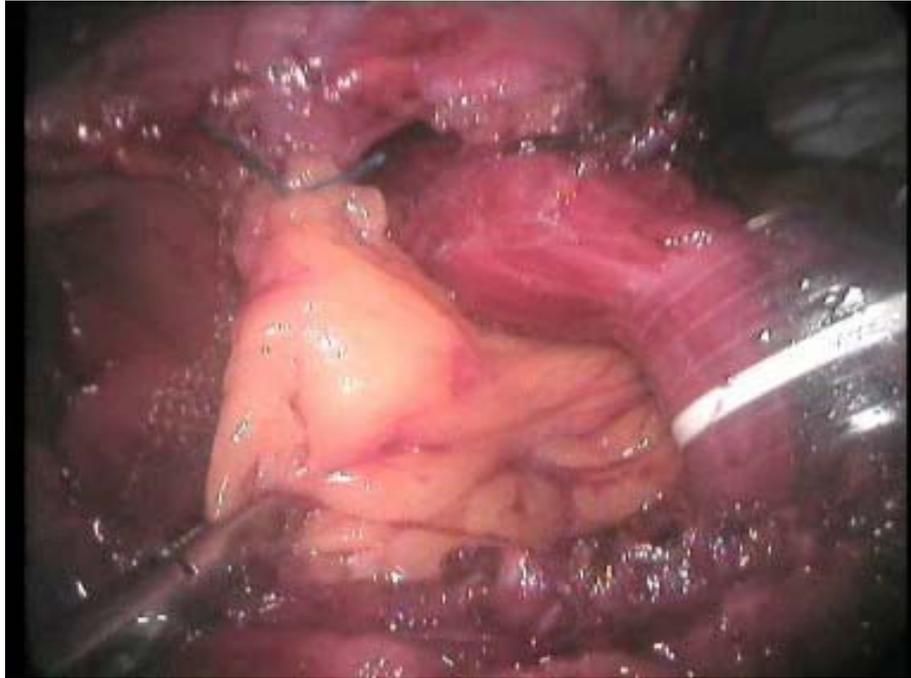


**Figure 14.** The teres ligament is used to cover the posterior hiatoplasty. It is sutured to the right and left crus at the same level creating a U-shaped reinforcement of the crura.

In Group C after the hiatal closure a polypropylene “U” shape mesh is introduced. It is then placed on the hiatoplasty at an onlay position and fixed with staples (Protac, Autosuture) (Figure 15). To avoid connection between the mesh and the esophagus or stomach, and therefore reduce the risk of mesh erosion, the omentum of the dissected great curvature is used. It is brought behind the esophagus and fixed to the right crus with non-absorbable stitches. In this position the omentum is between the mesh and the cardia and covers the mesh completely (Figure 16). In all cases a Nissen fundoplication is also added.



**Figure 15.** A “U”-shape polypropylene mesh is fixed in onlay position to the posterior hiatoplasty



**Figure 16.** The omentum of the dissected greater curvature is pulled between the esophagogastric junction and the mesh to avoid any connection between the mesh and the esophagus

#### *Statistical analysis*

Statistical analysis was performed with Chi<sup>2</sup> with Yates correction. P values < 0.05 were considered significant.

#### **4.2.3. Results**

##### *Perioperative data*

In Group A the mean operative time was 93 minutes (range 78-110). The conversion rate was 16%, 2 cases due to bleeding, 1 because of cardiopulmonary reasons and 2 for adhesions due to previous operations. Mean hospital stay was 7,3 days (range 4-16). No mortality was observed, perioperative morbidity was 9,6 % which included 2 bleedings and one pneumothorax. In Group B the mean operative time was 115 minutes (range 96-130). There was no perioperative mortality. 6 conversions (23%) to open surgery were performed all of them were redo operation. The morbidity was 11,5% which included 1 intraoperative

pneumothorax, 1 wound disruption after conversion and 1 late subdiaphragmatic abscess on the left side. Mean hospitalization time was 7,4 days (range 4-30 days). In Group C the mean operative time was 110,5 minutes (range 90-145). There were no conversions to open procedure. Mean hospital stay was 5,7 days (range 3-7). Mortality rate was 7,7%. One patient died due to the consequence of esophageal perforation. In this latter case we think that the perforation was caused by the bougie, because it was at the level of tracheal bifurcation. Unfortunately the routinely used esophagogram on the first day did not show any leakage and the perforation was discovered only the fifth postoperative day. Reoperation was performed with esophageal suture and drainage but the patient died on the 10 th postoperative day. Results of surgery comparing the three groups are shown in Table 7.

**Table 7.** Operation time, hospital stay, morbidity, conversion rate and mortality in the three groups

|                          | I. Group<br>N=31 | II. Group<br>N=26 | III. Group<br>N=13 |
|--------------------------|------------------|-------------------|--------------------|
| Operation time (minutes) | 93 (78-110)      | 115 (96-130)      | 110,5 (90-145)     |
| Hospital stay (days)     | 7,3 (4-16)       | 7,4 (4-30)        | 5,7 (3-7)          |
| Morbidity                | 9,6 %            | 11,5%             | 0                  |
| Conversion               | 5 (16%)          | 6 (23%)           | 0                  |
| Mortality                | 0                | 0                 | 1 (5,5%)           |

#### *Follow-up data and recurrence rates*

In Group A through an average of 34,6 months (until the beginning of the teres study) follow-up there were 2 anatomic and 8 symptomatic recurrences with hiatal hernia on barium X-ray. The latter 8 patients all underwent remedial surgery. Unfortunately the primary preoperative data of this historical control group was not sufficient enough to further evaluate these patients in order to determine what led to recurrence. The

average time elapsed after the primary operation was 25,6 months (range 6-42).

In Group B the follow-up was 13-46 months with an average of 30,9 months. 2 patients reported reflux symptoms postoperatively one and two years respectively. They were evaluated with esophagogastrosopy, stationer manometry and 24-hour esophageal pH monitoring. Neither signs of abnormal reflux nor anatomic recurrence was detected by these patients. 1 patient had severe pain after eating 18 months after the operation. Investigations revealed a 3 cm paraesophageal recurrent hernia. This patient underwent remedial surgery. 1 patient had temporary mild dysphagia and fullness after eating 2 years after surgery. Barium swallow showed slippage of the fundoplication into the mediastinum. Barium swallows revealed anatomic recurrence with slipped fundoplication in another two asymptomatic patients, 12 months after the operation. The latter 3 patients are now under strict surveillance, repeated barium swallows showed no changes in the size or type of recurrent hiatal hernia and no renewal of symptoms were recorded until this time. Out of these three patients two were predictable for failure due to the very thin right crus observed during the operation. From the 4 patients who had anatomic recurrence 3 had extreme large hiatal hernia (diameter was  $\geq 9$  cm) at the primary operation and one was a redo. From the 26 patients who entered the study 21 patients had a smaller hiatal hernia diameter than 9 cm. Among these 21 patients only one (4,7%) (who had recurrent hiatal hernia at primary operation) anatomical recurrence was observed. From the 5 patients who had a hiatal hernia greater than 9 cm in diameter, 3 (60%) had anatomic recurrence which was statistically significant ( $p=0,02$ ). Regarding to symptomatic recurrence no recurrence was observed from the 21 patients with hiatal hernia size between 6-9 cm and one recurrence was found in the 5 patients who had extreme large hiatal hernia. This difference also reached statistical significance ( $p=0,037$ ). A detailed outcome table is shown in table 8. Failed previous antireflux operations did not affect the anatomic recurrence rate. Out of 6 patients who had the ligamentum teres operation as a redo only one (16,6%) had recurrence,

while in the remnant 20 patient without previous fundoplication 3 (15%) had anatomic recurrence.

In Group C with a shortest average follow-up of 6,5 months there were no symptomatic or anatomic recurrence on barium X-ray. Summary of the anatomical and symptomatic recurrence of the three groups is shown in table 9. Statistical analysis of the three groups showed that reinforcement of the hiatal closure with teres ligament did not significantly reduce the overall recurrence rate compared to primary closure alone ( $p=0,14$ ). Although the number of patients in Group C is low and the follow-up time is also not comparable to the other groups, modified mesh hiatoplasty seemed to decrease the overall recurrence rate significantly compared to hiatoplasty alone ( $p=0,02$ ), but not compared to teres ligament reinforcement ( $p=0,135$ ). Anatomical recurrences showed no statistical differences at all between the three groups. Symptomatic recurrence was significantly reduced by both teres ligament ( $p=0,024$ ) and modified mesh ( $p=0,043$ ) reinforcement compared to the historical control group, but between the two reinforcement technique no significant difference was found ( $p=0,474$ ).

**Table 8.** Outcome of hiatal hernia repair with teres ligament (Group B) regarding to the size of the hiatal hernia

| Number of patients     | N=21      | N=5      | P value |
|------------------------|-----------|----------|---------|
| Size of hiatal hernia  | 6-9 cm    | > 9 cm   |         |
| Anatomic recurrence    | 1 (4,7 %) | 3 (60 %) | 0,022   |
| Symptomatic recurrence | 0         | 1 (20%)  | 0,037   |
| All recurrences        | 1 (4,7 %) | 4 (80 %) | 0,0001  |

**Table 9.** Outcome table comparing the three different surgical procedures for treatment of large hiatal hernia

|             | I. Group<br>N=31 | II. Group<br>N=26 | III. Group<br>N=13 |
|-------------|------------------|-------------------|--------------------|
| Recurrences | 10 (32,3%)       | 4 (15,3%)         | 0                  |
| Anatomic    | 2 (6,5%)         | 3 (11,5 %)        | 0                  |
| Symptomatic | 8 (25,8%)        | 1 (3,8 %)         | 0                  |

#### 4.2.4. Discussion

Laparoscopic antireflux surgery for gastroesophageal reflux disease, whether associated or not with type I hiatal hernia has an excellent long term result. On the other hand outcome after laparoscopic repair of large type II and III hiatal hernias is controversial. Early reports showed low rates of recurrence, but without objective radiologic follow-up data or with relatively short follow-up. Series with radiological midterm follow-up after laparoscopic repair of large hiatal hernia without a mesh showed a recurrence rate of 0-42 % (185-187). In this present study objective radiologic follow-up was observed in all patients with a mean follow-up of 34,6 months in Group A, 30,9 in Group B and 6,5 in Group C respectively.

Another concern regarding laparoscopic repair of paraesophageal hernias is the surgical technique. Question remains whether prosthetic meshes should be used or not. Several techniques were developed with different shapes of meshes and different techniques of placement (onlay, tension free) of a prosthetic mesh (polypropylene, PTFE, composite) as a reinforcement of the hiatal closure (188-190). In this present study we used the teres ligament and a polypropylene “U” shape mesh for reinforcement of the posterior hiatoplasty. These techniques were compared to primary closure. We suppose that the benefit of the teres ligament technique is, not only that it uses the patients own material, but the ligament teres, which is a fatty tissue both sides covered with peritoneum, fills the space between the esophagus and the cruras. It also

pushes forward the esophagus leaving no gap for possible recurrence on the anterior part. One might think that it can cause dysphagia or distorsion of the esophagus, but our pilot manometric vector volume study showed no asymmetry at the lower esophagus, and also no dysphagia was recorded on follow-ups.

Although a few prospective randomized (191-193) and other retrospective studies (194-196) comparing hiatal repair with or without mesh showed lower recurrence rate in favor of mesh cruroplasty there is still little Level I medical evidence in support of the superiority of one technique over the other. Unfortunately our study is also only a retrospective comparative study, but in accordance to the others we found that reinforcement of the hiatal closure reduces the rate of recurrence following large hiatal hernia repair. On the other hand recurrences also can be observed after laparoscopic mesh cruroplasty about 1 % to 14 % (197-200). In our study the overall recurrence rate was 15,3% with ligament teres, which was lower than primary closure alone (32,3%), and comparable to those with mesh hiatoplasty. The best results were observed after our modified mesh cruroplasty, but the number of patients and the short follow-up makes this result questionable.

Another argument against mesh reinforcement could be the additional costs and the possibility of complications such as severe adhesion, migration or perforation. Frantzides et al (201) showed that the cost of the hiatoplasty with PTFE prosthesis is around \$1000 more than the hiatoplasty alone. Regarding to mesh complication Carlson (202) et al published one case of mesh erosion (2,3%) into the fundus from 43 patients with polypropylene mesh repair after a mean of 52 months follow-up. A dislocation of a PTFE mesh into the cardial lumen (203), and a Dacron mesh into the esophageal lumen (204) was also published. Although mesh related complication is relatively rare, but follow-up time after laparoscopic repair of hiatal hernia with a mesh is still short. A late complication was published recently by Dutta (205), in a child 9 years after hiatal hernia repair. In this case an esophageal obstruction was caused by an eroded PTFE prosthesis. To avoid complication with a foreign material in this present study we used the teres ligament for reinforcement of the

hiatal closure in one group and we did not not observed any complications so far in connection with the usage of this ligament. In the other group we also used the patients own material, but not for reinforcement, but to cover the mesh. The omentum of the dissected greater curvature was brought behind the esophagus and placed between the esophagogastric junction and mesh to ovoid any connection and later any complication related to the mesh. In Group C there were no complications related to mesh so far. Other techniques were also developed to eliminate the possibility of mesh related complication. Early results with mesh derived from porcine small intestinal mucosa (SIS) (206) and mesh-human acellular dermal matrix (ACDM) (207) are promising.

The third debate regarding laparoscopic repair of large hiatal hernias is the definition of recurrence. It is still questionable whether a small recurrent sliding hiatal hernia has any clinical relevance. Andujar et al (208) reported a total of 166 patients after laparoscopic repair of large paraesophageal hernia. From that radiographic surveillance was observed in 120 patients. Six (5%) had recurrent paraesophageal and 24 (20%) had a sliding hernia. In our teres study one patient (3,8%) had recurrent paraesophageal hernia, who later underwent remedial surgery, and three (11,5%) had asymptomatic sliding hernia. The latter three did not required reoperation and have remained asymptomatic without any enlargement of hiatal hernia size at an individual follow-up of 17, 21, 22 months. Subanalysis of the 4 anatomic recurrence patients revealed, that the size of the hiatal hernia is at great importance, while previous hiatal hernia repair had no effect on recurrence rate. A possible failure, due to weakened right crus, was predicted in two of three patients, who had later anatomic sliding recurrence. In these cases, even with the possible risk of mesh associated complication, we assume that mesh reinforcement would have been a better solution. Therefore recently we decided to perform a modified mesh cruroplasty in patient with extreme large hiatal hernia associated with weakened right crus. Although with this recently used technique we did not observed neither any symptomatic nor anatomic recurrences, but more patients nor longer follow-up are needed to further evaluate the safety and efficacy of this modified mesh cruroplasty.

#### **4.2.5. Conclusion**

Our result suggests that laparoscopic reinforcement of large type II and III hiatal hernias with the teres ligament or with the modified mesh are reduces recurrences. Both are safe and effective. Teres procedure has the advantages that it carries no risk of a foreign material and applies no additional costs, and also prevents recurrences in the majority of patients. It seems that the only limitation of this technique is the size of the hiatal hernia and possibly the weakness of the right crus, therefore we presume that in such cases of extreme large hiatal hernia a prosthetic mesh would be probably advisable. In order to avoid any mesh related complication we prefer to cover the mesh with the omentum.

### **4.3. Duodeno-gastroesophageal reflux**

#### **4.3.1. Introduction**

Pathologic duodenogastric (DGR) and duodeno-gastroesophageal reflux (DGERD) can be detected in 10% to 50% of all reflux patients (209,210). Although duodenogastric reflux is a physiologic phenomenon which occurs normally nights and postprandial (211,212), excessive or pathologic duodenogastric reflux has been implied in the development of gastritis, gastric ulcer disease, dyspepsia, and even carcinoma (213-215). When duodenogastric and duodeno-gastroesophageal reflux present at the same time grade of the esophageal mucosa injury is strongly correlated with the amount of bile and acid refluxated into the esophageal lumen. Studies showed that in patients with more severe complication of GERD such as Barrett's metaplasia or esophageal strictures significantly more acid and bile was detected on esophageal pH and bilirubin monitoring in the esophageal lumen, compared to healthy volunteers or in patients with less severe grade of esophagitis (210,216,217). The effect of pathologic duodenogastric reflux and its toxic components on the esophageal mucosa have been demonstrated also in several experimental animal models (218,219).

Although many facts are known about the association of alkaline duodenogastric and gastroesophageal reflux, the therapeutic implications are still controversial. One of the reasons for that is, that the diagnosis of pathologic duodenogastric reflux, the accurate assessment of this abnormal condition, is very difficult to establish. The detection of alkaline reflux and/or the detection of its different components have been difficult and unreliable (220,221). Prior methodologies employed for measuring DGER, including endoscopy, aspiration studies (both gastric and esophageal), scintigraphy, and ambulatory pH monitoring, have technical difficulties and do not accurately measure DGER (217). Currently, the most commonly used means of assessing DGER is the ambulatory esophageal and gastric bilirubin monitoring system (Bilitec) (222). Although measuring bile reflux with

Bilitec can help to ensure the diagnosis of abnormal duodenogastric and duodeno-gastroesophageal reflux, indications for surgical intervention is still unanonymous. Furthermore the precise surgical intervention is not yet widely agreed and accepted. The most often used technique is a biliary diversion with Roux-en-Y suprapapillary duodenojejunosomy also called duodenal switch.

#### **4.3.2. Patients and methods**

In those patients where symptoms were susceptible for DGR or DGER beside our routine preoperative workup (barium X-ray, endoscopy, manometry, 24-hour esophageal pH monitoring) bilirubin monitoring with Bilitec 2000 was performed. Bilirubin exposure was analyzed above the 0,25 absorbance level in the stomach and 0,14 in the esophagus. Abnormal bile reflux was defined when the exposure exceeded the 95<sup>th</sup> percentile of healthy controls, which was 24,8 in the stomach and 11,8 in the esophagus (223). From 241 GERD patients who underwent a laparoscopic antireflux procedure 45 patients had two-channel (esophagus and stomach) 24-hour bilirubin monitoring before the operation because suspected duodeno-gastroesophageal reflux or because normal pH monitoring results. A further 16 patients had Bilitec after their initial antireflux operation for recurrent and atypical symptoms with normal 24-hour esophageal pH monitoring. From these 61 patients four (6,5%) underwent a duodenal switch procedure. They all were females with a mean age of 41,8 years (range 32-53).

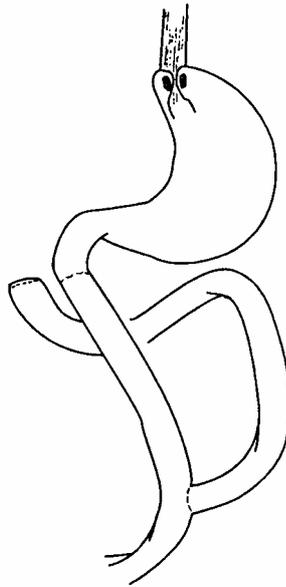
#### *Surgical procedure*

Our preference is to perform the biliary diversion procedure through a right subcostal upper abdominal incision, but other authors prefer an upper midline incision. When the Roux-en-Y suprapapillary duodenojejunosomy is begun, the duodenum is mobilized by a Kocher maneuver to feel the head of the pancreas and especially the position of the papilla of Vater as accurately as possible. Care must be taken to dissect an area around the duodenum well above the papilla and without devascularizing the proximal duodenum. Using the thumb and index finger

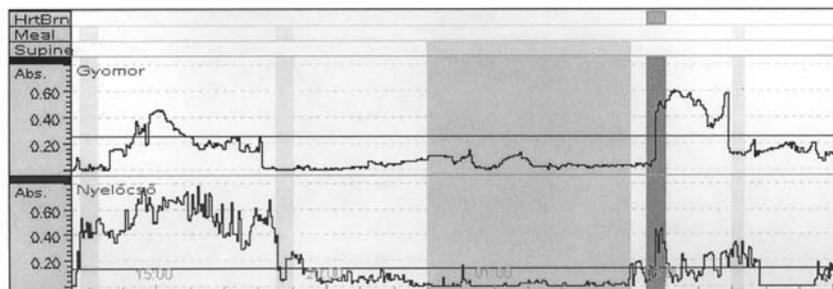
around the duodenum, it is usually possible to feel the closest approximation at a point along the medial duodenal border just proximal to the papilla at approximately 3 to 7 cm distal to the pylorus, depending on the anatomic situation of the patient. At this point the duodenum is dissected free of the head of the pancreas by carefully dividing the small vessels. It is essential to keep a minimal of 3 cm of postpyloric duodenum because only in this case remains enough receptor in this region for duodenal inhibition of acid secretion. It is important to reduce the risk of jejunal ulcers. Precautions must also be taken to avoid damage to the intrapancreatic common bile duct. When the channel between pancreatic head and duodenum is completed, the duodenum can easily be divided and closed with a linear stapling device. Since the dissection is carried down to the most distal point just proximal of the papilla, it is not advisable to oversew the stapling suture to avoid obstruction of the common bile duct. The first or second jejunal loop, depending on the vascular status of the mesentery, is pulled supracolically into the area of the duodenal bulb through an opening in the transverse mesocolon, and to the right of the midcolic vessels. A dissection point in the jejunal loop is identified to prepare a limb that is long enough to complete the Roux-en-Y jejunojejunostomy without tension. The distal jejunal loop is then sutured to the proximal duodenal stump in an end-to-end anastomosis. The proximal jejunal limb is anastomosed end-to-side to the distal jejunal limb 40 to 50 cm distal to the duodenojejunal anastomosis. (Figure 17.) The opening in the mesocolon is closed.

#### **4.3.3. Results**

From the 45 patients who had Bilitec before their antireflux operation 18 (40%) patients had abnormal duodeno-gastroesophageal reflux (Figure 18).



**Figure 17.** The duodenal switch procedure



Reflux Table - Gyomor

|                                   | HrtBrn | Total | Meal  | Supine | Upright | PrePra | PostPr |
|-----------------------------------|--------|-------|-------|--------|---------|--------|--------|
| Duration of Period (HH: MM)       | 00:30  | 22:42 | 01:20 | 06:00  | 16:42   | 15:22  | 06:00  |
| Number of Refluxes                | 1      | 27    | 0     | 2      | 25      | 17     | 11     |
| Number of Long Refluxes(>5 (min)) | 1      | 4     | 0     | 0      | 4       | 3      | 2      |
| Duration of longest reflux (min)  | 17     | 130   | 0     | 0      | 130     | 130    | 31     |
| Time abs >0.25 ((min))            | 17     | 248   | 0     | 1      | 247     | 187    | 60     |
| Fraction Time abs >0.25 ((%))     | 59.6   | 18.3  | 0.0   | 0.4    | 24.7    | 20.3   | 16.9   |

Reflux Table - Nyelőcső

|                                   | HrtBrn | Total | Meal  | Supine | Upright | PrePra | PostPr |
|-----------------------------------|--------|-------|-------|--------|---------|--------|--------|
| Duration of Period (HH: MM)       | 00:30  | 22:42 | 01:20 | 06:00  | 16:42   | 15:22  | 06:00  |
| Number of Refluxes                | 3      | 80    | 5     | 7      | 74      | 64     | 18     |
| Number of Long Refluxes(>5 (min)) | 2      | 11    | 3     | 0      | 10      | 11     | 3      |
| Duration of longest reflux (min)  | 18     | 359   | 29    | 3      | 359     | 194    | 119    |
| Time abs >0.14 ((min))            | 25     | 641   | 70    | 7      | 634     | 385    | 184    |
| Fraction Time abs >0.14 ((%))     | 83.6   | 47.1  | 88.0  | 2.1    | 63.2    | 41.7   | 51.3   |

**Figure 18.** Bilitec monitoring of the patient who later underwent a duodenal switch operation. Both esophageal and gastric tracing showed abnormal bile reflux

After a successful laparoscopic fundoplication only one (5,5%) patient had remnant symptoms susceptible for duodenogastric bile reflux. In this patient, symptoms appeared after ERCP, EST and stone extraction from common bile duct followed by a laparoscopic cholecystectomy. After the antireflux procedure, reflux symptoms disappeared and only epigastric pain and loss of appetite remained. Conservative treatment was started with sucralfate and prokinetic drugs with little effect. Because persistent symptoms of duodenogastric reflux a duodenal switch was performed half year after the laparoscopic fundoplication. Functional investigation before biliary diversion, showed no recurrent gastroesophageal reflux. At follow up patient was symptom free, and she returned to her normal eating habit.

From the 16 patients who had bilirubin monitoring after the antireflux operation, due to renewal of partially reflux symptoms and atypical epigastric symptoms, 3 (18,7%) had abnormal duodenogastric reflux. They all had epigastric and right subcostal pain, weight loss and loss of appetite. One of them also had typical symptoms of gastroesophageal reflux. The latter patients had a laparoscopic cholecystectomy 2 years ago and in the same time gastrotomy and removal of a gastric polypus was performed. Due to acute gastric hemorrhage reoperation was performed and the site of polypectomy was sutured from a pyloromyotomy. One year after that a Toupet fundoplication was performed because of gastroesophageal reflux disease. Barium swallow and endoscopy showed a small hiatal hernia and esophagitis SM II grade. Abnormal esophageal acid exposure was detected on 24-hour pH monitoring and incompetent LES was observed on manometry. 24-hour bilirubin monitoring revealed abnormal duodenogastric and gastroesophageal bile reflux. A duodenal switch and a revisional Toupet fundoplication were performed. One year after surgery the patient was symptom free and gained 2,2 kg. At two year follow-up, reflux symptoms renewed and functional testing proved recurrent abnormal esophageal acid exposure. Patient was put on PPI and she is now free of symptoms.

The other two patients had antireflux operation for GERD and histologically proven Barrett's metaplasia one and two years earlier. One of them also had cholecystectomy before. They had no reflux symptoms but epigastric and right subcostal pain, weight loss and appetitelessness were present. On 24-hour esophageal pH monitoring no abnormal acid reflux was observed. Bilirubin monitoring showed excessive bile reflux in the stomach, but in the esophagus no abnormal bile reflux was detected. A duodenal switch was performed in both patients. One of them had a small wound healing problem after surgery and the other had reflux symptoms one year after surgery but functional testing showed no abnormal acid reflux into the esophagus. The patient who had wound healing disturbance had an abdominal hernia repair two years after the duodenal switch.

There were no intraoperative complications, or major perioperative morbidity. Mortality was not observed. After an average of 24,3 months follow-up (range 21-30) all patients were symptom free. There was no progression or regression of the two Barrett's metaplasia. The three patients with symptoms of weight loss regain 2,2; 2,5 and 12 kg respectively. One patient is still on PPI because of recurrent gastroesophageal acid reflux. With this therapy she is symptom free.

#### **4.3.4. Discussion**

Gastroesophageal reflux can be differentiated into acidic, mixed (acidic and alkaline), and alkaline reflux by use of pH measurements. However, the actual pH value in the esophageal lumen does not distinguish the precise reflux components. Esophageal pH monitoring is an excellent method to provide information about acid reflux, but the pH environment in the esophagus is influenced by saliva, possibly even bicarbonate secretion from the esophageal mucosa, and acid and alkaline fluids, which may reflux from the gastric lumen (224,225). Intraesophageal pH monitoring is therefore an accurate method only if alkaline components play a minor role. The term duodeno-gastroesophageal reflux refers to regurgitation of duodenal contents through the pylorus into the stomach, with subsequent reflux into the

esophagus. Previously, the terms bile reflux or alkaline reflux were used to describe this process. However, duodenal contents contain more than just bile, and recent studies have shown that the term alkaline reflux is a misnomer because  $\text{pH} > 7$  does not correlate with reflux of duodenal contents. Therefore if there is a suspicion of DGR or DGER proper diagnostic tool should be used to adequately measure the bile component of the refluxate. Nowadays the best semi quantitative method for detection of bile reflux is the bilirubin monitoring system. In our study all of our patients who had suspected DGR or DGER underwent an esophageal and gastric 24-hour bilirubin monitoring (Bilitec 2000).

Although it is well known that acid and bile together is more harmful to esophageal mucosa than acid or bile alone (218), that is also well established that a successful antireflux operation has an excellent long term effect to control both acid and bile reflux (216,226). So even if pathologic duodeno-gastroesophageal reflux has been documented in the preoperative investigations there is no place for a duodenal diversion in those patients with primary reflux disease caused by an incompetent lower esophageal sphincter because surgical augmentation of the lower esophageal sphincter will probably prevent possible both acid and alkaline reflux into the esophagus successfully (227). In other words since the success rate of a Nissen fundoplication can be as high as 90% to 95% in primary reflux patients with an isolated sphincter defect, one can speculate that the necessity for a combined total duodenal diversion procedure together with a fundoplication is likely to be very unusual. In our treatment strategy for DGR and DGER we also think that the first step should be a laparoscopic antireflux procedure which is much less stressful for the patient. Therefore it is also an advisable strategy because most patients with DGER can not divert the different symptoms from each other. So if the patient became symptom free after a successful antireflux operation, there is no need for a duodenal diversion. This is supported by our finding that from the 18 patients who had duodeno-gastroesophageal reflux before the antireflux operation, only one patient (5,5%) had to be undergone a duodenal switch.

For the treatment of DGR and DGER the duodenal switch is one of most widely accepted procedure also used by us for biliary diversion. It was first published by DeMeester et al (228). A study from Klingler et al. (229) showed a 94% success rate 4 years after duodenal switch in 32 patients with duodenogastric reflux. An objective follow-up study with bilirubin monitoring from Collard et al. (230) showed that only 1 of 21 (4.7%) patients had abnormal bile reflux after a duodenal switch procedure compared to Henley's loop interposition. The most recent study on the largest patient sample after duodenal switch was published from the same group (231). From the 48 patients with a median follow-up of 81 months gastric symptoms were nil, had improved, and remained unchanged in 29 (60.4%), 16 (33.3%), and 2(4.2%) patients, respectively, and 1 patient experienced symptomatic recurrence after a 92-month symptom-free period (2.1%). Among the 44 patients who had postoperative upper GI endoscopy, 42 (95.5%) had no gastritis whereas 5 (11.3%) had an ulcer at the duodenojejunostomy. Gastric exposure to bile at postoperative 24-hour intragastric Bilitec test in 36 patients was nil, within the normal range, and still slightly pathologic in 15 (41.7%), 19 (52.8%), and 2 (5.5%), respectively. An extension of duodenal switch with fundoplication and superselective vagotomy was advocated by Csendes et al. (232) in patients with Barrett's metaplasia. They observed significant reduction in both acid and bile reflux in 65 patients 6 months after the operation. On long term follow-up 90% success was detected. Although these results are very promising, but probably because of an extended operation, the morbidity was also elevated to 14 % in this series. In our study there was no major morbidity or intraoperative complications.

The third surgical choice for biliary diversion is the choledocho-jejunostomy. Madura et al. (233) published a series of 31 patients who underwent a choledocho-jejunostomy for duodenogastric reflux. They found a 87% of success rate after an average of 51 months follow-up. Although there were no published complications we assume that this technique is technically more demanding (normal choledochus) and always carries the risk of anastomotic stricture. These patients usually have

a long life expectancy, so we assume that with longer follow-up there is a high possibility of reoperation for stricture of the choledocho-jejunostomy.

In our study we found that three of the four (75%) patients had cholecystectomy prior to appearance of their symptoms. Especially one patient complained that her symptoms started right after ERCP, EST followed by cholecystectomy. This finding is in accordance to some reports stating that cholecystectomy can predispose to abnormal duodenogastric bile reflux (234,235). On the other hand others studies did not find any association between cholecystectomy and excessive bile reflux into the stomach (236,237).

#### **4.3.5. Conclusion**

Patients with suspected duodeno-gastroesophageal reflux must be studied thoroughly using all current diagnostic measures to determine the probability of the pathophysiologic importance of such a finding. Indications for a duodenal diversion operation should be based on a spectrum of investigative results, including upper gastrointestinal endoscopy to detect ulcers, scars, strictures, or duodenal bulb deformities; esophageal manometry to detect esophageal peristaltic disorders and lower esophageal sphincter incompetency; antroduodenal manometry to verify gastric and antroduodenal motility disorders; 24-hour esophageal and gastric pH monitoring to confirm acid and alkaline reflux; fiberoptic 24-hour bile monitoring of the esophagus and stomach; gastric-emptying scintigraphy for evidence of delayed gastric emptying; and a barium study to detect gastric wall abnormalities. Previous cholecystectomy could predispose to duodenogastric or duodeno-gastroesophageal reflux.

If excessive alkaline reflux into the esophageal lumen is identified, the patient should be clearly informed that the planned antireflux operation, usually a laparoscopic Nissen fundoplication, may possibly be only the first step of the procedures that are necessary to bring constant relief. If complaints diminished after the antireflux procedure there is no need for a duodenal switch. Also in patients after primary antireflux operation for GERD appearance of atypical, epigastric symptoms should always bring attention to abnormal duodenogastric reflux. A preoperative

medical therapy to neutralize alkaline refluxed should be the first step in those patient. A duodenal diversion operation after laparoscopic antireflux surgery is indicated only in patients who have had a history of continued severe symptoms despite medical therapy and have clearly documented duodenogastric reflux. In these cases good results can be achieved with duodenal switch procedure.

## 5. Summary

Gastroesophageal reflux disease is one of the most common functional foregut disorders in civilized countries. A half century ago the concept of gastroesophageal reflux disease were characterized and the classical surgical correction initiated. Better understanding of the pathophysiology of GERD, technological advances of the last decade and outcome studies, with 5-year or longer follow-up after Nissen fundoplication showing patient satisfactions of 86% to 96%, have made the laparoscopic Nissen fundoplication the gold standard for antireflux procedures.

From 1998 to 2006 at time interval of 9 years 241 patients underwent a laparoscopic Nissen fundoplication for gastroesophageal reflux disease at the Surgical Department of Medical faculty, University of Pécs. Before the operation, all patients underwent a well established and standardized functional foregut investigation which contains esophago-gastroscopy, barium X-ray, esophageal manometry, 24-hour esophageal pH monitoring and in some cases 24-hour bilirubin monitoring. Our midterm follow-up of 48,5 months showed a 8,3 % failure rate which is comparable to other studies in the medical literature. Major intraoperative complications occurred in 15 cases (6,2%). Mortality rate was 0,82% due to delayed recognition of esophageal perforation. Conversion to laparotomy was performed in 13 (5,4%) of 241 patients. Analysis of failed antireflux operations showed that the most common reason for failure was a recurrent hiatal hernia.

We also looked for prognostic factors which may have influence on failure. By a univariate analysis we found that from the seventeen evaluated parameters three had significant effect on outcome after laparoscopic antireflux surgery. Hiatal hernia with a size greater than 3 cm, shortening of the esophagus on endoscopy and no response to PPI had significantly influenced the outcome of antireflux operation in a negative way.

During these 9 years we have met some special cases in connection with gastroesophageal reflux disease. The most interesting

observation was that hypertensive conditions of the lower esophageal sphincter, although it seemed paradoxical, can be associated with gastroesophageal reflux disease. The hypertensive lower esophageal sphincter, which is characterized by an elevated LES pressure with normal relaxation and no esophageal body motility disturbances, was observed in 7 patients. The first patient underwent a laparoscopic cardiomyotomy with anterior fundoplication as a recommended operation for hypertensive lower esophageal sphincter. Later this patient had severe gastroesophageal reflux and a revisional operation with a new complete fundoplication must be performed. From the medical literature we found out that HLES can be associated with GERD, therefore a prospective study was started to evaluate the effect of a fundoplication on HLES associated with GERD. We found that after a laparoscopic antireflux procedure the high pressure of LES can return to a normal level and the patients became symptom free (238).

Three interesting patients with achalasia were presented, who were treated for GERD for years. Evaluation of these patients showed that they all had long standing GERD with typical symptoms. Suddenly their reflux symptoms diminished and dysphagia developed. Functional investigation showed typical signs of achalasia in all of them. Two also had abnormal acid exposure on 24-hour pH monitoring. It was also interesting to see that those patients with GERD associated achalasia the pressure of LES was lower than of those with pure achalasia. We hypothesized that achalasia developed in the settings of long standing GERD (239), and they all underwent a laparoscopic Heller's cardiomyotomy with a Nissen fundoplication. We concluded that there is a subgroup of achalasia patients where achalasia develops due to long standing GERD. If preoperative examinations produce a strong suspicion of achalasia, which developed on the basis of GERD, we suppose that instead of an endoscopic dilatation a Heller's myotomy should be considered with a proper 360 degree fundoplication. We also hypothesized that both HLES and achalasia can occur as a consequence of gastroesophageal reflux. This hyperreaction of the LES can be explained as a protective action of the sphincter against abnormal acid exposure.

Evaluation of our outcome data showed that the most troublesome part of the antireflux operation regarding to recurrence is the hiatal closure. Not to mention that unacceptable high rate of recurrence was observed after laparoscopic repair of type II and III hiatal hernias. To overcome this problem the teres ligament was used to reinforce the hiatal closure in patients treated for large hiatal hernia. This procedure was used on 26 patients with large hiatal hernia. Our midterm results with an average of 30 months follow-up, showed that laparoscopic reinforcement of large type II and III hiatal hernias with ligament teres is safe and effective. It reduces the recurrence rate compared to hiatoplasty without reinforcement. A significant reduction of recurrence was found in symptomatic recurrences. It also carries no risk of a foreign material and applies no additional costs. Our results showed that the only limitation of this technique is the size of the hiatal hernia and possibly the weakness of the right crus, therefore we started another study with laparoscopic mesh hiatoplasty. 13 patients with extreme large hiatal hernia underwent laparoscopic mesh reinforcement for large hiatal hernia. In order to reduce the risk of mesh related complications a modification of the technique was applied. The omentum of the dissected greater curvature was used to cover the onlay "U" shape polypropylene mesh. With this modification the mesh cannot get into connection with the esophagus, cardia or the stomach. Results of the reinforcement of the hiatoplasty with an omentum covered mesh, seems promising but follow-up is short and more patient enrollment is needed.

Duodenal switch procedure was designed to eliminate abnormal bile reflux. During these 9 years we performed four such operations. All patients had an antireflux procedure as the first step and later a duodenal switch operation. One patient already had the diagnosis of abnormal duodenogastric and duodeno-gastroesophageal reflux before the laparoscopic Nissen fundoplication, the other three patients presented symptoms only some time after fundoplication. In one of four patients the fundoplication was also failed so a duodenal switch and a refundoplication were performed. Three out of four patients had cholecystectomy previously. In conclusion we suppose that patients with DGR and DGER

the first step should be a laparoscopic antireflux operation which is less stressful for the patients. This also helps choosing the right therapeutic option afterwards, because patients can not always divert the different types of reflux (GER,DGR,DGER) symptoms from each other. If the patient became symptom free no duodenal switch is needed. After antireflux surgery if the patient has atypical symptoms and the failure of the antireflux operation can be excluded one should always think about abnormal duodenogastric reflux. If DGR in these cases is objectively proven and the patient has severe symptoms despite of medical therapy, than a duodenal switch can be performed with good results. Previous cholecystectomies can also predispose to abnormal duodenogastric reflux. In good selected patients duodenal switch provides excellent symptomatic relief (240).

## 6. New findings

1. We suppose that there are two types of HLES patient. One with dysphagia and chest pain, who respond well to cardiomyotomy and the other is the GER associated HLES in whom the hypertension of the LES is a consequence or complication of gastroesophageal reflux. In these patients instead of a cardiomyotomy a 360 degree fundoplication should be performed.

2. Achalasia could develop in the settings of long standing gastroesophageal reflux. There are three factors that can predict GERD associated achalasia. First, if there is long standing reflux symptoms in the patients' history and reflux symptoms diminish after dysphagia developed. The second suspicious factor is a hiatal hernia accompanying achalasia. And third is, if pH monitoring shows abnormal acid reflux. The setpoint should be changed to pH 3 in these cases to exclude artifacts from acidic fermentation in the esophageal lumen.

3. We suppose that if preoperative examinations produce a strong suspicion of achalasia, which developed on the basis of GERD, a proper 360 degree fundoplication should be considered after Heller's myotomy, as anterior hemifundoplication does not protect fully against reflux.

4. A new laparoscopic technique was developed in our institute to prevent recurrence after laparoscopic repair of large hiatal hernia. The teres ligament was used to reinforce the hiatal closure in patients treated for large hiatal hernia. This is a completely new operation and it was never published before.

5. Although reinforcement of the hiatal closure with teres ligament was sufficient in most of the cases, recurrence was found in patients with extreme large hiatal hernia and weakened right crus. In these cases a modification of mesh cruroplasty was applied. This modification was also developed by our unit. To reduce the risk of mesh associated complications the mesh was covered with the omentum of the dissected greater curvature to avoid connection of the mesh and the cardia.

6. Experience with duodenal switch procedure, which was designed to eliminate abnormal bile reflux, has not been published in the Hungarian medical literature so far. We reported on four cases.

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## 9. Publications

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6. **G. Varga**, L. Cseke, K. Kalmár, ÖP Horváth. Laparoscopic repair of large hiatal hernia: comparison of three different techniques and modification of mesh hiatoplasty to prevent mesh related complications. Irish Journal of Medical Science 2007 Volume 176 Suppl 5 S208 (Abstract)

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19. A Papp, L Cseke, **G Varga**, K Kalmár, G Horváth, S Márton, ÖP Horváth: Chemo-radiotherapy in locally advanced oesophageal cancer – are upper third tumours more responsive? *Diseases of the Esophagus* 17 Suppl 1: A41, 2004. IF: 0,797
20. A. Papp, L. Cseke, G. Pavlovics, R. Farkas, S. Márton, **G. Varga**, L. Potó, ÖP Horváth. Locally advanced squamous cell cancer of the cervical oesophagus: the role of multimodal therapy. *Irish Journal of Medical Science* 2007 Volume 176 Suppl 5 S216 (Abstract)

## 7. Presentations (Not in connection with Thesis)

1. **Varga G**, Róth E, Szmolenszky AM. Changes of citrate synthase enzyme activity compared with creatin kinase following heart ischaemia. MST Kísérletes Sebészeti Kongresszus 1996, Hungary
2. **Varga G**, Jaberansari MT, Borsiczky B, Róth E, Paróczai M. Does bisaramil (a new anti-arrhythmic drug) have any cardioprotective and haemodynamic effect in an experimental ischemia–reperfusion model? MST Kongresszus 1998 Budapest, Hungary
3. **Varga G**, Cseke L, Pataki N, Horváth ÖP. Mesenterio-axiális gyomorvolvulus műtéti megoldása laparoskopos gasztropexiával – Esetismertetés MST Kongresszus 1998 Budapest, Hungary
4. **Varga G**, Király Á, Horváth ÖP. Relation between different investigating techniques in patients with gastroesophageal reflux disease MGT 41. Nagygyűlése 1999, Balatonaliga, Hungary
5. **G.Varga**, M.Fein, K.H.Fuchs, S.M.Freys, J.Maroske , H.Tigges . Indication, technique and results of laparoscopic treatment of achalasia. ISDE Congress 2001 Sao Paulo, Brasil
6. **G.Varga**, M.Fein, K.H.Fuchs, S.M.Freys, J.Maroske , H.Tigges, A. Thiede Interaction between gastric pH, Helicobacter pylori and

duodenogastric reflux in patients with gastroesophageal reflux disease ISDE Congress 2001 Sao Paolo, Brasil

7. **Varga G.**,Fein M.,Freys S.,Marosle J.,Tigges H., Fuchs K. Az achalasia sebészi kezelésének korai eredményei MST Kongresszus 2001 Pécs
8. **Varga G**, Cseke L, Horváth ÖP. Gastrooesophageális reflux ritka szövődménye: Barrett oesophagus talaján kialakult nyelőcső adenocarcinoma és subglotticus trachea stenosis – esetismertetés MST Kongresszus 2002, Hungary
9. **Varga G**, Cseke L, Horváth Ö.P. Subglottic trachea stenosis as a consequence of long time gastroesophageal reflux - Case report MGT 44. Nagygyűlése 2002, Balatonaliga, Hungary
10. A. Papp, L. Cseke, G. Pavlovics, R. Farkas, S. Márton, **G. Varga**, L. Potó, ÖP Horváth. Locally advanced squamous cell cancer of the cervical oesophagus: the role of multimodal therapy. ESS Congress 2007 Dublin, Ireland

#### **8. Invited lectures:**

1. **Varga G**, Cseke L, Kalmár K, Horváth ÖP. Nagyméretű hiatus hernia kezelése: Új laparoscopos módszer III. Pécsi Nyelőcsőnap 2004, Pécs, Hungary
2. **Varga G**. Nyelőcső motilitászavarok a sebész szemszögéből. III. Pécsi Nyelőcsőnap 2004, Pécs, Hungary
3. **G. Varga**, L. Cseke, K. Kalmár, Ö. P. Horváth. Difficult closure of hiatus with Ligamentum teres – prevention of recurrence-Early results. EAES Congress 2005 Venice, Italy
4. **Varga G**, Cseke L, Horváth ÖP. A duodeno-gastroesophagealis refluxbetegség diagnózisa és sebészi kezelésére MST Jubileumi kongressusa 2006 Budapest, Hungary

5. **Varga G.** Die Beziehung Achalasie und Hiatus Hernie Symposium un Kurs Gastrointestinale und Kolorectale Funktionsstörungen 2007 Frankfurt , Germany

## 9. Participation in Research Grants

1. ÖP Horváth, **G Varga**, K Kalmár, Á Király, I Kiss, E Kálmán, T Aikou, H Feussner, KH Fuchs: A gyomor és a gastro-oesophagealis átmenet rosszindulatú daganatainak komplex kezelése FKFP-0361/2000
2. FT Molnár, ÖP Horváth, Á Király, E Kálmán, I Kiss, **G Varga**, K Kalmár: A gastro-oesophagealis reflux betegség szövődményeinek pathogenesisise, megelőzése és kezelése OTKA 2001
3. ÖP Horváth, L Cseke, D Kelemen, K Kalmár, **G Varga**: Aborális pótygyomor prospektiv randomizált összehasonlítása hagyományos orális pótygyomorral totális gastrectomia után OTKA T 042726/2003
4. Horváth ÖP, Cseke L, Kalmár K, Papp A, **Varga G**: Módszerek a nyelőcsőrák sebészi kezelése eredményeinek javítására ETT 2003.

