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1955

**Management of Gastro-oesophageal Reflux Disease  
by Antireflux Surgery**

Studies on Pathophysiology and Mode of Optimising Surgical  
Therapy

by

Lars Rydberg



Göteborg 1999



# Management of Gastro-oesophageal Reflux Disease by Antireflux Surgery

## Studies on Pathophysiology and Mode of Optimising Surgical Therapy

### AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att  
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- II. Rydberg L, Ruth M, Lundell M. Does oesophageal motor function improve with time after successful antireflux surgery ? Results of a prospective randomised clinical study. *Gut* 1997 Jul;41(1): 82-6.
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- V. Rydberg L, Ruth M, Lundell L. Characteristics of secondary oesophageal peristalsis in operated and non-operated patients with chronic gastro- oesophageal reflux diseases. In press

# Management of Gastro-oesophageal Reflux Disease by Antireflux Surgery Studies on Pathophysiology and Mode of Optimising Surgical Therapy

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## ABSTRACT

The pathogenesis in GORD is unclear. Motor dysfunctions in the oesophageal body, as well as in the gastro- oesophageal junction, are commonly seen. An important question is whether these motor disturbances are of primary pathogenetic nature or appear as a consequence of the mucosal inflammation caused by chronic reflux? Antireflux surgery is effective concerning reflux control. It is, however, unclear whether a partial fundoplication (Toupet, 180- 200° fundic wrap) is as effective as a total fundoplication (Nissen- Rossetti, 360° fundoplication). One method to establish the efficacy of the surgical therapy is to carry out studies with long-term follow-up, and evaluate the degree of reflux and symptom control at predefined time intervals. Furthermore, a pivotal question is how to select patients with GORD to optimise the clinical results and to minimise the postoperative sequelae?

**Methods:** The background patient material consisted of 137 chronic GORD patients suitable for surgical therapy. They were randomised to either a total or a partial fundoplication. The postoperative follow up extended to at the most 5 years and were carried out, at regular time intervals, by an independent physician. The investigations included clinical assessment, upper endoscopy, 24 hour pH monitoring, and manometry of the oesophageal body as well as of the lower oesophageal sphincter (LOS). For assessment of the LOS tone and function two techniques were used. Firstly the LOS tone was assessed by use of a "station pull through" technique and was carried out by a water perfused triple lumen catheter with 3 side holes positioned 120° apart. In order to assess LOS tone over long time periods and to study the transient lower sphincter relaxations (TLOSR:s), we used the "sleeve" technique. To trigger TLOSR:s, 750 ml of air was insufflated into the stomach. The manometric investigation of the oesophageal body was performed by use of a water perfused catheter assembly with lateral side openings at 5 cm intervals. The primary peristalsis was analysed after water swallows and secondary peristalsis after boluses of air injected into the mid oesophagus. Interpretation and calculation of all manometric findings were carried out by one person, without knowledge of the nature of surgery undertaken in each patient and also unaware of the group affiliation of the subject.

**Results:** Since no change in the motor function with time was observed, despite postoperative perfect reflux control, our results did not support the hypothesis that the motor dysfunction arises as a result of transmural inflammation caused by uncontrolled reflux. Furthermore, no apparent change in the deficient ability to excite secondary peristalsis was observed after successful surgery. We were unable to observe any correlation between findings at preoperative manometry and the postoperative clinical outcome, irrespective of the type of fundoplication. The two surgical procedures (total and partial fundoplication, respectively), were equally effective concerning reflux control. However, we demonstrated important differences in that symptoms of obstructive nature in the early postoperative period and complaints of rectal flatulence later during the follow-up period were more frequently seen after a total fundoplication. This favourable effect of the partial fundoplication could be explained by the fact that a partial fundic wrap was followed by a lower basal tone in the LOS, lower nadir pressure at maximal LOS relaxation and a greater ability to vent air from the stomach.

**Conclusions:** Preoperative manometry is not the tool, which allows us to tailor the surgical procedure in order to minimise postoperative side effects. The partial fundoplication (Toupet fundoplication) seems to be superior to the total fundoplication (Nissen- Rossetti) depending on equal effectiveness in controlling GORD but fewer adverse sequelae. Finally our data on motor function of the oesophagus add to the notion that motor dysfunctions observed in GORD are of primary pathogenetic nature.

From the Department of Surgery, University of Gothenburg, Sweden

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## Index

<b>Introduction</b> .....	5
<b>Prevalence and incidence of GORD</b> .....	6
<b>Pathophysiological aspects on:</b> .....	8
Oesophageal body function.....	8
Gastro- oesophageal junction.....	10
Mucosal resistance .....	11
<b>Surgical therapy</b> .....	12
Indications for therapy .....	13
Historical aspects .....	14
<b>The aim of the study</b> .....	15
<b>Patients and methods</b> .....	17
Clinical assessments .....	17
Endoscopy .....	18
24 hour pH monitoring .....	18
Lower oesophageal sphincter pressure .....	19
The sleeve techniques .....	20
Oesophageal body manometry .....	21
Triggering of transient lower oesophageal sphincter relaxations .....	22
Operative procedures .....	23
Patients .....	24
Study I .....	24
Study II .....	24
Study III .....	25
Study IV .....	25
Study V .....	25
Statistics .....	26
<b>Results and comments</b> .....	27
Do funduplications work – and how? (Studies I, III, V) .....	27
Oesophageal motor dysfunction- of pathogenetic concern? (Studies II, V)...	36
<b>Summary and concluding remarks</b> .....	42
<b>Acknowledgements</b> .....	44
<b>References</b> .....	45



This thesis is based on the following papers, which will be referred to in the text by their Roman numerals .

- I. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen- Rossetti) or semifundoplication (Toupet) for gastro- oesophageal reflux. *Br J Surg* 1996 Jun;83(6): 830-5.
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## INTRODUCTION

Gastro-oesophageal reflux disease (GORD) can broadly be defined as "symptom, combined with or without oesophageal mucosal damage, which occur as a consequence of the reflux of gastric juice". In a recent expert consensus conference this definition was further expanded upon and the panel agreed that GORD should be used to include "all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinical significant impairment of health related well-being (quality of life) due to reflux related symptom, after adequate reassurance of the benign nature of their symptoms".

GORD is a disease in transformation. It used to be a rare finding in individuals referred for upper GI-endoscopy during a time when peptic ulcer disease was far more prominent. More recently, GORD has occupied a central role in the clinical practice of gastroenterologists, and much interest has been focused on the management of oesophagitis patients. The healing of oesophagitis was considered mandatory to prevent complications from occurring. Clinical evidence has, however, indicated that a substantial number of GORD patients do not have macroscopic lesions at endoscopy despite severe and long lasting reflux symptoms. Awareness of this, alongside with high and increasing prevalence of similar complaints, has led to the clinical management of such patients being moved from the gastroenterologists to the general practitioner. The efficacy of modern therapies has allowed a change of strategy from the use of endoscopy as an initial mainstay diagnostic workup initiative towards a focus on symptom analysis and assessment of symptom response to short term, profound acid inhibition therapy. Consequently a different view on long-term treatment strategies has emerged. Recognition of the impact of the disease on quality of life of the patients and the effect of therapy has introduced new dimensions to the disease perspective. Furthermore, new technologies have a particular impact on the feasibility and attractiveness of surgical long-term therapy of chronic GORD, not the least by the increasing knowledge of the mode of action of different surgical procedures with the potential to reduce adverse complaints associated with similar operative therapies. Therefore during a time period characterised by a dynamic and even changing view on the management of GORD, it is of significance to focus on long-term therapeutic alternatives in general and surgical therapy in particular. A comprehensive overview on antireflux surgery should include aspects on efficacy, durability, safety and how to minimise the risk for adverse effects.

## PREVALENCE AND INCIDENCE OF GORD

Although GORD is clearly an extraordinarily common disorder, the epidemiology of GORD is not well defined. One problem relates to the lack of "gold standard" for establishing the diagnosis. Symptoms do not, however, reliably predict the presence of oesophageal inflammation. Heartburn, which is widely regarded as the cardinal symptom of GORD, may even be absent in patients with verified reflux oesophagitis. In one study 65% of patients with anatomical evidence of oesophageal inflammation complained of frequent heartburn whereas approximately 25% of patients with Barrett's oesophagus (complication of severe GORD) had no symptoms of oesophageal disease (1). The prevalence of heartburn has been reported to range from 2 % up to 40% of the adult population, depending on how the disease and the population are defined. When the diagnostic criteria are restricted to patients with endoscopic oesophagitis, the prevalence has been estimated to be about 2% in the Western world (2). Over the 10-year period 1977 to 1986 establishment of open access endoscopy units in the UK increased availability of endoscopy and the proportion of patients diagnosed as having reflux oesophagitis increased from 3 to 19% (3). Endoscopic oesophagitis is found in about one third to two thirds of patients with reflux symptoms who have been referred for investigation (4, 5).

The prevalence of heartburn, on the other hand, in the general population ranges from 17 to 40% (6- 14). Heartburn is, however, a common symptom in patients with upper abdominal complaints (14- 16), but to be predictive for GORD it should be the predominant symptom (17). It is also known from 24 hour pH studies that more than half of the patients with high levels of oesophageal acid exposure suffer from symptoms other than heartburn (4, 17) and heartburn is not always present even in patients with reflux oesophagitis (18- 19). Out of 377 randomly selected adults in Sweden who responded to a questionnaire about symptoms of GORD, 21% complained to have heartburn. Typically, patients who suffer from symptoms of GORD do so for many years before seeking medical help. In one large study investigating patients with severe reflux oesophagitis, the duration of symptoms before hospital presentation was < 1 year in 18 %, < 3 years in 50% and > 10 years in 24% (20).

The annual incidence has been reported to have increased during the last 30 years. In Switzerland the estimated annual incidence of oesophagitis seemed to have increased from 10 per 100,000 in 1963 to 43 per 100,000 in 1970 which increased further to 139 per 100,000 in

1980 (21). In a similar Swedish study (22) based on endoscopy reports accumulated during 2 years between 1988 and 1990, the annual incidence of oesophagitis was calculated to be 120 per 100,000 and 88% of these cases were uncomplicated endoscopic findings. Male to female ratio was 2:1, which contrasts to the old figures reported from Scotland in 1969 (23) with severe oesophagitis including complications of stricture and ulcerations collected during the time period 1951 to 1967.

The general opinion has traditionally been that GORD evolves from symptoms of reflux without oesophagitis to erosions and more severe extensive mucosal breaks ending up with complications in the form of stricture ulcer and columnar lined oesophagus. There is, however, little evidence to support this view and studies focused on the natural history of a mixed group of endoscopy negative and positive patients with abnormal oesophageal acid exposure it was found that most patients remained to be symptomatic and the endoscopic findings were essentially stable over a 3 year period (24). Similarly McDougall and co-workers found over a 10-year period when studying patients with reflux oesophagitis similar findings (25). In a recent Finnish study following patients between 17 to 22 years after initial diagnosis of GORD, symptoms had improved in a significant proportion of the 50 conservatively treated patients but the majority of those still had endoscopic findings suggestive of GORD (26). In a huge study (27) comprising of 194,527 patients with GORD who were followed between 1981 and 1994 the investigators confirmed the finding that severe oesophagitis and complications are more common in elderly subjects (22, 23) but they could not find a clean cut progression between different manifestations of GORD.

The oesophageal complications of GORD include Barrett's oesophagus, ulceration, bleeding, perforation and stricture. Data on the prevalence of these complications derive primarily from studies of hospitalised patients with substantial reflux and oesophagitis. Hence, the complication rates observed may have overestimated the true prevalence of these problems among patients with GORD when extrapolated to the general population. This may not be true, however, for Barrett's oesophagus. This condition has been found in approximately 12% of patients undergoing endoscopic examination for symptoms of GORD (28). The post-mortem prevalence of Barrett's oesophagus was investigated in Olmsted county, Minnesota and was found to be 376 per 100,000 (29). Most of these cases were found at autopsy and not recognised during life and the investigators concluded that this was due to the fact that most patients with Barrett's oesophagus do not seek medical attention for this condition. Barrett's

oesophagus is clearly a risk factor for oesophageal adenocarcinoma (30, 31). It has been proposed that even uncomplicated reflux oesophagitis (without Barrett's oesophagus) predisposes to oesophageal neoplasm. A recent epidemiological study from Sweden clearly emphasises the paramount impact of chronic reflux symptoms on the subsequent risk of developing adenocarcinoma of the oesophagus (32).

Apart from reports on Barrett's oesophagus there are few studies addressing the issue of prevalence of oesophageal complications to GORD. The estimate of less than 2% of gross oesophageal haemorrhage seems reasonable, but occult bleeding from the oesophagus may be far more common (33). The prevalence of complications in patients with GORD has been estimated to be; 10-15% Barrett's oesophagus, 2-7% oesophageal ulcer, <2% oesophageal haemorrhage, <0.2% oesophageal perforation and 4-20% oesophageal stricture (34). The benign character of the disease has been emphasised by many clinical investigators. A recent population based study from Finland (35), however, suggested that a larger proportion of patients with GORD might experience a fatal outcome due to severe complications than previously has been recognised.

## **PATHOPHYSIOLOGICAL ASPECTS ON:**

### **Oesophageal body function**

The oesophagus is not simply a tube through which food passes. It is an organ with its own movement patterns and its own innervation. At rest the oesophagus is tightly closed above and below with the upper oesophageal sphincter consisting of straightening muscle tissue creating a high-pressure (40-120 mm Hg). The lower oesophageal sphincter consists of smooth muscle tissue establishing a pressure zone amounting to 10-15 mm Hg in the normal state. At swallowing, a co-ordinated pattern of relaxation and contraction is initiated starting in the hypopharynx, upper oesophageal sphincter, the oesophageal body and lower oesophageal sphincter. In a normal swallow movement the peristaltic contraction of the oesophageal body is propagated towards the stomach and before the peristaltic contraction reaches the distal oesophagus, the LOS opens for a few seconds (36). The peristalsis observed with normal swallowing is called primary peristalsis. If gastric juice is refluxed into the oesophagus or parts of the bolus retained in the organ, the oesophageal wall stretches which also triggers peristaltic movements, so called secondary peristalsis. This type of peristalsis also coincides

with a relaxation of the lower oesophageal sphincter (LOS) (37, 38). The primary peristaltic wave clears the oesophageal lumen of the bolus and in case of reflux also of the refluxed material. Oesophageal clearance may be impaired in patients with GORD due to impaired peristalsis (39, 40, 41), but the relationship between peristaltic dysfunction and acid clearance has not been well fully explored. The peristaltic wave itself does not suffice to restore oesophageal pH to the normal level in case of acid reflux. There are two major factors affecting the acid clearance time (42): the volume clearance which is dependent on the oesophageal peristalsis and secondly the salivary function (43). With the clearance of the bolus, acidification of the oesophageal lumen is substantially reduced by the first swallow induced by the peristaltic wave, but then it takes several minutes before the oesophageal pH has returned to normal level due to repeated swallowing and neutralisation of the remaining acid by the bicarbonate of the saliva (44). In this context it is important to note that in the majority of GORD patients the salivary volume and bicarbonate secretion do not differ from healthy controls but still has the oesophageal acid been shown to be impaired in many patients with GORD (43). Patients with hiatal hernias are also more likely to have abnormal acid exposure, which is probably related to the delayed clearance of oesophageal content due to the anatomical displacement of the gastro-oesophageal junction (45, 46).

Motility defects in the oesophageal body have been described which per se cause impaired oesophageal clearance of refluxed material (43, 47- 53). Although the figures vary between different series, as many as 40% of patients with severe GORD might have delayed gastric emptying which per se also facilitates reflux of noxious material into the oesophagus (54, 55). Recent data have demonstrated an association between impaired motor function recorded in the oesophagus and delayed emptying of food components from the stomach in these patients (56). Oesophageal primary peristalsis contraction amplitudes below the 25th percentile of the normal, at the level of the oesophagus, are considered failed contractions. Contraction velocity between two contraction peaks of  $> 20$  cm/second are considered to be simultaneous rather than peristaltic. Using these definitions, failure of oesophageal body motor function can be identified by the presence of a contraction amplitude below 20 mm Hg in one or more of the three lowest 5 cm oesophageal segments, or a prevalence of  $> 20\%$  simultaneous waves in these segments. Furthermore, impaired bolus clearance follows a peristaltic amplitude  $\leq 30$  mm Hg in the distal third of the oesophagus (43, 47, 48).

## **Gastro-oesophageal junction**

Reflux of contents from the stomach into the oesophagus is a normal physiological phenomenon that occurs at least a few times daily in adults provided that intergastric pressure supersedes the competence of the reflux preventing mechanisms in the oesophago-gastric junction. Reflux is prevented by a barrier at this anatomical site, comprising of both functional and structural components. The different constituents of this barrier have been suggested to be the mucosal valve, the angle of His, the intraabdominal portion of the oesophagus, the crural diaphragm and perhaps the most significant component being the lower oesophageal sphincter. In normal subjects, the majority of reflux episodes seem to be associated with and probably caused by transient lower oesophageal sphincter relaxation's (TLOSR) which are by definition not swallow induced (57- 60). These TLOSR:s are probably mainly triggered by gastric mechanisms in the form of mechano-receptors located in the proximal part of the stomach (57, 61). These mechanisms are very similar to those operating during normal venting of air during belching (62, 63). It seems as if the triggering of TLOSR:s is counteracted by some postural changes, anaesthesia as well as sleep. At the time of transient lower oesophageal sphincter relaxations a concomitant inhibition of the crural diaphragm occurs (58).

In patients with GORD, the level of oesophageal acid exposure is markedly increased due to the frequent episodes of reflux. There seems to be a correlation between the severity of mucosal breaks according to the Los Angeles classification system and the magnitude of acid exposure (64). The majority of reflux episodes are preceded by TLOSR:s (62, 65- 67). In the fasting state the number of TLOSR:s is very low and food intake is a strong stimulus to transient lower oesophageal sphincter relaxations also explaining the postprandial character of abnormal reflux in the majority of patients with GORD (58, 60, 68, 70). In patients with severe oesophagitis, on the other hand, both day time and night time acid exposure are important and other aspects on the incompetence of the antireflux barrier contribute to the relative high level of acid exposure. In these patients, the remaining reflux episodes seems to be associated with either absent LOS tone or with abdominal straining where the increase in gastric pressure overcomes the pressure of the tone of the lower oesophageal sphincter (58, 59, 66). Since the contractions of the crural diaphragm increases the intraluminal pressure at the oesophago-gastric junction it prevents reflux by compressing the distal oesophagus. It is important to realise that antireflux barrier is therefore compromised in patients with large

hiatal hernias and the presence of hiatal hernias has recently been shown to correlate to abnormal acid exposure also in randomly selected subjects recruited from the normal population (45, 59, 71, 72).

### **Mucosal resistance**

The components of the refluxate, including H<sup>+</sup> ions, pepsins, bile salts and pancreatic enzymes are potentially able to permeate the oesophageal squamous mucosa and cause injury (73, 74). These agents may act individually or in combination, although present information would firmly suggest that the most predominant effects are exerted by the acid component. The mucosal barrier opposes the effects of these damaging agents constituting an integrated complex of anatomical physiological components which together act to maintain the integrity of the mucosa (75, 76). Oesophagitis results from excessive reflux of gastric content rather than excessive gastric secretion (77). It has been proposed that bile acids play a major role in the patients with complicated reflux disease since increased concentrations of bile acids are found in the oesophagus of patients with Barrett's oesophagus (73). Several studies have demonstrated a correlation between mucosal contact time with the refluxate and the endoscopic severity of the oesophagitis (78, 79), but a similar relationship between the intensity of symptoms and the magnitude of acid reflux has not been clearly shown (80- 82). Additional data also support the view that mechanisms within the epithelial barrier of the oesophageal mucosa may be important for the development of oesophageal injury and symptoms in patients with GORD (83). The morphological barrier that prevents or retards diffusion of noxious luminal contents through the epithelium has been characterised as a string of apical cell membranes combined with intracellular junctional structures throughout the upper cell layers of the stratum corneum of the squamous epithelium (84). The mucosal resistance, which is dependent on the inherent resistance to these ionic movements, seems to be a function of these tight junctions and also the intercellular glycoconjugate. In GORD, the ability to resist acid is probably weakened and acid passes relatively more easily from the oesophageal lumen into the upper layers of the epithelium (85). Differences in epithelial resistance between individuals may then explain why the same level of acid exposure causes symptoms and oesophageal damage in one individual but not in another (86, 87).



## SURGICAL THERAPY

For many patients GORD is a chronic relapsing problem. This becomes readily apparent when confronted with the very rapid and almost universal symptomatic and/or endoscopic relapse after prior healing of reflux induced oesophageal damage with e.g. acid inhibitor drugs (88, 89). One explanation for the chronic nature of GORD is the failure of the medical therapy to correct the underlying motor abnormalities responsible for the disease (90- 92). As no medical therapy is capable of providing permanent correction of the motor disorders it is to be expected that reflux will recur as soon as therapy is stopped. However, with modern medical therapy in the form of proton pump inhibitors (PPI), patients can be kept in clinical remission for years (93- 95). There are, however, short comings and drawbacks with pharmacological maintenance therapy (96). H<sub>2</sub> receptor antagonists insufficiently interfere with food stimulated acid production and a striking tachyphylaxis and subsequent acid rebound is frequently seen (97). For more severe reflux disease twice daily doses of proton pump inhibitors are often necessary and occasional acid rebound is also demonstrable after stopping proton pump inhibitor therapy (98, 99). Furthermore, there is sometimes an insufficient control of volume reflux, nocturnal symptoms and retrosternal pain. With time dose escalation may be necessary and particularly divided doses of acid inhibitory drugs are required (100). Acid break through during the night has recently been recognised and a novel medical management strategy has subsequently been designed with the addition of nighttime H<sub>2</sub> receptor antagonists (99). Another aspect causing some concern is of course the worsening of the inflammation of the gastric mucosa during PPI therapy, especially within the corpus area in *Helicobacter pylori* infected patients. This topic has been quite vigorously debated recently (101, 102). The ongoing controversy relating to non-acid reflux (bile and pancreatic juice reflux) and its potential effect on the occurrence of columnar lined metaplasia and therefore also the increasing problem with adenocarcinoma of the oesophagus has always to be born in mind (103-105). The rising incidence of adenocarcinoma of the oesophagus and gastric cardia seems to be strongly associated with chronic reflux particularly in obese patients (32, 106). These many concerns will in the future have important impacts on the attitudes towards complete control of reflux and the reconstruction of the physiology of the gastro-oesophageal junction by an antireflux operation.

## Indications for therapy

Surgical treatment of gastro-oesophageal reflux disease has previously been limited to patients with chronic complicated reflux or those with very long-standing severe symptoms. There is now an increasing tendency in many countries to utilise surgery in the early stage of reflux. This is due to changes in the surgical technique and also perhaps paradoxically because of the improvement of medical therapy (107). Patients with reflux can be divided into two groups. Those who have complicated reflux and those with straightforward disease without complications. The treatment of peptic strictures has been greatly improved by introduction of PPI:s. In past surgery was the only effective treatment for strictures and when the stricture tight and fibrotic this often required a resection of the oesophagus (108). Dilatable strictures in young fit patients are still an indication for fundoplication and dilatation (109, 110). Respiratory complications include recurrent pneumonia, bronchitis, asthma, posterior laryngitis and chronic cough (111, 112). This is a firmly established indication for antireflux surgery although we must admit that the scientific evidence for the true benefit of antireflux surgery has still to be gained (113-115). There is no consensus on whether Barrett's oesophagus (columnar lined mucosa) remains an absolute indication for antireflux surgery. Evidence, however, suggests that continued reflux may be deleterious for the process of neoplastic changes in the oesophageal mucosa (103) and in fact the results of a randomised trial, presented some years ago suggested that antireflux surgery had advantages over medical therapy (116). The modern updated use of PPI:s, however, has to be compared to antireflux surgery in order to reach a more comprehensive view of the potential merits of respective therapy. Another important aspect is of course the data suggesting that dysplastic lesions do not occur after successful antireflux surgery as compared to the situation in those who experienced relapse after the surgical procedure (117). Recent circumstantial information would indicate that antireflux surgery has the potential to reverse the metaplastic lesions in the cardiac region but continued follow-up and more extensive clinical research are required.

In patients with uncomplicated reflux antireflux surgery used to be indicated in those where medical treatment could not prevent the disease from significantly deteriorating the patients quality of life. Historically, failure to respond to medical treatment has been the main determinant for those referred for antireflux surgery. This indication still remains valid but modern medical therapies are so effective that only a small minority of patients do not get substantial or complete relief of their symptoms (89). However, if patients cease their use of

PPI:s reflux symptoms recur rapidly and sometimes even with greater severity than before treatment (118). Also many patients with reflux do not want to be reliant on a form of medical therapy that is yet to establish its record of safety over many years (> 10 years) of continuous use.

### **Historical aspects**

Originally the hiatal hernia was regarded as the dominant pathogenetic factor in GORD hence the surgical approach was to correct this anatomical defect in patients with reflux oesophagitis (119). By the technique introduced by Allison the hiatal hernia was reduced by incising the phrenico oesophageal ligament and resuturing it to the inferior diaphragm and also approximating the crural components of the diaphragm. Subsequent follow-up proved this operative approach to be ineffective (120, 121). In 1955 Rudolf Nissen performed the first fundoplication (360°) after that he had observed its beneficial effects in a patient in whom he resected the gastro-oesophageal junction and reconstructed with an oesophago-gastrostomy (122, 123). After a series of technical developments Belsey introduced his antireflux procedure in 1952 and later Skinner and Belsey reported successful results in a substantial proportion of patients (124). This procedure was done transthoracically with the wrap encircling about 270° of the oesophageal circumference. Many modifications have thereafter been introduced based on the original Nissen total fundoplication. Rossetti and Hell (1977) used a technique which incorporated only the anterior fundic wall which was encircling the entire circumference of the oesophagus and they fixed the wrap to the cardia in order to prevent wrap migration (125). Quite soon it became evident that patients after a total fundoplication had not only some obstructive complaints but also had difficulties in venting air from the stomach and also inability to vomit. In order to prevent gas bloat complaints a more floppy technique was launched including full mobilisation of the fundus of the stomach with construction of the wrap around a large bougie introduced into the oesophagus and straightening the gastro-oesophageal junction (126). Subsequent studies also tried to gain data to support the view that the wrap should be even shortened in order to prevent some of these complaints (127).

The original Nissen fundoplication (123) was done by laparotomy through a mid-line incision with dissection and visualisation of the oesophago-gastric region allowing also mobilisation

of the distal oesophagus. Usually these operations were combined with a crural repair with application of a couple of sutures approximating the posterior part of the crural diaphragm. The fundus is brought behind the oesophagus and sutured in front of the oesophagus with or without mobilisation of the short gastric vessels. Various methods have been presented to prevent disruption and slippage of the wrap (128). For instance teflon patches applied externally between the fundic wall and the oesophagus and other techniques including placing the sutures in two layers have been presented. Measures to prevent migration of the wrap have been advocated including incorporation of the oesophagus in the sutures, suturing the upper border of the wrap to the oesophagus or to include the anterior gastric wall in the lowest sutures fixing the left side of the wrap to the cardia.

The partial posterior fundoplication was popularised by Toupet (1963) (129), an operation which is performed by mobilising the oesophagus as previously mentioned and thereafter the left and right side of the wrap, the wrap is anchored to the crura as well as to the oesophagus with or without addition of a crural repair. Thereby, about 200° of the oesophagus is encircled by the wrap. The wrap may also be anchored to the arcuate ligament and the preaortic fascia thus reinforcing the flap valve mechanism (130)

The Hill procedure (131) includes reduction of the hiatal hernia, hiatal closure and suturing the anterior and posterior phrenico-oesophageal bundles to the preaortic fascia. Successful reconstruction has been suggested to be confirmed by intraoperative manometry (132). It has been claimed that this procedure restores the intraabdominal oesophagus, the angle of His and thus reconstructs the physiology of the gastro-oesophageal junction.

## **THE AIM OF THE STUDY**

Fundoplication operations have become the most widely used form of antireflux surgery and the efficacy of these operations has been established by clinical and endoscopic follow-up and also by oesophageal 24 hour pH monitoring (133- 139). Under the decades, a number of modifications of the original fundoplication operations have been launched but not every surgeon using the actual technique is as satisfied with the clinical outcome as the originator. When compiling data from clinical studies it is difficult to obviate clinical important differences in the efficacy between different antireflux procedures when assessing the GORD

relapse rate. The most comprehensive and scientifically valid way of establishing an eventual advantage of one therapeutic strategy over another is to carry out comparative, randomised and clinical trials. There are a number of obstacles that make the design and logistics of similar trials in the surgical field complicated. Since the introduction of the Nissen total fundoplication there has been some concern about the incidence of troublesome mechanical complications which have necessitated several modifications reducing the over all incidence of these complications to about 15% (140). Persistent postprandial adverse symptoms in the form of dysphagia, inability to belch and vomit, postprandial fullness, bloating and pain and socially embarrassing rectal flatulence can mar on otherwise excellent result in a small but significant group of patients after these procedures. The frequency by which these postfundoplication symptoms have been reported varies considerably between series (135, 136, 141, 142). Since we lack effective treatment of established severe postfundoplication symptoms prevention is of primary concern. A number of technical considerations have been focused on and alleged to counteract some of these problems.

The present thesis therefore can be subdivided into two major parts; one dealing with the pathogenesis of GORD and the other by the refinement of antireflux surgery based on an increased knowledge of the mode of action of similar procedures.

The following questions were addressed:

1/ Can a posterior partial fundoplication control reflux and symptoms of GORD as effectively as a total fundoplication?

2/ Is a partial fundoplication followed by less complaints of gas bloat character than a total fundoplication? If so, which mechanisms are involved?

3/ Does the motor characteristics of the body of the oesophagus influence the outcome of antireflux surgery? Is it possible to tailor the surgical procedure based on similar preoperative manometric information?

4/ Does oesophageal motor function improve with the time of reflux control?

5/ Are motor disturbances (primary and/or secondary peristalsis) genuine pathogenetic deficiencies in GORD or do they occur as a secondary phenomenon and thereby having the potential of being reversible?

## PATIENTS AND METHODS

### Clinical assessments

Except for the preoperative situation all patients were during the postoperative follow-up investigated and interviewed by an independent physician in order to increase the precision of the clinical and endoscopic information. Symptoms both relating to GORD and postfundoplication complaints were graded from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe, incapacitating symptoms).

All follow-up visits were scheduled according to a predefined protocol (Figure 1) up to 3 years after the operation. In case of troublesome symptoms and/or relapse the patients were asked to contact the respective clinician in charge or the research nurse who were responsible for the logistic aspects of the follow-up procedures.

	Pre op	Post op				
		3 mos.	6 mos.	1 yr.	3 yrs.	5 yrs.
Clin. assessment	X	X	X	X	X	X
Endoscopy	X			X	X	X
24 h pH- metry	X		X		X	
Manometry	X		X		X	

Fig. 1. Protocol followed for the assessment of antireflux surgery.

## **Endoscopy**

Endoscopic investigations of the oesophagus, stomach and proximal duodenum were carried out on an out-patient basis with the patient fasted over night and local anaesthetics applied to the posterior pharynx. Videoendoscopes or in the early part of the investigation period, Olympus GIF XQ endoscopes were regularly used. Again the postoperative endoscopic investigations were performed by an independent endoscopist who was not aware of the details of the actual surgical procedure or manometric findings.

A modification of the Savary-Miller endoscopic classification system was used to describe the signs of oesophagitis, which has been described in detail elsewhere (143). The following gradings were used:

Grade 0 = normal oesophageal mucosa, no abnormalities noted.

Grade 1 = erythema or diffusely red mucosa: oedema causing accentuated folds.

Grade 2 = isolated round or linear erosions extending from the gastro-oesophageal junction upward in relation to the folds.

Grade 3 = confluent erosions extending around the entire circumference or superficial ulceration but without stenosis.

Grade 4 = complicated: erosions as described above plus deep ulceration, stricture of columnar lined oesophagus.

We separately analysed the presence or absence of columnar lined oesophagus defined as columnar lined metaplasia extending (3 cm above the gastro-oesophageal junction).

## **24 hour pH monitoring**

A monocrystalline antimony pH electrode (Metronic, Stockholm, Sweden) was passed through and secured to the nose with the electrode positioned 5 cm above the high-pressure zone as located by the preceding manometric investigation. A reference electrode was

attached to the skin of the chest. Each pH electrode was calibrated before and after the respective investigations and the pH data were acquired every 4th second and stored in a digital memory. All patients carried out these investigations on an ambulatory basis when they were instructed to follow their usual pattern of living. Reflux symptoms, meals including drinking, smoking and resting periods were recorded by the patients in a diary.

### **Lower oesophageal sphincter pressure**

The manometric techniques used were aimed at investigating the motor activity of the body of the oesophagus and the basal tone and function of the lower oesophageal sphincter (LOS).

For assessment of lower oesophageal sphincter tone and function two techniques were used: firstly the LOS tone was assessed by use of a station pull-through technique where the pressure characteristics of the gastro-oesophageal junction were measured by a water perfused triple lumen catheter with 3 side holes positioned 120° apart. The catheter was connected to a transducer assembly, placed at the oesophageal level of the subject when supine. Each channel was perfused with water (0.5 ml /minute) by a low compliance capillary system (Arndorfer Medical Specialities, Green Dale, Wisconsin, USA). The probe was introduced through the nose in subjects being fasted over night. When the station pull-through technique was used the probe was withdrawn 0.5 cm each time and kept at this level for at least 30 seconds or until recordings became stable. The high-pressure zone was defined as the mean of the highest pressure plateau recorded by each of the 3 ports minus the pressure in the gastric fundus measured at the end of expiration. The length of the intraabdominal portion of the high pressure zone was calculated from the pressure profile as the distance from the point of the first stable pressure elevation above the fundus pressure to the first point of negative pressure to change on inspiration.

Each catheter assembly was connected to a transducer placed at the oesophageal level of the subject in a supine position. All pressure recordings were traced on line on a computerised system (Synectics, Polygram, Stockholm, Sweden, version 6.40).



### The sleeve technique

In order to compensate for the potential inaccuracies with the station pull-through technique, depending on the movements of the LOS region with breathing and swallowing (144) and also to allow longer periods of continuous assessment of LOS tone, we also used the sleeve sensor as originally described by Dent in 1976 (145). This catheter assembly had at the distal end a sleeve sensor, which was positioned to straddle the oesophageal junction. In the side hole distal to the sleeve the intragastric pressure was measured continuously. The sleeve sensor consists of a 6 cm long thin wall rubber sleeve that was glued along with the catheter. The sleeve was constantly perfused with water and the lower oesophageal sphincter squeezed this sleeve membrane to cause an increased resistance to flow of water throughout the length of the sleeve. The increased resistance to water perfusion has been shown to be directly related to the squeeze pressure inflicted on the sleeve. At each assessment, the LOS pressure was related to the corresponding intragastric pressure as assessed during expiration. By use of the sleeve technique we could assess LOS tone over a substantial period of time but in addition to that the technique offered a unique prerequisite for analysing LOS function such as the triggering of transient lower oesophageal sphincter relaxations and the nadir pressure of the LOS during repeated water swallows.

The transient lower oesophageal sphincter relaxations were defined as abrupt ( $< 1$  mm Hg/second) fall in LOS tone exceeding 5 mm Hg to a level of  $\leq 2$  mm Hg above the intragastric pressure with a duration of these events extending to at least 5 seconds (146). No swallows were allowed during the 5 seconds preceding the onset of the LOS relaxation. Postswallowing transient lower oesophageal sphincter relaxations were, however, included in the analysis.

In one investigation the ramp pressure immediately oral to the LOS was investigated (147). The ramp pressure in this context was identical to the intrabolus pressure assessed in the distal third of the oesophagus just proximal to the sleeve sensor. It was defined as the plateau of pressure ( $\leq 2$  mm Hg) above the intraluminal baseline pressure which was established immediately before the steep up stroke of the peristaltic contraction. The ramp pressure was calculated as the mean pressure level above intraluminal pressure occurring during 10 consecutive water swallows.

## Oesophageal body manometry

Manometric investigation of the oesophageal body was performed by use of a single catheter assembly containing 5 polyethylene tubes bound together with 5 lateral openings placed at 5 cm intervals from the distal end of the catheter. The catheter was perfused with water at 0.5 ml/minute with a low compliance capillary system as described above. The function of the oesophageal body was assessed by placing the proximal side hole 1 cm below the upper oesophageal sphincter and the main side hole at 5 cm:s interval covering the entire length of the oesophageal body. In order to analyse the primary peristalsis, ten swallows of 5 ml volume, at room temperature, were performed with at least 15 seconds intervals. The peristaltic characteristics were analysed as follows: The mean contraction amplitude was assessed in the distal third of the oesophageal body as the peak pressure in relation to the end expiratory intraluminal pressure of the oesophageal body. The duration of each contraction was defined as the length of the time in seconds between the intercept points of the steep up and down stroke of the contraction and estimated in relation to the base line intraluminal pressure. The time delay between peaks of the oesophageal pressures at consecutive recording points was used to calculate the speed of the peristaltic wave. Simultaneous contractions were defined to have a propagation speed of  $> 20$  cm/second. In addition, the frequency of failed primary peristalsis was determined and characterised when a peristaltic sequence reached an amplitude of less than 10 mm Hg at any side hole and onwards when the water swallow induced peristalsis was followed through the oesophagus. An "aperistaltic oesophagus" was defined as a situation when water swallows never elicited a peristaltic response in any level of the oesophagus, which reached an amplitude of 20 mm Hg.

Secondary peristalsis (38) was triggered by insufflation of a 10 ml air bolus rapidly into the mid portion of the oesophagus with at least 20 seconds intervals. After each air bolus insufflation the peristaltic response in the distal third of the oesophagus was investigated. After each recording session a dry swallow was followed before the next air bolus was insufflated to clear the oesophagus from any remaining material. Otherwise the peristaltic characteristics of the secondary peristalsis were analysed as described for the primary peristalsis.

Common cavities in the oesophageal body after gastric distension (63) was assessed and defined as an abrupt increase ( $> 0.5$  mm Hg/second) in intraoesophageal pressure above the



The completeness of the transient lower oesophageal relaxations was assessed in relation to the nadir pressure during repeated water swallows (148). This is of particular importance after fundoplication procedures, which exposes the native LOS to external compression by the fundic cuff (Figure 2).

Therefore, separate notes were made on transient relaxations in which the nadir pressure reached below 2 ml Hg relative to intragastric pressure.

### **Operative procedures**

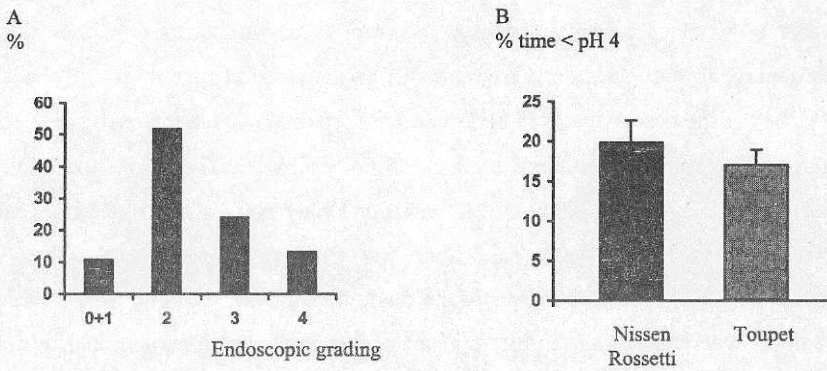
All operations were done through the abdominal route. A posterior crural repair was done only if preoperative barium meal radiography and endoscopy revealed an obvious hiatus hernia and if the operating surgeon considered the hiatus to be remarkably wide. The fundus of the stomach was generously mobilised by dividing the short gastric vessels. The distal oesophagus was exposed through the hiatus by opening the phrenico-oesophageal membrane and a 2-4 cm wide opening made above the hepatic branch of the anterior vagus nerve. The fundus could then be wrapped behind and around the oesophagus without tension. Care was taken to avoid damage to the vagus nerves. The partial fundoplication according to Toupet, encircled 180 - 200° of the oesophageal circumference and proximal sutures on each side also fixed the fundus to the crura and the lateral margins of the oesophagus. The right suture row continued distally with 2-3 stitches between the fundus and right margin of the oesophageal wall. The right posterior part of the fundoplication was fixed to the right crus with 2-3 separate non-absorbable sutures. The left part of the fundoplication was fixed to the left crus by at least 2 sutures whereafter the left posterior part of the fundoplication was fixed in the same manner as the right side, making the length of the fundus cuff 2-3 cm.

When performing a 360° fundoplication according to Nissen-Rossetti, a more extensive mobilisation of the greater curvature of the stomach was usually done. All short gastric vessels were regularly divided. The anterior part of the fundus encircled the oesophagus and was subsequently reattached to the anterior aspects of the fundus by non-absorbable sero-muscular sutures. The oesophageal wall was not included in these stitches and great care was taken to make the fundoplication "floppy" and about 2-3 cm in length. An index finger could easily be passed between the cuff and the oesophagus.

## Patients

### Study I

The background patient material consisted of 137 consecutive patients referred to our unit for surgical therapy with chronic GORD (38% males) with a mean age of 53.2 years (range 25-74 years). All patient had a clinical history indicating GORD, including complaints of acid regurgitation and heartburn and 8% had mild dysphagia. The respective endoscopic criteria are given in Figure 3 and 22 patients had Barrett's oesophagus extending at least 5 cm above the gastro-oesophageal junction but none had dysplasia at biopsy. In the same Figure is also given the preoperative 24 hour pH metry data. Sixty-five patients were randomised to a total fundic wrap according to Nissen-Rossetti and 72 to partial fundic wrap essentially according to the principles outlined original by Toupet. Forty-five % of the patients had a posterior crural repair based on the indications described above. The follow-up procedures are outlined in Figure 1.



**Fig. 3.** Preoperative endoscopic severity of oesophagitis (A) and acid reflux as assessed by ambulatory 24 h pH monitoring in patients submitted to antireflux surgery. Data are modified from Lundell L, Abrahamsson H, Ruth M, Sandberg N, Olbe L. Lower esophageal sphincter characteristics and esophageal acid exposure, following partial or 360° fundoplication: Results of a prospective, randomized clinical study. *World. J. Surg.* 15, 115- 121, 1991.

### Study II

In study II 33 of these chronic GORD patients (22 males) with a mean age of 53 years (range 25-71 years) agreed to participate in a more extensive manometric investigation program. An

additional selection criteria was that these patients had a clinical and investigational history of long-term successful outcome of the surgical procedure. The success of the operation was established by use of symptom assessment, endoscopic findings and 24 hour pH monitoring at 3 years after the operation. Eighteen of these patients had been randomised to partial fundic wrap and 15 to total fundoplication. Four had Barrett's oesophagus.

### Study III

From the originally recruited study population of 137 patients we could only use data from 106 patients for the study on the significance of tailoring antireflux surgery. This was due to the fact that 16 patients had initially to be excluded due to technical imperfections in the preoperative manometry. Furthermore, the study analysis was based on a minimal follow-up of 3 years and during that time period 3 patients were lost to follow-up, 2 died during the subsequent course and the rest had either a reoperation due to intrathoracic herniation of the fundoplication or gastro-oesophageal reflux relapse. The remaining 106 patients available for analysis (65 males) had a mean age of 53.5 years (range 25-74 year). Fifty-three of those were randomised to total fundoplication according to Nissen-Rossetti and 53 had a Toupet partial fundoplication.

### Study IV

Twenty-four of the originally enrolled patients agreed to undergo complete study program at the time of long-term follow-up after the original operation. The relevant investigations were carried out after a mean of 54.5 months (range 35-85 months) after the operation. Thirteen patients, with a mean age of 49.8 years (range 35-61 years) had originally a total fundoplication (11 males) and 11 subjects had a partial fundoplication of whom 7 were males (mean age 47.9 years, range 25-68 years). Again all patients had complete control of their reflux disease as assessed by symptoms, endoscopic investigation and ambulatory 24 hour pH monitoring.

### Study V

Three groups of subjects were included into this investigation. One comprised of 8 healthy volunteers with a mean age of 40 years (range 20-66 years) of whom 4 were males. The

second investigational group comprised of 23 GORD patients with a mean age of 44 years (range 34-60 years) of whom 15 were males and a GORD history extending up to 7 years. These patients had erosive oesophagitis and an abnormal 24 hour pH monitoring as inclusion criteria. Thirdly 21 successfully operated GORD patients were included who had a mean age of 48 years (range 25-68 years) and 16 of those were males. Eleven patients had been previously operated on with a total fundoplication and 10 by a partial posterior fundoplication. The investigations were carried out more than 3 years after the operation. The details of respective investigational procedures have been given previously.

### Statistics

In study I, the pre- and postoperative 24 hour pH monitoring and manometry data were evaluated by the non-parametric Mann-Witney U-test. Analysis of variance, by use of the Anova-test, was applied for the comparison between the two procedures concerning postoperative complaints of both GORD related character and postfundoplication type.

In study II, the manometric parameters; peristaltic amplitude, duration and propagation speed of the peristaltic wave, occurrence of failed, bifasic and simultaneous contractions were analysed by use of the Anova test for repeated measures and the non-parametric Wilcoxon signed rank test when appropriate. Preoperative peristaltic amplitudes in the two surgical groups were compared by the Student's *t*- and Wilcoxon signed rank tests. Student's *t*- test was also applied for analysis of postoperative ramp pressures.

In study III, simple regression analysis was initially applied followed by multiple stepwise regression analysis. In order to relate the preoperative manometric data and the clinical complaints, we applied the Chi-squared test.

In study IV, we applied the Student's *t*- test to compare the postoperative LOS properties and functions. The Chi-squared, Mann-Whitney and Wilcoxon signed rank tests were used to describe the occurrence of "common cavities" in the two patient groups.

In study V, the difference in response rate between stimuli in the three groups were analysed by use the Mann-Whitney U-test and for comparison between manometric properties relating

to primary and secondary peristalsis we applied the Wilcoxon-signed rank test and analysis of variance (Anova test). In all calculations  $p < 0.05$  was considered to be significant.

## RESULTS AND COMMENTS

### Do funduplications work- and how ? (Studies I, III ,V)

Preoperative data on the abdominal length and magnitude of the high pressure zone in the gastro-oesophageal junction were available in 85 patients when the station pull-through technique had been used. LOS tone was found to be  $7.1 \pm 0.6$  (SE) mm Hg and the intraabdominal length  $11 \pm 0.3$  mm. At 6 months after the operations the corresponding values were  $15.1 \pm 0.9$  mm Hg and  $20.5 \pm 1.0$  mm respectively. The basal pressure of the LOS region was significantly higher in patients having a total fundic wrap ( $p < 0.01$ ) a difference, which persisted with the passage of time. When the LOS tone was assessed by use of the sleeve technique in study V we found that the basal tone was quite stable in both fundoplication groups but was significantly higher in those who underwent total fundoplication both in the sitting as well as in the recumbent position ( $p = 0.01$ ). At these long-term follow-up investigation we again found no difference in the intraabdominal length of the high pressure zone between the two operative procedures.

During the study period we defined a relapse of GORD to be recurrent symptoms of similar character to those assessed before the operation and/or endoscopic signs of oesophagitis. The symptom should be severe enough to require at least intermittent medical therapy and not managed only by modification of life style. The recurrence of reflux during the first 3 years occurred in 7 patients, 4 (6%) in the partial fundoplication group and in 3 (5%) in the Nissen-Rossetti group. Five of these patients had a relapse within 6 months of the operation. With regard to clinical assessment, endoscopic investigations and 24 hour pH monitoring variables we found no significant differences between the two study groups neither at the early, nor at the long-term follow-up investigations.

Specific postfundoplication symptoms such as inability to vomit were reported by the patients with a similar frequency in both groups (85%) at three months and corresponding figures were



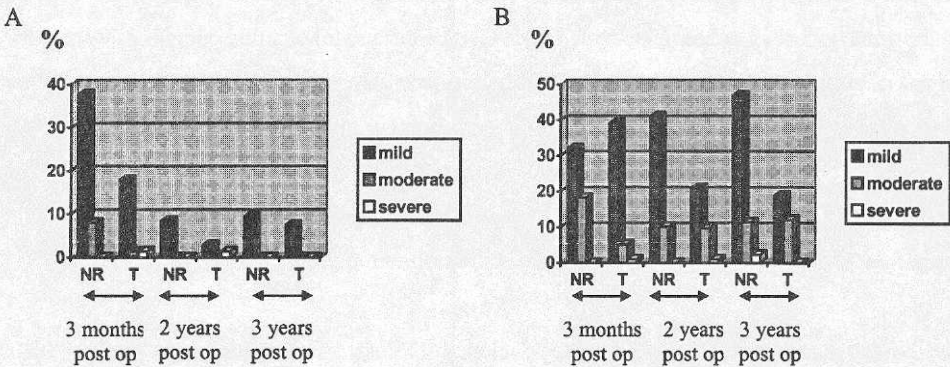
obtained at 3 and 5 years (88 and 90% respectively). It is important to note that only 5% of these patients indicated that their inability to vomit exerted detrimental effect on their quality of life either in the early or in the late postoperative period. At 3 months after the operation, 82% reported an ability to vent air from the stomach and 80% indicated a similar ability 3 and 5 years later. Consequently, when asked specifically about this most patients were able to belch after surgery with no difference between the two procedures. Dysphagia was more frequently reported in patients who had Nissen-Rossetti total fundoplication at the early postoperative investigation ( $p < 0.05$ ), a difference which subsequently disappeared. Several postprandial symptoms were evident in the early postoperative phase and there was a tendency towards an improvement with time. However, a significant difference emerged between the two study groups with respect to complaints of rectal flatulence showing that significantly fewer patients who had a Toupet posterior partial fundoplication complained of this during the follow-up period ( $p < 0.05$  at 2 years and  $p < 0.01$  at 3 years) (Figure 4).

Five patients who had a "floppy" Nissen-Rossetti experienced a herniation of the fundoplication into the thoracic cavity, giving rise to symptoms ranging from signs of pure obstruction to postprandial pain but none had reflux. No one in the Toupet group had a similar herniation diagnosed. This complication was diagnosed at variable time intervals after the operation. Noteworthy is that only one of these 5 patients had a crural repair at the primary operation. As a consequence of this specific complication, the total failure rate was higher among those allocated to a Nissen-Rossetti total fundoplication ( $p < 0.05$ ).

The nadir pressure of the lower oesophageal sphincter region investigated by the sleeve technique and assessed during water swallows was significantly higher in patients with the total fundoplication ( $10.1 \pm 1.7$  mm Hg) ( $m \pm SE$ ) than the value of  $3.4 \pm 0.5$  mm Hg in those who had a partial fundoplication ( $p = 0.003$ ). The number of transient lower oesophageal sphincter relaxations in the recumbent and sitting position was very low in the two groups, with an average number less than one transient lower oesophageal sphincter relaxation per 30 minutes period.

A marginal increase in the number of TLOSRS was noted after gas insufflation into the stomach. The few transient LOS relaxations elicited by gastric distension occurred in the first 10 minutes after gas insufflation and there were numerically more in the posterior

fundoplication group but otherwise there was no significant difference between the two study groups. The nadir pressure during transient LOS relaxations was  $6.5 \pm 2.6$  mm Hg in those having a total fundic wrap which was higher than the value of  $2.6 \pm 0.8$  mm Hg in those having a Toupet fundoplication (not significant). On recording the number of common cavities during transient lower oesophageal sphincter relaxations after gas insufflation into the stomach, 9 events were noted in 7 patients who had a partial fundoplication and only one in those with a total fundoplication ( $p=0.005$ ).



**Fig. 4.** Dysphagia score (A) and assessment of rectal flatulence (B) after total (NR) and partial (T) fundoplication.

Returning to the preoperative assessment of the study population, dysphagia (moderate to severe in 8%) was present in 20% of patients with no difference between the study groups. We observed no correlation between the prevalence of preoperative symptoms and the presence of abnormal manometric findings except between regurgitation and failed primary peristalsis ( $p=0.01$ ). Motor dysfunction (defined as peristaltic amplitude  $\leq 30$  mm Hg, failed primary peristalsis and/or simultaneous contractions in more than 20% of the peristaltic waves) was noted in 34 patients among those subsequently operated on with a total fundic wrap and in 33 patients having a partial, posterior fundoplication. Among these patients 15 had both a low peristaltic amplitude and failed primary peristalsis whereas 8 had a combined failed primary peristalsis and simultaneous contractions. The other patients had only one of these motor dysfunction characteristics, but again with no difference between the study groups. An "aperistaltic oesophagus" was preoperatively found in 4 patients later having a

Nissen-Rossetti and in 3 operated on with a posterior partial Toupet fundoplication. Again these patients could not be separated from the others by their preoperative symptom profile.

Postoperatively the point prevalence of dysphagia (always mild) decreased to a level of 8% at 3 years again with no difference within the surgical procedures. However, significantly fewer patients complained of rectal flatulence in the partial fundoplication group ( $p < 0.01$ ). Furthermore, we were unable to demonstrate a relationship between the preoperative symptom profile and postoperative outcome ( $r < 0.3$ ). We found no relationship ( $r < 0.3$ ) between preoperative manometric findings and postoperative symptoms both when assessed in the total group or when subdivided by the type of fundoplication operation. When the groups of patients representing motor dysfunction (see above) were specifically analysed we again were unable to demonstrate a difference in outcome between those having a total or a partial fundoplication. Considering the very few patients presenting with an "aperistaltic oesophagus", 6 patients reported no obstructive symptoms postoperatively and only one mild dysphagia, whereas one had some concern with regurgitation at 3 years postoperatively.

The Nissen-Rossetti and Toupet groups included 11 and 16 patients, respectively with a preoperative BMI  $> 28$  kg/m<sup>2</sup>. When the relationship between body mass and the surgical outcome in general was analysed we found that BMI had no impact on the clinical outcome. This was also true when those were compared having a BMI above and below 28 kg/m<sup>2</sup>, respectively.

Dysphagia is a quite common symptom in patients with long standing GORD and we observed that 20% complained preoperatively of some degree of dysphagia. Motility disturbances associated with GORD have been characterised and found to induce impaired volume clearance (47, 50, 149). It has been suggested that between 25-50% of patients with peptic oesophagitis have peristaltic dysfunction (48, 49, 53). Although we, like others, have not found obvious correlation between manometric findings and symptoms (150), the difference in prevalence of dysphagia between series may be due to selection criteria. Irrespective of these potentially confounding factors we were, however, unable to demonstrate any relationship between preoperative symptoms of obstructive nature and subsequent clinical response to different types of fundoplication.

A number of mechanisms have been suggested to be involved in the development of obstructive symptoms after fundoplication with a particular focus on motor dysfunction of the oesophageal body with its inherent association with impaired bolus clearance. Although the clinical significance of it has to be determined, total fundoplication indeed causes a partial obstruction at the gastro-oesophageal junction why it is tempting to believe that this surgical procedure is prone to induce obstructive complaints in reflux patients with impaired motor function. Accordingly, patients with preoperative poor oesophageal motility have been recommended to be operated on with partial fundoplication rather than a total fundic wrap to avoid adverse consequences of the operation (127, 151- 154). However, in our entire material we were unable to demonstrate any predictive value of the preoperative manometric findings on the subsequent outcome after either a total or a partial fundoplication. This analysis was broken down into greater detail, by specifically analysing those who had a preoperative peristaltic amplitude of less than 30 mm Hg in the distal oesophagus, those with failed primary peristalsis and increased frequency of simultaneous contractions thus being exposed to the highest theoretical risk. Still we were unable to demonstrate any impact of these preoperative manometric observations on the subsequent clinical outcome. During recent years, results have been published from another two studies, which have a bearing of this clinical topic. In a cross-sectional study, Mughal and co-workers investigated 176 consecutive patients who had a floppy Nissen fundoplication irrespective of the preoperative manometric characteristics (155). The authors concluded that preoperative oesophageal studies, other than those required to make an accurate diagnosis, were of no value in designing the suitability of patients for surgical correction of GORD with a total fundic wrap. In another series of 345 consecutive patients operated on with a laparoscopic Nissen fundoplication, Baigrie and co-workers found 31 patients who had severely disordered peristalsis preoperatively (156). These patients reported postoperatively very similar clinical results as in the larger group of patients with normal motor function of the oesophagus, which suggested to the authors that similar manometric findings are not a contraindication to a Nissen fundoplication. Taken together these reports indicate that the principle of tailored type of fundoplication, based on the preoperative motor function of the oesophagus in chronic GORD patients, lacks firm scientific support. Similarly, the alleged preference of a transthoracic approach in obese patients found no support by the present results either (154, 157). In fact, we recorded no impact of obesity on the outcome of antireflux surgery all performed through the abdominal route.

Fundoplication has become the most widely used form of antireflux surgery and the efficacy of the procedure has been established by clinical examinations, endoscopic follow-up and oesophageal pH monitoring (133- 139, 158). However, the prevention of reflux alone does not always provide an optimal result for the patient and persistent postfundoplication symptoms can jeopardise an otherwise excellent result because of dysphagia, inability to belch and vomit, postprandial fullness, bloating, pain and sometimes socially embarrassing rectal flatulence (135, 136, 141, 142). A number of technical considerations may counteract some of these problems but available data from controlled clinical trials have hitherto not allowed firm conclusions (140, 142, 154, 159- 161). This study was designed to address two clinical questions. First is it necessary to encircle more than half of the oesophageal circumference by the fundic wrap to control gastro-oesophageal reflux? Secondly, is a semifundoplication followed by fewer symptoms of gas bloat type than a total fundoplication?

Information from controlled, randomised clinical trials shows that various fundoplication procedures extensively used in clinical practice result in very similar long-term control of reflux symptoms (130, 162- 170). Many of the clinical trials carried out so far have enrolled a limited number of patients allowing a significant risk of type II error. These may yet be differences in efficacy and complications rate between various antireflux procedures. The total fundoplication with its modifications is the method of choice in many centres throughout the world, however, a total fundic wrap may need to be re-evaluated based on the preponderance of postoperative symptoms, as seen in the present study and also reported by others, when more specifically focused on these complaints. This is particularly significant since we found that the partial fundic wrap controls reflux equally well and durably when assessed objectively by a clinical assessor, at endoscopy and 24 hour pH monitoring. A particular risk of intrathoracic herniation of the fundoplication with its potential hazard and danger to the patient seems to be associated with the total fundoplication when a crural repair is not done (172, 173). Although not strictly studied present circumstantial information strongly indicates the necessity of always reconstructing the hiatus. The explanation for the fact that we saw no such complications in the Toupet group can be found in the technical aspects and differences between the two surgical procedures.

The key mechanisms behind side effects after fundoplication procedures may reside in the function of the lower oesophageal sphincter and its capacity to relax on appropriate stimulation (148). Transient lower oesophageal sphincter relaxations are known not only to

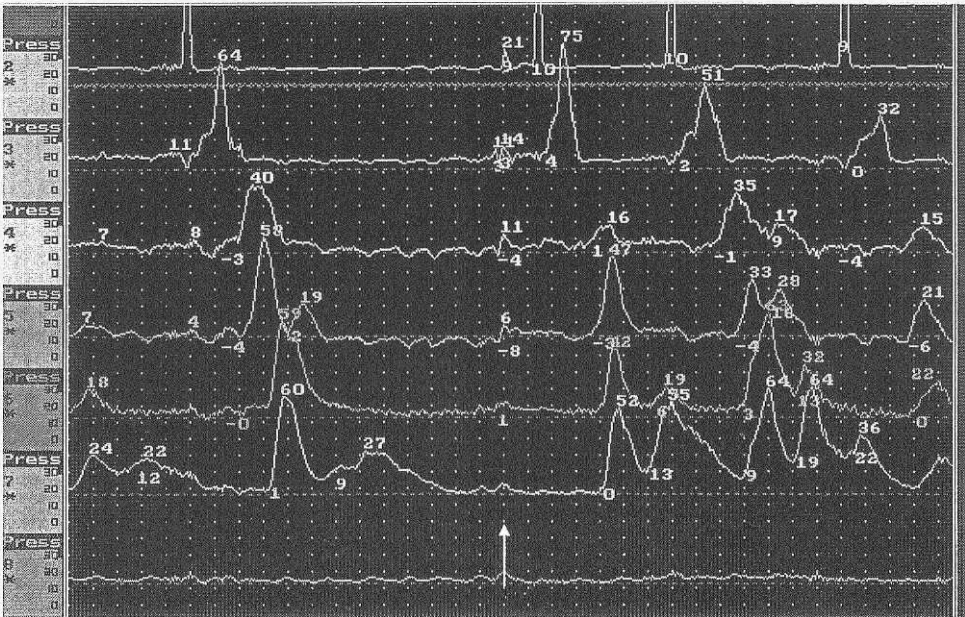
be of particular pathogenetic importance in GORD (59, 60), but also to play a pivotal role in our ability to adequately vent air from the stomach (62, 63, 171). We found that patients after total fundoplication more frequently complained of socially embarrassing flatulence, which might just be caused by an impairment in the ability to vent air from the stomach. Hypothetically, these operations might therefore exert different effects on important reflux preventing mechanisms such as LOS tone, inability of the LOS to relax on proper stimulation and on the frequency of transient LOS relaxations. Different studies done in patients submitted to fundoplication operations have shown an increase in LOS tone (174- 181). Our continuous assessment of LOS tone over a longer period of time, by use of a sleeve sensor, revealed that the pressure was substantially higher after total fundoplication than after posterior partial fundoplication. In the latter group the pressure levels recorded in the LOS were very close to what is seen in normal healthy subjects. In this context it is relevant to recall the previously expressed view that the total fundoplication might overcorrect the mechanical deficiencies in the gastro-oesophageal junction, creating a supercompetent cardia. It has to be shown whether a shorter and "looser" total fundoplication might counteract some of these mechanical consequences (154, 178). Irrespective of the type of operation, basal LOS tone did never reach a level at which free reflux is considered to occur. Some of the mechanical consequences may also induce obstructive complaints and/or manometric sequelae.

Recent studies have shown that a total fundic wrap reduces postprandial reflux by affecting amongst others the frequency of transient LOS relaxation (148). Similar studies have also demonstrated that these operations render swallowing induced LOS relaxations incomplete presumably by mechanical compression of the LOS segment (182). These observations are of major clinical significance since they suggest that these operations restore the physiology of the gastro-oesophageal junction. We, as others (148), realise that the definition of transient LOS relaxations has to be modified in similar studies where the patients in the postoperative setting have significantly higher basal sphincter tone and consequently when the nadire pressure is seldomly recorded at a level which is considered to allow free reflux (< 2 mm Hg).

We found a low frequency of transient LOS relaxations when assessed in the recumbent as well as in the upright body position when our patients were investigated about 3 years postoperatively. Similarly, gas insufflation into the stomach seldomly elicited transient LOS relaxations. Despite the fact Toupet fundoplication only encircles half of the oesophageal

circumference it was not possible to demonstrate a difference in the frequency of transient LOS relaxations between the two fundoplication groups both in the basal state and after gas insufflation into the stomach. A frequent observation was, however, that the nadire pressure during transient LOS relaxations was lower in the patients who had partial fundoplication.

An important indication of venting of air from the stomach is the occurrence of common cavity during manometry (Figure 5) (63). This event is represented mechanically by an intragastric pressure superseding the sphincteric pressure during relaxation and transmitted into the lumen of the body of the oesophagus. Significantly fewer, common cavities were recorded in patients having a total fundoplication. Therefore, these results provide an explanation for the clinical finding of fewer problems with rectal flatus after partial fundoplication.



**Fig. 5.** Manometric tracing from the oesophageal body and gastro- oesophageal junction, illustrating an "common cavity"- phenomenon.

Fundoplication surgery is, however, more than just wrapping the stomach around the distal oesophagus causing a mechanical buttressing of the area. The operation reduces the hiatal hernia by dissection and mobilisation of the oesophagus and positioning of the crural sutures. This anatomical restoration might in itself have the potential to prevent reflux by reducing the

hiatal hernia and by improving oesophageal clearance and crural function. Incomplete LOS relaxation after operation might also be induced by neural mechanisms since mobilisation of the fundus of the stomach divides connections between gastric mechanoreceptors in that area and the lower oesophageal sphincter region. Animal experiments may be interpreted in favour of a local denervation after similar operations (171, 183). The complete division of the short gastric vessels as carried out in the present series in patients undergoing a total fundic wrap might be followed by more complete denervation.

Therefore, it can be concluded that partial fundoplication procedures, which augment various constituents of the valvulo plastic components of the gastro-oesophageal junctional competence and utilise a lesser degree of fundoplication seem to be associated with a lower incidence of mechanical complications and an updated compilation of clinical data would suggest that a well conducted partial fundoplication procedure is as effective and durable in reflux control as a total fundoplication. This issue has even been more intensified since the advent of laparoscopic fundoplication and several reports have high-lighted the increased incidence of mechanical complications following a laparoscopic Nissen fundoplication compared with the open approach (184). Similar consequences may be associated with altered geometry and other factors inherent in the laparoscopic fundoplication techniques to which may be added the lack of tactile feedback. Data from recent, non-randomised, studies have, however, shown that laparoscopic partial fundoplication procedures may be associated with a similar low incidence of mechanical complications and a negligible reoperation rate as an open operation (185-188).

The clinical importance of reducing troublesome rectal flatulence by a partial fundoplication has to be recognised. Observations of particular significance on this issue come from a recent multicentric Nordic clinical trial where patients were prospectively interviewed both before and after antireflux surgery as part of a protocol comparing medical and surgical therapy (139). Hereby flatulence was found to be one of the few, so called postfundoplication symptoms, which indeed increased after the operation. A similar trend has previously been found in the Veteran Administration Study comparing medical and surgical therapy for complicated GORD (134). With the clinical goal of technically adjusting antireflux surgery to a level where reflux is not only effectively and durably controlled but also avoids adverse therapy specific symptoms, these observations have an apparent significance on the choice of antireflux procedure.



The question has also to be considered which factors are of importance when selecting patients for different surgical procedures? Gastric function studies have been emphasised but prospective, controlled clinical data are still lacking to support its significance (189). Furthermore, it has been argued that patients who suffer predominantly from upright (daytime) acid reflux, without endoscopic evidence of oesophagitis are less likely to respond favourably to antireflux surgery (157). The recognition of the importance of transient lower oesophageal sphincter relaxations in the pathogenesis of reflux suggests that postprandial reflux is a dominating pathogenetic mechanism giving more focus on daytime acid reflux variables (58). In fact, a recent study reported similar results in endoscopy negative compared to endoscopy positive GORD patients (186). Another issue is whether patients not responding fully to modern acid inhibition therapy are likely to respond less favourably to antireflux surgery? Given that a partial clinical response to such therapy is registered, our data would suggest a beneficial effect of fundoplication also in those few patients (139). However, manometric investigations and manometric data cannot be used to tailor the type of antireflux procedure but instead the most obvious objective for the manometric investigation in the preoperative setting should be to exclude other non GORD causes of symptoms and to establish a physiological reference point to which the positioning of the pH electrode for 24 hour pH monitoring can be related (190).

#### **Oesophageal motor dysfunction – of pathogenetic concern? (Studies II, V)**

Numerous investigators have demonstrated a resting tone of the lower oesophageal sphincter in the lower ranges in patients with reflux oesophagitis (47, 50, 174) and also a dysfunction relating to the occurrence and triggering of secondary peristalsis (37, 191- 193). These manometric events have also been observed to coincide with impaired oesophageal peristalsis, the more severe the endoscopic findings the greater disturbances in oesophageal motor function (40, 47, 50,194). With the occurrence of similar peristaltic deficiencies oesophageal transit may be retarded which causes a deficient clearance of installed acid into the oesophagus and consequently also of refluxed material during the instances of absent sphincter pressure or increased intraabdominal pressure. Whether these motor abnormalities are primary phenomena or occur as a consequence of repeated injury caused by acid reflux induced by inflammation is an area of controversy. Oesophageal peristalsis is still the major mechanism of oesophageal acid clearance firstly by the initial removal of the bulk of the

refluxate and secondly by the transport of swallowed saliva to neutralise acid components of the refluxate (39-41, 43). Secondary peristalsis which are triggered by oesophageal distension caused e.g. by reflux also contributes to the oesophageal volume clearance and consequently have been observed to occur less frequently in patients with reflux disease suggesting triggering defects hereby in these patients (191, 192, 194). Surgical observations have been presented to suggest that motor function may improve after fundoplication operations in terms of increased peristaltic amplitude and also a decreased percentage of failed primary peristalsis (174- 177). These observations would imply that these motor dysfunctions are secondary phenomena and also that reflux control is mandatory to prevent further progression. Furthermore, it has been suggested that fundoplication procedures should be performed before the mean contraction amplitude has fallen below 35 mm Hg i.e. before irreversible damage to the oesophageal muscle function has occurred (176). We addressed these issues in our patients randomised to either a total or a partial fundoplication in order to assess these patients also 3 years after the actual operative procedure. All patients studied pre- and postoperatively had a complete control of reflux as indicated by endoscopic, clinical and 24 hour pH monitoring observations. The positioning of the manometric catheter was related to the upper oesophageal sphincter in order to prevent any inaccuracies relating to the repositioning of the gastro-oesophageal junction into the abdominal cavity by the operative procedure.

Unfortunately, we were unable to recruit data on triggering of secondary peristalsis in these patients hence we in this respect have to compare the actual postoperative information with the corresponding values from controlled subjects and patients with reflux oesophagitis investigated in our laboratory for other purposes.

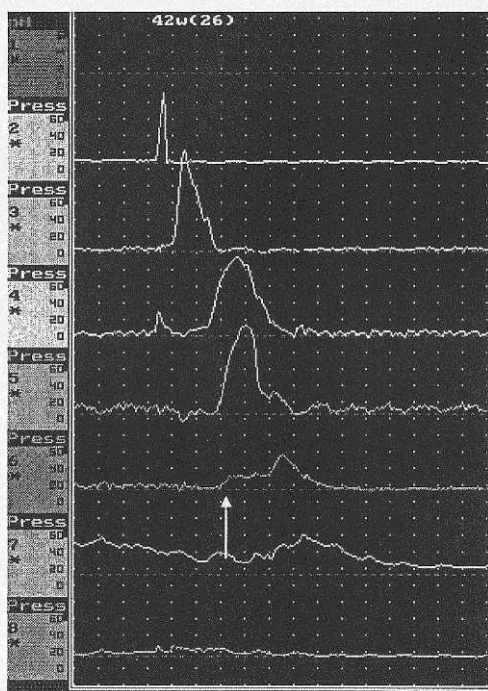
A somewhat, although not significant, lower mean peristaltic amplitude was found preoperatively in those patients who subsequently were allocated to Nissen-Rossetti total fundoplications. Similarly, a non-significant but somewhat high frequency of failed primary peristalsis was recorded in this group. In total 12 patients had a peristaltic amplitude preoperatively which was less than 35 mm in the distal oesophagus.

When reassessed 3 years after respective antireflux procedures, the peristaltic amplitude in the mid third of the oesophagus was significantly increased from  $43.3 \pm 17.8$  to  $58.8 \pm 22.6$  mm Hg (mean  $\pm$  SD,  $p < 0.05$ ). A significant increase ( $p < 0.05$ ) in the peristaltic amplitude was

correspondingly observed in the distal third of the oesophagus. No differences were, however, noted either in the peristaltic propagation speed or in the duration of the contractions. When the two fundoplication groups were separately analysed an increase in amplitude was recorded only in patients operated on with a Nissen-Rossetti fundoplication, whereas relatively unchanged values were recorded in those having a Toupet partial fundoplication. A significant decrease in the frequency of failed primary peristalsis ( $p < 0.05$ ) was recorded in the entire study group but again this difference was strictly confined to the patients allocated to a total fundic wrap. Manometric data from investigations using the sleeve sensor were obtained in 11 patients in the total fundic group and 15 in the partial posterior fundoplication group. Similar tracings were also obtained at least 3 years after the actual operative procedures. With the sleeve sensor straddling the gastro-oesophageal junction we were allowed to determine the ramp pressure by use of a similar type of analysis as has previously been done in the upper oesophageal sphincter (146). The mean ramp pressure after water swallows was  $3.1 \pm 3.8$  (mean  $\pm$  SD) mm Hg in the Toupet group whereas a somewhat higher figure of  $3.8 \pm 4.2$  mm Hg was established in those having a total fundic wrap. This difference did, however, not reach significance (Figure 6).

Secondary peristalsis stimulated by air insufflation into the mid oesophagus occurred in  $65 \pm 13.2$  % (mean  $\pm$  SD) of the healthy subjects which was higher than in the GORD patients ( $46.3 \pm 7.7$  %). In the chronic GORD patients who were investigated  $> 3$  years after successful antireflux surgery, secondary peristaltic wave was elicited in only  $26 \pm 7.2$  % of the attempts which was significantly lower than the  $46 \pm 7.7$  % of the secondary peristaltic waves triggered in the non operated GORD patients ( $p < 0.05$ ). When doing a direct comparison between motor characteristics of primary and secondary peristalsis we found that in general the secondary peristaltic waves had significantly lower amplitudes than the primary waves both in the non operated as well as in the operated patients. No significant differences were otherwise revealed between secondary and primary peristaltic wave duration and propagation. A separate analysis was also carried out comparing the 10 Toupet and 11 Nissen-Rossetti operated patients. Patients having a total fundic wrap presented with a higher amplitude when investigated 3 years after the operation whereas the motor characteristics otherwise did not differ between the two study groups. Accordingly the secondary peristaltic amplitudes remained somewhat higher in patients having a total fundoplication (not significant). The frequency of secondary peristaltic waves triggered by air insufflation was  $30 \pm 10.2$  % in those

having a partial fundoplication compared to  $23 \pm 10.4\%$  in those having a total fundic wrap (not significant).



**Fig. 6.** Ramp pressure (intrabolus pressure) after a water swallow in a patient previously operated on with a total fundoplication (the arrow indicates the onset of pressure rise).

What evidence supports the hypothesis that impaired motor function in GORD occurs as a consequence of reflux induced smooth muscle damage? Experimental studies have shown acid perfusion of the feline oesophagus to produce an inflammatory process, which seems to be associated with a reduction in lower oesophageal sphincter pressure (195, 196). This reduction is reversible and disappears concomitant with the healing of the oesophageal inflammation. In vitro studies have also shown that basal active forces of the circular muscle of the LOS to be reduced on acid challenge to the mucosa, a reduction which seems to be dependant of the degree of mucosal injury (197). Inflammatory reactions induced by oesophageal acid perfusion tend also to impair the transduction pathway, which mediates the contraction of the LOS (198). As previously mentioned studies on motor impairments in GORD suggest also that the degree of motor dysfunction becomes progressively more severe with advanced grades of oesophagitis (40, 47, 50, 194). Furthermore, surgical studies have presented data to suggest that motor function improve with time after fundoplication in terms of increased peristaltic amplitude and also decreased percentage of failed primary peristalsis

(174-177). Similar observations taken together would indicate that motor dysfunction in GORD is a secondary phenomenon with the potential to improve as a consequence of adequate and complete reflux control.

The question then is why we were unable to demonstrate an improvement in motor function of the distal oesophagus in our Toupet operated patients despite the fact that they had an equally durable and effective control of their reflux disease as those having a total fundoplication? Our study groups were also essentially identical with respect to other relevant clinical and laboratory indices of reflux disease. One possible explanation to our results could, however, be that the recorded increase in peristaltic amplitude in the Nissen-Rossetti group occurred solely as a consequence of an outflow obstruction in the gastro-oesophageal junction and therefore should be classified as a secondary phenomenon. The Toupet fundoplication raises the lower oesophageal sphincter tone to a level, which is significantly lower than after a total fundic wrap despite otherwise similar mechanical consequences on the intraabdominal length of the high pressure zone. We have data to support that these differences in the estimated tone of the lower oesophageal sphincter might explain the occurrence of dysphagia in the early postoperative period after a total fundoplication. Giving additional support to the idea of mechanical obstruction in the gastro-oesophageal junction we found numerically higher ramp pressures in patients having a total fundoplication.

Although our study design and methodology were not specifically focused on this issue, the data would thus imply higher intrabolus pressure in Nissen-Rossetti operated patients to overcome the subclinical outflow obstruction. As a consequence of such a mechanical situation, an increased amplitude of the peristaltic wave is to be expected why it can be argued that the recorded lower frequency of also failed primary peristalsis after total fundic wrap is a quite predictable and logic finding. This is particularly true as we applied a cut off level of  $\leq 10$  mm Hg of the peristaltic amplitude as a criteria for failed primary peristalsis. Our long-term findings after successful antireflux surgery showing no true improvement in oesophageal motor function are supported by data from studies in which reflux diseases was effectively controlled by medical means such as profound acid inhibition therapy (70, 90- 92, 199).

Secondary peristalsis is an important mechanism for the complete clearance from the oesophagus of either an obstructed bolus or juice refluxed from the stomach (57, 193).

Therefore defective secondary peristalsis might be a mechanism contributing to the pathogenesis of reflux disease and/or dysphagia (39, 40, 191-194). We obtained data to support previous findings suggesting that chronic GORD patients have a defective triggering of secondary peristalsis compared to healthy controls but otherwise the secondary motor functions of the oesophagus have similar characteristics compared to the primary peristaltic motor responses induced by water swallows. Furthermore, we observed that patients investigated > 3 years after successful antireflux operations had a higher threshold for eliciting secondary peristalsis when triggered by an air bolus injected into the mid portion of the oesophagus compared to chronic non-operated GORD patients and definitely so to healthy subjects. Although, it has to be mentioned that the present study groups should not be strictly compared, there are, however, important pieces of circumstantial information, which can be gained from the study. The presently observed lower primary peristaltic amplitude in the operated group compared to the non-operated GORD patients suggest that the former group already at the preoperative state had a more deteriorated motor function of the body of the oesophagus. Again we were unable to demonstrate any improvement in the peristaltic responses when the pre- and postoperative investigations were compared. Based on these observations it was predictable to find lower response rates also regarding the secondary peristalsis. In fact, if a significant improvement in motor function had appeared with time after antireflux surgery we would have expected a closer equality in the accuracy by which an air bolus would trigger secondary peristalsis when comparing the two chronic GORD study groups.

Therefore, it is reasonable to conclude that the present observations regarding primary peristalsis as well as secondary peristalsis support the hypothesis that GORD is pathogenetically linked to a primary defect in the oesophageal motor function and does not change with time of adequate reflux control.

## SUMMARY AND CONCLUDING REMARKS

An ideal antireflux procedure should be safe, effective, durable be relatively easy to teach and perform, and be free from troublesome mechanical complications. The total fundoplication in the form of the Nissen procedure is the most widely used antireflux operation world-wide. Although its efficacy is well documented, the clinical success relating to GORD control is frequently compromised by troublesome mechanical. These side effects seems to be related to the construction of a supercompetent antireflux barrier at the gastro-oesophageal junction, the consequences of which are inability to adequately vent air from the stomach. In patients operated on with a total fundoplication our data strongly suggest that compensatory mechanisms are operating to overcome an outflow obstruction in the gastro-oesophageal junction again emphasising the overcorrection of the physiology. It has been suggested that these mechanical adverse consequences may be counteracted by making the wrap shorter and looser. The ultimate goal for antireflux surgery has to be to restore the physiology of the antireflux mechanisms in the gastro-oesophageal junction to normalise the anatomy without adding adverse effects. In this thesis have results been presented to indicate that a partial posterior fundoplication achieves the same level of reflux control as a total fundoplication but is accompanied with a lower frequency of mechanical complications and also a more efficient ability to vent air from the stomach. The key mechanisms behind side effects after fundoplication procedures seems to reside in the function of the lower oesophageal sphincter (LOS) and its capacity to relax on appropriate stimulation. Our results would tentatively suggest that a partial posterior fundoplication normalises the LOS tone, significantly reduces the inability of the LOS to relax on proper stimulation and on the triggering on transient LOS relaxations. Furthermore, the mechanical consequences of a partial fundoplication are that the LOS tone approaches the level, which is seen in healthy subjects. Importantly only exceptionally were LOS pressure levels seen  $< 2$  mm Hg which is considered to allow free reflux.

The question of selecting patients for different surgical procedures is of highest clinical significance. Provided that an adequate diagnosis of GORD is established and the chronicity of the disease is obvious our data strongly suggest that manometric characteristics of the motor function of the body of the oesophagus cannot be used as a tool to tailor the surgical approach. The role of the manometric investigation in the preoperative settings should be to exclude

other non-GORD causes of symptoms and to establish a physiological reference point, to which the positioning of the pH electrode for 24-hour pH monitoring can be related.

There is a widespread consensus that GORD is pathogenetically linked to primary defects in the motor function of the oesophagus and gastro-oesophageal junction. Circumstantial evidence does, however, indicate that there is a deterioration of motor function with time of continuous injury caused by reflux damage to the mucosa and other oesophageal wall tissues. The data presently presented from relating to both primary and secondary peristalsis give support to the notion that GORD is a disease primarily affecting the motor function of that particular area. This information creates an important target for the development of future drug therapies.



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