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# Studies of preoperative evaluation and surgical procedures for gastroesophageal reflux disease

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# ABSTRACT

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## Introduction

Gastroesophageal reflux disease (GERD) is defined as the non-physiological movement of gastric contents from the stomach to the esophagus, which causes various degrees of troublesome symptoms and/or esophageal mucosal injury. Symptoms of GERD such as heartburn and regurgitation are common and the prevalence has been reported to vary between 7-20 % in the Western world. Although pharmacological treatment is the primary choice, surgery is an alternative when the effect of acid reducing agents is unsatisfactory.

## Objectives

The overall objectives of this thesis were to investigate different clinical aspects of preoperative evaluation and surgical procedures for the treatment of GERD.

## Methods and results

**Study I** investigates the predictive ability of preoperative esophageal manometry on postoperative dysphagia in 191 patients who underwent open antireflux surgery. Dysphagia was a common preoperative finding, as was any type of preoperative esophageal motor abnormality. Postoperatively, dysphagia was reduced irrespective of the presence of preoperative dysmotility or not.

**Study II** tests the hypothesis that laparoscopic partial fundoplication differs in clinical outcomes compared to open surgery in a randomized study including 192 patients with GERD. In the short term, open surgery was associated with a higher incidence of perioperative complications and a prolonged recovery. At 1 and 3 years postoperatively, esophageal acid exposure was reduced similarly after open and laparoscopic surgery, as was control of GER symptoms. During 3 years of follow up, the recurrence rate was higher in the laparoscopic group. However, total need for reinterventional surgery was at similar levels, due to increased rates of incisional hernia operations in the open group.

**Study III** investigates the symptomatic and physiological effects of endoscopic gastroplication (EGP) in 46 patients with GERD in a randomized placebo-controlled setting. Endoscopic gastroplication resulted in significant reduction of PPI consumption and GER symptoms during 1 year of follow up. However, there was no difference between the EGP and the placebo treated controls. EGP did not alter esophageal acid exposure or LES pressure.

**Study IV** investigates agreement, concordance of diagnostic yield, and subjective quality of life parameters between traditional 24 h catheter based and 48 h wireless esophageal pH monitoring in 55 GERD patients and 53 healthy volunteers. Wireless pH monitoring consistently underestimated esophageal acid exposure compared to traditional technique. Although there was a high correlation between the two techniques, the agreement between the methods as assessed by Bland-Altman analysis was low.

## Conclusions

Preoperative esophageal manometry does not predict development of postoperative dysphagia. Open and laparoscopic partial fundoplication are equally effective alternatives for the surgical treatment of GERD. However, fewer complications and faster recovery makes laparoscopic approach the primary choice. EGP has no treatment effect over placebo and should therefore not be recommended for the treatment of GERD. Wireless esophageal pH monitoring is not immediately interchangeable with traditional pH monitoring for use in clinical practice.





# List of papers

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

- I.       **Preoperative oesophageal motor activity does not predict postoperative dysphagia.**  
Håkanson B, Thor K, Pope CE 2nd.  
Eur J Surg. 2001 Jun;167(6):433-7.  
Reprinted with permission from Taylor & Francis group.
  
- II.       **Transabdominal versus laparoscopic partial fundoplication. A prospective randomized trial.**  
Håkanson B, Thor K, Thorell A, Ljungqvist O.  
Surgical Endoscopy, in press.  
Reprinted with permission from Springer Science & Business Media Inc.
  
- III.       **Twelve months follow-up after treatment with the EndoCinch endoscopic technique for gastro-oesophageal reflux disease – a randomised placebo-controlled study.**  
Montgomery M, Håkanson B, Ljungqvist O, Ahlman B and Thorell A.  
Scand J Gastroenterol 2006, in press, (2006, 1-8, prEview article, June 22).  
Reprinted with permission from Taylor & Francis group.
  
- IV.       **Comparison of wireless 48-hour Bravo™ versus traditional ambulatory 24-hour esophageal pH monitoring.**  
Håkanson B, Berggren P, Granqvist S, Ljungqvist O and Thorell A.  
Submitted.



# ABBREVIATIONS

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ARS	Anti Reflux Surgery
ASA score	American Society of Anesthesiologist score
BE	Barrett's Esophagus
BMI	Body Mass Index
CLE	Columnar Lined Esophagus
EGJ	Esophago Gastric Junction
ERD	Erosive Reflux Disease
GER	Gastro Esophageal Reflux
GERD	Gastro Esophageal Reflux Disease
GEV	Gastro Esophageal flap Valve
GI	Gastro Intestinal
GSRS	GastroIntestinal Symptom Rating Scale
h	hour
HH	Hiatal Hernia
HRQL	Health Related Quality of Life
IM	Intestinal Metaplasia
LA A-D	Los Angeles classification of esophagitis, A through D
LES	Lower Esophageal Sphincter
LESP	Lower Esophageal Sphincter Pressure
LOS	Length Of Stay
NARD	Non Acid Reflux Disease
NERD	Non Erosive Reflux Disease
PPI	Proton Pump Inhibitor
SCJ	Squamo Columnar Junction
SF-36	Short Form -36
SGV	Short Gastric Vessels
SM I-IV	Savary-Miller classification of esophagitis, I through IV
TLESR	Transient Lower Esophageal Sphincter Relaxation



# INTRODUCTION

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In the developed world, a considerable part of the population suffers from symptoms related to gastroesophageal reflux (GER). These complaints typically include heartburn and regurgitation and have been reported in 7-20 % of the population <sup>1,2</sup>. GER symptoms frequently impact health related quality of life (HRQL) perceptions and, accordingly, require treatment. The first line treatment is pharmacological, commonly for prolonged time periods. When medical treatment fails or is unsatisfactory to the patient, surgery is a remaining alternative, aiming at correcting the underlying cause for GER. Different opinions prevail regarding effects and appropriateness of long-term pharmacological treatment versus long-term results of antireflux surgery <sup>3</sup>. There is no clear consensus as to which preoperative investigations that are mandatory in order to facilitate and rationalize the decision making at the prospect of surgery. New techniques have made several options available when choosing surgery. The present studies focus on preoperative investigations and outcomes of surgical antireflux treatments.

Within the context of the present thesis GERD is defined as the unintentional non-physiological movement of gastric juices and contents, from the stomach to the esophagus, which causes various degrees of troublesome symptoms or esophageal mucosal injury <sup>4</sup>.

## Anatomy and physiology

The esophagus is a muscular tube of approximately 25 cm length connecting the lower pharynx to the stomach. The esophageal

mucosa has a squamous epithelial lining. The esophagus' primary function is to propel boluses of fluids and solids from the hypopharynx to the stomach. The esophageal wall has a two layer muscular structure with an inner layer of circular muscle and an outer layer of longitudinal muscle. The upper approximate third of the esophageal muscle wall is an extension of the lower pharyngeal constrictor muscle, continuing down from the hypopharynx and is composed of striated muscle cells. The distal two thirds of the esophageal muscle wall is constituted of smooth muscle cells. At the most distal part of the esophagus there is a thickening of the muscular wall, which represents the lower esophageal sphincter (LES). Within the LES, the squamocolumnar junction is normally situated where the esophagus continues down and enters the stomach in an oblique fashion, creating the acute angle of His at the cardia. The collar sling musculature of the gastric cardia is responsible for maintaining the acute angle of His <sup>5,6</sup>. The intraluminal extension of the angle of His creates the musculomucosal fold at the cardia, endoscopically apparent as the gastroesophageal flapvalve (GEV) <sup>5,7</sup>. This allows for a one-way passage of ingested contents into the stomach and prevents reflux due to the flap valve opposing the lesser curvature of the stomach. The LES is normally contracted and relaxes at the beginning of each swallow, for the duration necessary to permit bolus to enter the stomach. Primary peristalsis is normally responsible for the propulsion of bolus through the esophagus. The stomach is a saccular reservoir with a robust muscular wall for grinding nutrients. The mucosa of the stomach has a columnar epithelial

lining that secretes mucous, hydrochloric acid and peptic substances for the digestive process. The gastric mucosa is, under normal conditions, resistant to the acidic peptic environment of the stomach, in contrast to the squamous epithelial mucosal lining of the esophagus, reflecting their different principal functions.

## **Protective mechanisms of the esophagus and esophagogastric junction**

The competence of the esophagogastric junction (EGJ) is crucial in order to avoid gastroesophageal reflux. Several factors within the esophagus, the EGJ, diaphragm, and stomach are together responsible for preventing gastric contents from entering the esophagus unintentionally and thereby act to prevent symptoms of GER.

Mucous secretion in the mouth, pharynx and esophagus lubricate swallowed contents and neutralizes refluxed acidic contents <sup>8</sup>. Normal motor activity in the esophageal body promotes clearance and prevents refluxed material from staying in the esophagus for a prolonged period of time <sup>9</sup>. The lower esophageal sphincter (LES) or the high-pressure zone (HPZ) <sup>6</sup> acts as a muscular barrier separating the esophagus from the stomach. The anchoring of the EGJ to the diaphragm and the subhiatal area by the phrenoesophageal ligament laterally and anteriorly, and by the esophagogastric mesentery posteriorly <sup>10</sup> is also an essential part of the preventive system. This anchoring is responsible for keeping the EGJ in an intra-abdominal position and consequently retaining the distal esophagus exposed to positive intra-abdominal pressure. The firm suspension of the hiatal area prevents the EGJ from excessive movement up and down the hiatal orifice and thus impedes a sliding of the EGJ into the lower chest as an hiatal hernia (HH). The alteration of the anatomic geometry of the EGJ with loosening of attachments of the cardia and eventual attenuation of the sling fibers, results in a more obtuse angle of His' and a gradual

deterioration of GEV of the cardia <sup>6, 11</sup>, a prerequisite for GER.

Moreover, the diaphragm exerts a pinching action on the lower esophagus that is alleged to make up an adjunct in the chain of defensive mechanisms, <sup>12</sup>.

The normal motor activity of the stomach and duodenum allows emptying of the contents of these areas into the mid-gut, avoiding excessive strain acting on the EGJ.

## **Pathophysiology**

Hiatal hernia (HH) is usually the displacement of the uppermost part of the stomach via the hiatal orifice, into the lower chest above the diaphragm. Hiatal Hernia is commonly found during upper gastrointestinal (GI) endoscopy for evaluation of gastroesophageal reflux disease or in the investigation of patients with other upper GI symptoms <sup>13,14</sup>. In 1926 Åke Åkerlund suggested the term hiatus hernia, instead of diaphragmatic hernia, which until then had been the prevailing term <sup>15</sup>. Åkerlund furthermore suggested a classification of HH subdivided into three general types of herniations <sup>15</sup>. A modification of this classification is commonly used at present; type 1 - the sliding hernia, the most typical type of HH in which the esophagogastric junction (EGJ) and the upper part of the stomach slides up through the hiatal opening into the chest; type 2 - the paraesophageal hernia, in which the fundic part of the stomach is herniated through the hiatal orifice into the mediastinum, typically leaving the EGJ in its normal position below the diaphragm; type 3 - mixed hernias, which are a combination of usually larger sliding hernias and a paraesophageal herniation or more or less complete gastric herniations, the latter sometimes referred to as type 4 herniations. Type 4 herniations are not infrequently incarcerated or complicated by a gastric volvulus <sup>16</sup>.

Several putative mechanisms for gastroesophageal reflux have been suggested. Alterations of anatomical geometry in the upper stomach including hiatal herniations make the gastroesophageal flap-valve mechanism (GEV)

more likely to become insufficient and allow gastroesophageal reflux to occur <sup>7</sup>. In a study with dissection on cadavers it was possible to demonstrate a pressure gradient over the EGJ by insufflation of the stomach, and also to eliminate this pressure gradient when the angle of His was made obtuse <sup>11</sup>. Defective lower esophageal sphincter (LES) is generally considered to be an important factor in the development of GERD and is usually defined as a very low resting pressure in the LES (< 8 mmHg) <sup>17, 18</sup>.

Transient lower esophageal sphincter relaxations (TLESR) are relaxations of LES not elicited by a swallowing maneuver. Transient lower esophageal sphincter relaxations are vagally mediated reflex responses to the physiological receptive relaxation of the stomach in the postprandial state <sup>19</sup>. TLESR are frequently encountered in the postprandial state both in healthy subjects and in patients with GERD. TLESR have been suggested to account for 70 and 100 % of GER episodes in patients and in healthy subjects with GERD<sup>19</sup>. Interestingly, TLESR has been reported to be less frequent in patients after open as well as laparoscopic fundoplication <sup>20</sup>. This effect has been suggested to be a result of the wrap encircling the lower esophagus and cardia, permitting only limited distension of these areas after a meal <sup>20, 21</sup>.

Moreover, non-specific esophageal motor disorder can give rise to defective peristalsis, which may enhance the risk for symptoms of gastroesophageal reflux. Finally, gastric stasis and gastroparesis with or without concomitant diabetes mellitus and autonomous neuropathy increases the strain on the esophagogastric junction and consequently enhances the risk for gastroesophageal reflux to occur <sup>22</sup>.

## Symptomatology

### *Primary symptoms*

Typical primary symptoms of GERD are heartburn, regurgitation, retrosternal and epigastric pain and some degree of dysphagia and odynophagia <sup>1, 2</sup>.

### *Secondary symptoms*

Secondary or extraesophageal symptoms are common and are principally of pharyngeal, laryngeal and/or of pulmonary origin, generating sore throat, hoarseness, cough, supine aspiration and non-allergic asthma <sup>23, 24</sup>. Laryngitis has been shown to be common <sup>25</sup> and GER has been reported at high rates of prevalence in patients with asthma (>50 %) <sup>26</sup>. The association between GERD and secondary symptoms might not always be obvious, and patients might present with secondary symptoms overshadowing the primary cause of their problem <sup>26</sup>.

Symptoms of gastroesophageal reflux can be described as the common pathway for several different pathophysiological processes. Therefore, the type of symptoms varies considerably between individuals and also over time in a person with GERD. For instance, failure of esophageal motor function and failure of the gastroesophageal flap valve mechanism do not necessarily give rise to the same type of symptoms intra- or interindividually. Overall, symptoms of gastroesophageal reflux disease have been shown to have a high impact on every day life as a whole, reducing quality of life to similar levels as in patients with ischemic heart disease and angina pectoris <sup>27</sup>.

## Complications to GERD

Complications related to GERD are frequent. The most common complications are esophagitis, esophageal stricture and Barrett's esophagus <sup>28</sup>. Esophagitis is an inflammatory response of the esophageal mucosa to an excessive exposure of noxious agents of chemical or infectious origin. The most frequent chemical irritant is gastric juice, mainly composed of hydrochloric acid and pepsin. In addition, several pharmacological agents are known to be deleterious to the integrity of the esophageal mucosa, e.g. potassium chloride. Another exogenous source to esophagitis is caustic agents, predominately lye, which may give rise to serious inflammation and stricture formation, a rare condition mostly affecting children.

Exposure to acid and pepsin do not explain all reflux induced esophagitis. Non-acid reflux of duodenal origin has been recognized as an important factor causing esophagitis and mucosal alterations in the esophagus. Duodenal juice containing bile and pancreatic proteolytic enzymes are important factors for development of metaplastic mucosal changes that occur at and above the EGJ, in particular the columnar lined esophagus (CLE)<sup>29, 30</sup>. Columnar lined esophagus in the presence of histologically verified intestinal metaplasia (IM) has been designated the eponym Barrett's esophagus (BE). Interest in BE has increased in past decades since it constitutes a premalignant condition that has been associated to the rising incidence of adenocarcinoma in the distal part of the esophagus in Western countries, especially among white male subjects<sup>31</sup>.

Other etiologies to esophagitis exist, like allergic or immunological disorders resulting in eosinophilic esophagitis, a condition that has increased in prevalence during the past ten years<sup>32</sup>.

Esophagitis sometimes results in stricture formation of the esophagus, either during ongoing active inflammation or as an endstage of healed esophagitis. Commonly, strictures obstruct the propulsion of bolus in the esophagus resulting in dysphagia<sup>33</sup>. A further complication of GERD is the specific dental erosion, which have been suggested to be a consequence of gastroesophageal reflux<sup>34</sup>.

GERD has traditionally been considered a continuum of disease, including non erosive reflux disease (NERD), erosive reflux disease (ERD) and Barrett's esophagus (BE). These descriptive entities have been commonly considered to be related in that NERD can progress to ERD and further to BE. Recent data are suggesting that most patients do not usually interchange between these groups<sup>35, 36</sup>. In accordance, it has been proposed that from an etiological point of view, NERD, ERD and BE should therefore be considered separate entities. This approach has been debated, and at the present time, its relevance is unclear<sup>37</sup>.

Even though the treatment of GERD in the individual patient is mainly dependent upon the severity of symptoms, this approach, from a gastroenterological and surgical point of view, may become of apparent clinical interest.

## Options of treatment

The ideal treatment of GERD, medical or surgical, should result in a high degree of symptomatic relief, heal secondary manifestations and have the ability to permanently restore the defective antireflux mechanisms, that causes gastric contents to enter the esophagus, while not causing side effects<sup>38</sup>.

## Medical therapy

Occasional or mild symptoms are usually treated conservatively with general and dietary measures aimed at educating the patient to understand why they have occurred and how to alleviate these inconveniences. More frequent or severe symptoms are treated pharmacologically with antacids and antisecretory drugs, such as H<sub>2</sub> receptor antagonist or proton pump inhibitors (PPI). The introduction of the latter has transformed and extended medical therapy for such upper gastrointestinal symptoms and manifestations, providing a high degree of symptomatic relief and reduction of esophagitis in the GERD population<sup>39-41</sup>. Severe and chronic symptoms of reflux disease might require continuous high doses of PPI for an indefinite period of time to alleviate symptoms and to prevent recurrence<sup>42</sup>. Long term regular or continuous medical therapy has been shown to result in similar degree of symptomatic relief as surgery<sup>43</sup>. However, recurrence rates after discontinuation of pharmacological treatment are high, and relapses have been reported to be in the range of 80 %<sup>44</sup>. This is probably because medical therapies as we know them today, relieve symptoms and heal secondary manifestations, but do not provide cure to the disease.



For patients with severe longstanding symptomatic reflux disease, with or without secondary manifestations, surgical procedures therefore represent an alternative to continuous medication. A minority of these patients are referred to a surgeon for evaluation with a prospect to have antireflux surgery.

## Surgical therapy

### *Preoperative considerations*

Careful assessments of patients before antireflux surgery is mandatory and traditionally includes standard esophageal 24 h pH monitoring<sup>45</sup> as the golden tool for evaluation, in addition to endoscopic investigation and esophageal manometry. The latter is performed to identify the upper border of the lower esophageal sphincter to enable placement of the esophageal pH sensor at the correct level for pH monitoring and also to rule out specific esophageal motor abnormalities. One argument for performing esophageal manometry is to aid decision making regarding which type of surgery is appropriate in order to avoid postoperative dysphagia; a concept known as tailoring<sup>46</sup>.

Recently, new techniques have been added to this armamentarium. Wireless esophageal pH monitoring has been introduced, a new device that makes pH catheters through the nose redundant<sup>47</sup>. This technique is being tested within the current thesis. High-resolution manometry<sup>48, 49</sup> and esophageal impedance<sup>50</sup> may prove clinically useful and give new insights to abnormalities of esophageal motility.

### *Surgical procedures and techniques.*

In the first half of the twentieth century hiatal hernia was merely considered a mechanical problem and efforts were made to find a solution, essentially by means of a herniorraphy. Not until the beginning of the 1950's did the relationship between gastroesophageal reflux, esophagitis, and hiatal hernia started to emerge, especially from the works of Barrett in 1950 and Allison in 1951<sup>51, 52</sup>. Angelo Soresi published the first series of elective surgical repair of hiatal hernia

in 1919<sup>53</sup>. Soresi performed a hiatoplasty in three patients. Surgical treatment of GERD became popularized in a wider perspective in the 1950's with the total fundoplication introduced by Rudolph Nissen in 1956, a procedure Nissen named gastroplication<sup>54</sup>. To this day the Nissen fundoplication is still the most performed procedure, presently mostly carried out with laparoscopic technique.

Hiebert and Belsey presented the Belsey Mark IV partial transthoracic fundoplication in 1961<sup>55</sup>. In 1963 André Toupet presented a partial fundoplication with posterior gastropexy as an adjunct to the Heller esophagogastromyotomy for achalasia cardiae<sup>56</sup>. The use of the partial fundoplication as a surgical approach for the treatment of GERD has had a wide spread to many centers, especially in European countries and Australia. However, the use of a partial fundoplication has, with some exceptions, been less frequently employed in the United States because of a common opinion that the partial fundoplication does not meet standards related to antireflux capacity as well as concerns on the durability of the procedure<sup>57, 58</sup>. On the other hand, the partial fundoplication has been suggested to be associated with fewer side effects postoperatively, such as short and long term dysphagia, inability to belch, bloating, abdominal distension and flatulence<sup>59-61</sup>. Several randomized prospective trials have dealt with these issues in open surgery and the majority of them show at least equal rates of symptomatic relief, antireflux capability as well as equal durability and lower rates of postoperative mechanical problems after partial compared to total fundoplication<sup>60, 62-67</sup>. One reason for surgeons choosing the Nissen operation might be that partial fundoplication is a more time-consuming and difficult procedure, at least when performed by laparoscopic technique.

Several additional variations on the theme of total or partial fundoplication have emerged through the years, of which some important modifications are shown in table 1.

The minimally invasive surgical revolution that started with laparoscopic cholecystectomy in the late 1980's was soon to be followed by

the first reports of laparoscopic fundoplication published in 1991<sup>68,69</sup>. Subsequently, virtually all previously described fundoplications and modifications have also been accomplished with the laparoscopic approach. In general, symptomatic relief after open or laparoscopic fundoplications have been reported to be in the range of 84 to 97 %<sup>70</sup>. Although these results are encouraging, concerns have been raised regarding the durability in the long term<sup>3,71,72</sup>. Several technical surgical details, of fundoplication by open or laparoscopic approach are still under debate and await to be resolved for optimal results. At present most surgeons would probably agree that a cruraplasty is mandatory in order to reduce the risk for reherniation. However, whether to perform a partial or a total fundoplication is less clear, as is the role of dividing the short gastric vessels (SGV)<sup>73</sup>. A few studies have dealt with cost-benefit ratio of antireflux surgery (ARS), comparing open versus laparoscopic surgery<sup>74-76</sup>. A majority of these studies conclude that, although laparoscopy commonly requires longer operating time, initial investment-costs for equipment and utilization of more disposable instruments, postoperative benefits such as shorter LOS, faster recovery and shorter time off work makes laparoscopic ARS at least cost neutral versus open surgery. A further controversy in the treatment of GERD, is the question whether to perform ARS in patients with BE. This question has two implications. On the one hand, the results following ARS in BE are generally held to be poorer with higher rates of symptomatic recurrences<sup>77</sup>. On the other hand, the risk of dysplastic progression of untreated BE into adenocarcinoma is felt to justify a more aggressive approach than in other, benign, indications. Although case series from successful ARS have reported regression of IM<sup>78-80</sup>, there is no evidence that ARS (or medication) at present, has decreased the risk for developing esophageal adenocarcinoma postoperatively<sup>3,81,82</sup>.

One of the most common findings after surgery for a large HH or paraesophageal hernia is reherniation, which has been reported to occur in 15 % to over 40 %<sup>83</sup>. In inguinal hernia repair, the use of mesh has been shown to be associated with considerable reduction of recurrence rates<sup>84</sup>. The use of prosthetic material has been relatively scarce in ARS, apart from pledgets to reinforce the cruraplasty or the fundoplication and the antireflux prosthesis of Angelchik<sup>85,86</sup>. This is to a certain extent due to the apprehension of placing artificial material in the proximity of the non-serosal surface of the esophagus. For this reason patches from more inert materials such as PTFE (polytetrafluoroethylene) have been used with promising results in terms of complications and strength of the reconstructed hiatal orifice<sup>87-89</sup>.

Although effective, open and laparoscopic fundoplication are associated with side effects, and relatively high degree of invasiveness. Following the rapid development of endoscopic techniques during recent years, it has been possible to offer patients less invasive endoscopic treatments for symptoms of GER. The first technique to become commercially available was the endoscopic gastroplication procedure, the EndoCinch<sup>TM</sup> (CR Bard, Billerica, Mass., USA). Several others have followed; the Stretta<sup>TM</sup> delivering radiofrequency energy (microwave) at the cardia (Curon Medical Inc., Fremont, Calif., USA), the Enteryx<sup>TM</sup> polymer injection technique (Boston Scientific, Mass., USA), the Gatekeeper<sup>TM</sup> technique with submucosal placement of prosthetic bars (Medtronic Inc., MN., USA), and most recently the full thickness plicator (NDO Surgical Inc., Mansfield, Mass., USA). As with the laparoscopic expansion during the early 1990's, endoscopic techniques became widely used many years before randomized controlled trials were performed, to assess the efficacy of endoscopic antireflux procedures.

**Table 1.** Overview of different surgical procedures for treatment of GERD.  
All procedures depicted were originally designed for open surgery but all have also been undertaken by laparoscopy.

year	author	procedure
1956	R Nissen <sup>29</sup>	total fundoplication
1957	L Collis	esophageal lengthening
1974	M Orringer <sup>43</sup>	Collis-Nissen
1977	M Rossetti <sup>44</sup>	anterior wall total fundoplication
1977	P Donahue <sup>45</sup>	floppy total fundoplication
1986	T DeMeester <sup>46</sup>	short floppy wrap, total fundoplication
<hr/>		
1961	C Hiebert <sup>47</sup>	transthoracic partial fundoplication, Belsey Mark IV
1962	J Dor <sup>48</sup>	partial fundoplication, anterior type
1963	A Toupet <sup>30</sup>	partial fundoplication with posterior gastropexy
1967	L Hill <sup>49</sup>	posterior gastropexy, calibration of cardia
1991	A Watson <sup>50</sup>	'physiological' partial fundoplication anterior type

## Effects of surgery - assessment of results

Objective measurements are important in the preoperative evaluation of patients to accurately assess manifestations of disease and monitor results and effects of treatment. Therefore, upper GI endoscopy, 24-hour ambulatory pH monitoring, and esophageal manometry are frequently utilized to ensue objective parameters.

Subjective parameters such as health related quality of life (HRQL) issues have become increasingly important in recent decades, not least in the context of treatment of benign diseases in medical practice. As a consequence, tools for measurement of subjective parameters have been developed and validated. These tools or quality of life protocols have been adjusted

to a majority of medical diagnoses. The short form 36 (SF-36) <sup>96</sup> is a validated quality of life protocol measuring several different aspects of general, physical and mental health. Gastrointestinal symptom rating scale (GSRS) is a validated quality of life protocol measuring aspects of gastrointestinal or abdominal well being <sup>97, 98</sup>.

## Overview of studies included

In Study I the predictive ability of preoperative esophageal manometry on postoperative dysphagia is investigated.

Since 1991 laparoscopy has become the main technique for surgery of benign diseases of the esophagogastric junction <sup>99, 100</sup>. Study II tests the hypothesis that laparoscopic partial fundoplication differs in outcome over a three year period compared to open surgery, with regard to control of esophageal acid exposure, symptomatic relief, complications, recovery and the need for reinterventions.

While laparoscopic antireflux surgery has evolved as the main surgical therapeutic modality for GERD, there has been an increasing demand for even less invasive, endoscopic procedures. As technical development of endoscopic suturing devices has gradually improved,

intraluminal endoscopic suturing has been accomplished in recent years. This technique aims to strengthen the lower esophageal sphincter and to augment the antireflux barrier in order to reduce gastroesophageal reflux and consequently, to alleviate symptoms of GERD. Study III investigates the effects of endoscopic suturing at the cardia with an endoluminal plication technique in a randomized placebo-controlled study.

Twenty-four hour ambulatory pH-monitoring is considered the principal diagnostic tool for the detection of increased esophageal acid exposure, gastroesophageal reflux and hence, the presence of gastroesophageal reflux disease <sup>45, 47</sup>. Traditional catheter based, transnasally placed pH sensors cause considerable discomfort to the patient. This has raised the question of to what extent pH monitoring can be considered representative for esophageal acid exposure (during normal daily life circumstances). A wireless system for determination of esophageal acid exposure has recently become available for clinical use. Study IV investigates feasibility, agreement, concordance of diagnostic yield and subjective quality of life parameters in simultaneous esophageal ambulatory 24 hour pH monitoring by catheter versus wireless 48 hour pH monitoring in healthy subjects and patients.

# AIMS

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The overall aim for these studies was to evaluate different aspects of preoperative workup and surgical procedures for gastroesophageal reflux disease. More specifically, the following questions have been addressed:

- I                      Does preoperative esophageal manometry predict the degree of postoperative dysphagia?  
  
Do preoperative symptoms of dysphagia relate to esophageal motor abnormalities as assessed by preoperative esophageal manometric examination?
- II                     Does open partial posterior fundoplication result in superior control of esophageal acid exposure and of GER symptoms compared to laparoscopic partial posterior fundoplication during three years of follow up?  
  
Does open partial posterior fundoplication result in better clinical perioperative, one, and/or three-year outcomes compared to laparoscopic partial posterior fundoplication technique?
- III                    Does endoscopic gastroplication procedure reduce PPI utilization and/or improve GER symptoms?  
  
Does endoscopic gastroplication procedure reduce esophageal acid exposure and/or improve LES sphincter characteristics in the treatment of patients with GERD?
- IV                    Is the agreement of esophageal acid exposure as assessed by traditional 24 hour pH monitoring versus 48 hour wireless pH monitoring sufficiently high to enable interchange of the two techniques in clinical practice?  
  
What is the concordance of diagnostic yield between traditional 24 hour pH monitoring and wireless 48 hour pH monitoring?



# METHODOLOGY

The methods used and reasons for choosing particular methods are described below.

## Patients and healthy subjects

In Studies I-IV, patients who were either accepted for surgical treatment or investigated for symptoms suggestive of GERD were included. Study IV also included 53 healthy volunteers. An overview of the number of patients and volunteers participating in the various studies, and their basic demographics are given in table 2.

## Ethics

All studies were performed in accordance with the Helsinki declaration. The local ethical committee approved studies II - IV. Study I was conducted as a retrospective analysis of data previously collected within the frame of a clinical quality project, which assessed routinely performed preoperative esophageal manometry and also pre and postoperative standardized questionnaires. Thus, at the time of the study, in

accordance with SFS 2003:460 (Swedish Codes of Statutes), no ethical approval was applied for. In studies II - IV patients and healthy subjects were informed, in writing and orally, of the nature and the purpose of the study. Informed consent was obtained before entering the studies (studies II – IV).

## Endoscopy

Upper GI endoscopy was used to evaluate the pre and post interventional status of the esophagus, stomach and duodenum in healthy volunteers and patients throughout the studies. A video-endoscope was used (Olympus GIF 130 or 160, Olympus AB, Solna, Sweden) in all studies, except for Study I, in which Olympus GIF Q20 or GIF 100 was used. Upper GI endoscopic evaluation was performed according to a protocol, which was developed in particular to standardize assessments with special attention taken to the EGJ. Distances from the incisives to the SCJ and the EGJ and to the hiatal diaphragmatic indentation were noted. The axial length from the EGJ to the hiatal

**Table 2.** Basic demographics for study I to IV.

Study	n	patients	volunteers	gender f/m	age	weight kg	BMI kg/m <sup>2</sup>
I	191	191	-	78/113	47 (18-83)	77 (46-112)	-
II	192	192	-	85/107	53 (22-82)	-	26.1 (19-36)
III	46	46	-	31/ 15	42 (19-66)	-	24.4 (16-37)
IV	108	55	53	64/ 44	49 (21-69)	-	25.3 (19-37)

n = number, f = female, m = male. Values are exact number, median (range).



diaphragmatic indentation was documented and a distance of more than 2 cm was required to define the presence of an HH. Biopsies from each quadrant of the lower esophagus, approximately 3-4 cm above the EGJ were obtained to preclude or verify esophagitis and columnar lining of the esophagus. Endoscopic esophagitis was classified according to Savary-Miller (grade 1 through 4) <sup>101</sup> in Studies I and II. In Studies III and IV macroscopic esophagitis was assessed according to the Los Angeles classification, LA grade A through D <sup>102</sup>. A modified gastroesophageal flapvalve classification according to Hill <sup>7</sup> was used in Studies II to IV. In Study III, the number of visible, retained sutures was also documented at follow up endoscopies.

In general, upper endoscopy is a relatively uncomplicated and short examination that is well tolerated by the majority of subjects and patients without sedation or general anesthesia. Endoscopy with the use of modern video techniques enables high precision examination of anatomy and of mucosal lining of the esophagus, stomach and the duodenum. Alternatively, a barium swallow could have been considered for use in the present studies. This investigation may allow examination of the same part of the gastrointestinal tract as upper endoscopy with even less discomfort to patients and volunteers and, thus, a higher compliance rate could be expected. Although upper GI barium series enables detection of HH <sup>14</sup> and gross anatomic changes with good precision, it has poor sensitivity for determination of esophagitis, GER, columnar lining of the esophagus, distances to SCJ and EGJ and for assessing the flapvalve<sup>103</sup>. In addition, barium swallow has the disadvantage of exposing the subject to radiation. Therefore, upper GI endoscopy was used for examination of the esophagus, stomach and duodenum throughout the studies included in the present thesis.

In order to standardize and facilitate appraisal of the EGJ, the presence of HH and the cardia in regards to the endoscopic appearance of

the gastroesophageal flapvalve and the cardiac competency, a modified gastroesophageal flapvalve classification according to Hill was adopted (grade 1 through 3). This classification system has been demonstrated to correlate with GERD for the higher grades of GEV (2-3) and has been found to be reliable and provide useful information for clinical purposes <sup>7, 104, 105</sup>.

In Studies I and II, the Savary-Miller classification was used to assess endoscopical esophagitis <sup>101</sup>. This classification represents a descriptive but non-validated method for assessing esophagitis, leaving a considerable degree of subjectivity to the endoscopist. Later, the Los Angeles classification of esophagitis was developed and validated and found to be reproducible and reliable for clinical purposes <sup>102, 106</sup> and was therefore used in studies III-IV.

Biopsies obtained from the lower esophagus were evaluated by the same pathology laboratory in all studies. Esophagitis was assessed histologically according to the Ismail-Beigi <sup>107</sup> classification. This histological classification divides esophagitis into three grades, where the two lower grades (basal cell hyperplasia and/or elongation of the papillae and infiltration of granulocytes) are not possible to visualize macroscopically. The microscopical grade 3 esophagitis with histological ulceration, on the other hand, corresponds to endoscopic visible esophagitis.

As previously mentioned, the columnar lined esophagus, when associated with intestinal metaplasia, is a premalignant condition (Barrett's esophagus) predisposing to the development of adenocarcinoma of the esophagus <sup>108, 109</sup>.

The columnar lining has been described by Paull et al <sup>110</sup> and is generally divided into three distinctive types; 1) the cardiac type of junctional epithelium, 2) the gastric fundic type of epithelium and 3) the intestinal metaplastic type (IM) of epithelium with goblet cells. The latter type of IM is recognized as the Barrett's esophagus when lining the esophagus, and thus requires a histological verification for diagnosis.



Because of the premalignant characteristics of IM, patients with columnar lining of the esophagus and histologically verified IM were excluded from studies II-IV.

## Manometry

Esophageal manometry was used for pre-operative evaluation in all patients and healthy volunteers included in Studies I-IV. Standard stationary manometry with a 6 or 8 luminal catheter was performed,<sup>111</sup>. The catheter was perfused with water using a low compliance Arndorfer pump at a rate of 0.5 ml per minute. In Studies I and II, the 6 lumen catheter was utilized. The distal 3 ports (positioned circumferentially at the same level) were placed in the central portion of LES and two ports were located five and ten cm, respectively, in a proximal esophageal direction. At least five swallows of 5 ml were ingested at 20 seconds intervals. In addition, to further evaluate esophageal body characteristics another 5 wet or dry swallows were performed after proximal repositioning of the manometry catheter. Manometry characteristics were analyzed using gastrosoft software (Synectics, Sweden). For Study I, the manometric tracings of all patients entering the study were reviewed by BH and CP according to prestudy defined manometric criteria. The manometric definitions are given in table 4. In Studies III and IV, an eight-lumen catheter was used. The 4 proximal channels had 5 cm spacing and the 4 distal channels (at the same level) were located 5 cm further below (single use manometric catheter,  $\varnothing$  4.5 mm). With this setting LES characteristics and esophageal peristaltic characteristics were obtained from a station pull through and from at least 10 repeated 5 ml water swallows separated by a minimum of 30-second intervals. Manometry characteristics were analyzed using Polygram Net software.

Esophageal manometry is commonly used for preoperative workup in patients evaluated for surgical treatment of GERD for several reasons. Firstly, it enables determination of the level of

LES' upper border, which could be used as a reference for the placement of the pH sensor. Typically, 5 cm above the upper border of LES has been a generally accepted standard position for the pH sensor in the lower esophagus<sup>45</sup>. Secondly, esophageal manometry enables detection of specific primary motor disorders of the esophagus that might generate symptoms clinically difficult to distinguish from GERD, such as achalasia, diffuse esophageal spasm and nutcracker esophagus. Thirdly, manometry has been commonly employed in order to identify patients at risk of developing postoperative dysphagia. Its use became more popular after the concept of "tailored antireflux surgery" was introduced<sup>46</sup>. Furthermore, some authors have advocated the use of esophageal manometry in order to verify the presence of GERD distinctive manometric patterns such as low amplitude peristalsis of the esophageal body, low degree of esophageal non-specific motor abnormalities and defective lower esophageal sphincter with a LESP of less than 6 mmHg<sup>18,112</sup>. However, these motor abnormalities are common findings both in subjects with and those without dysphagia or GERD. Moreover, the prevalence of such findings has been shown to increase with age and therefore such motor abnormalities are not necessarily clinically relevant in the evaluation of a particular patient for surgical treatment of GERD<sup>113-115</sup>.

## pH monitoring

In Studies I-III, standard ambulatory transnasal 24 h pH monitoring technique was employed. A dual probe antimony catheter, non-disposable ( $\varnothing$  2.1 mm Synectics, Sweden) or disposable, (slimline  $\varnothing$  1.8 mm, Medtronic, Sweden) with 15 cm spacing of the sensors was used. The esophageal sensor was placed 5 cm above the upper border of the LES as previously determined by manometry<sup>45</sup>. This distance was chosen in order to ensure an intraesophageal positioning of the pH sensor, since the catheter is fixed to the nares and therefore, its esophageal sensor is subjected to considerable movements

up and down the distal esophagus as a result of respiration and swallowing. The catheter was passed transnasally down the esophagus with the patient in an upright sitting position or in a left lateral supine position.

In Study IV, esophageal pH monitoring was performed for a period of 48 hours of which the first 24 hours were simultaneously monitored with both traditional and a newly developed wireless technique (see further below). The study comprised two series. A first series of 32 symptom free volunteers and 29 patients with a suspicion of GERD was initially performed. Since the results from the first series suggested consistently higher values of esophageal acid exposure time with conventional technique and large differences in distances between the catheter and the capsule pH sensors, a second series was performed with fluoroscopic verification of identical positioning of the two pH sensors. The second series included 21 volunteers and 26 patients. The slimline system samples pH data at 0.25 Hz whereas the Bravo system samples pH data at 0.17 Hz. Data of concurrent esophageal pH from the slimline and Bravo sensors was stored in data-loggers and afterwards uploaded to Polygram Net software for analysis.

The Bravo system consists of a rectangular capsule with the dimensions of 6.0 x 6.3 x 26 mm, which is attached to the esophageal mucosa by a delivery device. The Bravo transmitter transfers a digital radiotelemetry signal with 2 current pH values, obtained at six seconds intervals, to a portable receiver every twelve seconds.

The Bravo capsule mounted on its catheter delivery assembly is passed into the esophagus, and positioned 6 cm proximal to SCJ. A well in the proximal part of the capsule is connected to a high performance vacuum unit and a sub-atmospheric pressure of 600 mmHg is applied to assure that the adjacent esophageal mucosa enters the well and is transfixed by a spring loaded stainless steel pin. The pin is finally released from the handle of the delivery assembly and the delivery system is withdrawn from the esophagus. The pH capsule detaches and passes through the intestine within the end

of the first week or during the second week, usually without the subject noticing.

In the first series, the Bravo capsule was passed transorally with the patient in an upright sitting position, after the endoscopy, and attached to the esophageal mucosa 6 cm above the SCJ compliant to manufacturer's instructions. This was immediately followed by the transnasal introduction of the pH catheter to the esophagus (with the patient in an upright sitting position). The proximal pH sensor was positioned 5 cm proximal to the upper border of the LES as previously determined by the manometric examination. The distance between the catheter and Bravo pH sensors was documented by a chest radiogram. In the second series the endoscopy and capsule delivery were both accomplished with the patient in the left lateral supine position, followed by the pH catheter placement to the identical level as the capsule pH sensor, as verified by fluoroscopy.

Radiography is an alternative not uncommonly used in clinical practice to evaluate GERD. Even though this modality is fairly simple and less discomforting from a patient's perspective, it has a considerable lack of sensitivity for GERD<sup>103</sup>. Esophageal pH recording is therefore commonly considered the most important tool for quantifying esophageal acid exposure and confirming gastroesophageal reflux. The type of pH electrode most frequently used is the antimony electrode, although the more expensive glass electrode has proved to be more stable and quicker in pH response as well as less subjected to pH-drift in a laboratory setting<sup>116</sup>. For clinical purposes, however, the antimony electrode provides similar results to the glass electrode. Moreover, it might offer less discomfort compared to the glass catheter, which has a wider diameter<sup>116</sup>.

There are a variety of studies regarding feasibility, sensitivity, specificity, reliability and the necessity of esophageal pH recording in patients with suspected GERD<sup>45, 117-120</sup>. A common consensus is that esophageal pH recording is advisable and should be performed

prior to surgery in order to verify increased esophageal acid exposure and to establish GER and possibly GERD<sup>118, 119, 121</sup>. Accordingly, pH recording has, since its wider introduction in clinical practice during the 1980's, been used to objectively assess the degree of GER. Although the contribution of pH recording in assessing foregut disease has been generally recognized, there are still some problems or potential shortcomings associated with the available techniques. In particular, traditional ambulatory pH recording utilizes catheters passed transnasally down to the esophagus. This is a common cause of complaints, which could cause a proportion of subjects to reduce their degree of potential reflux-generating activities, such as food intake and physical activity. This, in turn, might raise doubts as to how representative the results from the investigation are in a particular individual<sup>122</sup>. In addition, some subjects will not accept the pH recording at all or, alternatively, choose to discontinue it prematurely. Moreover, some patients undergoing investigation for symptoms thought to arise from the upper GI tract have non-acid reflux<sup>123</sup>. Until recently, non-acid reflux has been difficult to quantify and assess since the pH sensor detects only acid. Dual probes with a distal sensor in the stomach have been used to indirectly correct for this<sup>124</sup>. The pH probe in the stomach, however, only provides information on the present gastric pH and does not supply data on non-acid GER. Due to these difficulties associated with interpretation of recordings with the dual probe technique, it has not gained wide acceptance for clinical use.

Another method for distinguishing between reflux of gastric and non-gastric reflux is the bilitech recording. This technique monitors bilirubin by spectrophotometry at a wavelength of 453 nm<sup>125</sup>. The necessity of two catheters and monitoring systems (one for acid and one for bilirubin) and the specificity to bilirubin has restricted its utility as a routinely performed investigation in patients with GERD. Accordingly, it has mainly been applied in order to record bilirubin duodeno-gastro-esophageal reflux in patients with Barrett's esophagus<sup>126</sup>.

In recent years, multi-channel intraluminal impedance with concomitant pH recording has emerged as a possible alternative. This technique records acid as well as gas and liquid movements within the esophagus, including non-acid reflux, and might therefore evolve into the next standard technique for evaluating GER<sup>127</sup>. However, it still involves the use of a transnasal catheter, which might limit its usefulness.

## Symptom and quality of life assessments

In recent decades, health-related quality of life (HRQL) issues have become increasingly recognized as important factors in assessing various aspects of health and disease. Thus HRQL measures have been used to assess outcomes in clinical trials and as indicators of quality of medical care and therapies in clinical practice. Chronic disease may have a profound impact on HRQL. Patients with symptoms of upper GI origin or symptoms suggestive of GERD have been found to have scorings of general wellbeing at the same levels as patients with angina pectoris and chronic obstructive pulmonary disease<sup>128</sup>. Several general and specific HRQL instruments have been developed and validated in terms of internal consistency and reliability, and scale construct validity.

In longitudinal studies, the variation in HRQL scores is dependent on many factors. Commonly, the investigated intervention provides a specific effect, i.e. the result of the treatment. However, nonspecific effects may have an influence on the outcome measures. The most obvious nonspecific effect is the placebo effect<sup>129</sup>. Another nonspecific effect is the Hawthorne effect, which can be defined as the tendency for subjects to change their behavior as a consequence of being subject to special attention and interest, i.e. participating in a study<sup>129</sup>. To compensate for this potential bias, the study design with randomization to a control group is usually employed.

In Studies I and II, dysphagia and GERD symptoms were evaluated by means of a structured questionnaire. The form consisted of 75 questions in six different domains covering reflux specific symptoms, general symptoms, symptom provoking factors, concomitant disease, alcohol and tobacco consumption, and current medication.

The patients scored reflux specific symptoms, according to frequency or severity, on a four-graded scale (table 3).

More recently, validated and disease-specific QoL instruments such as SF36 and GSRS emerged and have become available for clinical use and were therefore used in Studies III-IV. The short Form 36 (SF-36) was developed from the Medical Outcomes Study, a 20-question short-form survey, to quantify general health in the US, as described in 1988 by Stewart et al.<sup>130</sup>. It was later expanded and validated in a 36 item short-form survey<sup>131</sup>. The SF-36 covers eight health domains: physical function, bodily pain, role-physical, general health, vitality, social function, role-emotional and mental health. The eight subscales of each domain scores 0-100, with higher values depicting improved health status. The SF-36 subscale scores have high reliability and the subscales have high construct validity. Subsequently, physical and mental summary component scores were developed<sup>132</sup> with good reliability and validity. A 3-point difference is considered clinically relevant. SF-36 have been transformed for different cultures and translated into different languages.

The GSRS (GastroIntestinal Symptom Rating Scale) is a symptom specific HRQL instrument, which was developed in the late 1980's<sup>133</sup>, initially for assessing peptic ulcer disease and irritable bowel syndrome. GSRS was later validated for a variety of abdominal symptoms. It comprises a questionnaire with 15 items covering 5 dimensions of abdominal symptoms: abdominal pain syndrome, reflux syndrome,

indigestion syndrome, obstipation syndrome and diarrhea syndrome. The subscales are 7-point Likert scales (1 to 7 points) where 1 depicts no symptoms and 7 the highest grade of symptoms. Results are calculated as mean item scores for each dimension. GSRS has been validated for GERD and has been found to have good reliability and validity<sup>134</sup>.

The visual analogue scale (VAS)<sup>135, 136</sup> was used in Studies II and III for assessing pain in patients and volunteers. The VAS scale has been used as a self-administered assessment for monitoring different clinical parameters, principally pain but also postoperative nausea and vomiting, and clinical entities such as asthma and dyspepsia. The verbal rating scale is an alternative but has the shortcomings of an ordinal scale<sup>137</sup>. The VAS has been found to be reliable and valid for clinical purposes. A general problem with all of the studies using subjective validations, VAS or Likert scales alike, is that all suffer from the fact that they are non parametric by definition. Thus, they only tell the investigator if one measurement is better or worse than the other and, no information about the level of difference between the two subjects of investigation is given.

## Statistical analyses

All values are given as median and range unless otherwise stated. Statistical significance was accepted at  $p < 0.05$  using Chi<sup>2</sup> and Fisher's exact test. Mann Whitney U-test was used for comparisons between the groups. The Wilcoxon test was used to determine within group differences over time. Student's t-test and the Friedman test were used when appropriate. Furthermore, correlations were analyzed with simple regression and analyses for determination of limits of agreement were performed using the Bland-Altman analysis<sup>138</sup>.

**Table 3.** Grading system for subjective symptoms, utilized in Studies I and II.

Grade	Symptom		
	Heartburn nos. of episodes per day	Regurgitation nos. of episodes per day	Dysphagia nos. of episodes per day
0	no episodes	no episodes	no episodes
1	< 1	< 1	< 1
2	1 – 5	1 – 5	1 - 3
3	> 5	> 5	> 3



# STUDY DESIGNS, RESULTS AND DISCUSSION

## Study I.

### Preoperative oesophageal motor activity does not predict postoperative dysphagia.

In study I, 200 consecutive patients who underwent transabdominal antireflux surgery were enrolled. The predictive value of preoperative esophageal manometry on postoperative dysphagia was evaluated retrospectively. Further, the relationship between preoperative motor abnormalities and preoperative dysphagia was assessed.

Standardized preoperative workup and surgical procedure according to clinical routines were applied for all patients, including preoperative upper GI endoscopy,

24 h ambulatory pH monitoring and esophageal stationary manometry. Esophago-gastro-duodenoscopy was performed to identify HH, esophagitis and specifically, stricture or stenosis that could explain any presence of dysphagia. Dysphagia (and GERD symptoms) was evaluated by means of a structured questionnaire prior to, as well as at least one year (range 1-

4 years) after surgery. Dysphagia, defined as a sense of arrest of the bolus in the esophagus, was assessed for both solids and liquids and scored by frequency in a four-graded scale, table 3. Definitions of manometric characteristics are given in table 4. All patients underwent transabdominal partial posterior fundoplication performed according to a standardized protocol, which included the creation of an approximate 270-degree wrap of the stomach behind the esophagus. The short gastric vessels were routinely divided to reassure a loose enough wrap. The wrap was sutured posteriorly to the left and right crurae as well as to the median arcuate ligament and anteriorly to the esophagus and the esophagogastric junction. The hiatal opening was tightened with a separate cruraplasty if it was notably widened during surgery. No esophageal dilator or bougie was used and no other specific surgical measures were taken in

**Table 4.** Definitions of manometric peristaltic characteristics.

manometric definitions	
aperistalsis	no peristaltic sequences
defective peristalsis	40 % or fewer peristaltic waves
low amplitude	mean amplitude < 30 mmHg
non specific motor disease	prolonged duration, increased amplitude,
normal	none of above



order to avoid postoperative dysphagia, on the basis of the preoperative manometry. Patients were, however, informed about the possibility of postoperative dysphagia.

Full records of history, questionnaire data and analyzable manometric tracings were obtainable in 191 of the 200 patients originally enrolled. Demographics are given in table 2. Preoperative total esophageal acid exposure time (pH <4) was 16 % (range 5 – 84). In summary, the results demonstrated that esophageal motor abnormalities were a common finding in preoperative esophageal manometry and that dysphagia was reduced postoperatively. Ninety-eight of 191 patients (51 %) experienced some dysphagia preoperatively. Fifty-two of these 98 patients (53 %) had neither motor disorder nor stricture to explain the dysphagia. The number of patients having dysphagia postoperatively was reduced from 98 to 43 (p<0.001). Twenty-five out of 59 patients (42 %) with preoperative motor disorder shown manometrically did not complain of preoperative dysphagia, as shown in table 5. New onset postoperative dysphagia was seen in eight patients of whom four had defective peristalsis and 4 had normal preoperative manometric findings.

The patients in this study had symptoms requiring regular pharmacological treatment for

symptoms of GERD and were, on preoperative examination, found to have esophageal acid exposure times within the range expected in a GERD population <sup>121</sup>. Patients were accepted for surgery after proper preoperative evaluation and information. The procedure performed was a transabdominal partial posterior fundoplication, which has been suggested to be associated with a lower risk for postoperative mechanical complications such as dysphagia and bloating, compared to total fundoplication. The prevalence of preoperative dysphagia of 51 % in this study was within the expected range compared to previous reports <sup>139-142</sup>. More than half of patients in the present study had no manometric finding or stricture to explain the dysphagia and almost one third of patients with no preoperative dysphagia had a motor disorder on the preoperative tracing. These findings might reflect the observation that GERD is frequently related to different patterns of dysmotility <sup>143</sup>. In addition, the presence of an HH itself has also been proposed to give rise to symptoms such as dysphagia <sup>144</sup>. Regardless of preoperative manometric finding, dysphagia was reduced in prevalence postoperatively. In addition, none of the patients that could be considered to be at higher risk of developing postoperative dysphagia, as judged by their preoperative manometric findings, (aperistalsis or low amplitude contractions) complained of

**Table 5.** Dysphagia and esophageal motor activity before and after transabdominal partial fundoplication.

	Transabdominal partial fundoplication				p
	preoperatively		postoperatively		
	preop motor abnormality		preop motor abnormality		
	yes	no	yes	no	
dysphagia	34	64	19	24	<0.001 <sup>1</sup>
no dysphagia	25	68	40	108	

<sup>1</sup> dysphagia preoperatively versus postoperatively.



dysphagia for the first time postoperatively.

In summary, the data from the current study demonstrates that, in patients scheduled for surgical treatment of GERD, other factors than esophageal motor disorders or strictures are likely to explain preoperative dysphagia. Furthermore, the data strongly suggests that evaluation of preoperative esophageal motor activity does not predict which patients will

develop dysphagia or have their preoperative dysphagia accentuated by the repair, after transabdominal partial posterior fundoplication. Therefore, these findings raise doubts as to the necessity of routinely performed preoperative esophageal manometry in clinical practice, when considering surgical options for the treatment of GERD.

## Study II.

### **Transabdominal versus laparoscopic partial posterior fundoplication. A prospective randomized trial.**

Study II is a prospective randomized controlled trial evaluating short- and medium-term (3 year) outcomes of open versus laparoscopic partial fundoplication. The objective was to assess the outcomes in terms of perioperative course, postoperative complications, symptomatic relief, recurrent disease and, in addition, the need for reinterventional surgery. Preoperative workup included upper GI endoscopy, esophageal manometry, 24 h pH monitoring and structured questionnaires for symptoms of GERD or other possible related upper G-I tract disorders. Inclusion criteria were: typical symptoms of GER, esophageal acid exposure of pH<4 for more than 4 % of monitored time and age above 17 years. In the case of an inconclusive pH monitoring, endoscopic esophagitis of no less than SM II was required to enter the study. Patients with CLE and IM on histology and/or previous major gastric or other abdominal surgery were excluded. However, earlier cholecystectomy was not an exclusion criterion. After giving informed consent to participate, eligible patients were assigned to either transabdominal or laparoscopic partial posterior fundoplication.

Surgery was performed according to a standardized protocol which required the surgeon to have experience of a minimum of 15 independently performed operations of either type before being allowed to participate

in the study. The presence of 2 surgeons was also required during the operation. General anesthesia was applied according to a standardized protocol for all patients during surgery. In the postoperative period patients were optimized relative to technique and routines for the two types of surgery, respectively and consequently, the patients in the transabdominal group were treated with an epidural catheter for postoperative analgesia<sup>145</sup>.

Patients had a partial posterior fundoplication performed by transabdominal or laparoscopic technique. The wrap was encircling the esophagus approximately 270 degrees leaving the anterior or right antero-lateral aspect of the esophagus and the EGJ uncovered. The length of the most anterior part of the wrap was typically at least 4 cm. The short gastric vessels (SGV) were divided according to routine for the transabdominal procedure, and as judged necessary when the laparoscopic technique was used. The wrap was sutured posteriorly to each of the crurae. In the transabdominal technique the wrap was also secured to the median arcuate ligament<sup>10</sup>, which was not dissected with the laparoscopic technique.

Operation time, peri- and postoperative complications, analgesics consumption, reoperations and reinterventions, hospital stay, time off work and recurrences and incisional herniations were assessed.

At six weeks postoperatively patients returned for an outpatient clinical control and were asked to fill out the questionnaire. One and three years postoperatively patients returned for a full investigation with endoscopy including biopsies, esophageal pH recording and manometry. Patients also filled out the questionnaire at one and three years after surgery. In addition, three years postoperatively questions assessing the consumption of acid suppressive agents, such as protonpump inhibitors and Histamin<sub>2</sub> receptor antagonists, taken during the previous six months were used to supplement the questionnaire. These questions included components of reason for any ongoing medical therapy as well as doses of specific pharmaceutical products.

Out of 205 patients initially accepting and giving consent to participate in the study four patients later declined surgery. Of the remaining 201 patients, 101 subjects were randomized to open surgery and 100 to the laparoscopic approach. Eight subjects were excluded due to reconsiderations of the possibility to comply with the study protocol and another subject was excluded because of perceived contraindications to the laparoscopic technique. Finally, of the 192 patients remaining and entering the study, 93 were randomized to open technique and 99 to laparoscopic technique. All patients were followed for 6 weeks and 191 subjects were followed for 1 and 3 years. One patient in the laparoscopic group, died during follow

up 2.5 months postoperatively from diabetic complications unrelated to surgery. An intention to treat protocol was applied for postoperative analysis during follow up.

Patient demographics regarding gender, age, BMI, duration of disease and the presence of preoperative endoscopic esophagitis were similar between groups (table 6). Preoperative esophageal acid exposure (table 7) or GER symptoms (figure 1) did not differ significantly between groups.

Five patients were converted from laparoscopic to open surgery, mainly due to limited access to the operative field for anatomical reasons. Blood loss, length of stay and sick leave were reduced in the laparoscopic group compared to the open group, while operative time was 15 minutes longer (table 8). The mean operative time was not reduced in the laparoscopic group during the second half compared to first the half of the study,  $p=0.85$ . Perioperative complications were lower in the laparoscopic group as compared to the open procedure group,  $p<0.05$ . Postoperative pain was reported less pronounced in the open group during the first 2 days after surgery ( $p<0.05$ ), presumably as a result of the epidural catheter used in the open procedure group. After day 2 however, the laparoscopic group reported less pain. The laparoscopic group demonstrated shorter time until first passage of flatus,  $p<0.001$  and in addition had shorter time until intake of solid food,  $p<0.001$ .

**Table 6.** Demographics prior to open and laparoscopic fundoplication. Values are exact number, median (range) or percentages.

	open	laparoscopic	p
gender (F/M)	35/58	50/49	0.07
age	52 (22-82)	53 (23-77)	0.80
BMI	25.9 (18.6-33.9)	26.2 (19.5-35.9)	0.18
duration of disease (years)	10 (1-44)	10 (1-40)	0.34
endoscopic esophagitis ( %)	76	70	0.09

Endoscopic esophagitis classified according to Savary – Miller.

Six weeks postoperatively, dysphagia of any type was significantly reduced postoperatively in both groups, as were symptoms of heartburn, regurgitation and chestpain,  $p < 0.001$ .

At one year postoperatively subjects expressed their general opinion of satisfaction or dissatisfaction with the procedure undertaken. Overall assessment one year after surgery was satisfactory in 93.5 % of patients in the open procedure group and in 88.8 % of patients in the laparoscopy procedure group, ( $p = 0.31$  between groups). Esophageal acid exposure time was highly significantly reduced within both groups at one year after surgery  $p < 0.001$ , with no statistical significant differences between groups, table 7.

At one year postoperatively, GER symptoms were effectively kept reduced at low levels, with no statistical differences between groups for heartburn, regurgitation, dysphagia or chestpain.

Dysphagia for solids was present in 8 and 7.5 % of subjects in the open and laparoscopic groups, respectively, ( $p = 0.78$ ). Five and 18 subjects in the open and laparoscopic groups, respectively, were found to have a hiatal herniation at endoscopy ( $p = 0.02$  between groups) but there were no significant differences in endoscopic esophagitis, presence of columnar lined esophagus or microscopic esophagitis.

At three years after surgery subjects again assessed overall satisfaction or dissatisfaction with the procedure undertaken. 93.5 % in the open group and 90.8 % in the laparoscopic group expressed such satisfaction ( $p = 0.59$ , between groups). Reduction of esophageal acid exposure time and symptoms was maintained within and between groups after both procedures, (table 7 and figure 2,  $p < 0.001$  for acid exposure and symptoms within groups).

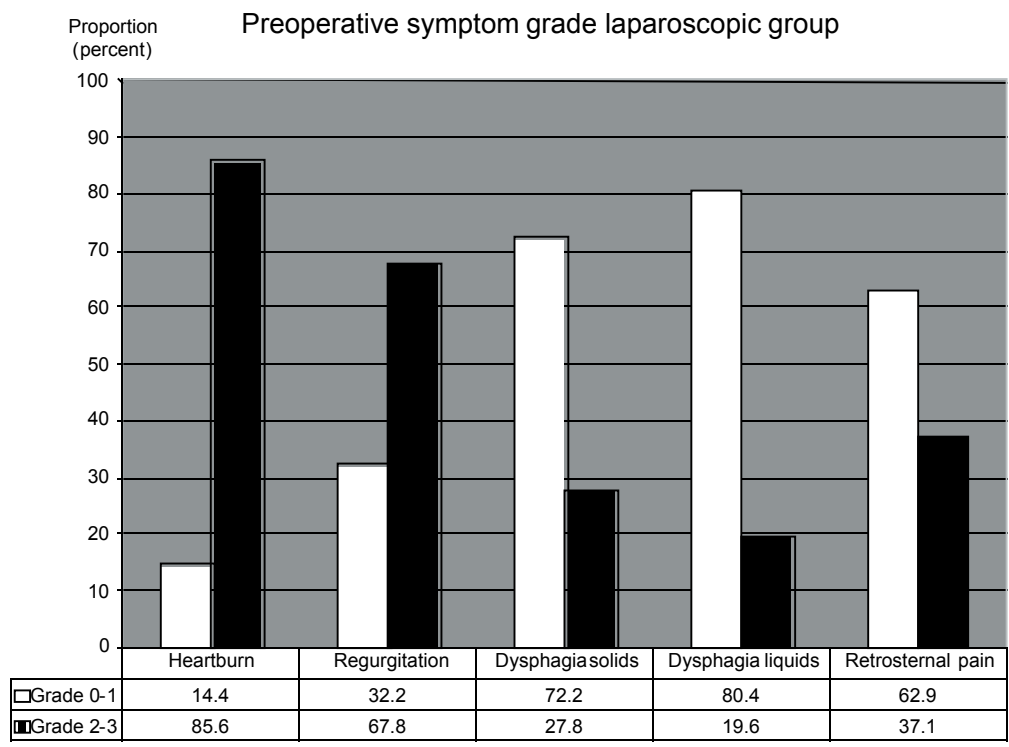
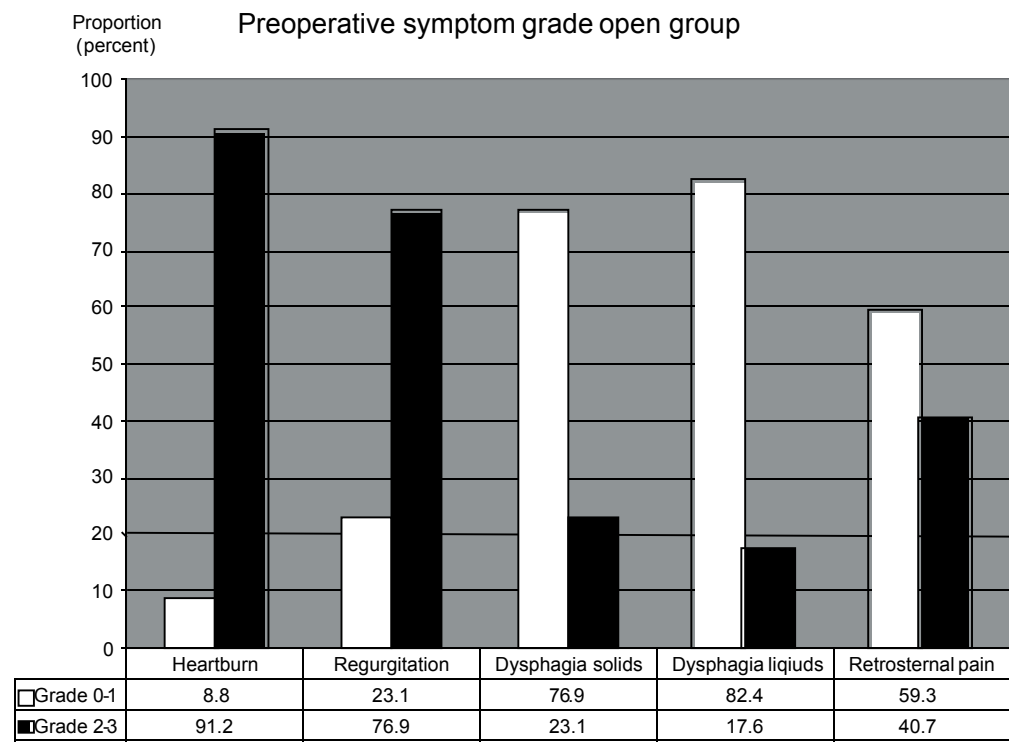
**Table 7.** Pre and postoperative esophageal acid exposure. pH < 4 in percent of monitored time, values are median (range).

	Esophageal acid exposure %		
	open	laparoscopic	p
preoperative	20.0 (4.0-88.7)	17.1 (4.0-79.1)	0.24
postoperative 1 year	2.1 (0.0-83.2)	3.8 (0.0-84.2)	0.06
postoperative 3 years	5.4 (0.0-69.5)	5.9 (0.2-88.1)	0.53

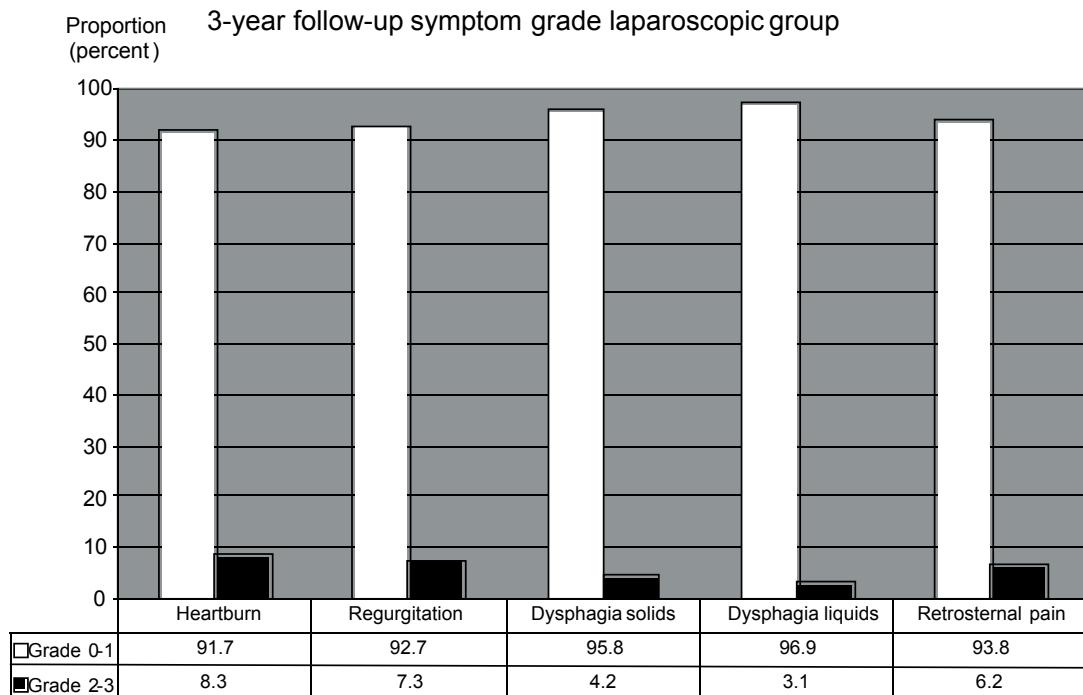
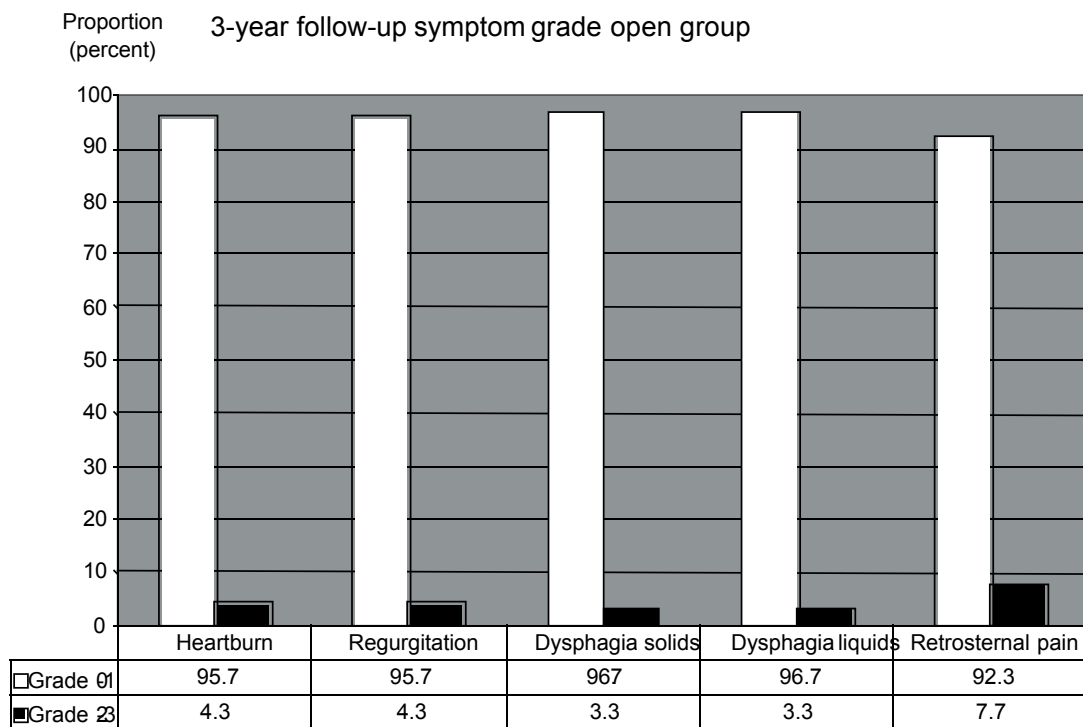
**Table 8.** Perioperative data in patients undergoing open and laparoscopic fundoplication. Values are median (range).

	open n = 93	laparoscopic n = 99	p
operation time, minutes	80 (50-230)	95 (50-265)	< 0.001
blood loss, ml	75 (0-350)	0 (0-1900)	< 0.001
length of stay, days	5 (2-36)	3 (1-12)	< 0.001
sick-leave, days	42 (10-76)	28 (0-108)	< 0.001

Figure 1.



Preoperative symptom scoring. White bars indicate no or low influence symptoms. Black bars indicate moderate or high influence symptoms.

**Figure 2.**

Postoperative symptom scoring at three years. White bars indicate no or low influence symptoms. Black bars indicate moderate or high influence symptoms.

Subjects having pharmacological acid reduction therapy to alleviate symptoms of GER at three years after surgery (5 and 10 patients, open vs laparoscopy) did not significantly differ between groups ( $p=0.28$ ).

During the entire follow up period there was one recurrence in the open procedure group and eight recurrences in the laparoscopic group that required a redo procedure due to symptoms of GER  $p=0.035$ . In addition, seven patients in the open procedure group required reoperation for incisional herniations. Thus, in total, there were eight reoperations in the open group and eight reoperations in the laparoscopic group  $p=1.0$ .

The present study demonstrates that, short and medium (3 year) term outcomes after open versus laparoscopic fundoplication are equally good regarding symptomatic and functional parameters, and are comparable to what have been reported for both open and laparoscopic full as well as partial wrap procedures<sup>63, 93, 146, 147</sup>. Patients participating in this study were carefully evaluated and found to have symptoms and signs consistent with GERD. The study groups were similar on preoperative evaluation and patients were operated and followed according to protocols with standardized procedures. The number of patients recruited for this study was calculated in order to detect

a two to three fold difference in symptomatic failures. In consequence, the possibility that a smaller difference does in fact exist cannot be fully excluded within the present protocol.

The higher recurrence rate from laparoscopic fundoplication suggested from our data is in line with previous studies<sup>71, 72</sup>. However, recurrences were successfully treated with a laparoscopic redo procedure as reported earlier<sup>148, 149</sup>. On the other hand, our study confirms previous reports that open, transabdominal surgery results in a higher frequency of abdominal wall hernias necessitating reoperations<sup>150, 151</sup>. Considering the higher rates of recurrences after laparoscopy and the higher rates of postoperative abdominal wall hernias after open surgery, the outcomes regarding the need for redo procedures following the different approaches could be considered similar.

In conclusion, the data from the current study suggests that open and laparoscopic partial posterior fundoplication are equally feasible and effective alternatives for the surgical treatment of GERD. However, the lower rate of surgical complications, shorter length of stay, faster postoperative recovery and shorter time off work, makes the laparoscopic approach the primary choice when considering a partial posterior fundoplication.

### Study III.

#### **Twelve months follow up after treatment with the EndoCinch endoscopic technique for gastro-oesophageal reflux disease – a randomised placebo-controlled study.**

Study III is a prospective randomized placebo-controlled study evaluating 1-year outcomes of endoscopic suturing at the esophagogastric junction (EndoCinch™ procedure). Primary outcome variable was post procedural consumption of PPI's. In addition, prevalence of GER symptoms, esophageal acid exposure, lower esophageal sphincter pressure and length,

procedure related complications and recovery time were assessed.

Forty-six otherwise healthy patients with typical and recurrent GER symptoms requiring regular PPI treatment were enrolled in this study. Inclusion criteria were: a history consistent with GERD, daily PPI treatment, endoscopic

confirmation of the flapvalve (GEV) to be insufficient (grade 2 or more), and total or upright esophageal acid exposure time exceeding 4 and 6 %, respectively. Patients having ASA>2, HH more than 3 cm of axial length, total esophageal acid exposure time exceeding 8 %, histologically verified BE, specific esophageal motor abnormalities or previous antireflux surgery were not allowed to enter the study.

Preoperative workup comprised upper GI endoscopy, esophageal manometry, 24-hour pH monitoring and assessment of general (SF36) and specific (GSRS, intestinal/abdominal) quality of life parameters<sup>132, 133</sup>. In addition, PPI consumption was documented as number of doses equipotent to 20 mg omeprazole per week. At 6 weeks after the procedure subjects answered QoL forms and reported PPI consumption. In follow up at 3 and 12 months, patients were assessed using the same investigations and forms as preoperatively.

The EndoCinch endoscopic sewing device is 6 x 29 mm (Ø x length) and is mounted on the top of the endoscope. The sewing device contains a chamber connected to a vacuum pressure channel. When vacuum pressure is applied at the desired level, the mucosa is pulled in to the chamber after which a needle with an attached prolene suture is driven through the mucosal

and submucosal layers. In order to accomplish a submucosal plication each suture consists of two stitches. Between the stitches the instrument is rotated 45-90 degrees. The knots are tightened and secured with a ceramic plug fixation device. Prior to launching the study, the two surgeons performing the procedures had formal training in another clinic and own experience from a total of 30 procedures, one assisting the other.

The study protocol required follow up of the subjects during one year postoperatively. Prior to randomization subjects were stratified by BMI; below or above 25kg/m<sup>2</sup>. A standardized protocol for anesthesia and postoperative analgesics was employed for all subjects. Randomization took place after general anesthesia was induced and the subjects were allocated to endoscopic suturing or a sham procedure.

Patients assigned to the EndoCinch group underwent the plication procedure with sutures placed immediately distal to the squamocolumnar junction. Two to four sutures were used, as judged necessary to give the desired luminal tightness from the plication. For both procedures subjects underwent endoscopy during an approximate half our. To facilitate access to EGJ an overtube was used in both groups through which the endoscope was brought in place. The number of movements up and down was made approximately equal in each group.

**Table 9.** Baseline characteristics of patients undergoing EndoCinch plication (treatment) or sham (control) procedure. Values are given as median (range). No differences between groups were noted.

	Treatment group <i>n</i> =22	Control group <i>n</i> =24
Age (years)	42 (22-66)	41 (19-66)
Gender (male/female)	6/16	9/15
BMI	24.2 (19-37.2)	24.5 (16.4-34.7)
Length of hiatal hernia (cm)	2 (0-2.5)	2 (0-2.5)



Thus, patients in the control group underwent the same anesthetic and endoscopic procedure with the exception that no sutures were placed. Postoperatively, patients resumed fluids after 2 hours and all subjects were discharged the first day after the procedure.

At follow up, patients and staff were blinded to which procedure was performed and the endoscopists performing the procedure were therefore not, within the study protocol, involved in any further patient contacts.

Of the 46 patients entering the study, 22 were assigned to the treatment group and 24 to the control group. Baseline demographics were similar between groups as shown in table 9. In

16 of the patients 3 sutures were placed and the remaining 6 patients received 2 or 4 sutures. Three patients, all in the control group, were excluded during follow up, one patient because of pregnancy and two due to escalating reflux symptoms that were not possible to control pharmacologically. Both these patients received a laparoscopic antireflux procedure.

There were no complications specific to endoscopy, placement of the overtube or the plication procedure. Minor side effects included sore throat, mild dysphagia and epigastric pain, which resolved within 3 days postoperatively during which paracetamol on demand was given.

**Table 10.** Esophageal manometry data (a) and acid exposure (b) before (baseline) and at 3 and 12 months post-procedure. Values are given as median (interquartile range).

a	Manometry characteristics	Baseline	3 months	12 months	
Treatment group	LES length (cm)	6.3 (5.3-7.3)	5.8 (4.0-6.8)	5.0 (4.0-7.0)	ns
	LES pressure, mm Hg	11.6 (6.5-16.8)	11.2 (7.5-15.9)	9.9 (5.9-13.9)	ns
Control group	LES length (cm)	4.7 (4.0-6.7)	5.7 (4.0-7.0)	5.5 (4.2-6.0)	ns
	LES pressure, mm Hg	10.3 (6.6-15.8)	13.9 (9.7-15.8)	14.0 (11.6-19.0)	ns
b	Esophageal acid exposure	Baseline	3 months	12 months	p
Treatment group	Total time pH<4 %	5.95 (3.78-6.73)	6.60 (1.4-11.6)	4.7 (3.18-7.13)	ns
	Upright time pH<4 %	8.1 (5.55-10.45)	5.6 (2.0-15.0)	7.8 (4.98-9.58)	ns
	Supine time pH<4 %	1.6 (0.18-3.25)	0.9 (0-5.2)	1.0 (0.5-3.0)	ns
Control group	Total time pH<4 %	5.90 (4.63-7.08)	7.2 (4.0-10.9)	7.4 (4.03-12.45)	ns
	Upright time pH<4 %	9.0 (5.48-12.13)	8.65 (6.93-14.7)	11.7 (4.5-19.2)	ns
	Supine time pH<4 %	0.85 (0.2-1.9)	1.05 (0-4.1)	0.5 (0-3.8)	ns



At baseline, 21 patients in the treatment group had a small HH ranging from 1.5 to 2.5 cm. In the control group, 22 patients displayed a HH ranging from 1.0 to 2.5 cm. Esophagitis was not commonly encountered, neither at baseline nor at follow up and there were no statistically significant differences between groups during the course of the study.

Baseline LES length and LESP were similar in both groups. However, LESP was generally in the lower ranges in both groups at baseline (table 10 a). At baseline and postoperatively there were no statistically significant changes within or between the groups. Compared to normal values, baseline esophageal acid exposure time characteristics were equally and

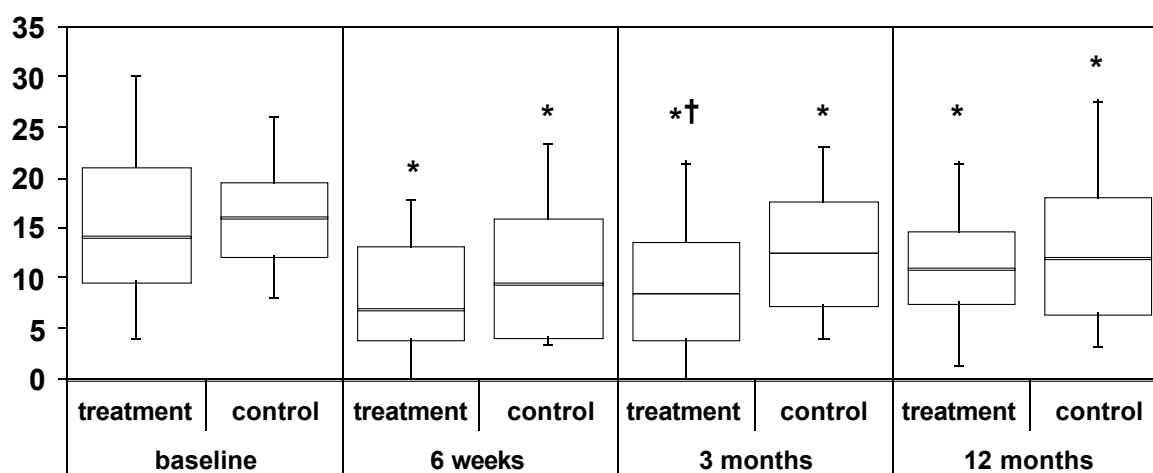
**Table 11.** PPI consumption as number of doses equipotent to omeprazole 20 mg per week.

	Baseline n=46	6 weeks n=43	3 months n=43	12 months n=43
Treatment group	7	1 (0-7) *	0,5 (0-7) *†	1 (0-7) *
Control group	7	3 (0,25-7) *	5 (1-7) *	3 (0,5-7) *

\*p<0.05 versus baseline

†p<0.05 versus control group

**Figure 3.** GSRS scores at baseline, six weeks, three and twelve months after endoscopic gastroplication or control procedure. Values are median, interquartile range and 5th to 95th percentile.



\*p<0.05 versus baseline

† p<0.05 versus control

slightly elevated in the treatment and control groups and they were similar between groups throughout the follow up (table 10 b). There were no significant changes within groups compared to baseline at 3 or 12 months after procedures.

The number of endoscopically verified remaining sutures decreased during the follow up. Sutures decreased from 100 % at baseline (median 3, range 2-4) to 67 % (median 2, range 0-3) at 12 months.

PPI consumption (number of doses equipotent to 20 mg of omeprazole per week) decreased significantly during the follow up at 6 weeks, 3 and 12 months within both groups but was no different between groups except at 3 months post procedural. At this time the treatment group had a lower PPI consumption,  $p < 0.05$ , table 11. The number of patients that were completely off PPI medication increased similarly and significantly in both groups, at 6 weeks, 3 and 12 months ( $p < 0.05$  within groups).

Compared to baseline, GSRS scores were reduced significantly in both groups at 6 weeks and after 3 and 12 months of follow up, (figure 3). GSRS scores were significantly lower in the treatment group at 3 months after procedure,  $p < 0.05$ . SF36 PC (physical component) scores were significantly increased 6 weeks after intervention in both groups and in the treatment group only at 3 and 12 months after the procedures,  $p < 0.05$ . MC (mental component) scores were at the same level as baseline in both groups throughout the follow up period except for a slight elevation at 3 months post-procedure in the control group (vs baseline),  $p < 0.05$ .

In the present study, it was confirmed that endoscopically sutured plication is feasible to perform and can be accomplished without any major complications. Moreover, it was also demonstrated that treatment with the EndoCinch as well as sham procedures reduced symptoms and PPI consumption while esophageal acid exposure remained unchanged and without any

significant differences between the treatment and control groups. Neither LESP or LES sphincter length nor esophageal acid exposure time was affected by the procedure or associated with the results. A possible explanation for the lack of improvement with the treatment compared to the sham procedure may be the considerable loss of sutures that was demonstrated after the endoscopic suturing technique, a finding consistent with several other authors<sup>152, 153</sup>.

The subjects included in the present study had low-degree GERD with typical symptoms requiring regular PPI treatment and a verified esophageal acid exposure time consistent with GER. In addition, subjects had only small HH and an insufficient flapvalve on endoscopy as well as mainly low grades of esophagitis. The presence of GERD was furthermore confirmed by the reduced QoL and increased symptom scores reported by the subjects. The surgeons performing the procedures had both formal training at another clinic and experience from 30 endoscopic suturing procedures prior to the study.

The endoscopic gastroplication technique has been reported to be possible to perform with or without the use of general anesthesia<sup>154</sup>. General anesthesia was used in this study for several reasons; firstly to diminish excessive movements of the EGJ during the procedure, secondly to make blinding of the procedures possible and thirdly, for the comfort of the subjects as an overtube was employed during the procedures.

Outcomes of standard laparoscopic anti-reflux surgery are encouraging regarding reduction of GER symptoms and healing of GERD complications. Nevertheless, surgical procedures are still associated with postoperative complications and, not least due to super competence in the EGJ, might result in varying degrees of bloating and flatulence in the short and long term<sup>64</sup>. A substantial part of symptomatic individuals can be categorized as having non erosive reflux disease (NERD) and will never develop complications to the disease in terms of esophagitis, stricture or columnar lining of the esophagus. However, as many of

these subjects are depending on continuous pharmacological treatment for relief of GER symptoms an even less invasive procedure than minimal invasive laparoscopic surgery with a fundoplication would therefore be desirable. Since the report from Swain et al in 1994 of the endoscopic suturing device, several different modalities of endoscopic antireflux procedures have rapidly evolved. Until recently, five different technical solutions have been developed and become commercially available. The first one to gain a wider spread and use is the technique evaluated in the present study, the EndoCinch plication technique (CR BARD, Billerica, Mass., USA). The other procedures, differing in technical solutions are; the Stretta procedure (Curon medical Inc, Freemont, Calif., USA) inducing structural submucosal changes in the EGJ by local microwave treatment, the Enteryx polymer injection technique procedure (Boston Scientific, Mass., USA), the Gatekeeper hydrogel prosthesis submucosal implant procedure (Medtronic Inc, USA) and recently, the endoscopic full thickness plicator (NDO). Not until recently, a few randomized sham controlled studies of these new techniques have been published <sup>155-157</sup>. Expectations from newly developed techniques that, at least in theory, seem promising and less invasive are often high. Therefore, such techniques tend to be widely spread as soon as being commercially available, even in the absence of previous randomized placebo controlled studies. Interestingly, two of the commercially available endoluminal techniques for treatment of GERD symptoms have recently been withdrawn by the producers (Enteryx and Gatekeeper), the first because of complications associated with the technique and the second because of insufficient treatment effect as shown in an as yet unpublished multicenter sham controlled study.

The most commonly used and most studied technique for endoscopic treatment of GERD is the EndoCinch plication procedure. In uncontrolled studies, positive effects <sup>154,158</sup> as well as no effects <sup>152</sup> have been reported. However, at the time of submission of the results from the present study, there were no data published

over effects by this technique from a placebo-controlled study. The main finding in the present study was that although symptoms of GER and PPI consumption were reduced postoperatively, there were no significant differences between EndoCinch or control groups at 12 months post procedure. Only at 3 months postoperatively there was a significant difference between the groups in symptom scoring and PPI consumption. However, since neither LES or esophageal acid exposure time underwent any significant changes postoperatively compared to baseline, this suggests that the symptomatic improvement and reduction in PPI consumption was more likely attributable to the placebo effect. On the other hand, these findings might also be explained by a genuine treatment effect that extended over 3 months postoperatively in the EndoCinch group.

The absence of demonstrable treatment effect seems closely associated to the considerable loss of sutures, a finding consistent with other authors' conclusions <sup>152, 153</sup>. The fact that loss of sutures over time is substantial might highlight another subsequent issue, i.e. the difficulty to have reliable and durable suturing or stapling performed from within the intestinal tract. Several plausible explanations might account for these difficulties, one being that the mucosal lining of the intestine is a stratum with a high rate of desquamation and regeneration which might affect the durability. Furthermore, the technique relies on the sutures to go deep enough into the submucosal layers, which might not always be accomplished <sup>159</sup>.

In summary, the EndoCinch gastroplication technique is feasible to perform and enables gastroplication without any major complications. Although a reduction in GER symptoms and PPI consumption was documented after EndoCinch gastroplication, this was not different from controls, suggesting that the effects are mainly attributable to a placebo effect.

Therefore, in conclusion, data from the present study demonstrates that although some short-term treatment effects cannot be excluded, failure of treatment is to be expected with the endoscopic plication technique of EndoCinch.

## Study IV.

### Comparison of wireless 48-hour Bravo™ versus traditional ambulatory 24-hour esophageal pH monitoring.

This prospective study evaluates feasibility, agreement, subjective symptoms, reproducibility and possible diagnostic gain of traditional catheter-based versus 48 h wireless esophageal pH monitoring.

53 healthy volunteers and 55 patients referred for evaluation of symptoms suggestive of GERD entered the study. Volunteers and patients were subjected to upper GI endoscopy, esophageal manometry and pH monitoring. Prior to investigations all subjects answered SF-36 and GSRS forms to assess general and upper GI as well as abdominal health. During each day of pH monitoring subjects estimated how often they had a meal, how much volume the meal consisted of, and to what extent physical activity was performed during monitoring as compared to a normal day.

Upper GI endoscopy was performed after standard esophageal manometry and before attachment of the capsule with the subjects in the left lateral supine position.

Esophageal pH monitoring was performed for a period of 48 hours of which the first 24 hours was simultaneously monitored with both the traditional and wireless techniques. During the second 24 hour period esophageal acid exposure was monitored only by the wireless technique. The study comprised of two series (see methods section). In summary, the differences in the protocol for series 2 compared to series 1 were, that in series 2 the Bravo capsule was placed with the subjects in the left supine position, the placement of the slimline sensor was adjusted to the same level as the Bravo sensor during fluoroscopy before documentation of the positions by a chest radiogram, and that 9 of the volunteers from series 1 had a repeat investigation performed.

Total esophageal acid exposure and correlation was analyzed and compared between both techniques for the first simultaneous 24 h period. In addition, the second 24 h and the total 48 h periods of wireless monitoring were compared to the 24 h slimline monitoring.

The cut off for upper limit of normal values of esophageal acid exposure time for the Bravo technique was calculated from the regression equation of slimline versus Bravo acid exposure time. The concordance of diagnostic yield was determined by dividing the sum of subjects in which the data from the 2 techniques rendered the same diagnostic conclusion with the total number of subjects <sup>160</sup>.

To investigate how well values obtained using the two techniques agree, the Bland-Altman analysis was performed <sup>138</sup>. This technique determines the range between limits of agreement for two methods assumed to measure the same determinant. The agreement between the methods was estimated by plotting the differences between measured slimline and Bravo acid exposure time values during the first 24 h period against their mean. The limits of agreement are defined as the mean difference of measured values with the two techniques  $\pm 2$  SD (Standard Deviation) of the mean. The range between limits of agreement thus represents the interval of 24 h esophageal acid exposure values in which 95 % of the population could be expected to be found.

There were no significant differences regarding sex or age between healthy subjects and patients (table 12), whereas BMI was slightly higher in patients ( $p < 0.01$ ). GSRS scores were higher in patients compared to controls and pretrial SF 36 scores (PCS and MCS) were higher in volunteers compared to patients ( $p < 0.001$  for all).

In total, seventeen patients in the first and second series had endoscopic esophagitis (31

%). Two volunteers were excluded from the study, one because of a finding of esophagitis on endoscopy and the other because of low degree heartburn revealed in GSRS. Two volunteers (4 %) and 34 patients (62 %) had a HH on endoscopy. No other pathologies were documented in volunteers or patients.

In both groups, a total of 16 failures were documented (14.8 %). 13 of these were failures of attachment or premature detachment (10.2 %) and 3 were failures of either data capture or refusal to have the slimline catheter. pH data was successfully captured in 98 % of all initially included subjects with the slimline as compared to 87 % for the Bravo capsule ( $p < 0.01$ ). The majority of problems associated with attaching or premature detaching of Bravo capsules occurred in the early phase of the study.

The mean distances between the slimline and Bravo capsule sensors in the first series were  $18.7 \pm 13.2$  (SD) mm in volunteers and  $24.9 \pm 15.6$  (SD) mm in patients ( $p = 0.11$  between groups). In relation to the Bravo sensor, the slimline sensor was located distal in 32 cases, and proximal in 23 cases. Figure 4 illustrates the relation between the inter-sensor distances and differences in recorded esophageal acid

exposure time between slimline and wireless pH recordings day 1 in all included subjects in series 1 ( $r^2 = 0.41$ ,  $p < 0.001$ ).

Complete pH data could be analyzed for 27 healthy volunteers and 26 patients in series 1 and for 18 volunteers and 21 patients in series 2 (In total 92 subjects).

Total esophageal acid exposure time in volunteers and patients is shown in tables 13 a and b. In general, slimline recordings of esophageal acid exposure time were approximately two-fold higher than Bravo generated data for day one, day two as well as for total 48 h Bravo recordings, ( $p < 0.01$ ). However, some exceptions were encountered. In patients, there were no statistical differences between 24 h slimline and Bravo recordings day 2 (both series) and 48 h total recordings, first series, table 13b.

There was a highly significant correlation ( $r^2 = 0.66$ ,  $p < 0.001$ ) between slimline and Bravo generated acid exposure time day 1 when all subjects were assembled for analysis (figure 5). By use of the regression equation and the cut-off value of 4.0 % as the upper limit for normal values of esophageal acid exposure time as determined by use of the slimline catheter<sup>160</sup>, cut-off for upper limit of normal values for use

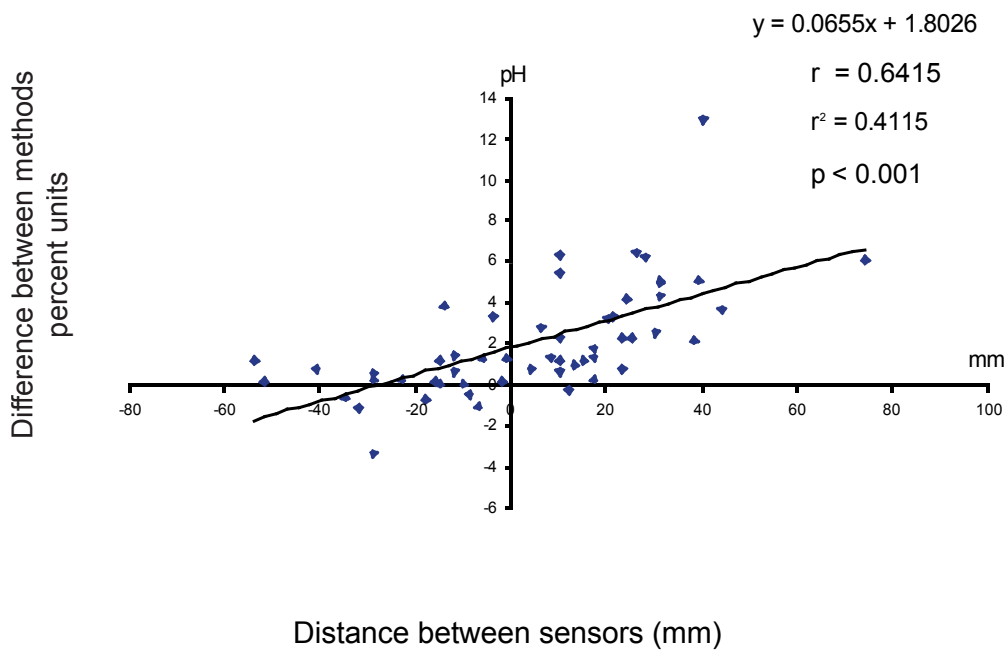
**Table 12.** Demographic data of volunteers and patients. Values are numbers, median and range.

	volunteers n = 52	patients n = 50	p
gender (f/m)	33f/19m	28f/22m	0.44
age	47 (21 - 68)	50 (23 - 69)	0.17
BMI	23.7 (18.8 - 30.9)	26.9 (22.8 - 37.0)	<0.01
GSRS	1.05	3.15	<0.001
SF36 PCS	57	46	<0.001
SF36 MCS	55	44	<0.001

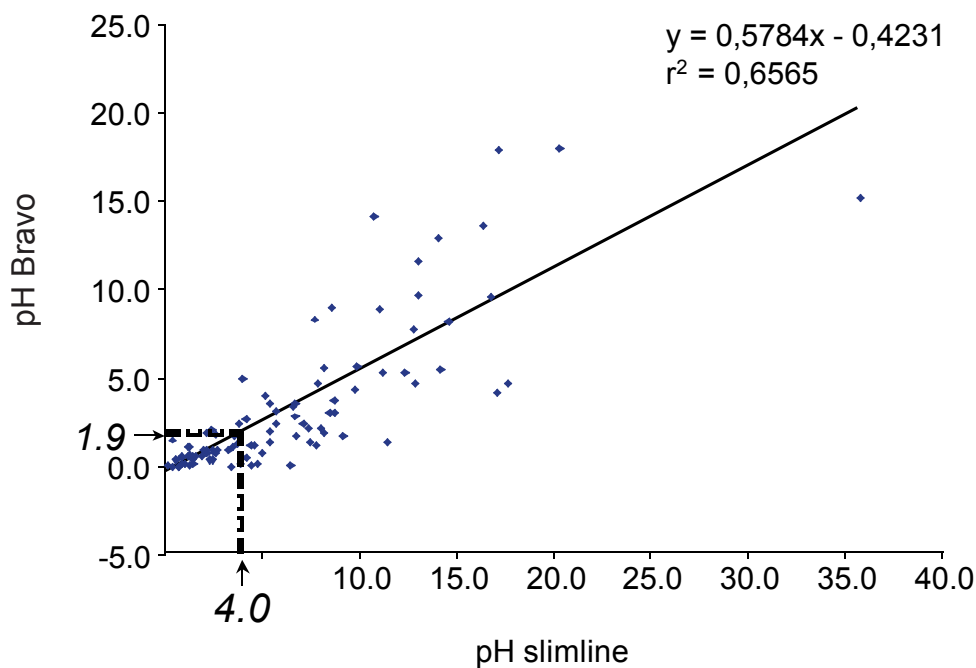
of the Bravo capsule was estimated to be 1.9 %, figure 5. When separate regression equations were used for volunteers and patients, cut-off for upper limit of normal values for the Bravo capsule were 1.9 and 2.0 %, respectively. Using these cut-off values, esophageal acid exposure was abnormal, as diagnosed with the slimline

catheter in 53 of the 92 subjects, with the Bravo capsule in 42 subjects, and with both techniques in 39. Conversely, esophageal acid exposure was normal with the slimline system in 39 subjects, with the Bravo system in 50 subjects and with both techniques in 36 subjects. With all subjects included, the concordance of diagnostic yield

**Figure 4.** Differences in esophageal pH vs slimline to Bravo sensor distances



**Figure 5.** Esophageal acid exposure Bravo vs slimline





was 81.5 %, (84.1 and 80.9 %, for volunteers and patients, respectively).

Differences in esophageal acid exposure time values between both techniques against their mean for all included subjects are illustrated in figure 6. The mean difference between slimline and Bravo generated acid exposure time data was  $3.2 \pm 3.4$  percent units, and consequently, the limits of agreement (mean  $\pm$  2SD) ranged from  $-3.7$  to  $10.0$  percent units.

Total esophageal acid exposure time for 9 healthy volunteers in which repeated measurements were

performed is given in table 14. For the slimline pH recordings, there was a statistical difference between series 1 and 2, with approximately two-fold higher values for series 2 ( $p < 0.05$ ), while there were no significant differences between Bravo recorded data day 1, day 2 or for total 48-h recordings. The mean between-measurement CV (Coefficient of Variation) was  $60.1 \pm 26.3$  % for slimline recordings, while corresponding values for Bravo day 1, day 2, and total were  $66.0 \pm 47.3$ ,  $68.4 \pm 50.8$ , and  $55.4 \pm 52.5$  % respectively ( $p = \text{ns}$  slimline versus Bravo for all). Limits of agreement for repeated measurements

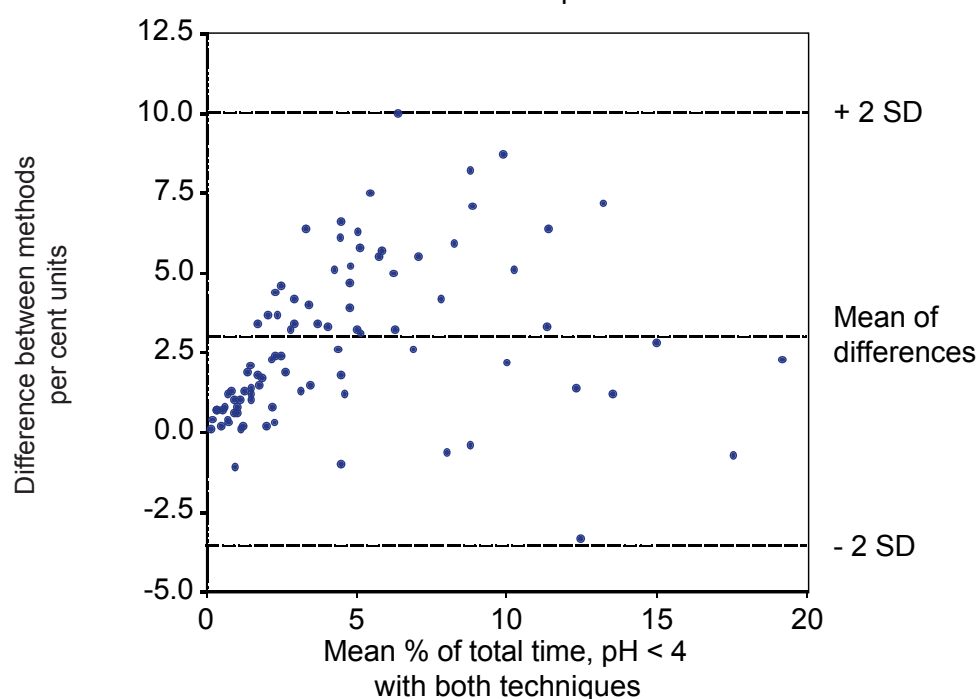
**Table 13 a.** Total esophageal acid exposure pH  $< 4$ , in % of monitored time in volunteers. Values are median, (5<sup>th</sup> – 95<sup>th</sup> percentile). Second series corrected for probe distances.

	Slimline	Bravo day1	Bravo day 2	Bravo total
Volunteers 1 <sup>st</sup> series n=27	2.1 (0.4-12.8)	1.1 (0.1-9.0)	1.4 (0.1-8.3)	1.2 (0.2-8.7)
p vs slimline		$<0.001$	0.034	0.004
Volunteers 2 <sup>nd</sup> series n=18	4.4 (1.2-12.4)	1.2 (0.1-5.3)	1.4 (0.6-8.1)	1.8 (0.4-4.5)
p vs slimline		$<0.001$	0.005	0.002

**Table 13 b.** Total esophageal acid exposure pH  $< 4$ , in % of monitored time in patients. Values are median, (5<sup>th</sup> – 95<sup>th</sup> percentile). Second series corrected for probe distances.

	Slimline	Bravo day1	Bravo day 2	Bravo total
Patients 1 <sup>st</sup> series n=26	6.8 (0.9-17.7)	3.2 (0.1-17.9)	6.9 (0.7-16.3)	5.2 (0.6-15.7)
p vs slimline		$<0.001$	0.77	0.08
Patients 2 <sup>nd</sup> series n=21	7.1 (0.7-17.1)	2.4 (0-9.6)	5.2 (0.2-14.8)	4.3 (0.1-12.8)
p vs slimline		$<0.001$	0.073	$<0.001$

**Figure 6.** Differences against mean for esophageal acid exposure in volunteers and patients



**Table 14.** Repeat simultaneous traditional and bravo pH-monitoring in volunteers. Total esophageal acid exposure pH <4 in % of monitored time. Values are median, (5<sup>th</sup> – 95<sup>th</sup> percentile). Second series corrected for probe distances.

	Slimline	Bravo day1	Bravo day 2	Bravo total
Volunteers 1 <sup>st</sup> series n=9	1,9 (0.7-4.6)	0.6 (0.0-1.9)*	1.2 (0.0-5.1)	1.0 (0.0-3.1)*
Volunteers 2 <sup>nd</sup> series n=9	4.4 (1.2-11.4)	1.3 (0.2-3.1) *	1.2 (0.6-5.5) *	1.3 (0.4-4.3) *
p vs first series	0.021	0.208	0.176	0.108

\* p<0.05 versus slimline.



day 1 ranged from -3.05 to 8.23 for the slimline and from -1.81 to 2.47 % for Bravo generated data (figures 7 and 8).

Data regarding relevant behavioral patterns during measurements for volunteers and patients are summarized in table 15. Compared to normal, food intake (frequency as well as volume) and physical activity was significantly

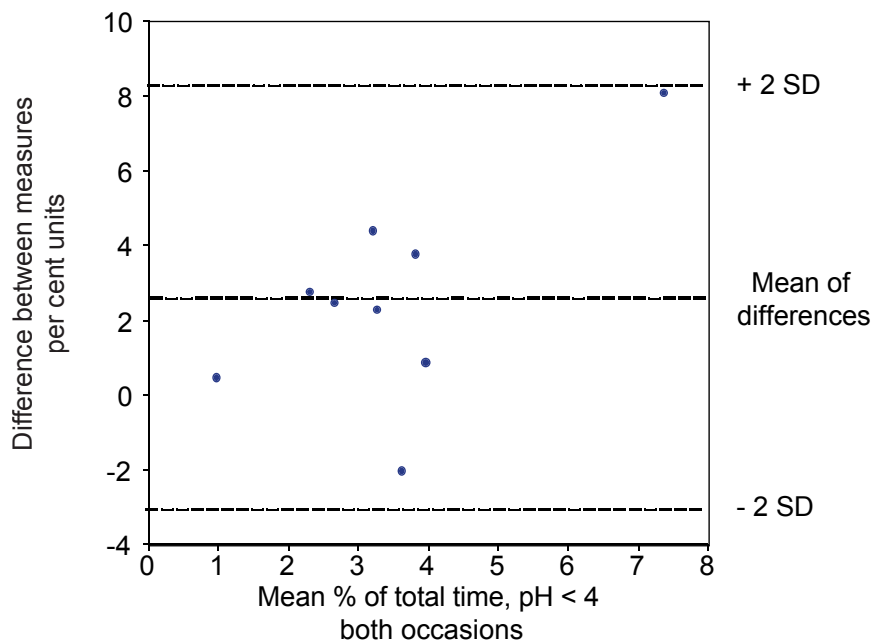
more affected day 1 than day 2 when the nasal catheter was removed ( $p < 0.05$ ).

No complications specific to techniques were observed and in no subject the pH catheter or Bravo capsule had to be removed prematurely.

In the present study, simultaneous esophageal pH recordings were performed using traditional slimline catheter pH sensor and wireless Bravo

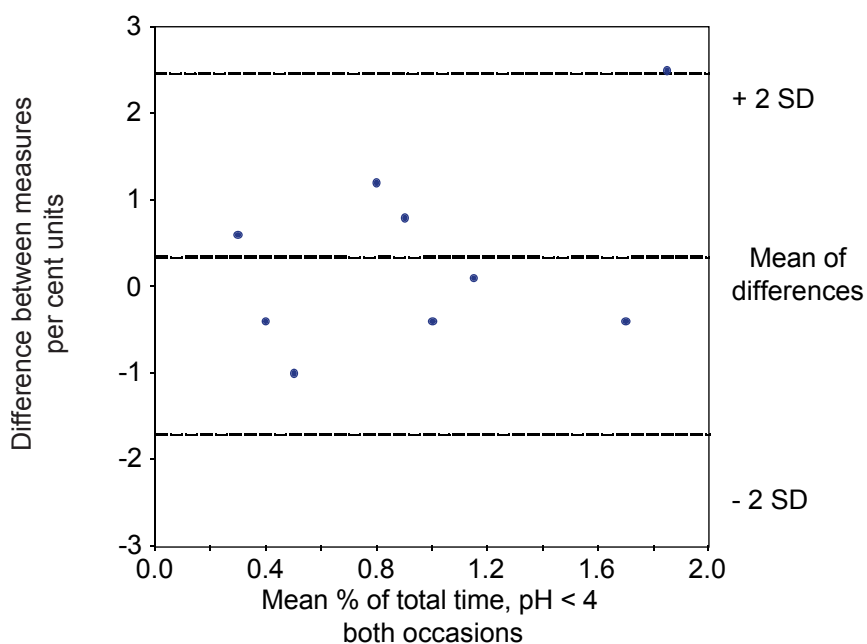
**Figure 7.**

Differences against mean for esophageal acid exposure in repeat slimline measures



**Figure 8.**

Differences against mean for esophageal acid exposure in repeat Bravo measures



capsule in healthy symptom free volunteers and in patients with symptoms suggestive of gastroesophageal reflux. In accordance with earlier reports, it was found that the Bravo capsule is feasible to use and well tolerated in the majority of volunteers and patients, that acid exposure time is significantly lower with the Bravo system, and that there is a highly significant relation between the two techniques in acid exposure time recorded. However, this does not mean that the agreement between methods is high and, indeed, there was a wide range in limits of agreement between the two techniques. This suggests that the two techniques are not immediately interchangeable for use in clinical practice. In addition, it should be noted that the present protocol did not allow distinguishing which technique was the most accurate.

Since esophageal acid exposure could be expected to vary over time, the only valid comparison between two different techniques involves simultaneous measurements in the same subject. A reasonable assumption is, that if positioned at the same esophageal level, both pH sensors are exposed to the same degree of acid reflux. Esophageal acid exposure has been suggested to vary with the distance from LES and our data suggest a relationship between the positions of the sensors and recorded esophageal acid exposure times for the two techniques (figure 4). Therefore, the difference in positioning of the pH sensors in first series of the present

study could be expected to be influential on the results. For this reason, identical positioning of the two sensors was assured in the second series by adjustment during fluoroscopy. As the differences in recorded acid exposure time between the two techniques were not reduced by this procedure, it indicates that different sensor positioning was not the sole explanation for differences in recorded pH-values.

It has been suggested that this difference is due to a flawed software scheme for electrode thermal calibration, and that accuracy of pH data sets can be improved by the use of an *in vivo* pH reference <sup>161</sup>. As a consequence, a correctional factor for electrode thermal calibration has now been introduced for the slimline system. However, our data demonstrates that, at least in the higher range of acid exposures of patients, the acid exposure time values as recorded by the Bravo system were higher during day 2 compared to day 1, table 13 b. In addition, there was a significant difference between Slimline and Bravo recordings day 1 while there was no difference between Bravo recordings day 2 and slimline acid exposure time in patients. One possible explanation for this observation could be that the removal of the slimline catheter itself after day 1 enables a more reflux-inducing lifestyle. Alternatively, a drift in calibration of the Bravo capsule could occur with time.

Cut-off levels for upper limits of normal Bravo values in the present study (1.9 %) were approximately 2 percent units below cut-off

**Table 15.** Ability to eat and physical activity during simultaneous slimline and wireless Bravo pH monitoring in volunteers and patients added, compared to normal food intake and normal daily activity.

	Day 1	Day 2	p
Food intake; less often	24	8	<0.05
Food intake; less volume	36	10	<0.05
Physical activity; less activity	42	14	<0.05

Numbers are patients and volunteers scores.

for normal values traditionally used for the slimline technique in our lab (figure 5), and approximately one percent unit below the cut-off value reported by des Varannes et al <sup>160</sup>. Concordance of diagnostic yield was similar between groups in our material and was in the same range as reported earlier <sup>160</sup>.

In the same report it was concluded that there was a strong correlation between the two techniques. Although this seems to be the case, it would be surprising if a significant relation between two techniques measuring the same parameter would not exist and this does by no means confirm that the two techniques agree satisfactory. A plot of the two measurements against each other will only yield data points clustered near the regression line which makes it difficult to assess the between-method differences. A plot of the differences between the methods against their mean is much more informative. In our study, this analysis displayed considerable lack of agreement between slimline and wireless techniques with differences up to 13.7 percent units (figure 6). Given the mean difference between the techniques (3.2 percent units) and a SD of 3.4, the calculated limits of agreement will be  $3.2 - 6.8$  ( $2 \times \text{SD}$ ) = -3.7 percent units and  $3.2 + 6.8 = 10.0$  percent units. Thus, if normally distributed, 95 % of differences between measured values with the two techniques could be expected to lie between these limits. Such large differences between measured values must be considered to be of clinical significance and therefore strongly suggest that the two techniques are not interchangeable. When examining the graph (figure 6), no obvious relation seems to be apparent between differences in measured exposure times and the mean values, suggesting that the differences do not vary in any systematic way over the range of measurements. Usually, when analyzing agreement between two methods, one does not necessarily have information of which method gives the true value. In this situation the mean of the two values obtained with the different techniques has to be used, and this will give the best estimate.

Reproducibility was estimated using repeated measurements with both techniques in 9 volunteers. The variability of esophageal acid exposure may be expected to be substantial over time <sup>162</sup>. Since a considerable amount of time elapsed between measurements the possibility to give a robust estimation of reproducibility within either technique was limited. Nevertheless, the present study was performed in volunteers who had no symptoms at either study occasion, and should therefore enable a reasonable comparison at least between the techniques. It was found that the CV was in the same range ( $60 \pm 26$ , and  $66 \pm 47$  %) for slimline and Bravo day 1 generated exposure time values ( $p=0.9$ ). However, as the range for limits of agreement between repeated measurements was much wider for slimline than for the Bravo technique, (figures 7 and 8) these data suggest that, if anything, the wireless Bravo technique may be superior to slimline in this respect.

The present self reported data over behavioral patterns during measurements with the two techniques are suggestive of improved patient tolerance demonstrating less influence on daily life parameters such as mobilization and eating habits once the slimline was removed (table 15). It should be noted, that the present protocol was not primarily nor optimally designed to explore this specific question. If, however, data that convincingly demonstrates superior tolerability with the Bravo capsule compared to conventional techniques emerges, it still needs to be demonstrated that this is also associated with improvements in estimation of the actual degree of esophageal acid exposure time.

In conclusion, the data from the present study demonstrates that the use of the wireless Bravo system is feasible, well tolerated and systematically underestimates esophageal acid exposure compared to conventional techniques. The new finding is that the agreeability between the two techniques is not as good as earlier suggested, indicating that the two techniques are not immediately interchangeable. Moreover,

the surprisingly large variability between methods in all subjects and CV within each method for volunteers indicates that data from both techniques should be interpreted with

caution and in relation to other variables such as symptoms and endoscopic findings when evaluating patients with a suspicion of GERD.

# CONCLUSIONS

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- I                      Preoperative esophageal manometric examination does not predict the development of dysphagia postoperatively, nor does preoperative esophageal motor abnormalities relate to preoperative dysphagia.
  
- II                     Open partial posterior fundoplication results in similar reduction of esophageal acid exposure, and control of symptoms of GER compared to laparoscopic partial posterior fundoplication during 3 years of follow up.  
  
Open partial posterior fundoplication results in an increase of peri- and postoperative complications, longer LOS and prolonged postoperative recovery compared to the laparoscopic approach. The need for revisional surgery due to incisional hernia following open surgery is similar to the need for redo surgery due to recurrence after laparoscopic partial posterior fundoplication.
  
- III                    Endoscopic gastroplication procedure reduces PPI consumption and GERD symptoms, only equivalent to that of placebo.  
  
Endoscopic gastroplication procedure does not result in a significant reduction of esophageal acid exposure time or improvement of LES characteristics.
  
- IV                    The degree of agreement of esophageal acid exposure as assessed by traditional 24 h pH monitoring versus 48 h wireless pH monitoring is not sufficiently high to enable immediate interchange of the two techniques in clinical practice.  
  
The concordance of diagnostic yield between the two methods is approximately eighty percent.



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