ENDOLUMINAL THERAPIES FOR GASTROESOPHAGEAL REFLUX DISEASE, OBESITY AND BARRETT'S ESOPHAGUS

Development of a new endoluminal device and a technique

Ph.D. Thesis

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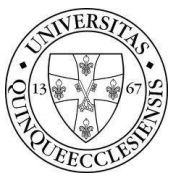

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ABBREVIATIONS

BMI	body mass index
ESD	endoscopic submucosal dissection
EMR	endoscopic mucosal resection
EWL	excess weight loss
GEJ	gastroesophageal junction
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GI	gastrointestinal
H2RA	H2 receptor antagonists
HRQL	heartburn related quality of life
HBSS	heartburn symptom score
HTS	hypertonic saline
IWQOL	impact of weight on quality of Life
IGLEs	intra-ganglionic laminar endings
LARS	laparoscopic anti-reflux surgery
LES	lower esophageal sphincter
LESP	lower esophageal sphincter resting pressure
PPI	proton pump inhibitor
RFA	radiofrequency ablation
SEMR	strip endoscopic mucosal resection
tLESR	transient LES relaxations
TIF	transoral incisionless fundoplication

1. INTRODUCTION

Gastroesophageal reflux (GER) is due to the failure of the gastro-esophageal barrier and may lead to gastroesophageal reflux disease (GERD) [1, 2]. The number of patients with GERD has dramatically increased in the last two decades particularly in the Western world. This has generated an extensive research and it led to a better understanding of the pathophysiology of this condition; however, the appropriate management of GERD continues to be debated [3, 4]. New anti-secretory medications, laparoscopic surgical techniques and novel endoluminal devices have been introduced for the treatment of GERD. The outcomes are encouraging but the cost of medication and surgery continues to be high [5].

Persistent reflux of acidic, bilious, small intestine and pancreatic contents of the stomach to the esophagus result in a chronic inflammation of the esophageal wall. Barrett's esophagus is thought to be a mucosal adaptation to this chronic exposure which often leads to a lower esophageal intestinal metaplasia characterized by columnar epithelium. Barrett's esophagus is a premalignant condition associated with an increased risk of esophageal adenocarcinoma [6]. There are many therapies for the containment of Barrett's esophagus. Primary mucosal removal such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have advantage over other techniques as pathological examination of the removed tissues is possible. These techniques are relatively safe and effective; however, they can be time consuming and difficult to perform [7]. It was shown that obese people, especially with abdominal adiposity, has an increased risk of developing Barrett's esophagus [8, 9].

The prevalence of obesity has more than doubled in the last two decades in the United States, as about 70% of adults are either overweight or obese [10]. If this trend continues, more than 80% of the adult population will be overweight or obese by 2030 and almost all American adults will be overweight by 2048 [11]. The association of chronic diseases with obesity is widely known. Guh et al reported 18 different co-morbidities attributable to obesity [12]. The most effective treatment for obesity is bariatric surgery. The number of surgical procedures for obesity has significantly increased in the recent past. However, due to its cost and the risk of complications, less invasive treatments are being developed.

The limitations of pharmaceutical and surgical therapies, in combination with the high incidence of reflux disease and obesity has created the need to develop less invasive procedures that effectively address the underlying problem and are devoid of the shortcomings of the surgical option. However, many of new transoral techniques for GERD and obesity have not fulfilled these requirements. A single technique that can be used to restore the gastroesophageal barrier and restrict the capacity of the stomach would be attractive.

1.1 Anatomical and physiological background of GERD

The lower esophageal sphincter (LES) and the geometric profile of the cardia are factors to prevent GER and are the targets of surgical and endoluminal GERD procedures. The LES is characterized by its length, relative position to the diaphragm and pressure. A decrease in pressure and/or the overall length or just the length of the abdominal segment of the LES predisposes to reflux, as it decreases the resistance imposed on the flow of gastric juice or bile from the higher pressure stomach. The most

common cause of a permanently defective sphincter is inadequate pressure but the efficiency of the sphincter can also be nullified by an inadequate abdominal length or an abnormally short overall length [1]. In patients with severe GERD, the LES or the "high-pressure zone" is virtually nonexistent or greatly reduced. However, the cause of reflux in milder disease with a normal lower esophageal sphincter resting pressure (LESP) is under considerable debate. It is believed that transient LES relaxations (tLESR), i.e. intermittent spontaneous decreases in LESP, are responsible for reflux events [13-16]. Recent electrophysiological data suggests that the relevant vagal afferent fibers terminate with specialized intra-ganglionic laminar endings (IGLEs). These deformity-sensitive transducers are lined in series with muscle fibers at the cardia and fundus and are believed to mediate both fundic receptive relaxation and elicitation of tLESRs [17].

The normal angle of His prevents the distensive forces generated within the stomach to be transmitted to the LES, thus preventing its subsequent "unfolding" [1]. As the normal geometry of the cardia disappears with increasing gastric distention, the abdominal segment of the LES becomes more exposed to the intragastric and abdominal pressure and loses its intraabdominal length. It is taken up into the stretching fundus (such as the uterine cervix during delivery). At a critical length of 1-2 cm, the LESP drops acutely and GER occurs [18].

Nissen fundoplication prevents LES shortening during gastric distension, thus minimizing GER [18]. In light of the above described pathophysiologic factors, endoscopic therapies should prevent reflux in one or more of the following ways; 1) alter the compliance of the cardia and prevent tLES shortening/relaxation, 2) increase baseline LES tone or, 3) increase baseline LES length.

1.2 Management of GERD

The treatment of GERD is individualized depending on the patient's co-morbidities, symptom severity, response to medication and physiologic test results. The treatment spectrum is wide; from simple life style changes to Roux-en-Y gastric bypass. Complete healing of esophagitis after intensive proton pump inhibitor (PPI) therapy has been reported to be as high as 90%, however, medication have no effect on the underlying anatomical defects [19, 20]. Acid-related symptoms can be eliminated with vigorous antisecretory therapy but alkaline reflux may also occur and leads to definitive changes in the esophageal mucosa. Administration of single daily dose of PPI is sufficient in the majority of patients but those with more advanced disease require higher doses [21]. Patients with low LES pressures are the most exposed to relapse of GERD after pharmacological therapy [22]. Moreover, 50% of patients continue to exhibit low intra-gastric pH and objective evidence of acid regurgitation despite complete symptomatic control on PPI therapy [23].

Despite the relative safety of these medications new data has increased concern about the long-term effects and safety of anti-secretory drugs [24]. Patients on long-term PPI therapy encounter a higher incidence of pulmonary infection, nutritional deficiencies such as hypocalcaemia, Vitamin B12 deficiency or hypomagnesaemia, an increased rate of hip fractures and increased incidence of Clostridium difficile infections [25-27]. These side effects plus the high cost of antisecretories remain a significant problem. Thus many patients must commit to other therapy to provide lifelong solution for GER and GERD.

Anti-reflux surgery is recommended for patients with refractory or complicated GER and provides excellent symptom control in 85%-90% of cases [28, 29]. With the

advent of laparoscopic anti-reflux surgery (LARS) the number of anti-reflux operations has doubled [30]. However, failure may occur and 3%-5% of patients undergo one or more remedial operations [31, 32]. In addition, LARS requires a general anesthetic, hospitalization, postoperative lifestyle limitations for days to lifetime, is expensive and is associated with post-operative morbidity and even a mortality rate [33].

Reoperative anti-reflux surgery is a feasible option for patients with recurrent disease, although the results are inferior compared with primary surgery [34, 35].

Endoluminal intervention for GERD is a relatively new and promising concept. It holds out reduced morbidity and mortality and may be easier to perform as a repeat procedure.

1.3 Endoluminal GERD therapies

In 1986, Paul Swain - a British gastroenterologist - developed a sewing capsule that was attachable to the tip of the flexible endoscope to perform limited surgical maneuvers in the gastrointestinal lumen [36]. The idea of minimizing surgical trauma by performing operative procedures within the gastrointestinal tract provided a new perspective. In the last 30 years a spectrum of new endoscopic techniques have been developed for the treatment of GERD [37]. The endoscopic anti-reflux procedures published to date can be categorized into three groups:

(1) ablation,

(2) injection or implantation,

(3) fixation.

1.3.1 Ablative technique

Stretta® procedure

The possibility of radio frequency ablation being used for GERD therapy was explored after successful treatment of snoring and sleep apnea [38]. The Stretta procedure applies radiofrequency to the smooth muscle of the LES by 4 or 8 radially arranged titanium electrodes, resulting in muscular hypertrophy, fibrosis as well as neurolysis at the level of the lower esophageal sphincter and gastric cardia. More than 4000 procedures were performed in the United States alone. The indications were confined to patients with early reflux disease. Although significantly better heartburn related quality of life (HRQL) scores at 6 and 12 month were seen in most studies, the pH normalization rate was only 30-40 % [39-43].

1.3.2 Injection/ implantation techniques

The goal of the injection therapies is to deliver a biologically inert, injectable substance into different depths of the LES region. The injectates are either placed into the submucosal to increase the volume of the LES or into the muscularis propria for granulation and fibrous capsule formation.

Enteryx®

Enteryx, an ethylene vinyl alcohol copolymer with tantalum dissolved in dimethyl sulfide. It is injected into the muscularis propria of the LES. Randomized control trials demonstrated that Enteryx implantation significantly improved the HRQL scores and medication usage compared to control groups, however, improvement in LES pressure, esophagitis and esophageal acid exposure did not occur [44, 45].

Gatekeeper®

The Gatekeeper Reflux Repair System is a dehydrated hydrogel prosthesis implanted into the submucosa at the level of LES. It hydrates to a 6 x 15 mm cylinder shape soft pliable cushion and is removable by endoscope [46, 47]. In a case series of 78 patients a significant improvement in heartburn, regurgitation, HRQL, medial LES pressure and medication use at 6 months was observed, although pH normalization occurred in only 40% of patients [46, 48]. The retention rate of the implant was 70% at 6 months and 15% of patients required a second treatment within 6 weeks of the primary procedure [48-50].

Durasphere GR®

Durasphere is a sterile, biocompatible injectable bulking agent composed of pyrolytic carbon coated graphite beads containing zirconium oxide, suspended in a water-based, absorbable polysaccharide carrier gel. The size of the beads ranges from 90 - 210 μm to prevent migration of particles. This agent has been widely used for the treatment of stress urinary incontinence and recently for fecal incontinence [51-53].

The gel is injected through a 20 G sclerotherapy needle into 4 quadrants of the submucosa within 1 cm of the Z-line. The procedure is considered complete when the esophageal walls are approximated at the GEJ.

Initial short-term results are available from a single-center trial of 10 patients with uncomplicated symptomatic GERD [54]. At one year follow-up esophageal pH normalization was achieved in 40%. Five patients underwent repeat treatment.

1.3.3 Fixation techniques

Endoluminal suturing techniques are based on intraluminal apposition of tissue by using either staples, suture fasteners or sutures. The procedures are visualized by use of commercially available or by specially developed endoscopes. The outcomes have been somewhat encouraging but better results are needed in terms of pH normalization.

EndoCinch® (Bard)

This device was originally developed by Swain to create a full thickness intussusception at the gastroesophageal junction by a transoral sewing technique [36].

The device includes a suturing capsule, suture tags and an anchoring system that secures the suture and cuts the strands. The procedure is done under conscious sedation. The device is passed into the esophagus and the gastric cardia is remodeled just below the GEJ. First the gastric wall is sucked into the sewing capsule and a non-absorbable suture is passed through it by using a straight needle. After the suction is discontinued the system is reloaded and a second stitch is placed adjacent to the first. The two stitches are pulled together and cinched by a ceramic plug and ring. Two to four plications were placed in different configurations.

The procedure is generally safe. Results of multicenter trials demonstrated only 39.7% pH normalization rate at 6 months follow up. The initial symptom and medication usage improvement was attributed to post procedure edema, submucosal hemorrhage and the sham effect [55].

It was found that an inverted intraluminal gastroplication does not result in fusion between mucosal folds, irrespective of suture depth. A flat scar is the final outcome and appears proportional to the amount of ischemia, foreign body reaction and suture depth [56].

Plicator® (NDO Surgical)

The NDO Plicator system was developed to create and fixate a gastric plication below the GEJ in the anterior cardia with serosa to serosa apposition. The system consists of a Plicator instrument, a helical shaped "corkscrew" tissue retractor and a pre-tied suture insert.

The plication is secured by a pre-tied, suture based implant that is placed in a retroflexed manner. The plicator system has no own imaging capability and the procedure is done under direct visualization by inserting a 6 mm flexible endoscope through the device. The procedure is performed under intravenous sedation. First the flexible Plicator is inserted into the stomach than the gastric cardia is showed by the endoscope. Under direct endoscopic visualization gastric tissue below the anterior cardia is engaged and then retracted between the device arms. The arms are closed and the pledged sutures deployed. One or two additional transmural sutures are placed if necessary. The single plication procedure is about 10 to 20 minutes long [57].

Mild or serious adverse events such as abdominal or chest pain, pharyngitis, dysphagia, pneumothorax, pneumomediastinum, gastric wall perforation and severe abdominal or chest pain were reported from prospective multicenter and sham controlled randomized trails [57-59]. Distal esophageal acid normalization occurred in only 23% to 30% after one year post-procedure follow-up [58, 60]. The endoscopic full thickness plication system has been shown to provide a modest effect on reflux symptoms and quality of life at five years.

EsophyX® (EndoGastric Solutions)

The EsophyX device is used to increase the competency of the anti-reflux barrier by restoring the angle of His. A valve is created at the GEJ by delivering multiple full thicknesses, non-resorbable polypropylene fasteners. The end result is an anterio-lateral, 200-300 º, 3-5 cm long partial fundoplication.

Two techniques for transoral incisionless fundoplication (TIF) have been developed. The TIF 1 results in a 220º, omega shaped nipple type valve on the greater curvature side. In the TIF 2 procedure the fastener deployment is initiated further posterior and anteriorly resulting in a 270º valve [61].

The main technical steps are: the device is inserted transoral over a 6mm endoscope into the esophagus. Gastric tissue from the opening of the GEJ is engaged and retracted. The device is then rotated wrapping the fundus toward the lesser curvature. Under visual control multiple, non-absorbable polypropylene "H" fasteners are fired circumferentially, creating a double-wall thickness valve, positioning the gastric wall above the GEJ.

The procedure has been demonstrated to be safe and in the majority of cases free from serious immediate and long-term complications, however, serious adverse events such as esophageal perforation, gross intraluminal bleeding, free abdominal air or pneumothorax may occur. Objective results are penurious. Post procedural esophageal pH monitoring was performed in one clinical trial at one year post-procedure. Normalization of distal esophageal acid exposure was seen in only 37% of patients [62]. Patients with a Hill grade I or II valve benefited most from the procedure.

MUSE® Endoscopy System (Medigus)

The Medigus SRS system is a special 15 mm thick endoscope that combines a surgical stapler, video camera and a sonar to create a 180º anterior fundoplication. The tip of the endoscope retroflexes to the endoscope's rigid, 6 cm long segment and brings the proximal gastric wall to the lower anterior esophagus, 2-3 cm above the GEJ. A serosa to serosa apposition is created between these structures by firing a cartridge of 5 staplers which located in the rigid segment of the endoscope. The tip of the endoscope functions as the stapler anvil. If is indicated a new cartridge is loaded and the procedure is repeated.

Recently 69 patients underwent a Medigus SRS fundoplication and 64 were followed up for 6 month in a prospective multi-center trial [63]. There were 10 postoperative complications such as pain, fever, pneumothorax, pneumomediastinum, esophageal leak or esophageal hemorrhage. At 6 months, at least 50 % reduction in GERD-HRQL score (off PPI) from pre-procedure values was achieved in 48 of 66 patients (73, 95 % CI 60–83 %). At the 6-month follow-up, forty-two patients (64.6 %) were no longer using any daily PPI or other acid reducing medications. On pH monitoring there was a statistically significant reductions in the mean for (%) total time pH $\leq$ 4; however, it did not decreased within the normal range [mean (SD) 10.9 (10.7) vs. 64 7.3 (5.1), $p<0.001$].

Table 1 shows the short term results of different endoluminal GERD procedures.

Technique	Device	Author	No of patients	Follow-up (month)	pH normalization (%)	Resolution of esophagitis
Ablation	**Stretta**	Triadafilopoulos et al.	94	6	0%	29%
		Corley et al.*	35	6	-	-
		DiBaise et al.	18	6	22%	0%
		Tam et al.	20	12	0%	0%
		Richards et al.	41	7	36%	-
Injection	**EnteryX**	Johnson et al.	81	12	39%	0%
		Cohen et al.	102	12	37%	25%
	Gatekeeper	Fockens et al.	69	6	40%	-
		Cicala et al.	9	6	33%	-
	Durasphere	Ganz et al.	10	12	40%	100%
Suturing	**EndoCinch**	Filipi et al.	64	6	30%	6%
		Mahmood et al.	27	3	48%	-
		Tam et al.	15	6	27%	0%
		Schiefke et al.	56	12	28%	14%
		Schwartz et al.	17	3	29%	-
		Soji et al.	44	6	-	65%
	NDO plicator	Pleskow et al.	64	6	30%	-
		von Renteln et al.*	41	12	-	-
		Rothstein et al.	78	3	23%	0%
		Khajanchee et al.	221	6	32%	-
	EsophyX	Cadiére et al.	16	12	68%	19%
		Demyttenaere et al.*	22	10	-	-
		Cadiére et al.	79	12	37%	40%

Table 1. Change in objective measures **(**esophageal pH exposure and resolution of esophagitis) after different endoluminal treatments for GERD.* Only subjective measures were evaluated.

1.4 Physiology of obesity

The pathophysiology of obesity is complex as it is influenced by environmental, behavioral, genetic, endocrine and neurotransmitter factors. Although obesity is simply a result of an imbalance between energy intake and expenditure, the various combinations of these factors results in heterogeneous clinical manifestations of obesity. Recent research implicates environmental and social-behavioral risk factors including poor quality nutrients, chronic stress, pre-and postpartum environment, sedentary lifestyle and exposure to chemical or pharmaceutical agents, such as antipsychotics, antidepressants or corticosteroids [64-67].

Gene-diet interactions on monozygotic twins demonstrate that the genotype has an unquestionable role on diet related obesity [68]. Recently reported genome-wide association studies have revealed several genes related to obesity risk. The insulin induced gene 2 (INSIG2) and the fat mass and obesity-associated (FTO) genes were identified as genes having influence on body mass [69]. Although the exact number of these gene variants is unknown, it is likely that many will have a modest effect on the phenotype [70].

Agents, called adipogenes interfering with the endocrine or neuroregulatory system influence adipogenesis and obesity. The gastrointestinal peptide hormone ghrelin is produced in the oxyntic glands of the gastric fundus and regulates food intake, body weight, adiposity and glucose metabolism [71]. Its blood level elevates with increased sensations of hunger and it stimulates gut motility and gastric acid secretion through receptors in the hypothalamic neurons [72].

The role of chemical agents in the development of obesity is well established but a better understanding of the molecular background is crucial. As our knowledge of the

pathophysiology of obesity increases, it is becoming clear that the treatment of obesity is complex and must be individualized.

1.5 Management of obesity

Present treatment options for obesity range from life style change and dieting to bariatric surgery. The efficacy of the former is variable and usually limited because the psychological, environmental and socioeconomic circumstances are usually not optimal. Currently available pharmaceutical options are used as an adjunct: (1) inhibitors of intestinal fat absorption, (2) sympathomimetic agents that suppress appetite, increase satiety or thermogenesis, and (3) antagonists of the endocannabinoid system [73]. The use of these drugs often results in only moderate weight loss and combination therapy is advocated for the majority of patients. For those with a BMI $\geq$ 30 and if conservative measures are ineffective, bariatric surgery can be the treatment of choice.

The spectrum of bariatric surgery is wide including adjustable gastric banding, sleeve gastrectomy, jejuno-ileal bypass, duodenal switch biliopancreatic bypass and Roux-en-Y gastric bypass. The number of bariatric surgical procedures has significantly increased in the recent past. Only in the United States 250,000 bariatric operations are performed annually, mostly laparoscopically [10]. The complication and cost of bariatric surgery has decreased, however, surgery is available only for a small part of the morbidly obese population. Despite the improved results a large proportion of patients still resist having operative intervention. In addition, many insurance companies do not cover bariatric surgery.

An effort to develop newer and less invasive techniques for the obese population is imperative. Endoluminal management of obesity is challenging as it must be safe, effective, durable and cost effective.

1.6 Endoluminal bariatric therapies

The increasing need for bariatric surgery and the initial feasibility of endoluminal therapy for GERD has stimulated interest in the endoscopic management of obese patients. The approach still is in its infancy but holds great promise for providing presurgical weight loss, postsurgical revisions and even primary intervention. The current and emerging endoscopic devices for obesity are numerous and can be categorized as

(1) space occupying devices,

(2) transoral endoluminal stapling or suturing devices,

(3) prosthetic gastric/duodenal sleeves,

(4) miscellaneous.

1.6.1 Space occupying devices

Intragastric balloon therapy is the most preferred endoscopic bariatric procedure worldwide. This popularity is based on its relative safety and short term efficacy as well as low price compared to other techniques. Balloons are usually placed under conscious sedation. After the device is positioned in the stomach it is inflated under direct endoscopic visualization. The patient is then advised to take a full liquid diet for 3 weeks, progress to half-solid food for one week then continue with regular meals. The device is usually removed at 6 months. Balloon therapy related weight loss is due to

mechanical and physiological effects. It provokes sense of satiety secondary to gastric distention and also has an effect on gastric motility through neurohormonal changes [74]. The most frequent device related complications are GERD and consequent esophagitis, nausea or vomiting which usually responds to medication, but serious adverse events such as gastric perforations; small bowel obstruction from a collapsed balloon and cardiac arrest have also been reported [75-78].

The BioEnterics *Intragastric Balloon (BIB) system* is a spherical, smooth silicone device filled with saline and has an adjustable volume (400 to 700 ml). In retrospective study data from 2,515 patients showed a 33.9 ± 18.7 %EWL in 6 month. Patients with concomitant hypertension and diabetes achieved significant improvements in blood pressure and glycemic control [75, 79]. However, other sham-controlled trials did not show significant weight loss from the BIB procedure [80, 81]. The *Heloisphere Bag (HB)* is an air-filled balloon inflated with 500-800 ml of air. Satisfactory weight loss was demonstrated in prospective multicenter studies (10-29.1 %EWL); however, high spontaneous deflation rate of 40% was also seen [82-84]. The Similed gastric Balloon (SGB) is filled with 700 ml of a saline. After 6 months 34.6% EWL occurred. In 21% of patients early device removal was necessary because of severe epigastric pain. More recently an expandable and degradable polymer pill has been developed that takes up space in the stomach [85]. This technology has not yet been clinically tested.

In summary, intragastric space occupying devices are generally safe, but durability of weight loss after balloon therapy continues to be a pitfall. They may have a role as a bridge to bariatric surgery to reduce perioperative complications in morbid obese population. There is no data to support their use as a standalone device for sustained weight loss.

1.6.2 Endoluminal incisionless stapling or suturing devices

EndoCinch (RS2) Suturing system (Bard)

The EndoCinch device was originally developed for the treatment of GERD, but long term results failed to demonstrate objective efficacy. The new RS2 Bard device is designed for transoral gastric volume reduction. The device sutures the anterior and posterior gastric fundus and body using a series of two or three stitches in a "quilting" pattern. This approach prevents the stomach from relaxing to receive food.

A nonrandomized, multicenter feasibility study with 18 patients (BMI ranging from 30 to 45 kg/m^2) showed at 6 and 9 months post procedure patients achieved a mean 30.4% and 34.4% EWL respectively [86]. The procedure may represent a treatment option for obesity; however, the data is limited in terms of size and follow up. No further studies have been published.

Incisionless Operating Platform (USGI Medical)

This surgical platform is used for translumenal, endoluminal or single incision surgery. For bariatric patients it is intended for either primary or revisional procedures. The IOP contains 4 channels, one for a flexible 4.9 mm endoscope for visualization and the other 3 for tissue manipulation. The specially designed tissue anchors provide durable tissue approximation because the holding force is widely distributed.

In a first short term studies, 20 patients with a dilated pouch and stoma were enrolled [87, 88]. Seventeen cases were considered successful. The mean stoma diameter and pouch volume was reduced by 65% and 36% respectively. The mean weight loss of successfully treated patients was 8.8 kg at 3 months. No major complications were encountered.

Horgan et al reported results of 112 patients who underwent the restorative procedure [89]. The mean stoma diameter was reduced by 50 % and the pouch length by 44% when placing an average of 6 anchors. At 6 months post procedure 96 patients lost 32% of the weight regained after bariatric surgery. Application of the IOP platform for revisional bariatric surgery appears to be safe. Further studies on procedure durability are planned.

StomaphyX® (EndoGastric Solutions)

The StomaphyX is a single-use device, designed to create large gastric tissue folds. A regular gastroscope is used through the device for direct visualization. Tissue is drawn into the distal part of the device and five to six gastric folds are created and stabilized one by one after delivery of non-resorbable polypropylene fasteners.

Results of revisional bariatric procedures from a single center are available. Thirty nine patients with an average pre procedure excess body weight of 51.1 kg underwent complicationless procedures. The mean EWL% at one year follow up was 20% [90]. Successful repairs of gastric pouch leaks with the StomaphyX device also have been reported [91].

TOGA®(Satiety Inc)

The TOGA system is an endoscopic stapling device to create a gastric sleeve parallel to the lesser curvature. The procedure is performed under direct visualization as a gastroscope can be advanced through the device and retroflexed. The stapler engages the anterior and posterior gastric walls by applying suction. After staple application the device is withdrawn and reloaded. The second staple row extends the sleeve distally creating an 8 cm long 2 cm wide sleeve with a maximum 10 mm outlet.

A total of 32 morbidly obese patients were enrolled in two studies [92, 93]. The follow up period was 6 months. The EWL was 24.4% using the first generation and 46% with the second generation device. The BMI decreased from 43.3 to 38.5 and from 41.6 to 33.1 respectively. No major complications occurred. The most common adverse events were transient pain, nausea and dysphagia. Using the second generation device, 82% of the staple lines were found to be intact at the 6 month follow up. An FDA multicenter trial resulted in failure with insufficient weight loss.

In summary, endoluminal suturing and stapling techniques are seemed to be safe and have demonstrated good to moderate weight loss on short therm. Durability of the modified gastric anatomy is related to scar tissue formation between opposed gastric walls. Mucosa to mucosa apposition does not provoke significant amount of scar tissue and will not last long.

1.6.3 Prosthetic sleeves

Prosthetic sleeves are tube-like plastic devices delivered and secured endoscopically in the proximal GI tract to restrict absorption of nutrients in the small intestine and/or exclude the stomach from the digestive process. The main advantage of the procedure is that it does not alter permanently the anatomy. Its potential disadvantages are difficulty in securing the device with the consequent potential of migration and small bowel obstruction.

Valen Tx

The Valen Tx gastric sleeve is designed to mimic the effect of the Roux-en-Y gastric bypass. The device is attached by transmural anchors to the GEJ, and extends

through the stomach and into the distal duodenum or proximal jejunum. The length of the sleeve is variable depending on the therapeutic goal.

In the first human clinical trial 12 patients were enrolled with a BMI ranging from 35-50 [94]. The device was delivered safely and anchored successfully to the GEJ. The implantation period was 12 weeks and no spontaneous anchor detachments occurred. The mean excess weight loss was 46% at three months post procedure. No complications occurred during the study period or at removal.

Endobarrier (GI Dynamics)

The Endobarrier is a 60 cm long, flexible sheath composed of a nutrient-impermeable fluoropolymer that is deployed in the duodenal bulb and extends to the jejunum. The device prevents nutrient absorption and mixing with digestive enzymes, mimicking one of the components of the RNY gastric bypass. A self-expandable crown-shaped, nitinol anchor holds the proximal orifice open and in place.

In a first human single center trial 12 patients with a mean BMI of 43 kg/m^2 were enrolled [95]. The devices were delivered and removed safely at 3 month. The mean EWL was 23.6%. The fasting glycaemia level in 4 diabetic patients improved and the hemoglobin A1c improved in three. In three short-term randomized controlled (device vs. sham or diet alone) trials and two long-term (1 year device treatment) trials EWL from 11,9% (12 weeks) to 47% (52 weeks) was demonstrated [96-99]. In another long-term study significant decrease inHbA1c% was achieved [100].

The precise mechanism behind the weight loss and metabolic effect of malabsorptive devices are unknown. There is also a lack of data regarding the durability of the prosthetic sleeves. Data after short-term implantation suggest a rapid weight

regain after device removal. The implantation of these systems carries a high (20%) failure rate and complications such as nausea, pain, device migration or GI bleeding.

1.6.4 Other therapies

Electrical stimulation

The bariatric effect of electrical stimulation therapy is based on a series of low-energy electrical impulses delivered to the smooth muscle of the stomach intended to create a feeling of fullness or gastroparesis. Laparoscopically delivered devices have been placed and an endoscopically delivered gastric pacemaker is in development. Natural orifice surgery may further support the wider applicability of electrical gastric stimulation.

Radiofrequency ablation

Localized tissue ablation using radiofrequency may have beneficial effects on weight loss. Radiofrequency ablation of the gastric antrum and pylorus may cause structural and functional changes that lead to decreased appetite and consequent weight loss. The device is endoscopically delivered and positioned in the stomach. For 3-5 minutes energy is applied for ablation. The theoretical treatment effects are as follows: (1) decreased appetite presumably due to mucosal lining changes resulting in reduced hormone and HCl release, (2) satiety due to gastric volume reduction and elasticity, and (3) a decrease in hunger by delaying gastric emptying and reduction of Ghrelin. The device is in its preclinical phase.

The development of these devices is in an early phase. Better understanding of neurohormonal changes after bariatric interventions may help to optimize their efficacy.

Table 2 cumulates the data from endoluminal obesity therapies.

Technique	Device	Author	No of patients	Follow up (month)	% EWL(mean±SD)	BMI reduction (mean±SD)
Space occupying devices	**BIB system**	Genco et al	2515	6	33,9±18,7	4,9±12,7
		Göttig et al	109	9	-	8,7±5,1
		Genco et al	16	3	38,5±5,1	5,8±0,5
			16	3	33,6±4,9	5,1±0,6
		Okta et al	17	5	27±9	-
		Doldi et al	132	4	-	5,2
	Heliosphere Bag	Foristieri et al	10	6	-	5,2±13,1
		Shastri et al	59	7	-	2,38
		Mion et al	32	4	-	3,25
	Similed Balloon	Carvalho et al	14	6	46,5±36,7	3,9
Stapling/suturing	**EndoCinch**	Ryou et al	151	12	29,9	-
	Bard RS2	Thomson et al	18	6	30,4	-
	USGI IOP	Mullady et al	20	3	-	(8,8kg)
		Horgen et al	96	6	32	-
	StomaphyX	Mikami et al	39	12	20	-
	TOGA	Deviére et al	20	6	26,5	2,2
		Moreno et al	11	6	46	-
Prosthetic gastric sleeves	**Valen Tx**	Swain et al	12	3	46	-
	Endobarrier	Rodrigez-Grunert et al	12	3	23,6	-
		Escalona et al	24	12	47	-

Table 2. Excess weight loss and reduction of BMI after different endoluminal therapies for obesity.

1.7 Endoluminal therapies for Barrett's esophagus

Persistent exposure of gastric content to esophageal mucosa creates an abnormal environment where after a cellular damage of the stratified squamous epithelium, intestinal metaplasia can develop. Barrett was the first to describe "The lower esophagus lined by columnar epithelium" [101]. This is a well-studied premalignant condition of esophageal adenocarcinoma.

In the era of minimally invasive procedures the treatment of Barrett's esophagus and early mucosal adenocarcinomas has been changed. Different endoscopic treatment modalities for mucosal destruction are available such as thermal, photodynamic, radiofrequency or endoscopic mucosal removal therapy.

Thermal therapies

This method results in destruction of columnar esophageal epithelium achieved by administration of heat form different sources. After elimination of esophageal mucosa regrowth of normal squamous lining occurs. The required thermal energy is applied by either using electrocoagulation, a heater probe, neodymium-doped yttrium aluminum garnet laser or argon beam plasma [102]. The laters are a non-contact electrical energy transfers to the tissue by means of electromagnetic radiation or ionized argon gas. Application of appropriate probes through an operating channel of an endoscope allows the use of these techniques in endoscopic surgery. In the case of argon beam plasma, mucosal injury occurs to a controlled depth of 1-2 mm [103]. The procedure is not devoid of risk and even major complications may occur. Results of thermal therapy show that eradication of Barrett's epithelium is not long lasting. Premalignant metaplastic cells may be hidden or reform under the regrown squamous

epithelium exposing the patient to the development of esophageal adenocarcinoma [104].

Photodynamic therapy (PDT)

This minimally invasive treatment utilizes a photosensitizing drug and laser light against high grade dysplastic cells and adenocarcinoma [105]. The photosensitizer is accumulated in the targeted cells and activated on a specific wavelength provided by a non-thermal laser light. As a result, singlet oxygen is generated which causes irreversible oxidation of essential cellular components [106]. Anti-tumor activity of photodynamic therapy is accelerated by vascular disruption and by elevation of anti-tumor immunity [107]. The unquestionable disadvantage of this technique is a prolonged general photosensitivity that can occur; however, new photosensitizing drugs are under investigation. The results have been inconsistent and this technique in now rarely used.

Radiofrequency ablation (RFA)

With this relatively new therapeutic method energy from a controlled radiofrequency source is applied to the Barrett's epithelium using a balloon catheter or a wired paddle. The controller of the RFA source is preset to deliver energy of 12 J/cm_2 which causes complete destruction beyond the lamina propria [108]. The inflated balloon in the esophagus releases energy circumferentially resulting in 360º mucosal destruction. The advantage of this procedure is that the depth of epithelial damage is better controlled in contrast to photodynamic therapy, but histological assessment is not possible. This method has been shown to be safe and effective in the treatment of patients with BE and high grade dysplasia [109].

Endoscopic mucosal removal

Endoscopic mucosal removal is being investigated extensively. The major advantage of this technique is that pathological examination after tissue removal is possible. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) were developed to remove superficial cancerous mucosa from the gastrointestinal tract. These methods have a bleeding rate of 8% to 16% and a perforation rate of 0% to 1 % in the esophagus and stomach [103,104]. EMR is performed either using a cap technique or band ligation. Results of focal EMR alone are inferior as the recurrence rate is up to 47%. [110]. Long-term complete response after circumferential or wide area EMR can be achieved in 76% to 100% of cases [111, 112]. Endoscopic submucosal dissection was developed for en bloc resection of superficial neoplasms or premalignant mucosal changes. The large mucosal lesions are removed in the submucosal layer by specially designed pulsed electrocautery knives. Endoscopic submucosal dissection is more often used to remove gastric mucosal lesions as manipulation in the thin walled esophagus carries more risk. Both techniques have a long learning curve.

1.8 Aims of the study

In the last decades extensive innovational effort has been addressed to endoluminal GERD and obesity therapies. Majority of these new devices have failed to demonstrate long-term efficacy and/or safety mostly due to the complex anatomy of the GEJ area and pathophysiology of these diseases. Data from previous studies suggest that mechanical changes to restore the angle of His and LES pressure for GERD and

restrictive bariatric techniques for obesity may have the greatest success. However, these techniques often fail due to the weakness of the fixation method.

The overall aim of the study was to develop a device and a procedure to create effective and durable gastroplasty to treat GERD and also to create a small proximal gastric pouch and outlet for obese patients. Our principal hypothesis was that gastric mucosal excision followed by full thickness suture placement is feasible, safe and provides long lasting tissue apposition and surgical effect. We also investigated the possibility to safely remove esophageal mucosa for Barrett's esophagus with a modified excision device. The aims of our work were:

► To develop and test a complex device that excises gastric mucosa and places full thickness sutures in one. We performed ex vivo and in vivo experiments to optimize device characteristics and to develop the operative technique.

► To demonstrate feasibility of mucosal excision and full-thickness suture apposition of the excision beds at the gastroesophageal junction by using a new generation of devices. We measured the GEJ compliance in a survival canine and determined the durability of the restrictive gastric pouch outlet in the obesity model. Histologic examination was also performed to visualize tissue healing and scar formation.

► To understand more how to augment scar tissue formation in the submucosa for more durable gastroplasties. We tested different hypertonic solutions in survival swine experiments.

► To evaluate the safety of the endoluminal gastroplasty procedure for GERD and obesity in a human pilot trial. We studied the effect of the gastroplasty procedure on

symptom scores, quality of life, antireflux medication usage and pH monitoring for GERD patients and excess body weight loss for obese patients.

► To develop a technique and evaluate the feasibility of strip endoscopic mucosal resection (SEMR) for Barrett's esophagus utilizing a modified gastroplasty excision device.

2. DEVELOPMENT OF THE DEVICE AND A NEW TECHNIQUE

2.1 Background

In the first phase of the study a complex transoral endoscopic device was developed. This was able to excise mucosa from both the GEJ and from the stomach and also to place full thickness sutures into the denuded areas [113]. Two procedures were designed: one to reduce tissue attenuation at the GEJ for GERD; another to create a small proximal gastric pouch for obese patients. The main focus of our initial laboratory work was feasibility, safety, quality, and reliability of mucosal excision and suture needle actuation.

2.2 Materials and methods

The device

The first generation device was a dilator shape instrument with handle, shaft and a distal integrated operating capsule that was capable both to perform mucosal excision and suture placement in one **(Figure 1/A)**. A short, flexible transition piece was integrated between the rigid capsule and the semi flexible shaft to provide flexibility for device insertion through the oropharynx. The 5 cm long rigid distal operating capsule contained vertical injection needles for submucosal epinephrine solution injection, horizontal running excision blade for mucosal removal and two, 3/4 circular needles for suturing each connected to a separate 2.0 Prolene suture **(Figure 1/B)**. The device was designed to be used with 5 mm - 6.5 mm diameter flexible pediatric gastroscope that enters into a dedicated channel at the handle and exits the device at the flexible transition segment. This endoscope provided direct visualization for the procedure. The

device shaft was marked with incremental graduations to indicate the distance from the distal tip to the incisors. Testing was performed in porcine, canine, baboon and human tissue.

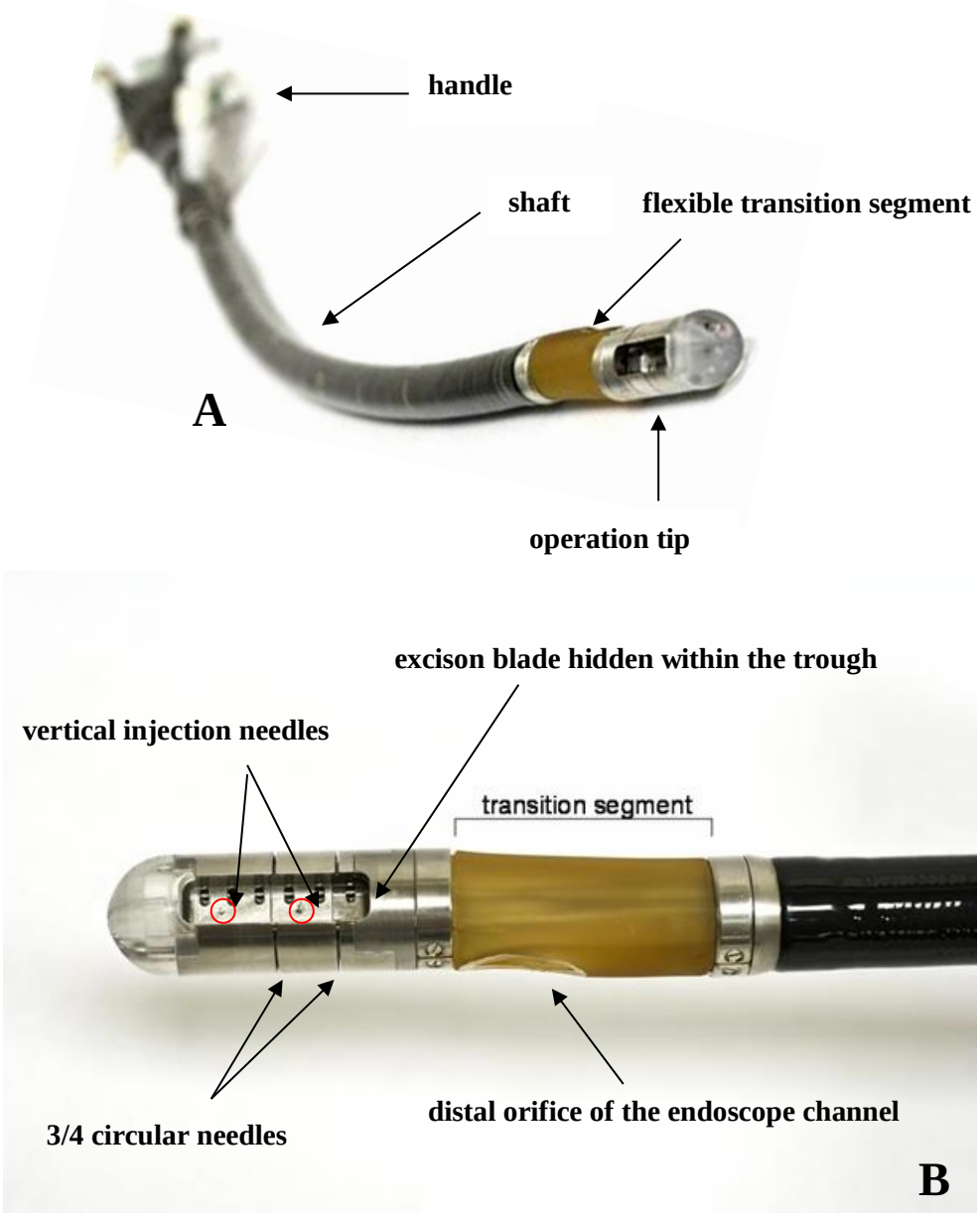

Figure 1. **A**: The general construction of the excision-suture device: handle; 65 cm semi-flexible shaft and a rigid operation tip. **B**: The 5 cm long operation capsule with two vertical injection needles for submucosal injection; with a horizontal running blade and with two ¾ circular suturing needles. A short flexible transition piece connects the

rigid tip to the shaft. The channel for the small diameter flexible endoscope exists at the transition piece of the device.

Ex vivo experiments

First ex vivo porcine tissue experiments were conducted on stomachs and esophagi to test feasibility of mucosal excision. Minor and major device and technique modifications were needed for more reliable mucosal excisions. Then both device and operative technique refinement were done on human esophagi and stomachs that were harvested from cadavers after organ donation. Histologic sections of the stomach wall were used to determine excision depth and excision overlap safety. Possible complication scenarios such as needle penetration into adjacent tissue were also tested by placing small intestine outside of the stomach at the suturing site.

In vivo experiments

Porcine in-vivo acute experiments (n=7) for GERD and obesity procedures were performed focusing on mucosal excision and suture actuation reliability (Creighton University, Omaha, NE, USA (IACUC PN-0785)). Each experiment was followed by necropsy with inspection of the abdominal cavity, excision placement, suture penetration and gastroplasty morphology.

For both GERD and obesity procedural efficacy data further survival studies were performed in baboons (Southwest Foundation for Biomedical Research, San Antonio, TX, USA (IACUC PN-1161)). The baboon stomach is similar to the human stomach in almost all respects, whereas the porcine model and canine models have thicker GEJs and proximal stomach walls.Total of 12 animals underwent GERD (n=6) or obesity (n=6). After euthanasia histologic and gross inspection were completed. First the abdomen was explored for injury to bowel, the liver, the spleen and other structures adjacent to the gastroesophageal junction. The whole stomach with approximately 5 cm

of the esophagus was removed. The proximal half of the stomach and the esophagus was opened along the lesser curvature. Documentation of tissue healing and measurement of the width and depth of the adhering tissue was performed. Specimens were than kept in formalin and cut in 2mm pieces in the caudad cephalad axis for histological examination.

The procedure

The main steps of the in vivo GERD operations were the following: under general anesthesia and endotracheal intubation the esophagus was dilated to 60Fr. The animal was placed in the left lateral decubitus position. The device was placed through the mouth into the stomach. A 6 mm pediatric flexible endoscope (FG-100 RE, Fujinon, Tokyo, Japan) was introduced through the dedicated channel of the device for direct procedural visualization. The device was positioned at the greater curvature for the first excision and the gastric wall was pulled into the trough of the operating capsule by applying 500 mm/Hg negative pressure. The submucosal space was injected with 15 ml of 1:200,000 adrenalin solution to lift the mucosal from the muscularis propria of the stomach wall and to create vasoconstriction for hemostasis. The horizontal cutting blade was then activated and mucosa excised. Suction was then discontinued and the mucosal strip was removed from the device trough with a grasping forceps. The excision bed was inspected for bleeding. Throughout all porcine and baboon experiments no excessive bleeding was encountered. The device was then positioned back on the excision bed for the first suture cycle. Suction was applied and after tissue capture the 3/4-circle suturing needles were rotated 360° through the captured tissue **(Figure 2)**. After the first excision-suture cycle the device was rotated to an anterior position, adjacent to the first excision, and the excision-suturing cycle was repeated. Suction was

discontinued and after endoscopic inspection the device was removed and the sutures were organized. A 10 mm endoscope was placed within the stomach to examine the sutures and excision sites and then the distal and proximal sutures were tied under endoscopic visualization by using a knotting device. The animal were then woken and fed with a clear liquid diet for 8 weeks.

The obesity procedure consisted of 3 overlapping excision-suturing cycles to create a vertical gastroplasty line to form a neo-esophagus with a small gastric pouch and restrictive outlet **(Figure 3)**. After euthanasia the intraperitoneal cavity was inspected followed by removal of the esophagus together with the stomach. Histologic examinations were also carried out for the baboons.

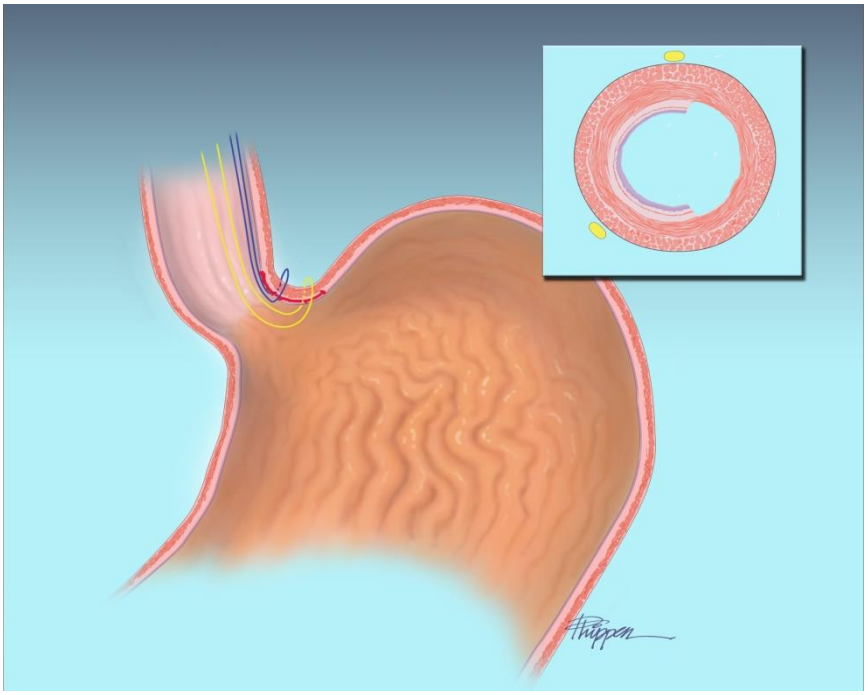

Figure 2. The gastroplasty for GERD consisted of a single excision-suturing cycle at the greater curvature side of the GEJ with excision pattern including 180° of the distal esophagus and proximal stomach. The excision pattern respects the location of vagal nerves in order to avoid their injury during suturing.

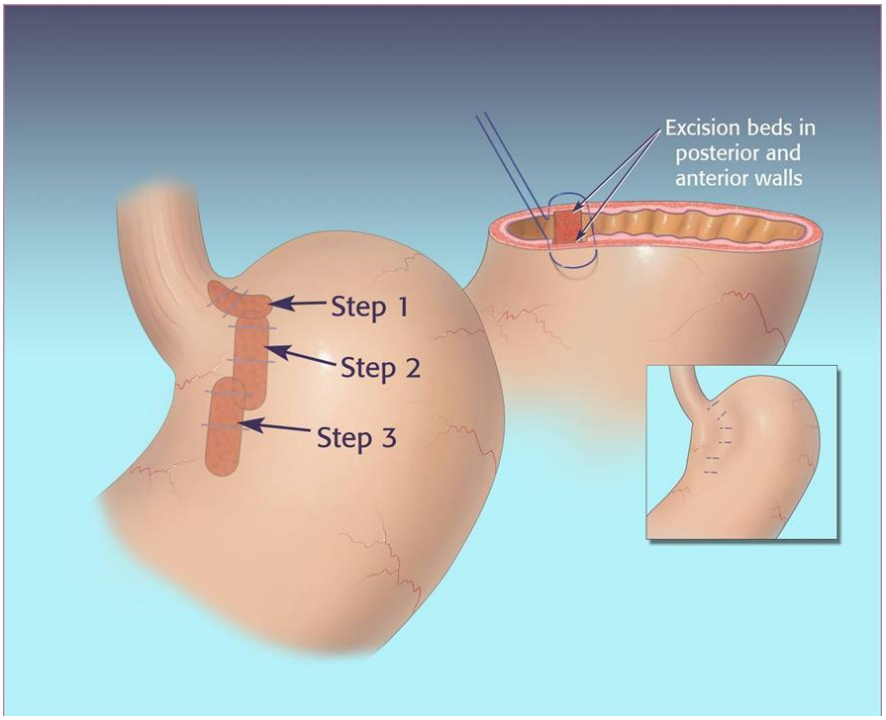

Figure 3. Schematic description of a 3 steps vertical gastroplasty with excision overlap and full-thickness sutures placement. A small proximal esophago-gastric pouch with a restricted outlet is created.

2.3 Results

Ex vivo

Total of 104 excisions and 55 suture actuations were performed. The size of the operative capsule trough and the depth of the excision blade provided reliable mucosal excision; however, full thickness injury occurred in 3 (2.9%) cases. The first generation combined excision-suture device showed consistent full thickness suture penetration depth but suture actuation reliability was poor as in 8 (14,5%) cases malfunctions occurred. Adjacent tissue suture entrapment experiments showed that the small intestine is not sutured when placed outside onto the sutured site of the stomach wall. The reason was that during suturing the suturing needles pushed the stomach wall ahead until it

reached the other wall of the trough pushing the small intestine out of the way. Based on these results injection needle positions and suturing mechanism of the device were modified. With these modifications more reliable submucosal injection to prevent full thickness injury and better device performance for safe suturing were achieved.

In vivo

During in vivo animal studies total of 82 excision-suturing cycles were carried out. In the baboon obesity group 1 (1.2%) stomach wall perforation occurred. The perforation was successfully closed endoluminal using the suturing device, and the animal was survived without incident. In the case mentioned the device entirely overlapped a previous excision site resulting in two excisions on a same location. In another obesity animal the suture pattern was placed inappropriate. The smallest excised mucosal strip was 10 x 14 mm and the largest 10 x 50 mm **(Figure 4)**. The overall suturing depth accuracy was low as 65%of the sutures were full thickness resulting in satisfactory stomach wall apposition and scar tissue formation **(Figures 5 and 6)**. Total of 3 from the survival procedures were considered to be satisfactory. Postoperative bleeding was noted in one of 12 survival animals with a single melanotic stool being passed. In 4 animals vomiting in the early postoperative period was noticed. After euthanasia no injury was found in the abdominal cavity in any of the 19 animals.

Figure 4. Example for an excised mucosal strip (10x28 mm) from the baboon study.

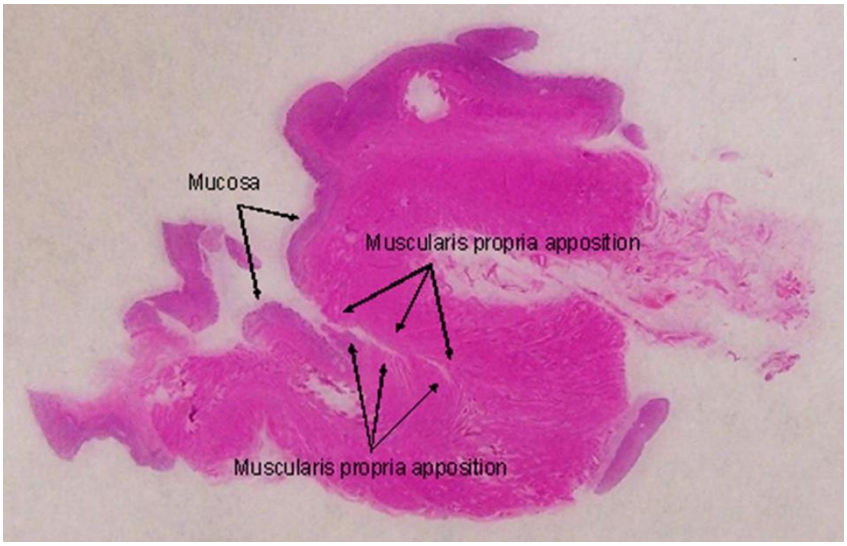

Figure 5. Histological (HE) picture of ideal excisions and excision beds apposition after suturing: muscularis propria to muscularis propria.

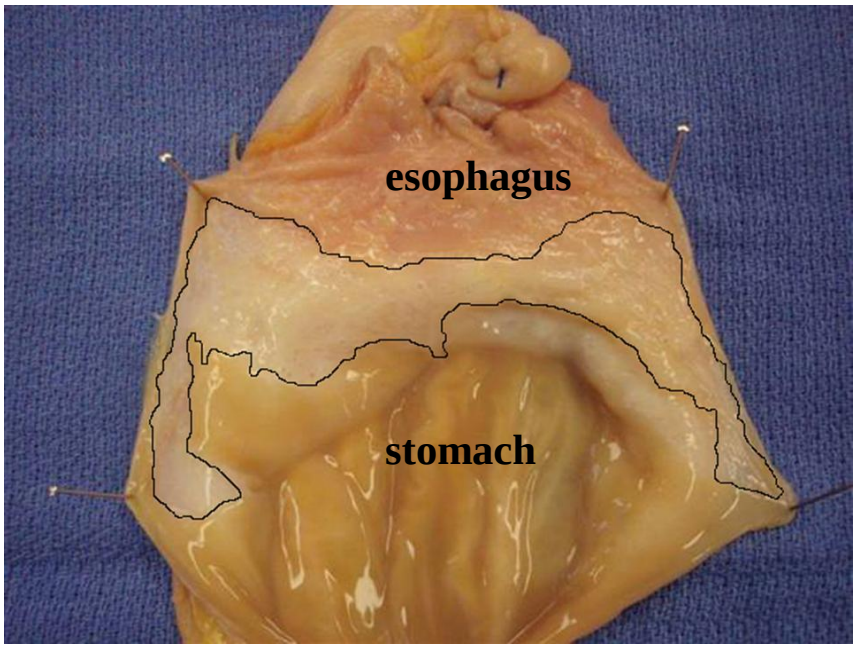

Figure 6. Gross picture of the three steps obesity gastroplasty: excisions with overlap are creating an inverted, continuous U shaped pattern. The specimen was cut open along the gastric and esophageal lesser curvature. The black line surrounds the scar tissue that was created.

2.4 Discussion

Laboratory results from ex vivo studies demonstrated gastric mucosal excision and suturing feasibility. However, in vivo survival animal experiments revealed inconsistent size mucosal excisions and poor suture penetration depth. Moreover, the three steps obesity gastroplasty procedure required significantly more effort to accomplish than acceptable. A correctable operator error caused one perforation, but the defect was sutured successfully by using the gastroplasty device. We learned that larger excisions first, followed by suturing with a separate, longer trough device would obtain more consistent full thickness suture penetration and a durable gastroplasty. Changes in the obesity procedure to reduce operation time and failure rate were also necessary.

3. SAFETY AND FEASIBILITY CANINE STUDY

3.1 Background

Data from the baboon survival study revealed that mucosal excision and full thickness suture placement to the excision beds is not optimal when using one combined device. It was also concluded that the 3 steps vertical gastroplasty was too time consuming and too complicated to perform and this would not work as an outpatient procedure in the future. Moreover, the sutures were approximating tissue from a relatively big distance that was under too much tension to stay approximated. To improve two separate devices were created: one for mucosal excision and another one for suturing. The gastroplasty procedure for obesity had been reduced in complexity as well. With this survival study our intention was to demonstrate safety, feasibility and efficacy of the new devices and the new gastroplasty technique [114].

3.2 Materials and methods

The new gastroplasty system

The excision and suturing devices were similar in construction each having an operational distal tip, flexible transition piece, a dedicated 5-6 mm endoscope channel, 60 Fr flexible insertion tube and a handle **(Figure 7/A)**. The trough of the excision device was wider and longer comparing to the previous combined excision-suturing device. Similar to the first prototype it contained vertical needles for tissue injection, suction ports and a horizontal blade for mucosal excision **(Figure 7/B)**. The suturing device was also longer and operated two circular needles 1 cm apart, each connected to a separate 2.0 Prolene suture **(Figure 7/C)**. There was nothing changed on the knotter **(Figure 7/D and E)**.

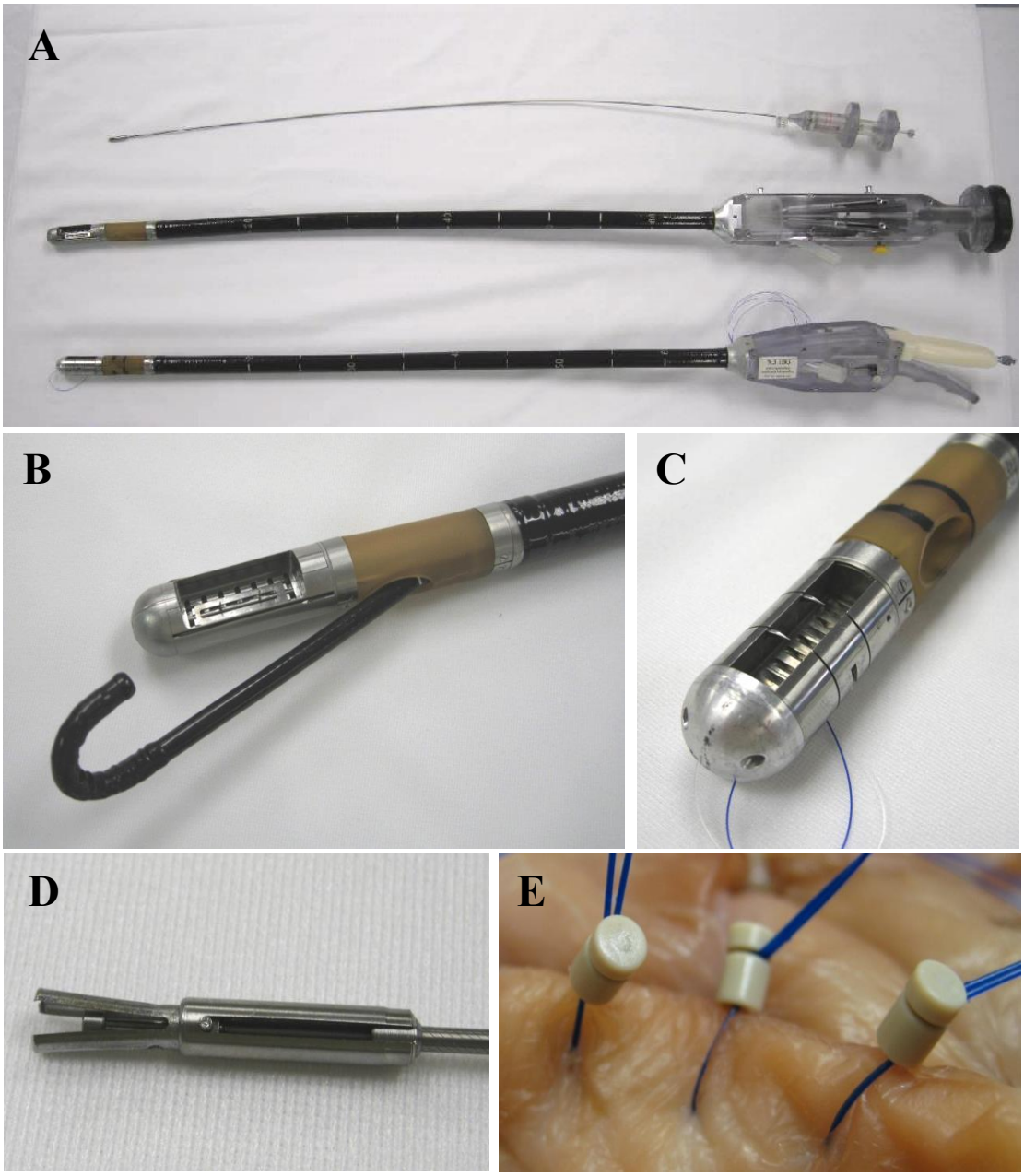

Figure 7. A. The Excision and Suturing Devices with the Knotter. **B**. The distal tip of the Excision Device showing the trough and suction ports. Vertical injection needles can be seen. The excision blade is retracted. **C**. The suturing capsule with transverse circular needles and attached sutures. The trough is 3 cm long and 0.8 cm wide. **D**. The knotter is 3 mm in diameter and pushes a cylinder with plug out with suture strands entrapped and after suture cinching it transects both suture strands. **E.** Knotting anchors with suture placed in porcine gastric tissue

Measurement of GEJ compliance

For the GERD procedure the Barostat device (G & J Electronics Inc, Toronto, Ontario, Canada) was used to measure compliance of the GEJ pre and post-procedure. The Barostat is a specially designed instrument used to maintain constant pressure in a closed chamber by means of a pneumatic pump. The flaccid bag is connected to a double channel catheter and inserted in a targeted part of the gastrointestinal tract. This allows measurements of the volume of the studied organ at different pressures **(Figure 8)**.

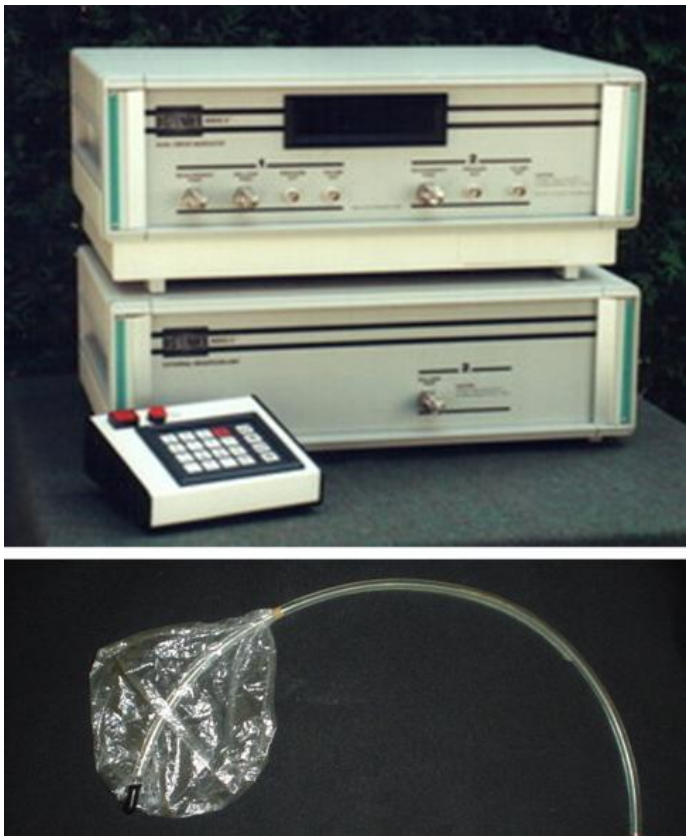

Figure 8. The Barostat and its catheter with the flaccid bag. After calibration of the Barostat, a balloon catheter was delivered and positioned endoscopically in the GEJ. Volumes of the GEJ at pressures from 3 to 21 mmHg in six steps were recorded. After completion the catheter was withdrawn.

Procedure

Seven mongrel dogs (ranging from 16 kg to 17.5 kg) were used for the study. The protocol was performed in the Creighton University (Omaha, NE, USA) and it was approved by the Institutional Animal Care and Use Committee under the number (IACUC PN-0813). Four dogs underwent the GERD procedure and three the obesity. The animals first were anesthetized with intravenous propofol, then endotracheal intubated, placed in the right lateral decubitus position and maintained under general anesthesia with Isoflurane. Initial endoscopy was performed to assess and record any anatomical variance as well as the distance of the GEJ from the incisors. The Barostat was then used to assess the compliance of the GEJ. A Savary guidewire was placed and the excision device was advanced over the guidewire into the proximal stomach. A 6 mm video endoscope (Fujunon EG-470N5) was inserted through a dedicated channel of the device and the stomach was insufflated with air. With the endoscope retroflexed the operating field and the tip of the device was visualized. The suction trough was positioned against the proximal gastric mucosa just below the GEJ on the greater curvature side, minus 500mmHg suction was applied and the mucosa was captured. Fourteen to 21 ml, 1:100,000 adrenaline solution with 40% Dextrose was injected into the submucosa creating a sustained and wide target zone for excision. The mucosa was then excised by a single forward motion of the horizontal excision blade and after removed by a flexible endoscope forceps. The excision procedure was repeated both on the anterior and posterior side of the first excision creating three, approximately 20 mm by 45mm adjacent excision beds. The excision device was then withdrawn.

The suturing device was inserted over the Savary guidewire and the 6 mm endoscope was advanced through a dedicated channel into position. The proximal

aspect of the two lateral excision beds were captured and in – 500 mmHg succession full thickness sutures were placed by two circular needles rotated 360º through the gastric wall. The device was then withdrawn and the sutures were reloaded. The procedure was repeated in the distal aspect of the excision beds for a total of 4 sutures. After suture device withdrawal the knotter was inserted under direct visualization and individual sutures sets were tied and cut in a single action. The visual result was recorded.

The technique for the obesity procedure was similar but the gastroplasty was placed 2 cm below the squamocolumnar junction and only two sutures were placed through the anterior and posterior excisions. The gastroplasty positioning was similar to that of the external gastric band when utilizing the pars flaccida approach. The sutures were separated further radially to create a restrictive procedure with the outlet on the lesser curvature side.

Following the procedure, dogs received 500 ml of subcutaneous physiologic saline and were kept without oral intake for 24 hours. From the first postoperative day to euthanasia they received a high protein high calorie pureed diet three times a day. There was no attempt made to create weight loss in the obesity group as the pureed liquid diet could go through a small outlet. Procedural complications, food intake, weight change were recorded throughout the study. All dogs were survived for 8 weeks. Mid-term endoscopies were carried out per protocol to evaluate the integrity of the gastroplasty. End term endoscopies and Barostat procedures for the GERD dogs were performed under general anesthesia. The measured and visual findings were recorded and the animals were euthanized with IV. sodium pentobarbital. The stomachs and

distal esophagi were explanted, examined, photographed and sectioned for histologic examination. The obesity explanted stomachs had a gel cast mold made of their GEJ.

3.3 Results

There were no intra or postoperative complications with all dogs surviving uneventfully. The GERD dogs lost an average of 0.13 kg and the obesity dogs gained an average of 0.5 kg at 8 weeks. No bleeding was observed, some animals did consume less in the first 10 days post procedure but eventually regained their weight. There was no evidence of swallowing problems such as increased salivation, retching or regurgitation. At end term endoscopy all 7 animals had a gastroplasty in place and there was no injury to the esophagus or stomach. The three obesity dogs had good gastric outlet apposition to a 6 mm endoscope with full insufflation as compared to a 1mm, 14mm and 12 mm spaces next to a 10 mm endoscope at initial endoscopy with full insufflation. The 4 GERD dogs had an average full insufflation gap to a 10 mm endoscope of 4 mm **(Figure 9)**.

Barostat tracings at baseline as compared to the post procedure 8 week study showed satisfactory results with a compliance decrease similar to that seen in a Nissen fundoplication. **Figure 10** shows a cumulative graph of all 4 animals' preoperative and postoperative tracings.

At autopsy there was no sign of perforation or injury of surrounding organs in any dogs. External fibrosis at the gastroesophageal junction was noted in 6 of the 7 animals. Thirteen of the 14 knotters placed in the 4 GERD dogs (4 in 3 dogs and 2 in one dog) were present and 6 of the 6 knotters placed in 3 obesity dogs were seen.

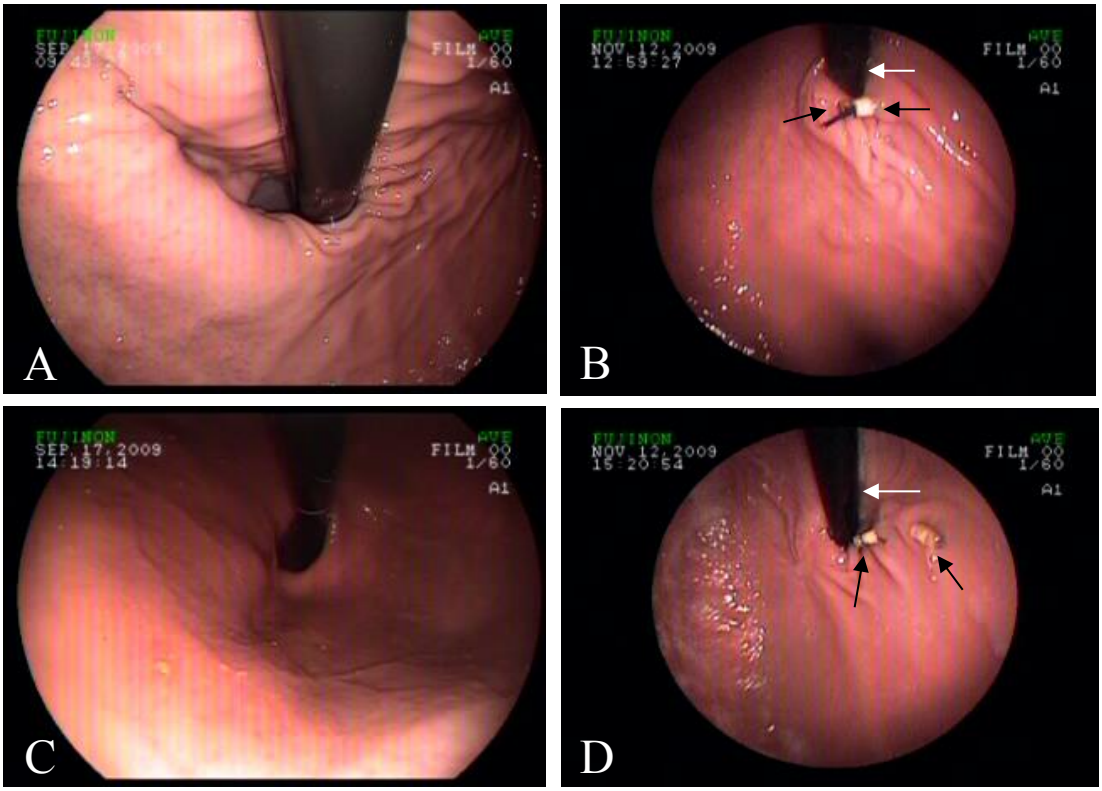

Figure 9. A. The pre-procedure incompetent valve with a 10 mm endoscope. **B.** The obesity post procedure outlet with a 6 mm endoscope at full insufflation. There is no gap visible (white arrow). **C**. Another pre-procedure valve for GERD at full insufflation with a 12 mm gap next to the 10 mm adult endoscope **D**. The post procedure valve at full insufflations with a 6 mm endoscope. The tightness is just proximal to the GEJ lip (white arrow). Black arrows show the cinches were stayed in place.

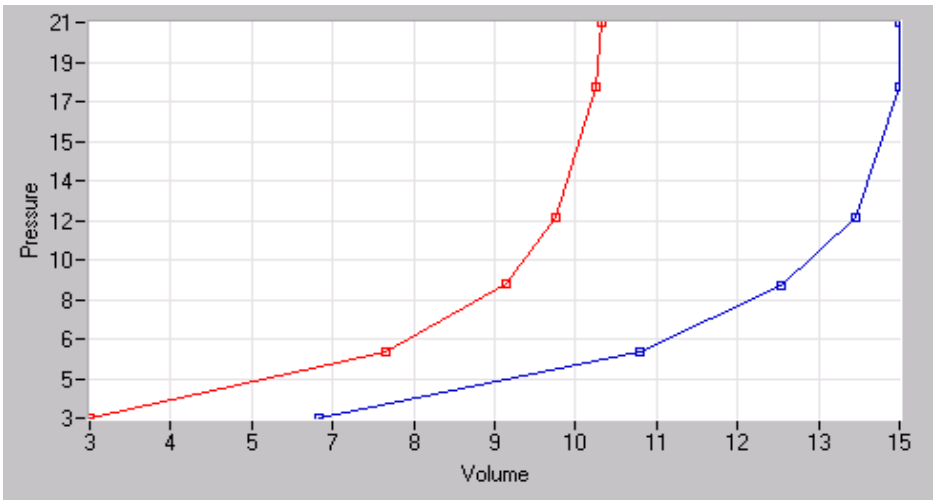

Figure 10. The cumulative Barostat graph of the 4 GERD animals. The blue line represents the mean preoperative compliance and the red line the decrease in the mean post procedure compliance. The pressures and volumes are expressed in mmHg and ml.

On histologic examination there was satisfactory scarring. Cicatrix formation was present within the submucosa and it was full thickness only in some areas **(Figure 11)**. The scar formation was concentrated at the angle of His in the GERD dogs but was on the average 42% circumferential in the obesity dogs. The desired circumferential scar involvement at this level was 50%. The gel cast mold of the GEJ in the obesity group showed an average outlet diameter of 8.6 mm with 10 mm being the desired diameter **(Figure 12.)**.

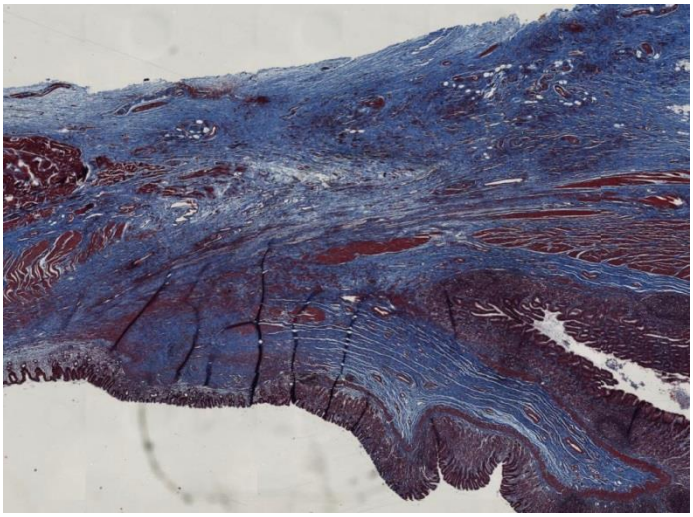

Figure 11. Trichrome stain of the stomach wall demonstrates full thickness scar formation. The fibrotic tissue stains blue.

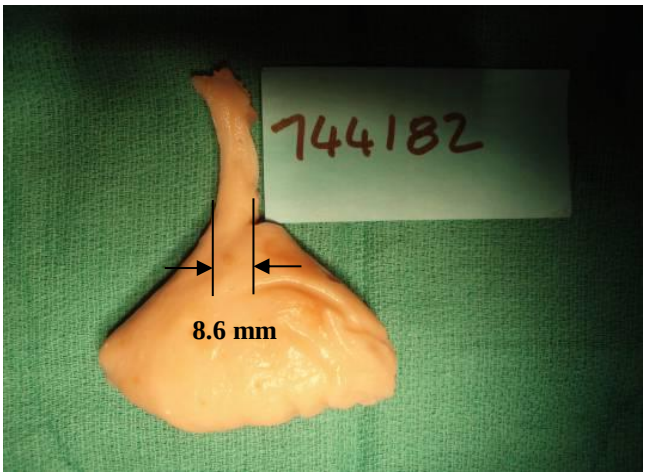

Figure 12. The distal esophagus and proximal stomach was filled with silicon free mold gel for 3D visualization of the GEJ area.

3.4 Discussion

We performed endoluminal proximal gastroplasty as an antireflux procedure and created a small proximal gastric pouch with a restricted outlet for obesity using the second generation of our gastroplasty system on total of 7 dogs. This study demonstrated that one step endoscopic gastric mucosal excision and suture placement at and below the GEJ is feasible and safe. All animals survived without complications. A significant decrease in GEJ compliance was seen in each animal after the GERD procedure. Good proximal gastric pouch outlet restriction was achieved after the obesity procedure. Scar tissue formation after mucosal excision and full thickness suturing was satisfactory but more fibrosis on the lesser curvature was needed for a long lasting obesity procedure. An injectable agent that generates more robust scarring would contribute to durability. In the next step of our study we examined different solutions that may fulfill this requirement.

4. GASTRIC SUBMUCOSAL FIBROSIS GENERATION

4.1 Background

Current bariatric and antireflux endoscopic treatment options include space restricting procedures using suture or staple gastric wall apposition to form a smaller gastric pouch or to restore the barrier between the stomach and the esophagus. Results are encouraging but probably not competitive with existing surgical procedures.

We hypothesized that significant submucosal fibrosis at the gastroesophageal junction would achieve better and more durable results after the sutured gastroplasty. Submucosal fibrosis rather than muscle or panmural fibrosis is also critical to success as the latter two can create excessive luminal compromise that would not respond to mechanical dilation of any kind.

Submucosal injection of hypertonic solutions can cause acute mucosal erosion with degradation of epithelial glands and congestion of capillary blood vessels on the day of injection [115]. Such tissue damage may create mucosal erosion with fibrosis of the submucosal layer resulting in permanent fibrotic deposition with luminal deformation and decreased tissue compliance [115]. The aim of this study was to determine if submucosal injections of hypertonic saline and dextrose solutions within the gastric wall will produce significant submucosal fibrosis.

4.2 Materials and methods

4.2.1 Preliminary study

A preliminary pilot study involving two female miniature swine (Sus scrofa domesticus) (21.4 and 24.4 kg) was conducted to determine if 4.2% hypertonic saline

(HTS) or 50% dextrose in water solution (D50W) forms more submucosal fibrosis. The protocol was approved by the Creighton University Institutional Animal Care and Use Committee under the number (IACUC MCL 0976) and carried out in the Central States Research Center (Oakland, NE, USA). We also investigated what volume of these solutions was optimal for fibrosis deposition.

With the minipig under endotracheal general anesthesia the abdomen was prepped and draped. A midline incision was made, the greater curvature vessels were cauterized and the larger ones were clamped and tied with 3-0 silk suture. A 7 cm gastrotomy along the greater curvature was created. The gastric wall submucosa was injected using either a HTS solution with 1:1000 epinephrine or D50W solution with 1:1000 epinephrine. Three, 6, or 9 ccs of solution were injected at pre-designated sites using a modified rigid gastroplasty excision device prototype.

For the first pig 3, 6 or 9 cc of 4.2% HTS with adrenaline was used and in case of the second pig 3, 6, or 9cc of D50W with adrenaline. At two sites in pig #1 9cc of 4.2% HTS was placed followed by mucosal excision. At another site in pig #1 normal saline with 1:1000 adrenaline was injected followed by mucosal excision as a control. The same was followed in pig #2 using D50W. A serosal suture was placed to mark each injection and excision site for later identification. The gastrotomy was closed and the animals recovered without incident. The animals were survived for 8 weeks and following the euthanasia each of the stomachs and distal esophagi were explanted. All 18 intervention sites were individually cut from the stomachs according to the serosal suture marks **(Figure 14)**.

The specimens were then kept in 10% formalin. Eighteen hours later the tissue was cut using a special rig with 7 pathology blades spaced 3 mm apart. Sutures if

present were left in situ. Each 3 mm wide block of tissue was cut each millimeter using a microtome resulting in three sections per block. The amount and level of fibrosis and other histologic features were recorded for each section. An H & E stain was used for the two outer sections of each block and a Trichrome stain for the middle section.

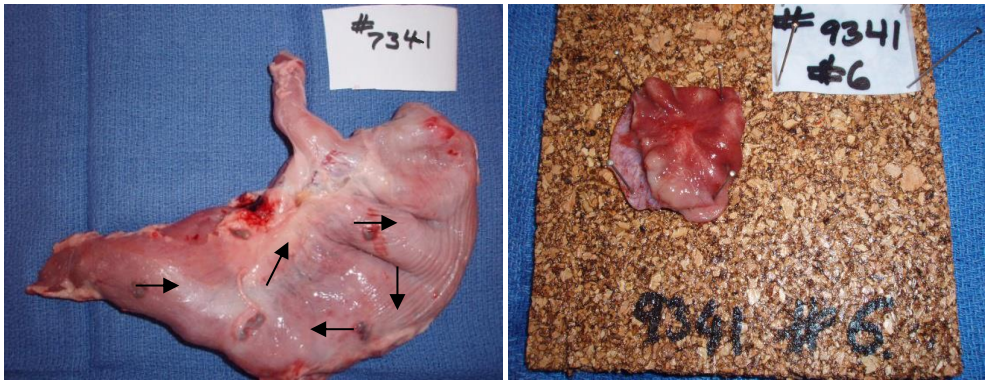

Figure 14. The explanted stomach with the serosal silk sutures labeling the injection sites. One of the excised injection sites with macroscopically visible fibrosis tissue in the middle.

4.2.2 A hypertonic saline study

Based on the results of the preliminary pilot study, a further experiment was conducted using 3 domestic pigs (Sus scrofa domesticus). Each animal underwent a series of gastric submucosal injections of different concentration HTS. A therapeutic adult flexible endoscope (GIF 140, Olympus, Tokyo, Japan) and endoscopic injection needles were used to deliver the hypertonic saline solutions into the gastric submucosa. The injections were placed every time in the fundus, body and antrum of the stomach. Each animal received 10 ccs of 4.2% HTS with Methylene Blue injections on three sites of the stomach. On Day 14 each animal was injected with 15 ccs of 5% HTS in three different sites as no ulcers were observed from the initial 4.2% HTS injections. Sites were changed to an untreated area of the stomach in a pre-determined manner. The

volume and concentration of HTS was increased to 20 ccs of 7.2% HTS on Day 30 as no animal had a healed ulcer greater than 1 cm in diameter.

Thirty days after the last procedure all 3 pigs were euthanized, the stomachs were explanted and each was opened on the greater curvature side. Using palpation and visual assessment, areas of fibrosis were identified and a corresponding 3-0 silk suture was placed on the serosal side.

The specimens were submerged in 4% formalin for 5 days. The same tissue cutting tool from the preliminary study was used but only one section from each 3mm thick cut was examined histologically. The same method of tissue staining, measuring and volume calculation was used.

Statistical analysis was performed using a t-test, Mann Whitney and ANOVA with SPSS version 17.0 (SPSS, Inc. Chicago, IL).

4.3 Results

Preliminary pilot animal study

In the first preliminary pilot study an abdominal partial wound separation occurred in one minipig. Antibiotic ointment and dressing were placed and the wound healed after two weeks. No other complications were encountered. Results showed that 3 cc of HTS and D50W caused no fibrosis after 8 weeks **(Table 3)**. The difference in fibrosis volume between 6 and 9 cc of 4.2% HTS was insignificant (p=0.683) as was the D50W 6 and 9cc difference (p=0.750). When comparing 6cc and 9 cc injections volumes of each solution the HTS injections caused a larger volume of fibrosis. D50W 3 cc, 6 cc and 9 cc injections showed an average fibrosis of 0.05 mm^3, 28.5 mm^3 and 16.5 mm^3 respectively. For 4.2% HTS the 3, 6 and 9 cc injections showed an average

fibrosis volume of 0 mm^3, 197 mm^3 and 138 mm^3 respectively. Areas were injection was combined with mucosal excision showed an average fibrosis volume of 101.5 mm^3 (4.2% HTS) and 62.5 mm^3 (D50W) but the sample size was too small for statistical analysis. The fibrotic change was within the submucosal layer in 100% of the cases **(Figure 15)**.

PIG #1 (HTS)				PIG #2 (D50W)			
Site	**Injectate volume (cc)**	**Fibrosis Width/ Length/ Thickness**	**Fibrosis Volume**	**Site**	**Injectate volume (cc)**	**Fibrosis Width/ Length/ Thickness**	**Fibrosis Volume**
1	3	0/0/0	0	1	3	0/0/0	0
2	6	20/9/1.4	252	2	6	0/0/0	0
3	9	13/6.1/1.6	127	3	9	0/0/0	0
4	3	0/0/0	0	4	3	2/0.47/0.1	0.1
5	6	13/9.1/1.2	142	5	6	9/9/0.7	57
6	9	17/3.8/2.3	149	6	9	9/6.1/0.6	33
7	9 (exc)	16/3.1/1.4	69	7	9 (exc)	12/7.7/0.9	83
8	9 (exc)	24/4/1.4	134	8	9 (exc)	6/7/1	42
9	9 NS (exs)	1/0/0.8	1	9	9 NS	12/0.6/0.2	1.4

Table 3: Scar tissue formation at 8 weeks post procedural after submucosal injection of different amount of 4.2 % saline and 50% dextrose solutions. NS-normal saline, (exc)-additional mucosal excision

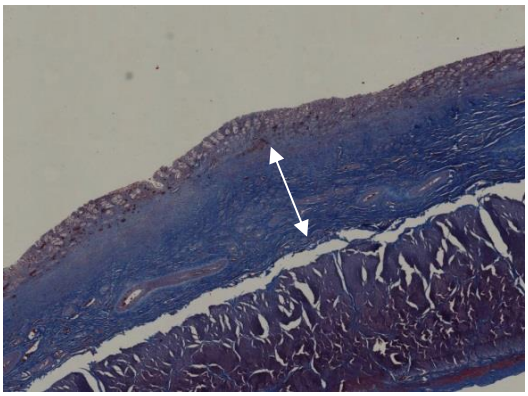

Figure 15. After controlled submucosal injection of hypertonic agents, fibrosis developed only in the submucosal layer indicated by the white arrow.

Hypertonic saline study

Total of 20 (74%) injection sites (fundus n=6, antrum n=8 and body n=6) had been identified visually and by palpation. From the 9-9 sites of the 4.2% and the 7.2% HTS injections 8-8 could be found, but only 4 of the 5% HTS injection sites could be detected. The average volume of fibrosis from the 4.2%, 5% and 7.2% HTS injection sites were 123±31 mm^3, 178±48 mm^3 and 354±57 mm^3 respectively. However, there was no statistically significant difference in volumes, although there was a trend for more fibrosis from 20cc of 7.2% HTS **(Figure 16)**. Fibrosis tissue was found in 88.9% of the cases within the submucosal layer.

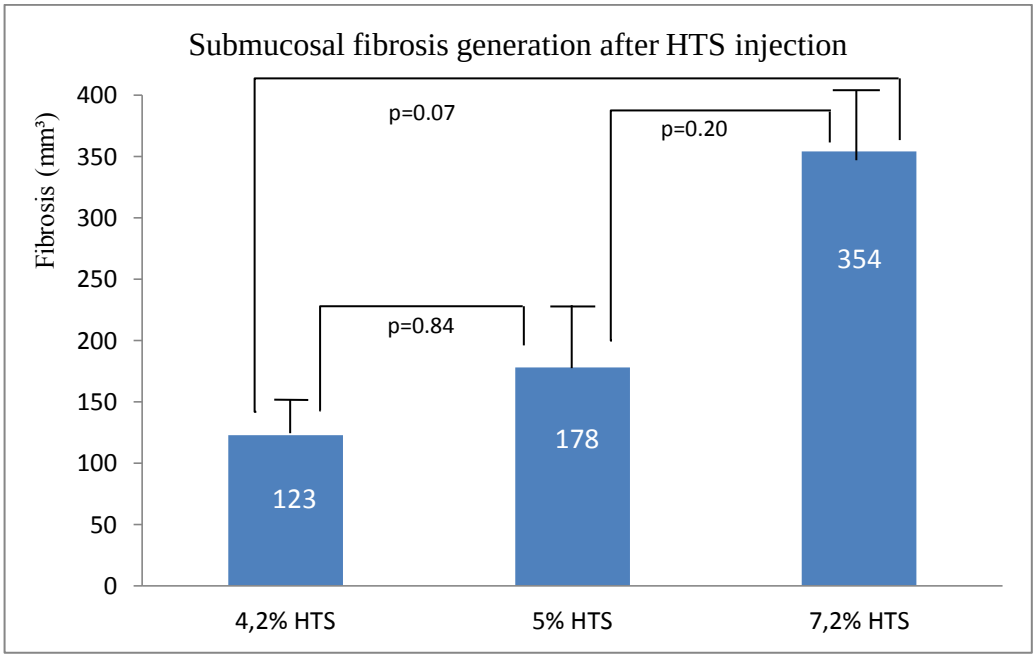

Figure 16. Volume of submucosal fibrosis after injection of hypertonic saline in different concentration.

4.4 Discussion

We demonstrated that gastric submucosal injection of hypertonic saline was superior to D50W in submucosal fibrosis induction. Increased concentration and volume of HTS solution appeared to induce more submucosal fibrosis. The difference in scar formation between different concentration of HTS was, however, not significant possibly because of small sample size. The increase in fibrosis may have been due in part to the larger volume used and the decreased time to euthanasia, although the maturity of fibrosis was unaltered between survival times. We demonstrated that highly accurate injection and consequent fibrosis can be achieved when using the excision device as in all specimens fibrotic tissue was only seen within the submucosal layer.

Hypertonic saline solution seemed to be optimal to provide a strong complementary line of scar tissue on the lesser curvature for the obesity procedure and more fibrosis for durable GERD gastroplasty.

5. A HUMAN PILOT STUDY

5.1 Background

After successful animal safety and feasibility studies numerous acute animal operations were carried out to refine technical and procedural details. Small device modifications were completed as well. The principal aim of the first human trial was to demonstrate safety and feasibility of the endoluminal gastroplication procedure. We were focused on restoring the angle of His and the compliance of gastric cardia to cease GERD and to create a durable restrictive subcardial area to demonstrate weight loss in obese patients. The effect of the procedure were studied using Heartburn Symptom Score (HBSS), GERD quality of life score (GERD-HRQL), GERD medication usage, distal esophageal pH and lower esophageal sphincter pressure in patients with GERD and by weight loss, blood pressure and laboratory changes in obese patients.

5.2 Materials and methods

Patients with symptomatic GERD and with obesity over BMI 35 kg/m^2 were included in the study. Data were collected prospectively and each subject served as their own control. The inclusion and exclusion criteria were:

Inclusion criteria

- For GERD patients: symptomatic reflux defined as a heartburn frequency score ≥ 2, when off medication, with or without erosive esophagitis (i.e., grade A or B on the Los Angeles Classification Scale); patients who were dependent upon PPI medication; documented acid reflux by pH monitoring (pH ≤ 4 for more than 4% for 24 hours following discontinuation of all GERD anti-secretory medications for 7 days), and

patients with an HRQL <10 on medication and HRQL >15 off medication. Signed informed consent form.

- For obesity: BMI > 35 or at least 45 kgs above ideal body weight and history of obesity for at least 5 years. Signed informed consent form.

Exclusion criteria

Pregnancy or intent to become pregnant during study participation; < 18 years of age; patients who were not candidates for general anesthesia or whose medical history classified them as level ASA 3 or higher; grade 2 or higher dysphagia (grade 2 - occasional trouble swallowing - 1 or 2 times per week); grade C or D erosive esophagitis while on medication; significant heart failure or a prosthetic heart valve; history of portal hypertension; previous gastroesophageal surgical procedures; endoscopic GERD therapy and/or thoracic surgical procedures; a disease state that is a general contraindication for an endoscopic procedures; condition which general surgery is contraindicated.

Special criteria for GERD patients: less than 30mmHg of pressure at any esophageal body level or more than 20% dropped or simultaneous waves; a hiatus hernia > 2 cm; if pH monitoring score is greater than 15% total time over pH of 4 or whose DeMeester score is >50. Special exclusion criteria for obesity were: achalasia; systemic lupus erythematosus or other autoimmune disorders and patients who are mentally challenged or emotionally unfit as determined by standard psychological evaluation

All patients after the screening process underwent a medical history, physical examination and upper endoscopy to rule out hiatal hernia > 2cm and any other major gastroesophageal pathology. Esophageal manometry and pH monitoring was performed.

For patients with GERD, symptom scoring questionnaire and GERD-HRQL (health related quality of life) evaluation were administered. Obese patients underwent upper endoscopy, physical examination, laboratory testing, IWQOL (Impact of Weight on Quality of Life) questionnaire and standard psychological evaluation.

The excision device had been modified with the tip of the operating capsule flattened and the through had a rhomboid shape for better tissue capture. The suturing devise handle was modified too for easier manipulation **(Figure 16)**.

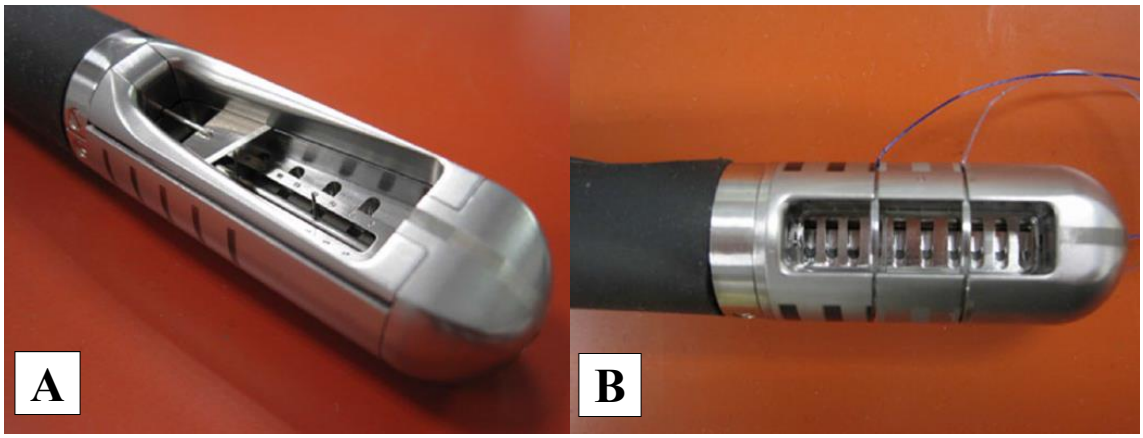

Figure 16. A.: The modified operating capsule of the excision device with the blade half way out. The flattened tip facilitates device insertion. The rhomboid shape through provides better tissue capturing and helps to avoid excision overlapping. **B.** The operating capsule of the suturing device: the tip and the edges were smoothened but the main dimensions of the trough were not modified.

The procedure

The protocol was approved by the Institutional Ethics Committee (IKEB 7255/2013) and the national Office of Health Authorization and Administrative Procedures of Hungary (35661/2011/OTIG). The procedures were performed in the Surgical Department of the Saint George University Teaching Hospital in Székesfehérvár, Hungary. Only patients who preoperatively signed the informed consent form were included.

The procedure was carried out under general anesthesia. A mouth opener was inserted and first an upper endoscopy was performed with the patient in the supine position. A Savary guidewire was than introduced followed by a 60 Fr esophageal dilation. We used a cautery snare to place marks along the lesser curvature for orientation. The lubricated excision device was inserted into the proximal stomach by no more than 2 lbs axial force with the patient's neck extended. We found the right lateral decubitus position optimal for the greater curvature tissue capture, injection and excision to prevent remote mucosal fold entrapment. Thereafter we used the right lateral decubitus position for all patients. Through the device dedicated channel a 6 mm video endoscope (Fujunon EG-470N5) was introduced for procedure visualization and the stomach was insufflated. With the excision blade retracted the device was positioned, -500 mmHg vacuum was applied; mucosa was captured and held in the trough. A 4.2% hypertonic saline (HTS) solution with 1:100 000 adrenaline solution was injected followed by discontinuation of the vacuum **(Figure 17/A)**. The device was gently retracted and the mucosal cushion inspected. If the cushion was satisfactory in size and position it was recaptured and injected again. After desufflation of the stomach and a short delay for appropriate vasoconstriction the excision blade was actuated. The

vacuum was discontinued and the stomach re-insufflated. The excised mucosal piece was elevated by a dedicated platform and removed by a foreign body forceps through the flexible endoscope. The removed tissue was inspected and measured. The procedure was repeated two more times for a confluent 3 excision denuded area at the GEJ **(Figure 17/B)**. In obese patients before suturing the lesser curvature side was injected with the HTS solution to form a 360^0 scarred submucosal ring after procedure completion for gastric pouch outlet restriction. The suturing device was than inserted over a Savary guidewire and its trough positioned on the third excision bed. The mucosa free gastric wall was captured by vacuum. The suture cycle was completed and suture position and penetration was checked. With sutures satisfactory in the excision bed the device was rotated to the first excision site and the procedure was repeated **(Figure 17/C)**. The sutures were inspected for position and the device was removed. The sutures were paired outside the patient's mouth. By endoscopic visualization first the distal suture was tied using the knotter device. The endoscope was retroflexed in the stomach to assured correct tissue apposition. The proximal sutures were secured in the same manner. After hemostasis was checked the outlet diameter was measured.

In obesity patients the procedure was carried out with small modifications. The excisions were positioned 2 cm distal to the GEJ and the sutures were more separated radially in the excised area to create a tighter gastric outlet and a small proximal gastric pouch **(Figure 17/D)**.

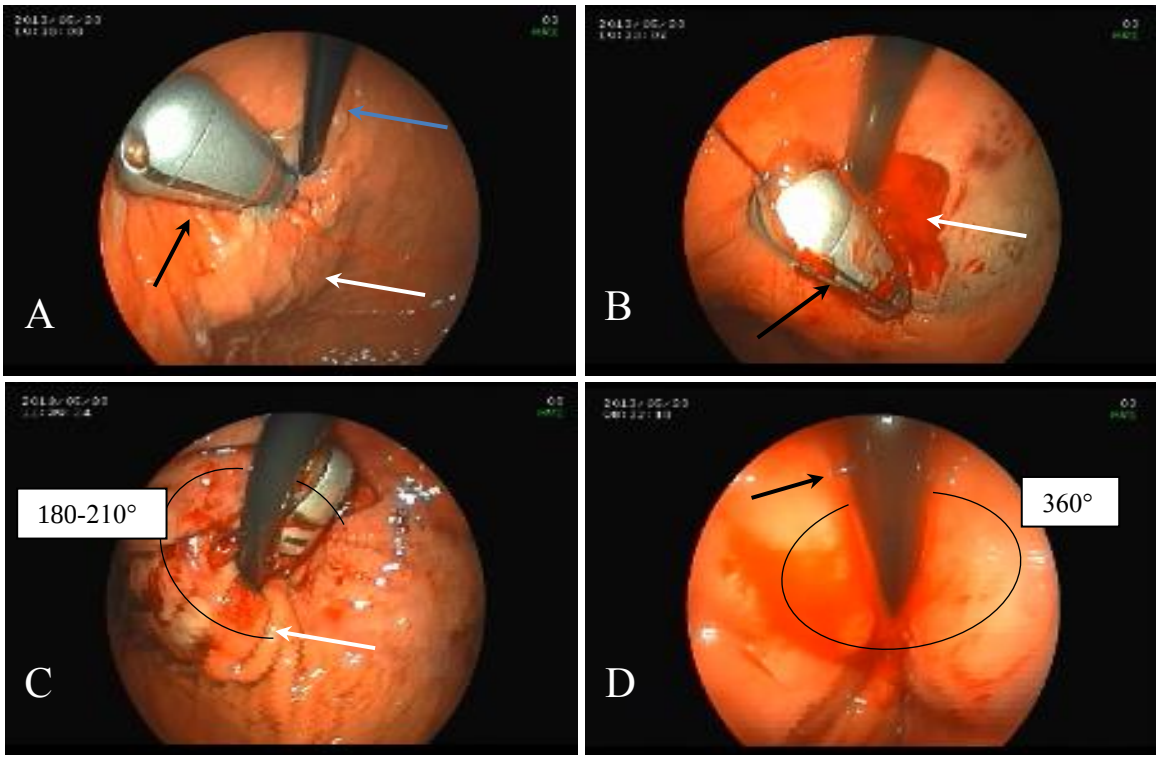

Figure 17. The main steps of the procedure: **A. After** submucosal injection of hypertonic solution the excision device is moved from the mucosal cushion for inspection prior to excision. The white arrow shows the elevated mucosa; the black arrow the posterior aspect of the excision device; the blue arrow indicates the 6 mm endoscope exiting from the flexible transition piece of the excision device for visualization. **B.** After the first excision is done (white arrow shows the 1st excision bed) the device is moved to a second excision site on the greater curvature (black arrow). **C.** The excision beds are sutured together to create a 180°-210° circumference small gastric pouch for obese (white arrow shows the pouch being created). **D.** The small proximal gastric pouch is completed to 360° by injecting hypertonic saline solution in continuation of the sutured pouch wall on the lesser curvature.

Patients were delivered to the Intensive Care Unit for a 12 hours long observation if needed. A chest x-ray was taken to check for stomach size and free air. Before extubation 8 mg intravenous ondansetron was administered to reduce the possibility of retching and vomiting. The obes patients received 2x0.4ml and the GERD

pateints 1x0.4 ml enoxaparine during their ICU stay. On the first postoperative day a gastrografin swallow study was performed to rule out an esophageal or gastric perforation in one patient.

Patients were kept on a Cleveland Clinic bariatric liquid diet and were given omeprazole 40mg two times a day for 1 month.

Follow up data was recorded by a study nurse on postop day1, 14, and 1, 3, 6, 12, 18 and 24 months after the operation. The follow up schedule for both groups are shown on **(Table 4 and 5)**.

Form Name	Baseline	Procedure	POD 1	POD 14	Month 1	Months 3	Months 6	Months 12	Months 24
GERD symptoms	x				x	x	x	x	x
GERD medications	x				x	x	x	x	x
GERD-HRQL	x				x	x	x	x	x
Esophageal Assessment									
Endoscopy	x	x					x	x	x
Manometry	x							x	x
pH monitoring	x							x	x
Procedure		x							
Adverse event		x							
Postop adverse event			x	x	x		x	x	x

Table 4. Schedule of preoperative evaluation and long term follow up for GERD patients. Abbreviations: GERD - gastroesophageal reflux disease; HRQL – heartburn related quality of life.

Form Name	Baseline	Procedure	POD 14	Month 1	Months 3	Months 6	Months 12	Months 24
H&P	x							
Medications	x		x	x	x	x	x	x
UGI symptoms	x		x	x	x	x	x	x
Body weight	x		x	x	x	x	x	x
Stool guaiac			x					
UGI series	x		x		x			
Assessment of comorbidities							x	x
Blood pressure	x	x	x	x	x	x	x	x
Fasting blood glucose	x	x		x	x	x	x	x
HbA1C	x	x			x	x	x	x
Urea breath test	x							
Lipid profile	x				x	x	x	x
IWQOL questionnaire	x			x	x	x	x	x
Endoscopy	x	x				x	x	x
Psychological evaluation	x							
Procedure		x						
Adverse events		x						
Postop adverse events			x	x	x	x	x	x

Table 5. Schedule of preoperative evaluation and long term follow up for obesity patients. Abbreviations: H&P – History and physical examination; POD – post operative day; IWQOL – Impact of weight on quality of life questionnaire.

5.3 Results

Fourteen patients were screened and total of 8 were included in the study (5 obese and 3 with GERD). Reasons for exclusion are seen in **Table 6**.

From the 8 patients originally included one obesity patient was excluded after procedural attempt as her anatomy did not allow us to dilate her upper esophageal sphincter safely. In two GERD patients the procedure was incomplete due to device and technical difficulties. These patients were excluded from the study as well. Total of 5 patients underwent a complete procedure and remained for follow up. There was no intraoperative significant bleeding or perforation encountered. The total procedural times were between 1h 30 minutes and 4h 45 minutes.

Patient#	Age	Gender	Pathology	Included	Reason for exclusion	ID # in the study
1	52	Male	GERD	NO	HH>2 cm	
2	61	Female	GERD	NO	DeMeester<14,7	
3	25	Female	GERD	YES		#8
4	38	Female	Obesity	YES		#4
5	45	Female	Obesity	NO	Emotionally unfit	
6	51	Male	GERD	NO	Esophageal dysmotility	
7	39	Female	Obesity	YES		#6
8	57	Female	Obesity	YES		#1
9	25	Female	Obesity	YES		#5
10	69	Female	GERD	YES		#3
11	39	Female	Obesity	YES		#7
12	61	Female	GERD	YES		#2
13	64	Female	GERD	NO	HH>2 cm	
14	58	Male	GERD	NO	Withdrawn consent	

Table 6. Candidate patients for the study and reasons for exclusion.

Procedure and follow up

Patient #4 (obese): she had no intraoperative or postoperative complication. Her initially 2 cm hiatal hernia was reduced in size on 6, 12 and 18 months endoscopy. At 24 month follow-up 67 % EWL plus normalization of her elevated baseline blood pressure were seen.

Patient #5 (obese): she had an uncomplicated procedure and postoperative period. However, on videotape review it was evident that the gastric outlet was 8 mm in diameter after suture tying (ideal would be 6 mm). The patient did not lose weight or experience food restriction at 6 and 12 months, but showed 12% EWL at 24 month follow-up.

Patient #6 (obese): she had a satisfactory intervention without any intraoperative or postoperative complication. She experienced intermittent dysphagia

with decreased frequency up to the 18 month follow-up. Her blood pressure had normalized. She had no other comorbidities. Her EWL was 34% at 24 months.

Patient #7 (obese): she had a complete procedure but vomited repeatedly in the Intensive Care Unit before extubation. Her initial chest X-ray was unremarkable but 12 hours postoperatively she had free abdominal air under both hemi-diaphragms. Laparoscopy and simultaneous upper endoscopy showed no perforation. A nasogastric tube was left in place, and she recovered uneventfully. However, on day 9 she developed vertigo with repeated vomiting and required re-hospitalization. At 6 month endoscopy her gastroplasty was loose and she had no food restriction. The 18 month endoscopy showed no change and this patient had no weight loss.

Tables 7-10 and **Figure 18** show the obesity patient cohort baseline information and study results.

	Baseline		6 Months		12 Months		18 Months		24 Months	
Patient	GERD symptoms	IWQOL	GERD symptoms	IWQOL	GERD symptoms	IWQOL	GERD symptoms	IWQOL	GERD symptoms	IWQOL
#4	None	68	None	72	None	81	None	87	None	92
#5	None	69	None	65	None	67	None	69	None	72
#6	None	44	None	69	Occasional dyspepsia	73	Occasional dyspepsia	79	Occasional nausea	84
#7	None	69	None	78	Occasional regurgitation	80	Occasional regurgitation	85	Occasional regurgitation	85

Table 7. GERD symptoms and IWQOL table of obesity patients. Note: higher IWQOL score is improvement

	Baseline			6 Months			12 Months			18 Months			24 Months		
Patient	Sleep apnea	BP (mmHg)	HgA1c (%)	Sleep apnea	BP (mmHg)	HgA1c (%)	Sleep apnea	BP (mmHg)	HgA1c (%)	Sleep apnea	BP (mmHg)	HgA1c (%)	Sleep apnea	BP (mmHg)	HgA1c (%)
#4	NO	135/100	5,5	NO	111/80	5,6	NO	115/90	5,6	NO	120/95	5,5	NO	120/80	5,2
#5	NO	141/100	5,8	Wake up 3x/night	135/95	5,7	Wake up 3x/night	150/110	5,9	NO	140/90	5,6	NO	135/95	5,8
#6	Wake up 3x/night	142/98	5,6	NO	110/70	5,4	Wake up 3x/night	110/80	5,2	NO	110/89	5,3	NO	120/82	5,1
#7	Wake up 3x/night	118/78	5,4	NO	115/80	5,4	Wake up 3x/night	110/70	5,6	Wake up 3x/night	125/80	5,3	Wake up 3x/night	115/75	5,4

Table 8. Co-morbidities of patients with obesity. BP- Blood pressure. Normal range for HgA1c. 4-5,6%

Patient	Baseline Hill classification	OP	6 Months	12 Months	18 Months	24 Months
# 4	Hill 3	2	0	0	0	0
# 5	Hill 3	2	2	2	2	*
# 6	Hill 3	2	0	2	1	0
# 7	Hill 3	3	3	4	5	*

Table 9. Endoscopy results in obesity patients

Patient	Baseline weight (kg/BMI/EW)	3 Months EWL(%)	6 Months EWL(%)	12 Months EWL(%)	18 Months EWL(%)	24Months EWL(%)
# 4	185/61/108	19	25	37	52	67
# 5	116/42/44	2	4	0	8	12
# 6	154/61/90	19	20	24	27	34
# 7	98/39/31	14	9	0	0	0

Table 10. Dynamics of excess weight loss for obesity patients (%EWL)

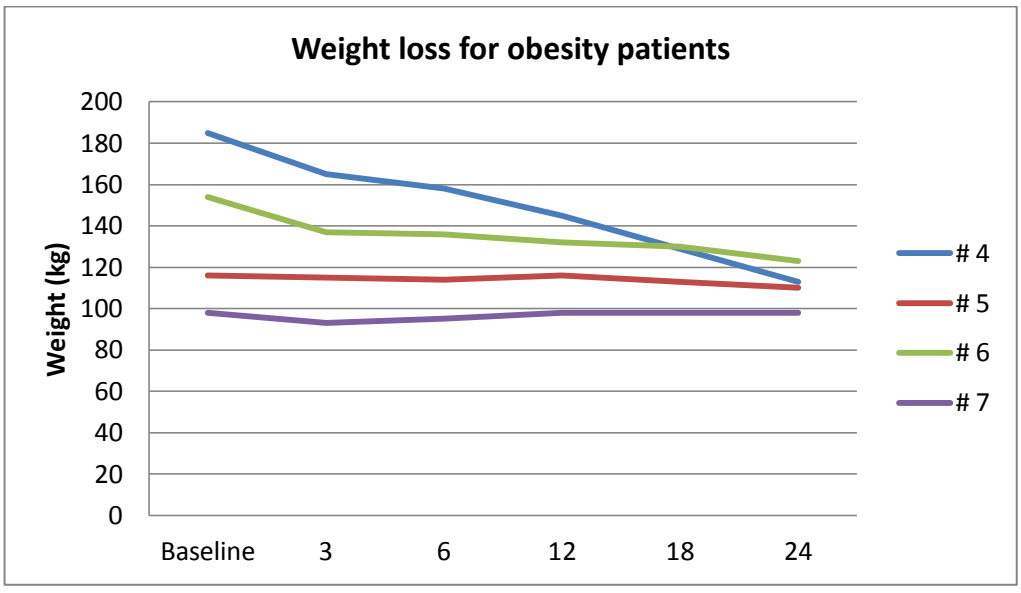

Figure 18. Dynamics of weight loss during the 24 months follow up.

Patient #8 (GERD): she had an uneventful operation without any postoperative complication. Her pre-operative HRQOL was 19 and the DeMeester score was 44. At 6 months her DeMeester score was 16 and at 12 months the HRQOL was 10. pH monitoring was not performed at 12 months due to equipment unavailability. Her 12 month endoscopy with a 10 mm endoscope and full insufflation is shown in **Figure 19**. No esophagitis was evident. At 18 month follow-up she remained asymptomatic and was off all anti-secretory medications. At 2 years her DeMeester score normalized and her HRQOL was the lowest since the procedure **(Table 11).**

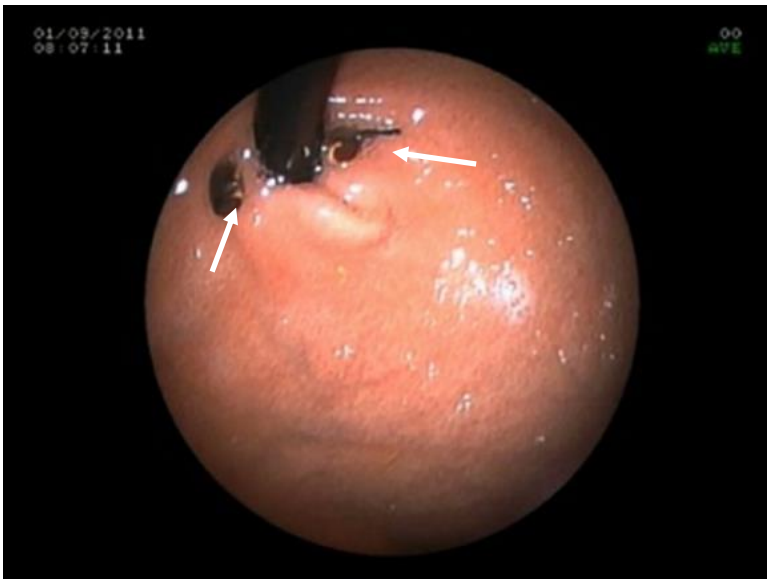

Figure 19. Control endoscopy at 12 months follow up shows a good tissue apposition to a 10 mm endoscope for Patient #8. The anchors are still in position (white arrows)

		Baseline	3 Months	6 Months	12 Months	18 Months	24Months
GERD symptoms		Occasional regurgitation and heartburn, Grade 2 dysphagia	Occasional regurgitation, Grade 2 dysphagia	Occasional regurgitation, Grade 2 dysphagia	Occasional regurgitation, Grade 2 dysphagia	Occasional regurgitation, Grade 1 dysphagia	Occasional regurgitation, Grade 1 dysphagia
Medication		PPI 1x30 mg	None	None	None	None	None
GERD-HRQL		19	14	13	10	13	6
Endoscopy		No esophagitis, 5 mm gap	_	No esophagitis, 0 mm gap	No esophagitis, 0 mm gap	*	No esophagitis, 0 mm gap
Manometry	Avg. Resting LESP	7 mmHg	_	36 mmHg	**	*	40 mmHg
	LES length	2cm	_	2cm	**	*	3 cm
	Failed propulsion	<10%	_	<10%	**	*	0%
pH monitoring	% pH < 4	9%	_	5%	**	*	3,3%
	Total pH<4	54	_	15	**	*	16
	DeMeester score	44.9	_	16	**	*	8.86

Table 11. Results of the GERD patient. Both objective and subjective measures improved during the 24 months follow up. *Missing data are due to lack of patient's cooperation. ** Missing data due to technical failure.

5.4 Discussion

We demonstrated that endoluminal gastroplasty for GERD and obesity is feasible and safe when using our new mucosal excision and suturing system. Initial patient outcomes showed that the procedure has the potential to effectively treat both pathologies [116].

During the first human study we learned the proper way to insert the devices which was simplified by the use of an adjustable mouth-opener and that the right lateral decubitus position is best for the proximal greater curvature tissue manipulation. The procedures were performed safely as no major complication occurred. Special care to avoid postoperative retching, gagging or vomiting is necessary to prevent tissue separation in the operative area. The submucosal fibrosis, which was created by mucosal excision and injection of hypertonic saline solution, served as a reinforcement to prevent expansion of the gastroplasty.

The GERD and obesity gastroplasty device described is the only transoral device that addresses two pathologies using similar operative techniques. Twenty four month patient follow-up showed promising results for both GERD and obese patients. Longer patient follow-up and a larger study are necessary to standardize the procedures and prove efficacy.

6. BARRETT'S STRIP ENDOSCOPIC MUCOSAL EXCISION

6.1 Background

Excision of pathologic mucosa from the esophagus may be necessary to prevent development of malignancies or to treat in situ superficial carcinomas. Based on our experience from the gastroplasty device our intention was to create a flexible instrument to excise and remove esophageal mucosa and muscularis mucosa safely, rapidly and with a low complication rate.

6.2 Materials and methods

Preliminary ex-vivo studies were carried out with porcine, canine, baboon and human esophagi. These experiments allowed us to determine the correct device characteristics necessary for consistent strip endoscopic esophageal mucosal resection (SEMR). Human esophagi were harvested from tissue donor patients with family informed consent under the auspices of the Nebraska Organ Recovery System.

The instrument shares the common characteristics with the gastroplasty device as it consisted of a handle and a flexible shaft with an integrated distal excision capsule **(Figure 20)**. The device has a dedicated channel for a standard 4.8 – 5.5 mm diameter endoscope with an opening on the handle and exiting on the proximal edge of the operating tip **(Figure 21/A)**. The device is mounted on the endoscope, and the endoscope acts as a visual and mechanic guide **(Figure 21/B.)**. The device is slided over the endoscope through the oropharynx and into the oesophagus. Target areas proximal to the GEJ are visualized anterograde by either an advanced or withdrawn straight endoscope. Mucosal changes near the GEJ can be visualized from the stomach with the retroflexed endoscope.

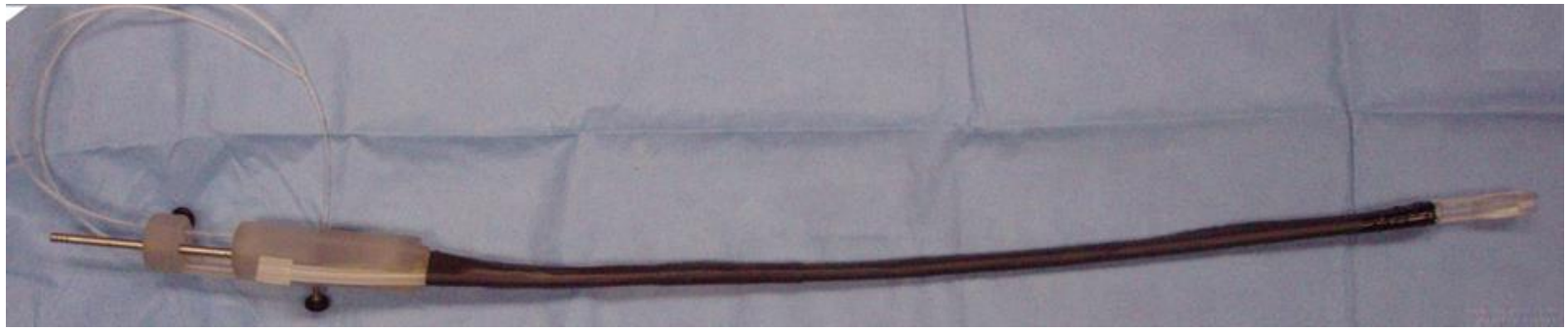

Figure 20. The working prototype of the Barrett's excision device with a flexible shaft, excision capsule and multifunctional handle.

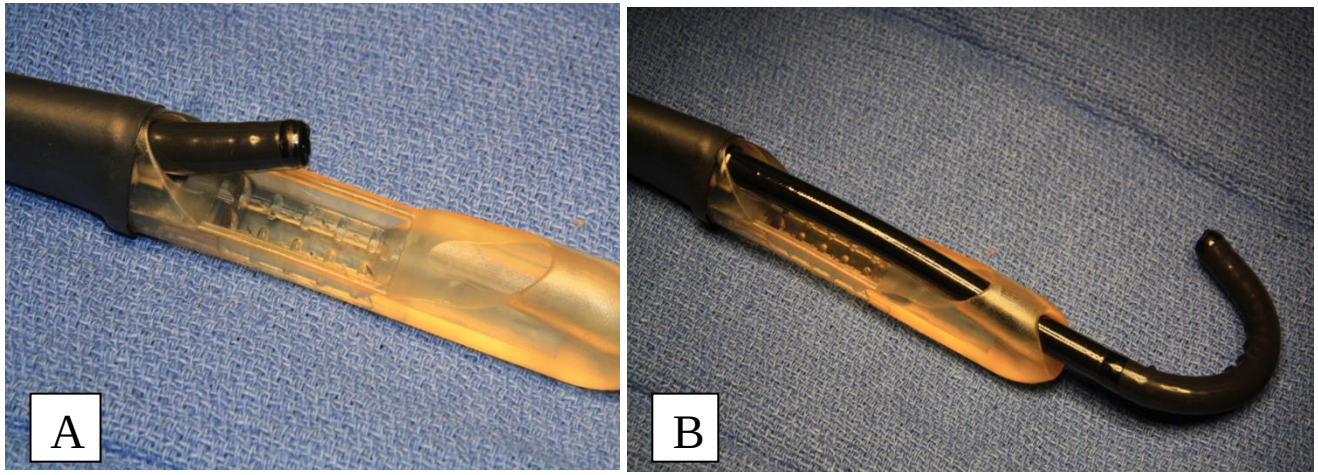

Figure 21. A 4.8-6 mm endoscope is passed through the device and down to the proximal trough for device positioning. The antegrade position provides visualization of the distended target area. **B.** If the target excision area is distal, the trans nasal endoscope is advanced through the tip of the device and retroflexed within the stomach for proper visualization.

The main steps of the procedures were the follows: first an esophageal cautery mark was placed prior to excision device introduction. The mucosa with cautery mark was excised to confirm correct positioning. The trough was positioned on the target points by direct endoscopic visualization. After device positioning the endoscope was retracted into the device shaft. After suction was applied the multiple suction ports pulled the mucosa into the capsule and the vertical anchor needles helped to hold the tissue in position. The longitudinal injection needle was forwarded above the bottom of the trough and a 1:100.000 Adrenaline solution was injected to assure the correct cutting depth and hemostasis.

To separate the muscularis mucosa from the muscularis propria thus increasing the "target space" and to provoke hemostasis, a 1:100.000 Adrenaline solution was injected trough an incrementally advanced longitudinal injection needle above the bottom of the trough **(Figure 22)**.

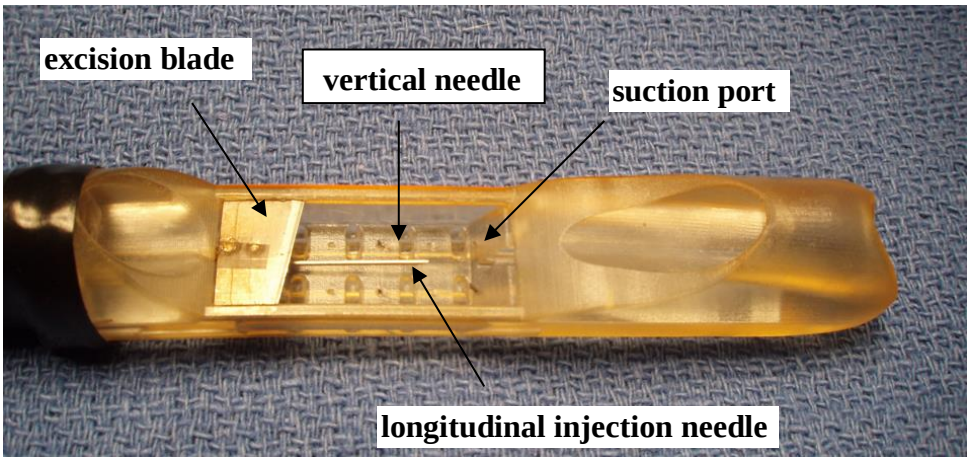

Figure 22. The trough contains vertical anchor needles and suction ports. The guillotine excision blade and longitudinal injection needle slide in the rigid, 50 mm x 16.7 mm excision capsule. The resection window is 2.8 cm long, 1.3 cm wide and 0.4 cm deep. The desired cutting depth through the first third of the submucosa assured complete removal of Barrett's mucosa and submucosal glands and the maximum of 2 excisions (270º of circumference) decreases the potential for stricture formation.

After injection the horizontal guillotine blade was advanced with a single motion and the mucosa was resected in a fixed plane. The device was then withdrawn from the esophagus with the specimen within the capsule **(Figure 21)**. This allowed the specimens to be easily orientated for histological analysis.

Figure 21. After the device is removed the excised mucosal strip remains within the trough for easy specimen orientation.

Additional animal tissues were used to assist in design modifications. Before in-vivo experiments the device was studied using fresh ex-vivo non-fixed human esophagi for completeness of mucosal resection and uniformity of excision depth. The excised human mucosal strips were assessed histologically. The excision depth was microscopically determined in 15 systematically separated locations within all tissue specimens. In vivo experiments were conducted in 1 canine and 2 porcine models. Total of 6 excisions were done to determine device efficacy and safety. In the porcine model, esophagi were myotomized from the gastroesophageal junction to the proximal 1/3 of the esophagus to provide a large enough esophageal lumen for comfortable device manipulation.

6.3 Results

The device allowed precise localization and positioning with satisfactory excision size and depth in ex vivo and in vivo specimens **(Figure 22)**. A total of 10 excisions were performed on 5 ex-vivo cadaveric human esophagi. The specimens ranged in size from 3 x 2.5 cm to 2.5 x 2.2 cm. The average thickness of the excised specimens was 0.297 mm with the excision level within the superficial submucosa (Sm1). One hundred and forty seven of 150 examined microscopic fields included the muscularis mucosa. In 30 excisions deep submucosal gland units were included.

The first non-survival canine and porcine experiments were promising in terms of safety. The device could be introduced without trauma in both canine and porcine models and 6 mucosal excisions were performed without bleeding **(Figure 23)**.

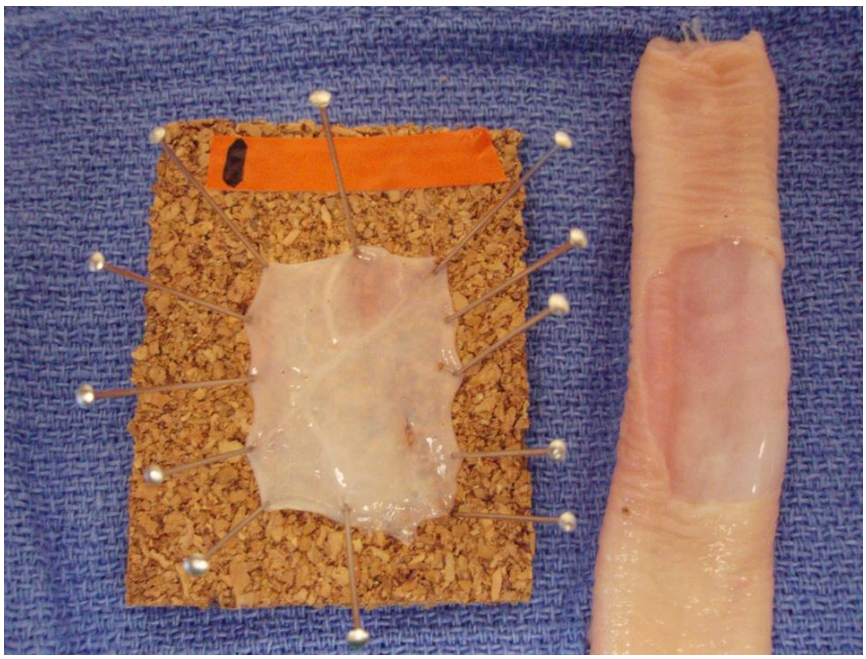

Figure 22. Excised mucosa (3 x 2.5 cm) after preparation for fixation, and an inverted ex-vivo human esophagus with the respective excision area.

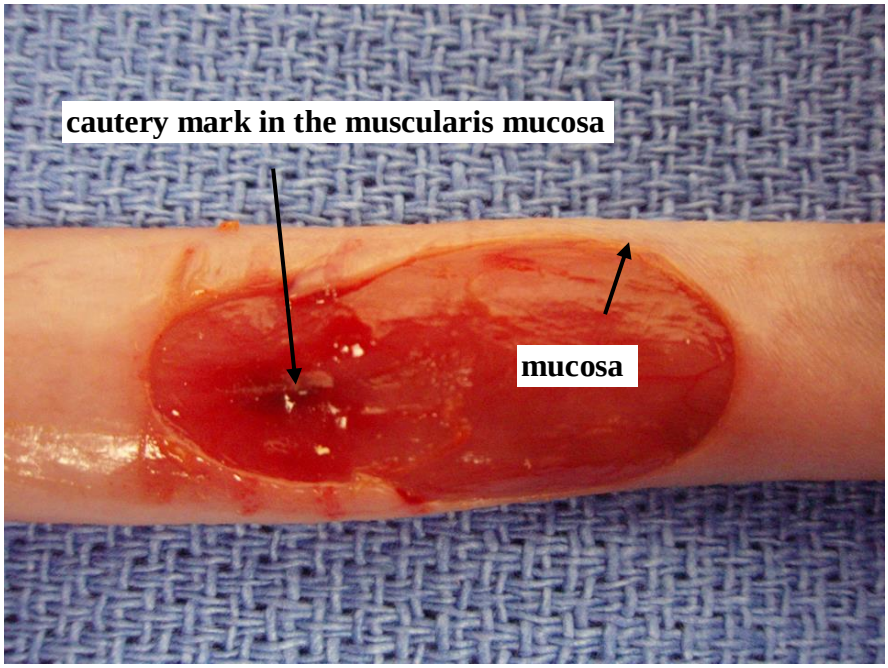

Figure 23. Mucosal excision after acute animal experiment. The esophagus is turned to inside out. The cautery marking still visible on the submucosa: There is no perforation visible.

Target cautery mark localization and accurate capsule placement was proven. No perforations occurred and none of the in vivo esophagi, after removal, showed evidence of excision penetration to the muscularis propria level.

6.4 Discussion

This new flexible endoluminal mucosa excision device fulfilled requirements for a successful endoscopic Barrett's mucosa excision device. Desired cutting depth and excision size was demonstrated, in 98% of cases. Large mucosal strip excisions using a cold blade technique without bleeding and esophageal wall perforation were performed in acute animal experiments. Other techniques have a long learning curve making the procedure operator dependent and time consuming [117-119].

This is the first automated endoluminal mucosal strip resection device that allows accurate deep and lateral margins and with relative ease of use. Further survival experiments and clinical trials will define the role of this device for endoscopic mucosal resection.

7. SUMMARY OF THE WORK

We were focused in our work on develop new techniques and devices for transoral endoluminal treatment of gastroesophageal reflux disease, obesity and - with some technical modifications- Barrett's esophagus.

The treatment of GERD is individualized. The spectrum is wide from simple life style changes to Roux-en-Y gastric bypass. Antisecretories often provide subjective and objective resolution of GERD; however they have no effect on the underlying anatomical defects or on the alkaline reflux. Moreover 50% of patients continue to exhibit low intra-gastric pH and objective evidence of acid regurgitation when reported complete symptomatic control on PPI therapy [23]. Despite the relative safety of these medications new data has increased concern about the long-term effects and safety of anti-secretory drugs [24]. Thus many patients must commit to other therapy to provide lifelong solution for gastroesophageal reflux. Anti-reflux surgery is recommended for patients with refractory, medication resistant or complicated GERD and provides excellent symptom control in 85%-90% of cases [28, 29]. In the era of laparoscopy the number of antireflux procedures has significantly increased. Notwithstanding of the minimally invasive nature of these interventions they are not devoid from complications. Early or late postoperative complications may prolong hospitalization, alter quality of life or require remedial surgical interventions. Reoperative anti-reflux surgery is a feasible option for patients with recurrent disease, although inferior results with a higher mortality and morbidity compared with primary surgery are seen [34, 35].

Present choices of weight reduction for the obese population are limited to life style change, adjunct pharmaceutical therapy and bariatric surgery. The spectrum of

bariatric surgery is wide and the number of bariatric surgical procedures has significantly increased in the recent past. Although majority of these procedures are performed laparoscopically the complication rate is still not negligible [10]. The cost of bariatric surgery is high and it is available for a small part of the morbidly obese patients. Despite the improved results a large proportion of patients still hesitate having operative intervention.

Advanced endoscopic therapy provides different treatment options for patients with Barrett's metaplasia. Thermal or photodynamic therapy and radiofrequency ablation destroy the columnar epithelium allowing the regrowth of physiologic stratified squamous epithelium. Endoscopic mucosal resection and submucosal dissection are other options. However, these techniques carry disadvantages; the formers do not provide tissue for pathologic examination, their durability is questionable and the procedure related complication rate is relatively high. The latter are time consuming and only endoscopists with significant experience are able to perform.

The increasing need for effective, safe, durable and inexpensive procedures dedicated to GERD and obesity resulted in new endoscopic treatment modalities. The numerous different procedures published to date can be categorized as ablative, injection/implantation, fixation, space occupying, transoral stapling, gastric sleeves and others. The idea of endoluminal management of these conditions is relatively new and devices providing long lasting effect have not been developed yet. Based on this new methods and instruments novel treatment options for other pathologies in the upper gastrointestinal tract – such as the Barrett's esophagus – also can be developed.

We used transoral endoscopic flexible devices to excise gastric mucosa and to place full thickness sutures in the excision beds to create an effective gastroplasty. With

some device modification we used this technique to excise mucosa from the esophagus for Barrett's disease.

Radiofrequency ablation and injection of different agents in the LES area has not fulfilled the expectations regarding to long term results in case of GERD. Fixation methods both for GERD and obesity are seem to be more durable but they are still along with high failure rate. We believe that the reason for failure is the lack of strong tissue apposition at the GEJ and the gastric fundus area where multidirectional and significant forces may arise.

In the first phase of our study we developed a multifunctional endoscopic device to excise gastric mucosa and place full thickness sutures in the excision beds creating a gastroplasty. We hypothesized that mucosal excision and apposition of the excision beds are necessary to prevent tissue separation. We placed the gastroplasty at the level of GEJ for GERD and first created a vertical gastroplasty line for obesity forming a neo-esophagus with pouch and restrictive outlet along the lesser curvature.

The in vivo laboratory work with baboons showed gastric mucosal excision feasibility and safety but durability of effect was lacking. However; we understood that separate excision and suturing device would be favorable to utilized to obtain optimal size mucosal excisions and consistent full thickness suture penetration.

From the first animal study we also learned that for ease of device adjustment to gastric tissue and for ease of procedure performance changes are required. In the second phase of the study changes in the design of the gastroplasty device as well as in the procedure were done. A separate excision and suturing device with different trough size were developed. These changes resulted in ease of use and accuracy in both excision and suturing. Procedural changes for obesity resulted that the gastroplasty positioning

was similar to that of the external gastric band when utilizing the pars flaccida approach.

We performed endoluminal gastroplasty as an antireflux procedure and as a gastric outlet restriction for obesity using the second generation of our gastroplasty system on 7 dogs. This study demonstrated that endoscopic gastric mucosal excision and suture placement at the GEJ is feasible, safe and easier with this devices. All animals survived without complications. A significant decrease in GEJ compliance was seen in each animal after the GERD procedure. Good gastric outlet restriction was achieved after the obesity procedure. Scar tissue formation after mucosal excision and full thickness suturing was satisfactory, however we assumed that more amount and greater extension of fibrosis may be needed. We believed that an injectable agent that generates more robust scarring would contribute to durability. In the next step of our study we examined different solutions that may fulfill this requirement.

Previous studies demonstrated that results of endoscopic GERD and obesity therapies often fail even in the short term. In many of these therapeutic options the main target site is the GEJ and the subcardial area. This is formed by a complex net of smooth muscle fibers resulting in a highly elastic and stretchable stomach wall where significant forces arise. This anatomy may be responsible for the high recurrence rate of GERD after endoluminal fixation methods. We hypothesized that generation of scar tissue in this area can prevent tissue disintegration to achieve more durable results.

We used different hypertonic solutions to create robust scar tissue in the submucosal layer. The level of scar tissue generation is critical as panmural fibrosis can be resulted in excessive luminal compromise that may be resistant to dilation of any kind. First we compared 4.2% hypertonic saline and 50% dextrose solutions to find

which is more effective in terms of scar formation. Results demonstrated that with submucosal injection of hypertonic saline stronger fibrosis was generated than with hypertonic dextrose.

Based on these results we used more concentrated saline solutions in larger volumes. It appeared that more intensive fibrosis after injection of more concentrated saline solution can be achieved. Injections by the excision device were more accurate than by endoscopic free hand injections. Further experiments to find an optimal saline concentration in terms of fibrosis formation are is progress.

In the first human mucosal excision and suturing gastroplasty pilot study we performed procedures to treat GERD and to reduce excess weight in obese patients. Total of 8 patients were included. Three with GERD having elevated DeMeester score without hiatal hernia and 4 patients over BMI 35 were included. Endoluminal gastroplasty at the level of LES and in the proximal stomach were created. The system and procedures were proven to be feasible and safe. Patients were followed up for two years by endoscopy and functional testing.

The mid-term results demonstrated that the procedure holds the potential either to rebuild the barrier function of the gastric cardia or to be a restrictive obesity procedure. The key for long term success is the scar tissue generated by mucosal excision and injection of hypertonic saline solution. Technical and procedural refinements are necessary to improve the results and reduce operating time.

We are planning to follow the patients and conduct a larger study to standardize the procedures.

Excision of pathologic mucosa from the esophagus in case of premalignant mucosal changes or in presence of in situ mucosal carcinomas is a treatment option.

Based on our experience from the gastroplasty device our intention was to create a flexible instrument to excise and remove esophageal mucosa and muscularis mucosa safely, fast and with low complication rate. Existing other techniques are along with high perforation and stricture rate or require a significantly higher level of endoscopic skill making the procedure operator dependent and time consuming.

We performed mucosal excisions from ex vivo human and in vivo dog and swine esophagi. Desired cutting depth and excision size was demonstrated without perforation. Accurate device positioning was demonstrated with relative ease of use. Further survival experiments and clinical trials will define the role of this device for endoscopic mucosal resection.

New statements from the study

1. We found that a safe gastric mucosal removal and suture placement for an endoluminal proximal gastroplasty is feasible by using a single transoral device; however in vivo acute and survival animal studies revealed insufficient excision size and poor full-thickness suturing accuracy.

2. We demonstrated safety and efficacy of the gastroplasty technique for both GERD and obesity by using two separate, excision and suturing devices for tissue excision and suturing.

3. We found that hypertonic saline solution is an effective and safe scar tissue generator when injecting into the gastric submucosa.

4. We showed safety and feasibility of the sutured gastroplasty after mucosal excisions both for GERD and obesity in humans.

5. We demonstrated that large esophageal mucosal pieces can be excised safe and with relative ease in a targeted fashion by using a cold blade technique.

6. This work is the first to demonstrate safety and feasibility of sutured gastroplasty after mucosal excision, suturing and submucosal hypertonic saline injection for GERD and obesity in humans. These findings support to conduct a larger human study to evaluate procedural efficacy and may serve to develop other effective treatment modalities for the endoluminal management of GERD, obesity and Barrett's esophagus.

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1. **András Légner**, Charles J. Filipi. (2010) Endoluminal therapies for gastroesophageal reflux disease and obesity. In Paul Alan Wetter (Ed) *Prevention and Management of Laparoscopic Surgical Complications 3rd edition.* (Chapt 22.)

Presentations

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2. Ferencz A**, Légner A**, Rőth E
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