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ORIGINAL ARTICLE

Endoluminal fundoplication (ELF) – evolution of EsophyX™, a new surgical device for transoral surgery

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Abstract
A novel endoluminal fundoplication (ELF) technique using a trans-oral and fastener-deploying device (EsophyX™, EndoGastric Solutions) was developed and evaluated for feasibility, safety and the treatment of gastroesophageal reflux disease (GERD) in a series of bench, animal, human (phase 1, phase 2, commercial registry) studies. The studies verified biological compatibility, durability and non-toxicity of the polypropylene fasteners as well as the feasibility of the ELF technique. The results of the preclinical testing indicated that the EsophyX™ device was shown to be safe, and capable of deploying fasteners directly into tissue and forming an interrupted suture line at the base of the gastro-esophageal valve (GEV). Moreover, the studies demonstrated that the ELF technique performed using the EsophyX™ device resulted in the creation of new GEVs of 3–5 cm in length and a circumference of 200°–310°, which maintained their anatomical aspects at six months. The ELF-created GEVs appeared similar to those created by laparoscopic anti-reflux surgery (LARS). The ELF procedure also resulted in reduction of all small hiatal hernias ($\leqslant 2$ cm in size) and restoration of the angle of His. The ELF procedure provides an anatomical approach similar to that of LARS for the treatment of GERD.

Key words: *Endoluminal, fundoplication, trans-oral, GERD, gastro-esophageal reflux, endoscopy*

Introduction

Endoluminal procedures have emerged as a new therapeutic option for the treatment of gastroesophageal reflux disease (GERD) (1). The following three categories of procedures have been evaluated and approved by the U. S. Food and Drug Administration (FDA). First, radiofrequency ablation to create submucosal thermal lesions in the smooth muscles of the lower esophageal sphincter (LES) and cardia (1–7). Second, the injection of biopolymer ethylene vinyl alcohol copolymer under fluoroscopy into the muscular layer of the LES (8–11). Third, transmural plication and suturing devices to create pleats in the gastroesophageal junction (GEJ) to enhance the competency of the gastric cardia pleating (12–17). The radiofrequency and injection procedures, however, have suffered from a variety of problems, including serious adverse events (SAEs) such as esophageal perforation (18) as well as short and medium-term efficacy falling short of initial expectations (1,19,20). As a result, these devices were removed from the market by the manufacturers or required additional sham-controlled trials to verify their effectiveness compared to placebo (1,20).

The trans-oral, endoluminal full-thickness plicators continue to provide the most promising alternatives to laparoscopic anti-reflux surgery (LARS) and medical anti-secretory therapies with proton pump inhibitors (PPIs) (1,19,20). Suturing procedures offer easy repeatability, short operative time, early discharge, little morbidity, and symptomatic improvement (1). Moreover, endoscopic gastroplication has proven short-term efficacy and has been demonstrated to be cost-effective for one to two years (1,14). A long-term sustainability of the plication and suturing approaches remains, however, unknown. Furthermore, the plication system appears limited in

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terms of placing more than one stitch because it would require a removal and re-entry of the device (1,14), which could increase the risk of perforation. This approach also does not reduce hiatal hernia nor create a robust gastro-esophageal valve (GEV).

The present study evaluates the use of EsophyX™ (EndoGastric Solutions, Inc., Redmond, WA, U. S. A.), a new flexible multi-channel endoluminal device that attempts to completely restore the valve at the gastroesophageal junction (GEJ) through a new endoluminal fundoplication (ELF) technique. The new ELF technique consists of inserting the EsophyX™ device trans-orally under direct visualization by an endoscope and creating a 3–5 cm long omega-shaped valve with 200°–310° of circumference through delivery of multiple fasteners acting like an interrupted suture line.

The safety of the EsophyX™ device have been evaluated using bench models and animal studies as well as phase 1 (feasibility) and phase 2 (pivotal) clinical trials and commercial registry. To date, the procedure has been successfully performed in Europe on close to 100 patients. The objective of the present article was to describe the evolution of the EsophyX™ device and ELF procedure and report the results on their technical feasibility, safety, and durability. The clinical results of the phase 1 trial with 17 GERD patients at three and six months after the procedure have been presented in detail in our previous publications (21,22) and are summarized in Table I for the purpose of discussion.

Material and methods

The EsophyX™ device and ELF procedure

The EsophyX™ is a disposable device that rides axially over a standard endoscope. The ELF technique is performed under general anesthesia by a team of two physicians, with one investigator operating the device and the other managing the endoscope to ensure proper exposure and visualization throughout the procedure. Each patient is positioned on the left side (left lateral decubitus position). The EsophyX™ device and the endoscope are passed transorally through the esophagus into the stomach (Figure 1). A proprietary esophageal invaginator incorporated into the device is used to engage the distal esophagus at the level of the Z-line and reduce hiatal hernia, if present, by advancing the device and esophagus aborally. Gastric tissue from the fundus is drawn between the body of the device and the tissue mold used to shape each portion of the GEV (Figure 1). Several polypropylene fasteners are delivered across the molded tissue to create a 3–5 cm long serosa-to-serosa flap (Figure 2). The process typically starts posteriorly at the greater curvature and continues anteriorly until creation of an omega-shaped valve with a 200°–310° circumference (Figure 3). After the EsophyX™ device withdrawal, the newly-created valve is examined and measured during endoscopic examination.

Preclinical testing

Bench and animal tests were conducted to verify whether the EsophyX™ device met pre-defined (input) product specifications and was safe and effective for the intended use. The verification testing was consistent with the U. S. FDA's Guidance on Premarket Notification [510(k)] Submission for Endoscopes used in Gastroenterology and Urology dated March 17, 1995. The device successfully passed the tests performed for mechanical integrity and characterization, including visual inspection,

Table I. Comparison of clinical effectiveness of the Endoluminal Fundoplication (ELF) procedure, laparoscopic anti-reflux surgery (LARS) and the Endoscopic Plication System (EPS) procedures

	ELF[1]	LARS[2]	EPS [3]
Mean percentage improvement in GERD-HRQL scores for patients off and on PPIs at baseline	Off PPIs 45% at 3 mo 64% at 6 mo On PPIs 63% at 3 mo 43% at 6 mo	n/a	Off PPIs 61% at 3 mo 58% at 6 mo
Mean percentage improvement in mean Mental / Physical SF-36 scores	43%/15% at 3 mo 10%/57% at 6 mo	n/a	11%/8% at 3 mo 8%/14% at 6 mo-
Percentage of patients off GERD medication	76% at 6 mo	92–96% at 6 mo	35% at 6 mo
Percentage of patients off PPI medication	88% at 3 mo 80% at 6 mo	92–96% at 6 mo	n/a 74 % at 6 mo
Percentage of patients with normal pH[4]	67% at 6 mo	91–96%	30% at 6 mo

[1]Data from (21) for 3 months and from (22) for 6 months [2]Data from (26,27,29,40), n=16 (mean age 45, 36–55) [3]Endoscopic Plication System (NDO Surgical, Inc., Mansfield, Mass) evaluated in n=64 (mean age 46.3, range 23–71) by (14) [4]Defined as <4.1% of time pH<4 or DeMeester score<14.7 PPI – proton pump inhibitor

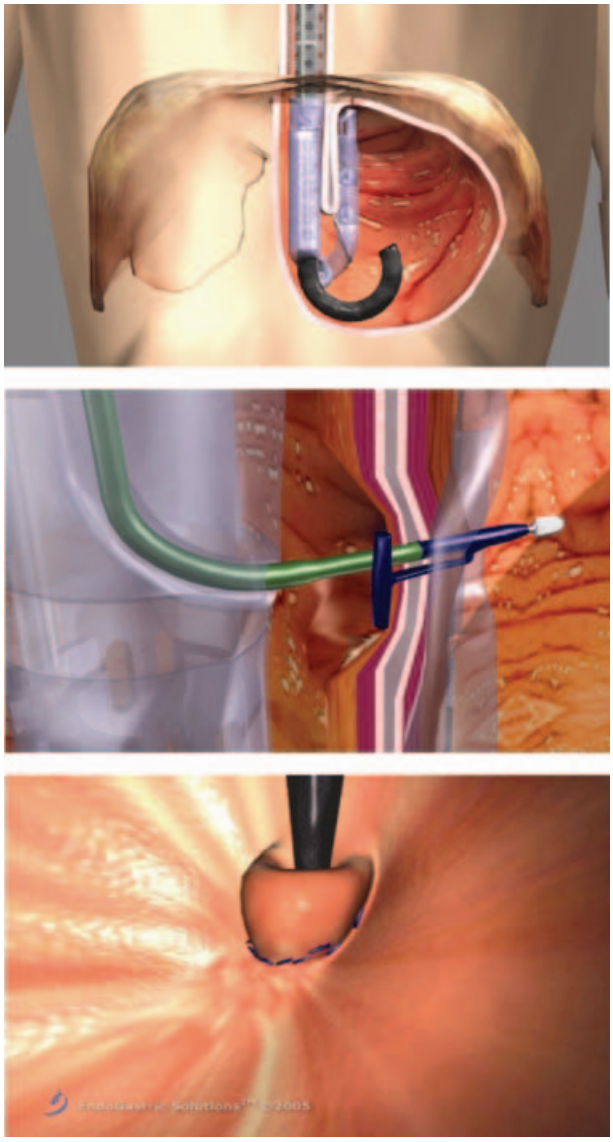

Figure 1. Schematic drawings illustrating endoluminal fundoplication (ELF) technique using the EsophyX™ device (top), polypropylene fasteners (middle) and gastro-esophageal valve resulting from the procedure (bottom).

surface finish inspection, dimensional inspection, seal leak tests and flow tests, and simulated use functional tests, safety interlock test, strength test, and flexibility test. Simulated use was evaluated in instrumented bench tests and with animal tissue. The tests allowed determination of the forces needed to penetrate the stomach tissue and optimization of the stylet's size and tip shape. The tests measured the forces needed to penetrate and deploy the fasteners through two layers of the stomach tissue and torque forces to penetrate the tissue with the helical retractor.

Biocompatibility testing was performed on the fasteners and construction materials used in the EsophyX™. The fasteners were tested for biocompatibility following EN ISO 10993 specifications and for pulling against the specification for a Class 1, 3-0 suture commonly used for stomach surgery as defined in USP 27-NE 22 Non-absorbable Surgical Suture Supplement. The materials utilized in the device construction were standard medical grade and tested for cytotoxicity using the ISO Elution Method – IX MEM extract, ISO intracutaneous studies, murine local lymph node assay and USP, and ISO systemic toxicity studies.

Six mature female canine models underwent the ELF procedure. The preoperative upper GI endoscopy revealed Hill Grade IV valve in one animal, Grade III valve in three, Grade II in one, and normal grade in one. Acute and chronic experiments were performed to investigate and confirm the ''valve theory'', based on strong evidence in the existing available medical literature. The ''valve theory'' claims that the GEV is necessary to stop GERD and that the LES is not by itself an effective antireflux barrier (ARB). One of the simplest proofs of well functioning valves in the absence of LES pressure was a consistent finding in excised pig stomachs, which were obtained through a meatpacking company. The finding indicated that, despite the presence of food and water and the absence of a working LES, the excised stomachs did not leak or reflux into and out of the esophagus. While the small bowel was tied off with a knot, the esophagus came consistently without such knot. Only in two out of the 300 examined stomachs the esophagus was tied off. The fact that the esophagus was not tied off in most of the excised stomachs indicated that reflux was effectively prevented by the GEV.

After extensive testing in 21 acute, short- and long-term chronic dogs, a GLP-study was performed using the EsophyX™ device and proprietary fasteners. A total of 19 mongrel dogs (hounds) were treated with the ELF procedure under general anesthesia. None of the treated animals had any procedure related complication, including side-effects such as bloating, dysphagia or other eating disorders. One dog died, but the cause of death was described by the two experts as completely unrelated to the ELF procedure. According to the protocol, nine animals were re-endoscoped at four weeks and subsequently sacrificed and esophagus and stomach resected, the remaining nine animals were re-endoscoped and resected at 12 weeks. The specimens were trimmed and were histopathologically examined.

Clinical trials

The ELF technique has been evaluated in two clinical trials and commercial registry involving close

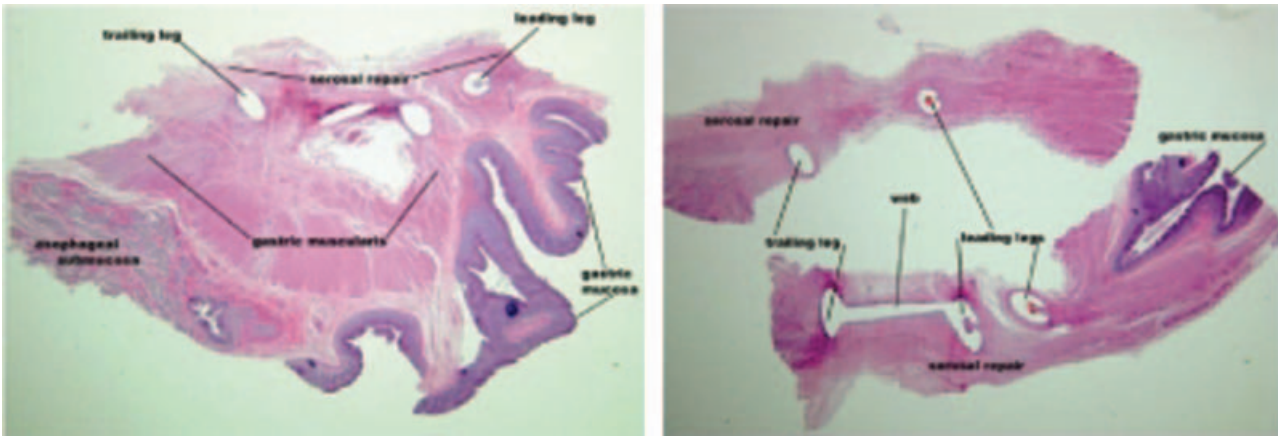

Figure 2. Longitudinal sections of canine gastro-esophageal junction showing the location of the ELF valve created using the EsophyX™ fasteners. The section on the left shows the adhesion bridge or serosal repair at the location of the gastric serosa plication. Note the position of the legs of the device in the gastric muscularis where they have produced a minimal fibrous and inflammatory reaction. The section on the right shows the gastric wall with a serosal repair and fastener in the tissue of the adhesion. Note the absence of fibrous or inflammatory reaction and the location of the legs of the device in the muscularis. Hematoxylin and eosin.

to 100 patients with a long history of GERD symptoms that had been treated with proton-pump inhibitors (PPIs) and referred for Nissen fundoplication. Both clinical trials were conducted in several university centers through Europe. The first clinical trial was designed as a one-year technical feasibility study (Phase 1) and included 17 patients. The results for the three-month and six-month follow-ups are summarized in Table I. The results of the 12-month follow-up are expected to be available shortly and will be presented in another publication. The phase 2 trial was designed as a one-year multicenter efficacy study with 70–90 GERD patients. The trial is in progress and the results of the six-month follow up are expected to be available by the end of the year. The registry is expected to provide a continuous source of data on the commercial cases in several European countries.

Results

Preclinical testing

The bench tests allowed determination of the best shape of the stylet tip, adequate lumen sizes and push tubes for the fastener deployment. Additional tests determined the adequate drive shaft strength for the helical retractor and the size and strength of the bail to hold and mold the tissue in a compressed state during fastener deployment. In the dog studies, the serosa-to-serosa full thickness valve created using the EsophyX™ device showed a solid serosal fusion at four weeks (Figure 2) and incorporation of the phrenoesophageal ligaments or membrane (PEM).

The results of the studies using canine model revealed a median procedure time (device in-device out) of 48 ± 19 minutes. A total of 146 fasteners were placed, with a median of eight per animal. A grand majority of fasteners (89%) were located at or below the Z-line and the remaining 11% were 1 cm above the Z-line. No fastener was found in the tubular esophagus. The dog cup-shaped GEJ anatomy contributes to a certain difficulty in placing fasteners precisely at the Z-line. The two thirds of fasteners located within 1 cm above the Z-line were placed during the first procedures. After the ELF procedure all dogs had Grade I valves while prior to the procedures only two out of six dogs had Grade I. The median length of the valves was 4 ± 0.6 cm postoperatively.

The bench tests in porcine stomachs showed a tenfold increase in yield pressure after an open or transgastric valvuloplasty. These valves were sutured over a rigid precursor of the current device, which also served as bougie, thus guaranteeing that the distal esophagus was not overly narrowed.

The tests of the polypropylene fasteners in short-term porcine model revealed a longitudinal intragastric fold of up to 5 cm in depth that was created surgically on the anterior aspect of the stomach with the fasteners. Histological examination at two weeks revealed a collagen shelf formed between serosal layers and a fusion in progress (Figure 2). No adverse events and inflammation occurred in response to the placement of the fasteners. The results of the fastener testing confirmed that the polypropylene was biocompatible, and safe to be used in humans based on the animal studies. The minimum specified tensile strength was 9.41 N. Pull

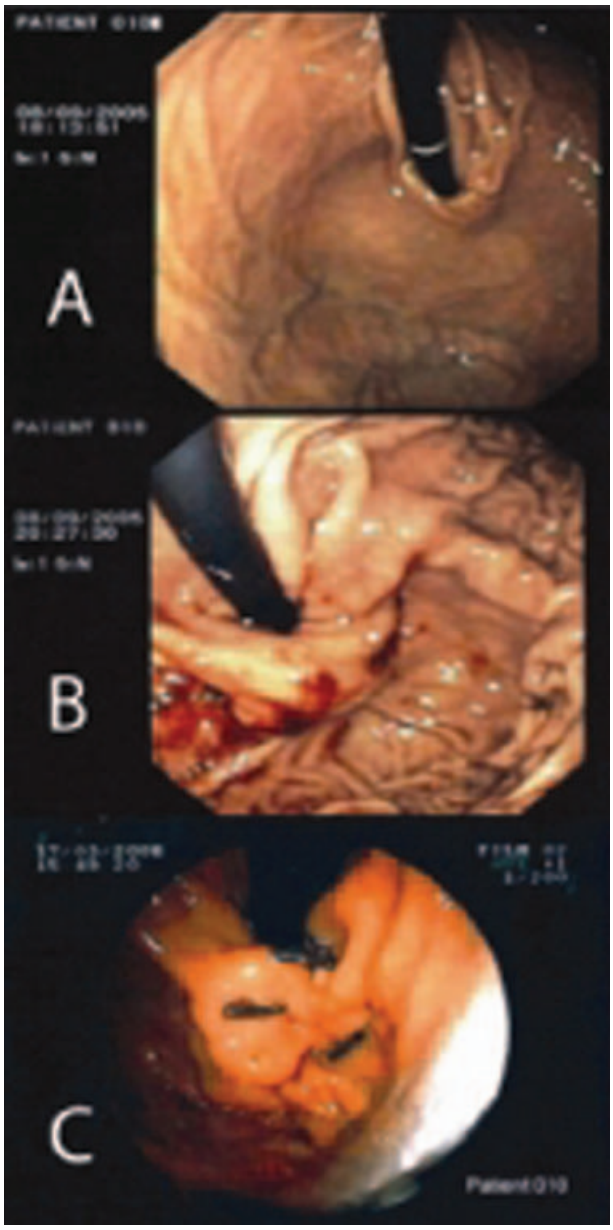

Figure 3. Endoscopic views of the gastro-esophageal valve (GEV) in the same patient at the baseline (A), at the time of the endoluminal fundoplication (ELF) procedure (B), and at six months after the procedure (C). Based on data from (22).

tests performed on 60 sterilized fasteners showed an average tensile strength of >11 N.

Clinical trials

The results of the Phase 1 trial have been published previously (21,22) and are only summarized in Table I. Endoscopic examination at six months showed a continued persistence of the valve (Figure 3) and maintenance of the valve configuration with a median circumference of 210° (range 150–250) and length of 3.5 cm (2.5–5.0). In the Phase 2 study, 55 patients were enrolled (average age 44.2 yr, range20–80) and 32 treated until now. The average procedure time was 94.9 ± 38.8 min, and an average of 15 ± 4 fasteners were used per patient. The average length and circumference of the ELF-created GEVs (n=32) were 3.8 ± 1.0 cm and 232.4 ± 30.9 degrees, respectively. The number of valves assessed as tight, moderate, and loose was 28 (86%), 4, and 0, respectively.

Discussion

The results of the preclinical tests demonstrated that the EsophyX^{TM} device was safe. The device was capable of deploying the fasteners directly into the stomach tissue and forming an interrupted suture line at the base of the ELF-created GEV. The animal and human studies demonstrated that the ELF technique performed using the EsophyX^{TM} device resulted in creating GEVs of 3–5 cm in length and a circumference of 200°–310° that maintained their anatomical aspects at six months (22). The procedure also resulted in reduction of all small hiatal hernias ($\leqslant 2$ cm in size) and restoration of the angle of His. The ELF-created GEVs appeared similar to those created by LARS (23–26). In contrast to the LARS (27–29), however, the ELF technique was performed without abdominal incisions and caused less pain, dysphagia, diarrhea, and gas bloating (Table II). The ELF technique also resulted in a much shorter hospitalization but much faster post-procedure recovery than LARS (Table II). The presence of fewer side effects such as dysphagia in the ELF-treated patients compared to those treated with LARS resulted most likely from the absence of PEM severing with no fundoplication behind the esophagus. The anatomical features and clinical and socio-economic benefits of the ELF procedure are compared with those of LARS and NDO's endoluminal plication system (EPS) in Table II and discussed in the paragraphs below.

A long-term efficacy and safety of surgical and laparoscopic restorations of the GEJ anatomy has been demonstrated in numerous publications (30–33). Considering that surgery is primarily performed in the most complicated cases, an average mortality rate of about 0.8%–1.0% is expected. The same reason is given for a morbidity rate in the range of 5% and a rate of re-operation of up to 16%. The overall outcome being reported is as high as 85–95% good to excellent in 15 to 20 year follow-up data. These numbers are based on objective data from the laboratory tests as well as on subjective data derived from patient interviews and quality-of-life

Table II. Comparison of technical performance and effectiveness of the endoluminal fundoplication (ELF) procedure, laparoscopic anti-reflux surgery (LARS), and the endoscopic plication system (EPS) procedures based on published studies cited in the present study

Criteria	ELF	LARS	EPS
Restore angle of His			
Restore valve			
Narrow LES	*		*
Narrow esophageal orifice			
Reduce hiatal hernia			
Narrow hiatus	*		
Tighten PEM (phreno-esophageal membrane)			*
Improve crural esophageal pinch			
Lengthen intra-abdominal segment of esophagus			*
Anchor valve/GEJ			*
Gastro-fundo- phrenicopexy	*		
Reproducible/standardized procedure/method			
Longevity of the treatment effect (years)	?	15+	?
Anatomical approach			
Emulate surgeries			
Level of required skills	++	+++	+
Reduction in PPI use	++	+++	+
Normalization of pH	++	+++	+
Improvement in QOL	++	++	++
Easy redo/revision			?
Limitation in number of redos			?
Dosage/customizable			
Procedure used to improve outcome of failed LARS			
Hospital stays (days)	1	2–11	0
Back to work (weeks)	1–3	3–4	?
Severity of side effect	+	++	+
Effect on esophageal clearance	better	better	?
Affects integrity of gastric reservoir		—	?

Black boxes indicate yes; white, NO; ?, not known;*, possibly

questionnaires (32). The same is true for patients in their eighties and older (31). In long-term comparative studies, the surgical treatments generated the results that were objectively and subjectively superior to those generated by the more conservative medical treatments (34,35). The studies also indicated that a durable improvement in reflux and regurgitation in patients with chronic severe GERD required intactness and integrity of the GEV.

The main goal of all surgical antireflux procedures is to restore the anatomical geometry of the GEJ (36,37). Surgery, whether open or laparoscopic, is directed toward restoring the ARB with its high-pressure zone (HPZ) to prevent reflux and regurgitation (27,38). Multiple steps, which most surgical procedures address differently, are required to reproduce the competency of the natural ARB. An evolution of open and now LARS over the last 60 years has resulted in close to perfect, yet very invasive, results (32,33,39). Over the recent years, medical treatments have also established a firm place in treating esophagitis (34). Although young, the endoluminal procedures have taken a permanent role in the treatment of GERD. The EsophyX^{TM} device and ELF procedure emulate many of the steps of LARS (Table II) and produce very promising early results (Table I).

Anatomists have described and demonstrated the GEJ anatomy since the early 17th century (38). Surgery restores the angle of His and re-establishes the GEV (23,24,39). Several studies have investigated and confirmed the importance of the valve to prevent reflux, even in the absence of a functional LES (36). As a result and depending on the technique used, LARS restores the antireflux valve and, concomitantly, the LES in its length and pressure. The EsophyX^{TM} device also restores a robust valve and improves the LES, whereas other endoluminal procedures focus primarily on having an effect on the LES or the esophageal orifice by narrowing, pleating, or injecting. None of these endoluminal procedures, however, restores a valve as described in Gray's anatomy.

All surgical procedures require dissection of PEM and the natural attachments between esophagus and diaphragm or crura. In contrast, endoluminal procedures such as ELF have no effect on extraluminal structures. In fact, the EsophyX^{TM} device pulls a 4 to 5cm long valve with the PEM incorporated in the serosa-to-serosa tissue approximation (Figure 2). Ultimately, the tissue fusion leads to a semicircular tightening of the PEM. Anchoring of the newly restored valve is an integral component of most surgical procedures and is achieved with the EsophyX^{TM} device by incorporation of the PEM. Moreover, by reducing hiatal hernia, the ELF procedure and surgery either lengthen the esophagus or partially or fully lengthen the intraabdominal segment of the esophagus. Gastro- or fundophrenicopexy, which are required to guaranty an extended longevity of the surgical repairs, may be available for the EsophyX^{TM} device in the near future.

In conclusion, the ELF procedure appeared to be safe and feasible. The procedure resulted in creation of tight and durable GEVs and reduction of GERD symptoms for six months. The ELF procedure provides an anatomical approach to the treatment of GERD that is more similar to LARS than that of the one-stitch tissue plication system by NDO (40). Furthermore, the ELF procedure offers additional advantages over the LARS because it is performed

without abdominal incisions, long-lasting GI side effects, prolonged pain, and long post-procedure recovery.

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