Fakultät für Medizin

Chirurgische Klinik und Poliklinik

The "therapeutic gap" in the treatment of gastroesophageal reflux disease: Systematic evaluation of endoluminal anti-reflux procedures- a complementary therapeutic approach? (EsophyX® and GERDX™ systems)

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Vollständiger Abdruck der von der Fakultät für Medizin der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Medizin (Dr.med)

genehmigten Dissertation.

Vorsitzender: Prof. Dr. Ernst J. Rummeny

Prüfer der Dissertation:

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Die Dissertation wurde am 12.06.2017 bei der Fakultät für Medizin der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 08.11.2017 angenommen.

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München 2017

Preface

This manuscript is the result of years of work at the department of surgery of Klinikum rechts der Isar. I would like to thank my supervisor Prof. Dr. med. Hubertus Feussner for his support, kindness, and freedom he gave me during the last 2 years. Thanks to my second supervisor Prof. Dr. med. Stefan von Delius, who gave me the opportunity to join in the team of endoscopy center. It was an incredible experience. Thanks to Ms. Sabrina Stoeppke, Ms. Helga Wirnhier, Ms. Alissa Jell, and all members of *MITI* group, who assisted to the data collection. I also feel grand gratitude for PhD Dr. med. Dirk Wilhelm and other members of *MITI* group who not only helped me with my study and work in the Klinikum rechts der Isar, but also helped me integrate into foreign country.

Thanks to all my friends and former colleagues here who made my every single day in this hospital very special. Thanks to every single person, who in one way or another, joined me during this special period. Thanks to my Chinese supervisor, Prof. Yongjun Chen, who understood, supported and encouraged me during all my time in Munich.

My greatest hug and deepest gratitude goes to my parents, my husband and daughter. Their unconditional love and support through out the last 2 years brought me to where I am now.

Last, thanks to my dear reader for reading the first page. I wish you a great journey through this manuscript.

February 2017

Suyu He

Abstract

Background A ”therapeutic gap” exists between medical therapy and anti-reflux surgery for the treatment of gastroesophageal reflux disease (GERD). Endoluminal sphincter augmentation (ESA) is a kind of endoscopic therapy which was developed in an attempt to close this “gap”. The aim of this study was to quantify the “ gap patients” and to evaluate the safety and efficiency of ESA using the EsophyX® and the GERDX™ system for the treatment of these “gap patients”.

Patient and methods Between November 2008 to December 2016, patients with chronic GERD referred to our surgical department were included. The proportion of patients received medical treatment, anti-reflux surgery (fundoplication) or ESA treatment was annually determined. The peri- and post-procedure data were evaluated in patients treated by ESA either with the EsophyX® or the GERDX™ system, and all these patients had a follow-up using standardized questionnaires and a telephone interview. Primary outcome measure was GERD-related symptom scores and quality of life. Second outcome measure was PPI usage.

Results The total number of gap patients who neither achieved treatment success with medication nor received anti-reflux surgery is 262 (16.0%, 262/1642). Among these 262 patients who have fallen into the “therapeutic gap”, 36 (13.7%, 36/262) underwent ESA using the EsophyX® device (17 patients) or the GERDX™ system (19 patients). 226 (86.3%, 226/262) patients were found to be unfit for ESA.

Of the 17 patients originally assigned to the EsophyX® procedure (EsophyX® patients), 12 patients finished the follow-up since the procedure failed in 2 patients, 3 patients (3/15, 20.0%)

received a re-intervention with Laparoscopic Nissen fundoplication (LNF). Of the 19 patients originally assigned to the GERDX™ procedure (GERDX™ patients), 15 patients finished the follow-up since 4 patients (4/19, 21.0%) relapsed after an interval. Among them, 2 patients without hiatal hernia (HH) received a second GERDX procedure and a LNF was performed in another 2 patients with HH≥2cm.

Both EsophyX® and GERDX™ procedures turned out to be safe, no severe adverse events occurred. The mean operation time was 54.9±11.3 minutes in EsophyX® patients and 31.3±11.0 minutes in GERDX™ patients respectively. The hospital stay was 4.4±1.1 days in the EsophyX® patients and 3.2±1.0 days in the GERDX™ patients respectively. Comparative analysis demonstrated longer operation time as well as hospitalization in the EsophyX® group (P<0.05). At the end of follow-up, 9 EsophyX® patients (9/12, 75.0%) and 10 GERDX ™ patients (10/15, 66.7%) achieved a reduction of PPI medication >50%. Both procedures resulted in significantly improved GERD-related symptom scores and quality of life (P<0.05).

Conclusion A "therapeutic gap" does exist between medical therapy and anti-reflux therapy for patients with GERD. ESA using the EsophyX® and the GERDX™ system can be a minimally invasive, relatively safe and efficacious complementary approach to close part of the "gap". Larger multi-center prospective randomized sham-controlled trials with a longer follow-up are needed to show if the positive initial results can be maintained.

Key words Endoluminal sphincter augmentation; Gastro-esophageal reflux disease management; Reflux; EsophyX; GERDX

Zusammenfassung

Hintergrund Es existiert im Rahmen der Behandlung der gastroösophagealen Refluxerkrankung(GERD) eine therapeutische Lücke zwischen der medikamentösen und chirurgischen Antirefluxtherapie. Die endoluminale Sphinkteraugmentation (ESA) ist eine endoskopische Intervention, die entwickelt wurde, um diese Lücke zu schließen. Das Ziel dieser Studie war, die Patienten, die mit einem derartigen Verfahren behandelt wurden zu quantifizieren und die Sicherheit und Effektivität der ESA zu evaluieren. Zum Einsatz kamen hierbei das sogenannte EsophyX® und GERDX™ System.

Patienten und Methoden Zwischen November 2008 und Dezember 2016 wurden Patienten mit einer chronischen GERD, die unserer chirurgischer Klinik überwiesen wurden, eingeschlossen. Das Verhältnis der Patienten, die medikamentös, endoskopisch oder chirurgisch im Sinne einer laparoskopischen Fundoplikatio therapiert wurden, wurde jährlich registriert. Der peri- und postprozedurale Verlauf wurde bei Patienten, die eine ESA mittels EsophyX® oder GERDX™ bekamen, mithilfe von standardisierten Fragebögen und einem Telefoninterview erfasst. Hierbei wurde das primäre Outcome anhand der GERD-assoziierten Symptome und der Lebensqualität gemessen. Das sekundäre Outcome bezog sich auf den Gebrauch von Protonenpumpenblockern (PPI).

Ergebnisse Die Gesamtzahl der Patienten, die in die oben erwähnte therapeutische Lücke fallen, ist 262 (16.0 %, 262/1642). Diese wurden nicht operiert und haben auch mithilfe einer medikamentösen Therapie keine Besserung der Erkrankung erfahren. Von diesen 262 Patienten wurde bei 36 Patienten (13.7%, 36/262) eine ESA durchgeführt. Bei 17 im Sinne

von EsophyX® und bei 19 Patienten kam GERDX™ zum Einsatz. Die restlichen 226 (86.3%, 226/262) Patienten waren nicht für derartige Interventionen geeignet.

Von den 17 Patienten, die eine ESA mit EsophyX® erhielten beendeten 12 Patienten das Follow-Up. Bei 2 Patienten schlug die Prozedur fehl und 3 Patienten (3/15, 20%) wurden schließlich mittels einer laparoskopischen Fundoplikatio nach Nissen (LNF) therapiert. Von den 19 Patienten, die mit GERDX™ therapiert wurden, ist schließlich bei 15 Patienten das Follow-Up beendet worden. 4 Patienten (4/19, 21.0%) hatten ein Rezidiv ihrer Erkrankung. Von diesen wurde bei 2 Patienten ohne eine Hiatushernie (HH) eine zweite GERDX™ durchgeführt. Die verbleibenden 2 Patienten hatten eine HH≥2cm und wurden schließlich operiert im Sinne einer LNF.

Sowohl EsophyX®, GERDX™ stellten sich als sicheres Verfahren ohne unerwünschte Nebenwirkungen dar. Die mittlere Interventionsdauer war bei EsophyX® 54.9±11.3 Minuten und 31.3±11.0 Minuten bei GERDX™. Die Krankenhausverweildauer war bei den ExophyX-Patienten 4.4±1.1 Tage und 3.2±1.0 Tage bei den GERDX-Patienten. Die vergleichende Analyse zeigte bei der EsophyX-Gruppe eine signifikant längere Operations- und Krankenhausverweildauer (P<0.05). Am Ende des Follow-Ups kann gesagt werden, dass 9 EsophyX® Patienten (9/12, 75.0%) und 10 GERDX™ Patienten (10/15, 66.7%) eine Reduktion der PPI von >50% erreichten. Beide Prozeduren erzielten eine signifikant verbesserte GERD-assozierte Symptomatik und Lebensqualität (P<0.05).

Fazit Es existiert eine therapeutische Lücke zwischen der medikamentösen und der operativen Therapie in der Behandlung der GERD. ESA im Sinne einer Versorgung mit EsophyX® oder GERDX™ ist eine endoskopische, relativ sichere und vor allem effiziente Methode, um diese

Lücke zu schließen. Zukünftig werden allerdings größere randomisierte, multizentrische Doppelblindstudien mit einem längeren Follow-Up-Zeitraum benötigt, um die positiven anfänglichen Ergebnisse zu bestätigen.

Schlüsselwörter Endoluminale Sphinkteraugmentation; Gastroösophageale Refluxerkrankung; Reflux; EsophyX; GERDX

Abbreviations

AEs	Adverse events
ARMS	Anti-reflux mucosectomy
DSQLD	Disease specialized quality of life questionnaire
EAC	Esophageal adenocarcinoma
EAE	Esophageal acid exposure
EGJ	Esophagogastric junction
ESA	Endoluminal sphincter augmentation
FDA	Food and Drug Administration
GERD	Gastro-esophageal reflux disease
GERD-HRQL	Gastro-esophageal reflux disease health related quality of life
HH	Hiatus hernia
LES	Lower esophageal sphincter
LF	Laparoscopic fundoplication
LNF	Laparoscopic nissen fundoplication
LPR	Laryngopharyngeal reflux
NERD	Non-erosive reflux disease
PPIs	Proton pump inhibitors
RCTs	Randomized clinical trials
RSI	Reflux symptom index
SAEs	Serious adverse events

TIF	Transoral incisonless fundoplication
TLESR	Transient lower esophageal sphincter relaxation

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1. Introduction

1.1 Overview of GERD

Gastro-esophageal reflux disease (GERD) is a disease spectrum caused by regurgitation of stomach contents causing troublesome esophageal or extra-esophageal symptoms as defined by the Montreal definition [1]. Either mild heartburn and/or regurgitation for at least 2 days per week or moderate to severe symptoms for at least one day per week qualifies as significant symptom-based diagnosis [2]. It is one of the most prevalent diseases in developed countries. An estimated 20-40% of Western adult populations suffer from reflux symptoms, characterized mainly by heartburn and/or regurgitation [3]. The prevalence of GERD in Asia is also increasing [4,5]. More importantly, even mild persistent reflux symptoms have been reported to impair physical and psychology well-being, consequently contributing to a significant adverse impact on patients' quality of life [4,6]. The social impact of GERD includes lost work days and increased health cost. Medically, there is a risk of developing esophageal adenocarcinoma (EAC). Barrett's esophagus will develop in an incidence rate of 0.8% per year [7]. GERD increases the risk of EAC by 8.6-fold [8].

1.2 Overview of treatments of GERD and their shortcomings

The objectives for GERD therapy are to eliminate symptoms, heal esophagitis, prevent recurrence of symptoms or progression of the disease. The initial treatment of GERD is geared toward reducing esophageal reflux. Dietary and lifestyle modifications as well as medication therapy (PPIs, antacids, H_2-receptor antagonists) has been used for such purpose. When standard medical therapies failed, surgery may be considered [9].

1.2.1 Dietary and lifestyle modifications

There has been increasing data supporting lifestyle intervention in the treatment of GERD. A recent systematic review summarized the results from several randomized clinical trials (RCTs) demonstrating that weight loss, early evening meals, and head-of-the-bed elevation were effective measures for reducing reflux symptoms and esophageal acid exposure [10]. Smoking is also found to be associated with the onset of GERD symptoms, and smoking cessation was proved to be effective for smokers' GERD symptoms control based on previous studies [11-12]. Although the association of these modifiable factors and GERD has been proved, and most patients can recognize that regular exercise, dietary habits and smoking cessation are important for the prevention and management of GERD, the fact is that the adherence to these prescribed lifestyle modification recommendations is challenging. The lack of communication from their provider and lack of ongoing support are two main reasons for this problem [10].

1.2.2 Medical therapy

The medical treatment of GERD primarily revolves around the use of anti-acids, including H_2-receptor-antagonists and more commonly and importantly, proton pump inhibitors (PPIs). Since the first introduction of PPI omeprazole in 1980s, PPIs has generally considered to be safe and widely used in clinical practice. Medical therapy with PPIs is the main therapy for most of the patients with GERD, and this therapy is also effective for the majority of GERD patients [9]. According to previous studies, 60-80% patients with GERD can get symptom resolution with PPI therapy [5,13-14]. Undoubtedly, it has an established role in the treatment of GERD.

However, there are still several shortcomings of PPIs for the treatment of GERD. First, not all of the patients can get complete symptom resolution with PPIs. There are patients with GERD whose symptoms fail to respond partially or completely to PPI after a sufficient period of therapy. The reported rates of PPI-refractory GERD vary among studies. A systematic literature review is available to identify the proportion of adults with GERD who experience partial or non-response of their reflux symptoms to PPI therapy, both in primary care and in community-based studies. Nineteen studies in individuals with GERD taking a PPI were included. These studies were from North America, Europe and Australia. It reported the partial or non-response to PPI therapy is 17% in interventional non-randomized primary care trials, 32% in randomized trials and 45% in observational primary care and community-based studies respectively [15]. Furthermore, GERD symptoms recur within 1 year in more than 90% of patients after PPI-withdrawal (the so called "rebound phenomenon"). It refers to the worsening of GERD symptoms upon PPI withdrawal, presumably due to acid overproduction from secondary hypergastrinemia [13,16]. The second problematic aspect of PPI is real or ostensible side effects. While the safety profile of PPIs was considered to be excellent, recent evidence suggests that chronic PPI use may be also associated with multiple adverse events. These include some health problems, such as nutrition deficiency, especially B_{12} deficiency [17], some infections, including clostridium difficile-associated diarrhea (CDAD) and pneumonia. A recent meta-analysis has found a 65% increase in the incidence of CDAD among hospitalized patients who were PPI users [18]. For pneumonia, the incidence of both community and hospital-acquired pneumonia was found increased in PPI users [19]. In addition, PPI use, especially chronic PPI use, may lead to the formation of gastric polyps. Previous studies have reported that PPI intake was the strongest risk factor associated with the

presence of fundic gland polyps [20]. Last but not least, the financial burden associated with chronic PPI use on patients and the entire healthcare system has to be taken into account. It has been estimated that over 10 billion dollars are spent on prescribed PPIs annually [21,22]. Each of these factors ultimately affect the patients compliance in a negative way, thus limiting the therapeutic efficacy of PPI.

1.2.3 Anti-reflux surgery

Anti-reflux surgery is often proposed as an alternative therapy for GERD patients, especially for patients who in principle, respond to PPI therapy but complain of side effects or do not wish to remain on chronic PPI treatment [23]. Anti-reflux surgery is designed to raise the tone of the LES by wrapping a mobilized part of the gastric fundus around the esophagus. With the advent of laparoscopic anti-reflux surgery, the two commonly used procedures are the Nissen fundoplication and the Toupet partial fundoplication [24]. The most frequently used surgical procedure, Nissen fundoplication (open or laparoscopic), comprehends the mobilization of the lower end of the esophagus and plication of the fundus of the stomach around it [25]. The surgery is usually performed on the day of admission and takes about 60-90min. In general, patients can be discharged from the hospital on the second post-operative day and return to work in 7 to 10 days. Other surgical options include Belsey partial fundoplication as well as Collis gastroplasty combined with Belsey partial fundoplication. Dependent on the skills and experience of the operating surgeon, anti-reflux surgery has been reported to have an efficacy rate of 90% [23].

Although anti-reflux surgery turns out to be safe and effective, several drawbacks of it are still prominent. The first one is the surgical risk. Despite being a minimally invasive procedure,

laparoscopic Nissen fundoplication (LNF) is associated with potential invasive risks and hospital stay [26]. While the risk for serious adverse effects following anti-reflux surgery is comparatively low, there is a number of well-recognized side effects associated with this procedure. Most of them are related with the integrity of the fundoplication. In some cases, the wrap is too high on the esophagus or too tight which can cause dysphagia or inability to vomit. Other reported symptoms include gas bloating, and uncontrolled flatulence [26,27]. The third one is the durability of LNF. In a previous study, it was reported that 10 years after anti-reflux surgery, 35.8% of partial PPI responders reported heartburn and 29.1% reported regurgitation. 18.2% patients resume PPI treatment for symptom management on 10 years follow-up [28]. Another drawback of anti-reflux surgery is re-operation. The complications from the fundoplication in a minority of patients may lead to a re-operation. Vignal et al. [29] did a study which included 595 patients. 7.9% patients (47/595) had required re-operation at a 16-year follow-up.

1.2.4 The "Therapeutic gap" between medical treatment and anti-reflux surgery

Although anti-reflux surgery has an established role in the treatment for GERD, the fact is that only 1-2% of all patients with GERD actually receive anti-reflux surgery [30]. It can only be done in selected patients with GERD. The relative contraindications include diagnoses where symptom overlap exists with GERD, but GERD is not the underlying etiology, patients with functional disorders, and patients unfit for surgery. So-called "secondary reflux disease" cases, such as patients diagnosed with gastroparesis, eosinophilic esophagitis, or collagen diseases are also not candidates for surgery [21]. Finally, for many patients, the "invasiveness" jump from PPIs to a laparoscopic fundoplication is just too great. Therefore, a large proportion of patients with incomplete symptom relief are stuck in the "therapy gap" that exists between

medical and surgical therapy. Not surprisingly a multitude of alternative options were attempted. Besides of countless modifications of the surgical approaches, the so-called "Angelchik" device deserves special notion which was temporarily in use about 30 years ago [31,32]. It was a sausage shaped silicone implant which was positioned around the cardia to stop reflux. Implantation was by far easier and faster than doing a fundoplication and the stay in the hospital was significantly shorter. So far, it was the first minimally invasive approach in anti-reflux surgery. Though it was effective in reflux prevention, it was soon left because of severe side effects. The foreign body around the cardia caused perforation or migrated [33].

Currently, at least three different less invasive alternatives to laparoscopic fundoplication are under evaluation (Figure 1):

1) LINX system The LINX system (LINX Reflux Management System; Torax Medical, Shoreview, MN) is a sphincter augmentation magnetic device which can be laparoscopically implanted at the GEJ to prevent reflux due to abnormal opening of the LES [34]. The aim of this procedure is to improve the barrier function of the sphincter without altering the hiatal and gastric anatomy or interfering with swallowing, belching, or vomiting. Previously studies reported the device not only decreased exposure to esophageal acid, improved reflux symptoms, but also allowed cessation of proton-pump inhibitors in selected patients with GERD [34,35]. The placement of a foreign body around the esophagus raises concern about erosion and hence the safety of the device. To date, severe erosions or migrations seem to be rare [36]. The risk over a longer period of follow-up is not known. The continued collection of data from the present study, existing registries, and current clinical use will allow assessment of the long-term risk of erosion.

2) Electrical stimulation of the LES is another therapeutic attempt. The LES stimulation system (EndoStim BV, The Hague, The Netherlands) can be implanted in the muscular layer at the anterior aspect of the LES using a conventional laparoscopic approach and under endoscopic visualization of the GEJ [37]. Previous studies in both animals and humans have demonstrated that electrical stimulation of the LES can increase resting LES tone. The procedure appears safe, with no significant perioperative complications noted and no post-procedure dysphagia reported [36,38]. However, long-term results, sham-controlled trials comparing LES stimulation with no-stimulation and comparative effectiveness trials with maximal anti-reflux therapy are still needed to further elucidate the role of LES stimulation in the management of GERD.

3) Endoluminal (flexible endoscopic) treatment It is an even more attractive alternative treatment of GERD. The idea is not entirely new but remains to be convincing. If it were possible to restore the valve function of the LES without surgery and general anesthesia via a flexible endoscopic treatment, the advantages would be evident. Even patients who are unwilling to undergo “real” surgery can be treated. The procedure is less time consuming than laparoscopic surgery, does not induce outside scars and is painless. Hospitalization is very short. Theoretically, endoluminal endoscopic treatment of GERD would, thus, be the ideal alternative to the life long medical treatment or surgical anti-reflux interventions. However, after more than 15-20 years of clinical trials with various techniques, a real breakthrough has not yet been reached. It is the purpose of this study to evaluate whether some comparatively new technique could be capable to acquire a relevant role in the clinical arrangement of reflux treatment.

Development of a minimally invasive endoscopic anti-reflux therapy as an alternative to chronic prescription drug use, without the morbidity related to surgery has attracted a great deal of interest. It could possibly close part of the "gap".

1.3 Rationale of endoluminal therapy for GERD

The fundamental abnormality in GERD is the pathological exposure of esophageal or supra-esophageal epithelium to gastric juice, resulting in mucosal injury or the elicitation of symptoms [39]. Some degree of gastro-esophageal reflux and esophageal acid exposure is considered normal or "physiological" associated with gas venting and belching. GERD results when the balance between what the epithelium is exposed to (related to the frequency of acid reflux, the effectiveness of acid clearance, and the causticity of that reflux) and what that epithelium can tolerate tilts in favor of the aggressive forces. Significant aberrations in one or more potential pathophysiological factors that augment the aggressive forces or deplete the defensive forces can result in shifting from a compensated condition to a decompensated one with the ensuing development of esophagitis or reflux symptoms [39,40]. Esophago-gastric junction (EGJ) competence is the most fundamental defensive factor preventing the complications of GERD [41], and also the focus of endoscopic therapies for GERD that are the subject of this manuscript. Although esophageal acid clearance, tissue resistance and causticity of the refluxate are also important factors in the pathogenesis of GERD, endoluminal therapies do not primarily target these pathophysiologic mechanisms. They primarily aim at the reinforcement of the LES.

Under normal conditions, reflux of gastric juice into the distal esophagus is prevented as a function of EGJ competence which maintains a closed barrier between the esophagus and the

stomach. The EGJ is an anatomically complex zone whose functional integrity as an anti-reflux barrier has been variably attributed to a number of factors: 1) intrinsic lower esophageal sphincter (LES) pressure, 2) extrinsic compression of the LES by the crural diaphragm, 3) the intra-abdominal location of the LES, 4) integrity of the phrenoesophageal ligament, and 5) maintenance of the acute angle of His promoting a "flap valve" function. Each of these components is operant under specific conditions and the global function of the EGJ as an anti-reflux barrier is dependent on the sum of the parts. The greater the dysfunction of the individual components that help maintain EGJ competence, the worse the overall anti-reflux function of the EGJ and as a consequence the severity of GERD [41].

Based upon these pathogenetic aspects of GERD, the mode of action of endoluminal therapies can be explained. All of these methods are intended to alter the mechanical properties of the EGJ to reduce the occurrence of reflux and, perhaps, the volume of the refluxate.

1.4 Overview of endoluminal therapies for GERD

The development of anti-reflux endoluminal therapy was an attempt at correcting GERD's pathophysiology by increasing the lower esophageal sphincter (LES) pressure, reducing the frequency of transient LES relaxation (TLESR), anti-reflux barrier construction, attenuation of esophageal sensation against refluxate, and anatomical reconstruction improving the angle of His or cardia for flap valve creation [42,43]. Some 30 years ago, the first endoluminal procedure was described by Swain and Mills [44]. Since then, many additional products appeared in the market. Generally, they can be divided into four groups: suturing or fundoplication techniques (EndoCinch, Plicator™ system， EsophyX®, MUSE™ system and

GERDX™ system) which aim at positioning sutures at the cardia, intramural injection or implants techniques (Enteryx, Gatekeeper) which create an anti-reflux barrier by a bulking effect at lower esophageal sphincter (LES) [45], radio frequency (Stretta, Mederi Therapeutics), which should reduce heartburn by causing contraction or stricturing of the LES, anti-reflux mucosectomy which attempts to shrink and remodel the gastric cardia flap valve by the scar formation after the mucosal resection [46] (Figure 1).

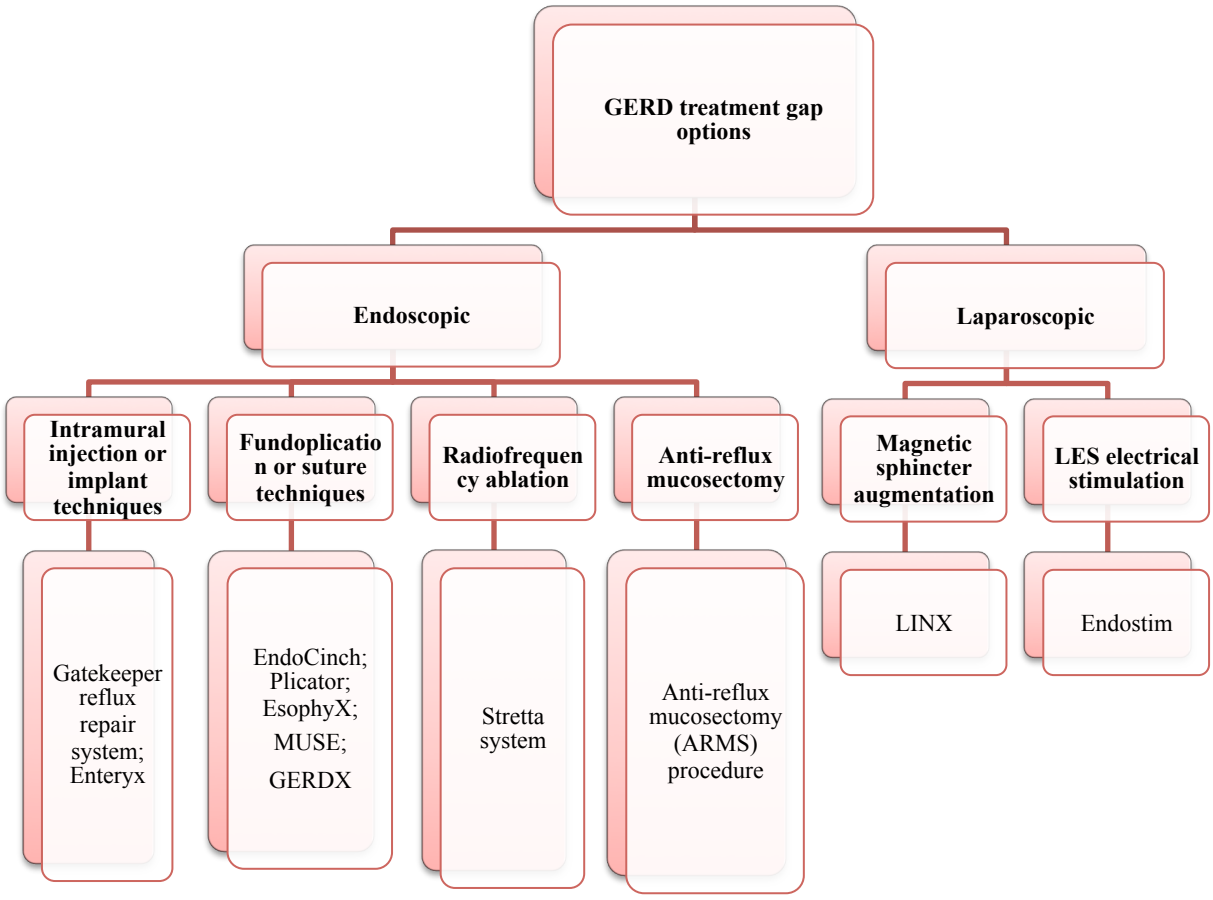


Figure 1 GERD treatment gap options: Endoscopic and laparoscopic techniques, classified according to different mechanisms to stop the reflux.

Although these endoluminal therapies seemed to be promising, many of them have shown poor long-term results. Products for intramural injection or implant technique were entirely removed from the market due to unsatisfactory benefits and various degrees of complications [45,47]. Currently, there are three endoluminal therapeutic procedures being used clinically-radio frequency treatment with Stretta system, anti-reflux mucosectomy and endoluminal fundoplication or suturing techniques with the EndoCinch, the Plicator™ system, the EsophyX®, the MUSE™ system and the GERDX™ system.

1.4.1 Stretta system

The Stretta procedure is one of the earliest endoscopic devices conceived to treat reflux. It was first FDA approved in 2000. The device consists of an ablation catheter and an electrical generator unit. The ultimate goal of the procedure was to augment the tone and integrity of the LES. 4 electrodes are inserted into the LES with RFA energy delivered under controlled temperature to produce a coagulation inflammation, necrosis, and fibrosis, causing contraction or stricture of the LES [48]. Accordingly, this procedure will do very little to improve the intrinsic LES function as the mechanism of action is defined as inducing fibrosis in the submucosa and muscle. Hence, this would lead to a less compliant distal esophagus and not impact the muscular function of the LES.

Published reviews of the literature are equivocal in their recommendations of Stretta in the management of GERD [49,50] The Stretta system revealed promising results with early open label trials. However, the randomized sham controlled trials did not support the findings of the open label trials [45,51]. The most recent systematic review concluded that was no evidence for the efficacy of Stretta system for the treatment of GERD [50]. High quality

evidence suggests that the Stretta procedure only provides a mild subjective improvement in symptoms but no objective improvement in reflux burden, EGJ function or reduction in PPI utilization [46,51]. The mechanism of the symptom improvement has been postulated to be related to alteration in esophageal visceral afferent fibers resulting from thermal injury. The lack of improvement in objective parameters, along with complications noted that are not much less frequent or severe compared to fundoplication make this approach less attractive.

1.4.2 Anti-reflux mucosectomy procedure

The mechanism of anti-reflux mucosectomy procedure (ARMS) is presumed to be due to scar formation after healing of the mucosal resection. This in turn results in shrinkage and remodeling of gastric cardia flap valve which strengthen the anti-reflux barrier and lead to the reduction of reflux events. Although the first case was performed more than a decade ago, the results of the first series were published in 2014 [52]. In the published pilot study including 10 patients, there was reduction in esophageal acid exposure (EAE) and improvement in flap valve grade observed on endoscopic examination. In addition, all of the patients could discontinue PPI after the ARMS therapy [52]. The advantages of ARMS include no requirement of any proprietary devices and no endoprostheses are left *in situ*. However, no randomized studies have been conducted so far, and durability of response is unknown either. In addition, the amount of mucosa to be resected for optimal results is not known and needs further evaluation. Furthermore, ARMS is only suitable for selected patients without hiatal hernia. Larger randomized studies with objective assessment and a longer follow-up are needed to prove the efficacy and durability of this procedure.

1.4.3 Endoluminal suturing techniques

Endoluminal suturing techniques aim at LES augmentation by emphasizing the lips of the cardia and re-shaping the angle of His. Among the presently available three techniques, this kind of technique has shown some promise in previous studies. Five different variants are available. They are the EndoCinch, the Plicator™ system, the MUSE™ system, the EsophyX® and the GERDX™ system. However, not all of them have shown good results. Some of them have shown poor long-term results. Among them, the EndoCinch and the Plicator™ system are no longer available on the market, and the EsophyX® is only available in the United States to date (Table 1).

1.4.3.1 EndoCinch suturing system

EndoCinch suturing system (C.R. Bard Inc., Murray Hill, NJ, USA), the landmark procedure, was first described by Swain and Mills in 1986 [44] and was subsequently approved by the FDA in April 2000. The plication achieved by EndoCinch is mucosal, and unlike the other products, it is not full thickness. The device is mounted on an endoscope and designed to create two, three or more plications at or below the esophagogastric junction (EGJ). It has been a popular option based upon well-studied research [53]. A substantial number of clinical trials of EndoCinch treatment have been published. Most of them were open-label with short to intermediate-term follow-up. Most complications associated with EndoCinch were mild and self-limited, such as a sore throat. Only a few severe adverse events were reported [54-57]. Mahmood et al. [55] reported three severe adverse events (defined as those events that were fatal or life-threatening or required prolongation of a current hospitalization) among twenty-six patients in their study. These events included two post-procedure bleeding and one gastric

mucosal tear. One post-procedure bleeding was also reported by Schwartz et al. [58]. With regard to safety, EndoCinch seems to be a relatively safe procedure.

Many studies have evaluated the short-term or intermediate-term efficacy of EndoCinch [54-56]. Among previous EndoCinch studies, two randomized, sham-controlled trials have been conducted. One of the randomized, sham-controlled study done by Schwartz et al. reported that despite early symptom improvement, EndoCinch failed to support a sustained symptom improvement. It also produced no significant control of the esophageal acid exposure [58]. The findings were confirmed in another sham-controlled RCT [59].

Studies for EndoCinch suggest that this device is relatively safe, but some severe adverse events can still happen during clinical use. There may be a possible modest, short-term benefit in clinical symptoms and medication, but this benefit is not durable. The lack of long-term benefit may be related to the loss of plications or the inability of the device to provide a full-thickness plication. Based on a number of studies to date, no strong evidence can support the conclusion that the EndoCinch device is clinically useful for the long-term management of GERD. This finding may be the main reason for which this device is no longer available (Table 2).

1.4.3.2 Plicator™ system

As the second endoluminal sphincter augmentation product, Plicator™ (NDO Surgical, Inc., Mansfield, MA) is slightly different from EndoCinch which involves only mucosal plication. The Plicator™ system was approved by the FDA in 2004 for the endoscopic treatment of GERD [60]. It consists of the reusable Plicator instrument, a single-use cartridge containing a suture-based implant, and a specially designed endoscopic tissue retractor. It accomplishes the

sphincter augmentation by delivering a transmural suture to create a full-thickness plication of the anterior gastric cardia.

According to previous studies, the Plicator™ system appears to be largely free of major complications and is generally well tolerated [61-63]. The majority of adverse events reported in previously published reports were mild and resolved spontaneously. Common adverse events after the procedure included abdominal pain, shoulder pain, chest pain, and sore throat. These events occurred either in the immediate 48-hour post-treatment phase or within 1 week of the procedure [61]. Severe adverse events were also reported. Pleskow et al. [62] reported three of 29 total patients developed severe adverse events after the procedure. Two patients developed dyspnea during the procedure shortly after placement of the overtube, and the third patient experienced a mucosal abrasion in the fundus due to instrument manipulation during the procedure. Other severe adverse events may have been associated with an inadvertent diaphragm injury during the deployment of the plication. Chuttani et al. reported some severe adverse events in their studies, including pneumothorax, pneumomediastium and perforations of the stomach [63].

Earlier studies have demonstrated the short-term and long-term efficacy of the Plicator™ system. Regarding the short-term result, one sham-controlled RCT performed by Rothstein et al. [64] was found. This study evaluated the 3-month results after the Plicator™ system procedure. Seventy-eight patients were randomly assigned to the Plicator™ group, and 81 patients were assigned to the sham group. Both the subjective data and objective data were evaluated and compared between groups at the 3-month follow-up. Both the improvement in symptom scores (56% vs. 18%, respectively, $P<0.05$) and the rate of discontinuation of PPIs are higher in the Plicator™ group than in the sham group (50% vs. 24%, respectively, $P<0.05$).

Regarding the pH data comparison, the percent reduction in median percent time at pH <4 was significantly improved with 18% in the treatment group but not in the sham group (-3%). Another open-label prospective study evaluated the 12-month follow-up results [65]. The follow-up was completed in 81 patients at seven centers. This study reported that 66% patients achieved symptom control and 58% patients achieved the discontinuation of PPIs at the 12-month follow-up. Regarding the long-term efficacy of the Plicator™ system, Pleskow et al. [62] reported five-year follow-up results. Thirty-three patients completed the 5-year follow-up in this study. At five-year follow-up, 50% of subjects achieved symptom control, Only 67% of subjects remained off daily PPI medication at the end of the follow-up. However, no additional objective data about pH or manometry were found in most long-term follow-up studies.

The data from the previous studies are encouraging. The Plicator™ system is relatively safe and effective in GERD symptoms control and PPI discontinuation. However, very few existing studies have demonstrated that it can improve the objective data and effectively reduce esophageal acid exposure. Further studies and long-term data regarding the safety and efficacy of this procedure would be necessary to define the value of the Plicator™ system. However, the company ceased operations in 2008, and the device is no longer clinically available [66,67] (Table 1).

1.4.3.3 EsophyX®

As one of the promising endoluminal sphincter augmentation products, the EsophyX® device (EndoGastric Solutions, Inc., Redmond, WA, USA) with serosa-fuse fasteners was designed to realize sphincter augmentation by reconstructing a full-thickness valve at the gastro-esophageal junction through tailored delivery of multiple fasteners during a single device

insertion. Because it also creates full-thickness plication, it is similar to the Plicator™ system. The main difference is the ability to perform circumferential, transmural plications with EsophyX®. The EsophyX® device was approved by the FDA in 2007 for the endoscopic treatment of GERD. The device consists of a flexible catheter that contains a tissue retractor and fasteners. The endoscope fits within this catheter. It is placed orally, and with the endoscope retroflexed in the stomach, the tissue retractor facilitates the apposition of the gastric cardia to the distal esophagus [68].

The EsophyX® system offers two different generation products. Despite the safety of both generations products are supported by previous studies [69, 70], some severe short-term adverse events also occurred following the use of both generation EsophyX® devices. According to previous reports, the incidence of severe adverse events is between 2.4% and 15.8% [71, 72]. The most common severe adverse events included perforations, post-procedure bleeding, pneumothorax, esophageal leak, and epigastric pain [71,73]. Mediastinal abscess is also common among the short-term complications [70].

Compared with other endoluminal sphincter augmentation products, the studies on EsophyX® device have reported the efficacy and persistency of the procedure at six months in most studies and for up to six years in one study. Both subjective data and objective data were analyzed in these studies, which include some double-blinded and sham-controlled studies.Håkansson et al. reported the short-term follow-up results of a double-blind sham-controlled study. At the 6-month follow-up, the symptom control, PPI consumption, and esophageal acid exposure were assessed and compared between the groups. Both subjective data and objective data were all in favor of the endoluminal sphincter augmentation using

EsophyX® procedure. Limitations of this study include its small size and limited follow-up duration [74].

Another prospective, sham-controlled trial was performed by Hunter et al. The investigators screened 696 patients with troublesome regurgitation despite daily PPI use. Patients with GERD and hiatal hernias (≤2 cm) were randomly assigned to groups that underwent sphincter augmentation using EsophyX® and then 6 months of placebo (n=87) or sham procedure and 6 months of once- or twice-daily omeprazole (controls, n=42). At the 6-month follow-up, the EsophyX® procedure eliminated the reflux symptoms in a larger proportion of patients than PPIs (67% vs. 45%, respectively, $P<0.05$). Regarding the objective data, the control of esophageal pH improved after the EsophyX® procedure (mean 9.3% before vs. 6.3% after, $P<0.001$) but not after sham surgery (mean 8.6% before vs. 8.9% after) [75].To evaluate the long-term efficacy of the EsophyX procedure, Testoni et al. followed patients for up to six years. Regarding symptom control, symptom scores off PPI were significantly lower at 12, 24, and 36 months. Regarding PPI usage, 79.6%, 87.8%, and 84.4% of patients stopped or halved the PPI therapy at 12, 24, and 36 months, respectively, after endoluminal fundoplication using EsophyX. The three-year figure remained stable up to 6 years. Impedance monitoring indicated significantly fewer total and acid refluxes after treatment ($P<0.05$) [76]. (Table 1).

Table 1 Endoluminal products using fundoplication or suturing technique

Products	Design	SAEs	Efficacy	Reasons withdrawal
EndoCinch	1) Mounted on an endoscope; 2) Mucosal plication.	0-13% (hypoxia, bleeding, gastric mucosal tear)[54-57].	1) Symptoms control: 60%-75% (slightly persisted to 12-month) [54,58]; 2) PPI discontinuation: 50%-65% (gradually decreased till 12-month follow-up [58,59].	Lack of durability [59].
Plicator™ system	1) Consists mainly of a Plicator instrument; 2) Full thickness plication.	0-1.5% (dyspnea, pneumothorax, pneumomediastium, perforation)[61,63].	1) Symptom control: 50-65% (persisted to 5 years)[62, 64-65]. 2) PPI discontinuation: 50-67% [62, 64-65].	Economical problems [66,67].
EsophyX®	1) Consists mainly of a flexible catheter; 2) Full thickness plication.	0-3% (perforation, bleeding, pneumothorax, esophageal leak, mediastinal abscess) [70-73].	1) Symptom control: 45-86%, average 69% [77-82]; 2) PPI discontinuation: 55-82%[77-83]. 3)	Not clear. Only available in the US now [82,83].
MUSE™ system	1) Consists mainly of a video- and endostapler; 2) Full thickness plication by stapling.	0-9% (esophageal perforation, pneumothorax, empyema, bleeding)[84-86]	1) Symptom control: 73-82% (persisted to 5-year)[84, 86-87]. 2) PPI discontinuation: 64-69.4%[76, 86-87].	Available on the market.
GERDX™ system	1) Based on the Plicator™ device; 2) Full-thickness plication [61,63].	0-8% (pneumonia) [88,89].	1) Symptom control: 83% (6-week follow-up)[89]. 2) PPI discontinuation: 83% [89].	Available on the market.

Note: SAEs: severe adverse event.

Although most results concerning endoluminal sphincter augmentation using EsophyX seem promising, device improvements should be made to reduce the procedure failure and the

risk of severe adverse events. Further studies are needed to identify the most appropriate subjects for this therapy. However, for some reason, it is not available both in Europe and most Asian countries any longer.

1.4.3.4 MUSE^{TM} system

The MUSE^{TM} device (Medigus Ultrasonic Surgical Endostapler , MUSE™, Medigus. Omer, Israel) applies anterior fundoplication to augment the barrier function of the lower esophageal sphincter. It was cleared by the FDA in 2014 and became CE-marked for use in European countries for the treatment of GERD in patients who require and respond to PPIs [84].

The MUSE™ system contains a video- and ultrasound-guided transoral flexible surgical endostapler and a digital console connected with it. With the ultrasound guidance, violation of surrounding structures can be avoided while the stapler is constructed to allow for a lasting and secure suturing of the gastric wall. Unlike other procedures, MUSE™ closely mimics surgical anterior fundoplication through transoral stapling. It enables a single operator to perform transoral partial fundoplication. It differs from all other sphincter augmentation procedures since it realizes augmentation by stapling which supposedly is more reliable than suturing. Furthermore, the ultrasonic range finder is engaged to display the thickness of the tissue that is ready for stapling when the direct visualization is impossible.

Only two clinical studies on this device are available until now. The first study by Danalioglu et al. reported one severe adverse event out of 11 patients after the procedure. One patient experienced chest pain and odynophagia soon after the procedure. This event was related to esophageal perforation, which completely recovered after over-the-scope clipping [85]. Two severe adverse in 69 patients were reported in another multi-center, prospective

study, including one empyema and pneumothorax, which were due to esophageal leak and upper gastrointestinal bleeding, respectively. However, neither event was life-threatening [84]. Both patients recovered smoothly after proper treatment. Esophageal perforation and leak turned out to the most common safety problem. Except for these severe adverse events, additional mild adverse events were reported for 5%-22% of patients. Among them, the most common were chest pain and sore throat after the procedure. The others included atelectasis, pain in the shoulder, and belching. All these resolved spontaneously and the majority of them were reported in the first 24-hour after the procedure only [84].

From the available two studies on the MUSE^{TM} device, both short-term and long-term results are available. Regarding the evaluation of the short-term efficacy, one study reported the outcomes of sphincter augmentation with the MUSE^{TM} device six months after the procedure [84]. Subjective data and clinical complaints, which were reflected by the GERD-HRQL score, improved by >50% in 73% (48/66) of patients. Regarding objective data, both PPI usage and esophageal acid exposure were evaluated. Regarding PPI usage, forty-two patients (64.6%) were off daily use of PPIs and of the 23 patients who continued to take PPIs following the procedure, 13 (56.5%) reported a ≥50% reduction in dose. Regarding esophageal acid exposure, the mean acid exposure as indicated by an esophageal pH <4.0 significantly decreased from baseline to 6 months (10.9% vs. 7.3%, respectively, P<0.001). For the same study, the 4-year follow-up results were available for 37 patients [78]. At the 4-year follow-up, the subjective data, reflected by the GERD-HRQL scores, significantly decreased from 29.1±5.6 to 8.9±8.3 at 6 months and 5.3±5.8 at 4 years post-procedures (P<0.01, compared to baseline and 6 months.) [84]. Regarding the objective data, the proportion of patients who remained off daily PPI use decreased from 83.8% at 6 months to 69.4% at 4 years (25/36).

However, regarding the esophageal acid exposure, no significant difference was observed for the percent of total time exposed to an esophageal pH <4.0 from the baseline to the 4-year follow-up (12.7% vs. 11.2%, respectively, *P*>0.05). As the collective for the 6 months assessment and 4 years follow-up was different, it is unclear whether the results indicate an lasting effect or if this is only simulated by a selection of patients that profited. According to the 4-years follow-up publication long-term follow-up included only patients of one center but not on the whole multi-center collective that was investigated after 6 months (Table 2). A second study on the MUSE™ device reported on long-term follow-up outcomes for 13 patients [87]. At the 5-year follow-up, regarding symptom control, 77% (10/13) patients showed at least 50% improvement in their off PPI GERD-HRQL scores. Regarding the PPIs usage, 64% (7/13) of patients had stopped, and another 23% (3/13) reduced PPI usage by 50% or more. However, no pH results were available in this study. Additionally, the study cohort was comparatively small and does not allow for reliable conclusions. However, results were almost equal to the study published by Zacherl et al.

From the available two studies, the results are promising. However, the small number of enrolled patients and the lack of a sham or control group are two important limitations of the studies presently available. Further study is needed to determine the safety and efficacy of endoluminal sphincter augmentation with the MUSE™ device.

1.4.3.5 GERDX™ system

As a new endoscopic antireflux system appeared on the market, GERDX™ system (G-SURG GmbH, Seeon-Seebruck, Germany) was designed based on the technology of the Plicator™ device and delivers transmural sutures to create a full-thickness plication of the anterior

gastric cardia to realize the augmentation of the barrier function of the LES. It got CE-marked for use in the European Union for endoscopic fundoplication for the treatment of GERD in patients who require and respond to PPIs. The GERDX^{TM} system includes an applicator instrument and an implant cartridge. The procedure is performed following a standard GERDX^{TM} system protocol under general anesthesia with endotracheal intubation in an operating room or an endoscopy unit by a team of a two-surgeons (surgeons and/or gastroenterologists). So far, two published studies concerning this new device exist. However, several clinical studies of this device have been in progress. Since the GERDX^{TM} system resembles the technology of the Plicator™ device, Spaun et al. did a study which compared the safety of endoluminal sphincter augmentation with Plicator^{TM} system to the augmentation with GERDX^{TM} system. Earlier studies have proved that the Plicator^{TM} system appears to be largely free of major complications and is generally well tolerated [61,65-66,71]. In this study, GERDX^{TM} system turned out to be safe and well tolerated as well as Plicator^{TM} system [88]. In another study done by Koch et al. reported that one patient among 13 patients who have accepted the procedure developed pneumonia after the procedure and required treatment with antibiotics. However, the complication was effectively controlled in a short time, the patient successfully recovered and was discharged [89].

The presently available preliminary short-term results of a prospective multi-center trial reported that the GERDX^{TM} system can improve symptom parameters as well as the esophageal acid exposure and improve the discontinuation rate of PPI medication. In this prospective study, routine gastroscopy has been performed in 12 patients, and an intact wrap was found in 10/12 (83%) patients, who were subjectively free of GERD symptoms. Two patients showed partly dispersed plication and also claimed persisting symptoms (2/12, 17%).

Both symptom scores and esophageal acid exposure improved after the GERDX™ system procedure [88].

Despite good safety and efficacy results have been got by the two previous studies, there is still a long way to go before the value of GERDX™ system can be reliably confirmed. Admittedly, it can be taken as a next generation device of the Plicator™ system with lots of good and validate data available, that support its functionality and effectiveness in principle. However, even then some further improvements, such as the reduction of the outer diameter of the overtube to ease advancement, modalities that allow for assessment of reliant and comptete suturing, and optimal number of sutures needed, seem necessary for GERDX™ system.

In conclusion, relevant scientific researches have reported some achievements of different endoluminal augmentation products by the present available three techniques, radio frequency treatment with Stretta system, ARMS, and suturing or fundoplication techniques with either the EndoCinch, Plicator™ system, EsophyX®, MUSE™ system or GERDX™ system. While most of available data suggest the Stretta procedure having an acceptable safety profile, the most recent systematic review concluded that there is no evidence for the efficacy of the Stretta system in the treatment of GERD [50]. The suturing or fundoplication technique seems to be promising. However, the EndoCinch and the Plicator™ systems are not available on the market any more (Figure 1). The EsophyX® device, as been reported in many studies, is available in Europe from 2008 to 2011. It is no longer available in Europe and most Asian countries at present (Figure 1). In our hospital (Klinikum rechts der Isar), we began to do endoluminal fundoplication with EsophyX® for GERD therapy in 2008 as long as it was available in European countries. However, it was no longer available in Europe since 2011 for some reason. As soon as it was no longer delivered, we switched to the second new device, the

GERDX™ system. In this study, we aim to evaluate the safety and efficacy of the EsophyX® device and the GERDX™ system for endoluminal sphincter augmentation on the treatment of GERD. By evaluating them both for the treatment of GERD we try to answer the question, whether the gap in anti-reflux therapy can be finally closed and whether there is a safe and less invasive interventional technique available which can avoid the need for PPIs intake.

1.5 Aims of this work

A less invasive interventional complement to laparoscopic fundoplication (LF) would be highly desirable since at least 1/4 of all patients treated with PPI are not completely content with the results [90], but only less than 1 % of these patients unhappy with medical treatment get an operation [30]. Obviously, there is a "therapeutic gap" which should be closed. The purpose of this work is two fold:

1) **To determine precisely the extent of the "therapeutic gap" in our own group of patients.** This includes a description of why medical treatment was not applicable/successful and why surgical treatment (fundoplication) was not performed.

2) **To evaluate the role of endoluminal anti-reflux treatment under practical conditions as an alternative treatment option to fundoplication.** After different attempts with various methods like submucosal infiltration etc. in our own patients, we focused on endoluminal fundoplication or suturing techniques since November 2008. By analyzing the short- and mid-term results, a first impression should be gained whether these promising new approaches are suitable to bridge – at least in part – this obviously existing therapeutic gap.

In particular, this study aimed at evaluating and comparing the safety and efficacy of endoluminal sphincter augmentation with the EsophyX® device and the GERDX™ system by doing a controlled follow-up study of patients with documented GERD and persistent or recurrent symptoms despite treatment with PPI in our hospital (Klinikum rechts der Isar).

2 Materials and Methods

2.1 Patients

All patients were included into this study who were referred to the laboratory for functional gastrointestinal diagnostics because of suspect esophageal reflux disease since 2008. 2008 was defined as the starting point, since endoluminal treatment became a standardized treatment option at our department with the beginning of that year. The proportion of patients who received medical treatment, anti-reflux surgery (fundoplication) or endoluminal treatment was annually determined.

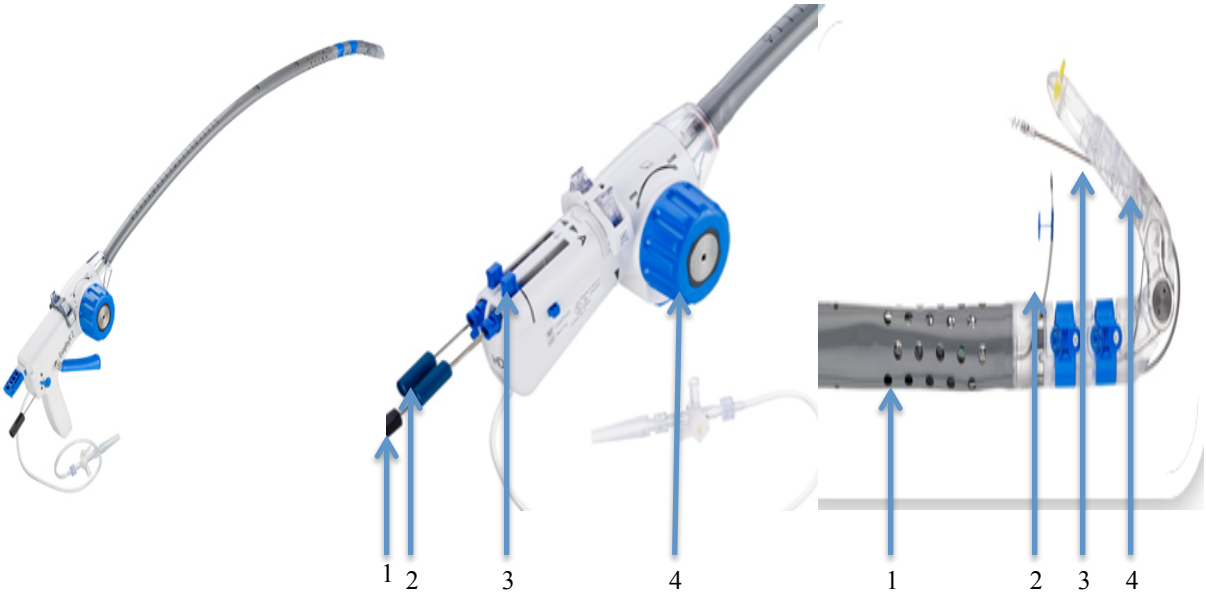
All patients who had been treated either by EsophyX or GERDX procedure had a follow-up using a standardized questionnaire and a telephone interview (December 2016/January 2017). Each of them was invited to have a functional check-up in case of complaints.

2.2 Devices and details of the procedures

2.2.1 EsophyX®

The EsophyX® device (EndoGastric Solutions, Inc., Redmond, WA, USA) (Figure 2) is composed of a handle, wherein the various controls are located, a chassis of 18 mm in diameter through which the endoscope is inserted and control channels run, side holes on the distal end of the shaft to which external suction can be applied (the tissue invaginator), a tissue

mold, which when brought into retroflexion pushes tissue against the shaft of the device, a helical screw, which is advanced into tissue to pull tissue caudally between the tissue mold and the shaft, two stylets, which advance from the shaft of the device through the plicated tissue and then through eyelets in the tissue mold, and a cartridge containing polypropylene H-shaped fasteners (or plicators), which are deployed over the stylets so that the trailing leg engages within the esophageal lumen and the leading leg engages within the gastric lumen [70].



A B C

Figure 2 EsophyX$_2$® device.

A: General view of the device. B: Close view of the control handle. The control handle mainly consists of: the retractor control (arrow 1), the fastener pushers (arrow 2), the stylet controls (arrow 3), the tissue mold knob (arrow 4); C: Close view of the working end. The tissue invaginator (arrow 1), enables to aspirate the esophageal tissue circumferentially and facilitates proper position of the fold caudal to diaphragm; The stylet and fastener (arrow 2), which approximates the tissue and maintains tissue compression throughout the healing process; The retractor (arrow 3), which engages and retracts the tissue, anchor gastro-esophageal junction during fundoplication; The tissue mold and chassis (arrow 4) which plicates and compresses the tissue. It rotates the fundus around the esophagus to create a partial wrap (arrow 3), which locks safely inside the tissue mold during insertion and removal.

The procedures were performed following a standard TIF2.0 protocol under general anesthesia with either nasal or transoral intubation by a team of two physicians (surgeons and/or gastroenterologists) [91,92]. The first physician controls the implantation of fasteners using the EsophyX device, and the second operates the endoscope and ensures continuous direct visualization. The device is inserted transorally into the esophagus with the patient in the prone position. The hiatal hernia, if present, is reduced by returning the squamocolumnar junction to its natural position below the diaphragm by fixing the esophageal wall by means of aspirating it to the shaft of the device. If the instrument is, then, advanced, the esophagus will be stretched automatically and lengthened. Plication is performed by deploying multiple H-shaped polypropylene fasteners, starting on the far posterior and anterior sides of the gastro-esophageal junction; then additional fasteners are deployed along the greater curvature part of the valve by rotating the tissue mold axially to slide the stomach over the esophagus. During a single insertion, a valve similar to that created by anti-reflux surgery is reconstructed by retraction of full-thickness plications and tailored placement of multiple fasteners circumferentially around the GE junction starting on the greater curve side of the valve [92] (Figure 3).

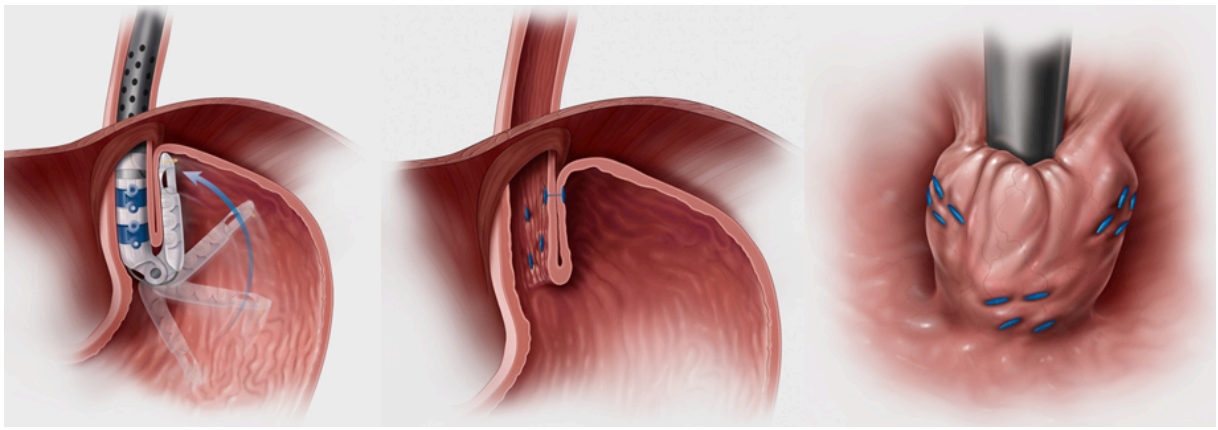


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Figure 3 EsophyX procedure overview.

A：The EsophyX® device is inserted into the esophagus through the mouth and is positioned at the junction of the stomach and esophagus. A small hiatal hernia is reduced by engaging suction (invaginator) and positioning the esophagus below the diaphragm. B: A full-thickness tissue fold at the gastro-esophageal junction is retracted, wrapped and anchored using implantable fasteners- equivalent to 3.0 sutures-which are delivered across the tissue to complete the plication. C: The valve is extended and multiple fasteners are delivered with a single device insertion. The TIF procedure reconstructs the primary components of the anti-reflux barrier, creating a tight 3-5cm valve enveloping the distal esophagus below the diaphragm.

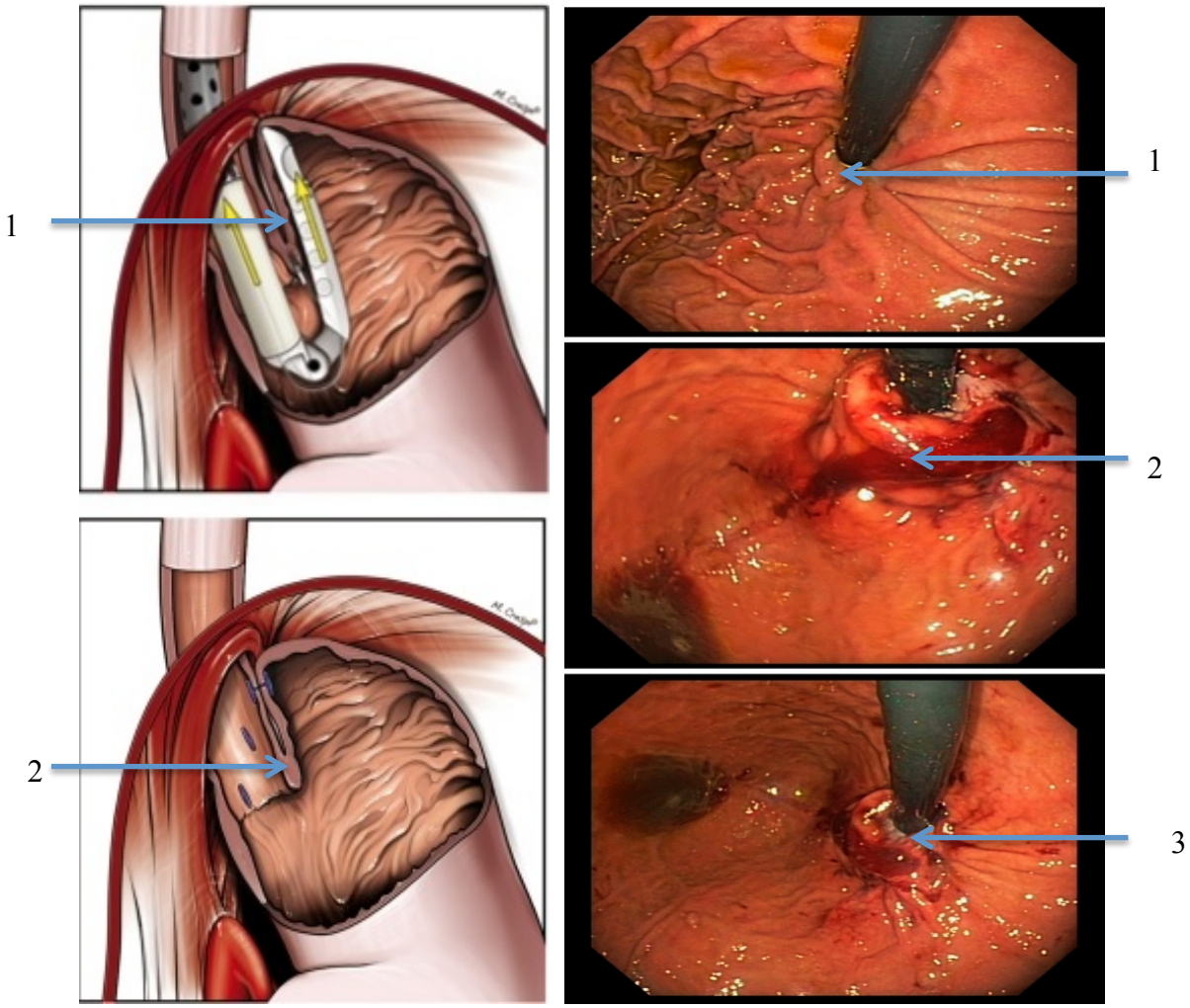


Figure 4 The schematic diagram of TIF2.0 procedure and the endoscopic images pre-and post-the procedure.

A: Schematic diagram of TIF2.0 procedure. B: Endoscopic images: The endoscope and the device are retroflexed and a helical retractor is engaged into the tissue slightly distal to the Z line. The fundus of the stomach is folded up (arrow 1) and around the distal esophagus utilizing the tissue mold and chassis of the device. After locking all the tissue manipulating elements, H‐shaped fasteners are then delivered through apposed layers of esophageal and fundus tissue (arrow 2). B: Pre-procedure and post-procedure view of the gastro-esophageal junction on retroflex endoscopy (the endoscopic images are the author's pictures) [70]. Pre-procedure, the gastro-esophageal valve (arrow1); The "Bell Roll" maneuver to create the new gastro-esophageal valve (arrow 2); The gastro-esophageal valve: immediately after the procedure (arrow 3).

Patients were instructed to consume a liquid diet during the first 2 weeks and a soft diet during the following 4 weeks. PPIs were discontinued 14 days after the procedure. In the event of symptom recurrence requiring medication, a ‘‘step-down’’ protocol was employed; and patients were returned to their pre-procedure dose of PPIs and then weaned from them if possible.

2.2.2 GERDX™ system

The GERDX™ system includes (Figure 5, A): 1) An applicator instrument used to achieve tissue approximation, plication and fixation. It consists of a control arm, the retractor handle and the brake, pump lever, retroflex control knob and knock and an endoscope channel (Figure 5, B); 2) An implant cartridge containing a non-resorbable suture with two bolsters and two retention bridges. The suture is standard USP size 2-0 monofilament polypropylene suture (Figure 5, C).

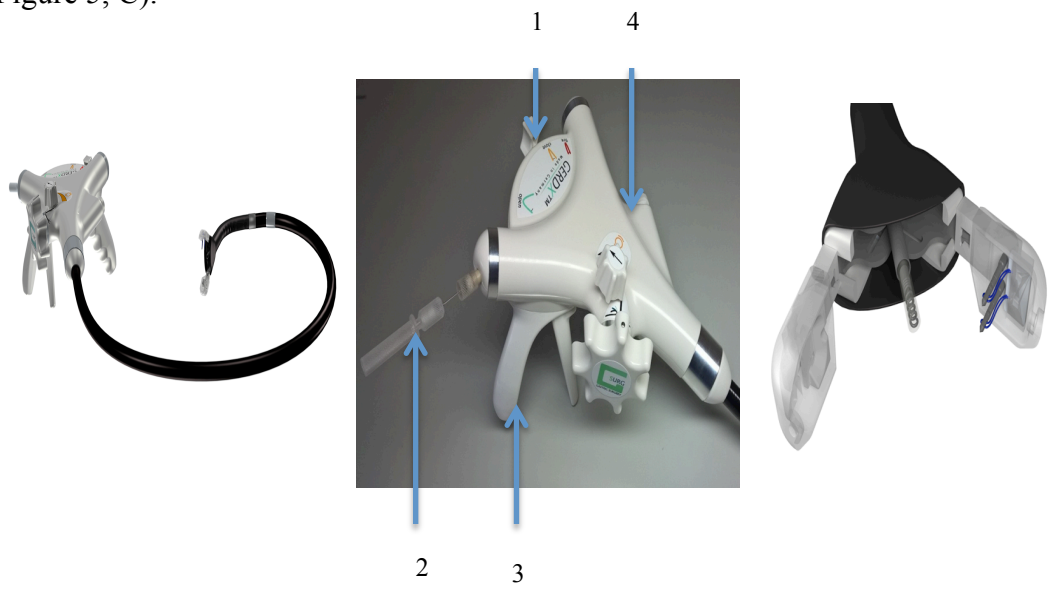


Figure 5 A: The GERDX™ system; B: The GERDX™-applicator consists of control arm (arrow 1), retractor handle (arrow 2), pump lever (arrow 3) and endoscope channel (arrow 4); C: The implant cartridge suture bolsters.

The procedure is performed following a standardized protocol with the patient under general anesthesia with endotracheal intubation in an operating room or an endoscopy unit by a team of a two-surgeons (surgeons and/or gastroenterologists). Generally, the first surgeon controls the whole process of tissue approximation, plication and fixation using the GERDX^{TM} applicator instrument, while the second operates the endoscope and ensures continuous direct visualization. The patient is placed in the supine position. Briefly, the procedure includes the following steps: 1) The distance measurement from GEJ to the incisors by a low profile gastroscope, (6.0 mm or smaller) and the insertion of a guide wire into the stomach; 2) insertion of the GERDX^{TM} applicator and the gastroscope; 3) distension of the stomach by air insufflation; 4) retroflexion of the instrument under endoscopic visualization to within 1 cm of the GEJ in the anterior position; 5) retraction of the targeted tissue by means of the retractor arms; 6) the deployment of the implant and evaluation of the plication with endoscope. The procedure is repeated to add additional plication if necessary and, according to the protocol, more than two sutures can be applied during the procedure (Figure 6, 7a and 7b).

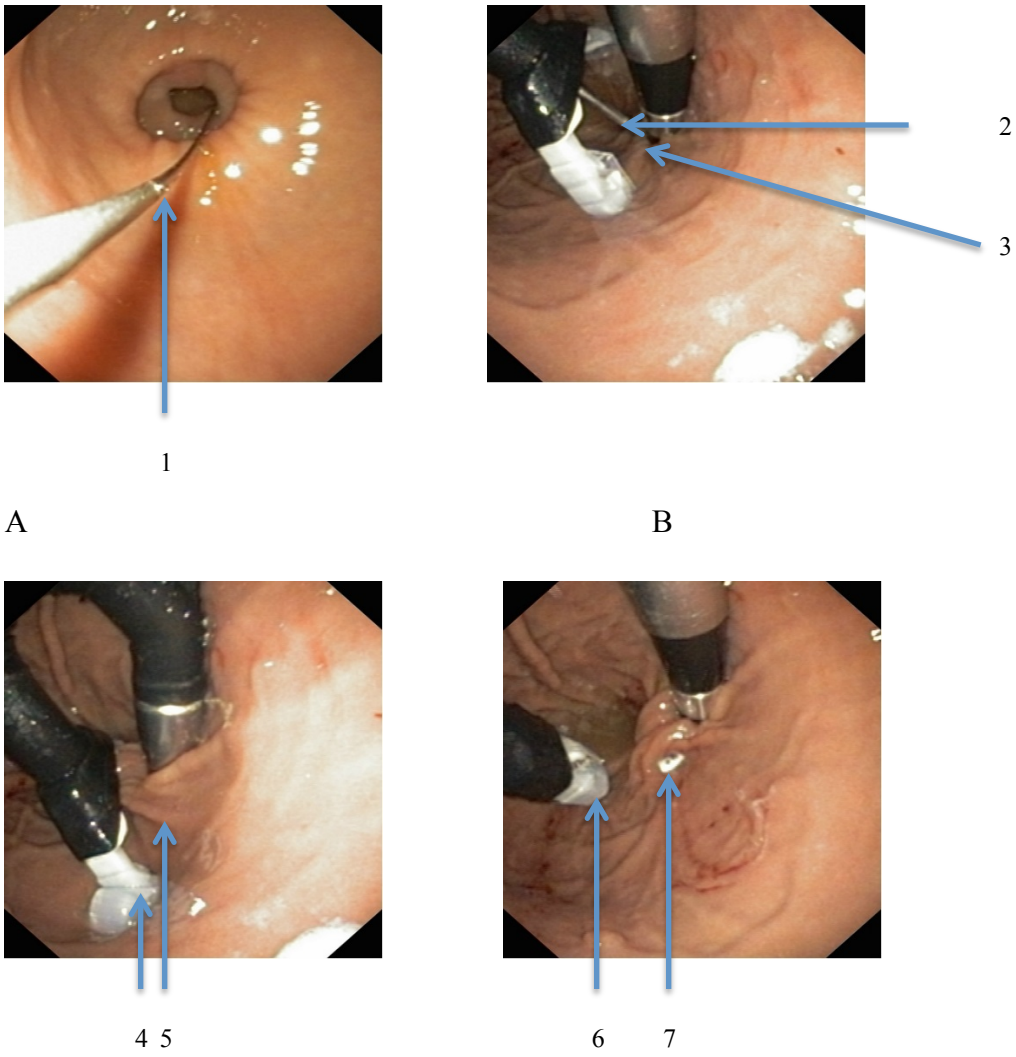
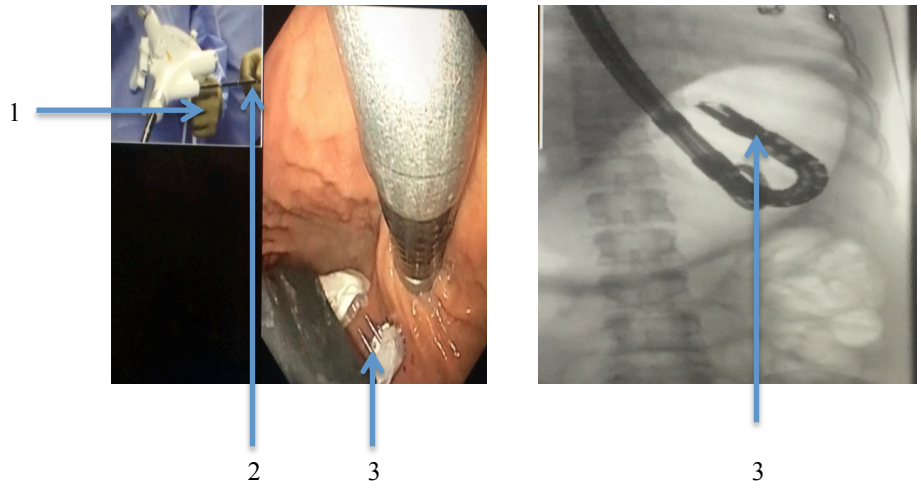


Figure 6 The procedures steps of the GERDX™ system

A: The guide wire is already introduced into the stomach through the gastroscope (arrow 1: the guide wire). The GERDX™ applicator is inserted over the guide wire. Then, the guide wire is removed; B: The instrument is retroflexed under endoscopic visualization to within 1cm the GEJ in the anterior position. The target tissue is retracted by the retractor (arrow 2: the retractor; arrow 3: the target tissue); C: The maximally bent tip with its two arms to grasp the tissue (arrow 4: one of the arm of the tip; arrow 5: the targeted tissue is being grasped); D: Endoscopic view of the plication after the implant has been deployed (arrow 6: the tip with two closed arms has been removed from the plication; arrow 7: the outside view of one deployed implant after the plication.).



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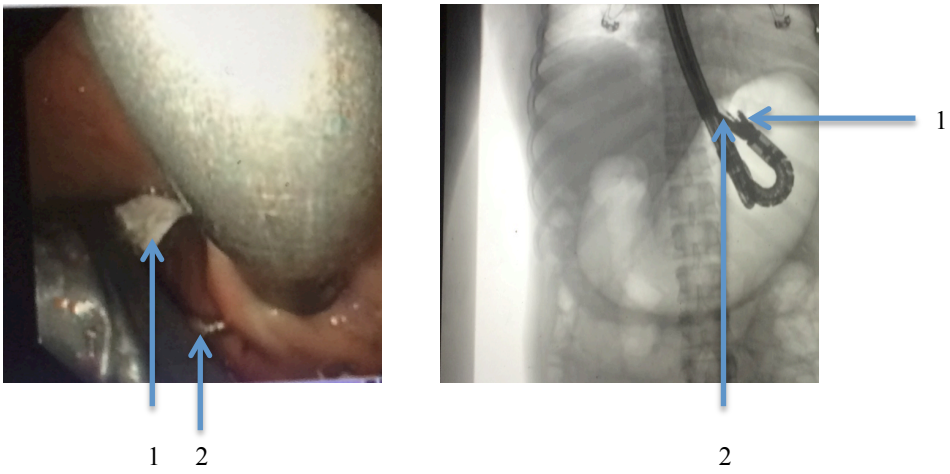
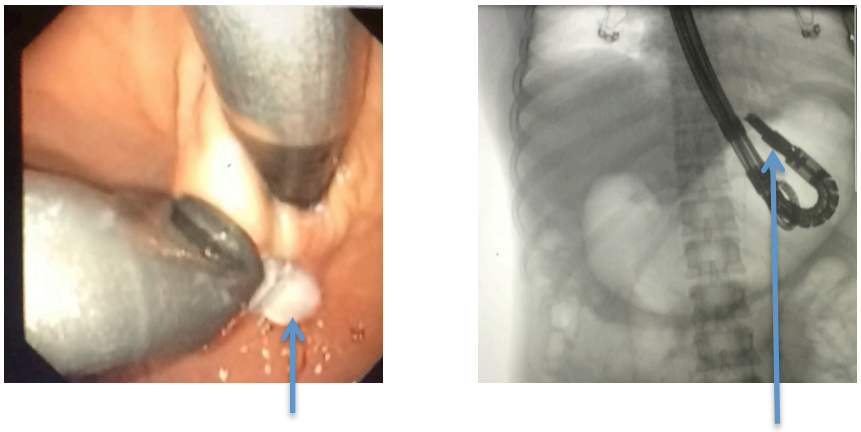


B

Figure 7a The procedure steps of the GERDX™ system under fluoroscopy: Steps before the deployment of the implant.

A. Left: the first surgeon controls the whole process using the GERDX™ applicator instrument (arrow 1), while the second surgeon inserts a low profile (6.0 mm or smaller) gastroscope down the esophagus and operates the endoscope to ensure continuous direct visualization (arrow 2). Right: Radiographic view: The instrument has been retroflexed under endoscopic visualization to within 1 cm of the GEJ in the anterior position (arrow 3). B. Left: The arms of the applicator have been opened (arrow 1). The retractor is inserted and pressed against the target tissue to gather tissue between the instrument arms (arrow 2). Right: Radiographic view.



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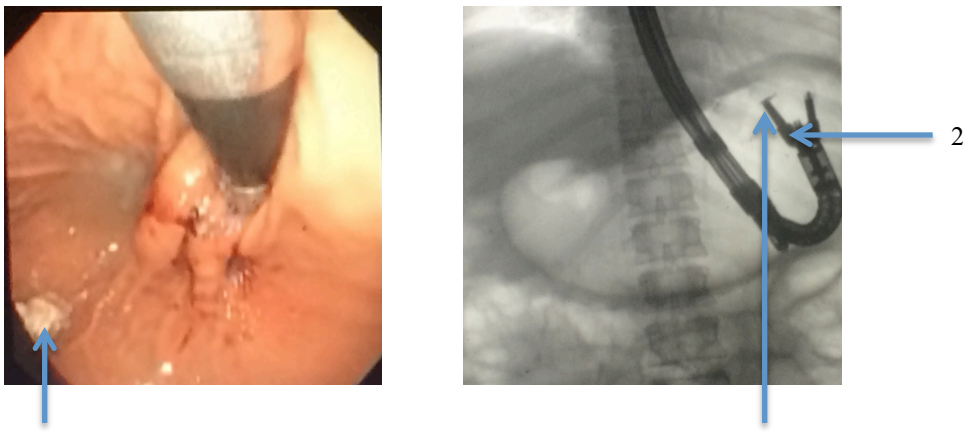


D

Figure 7b The procedure steps of the GERDX™ system under fluoroscopy: the deployment of the implant and after the deployment.

C. Left: The arms of the applicator are closed and the implant is deployed (arrow 1). Right: Radiographic view: The arrow positioned at the fornix region. D. Left: Completion of the procedure. Two arms of the applicator have been opened (arrow 1). The retractor is disengaged and pulled back completely into the applicator (arrow 2). Right: Radiographic view: In this free position within the fundus, the two arms can be occluded again. The tip is straightened and the device can be removed.

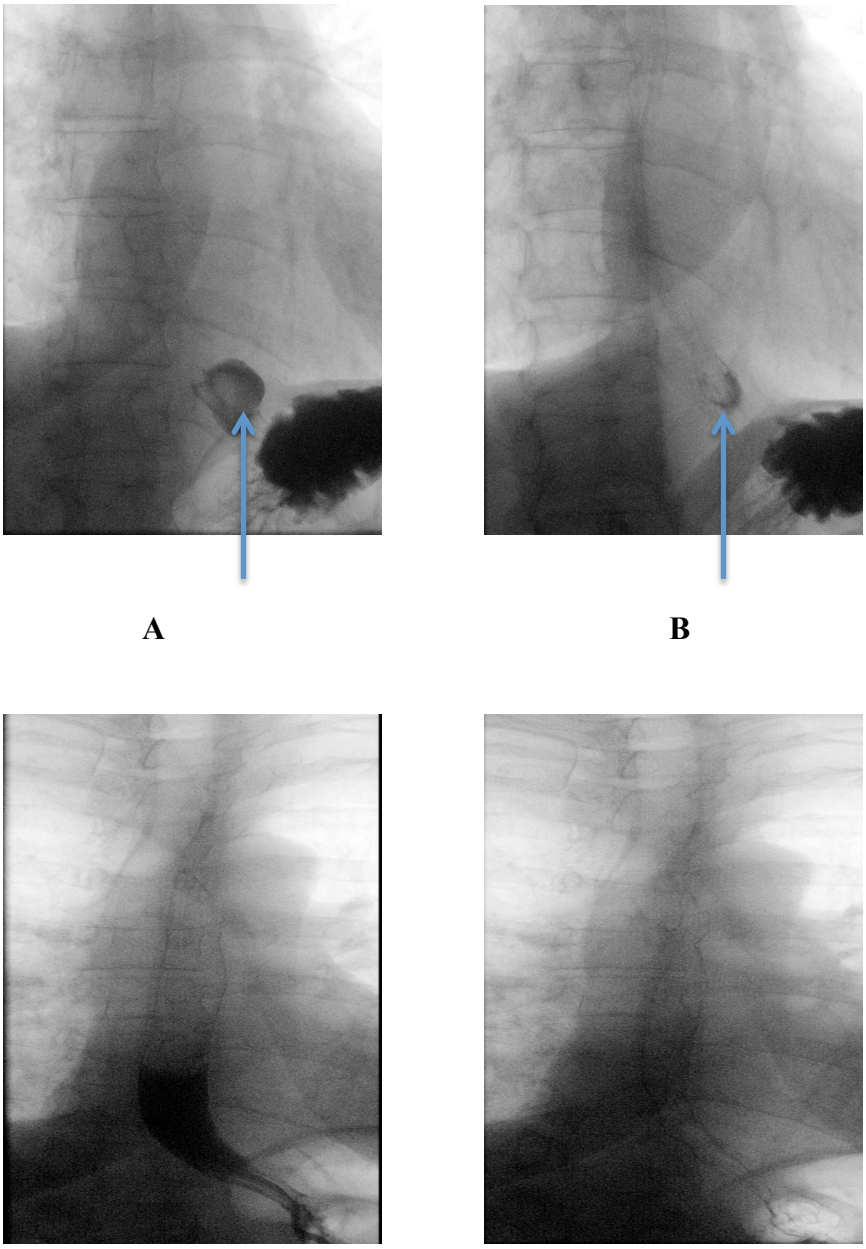


Figure 8 X-ray images of the esophagogastric function before and after GERDX (two days after the GERDX procedure) A,B: Pre-procedure: Small hernia with spontaneous reflux of the contrast medium (arrow); C: Post-procedure: Hernia no longer apparent; D: Post-procedure: Even under provocation no reflux visible.

2.3 Safety assessment

The incidences of anticipated or unanticipated adverse events (AEs) after the procedures were all carefully recorded. Here, AEs were assessed conventionally as serious or not. A serious adverse event (SAE) was predefined as any event resulting in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization or persistent disability/incapacity [93,94].

2.4 Assessment of effectiveness

The primary end point of this study was the frequency and severity of typical and/or atypical GERD symptoms and quality of life which was evaluated by a series of standard questionnaires as shown in 2.4.2. The second end point is medication use. Patients were evaluated at baseline for their typical or atypical GERD symptoms, quality of life and their medication use. Short and intermediate subject follow-up were completed to evaluate the effectiveness of the procedures. Each subject's follow-up result was compared with his/her result of the baseline.

2.4.1 Follow-up time

The follow-up for all patients was calculated from the intervention date to 15th December 2016. To all of them, a functional check-up was offered, in particular in case of complaints.

2.4.2 Follow-up measures

A series of standardized questionnaires and telephone interviews were used to collect relevant data. Three standard questionnaires were used for the evaluation of symptom and quality of

life. Comparisons were made between pre-procedural and post-procedural index values. These investigational tools included:

1) GERD-Health Related Quality of Life (GERD-HRQL) GERD-HRQL questionnaire was used to assess symptomatic outcomes for the typical symptoms of GERD [95]. The questionnaire contains a total of 10 items which are scored, and a patient-reported global satisfaction assessment which is not added to the total GERD-HRQL score (Questionnaire 1) [96];

2) Reflux Symptom Index (RSI) It is a validated, self-administered, nine-item reflux symptom index for the assessment of symptoms in patients with atypical GERD symptoms, especially for laryngopharyngeal reflux (LPR) (Questionnaire 2) [97];

3) Disease Specific Quality of Life Index It is a self-administered, five-item survey for assessment of atypical symptom, especially LPR impact on daily living (Questionnaire 3) [98].

2.5 Statistical analysis

Statistical analysis was performed using SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA). Aggregate data including patient demographics, baseline characteristics, safety and efficacy were summarized by descriptive statistics. The mean and standard deviation were generally reported for continuous variables. Medians and ranges were reported for data with skewed distribution. *P* values for changes at follow-up compared with those at baseline were calculated using the Mann-Whitney U and paired *t* test. Values with $P<0.05$ were considered significant.

3 Results

3.1 Final therapeutic stratification

A total of 1642 patients were diagnosed to suffer from GERD in the standard diagnostic work up of the surgical gastro-labor during the study period which comprehended 24-pH monitoring and impedance measurement. 1228 patients (74.8%, 1228/1642) achieved treatment success with PPIs and/or H_2-blocker. The remaining 414 patients (25.2%, 414/1642) were allocated to the treatment failure group with medication (Figure 9). Of these, 152 patients (9.2%, 152/1642) underwent anti-reflux surgery during the study period. The total number of "gap patients" who neither achieved treatment success with medication nor received anti-reflux surgery is 262 (16.0%, 262/1642) (Figure 9). Among these 262 patients who have fallen into the "therapeutic gap", 36 patients (13.7%, 36/262) were selected for an ESA using the EsophyX® device (17 patients) or the GERDX™ system (19 patients). (Figure 9)

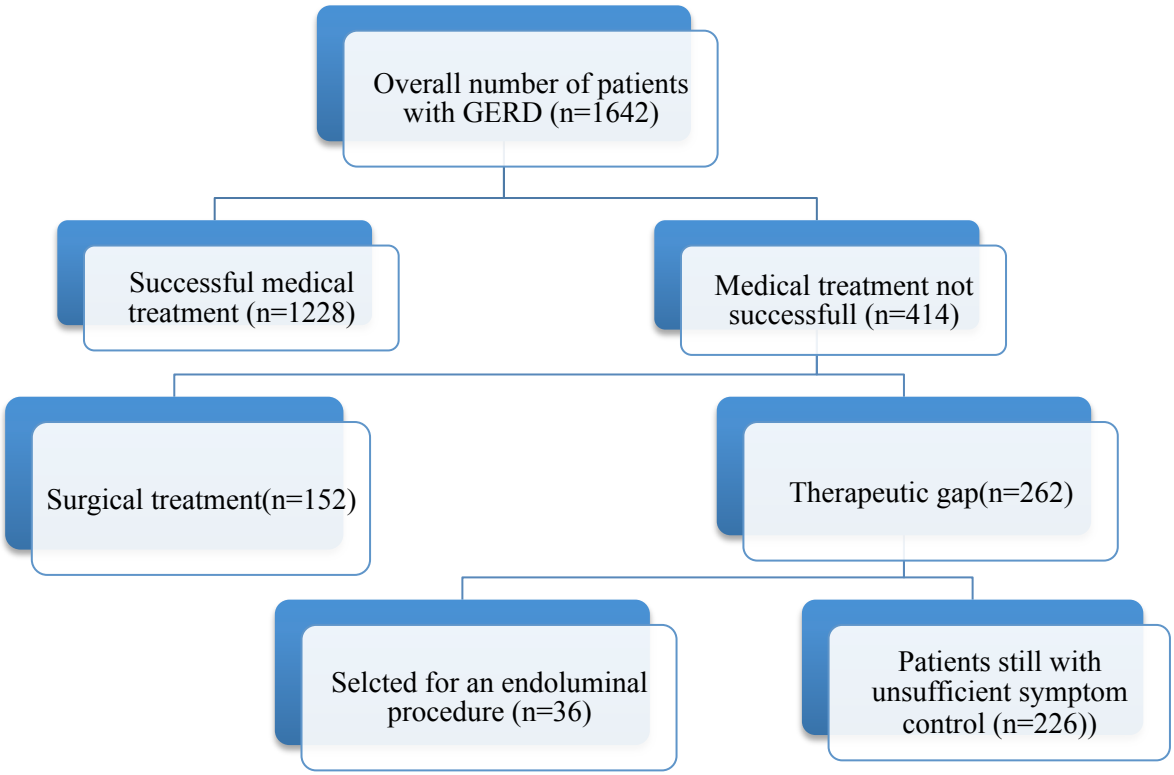


Figure 9 The final therapeutic stratification: Of n=1642 patients enrolled, only n=36 (2.2%) were selected for an endoluminal treatment. The "therapeutic gap" means patients with confirmed GERD who neither achieved treatment success with medication nor received anti-reflux surgery.

3.1.1 Non-applicability of endoluminal sphincter augmentation

Among the 262 patients who did fall into "therapeutic gap", 86.3% (226/262) patients were found to be no suitable candidates for endoluminal sphincter augmentation. The reasons of non-applicability conditions were methodical contraindications, refusal by the patient, or the inability to tolerate general anesthesia (Table 2). For another n=33 patients, the reasons were unclear.

Table 2 Reasons for non applicability of endoluminal sphincter augmentation

Contraindications:	1) Large hiatal hernia>2cm); 2) Non-effective esophageal motility; 3) Esophagitis severer than Los Angeles B; 4) Other esophageal diseases (e.g. varices, ulcers, tumors); 5) Previous anti-reflux surgery.
Refusal by the patient	
Patients unfit for general anesthesia	

In most cases, the presence of a large hiatal hernia was the reason not to perform ESA (Figure 10). Concomitant diseases comprehended esophageal varices, systemic scleroderma, and intestinal dysmotility. The majority of patient who denied to get an ESA was found in the early years (2008-2011). Maybe, this was due to a very cautious and comprehensive information of the patient by the surgeon before getting the informed consent. With growing experience and confidence, the surgeon became more inclined to recommend ESA explicitly.

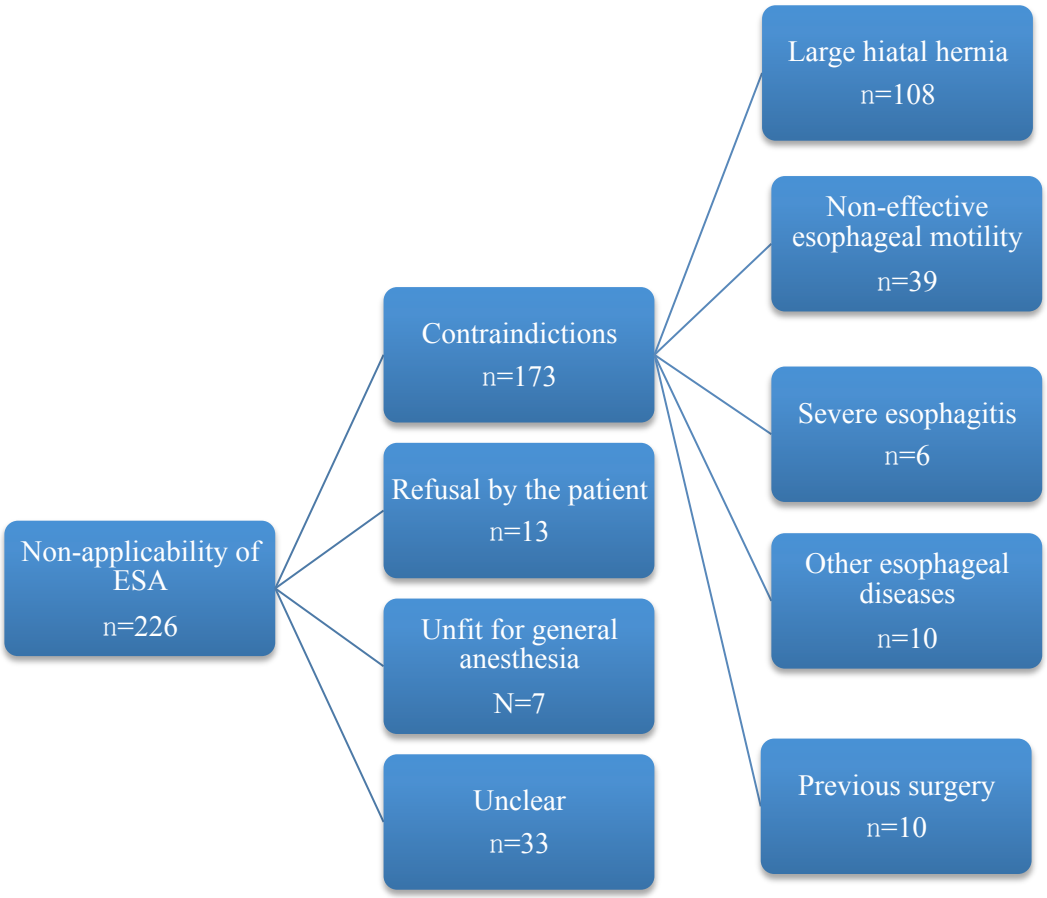


Figure 10 Conditions for non-applicability of endoluminal sphincter augmentation

The leading causes for non-applicability are depicted in Figure 10. However, an overlap of different reasons existed in individual cases. Evidently, ESA was indicated very cautiously in the beginning. Later on, the range of ESA applications became wider.

3.2 Outcome of ESA (EsophyX® or GERDX™)

A total of 36 patients selected for ESA using EsophyX® device (17 patients) or the GERDX™ system (19 patients) from November 2008 to December 2016 were enrolled in the study. All patients gave their permission to access their data. All patients in whom ESA could be successfully performed (15 patients in EsophyX® group and 19 patients in GERDX™ group)

were available until the end of follow-up. Among them, a re-intervention was done in 3 patients (3/15, 20%) in EsophyX® group and 4 patients (4/19, 21.1%) in GERDX™ group (Figure 11). All patients completed the symptom and quality of life questionnaires for the follow-up after the procedures. The average follow-up time for patients in EsophyX® group is 91 months (range=74-100), while the average follow-up time for patients in GERDX™ group is 18 months (range=1-30).

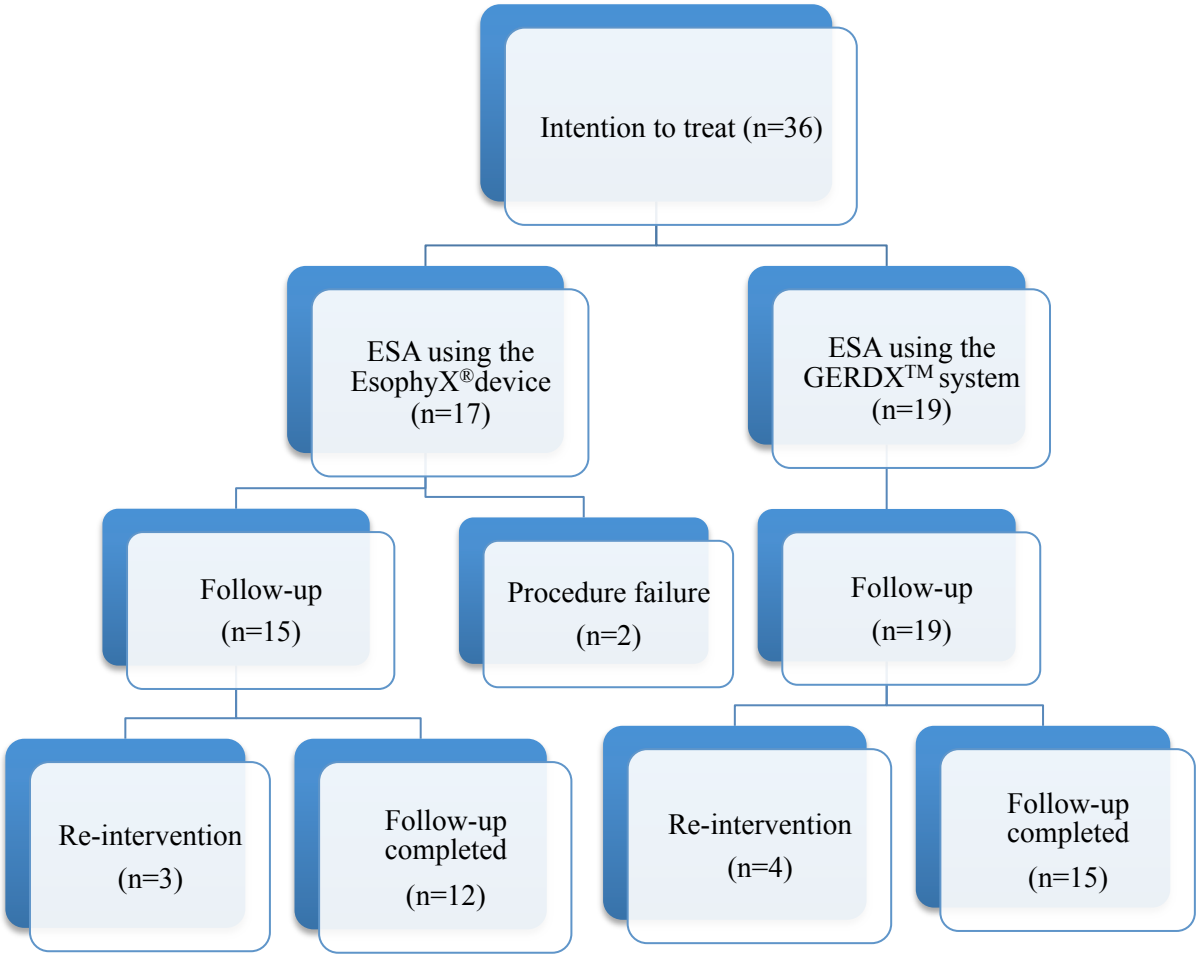


Figure 11 Flow chart on n=36 patients initially selected for ESA.

3.2.1 Preoperative data

Patient characteristics at baseline The enrolled 17 patients in the EsophyX® group all had documented chronic GERD for a median of 8.5 (range from 1 to 45) years and 16 patients (16/17, 94.1%) were on PPI medication, 1 patient (1/17, 5.9%) was on H_2-blocker medication. Median age was 52.2 years (range= 24-73), median BMI was 25.3 kg/m^2 (range=19.5-30.1), the gender structure is 9/17 (male/total). The enrolled 19 patients in the GERDX™ group all had documented chronic GERD for a median of 6.6 (range from 1 to 16) years and 19 patients (19/19, 100%) were on PPI medication before the procedure. Median age was 47.7 years (range from 21 to 71), median BMI was 26.2 kg/m^2 (range from 20.6 to 37.1), the gender structure is 10/19 (male/total), about 1/3 of the EsophyX® patients and roughly the half of the GERDX™ patients presented with esophagitis (Table 3). (The detailed basic characteristics of patients in both EsophyX® and GERDX™ group can be seen in the appendix table 1 and table 2)

Table 3 The average basic characteristics of patients in EsophyX® and GERDX™ group

	EsophyX	**GERDX**
Age	50.2±14.2	47.7±14.0
BMI (kg/m^2)	25.3±2.8	26.2±4.2
Gender (Male/Total)	9(17)	10(19)
History of GERD (year)	7.4(1-18)	6.6(1-16)
PPI (Pre-,%)	88	100
Esophagitis (%)	33.3%	47.4%
DeMeester Score	27.7±20.1	25.0±12.9

Note: The mean and standard deviation were reported for continuous variables. Medians and ranges were reported for data with skewed distribution.

3.2.2 Perioperative results

All ESA procedures using the EsophyX® device or the GERDX™ system were performed under general anesthesia, and all procedures were conducted by a team of one surgeon and one gastroenterologist.

3.2.2.1 Operation time

The length of the intervention varied considerably. A learning curve was evident (Figure 12). The mean operation time was 54.9±11.3 minutes in the EsophyX® group and 31.3±11.0 minutes in GERDX™ group. Comparative analysis demonstrated longer operation time in the EsophyX® group (P<0.005).

In the EsophyX® group, 9 interventions (60%, 9/15) could be done in 50 minutes, 4 interventions (26.7%, 4/15) with hiatal hernia (HH) required more than 65 minutes operation time. There were another 2 interventions (13.3%, 2/15) performed in 63 minutes and 60 minutes respectively without any special anatomical reasons.

In GERDX™ group, 17 interventions (81.0%, 17/21) were performed within 30 minutes. The operation time of one intervention (4.8%, 1/21) was over 60 minutes since it was performed by a trainee under the supervision of his trainer. Another 3 interventions (14.3%, 3/21) were done over 40 minutes. Two of them (9.5%, 2/21) had small HH, another one (4.8%, 1/21) had unexpectedly a severe esophagitis.

In both groups, two fasteners or sutures respectively were applied.

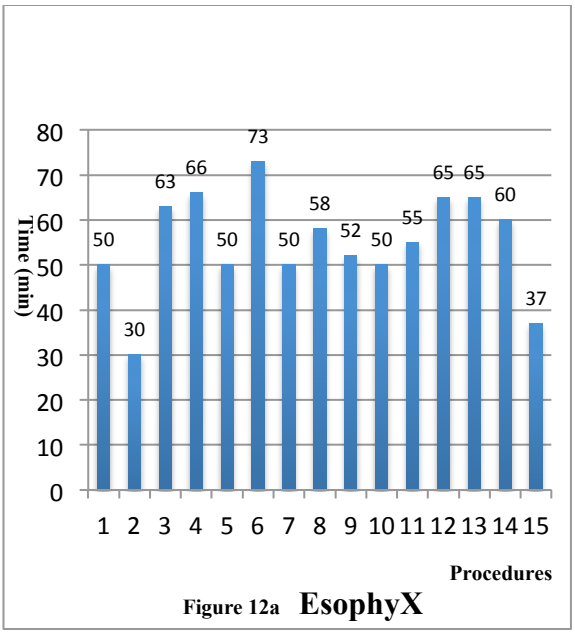


Figure 12a EsophyX

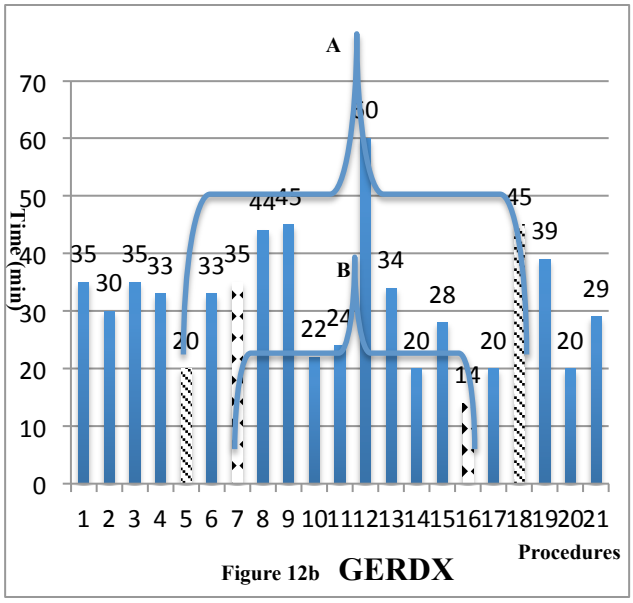


Figure 12b GERDX

Figure 12 Length of the endoluminal sphincter augmentation using the EsophyX® (Figure 12a) and the GERDX™ system (Figure 12b). There were 19 patients receiving a total of 21 interventions of the procedure using the GERDX™ system. Procedure 5 and 18 were done in the same patient (A); Procedure 7 and 16 were done in another single patient (B).

3.2.2.2 Complications and side effects

EsophyX® During the study time, a total number of 17 patients were considered to have ESA using the EsophyX® device. The procedure failed in 2 patients (2/17, 11.8%) since it appeared to be impossible to intubate the esophagus with the EsophyX device. The procedure was stopped for fear of hypopharyngeal perforation. The instances occurred in the beginning of the series when experience with the technique was still low. Otherwise, there were no severe adverse events during the EsophyX® procedure. Mild side effects occurred in 2 patients (13.3%, 2/15) after the procedure. 1 patient (1/15, 6.7%) complained of epigastric pain in the

first 24 hours after the procedure. 1 patient (1/15, 6.7%) suffered from temporary dysphagia in the first week. All of these adverse events were mild and resolved spontaneously.

GERDX™ system A total number of 19 patients underwent this procedure during the study time. All procedures with the GERDX™ system were completed successfully. No severe side effects were registered among these 19 patients in the follow-up. Side effects were reported in 4 patients (21.0%, 4/19). 2 patients (10.5%, 2/19) complained of occasional epigastric pain, 1 patient (5%, 1/19) had temporary chest pain and 1 patient (5%, 1/19) reported a sore throat. All these symptoms appeared in the first week and the majority of them occurred in the first 24-hour after the procedure. All these symptoms were soon alleviated with medication.

3.2.3 Postoperative results

3.2.3.1 Hospitalization

Average length of hospital stay was 4.4±1.1 days in the EsophyX® group and 3.2±1.0 days in the GERDX™ group respectively. A leaning curve was evident (Figure 13). Comparative analysis demonstrated longer hospitalization in the EsophyX® group (P=0.002).

In the EsophyX® group, a total of 15 interventions were performed in 15 patients. After 9 (60.0%, 9/15) interventions, patients were able to be discharged in 4 days. There were 3 (20%, 3/15) interventions after which patients were discharged in 5 days. The length of the hospital-stay was up to 6 days after 3 (20%, 3/15) interventions. Two of them complained of pain and required post-procedure analgesia over 24 hours, another one patient complained of dysphagia required of longer observation after the procedure.

In GERDX™ group, a total of 21 interventions were performed in 19 patients. The length of hospital-stay was no more than 3 days for 14 interventions (66.7%, 14/21). The length of the hospital-stay was up to 5 days after 2 (9.5%, 2/21) interventions. And these two interventions were performed in two different patients who complained pain and required analgesia over 24 hours after the procedure. There was one intervention (4.8%, 1/21) after which the hospital-stay was up to 6 days since the patient complained sore throat after the procedure.

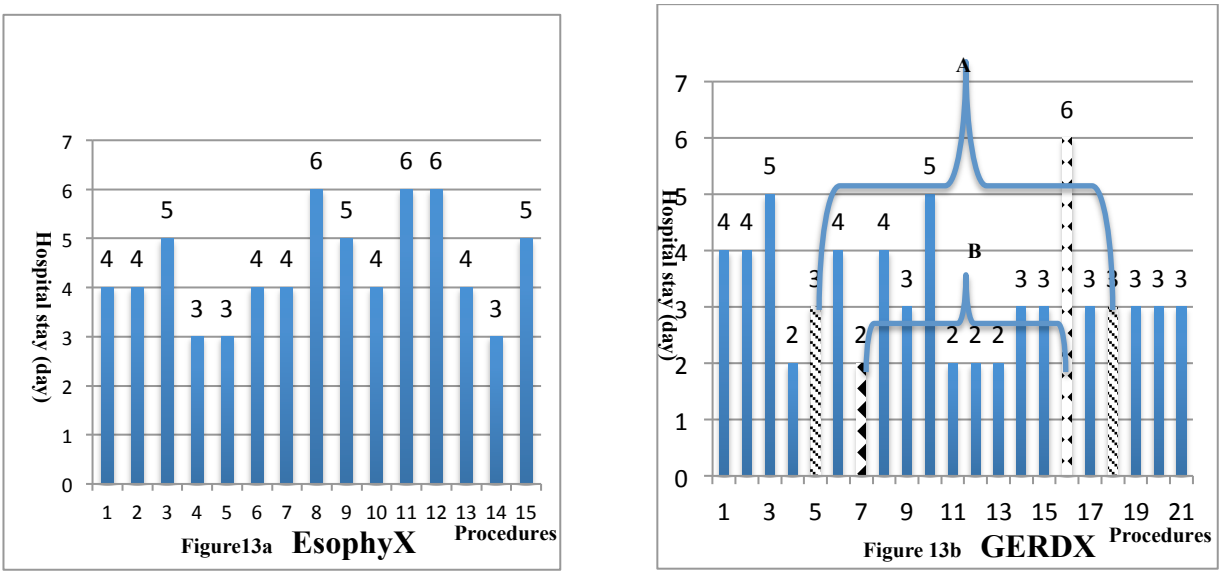
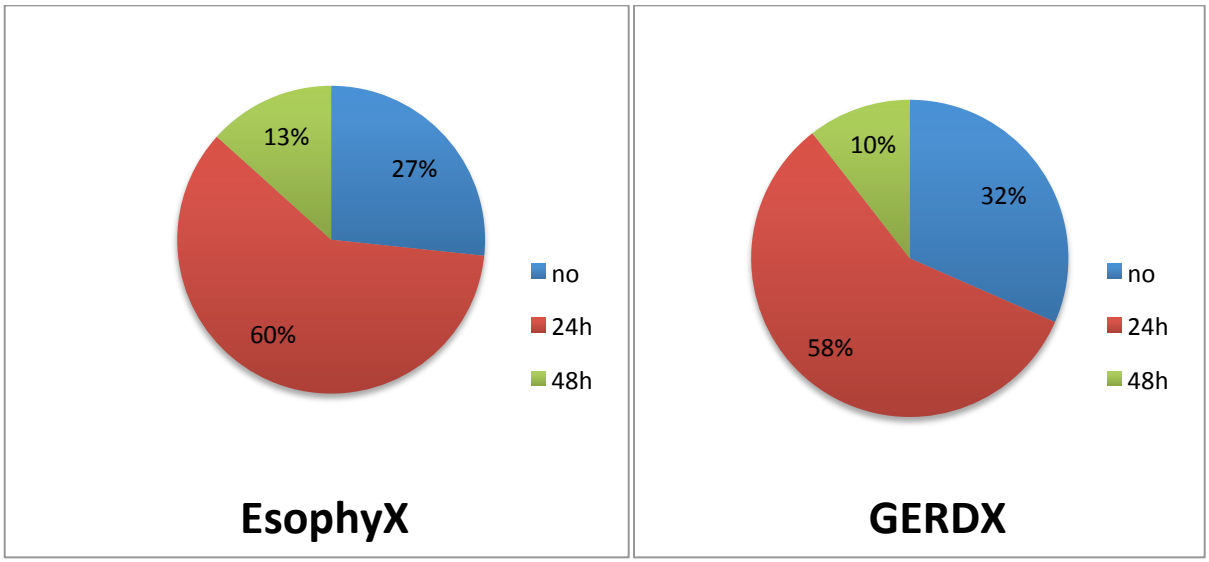


Figure 13 Length of hospital-stay of the patients in the EsophyX and GERDX group. Figure 13a: EsophyX, Figure13b: GERDX. There were 19 patients receiving a total of 21 interventions of the procedure using the GERDX™ system. Procedure 5 and 18 were done in the same patient (A); Procedure 7 and 16 were done in another patient (B).

3.2.3.2 Postoperative analgesia

Regarding the post-procedure analgesia, 60.0% (9/15) patients in EsophyX® group and 57.9% (11/19) patients in the GERDX™ group required post-procedure analgesia in the first 24 hours after the procedure. 13.3% patients (2/15) in EsophyX® group and 10.5% (2/19) patients in the

GERDX™ group required more than 24 hours analgesia. The total amount of post-procedure analgesia (NSAID requirements) required was similar for both EsophyX® group with a median of 19.0 (range=0-45.3) mg/kg and GERDX™ group with a median of 16.5(range=0-58.8) mg/kg. (Figure 14)



A B

Figure 14 Post-operative analgesia in the EsophyX® and GERDX™ group. The analgetic requirement and duration post-operation in EsophyX® group (A); The analgetic requirement and duration post-operation in GERDX ™ group (B). " no " means no analgetic was prescribed, "24h and 48h" means the analgetic requirement lasted for 24 hours or 48 hours.

3.2.4 Functional outcome/Follow-up results

3.2.4.1 Use of PPI-medication

In the EsophyX® group, of the total 15 patients, 3 patients required a second procedure (**Results 3.2.4.2**), 12 patients completed the follow-up. Of these 12 patients, all had had pre-

operative PPI (11 patients) or H_2RA (1 patient). At the end of follow-up, complete PPI or H_2RA cessation was achieved in 6 patients (6/12, 50.0%). The one patient entering the study on baseline daily H_2RA therapy remained off all antacids therapy. 3 patients (3/12, 25.0%) were taking non-daily, on-demand PPI. Another 3 patients (3/12, 25.0%) continued to take daily PPI.

In conclusion, 9 (9/12, 75.0%) of these 12 patients achieved a reduction of PPI medication >50% at the end of follow-up. Overall treatment effect remained stable for these 9 patients.

In the GERDX™ group, of the total 19 patients, 4 patients required a second procedure (**Results 3.2.4.2**), 15 patients completed the follow-up. Of these 15 patients, all had had pre-operative PPI therapy. At the end of follow-up, complete PPI cessation was achieved in 4 patients (4/15, 26.7%). 6 patients (6/15, 40.0%) were taking non-daily, on-demand PPI. Another 5 patients (5/15, 33.3%) continued to take daily PPI.

In conclusion, 10 (10/15, 66.7%) of these 15 patients achieved a reduction of PPI medication >50% at the end of follow-up. Overall treatment effect remained stable for these 10 patients.

3.2.4.2 Re-interventions

Regarding the group of EsophyX®, all patients were free of reflux symptoms when they left the hospital. However, 3 (3/15, 20%) of the 15 EsophyX® patients relapsed after an interval, complaining of reflux symptoms again (Table 3).

Table 3 Findings in 3 EsophyX® patients with recurrent symptoms after the EsophyX® procedure.

Patients	Symptom free interval (month)	Endoscopy		DeMeester Score		Procedure
		Pre-GERDX	Pre-second procedure	Pre-GERDX	Pre-second procedure	
1	4	NE	NE, no stitch report	23.4	28.5	LNF
2	2	NE HH<2cm	NE, HH<2cm,no stitch report	6.7	8.6	LNF
3	3	LA B	LA B, HH loosened stitches.	6.4	7.5	LNF

NE: No esophagitis; LA B: Los Angeles B; LNF: Laparoscopic Nissen fundoplication. HH: Hiatal hernia; "-" means the patient has no relevant result.

In all of them, it was decided to perform a Nissen fundoplication. There were no complications. Up to now, no reflux reoccurrence was observed.

As for the group of GERDX™ patients, 4 (4/19, 21.1%) of 19 patients presented again with recurrent reflux and received a second procedure (Table 4). With regard to these 4 patients, a Nissen fundoplication was performed in 2 patients with big hiatal hernia (≥2cm), and a second GERDX™ was decided to perform in another 2 patients. There were no complications. To date, all 4 patients have maintained good symptom control as well as discontinuation of PPI.

Table 4 Findings in 4 GERDX™ patients with recurrent reflux symptoms after GERDX™ procedure

Patients	Symptom free interval (month)	Endoscopy		DeMeester Score		Procedure
		Pre-GERDX	Pre-second procedure	Pre-GERDX	Pre-second procedure	
1	0.5	LA C, 3cm HH	LA C, 2cm HH, two stitches in situ	36.9	5.7	LNF
2	4	LA B, >3cm HH	LA B, >3cm HH, one stitch in situ	18.9	42.3	LNF
3	3	NE	NE, one stitch in situ	52.3	3.6	GERDX
4	4	LA A	LA B, no stitch	22.2	39.3	GERDX

NE: No esophagitis; LA A-LA C: Los Angeles A-C; LNF: Laparoscopic Nissen fundoplication. HH: Hiatal hernia.

3.2.4.3 Long-term control of symptoms after ESA

Of the 17 patients originally assigned to the EsophyX® procedure, only 12 patients were available for follow-up since the procedure had not been carried out in 2 patients, and a fundoplication was required in another 3 of them. All 12 patients (12/12, 100.0%) finished the follow-up during the study period.

In the group of GERDX™ patients, 19 patients were originally assigned to GERDX™ procedure. Technically, all procedures had been done successfully. 15 patients were available for the follow-up since 4 out of the 19 patients received a second procedure. Among these 4 patients, 2 patients received the second time GERDX™ procedure since the loss of the sutures or the loosened sutures had been found, and a fundoplication was required in another 2 of them. All the 15 available patients (15/15, 100%) finished the follow-up period.

3.2.4.4 Detailed symptom evaluation with questionnaires

At the end of follow-up after the procedure, 12 patients in the EsophyX® group and 15 patients in the GERDX™ group finished all the questionnaires and interviews (Figure 11). Typical symptom severity evaluated by the GERD-HRQL scores, were improved significantly compared with the baseline scores. The median scores were improved from 35 (range=6-41) to 4 (range=0-24) in the EsophyX® group (*P*=0.002), and from 32 (range=6-46) to 10 (range=0-47) in the GERDX™ group (*P*=0.006)

Atypical symptom severity, especially for laryngopharyngeal reflux (LPR), assessed using the RSI, also showed a significant improvement at the end of follow-up post procedure versus the baseline before the procedure. The median RSI scores improved from 10 (range=4-22) to 0 (range=0-9) (*P*=0.004) in EsophyX® group, and from 24 (range=6-39) to 8 (range=0-39) *(P*=0.013*)* in GERDX™ group (Table 5, 6). (The detailed questionnaire data of each patient is in appendix table 3, 4).

3.2.4.5 Quality of life

Quality of life scores were significantly improved at the end of follow-up after the procedure compared to the baseline of each group (Table 5, 6). The median scores improved from 7 (range=4-21) to2 (range=0-8) in EsophyX® group (*P*=0.005), while from 17 (range=0-26) to 4 (rang=0-26) in GERDX™ group (*P*=0.002). No difference was observed in quality of life between EsophyX® group and GERDX™ group (Table 5, 6). (The detailed questionnaire data of each patient is in appendix table 3, 4.)

Table 5 GERD symptoms and quality of life scores before and after EsophyX® procedure

Questionnaire	Baseline	At the end of follow-up	Reduction from baseline
GERD-HRQL score			
Median (range)	35(6-41)	4(0-24)	27(1-39)
***P*-Value**	0.002		
RSI score			
Median (range)	10(4-22)	0(0-9)	9(-2-22)
***P*-Value**	0.004		
DSQL score			
Median (range)	7(4-21)	2(0-8)	6(-3-18)
***P*-Value**	0.005		

GERD-HRQL: Gastroesophageal relux disease health related quality of life questionnaire; RSI: Reflux symptom index questionnaire; DSQL: Disease specialized quality of life questionnaire;

Table 6 GERD symptoms and quality of life scores before and after GERDX™ procedure

Questionnaire	Baseline	At the end of follow-up	Reduction from baseline
GERD-HRQL score			
Median (range)	32(6-46)	10(0-47)	21(-4-36)
***P*-Value**	0.006		
RSI score			
Median (range)	24(6-39)	8(0-39)	8(-8-29)
***P*-Value**	0.013		
DSQL score			
Median (range)	17(0-26)	4(0-26)	3(0-21)
***P*-Value**	0.002		

GERD-HRQL: Gastroesophageal relux disease health related quality of life questionnaire; RSI: Reflux symptom index questionnaire; DSQL: Disease specialized quality of life questionnaire;

4 Discussion

Dietary and lifestyle modifications combined with medication therapy and anti-reflux surgery have been the mainstay of GERD treatment. Most patients with GERD can achieve satisfying results with these treatments. However, there is a certain group of patients whose symptoms are not adequately controlled on medication but who are no candidates for anti-reflux surgery. The patients in this segment are belonging to the "therapeutic gap".

The existence of the "therapeutic gap" has led to the development of various endoluminal therapies which aim to cover this gap with a minimally invasive approach.

Three major findings of this study about the "therapeutic gap" and the possible endoluminal anti-reflux procedure for this "gap" were as follows: a) There is a "therapeutic gap" between medical and surgical treatments which can partly covered by ESA; b) ESA using EsophyX® or GERDX™ procedure is safe and efficacy in selected patients; c) Re-intervention with anti-reflux surgery or ESA procedures is feasible and a safe option in a patient who has persistent symptom or symptom reoccurrence after a ESA procedure.

Our first result not only proved the existence of "therapeutic gap", but also quantified and further classified the "gap". Our study found that 74.8% patients achieved treatment success with PPIs and/or H_2-blocker among patients diagnosed with GERD in the surgical gastro-labor during the study period. This is in accordance with the previous studies which reported 60-80% patients can achieve treatment success with the PPI therapy in patients with GERD [14,93]. 16.0% patients fell into the "therapeutic gap" except the 9.2% patients received anti-reflux surgery. This seemed to be different from earlier study which reported that only 1-2% of all patients with GERD actually receive anti-reflux surgery [30]. The ratio of our patients who have received the anti-reflux surgery is much higher than 1-2%. We speculated that this might

be because we are surgical department where patients are more inclined to choose surgery as a treatment for GERD.

In order to know whether ESA can cover the “gap”, we did a statistical analysis among the patients fallen into the “gap”. We found that among these “gap” patients, 13.7% underwent ESA using EsophyX® device or the GERDX™ system. Another 86.3% patients in the therapeutic gap were still with un-sufficient symptom control since they were found to be no suitable candidates for ESA.

From our results, we can answer the initial question whether by application of these devices the gap in anti-reflux therapy can be finally closed. ESA could certainly contribute to this problem. It offers an alternative treatment option for an increasing percentage of patients. The “ therapeutic gap” is apparently growing and due to the reported side effects of PPIs and behavioral changes in patients (refusal of medical therapy) it is estimated to increase from currently 20-30% to about 50% [30,99].

The result of our study proved that the ratio of the patients who received an ESA procedure accounted for only 13.7% (36/262) of the total “gap” patients. ESA will certainly not close the “therapeutic gap” completely. Several reasons may be attributed to this answer.

The first reason is that ESA with EsophyX® device or GERDX™ system can only be effective and safe in selected patients. The ideal candidates for ESA using the EsophyX® device or GERDX™ system are chronic GERD patients with partial but inadequate symptom control on high-dose PPI therapy, because these patients require an alternative therapy than PPIs, but laparoscopic fundoplication might be too invasive and an overtreatment. For proper patient selection the following aspects also have to be taken into account 1) presence of only a mild to moderate deterioration of the GEJ (absent or small hiatal hernia≤2cm, thus Hill grade I

or II); 2) proved effective esophageal motility assessed by fluoroscopy or manometry; 3) absence of esophagitis or a mild esophagitis not severer than grade B according to the Los Angeles classification; 4) absence of other esophageal diseases, such as ulcers, varices and tumors [100].

The second reason is that some patients are found to be unable to tolerate general anesthesia. While the ESA procedure is still a kind of invasive procedure, traditional esophagogastroduodenoscopy (EGD) anesthesia techniques (sedating) have been found to be insufficient and can negatively impact surgical technique [70]. General anesthesia is required for ESA which means any condition of the patient that might lead to the intolerability of general anesthesia should be excluded.

The third reason is refusal by the patient. Although the emerging role of ESA is undeniable, some patients are reluctant to accept any intervention, even if it is only an endoscopic one. Others do not trust in ESA because of the limited experience.

The second main finding of this study is the clinical safety and efficacy of ESA using EsophyX or GERDX. We performed ESA with EsophyX® in 17 patients and 19 patients with GERDX™ system. We followed up these patients from their respective intervention date till 15th December 2016. Our results demonstrated that both the ESA procedures with EsophyX® and GERDX™ were safe and effective. It helps to reduce PPI medication in 75.0% patients in the EsophyX® group and 66.7% in the GERDX™ group. And it allows for totally discontinuation of PPI in 50.0% of EsophyX® patients and 26.7% of GERDX™ patients. Review of the relevant literature, numerous studies have evaluated the efficacy of ESA, especially ESA with EsophyX® device. There are a number of prospective observational studies published up to now. The studies on ESA with EsophyX® have reported the efficacy

and persistency of the procedure at six months in most studies and for up to six years in one study. Both symptom control and PPI discontinuation were analyzed in these studies, which include some double-blinded and sham-controlled studies. With regard to short-term follow-up outcomes after ESA with EsophyX®, previous studies showed that 75%-93% and 72%-85% of patients had either discontinued PPI or halved the dose [101-105]. To evaluate the long-term efficacy of the EsophyX procedure, Testoni et al. [76] followed patients for up to six years. Regarding symptom control, symptom scores off PPI were significantly lower at 12, 24, and 36 months. Regarding PPI usage, 79.6%, 87.8%, and 84.4% of patients stopped or halved the PPI therapy at 12, 24, and 36 months, respectively, after ESA using EsophyX. The three-year figure remained stable up to 6 years. In our study, the average follow-up time for patients EsophyX® group is 91 months (range=74-100), there's no SAEs occurred after the procedure. However, 2 patients (2/17,11.7%) failed with the procedure and only 6 patients (6/12, 50.0%) achieved complete PPI discontinuation. The different results with the previous studies might be explained by both technical expertize, the quality of the tailored valve, careful post-procedure patient management as well as the patient-related reason, for example, hiatal hernia larger than 2cm. According to the previous studies, all these factors have been identified as key factors for achieving the post-procedure outcomes through ESA [70,82].

Although the results of ESA using EsophyX were good and seemed to be promising, 7 years ago, for some reason, the EsophyX was no longer available both in Europe and most Asian countries. We continued our ESA study with another procedure: the GERDX™ system. The GERDX™ system is a more recent development which explains that clinical data on it are still scarce. The device is currently being evaluated in several prospective studies. So far, only two studies about the GERDX™ system are available. Spaun et al. performed a study that

compared the safety of the already proven Plicator™ system [61,62] with ESA using the GERDX™ system. In this study, the GERDX™ system turned out to be as safe and well tolerated as the Plicator™ system [88]. In another study, Koch et al. [89] reported that one patient among 13 patients who had undergone the GERDX™ procedure developed pneumonia after the procedure and required antibiotic therapy. However, this complication was effectively controlled in a short time. With regard to the efficacy, routine gastroscopy has been performed in 12 patients at 6-week follow-up in this study, and 10(10/12, 83%) patients, who were subjectively free of GERD associated symptoms. Two patients showed partly dispersed plication and also claimed persisting symptoms (2/12, 17%). Both symptom scores and esophageal acid exposure improved after the GERDX™ system procedure [89]. In our study, the GERDX™ system turned out to be as safe as it has been proven in previous studies. No SAEs appeared so far. However, our follow-up time is much longer than the previous two studies. The average follow-up time for patients in GERDX™ group in our study is 18 months (range=1-30). Although the GERD-HRQL scores were improved from 32 (range=6-46) to 10 (range=0-47) at the end of follow-up, the complete PPI discontinuation achieved only in 4 patients (4/15, 26.7%) in our study. More performing experiences as well as device improvements are required for this new system. For example, until now, it is rather unknown for GERDX™ system that how many sutures are exactly required to provide a long-lasting and effective augmentation of the sphincter without causing negative side effects. Long-term benefits of ESA with the GERDX™ procedure still need to be observed.

Beyond the clinical safety and efficacy of this study related to ESA, we also found that reflux control may be ineffective in a subset of “gap” patients after ESA. Regarding these patients, re-intervention with either LNF or a second ESA is feasible and safe. In our study, a

total of 7 patients (7/36, 19.4%) were found to have a relapse after an interval complaining of reflux symptoms again in our study. Stitch loss was confirmed in 5 patients and functionless stiches were found in the other 2 patients. Subsequent LNF was done in 5 patients, and a second ESA procedure using the GERDX™ system was done in 2 patients. All the re-interventions have been done without complications and good reflux control were all achieved after the re-intervention.

Our findings were consistent with earlier studies evaluated the outcomes of re-intervention with LNF after ESA. A study done by Perry et al [106] evaluated outcomes of performing a revisional LNF procedure in 7 patients from a cohort of 66 patients using ESA with the EsophyX®. It found that two of these patients had persistent symptoms immediately after EsophyX®, while the remaining five developed recurrent symptoms between 5 and 33 months due to the partially dislodged fasteners. There were no instances of gastric or esophageal perforations after the re-intervention with LNF. This is consistent with our findings in which one patient was found to have persistent symptoms immediately after ESA, Another 2 patients reported symptom recurrence after 24 months and 36 months respectively. We speculate that these two late symptom reoccurrence might be related with the loss of the stitches.

However, there are some studies reported SAEs after the re-intervention with LNF. Witteman et al [107] reported perforation after the re-intervention. In this study, they followed 15 patients who underwent revisional LNF from a cohort of 43 patients who received an ESA with EsophyX® device. 11 patients (11/15,76%) were confirmed to have no function or disruption fasteners. All revisional procedures were performed laparoscopically without a need to convert to an open surgery. There was one reported instance of gastric perforation during dissection of the endoscopic fundoplication. And a statistically significant improvement in

quality-of-life measures in comparison to baseline were found after the revisional LNF. The same complication with re-intervention after ESA also been reported by Furnée et al [108]. Although the esophageal acid exposure had been normalized following the revision in this study, dysphagia followed by the revisional LNF which was refractory to dilation appeared in three patients. Furthermore, two instances of gastric perforation occurred during the LNF.

Despite these previous relevant studies documented the technically challenging of the revisional operations which could involve significant lysis of adhesions that may lead to the gastric perforations and conversions to open surgeries [19], the absence of operative complications in our patients suggest that revisional LNF can be safely performed in experienced surgeons. Additionally, the higher rates of dysphagia and the inferiority of symptom resolution were not observed in our patients, either.

Furthermore, no study has been done to prove the safety and efficacy of the re-intervention with the GERDX^{TM} system so far. In our study, a second ESA with the GERDX^{TM} system was performed in 2 patients without hiatal hernia or any other contraindications for ESA. There were no complications. To date, both 2 patients maintained good symptom control as well as discontinuation of PPI. Although the sample size is very small, it proved that a second GERDX^{TM} procedure in selected patients without HH or any other contraindications for ESA could be a feasible choice particularly in case of reflux reoccurrence. A further study has been planned to evaluate the long-term effectiveness of a second procedure with the GERDX^{TM} procedure.

Although ESA with both the EsophyX$^{®}$ and the GERDX^{TM} system seem to be safe and effective, the results of this study should be approached with caution because of the inherent

limitations. Firstly, the follow-up period was short, especially for patients in GERDX^{TM} group. Longer follow-up data are needed for further evaluation of the treatment effect. Secondly, the sample size is very small. The fact is, for ESA with EsophyX$^{®}$, we cannot get more patients from it any more since the product is no longer available in Germany. However, we will continue to apply ESA with the GERDX^{TM} system in our hospital.

Thirdly, comparison with either a sham procedure or another kind of treatment for GERD, such as laparoscopic anti-reflux procedure was not undertaken. Some comparative analysis about this is considered in the future study.

In conclusion, the outcomes of the study showed that a "therapeutic gap" does exist between medical therapy and anti-reflux therapy for patients with GERD. ESA can be a minimally invasive, relatively safe and efficacious complementary approach to medical therapy and surgery for the "gap" patients. With the evolving technique and increasing experience, ESA is gradually playing an emerging role for the management of selected patients with GERD. However, larger multi-center prospective randomized sham-controlled trials with a longer follow-up and comparison between PPIs and LFP for the treatment of GERD are needed to ascertain the true benefit of ESA for GERD treatment before it can be adopted as a standard alternative therapy for patients with GERD.

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LIST OF TABLES

Questionnaire 1 The Gastro-esophageal Reflux Disease-Health Related Quality of Life questionnaire

Questions	
__ 1. How bad is your heartburn?	0 1 2 3 4 5
__ 2. Heartburn when lying down?	0 1 2 3 4 5
__ 3. Heartburn when standing up?	0 1 2 3 4 5
__ 4. Heartburn after meals?	0 1 2 3 4 5
__ 5. Does heartburn change your diet?	0 1 2 3 4 5
__ 6. Does heartburn wake you from sleep?	0 1 2 3 4 5
__ 7. Do you have difficulty swallowing?	0 1 2 3 4 5
__ 8. Do you have pain with swallowing?	0 1 2 3 4 5
__ 9. Do you have bloating or gassy feelings?	0 1 2 3 4 5
__ 10. If you take medication, does this affect your daily life?	0 1 2 3 4 5
__ How satisfied are you with your present condition? Satisfied __ Neutral __ Dissatisfied __	

Scale: No symptoms = **0**; Symptoms noticeable, but not bothersome = **1**; Symptoms noticeable and bothersome, but not every day = **2**; Symptoms bothersome every day = **3**; Symptoms affect daily activities = **4**; Symptoms are incapacitating, unable to do daily activities = **5**

Questionnaire 2 The Reflux Symptom Index (RSI)

Within the last month, how did the following problem affect you?	**0=No problem** **5 = Severe problem**
1. Hoarseness or a problem with your voice	0 1 2 3 4 5
2. Clearing your throat	0 1 2 3 4 5
3. Excess throat mucous or postnasal drip	0 1 2 3 4 5
4. Difficulty swallowing food, liquids, or pills	0 1 2 3 4 5
5. Coughing after you ate or after lying down	0 1 2 3 4 5
6. Breathing difficulties or choking episodes	0 1 2 3 4 5
7. Troublesome or annoying cough	0 1 2 3 4 5
8. Sensations of something sticking in your throat or a lump in your throat	0 1 2 3 4 5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0 1 2 3 4 5
	TOTAL

Questionnaire 3 Disease specific quality of life index

Within the last month, how often did the following problem affect you?	0=No problem 5 = All the time
1. Did you have to clear your throat before talking on the phone?	0 1 2 3 4 5
2. Did throat discomfort or pain interfere with your normal work or daily activities?	0 1 2 3 4 5
3. Did you limit the amount of time you spent talking to other people due to problems with your voice?	0 1 2 3 4 5
4. Did coughing interfere with your work or other activities?	0 1 2 3 4 5
5. Did breathing problems interfere with your work or other activities?	0 1 2 3 4 5
	TOTAL

Table 1 Basic characteristics of patients in the EsophyX® group

Number	Age	BMI (kg/m^2)	Gender	GERD history (year)	PPI (Pre-)	Esophagitis	DeMeester score
1	55	29.7	Female	3	PPI	no	0.9
2	54	24.6	Female	2	PPI	no	42.9
3	38	22.7	Female	2	PPI	A	0.9
4	24	24.0	Male	6	PPI	A	19.7
5	37	24.0	Male	2	PPI	no	9.6
6	61	25.7	Male	18	PPI	A	122.8
7	49	30.1	Male	7	PPI	B	37.6
8	71	24.9	Female	18	H2	no	9.5
9	59	25.4	Female	7	PPI	no	6.7
10	34	27.8	Male	17	PPI	B	26.4
11	39	19.5	Female	1	PPI	no	26.5
12	41	23.8	Male	7	PPI	no	17.9
13	73	27.1	Male	12	PPI	no	51.3
14	58	22.7	Male	4	PPI	A	23.4
15	60	26.8	Female	5	PPI	no	20.0
16	71	26.8	Male	9	PPI	no	-
17	60	26.4	Female	5	PPI	no	-

Note: BMI: body mass index; PPI: proton pump inhibitor; Pre-: pre-procedure. "-" means the procedure failed or without using any pain medication. ★ means pain last more than 24 hours.

Table 2 Basic characteristics of patients in the GERDX^{TM} group

Number	Age	BMI (kg/m^2)	Gender	History of GERD (year)	PPI	Esophagitis	DeMeester score
1	39	25.2	Female	3	PPI	no	32.4
2	71	33.2	Female	8	PPI	A	32.0
3	43	24.1	Female	5	PPI	no	27.9
4	36	20.6	Male	8	PPI	B	13.2
5[v]	30	24.2	Male	2	PPI	no	52.3
6	33	26.9	Male	12	PPI	A	33.2
7	43	27.8	Male	10	PPI	A	38.2
8[v]	63	22.9	Male	5	PPI	A	20.3
9	35	20.7	Female	3	PPI	no	18.8
10	60	30.1	Male	2	PPI	A	5.3
11	21	26.6	Male	6	PPI	no	44.3
12	65	37.1	Male	1.5	PPI	A	18.5
13	42	27.8	Male	16	PPI	C	36.9
14	47	23.4	Female	10	PPI	no	13.5
15	67	21.7	Female	5	PPI	B	16.4
16	44	25.6	Female	1.0	PPI	no	20.0
17	57	23.7	Female	13	PPI	no	22.4
18	60	28.4	Female	5	PPI	no	14.5
19	50	27.4	Male	10	PPI	no	7.2

Note: BMI: body mass index; PPI: proton pump inhibitor; Pre-: pre-procedure. [v] means twice GERDX procedures have been done for one patient. ★ means pain last more than 24 hours.

Table 3 The Pre- and Post- (at the end of follow-up) questionnaire results of each patient in EsophyX® group.

Patients	GERD-HRQL		RSI		DSQL	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
1	26	18	17	0	18	0
2	6	5	22	0	16	0
3	37	24	7	9	5	8
4	35	6	4	0	4	2
5	41	8	6	5	7	4
6	28	3	10	2	5	1
7	36	0	5	0	5	0
8	39	0	9	0	6	0
9	23	0	21	0	18	3
10	40	6	16	0	20	2
11	35	0	4	0	4	3
12	20	0	14	3	21	5

GERD-HRQL: Gastroesophageal relux disease health related quality of life questionnaire; RSI: Reflux symptom index questionnaire; DSQL: Disease specialized quality of life questionnaire;

Table 4 The Pre- and Post- (at the end of follow-up) questionnaire results of each patient in GERDX™ group.

Patients	GERD-HRQL		RSI		DSQL	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
1	46	47	39	39	26	26
2	30	1	11	1	0	0
3	36	0	29	0	21	0
4	35	29	25	22	21	19
5	28	29	26	34	17	15
6	29	7	9	1	1	1
7	36	0	10	0	5	0
8	35	3	26	7	21	1
9	15	11	24	19	11	4
10	37	16	39	17	26	11
11	30	5	6	6	8	5
12	6	8	16	8	18	6
13	38	10	25	6	15	4
14	28	25	8	10	6	3
15	32	36	18	22	18	16

GERD-HRQL: Gastroesophageal relux disease health related quality of life questionnaire; RSI: Reflux symptom index questionnaire; DSQL: Disease specialized quality of life questionnaire;

ACKNOWLEDGEMENTS

I would like to express the deepest appreciation to my supervisor Prof. Dr. Hubertus Feussner. He gave me the opportunity to do my M.D. research in his gastrolabor and always supports for M.D project. Whenever I have difficulties, I can always get advice and help from my supervisor. Prof. Dr. Hubertus Feussner always tries to make time to solve my problems no matter how busy he is. He encouraged me to face the difficulties of the project and forgave me of the mistakes that I made during the studies. Most importantly, he taught me how to do a scientific research with a rigorous and scientific attitude. The rigorous but relaxed research environment in his gastrolabor allowed me to finish my dissertation in a pleasant way. Prof. Dr. Feussner fully understands the difficulties I encountered in daily lives as a foreigner in Germany, and he is always willing to offer a hand. Without his supervision and constant help this dissertation would not have been possible.

I would like to thank for my thesis committee mentor Prof. Dr. med Stefan von Delius. As my mentor, he gave me the opportunity to study and work in the endoscopy center. He taught me how to work as an endoscopist. He helped me know that only when I understood how to do endoscopy skillfully, can I really do my thesis related with endoscopic therapy. whenever I encounter problems in techniques related with endoscopy, I would turn for him for help first, and he would guide and discuss with me about the problems. With his help, we solved many bottleneck problems together through countless of tries and tests.

I would like to thank Ms. Sabrina Stoeppke, Ms. Jell and Ms. Helga Wirnhier of the Research Group Minimally-invasive interdisciplinary therapeutical intervention, Klinikum rechts der Isar of the Technical University Munich, Germany (*MITI* group) who helped me collect the relevant clinical data. Whenever I have difficulties or problems, I can always find some of

them for help. Besides research, they also gave me many useful suggestions in the daily life problems I encounter. I would like to thank them for all the helps in both academic and daily life problems. This is a real team in which the team spirit is so strong that one's confidence and potentials can be easily found and revealed here. I would thank this whole team since the team gave me a feeling like I'm at home when I do my clinical research here.

I would like to thank Prof. Dr. Helmut Friess. He is the leader of the surgical department. With the invitation and help both from Prof. Dr. Hubertus Feussner and Prof. Dr. Helmut Friess, such a precious opportunity can be given to me at the very beginning of my study when I was still a visiting scholar from China. He also gave me encouragements during my study and work in the surgical department of Klinikum rechts der Isar. The friendly and relaxed communication with Prof. Dr. Helmut Friess is impressive to me and encourages me to fulfill my study.

I would like to thank PD. Dr. Dirk Wilhelm. He not only gave me some good advice about my thesis, but also helped me revise the thesis related review. He always gave me new ideas and new visions from a new angle. He has showed me how to be a successful doctor and a good scientific researcher. During the hardest time of my study here, PD. Dr. Dirk Wilhelm gave me a hand and very helpful advice to help me conquer the difficulties that I met. He used his own way to reveal to me how a perfect doctor should be like.

I would like to thank Prof. Dr.med Mother Bajbouj. As a gastroenterologist and endoscopist, he gave me very good advice about my thesis. Without his support for the endoscopic techniques, I cannot understand the relevant endoscopic skills of my thesis. He also offered me timely help when I need some pictures for my publication. Without the help of Prof. Dr. med

Mother Bajbouj, the M.D. project may proceed so smoothly. I really appreciate much to all his help for me, especially for his critical advice for my thesis related review.

I would like to thank Dr. Bo Kong for his help for my application for the M.D. in TUM as well as some steps that are important for the preparation of the dissertation. Dr. Kong set a good example of being a good doctor in a foreign country. He helped me integrate into this new foreign environment. And he also gave me some good advice about learning a second foreign language which is very important for my application and further work with my M.D project.

I would like to thank Dr. Simon Nennstiel for the clinical data collection for me. Dr. Nennstiel offered me much help since I cannot speak very fluently Germany. He helped me communicate with the patients and collected part of the questionnaires' result for me. Besides, he gave me very good recommendations when I wrote my thesis related review. His revisions and recommendations are very impressive and helpful.

I would like to thank Dr. med. Fingerle Alexander from the department of radiology. He offered me great help when I need to check the photography of the relevant patients. With the help of Dr. med. Fingerle Alexander, the high quality imaging can be added to the dissertation.

I would like to thank my dear friends Dr. Zhen Liu, Dr. Juan Liu, Dr. Shuo Zhao, Dr. Yi Miao, Dr. Xinyi Zhao for the advice and data analysis for my dissertation.

I can't image two years' life without you.

In the last, I would express my deepest appreciation to my husband Dr. Yijun Liu, my parents and my daughter. Without your endless supports and help, I cannot finish my study in German.