Endoluminal Therapy for Treatment of Gastroesophageal Reflux Disease

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Pier Alberto Testoni, Sabrina Testoni, and Giorgia Mazzoleni

7.1 Introduction

Gastroesophageal reflux disease (GERD) is a very common disorder that can be currently treated by medical therapy and surgical or endoscopic transoral interventions.

Medical therapy represents the most common approach: proton pump inhibitors (PPIs) relieve symptoms and improve the patient's quality of life in the majority of cases. However, concerns related to potential side effects of continuous long-term medication, drug intolerance, or unresponsiveness and the need of high dosages for long periods to treat symptoms or prevent recurrences have increased in the recent years. Moreover, medical therapy may be inadequate to treat symptoms occurring in the presence of weakly acidic reflux and has high cost in the long term for either patients or healthcare system, if started at a young age and maintained for many years.

On the other hand, patients suffering from a mild GERD are in general reluctant to undergo surgical repair of the valve, considering its invasiveness. Surgery may also have in some cases consequences characterized by long-lasting dysphagia, flatulence, inability to belch or vomit, diarrhea, or functional dyspepsia related to delayed gastric emptying [1–4]. Even for interventions performed in centers of excellence, incisional hernias in the site of trocar insertion have been reported in up to 3 % of cases [5].

P.A. Testoni (✉) • S. Testoni • G. Mazzoleni
Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University – Scientific Institute San Raffaele, Via Olgettina 60, 20134 Milan, Italy
e-mail: pieralberto.testoni@unisr.it; testoni.pieralberto@hsr.it

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For these reasons, in the last 15 years, technological innovations have led to the development of a variety of transoral endoscopic techniques as alternatives to antisecretory therapy or antireflux surgery [6]. All these techniques would aim at reinforcing the barrier function of the lower esophageal sphincter (LES), similarly to surgery, and thus controlling reflux but with a lower invasiveness and costs compared to surgery.

Endoluminal therapies gained popularity and showed significant symptom control in the short-term period in the majority of published studies. However, most of them showed disappointing long-term results and have been abandoned [7–9]. Although an American Gastroenterological Association Institute Medical Position Statement established in 2008 that "the current data suggest that at present there are no definitive indications for the use of endoluminal therapy in gastroesophageal reflux disease" [10], transoral procedures have been offered to a selected group of patients with documented symptomatic chronic GERD (pathological reflux at pH and impedance recording and positive correlation between reflux and symptoms), responsiveness to PPI therapy and dependence on antisecretory drugs, hiatal hernias less than 2–3 cm, absence of Barrett's esophagus, and mild esophagitis. Patients with Barrett's esophagus, large hiatal hernias, obesity, severe medical comorbidities, esophageal primary motility disorders, or proximal reflux symptoms have been in general excluded from these transoral approaches.

Endoluminal techniques include three major categories: implantation or injection of foreign materials, application of radiofrequency ablation, and endoscopic tissue apposition techniques.

7.2 Endoluminal Techniques

7.2.1 Implantations and Injections

The theory on the basis of this technique is to instill a bulking agent at the level of LES, in order to increase its natural mechanical barrier to gastroesophageal reflux. Over the years, several attempts with various bulk-forming agents were made, but none remained on the market due to the occurrence of serious adverse events and/or lack of clinical efficacy. The first trials involved injection of polytetrafluoroethylene paste (Teflon, DuPont™, Wilmington, Delaware, USA, and Polytef, Mentor O&O Inc., Santa Barbara, California, USA) and bovine collagen that showed increased gastric yield pressures and decreased esophagitis, but a lack of durability (<6 months) [11].

Subsequent technologies involved the submucosal injection of polymethylmethacrylate (Plexiglass, Artes Medical Inc., San Diego, California, USA) into the LES, but it wasn't effective beyond 6 months [12]. Therefore, all these products were withdrawn from the market.

The most promising of the injectables was Enteryx (Boston Scientific Corporation, Marlborough, Massachusetts, USA), an implantable and biocompatible polymer, consisting of ethylene vinyl alcohol 8% mixed with powder of tantalum, a

radiopaque agent, in an organic liquid solution of dimethyl sulfoxide. It was injected as liquid form around the gastroesophageal junction in a circumferential manner. Once injected into the tissue, the agent forms a spongy, more solid material at the target site of injection at the esophagogastric junction (EGJ). It was a reproducible procedure in the event of inadequate control of the symptoms, but not reversible. In an international multicenter study involving 85 patients, Enteryx was effective concerning pH normalization (38.8 % at 12 months) and cessation of PPI therapy (74 % at 6 months). The scores of symptomatic questionnaires were comparable with those obtained with the antisecretory therapy. However, the device was withdrawn from the market because of procedure-related complications, such as chest pain (92 %), dysphagia (20 %), re-intervention (up to 25 % within 2 years), and a case of death due to the injection into the aortic wall [13–15].

Another injectable has recently been developed, Durasphere (Carbon Medical Technologies, St. Paul, Minnesota, USA), that is, a sterile non-pyrogenic bulking agent composed of pyrolytic carbon containing zirconium oxide beads, suspended in a water-based carrier gel containing beta-glucan. Durasphere is injected into the submucosa in order to create increased tissue bulk and subsequent coaptation of the LES. Over time, collagen is deposited around the pyrolytic carbon-coated beads, with the final bulking result due to the combination of the pyrolytic-coated beads and the body's own collagen. A pilot study on ten patients showed that 70 % of patients with mild to moderate GERD was able to discontinue medical treatment at 12-month follow-up, while 90 % of patients had reduced PPI use by 50 %, and 40 % had normalized pH [16]. However, further studies are needed to confirm its safety and effectiveness.

Among implantation techniques, a hydrogel prosthesis has been proposed (Gatekeeper Reflux Repair System, Medtronic Europe Inc., Tolochenaz, Switzerland). The aim of this technique was to narrow the diameter of the distal esophagus through endoscopic implantation of an expandable, removable, and radiopaque prosthesis in polyacrylonitrile hydrogel in the submucosal layer of the gastroesophageal junction. It was a repeatable and reversible procedure and has shown improvement in the control of reflux symptoms at 6-month follow-up. In 68 patients treated by this procedure, distal esophageal acid exposure (measured by pH monitoring), LES pressure, and symptom scores improved. Normalization of pH was observed in 40 % of patients. However, the device was withdrawn from the market due to related complications, such as pharyngeal perforation and severe postprandial nausea [17, 18].

7.2.2 Radiofrequency Ablation

The Stretta System (Mederi Therapeutics, Norwalk, Connecticut, previously Curon Medical, Sunnyvale, California, USA) was first introduced in 2000 and then refined over the years. This technique provides the ablation of the muscular layer by straddling the gastroesophageal junction with radiofrequency energy, performed with low power and controlled temperature. The device consists of a special flexible

catheter with a balloon-basket assembly and curved needles, distributed radially, which is inserted orally up to the cardia. Each needle is equipped with titanium electrodes to deliver the radiofrequency energy into the esophageal wall and LES, heating the water molecules of the muscle tissue and leading to collagen contraction and tissue constriction while irrigating the overlying mucosa to prevent thermal injury [19]. The ablation is repeated by rotating the device and varying its linear position between 2 cm above and 2 cm below the Z line. The procedure induces irreversible changes, resulting in tissue healing and thus tightening of the LES.

A randomized controlled trial has shown improvement in both symptom control and quality of life at 6-month follow-up, but the technique did not significantly reduce the need to take PPIs, the LES pressure, and the time of distal esophageal acid exposure [20]. The Stretta System was also able to reduce the frequency of the transient LES relaxation, because of the tissue fibrosis and retraction at the level of gastric cardia [21, 22]. The Stretta procedure reported few adverse events. The most common complications reported in studies of case series included transient epigastric pain (66 %), chest pain (15 %), fever (7 %), tears of the mucosal surface (4 %), esophageal ulceration (4 %), and dysphagia (3 %). Major adverse events were reported in less than 0.1 % of patients [23, 24].

No difference was observed between the Stretta procedure and the laparoscopic fundoplication regarding the quality of life in GERD, but 97 % of patients no longer required therapy with PPIs after laparoscopic surgery compared with 58 % of patients who underwent the Stretta procedure [25].

In a systematic review and meta-analysis (20 studies), involving 1441 patients, the authors found that the Stretta procedure improved GERD symptoms (decreased heartburn symptom in 525 patients (36.4 %) over 24.1 months, decreased quality of life scores in 433 patients (30.0 %) over 19.8 months, and improved DeMeester scores in 267 patients (18.5 %), but did not normalize esophageal acid exposure and did not significantly increase the LES pressure [26]. In an 8-year follow-up on 26 patients, Dughera et al. found a significant decrease in heartburn and GERD-HRQL scores, and 77 % of patients completely stopped PPIs. The only complication reported was a case of severe gastroparesis requiring long-term hospitalization [27].

In summary, Stretta provided safe, effective, and durable suppression of GERD; thus it is strongly recommended by the SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) for "patients who have had symptoms of heartburn, regurgitation or both for 6 months or more, who have been partially or completely responsive to antisecretory pharmacological therapy, and who have declined laparoscopic fundoplication" [28].

7.2.3 Endoscopic Tissue Apposition Techniques

Several endoscopic suturing and apposition devices have been developed, in order to mechanically sustain the LES or improve the antireflux barrier creating tissue plication around the gastroesophageal junction.

The EndoCinch (Bard Endoscopic Technologies, Murray Hill, NJ, USA) was initially approved in the USA in 2000. It consists of a suture system that is attached at the end of a standard flexible endoscope and has a cavity that permits the suction of a tissue fold. The device is inserted until reaching 1 cm downstream the Z line. A T-tag secures the submucosal tissue, and the physician lowers the suturing system to the gastroesophageal junction, where other series of sutures are placed below the LES, in order to create two to three gastric plications, forming a valve that works as a barrier against GER [13]. Several studies have evaluated EndoCinch as compared to sham or laparoscopic fundoplication. A noncontrolled trial, carried out in a single center on 70 patients, demonstrated the long-term failure of the treatment, mainly because of the loss of the sutures. Eighteen months after treatment, 56 patients (80 %) did not get improvement in the severity of reflux symptoms or use of PPIs. Endoscopic examination showed all the sutures in place in 12 patients (17 %) and no suture in 18 patients (26 %). In 54 and 50 patients tested, respectively, any significant change was not observed in the 24-h pH monitoring or pressure in the LES, while the length of the LES was only slightly increased [29]. A double-blinded, randomized study of EndoCinch versus sham demonstrated a significant improvement in the use of PPIs, the GERD symptoms, and the time of acid exposure up to 12-month follow-up, compared with the observation group, but did not show any significant improvement over the sham group. Of the EndoCinch group, 29 % of patients required re-treatment during the 12-month follow-up [30]. Moreover, in a study comparing EndoCinch to laparoscopic fundoplication, the authors found EndoCinch less effective than surgical fundoplication [31]. Thus, although a good safety profile, the device was no longer manufactured due to the lack of long-term efficacy.

Another device no longer available in the market for clinical use was the endoscopic suturing device (ESD, Wilson-Cook Medical, Bloomington, Indiana, USA) that consisted of an external accessory channel, attached to a flexible endoscope, which allowed the passage of the other two components of the device, the flexible systems Sew-Right and Ti-Knot. Sew-Right was a dual system of needles that used a single suture loop to create the tissue plication. The target tissue was sucked into a suction chamber; a suture was then passed through the tissue collected within the chamber. It was used as a continuous and single suture loop to sew two adjacent areas in the proximal stomach in order to form the plication, and it was possible to create two to three plications during a single treatment. Studies revealed the early loss of the sutures; at 6 months, only 5 % of the sutures were found still in place. There were no significant changes in the healing of esophagitis, time of esophageal acid exposure at 24-h pH monitoring, LES pressure, and PPI use [32]. In case series, this procedure has been associated with transient chest pain, abdominal pain, nausea, and self-limited bleeding, with rates similar to those observed with EndoCinch.

The endoscopic full-thickness plication system NDO Plicator (NDO Surgical Inc., Mansfield, MA, USA) was approved by the FDA in 2004. It was designed to create a transmural, full-thickness, serosa-to-serosa plication below the

gastroesophageal junction at the angle of His, under endoscopic direct retroflexed view by means of a flexible pediatric endoscope (5.9 mm) inserted through a dedicated channel of the device. A pretied suture-based pledget is delivered to create the plication, performed between the anterior gastric wall and the fundus [33]. A randomized controlled trial on 78 patients who underwent the procedure reported a significant reduction in the time of distal esophageal acid exposure, measured with pH monitoring, PPI use, and improvement of esophagitis at 6 and 12 months [34, 35]. Another randomized trial by Rothstein et al. reported an extended improvement in quality of life and PPI usage at 5 years compared to the sham group [36].

This device was withdrawn from the market, too, because of several complications: persistent abdominal pain (20 %), sore throat (41 %), chest pain (17 %), dysphagia (11 %), burping (14 %), nausea (6 %), pneumothorax (1.6 %), pneumoperitoneum (1.6 %), and gastric perforation (1.6 %) [37].

The treatment of GERD with endoscopic procedures continues to evolve, as two FDA-approved endoluminal platforms now exist, that allow endoscopists to bring the surgical principles of an anterior partial fundoplication to patients without the worry or risk of the post-fundoplication complications seen with traditional laparoscopic surgery. In the last years, transoral incisionless fundoplication (TIF) has been shown to be an effective and promising therapeutic option in alternative to medical and surgical therapy; the procedure achieves long-lasting improvement of GERD symptoms (up to 6 years), cessation or reduction of proton pump inhibitor (PPI) medication in about 75 % of patients, and improvement of functional findings, measured by either pH or impedance monitoring. TIF reconfigures the tissue to obtain a full-thickness gastroesophageal valve from inside the stomach, by serosa-to-serosa plications which include the muscle layers: the new valve is capable to boost the barrier function of the LES with patient's less discomfort and possibly fewer technique-related complications and side effects, compared to surgery.

The endoluminal platform for TIF with the greatest global experience so far is that performed by using the EsophyX® device (EndoGastric Solutions Ltd., Redmond, WA, USA), with over 10,000 procedures performed to date. TIF with this device has been proven to be good, durable, long-term follow-up data in most of the series, mainly using the TIF 2 technique. The newest endoluminal fundoplication device to gain FDA approval was the MUSE™ (Medigus Ultrasonic Surgical Endostapler – Medigus Ltd., Omer, Israel).

EsophyX® constructs an omega-shaped valve 3–5-cm long, in a 250–300° circumferential pattern around the gastroesophageal junction, by deploying multiple nonabsorbable polypropylene fasteners through the two layers (the esophagus and stomach) under endoscopic vision of the operator. MUSE™ staples the fundus of the stomach to the esophagus below the diaphragm using multiple sets of metal stitches placed under an ultrasound-guided technique and creates an anterior fundoplication functionally similar to standard surgical Dor-Thal operation. In the case of sliding hiatal hernia, the procedure can be performed only if the hernia can be reduced below the diaphragm.

7.3 Techniques for Transoral Incisionless Fundoplication

7.3.1 Pre-procedure Evaluation

Preoperative upper GI endoscopy is mandatory to determine the distance between the incisor teeth and both the esophagogastric junction (EGJ) and the diaphragmatic hiatus and the greatest transverse dimension of the hiatus under full gastric distension. In fact, with the current TIF technique, only a hiatal hernia not exceeding 3.0 cm in length can be fully reduced below the diaphragm, while a plication performed in a hiatus with a transverse dimension >3.0 cm can end up in the thorax, situation that reduces the efficacy of the newly created valve. Prior to the procedure, patients should always undergo esophageal manometry, to exclude primary motility disorders, and 24-h pH-impedance monitoring to avoid the inclusion of patients with functional heartburn. If the MUSE device is used, barium swallow should be performed to assess the reducibility of the hernia, being its irreducibility a contraindication to the procedure.

7.3.2 Transoral Fundoplication by EsophyX® Device

The EsophyX® device is composed of:

(a) A handle, wherein controls are located
(b) An 18-mm diameter chassis, through which control channels run and a standard front view 9-mm diameter endoscope can be inserted
(c) The tissue invaginator, constituted of side holes located on the distal part of the chassis, to which external suction can be applied
(d) The tissue mold, which can be brought into retroflection and pushes the tissue against the shaft of the device
(e) A helical screw, which is advanced into the tissue and permits to retract the tissue between the tissue mold and the shaft
(f) Two stylets, which penetrate through the plicated tissue and the tissue mold, and over them polypropylene H-shaped fasteners can be deployed
(g) A cartridge containing 20 fasteners

The device has been recently updated and improved in a new generation instrument: the EsophyX® 2. The fastener deployment is similar to a surgical stapler firing mechanism with a reduction of control complexity and dual fastener deployment and is improved by managing trailing leg; the crossing profile has been reduced with the elimination of tissue mold elbow and increase of tissue mold lateral stiffness; the tissue mold tip covers stylets during deployment.

Details of the first- and second-generation devices are illustrated in Fig. 7.1.

The procedure is performed by two operators: one controls the device and the other one operates the endoscope.

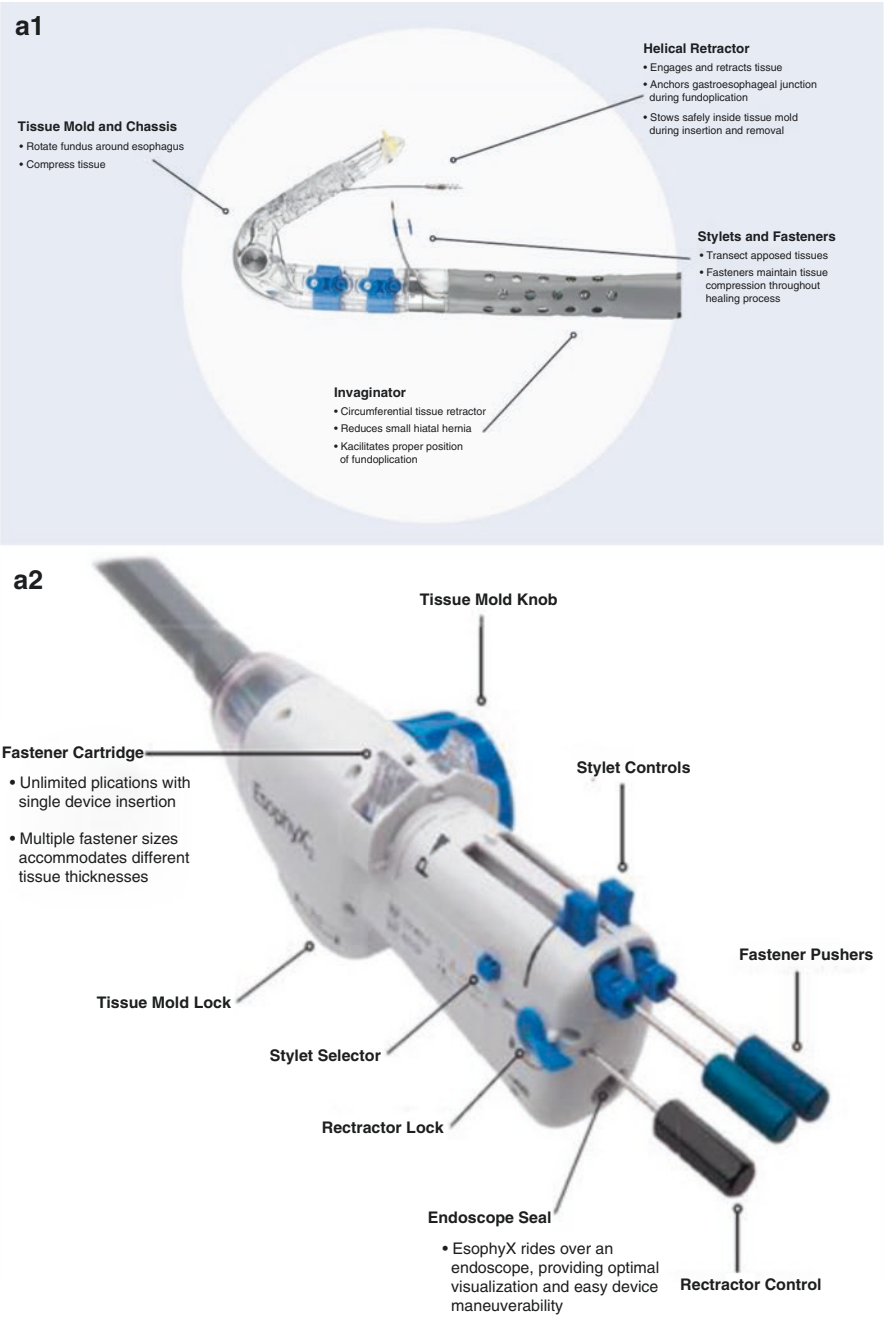

Fig. 7.1 The EsophyX® device: first- and second-generation devices (courtesy of EndoGastric Solutions, Inc. Redmond, WA, USA). (**a1**, **a2**) The device currently used (*©2014 EndoGastric Solutions*, Inc.). (**b1**, **b2**) The new generation device (*©2014 EndoGastric Solutions*, *Inc*.)

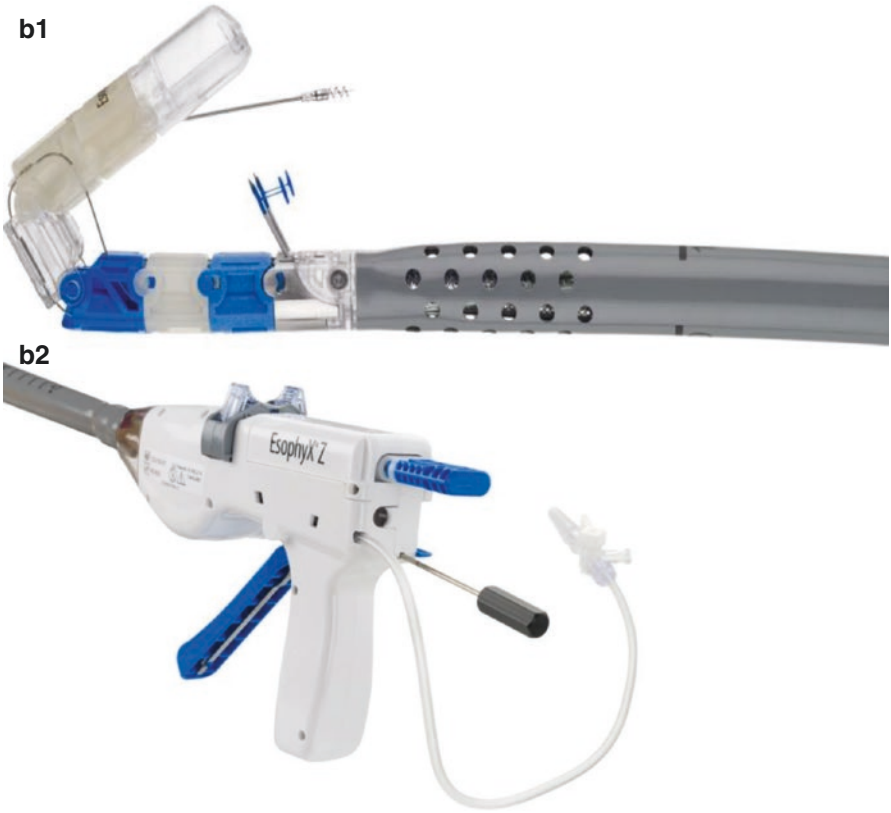

Fig. 7.1 (continued)

The device is inserted transorally with the patient in the left lateral or supine position, under general anesthesia. Hypopharyngeal perforation has been reported in this phase of the procedure if the device is introduced without an adequate caution; in difficult cases, the device can be gently rotated to pass the upper esophageal sphincter.

Once into the stomach, air or CO_2 is insufflated to distend the gastric cavity and permit an adequate vision of the gastric fundus and EGJ; CO_2 is preferable, because it leads to a faster and more sustained gastric insufflation and induces less discomfort to patients. With the endoscope placed in retroflexion position, the lesser curve is located at the 12 o'clock position and the greater curve at the 6 o'clock in the patient placed in left decubitus. Once the tissue mold is retroflexed, it is closed against the EsophyX® device, rotated to 11 or 1 o'clock position (lesser curve), and pulled back to place its tip just inside the esophageal lumen. At this point, the helical screw is advanced to engage the tissue under direct vision just below the Z line, the shaft of the device is advanced caudally, the tissue mold is opened, and the helical screw cable freed from the tissue mold. Then, a tension is applied to helical retractor, while a slight opening and closing of the tissue mold allow the fundus to slide

through the tissue mold; in this phase the stomach is being desufflated. Failure to desufflate the stomach during this phase of the procedure limits the size of the fundoplication.

After completing this maneuver, both helical retractor and tissue mold are locked in place; suction is applied to the tissue invaginator for approximately half a minute, and the device is then advanced caudally into the stomach, which has been re-insufflated. The latter maneuver ensures that esophagogastric plication is performed in an intra-abdominal position and reduces hiatal hernia, when present.

Plication is carried out by deploying multiple polypropylenes, H-shaped fasteners advanced over two stylets, one anterior and the other posterior. The fastener deployment process initiates on the far posterior and anterior sides of the esophagogastric valve adjacent to the lesser curvature and then is extended to the greater curvature by rotating the tissue mold axially to slide the stomach over the esophagus, resulting in circumferential tightening and a new valve circumference of >240°. The stylet is advanced under direct endoscopical vision through the tissue molded until its tip is seen by the operator. The fastener is then advanced over the stylet and deployed to create a serosa-to-serosa plication. Once the tip of the fastener becomes visible at the tissue mold, the stylet is pulled back while the fastener is maintained in place; by this way, the leading leg of the fastener is derailed and the fastener is deployed. Fourteen fasteners allowing seven plications are needed to construct a satisfactory circumferential gastroesophageal valve; however, the higher is the number of fasteners deployed, the more continent is the newly created valve. Details of the EsophyX® device's technique are shown in Fig. 7.2.

Endoscopic pre- and post-procedural findings are reported in Fig. 7.3.

Besides the standard procedure, two modified techniques have been reported over time to create the fundoplication. The technique we used in the last years engages the tissue by advancing the helical screw just below the Z line on the far posterior and anterior sides of the esophagogastric valve adjacent to the lesser curvature (11 and 1 o'clock position). Before inserting the stylet, a torque is applied by rotation (clockwise and counterclockwise at 11 and 1 o'clock, respectively) of the tissue mold locked; such a maneuver allows part of the fundus to rotate around the esophageal wall and more tissue to be engaged by the stylet. Four fasteners for each site are deployed at 1 and 11 o'clock and two fasteners for each site in the middle part of the valve, at 4, 6, and 8 o'clock position, to reinforce and prolong caudally the plication. This technique increased by 30 % the success rate of the procedure. With the standard TIF technique, 11/27 patients (40.7 %) didn't take PPI therapy at 12 months; with the application of the rotational TIF technique, 14/22 patients (63.6 %) were full responders.

Bell R. et al. have developed a rotational fundoplication, the so-called Bell Roll maneuver [38]. The helical retractor is engaged at 12 o'clock, and the tissue mold is placed at 6 o'clock; then the tissue mold locked is rotated toward the lesser curve by a radial motion of the handle of the device to the 12 o'clock position. This maneuver rolls the fundus over and around the distal esophagus to the 1 o'clock position.

At the end of the plication, an immediate endoscopy is performed to evaluate the pharynx, the esophageal lumen, the gastric fundus, and the fundoplication.

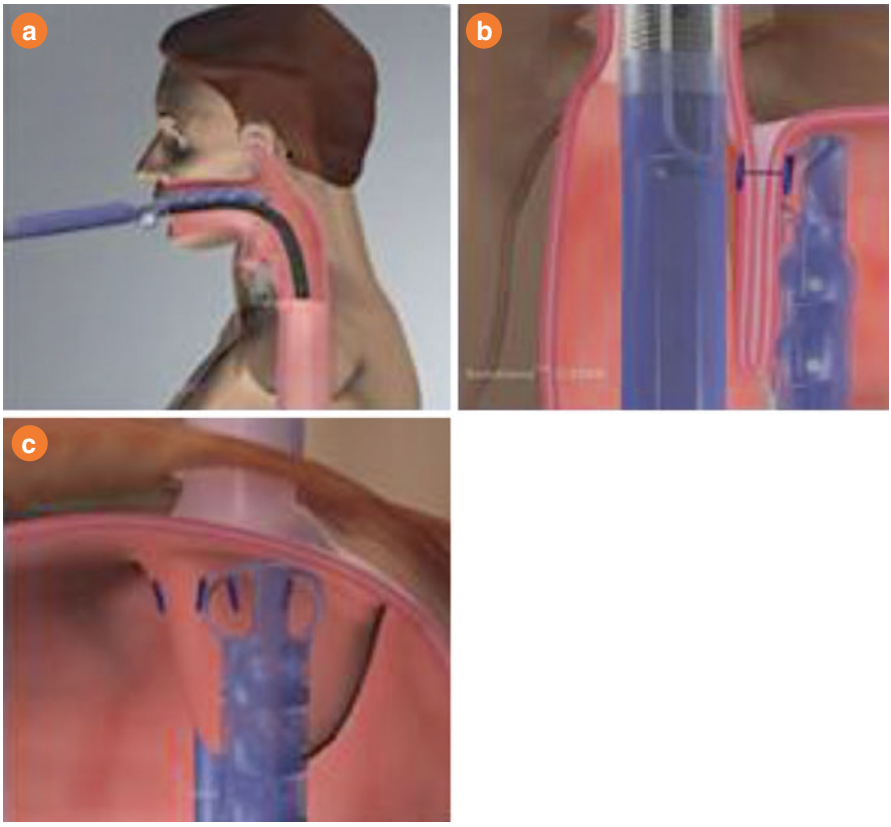

Fig. 7.2 Schematic representation of the procedure with EsophyX® device (Courtesy of EndoGastric Solutions Inc. Redmond, WA, USA). (**a**) The EsophyX® device enters the esophagus through the mouth and is positioned at the gastroesophageal junction; (**b**) the device wraps the fundus around the distal esophagus and fastens a tissue fold; this step is then repeated multiple times to reconstruct a robust, tight valve (**c**) (*©2014 EndoGastric Solutions, Inc.*)

7.3.3 Transoral Fundoplication by MUSE™ System

The MUSE™ system includes the endostapler and a console connected with the endostapler, containing a controller for the camera, ultrasonic range finder and various sensors, a pump for insufflation and irrigation, a suction system, and power and controls for the LED.

The endostapler has:

(a) A handle, wherein controls are located
(b) An insertion tube 15.5 mm in diameter, 66 cm long, containing the suction, insufflation/irrigation channels, and electrical and mechanical cables which operate the device

(c) A rigid section 66 mm in length that contains the cartridge. Each cartridge contains five standard 4.8-mm titanium staples, the ultrasound mirror, one alignment pin funnel, and two anvil screw funnels
(d) The distal tip, similar to that of an endoscope, with suction, irrigation, illumination (via LED), and visualization (via miniature camera) capabilities

The anvil, alignment pin, anvil screw, and ultrasound are all designed to ensure proper alignment and positioning of the device during stapling. The distal tip may be articulated in one direction to align with the rigid section and cartridge, with a bending radius of 26 and 40 mm.

Details of the device are illustrated in Fig. 7.4.

The procedure can be performed by one operator in experienced hands. The patient is placed in the supine position, under general anesthesia with endotracheal intubation. Positive end-expiratory pressure (PEEP) of at least 5 mmHg (7.5-cm H_2O) is administered. After a preliminary endoscopic assessment of the esophagus and stomach and once no contraindications are found, an overtube is placed. Then, the endostapler is inserted transorally through the overtube and gently advanced into the stomach under direct vision; passing the rigid section across the

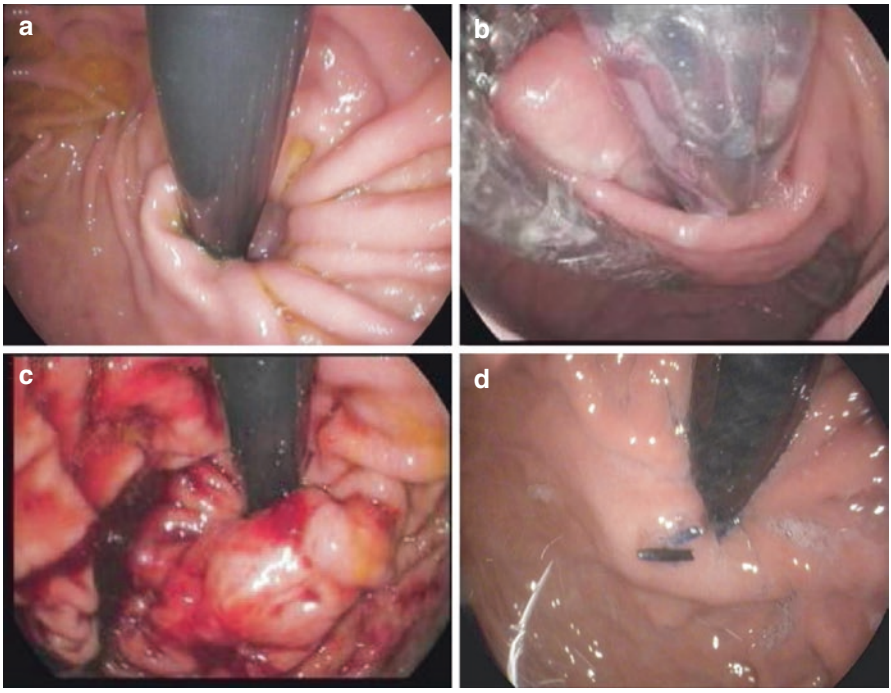

Fig. 7.3 Endoscopic views of the gastroesophageal valve before and immediately after the TIF procedure by EsophyX® device (authors' case). (**a**) The gastroesophageal valve: before the procedure with the EsophyX® device; (**b**) the "Bell Roll" maneuver to create the new gastroesophageal valve; (**c**) the gastroesophageal valve: immediately after the procedure with the EsophyX® device; (**d**) the gastroesophageal valve: 6 months after the procedure

pharyngoesophageal junction may encounter some resistance. In order to avoid applying excessive force and risk to injure the esophagus, the overtube may be withdrawn approximately 5 cm and then advanced with the endostapler as a unit. This maneuver can be repeated until the system reaches the esophageal midbody. Flexing the neck may make passage easier.

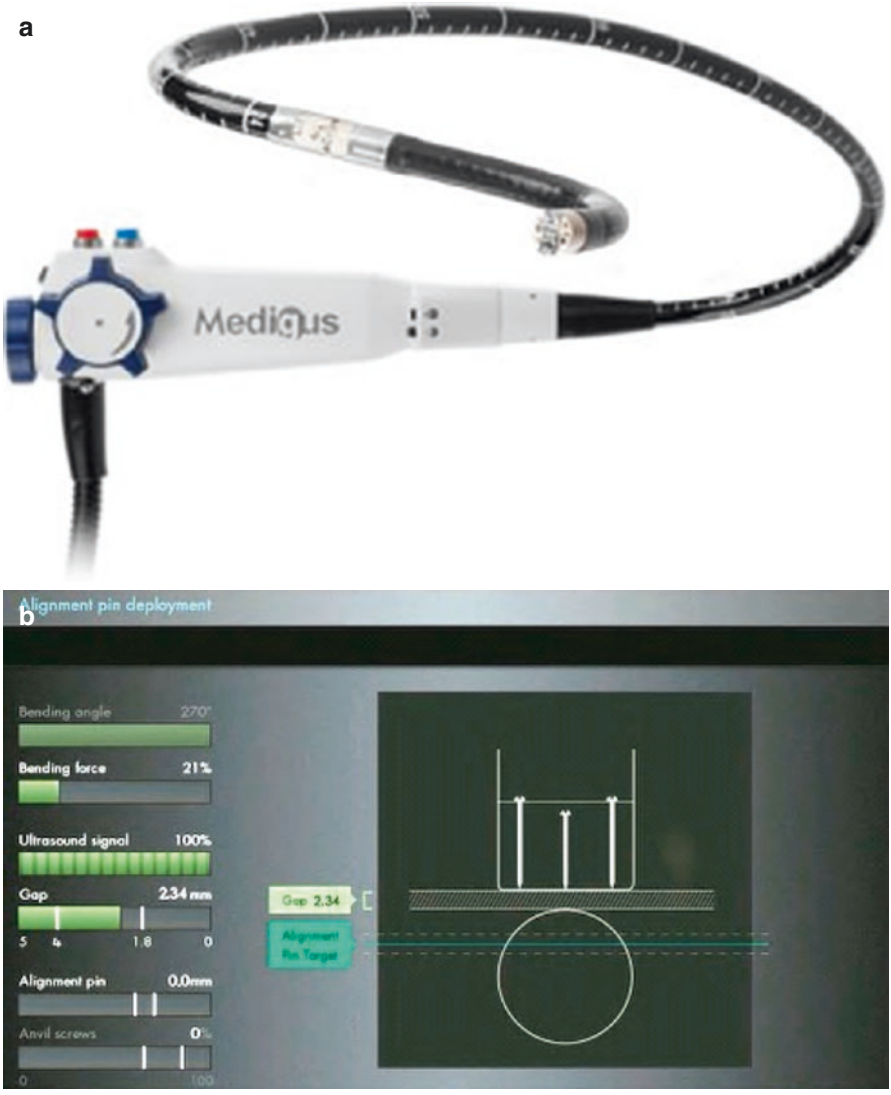

Fig. 7.4 The Medigus Surgical Ultrasonic Endostapler system, MUSE™ (Courtesy of Medigus Ltd., Omer, Israel). (**a**) The MUSE™ system (© *All rights reserved to Medigus Ltd. 2008–2015*); (**b**) the console connected with the endostapler, containing a controller for the camera, ultrasonic range finder, and various sensors (bending angle, bending force, alignment pin, anvil screws, gap) (© *All rights reserved to Medigus Ltd. 2008–2015*)

Once into the stomach, distended by insufflation of air or CO2, the stapler is advanced until the tip is approximately 5 cm past the EGJ and then retroflex by 180° to obtain an adequate vision of the gastric fundus and EGJ to select stapling location.

The most important stapling location is the leftmost location, which is typically performed first. This is the anchoring point for the fundus and should be placed as far to the left of the esophagus as possible. At times, depending on anatomy, it may be easier to perform the first stapling in a more central location. The additional stapling locations should be within 60–180° as long as the rightmost stapling should not be done on the lesser curve, because stapling in the lesser curve may attach the antrum to the esophagus and open the esophagogastric junction rather than close it. Additional staplings may be placed between the leftmost and rightmost. Once the correct location for stapling has been identified, all the procedures are performed under ultrasound guidance. Subsequent phases of the procedure include clamping tissue, deploying alignment pin, advancing anvil screw, stapling, and retrieving anvil screws [29]. Details of the MUSE™ device's technique are shown in Fig. 7.5.

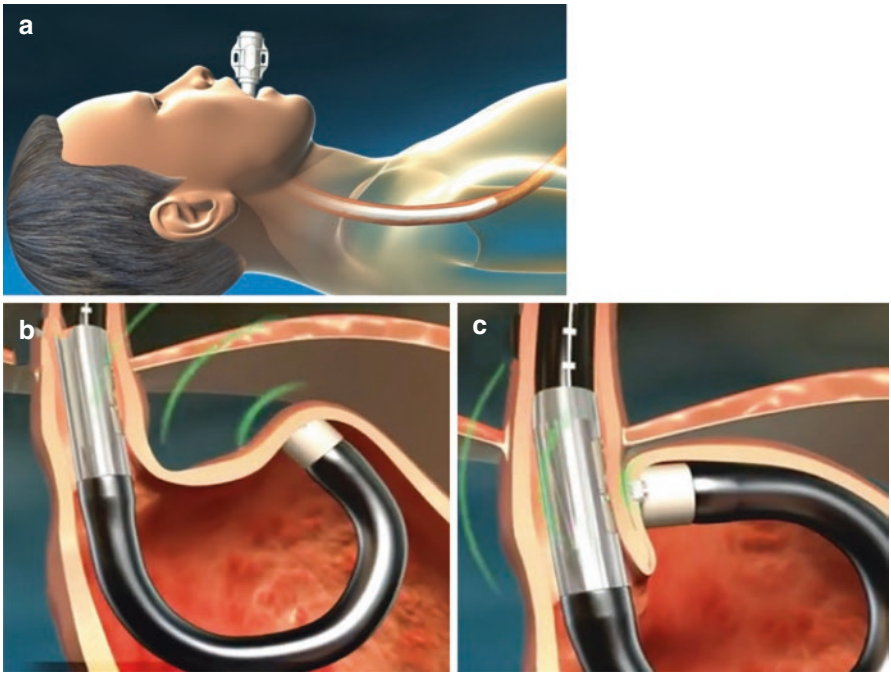

Fig. 7.5 Schematic representation of the Medigus Ultrasonic Surgical Endostapler (MUSE™) procedure (Courtesy of Medigus Ltd., Omer, Israel). (**a**) The endostapler is inserted transorally through the overtube and gently advanced into the stomach under direct vision; (**b**) once in the stomach, distended by insufflation of air or CO2, the stapler is advanced until the tip is approximately 5 cm past the EGJ and then retroflexed 180° to give adequate vision of the gastric fundus and EGJ to select the stapling location. The tissue is clamped and stapled under ultrasonic guidance; (**c**) this step is then repeated at least twice to reconstruct a robust, tight valve. Additional stapling locations should be within 60–180° of the valve circumference. EGJ, esophagogastric junction (© *All rights reserved to Medigus Ltd. 2008–2015*)

Endoscopic pre- and post-procedural findings after TIF with MUSE™ system are reported in Fig. 7.6.

7.3.4 Postoperative Care

Antiemetic prophylaxis with at least two drugs (according to the ASA recommendations for interventions with high risk of post-procedure nausea and vomiting) and full muscle relaxation throughout the procedure are mandatory for TIF. Antiemetic prophylaxis is maintained i.v. for 24 h, while broad-spectrum antibiotic therapy is maintained i.v. for 48 h and then by oral route over a 5-day period.

Almost all patients complain of transient pharyngeal irritation, as a result of insertion and manipulation of the device, and some have mild to moderate epigastric pain in 6 h after the procedure. Pain persisting for 2–4 days may require analgesics and should be considered for esophageal or gastric leak; CT scan and hydrosoluble contrast X-ray investigation should be carried out in these cases. Dysphagia and gas bloating are generally not reported by patients. White blood cell count may be slightly increased after the procedure. At discharge, patients are instructed to follow a liquid diet for the first 2 weeks and a soft diet for the next 4 weeks. PPIs are

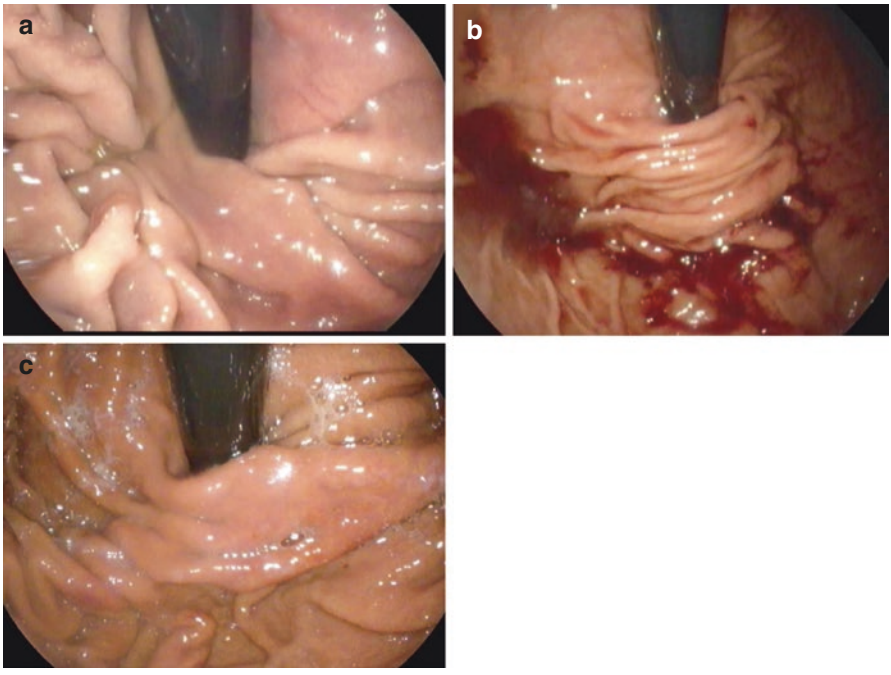

Fig. 7.6 Endoscopic views of the gastroesophageal valve before and after the TIF procedure with the Medigus Ultrasonic Surgical Endostapler (MUSE™) (authors' case). (**a**) The gastroesophageal valve: before the TIF procedure with the MUSE™ system; (**b**) the gastroesophageal valve: immediately after the TIF procedure by MUSE™ system; (**c**) the gastroesophageal valve: 6 months after the TIF procedure by MUSE™ system

discontinued 7 days after the procedure. Patients are also asked to refrain from vigorous exercise for 4 weeks.

7.4 Outcomes

To date, 20 prospective studies and one retrospective study, most of them observational and carried out in a limited number of patients, have been published on short- and medium-term follow-up (1–3 years) after TIF using EsophyX® device [38–58]. One study evaluated patients' outcomes up to 6 years after the procedure [56]. Sixteen studies assessed symptoms by means of the GERD health-related quality of life (HRQL); 11 evaluated pre- and post-procedure pH ± impedance recordings. A multicenter prospective study compared the efficacy of TIF versus omeprazole in a randomized controlled trial [59].

Overall, in 17 studies TIF was proven to discontinue antireflux medications or markedly decrease their dose; three studies arose concerns about the effectiveness of the procedure [45, 46, 49].

In the observational, nonrandomized studies, 6- and 12-month outcomes after TIF showed that 75–84 % and 53–85 % of patients had either discontinued PPI use or halved the dose of PPI therapy. Normalization of esophageal acid exposure, in terms of total acidic refluxes, number of refluxes, and DeMeester score, was reported in 37–89 % of patients.

Twenty-four months after TIF, daily high-dosage PPI dependence was eliminated in 75–93 % of patients. Endoscopic findings comparing fundoplication immediately after the procedure and 2 years later are reported in Fig. 7.7. In the two series reporting a 3-year follow-up, persistent discontinuation of daily PPI ranged from 74 to 84 % of cases [54, 56].

Only one study evaluated outcomes 6 years after TIF in 14/50 patients who underwent the procedure. High-dosage PPI dependence was eliminated in 86 % of patients, and approximately half of them completely stopped PPI use [56], providing evidence of the long-lasting effect of TIF on symptoms and PPI usage. Results are summarized in Fig. 7.8. Unsuccessful outcomes of TIF occurred mainly between 6 and 12 months after the procedure, while between 12 and 36 months, the results did not substantially differ. Six-year results were substantially similar to those reported at 36 months. These findings show that an appropriate patient selection plays a pivotal role in achieving clinical success after TIF and confirm that factors negatively affecting postoperative outcomes play a role early in the postoperative period in most patients. Operator's experience plays an important role in TIF outcomes, too. All TIF failures observed in our series occurred in patients who underwent the procedure early in the operator's learning curve. A retrospective study in 124 unselected patients carried out in two community hospitals and reporting, respectively, 75 and 80 % of patients free of typical and atypical GERD symptoms over a mean follow-up of 7 months confirmed that the operator's experience plays a major role in successful outcomes [52].

Only three prospective, randomized controlled trials have been so far published. Two assessed the 6-month efficacy of TIF versus omeprazole therapy: one showed

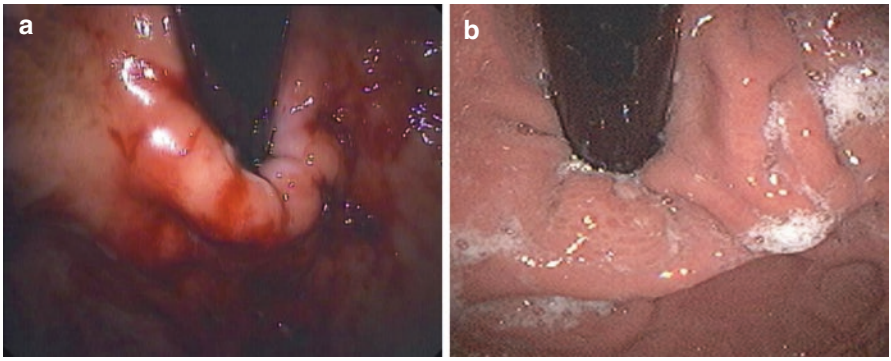

Fig. 7.7 Endoscopic views of the gastroesophageal valve immediately after and 24 months after the TIF procedure with EsophyX® device (authors' case). (**a**) The gastroesophageal valve: immediately after the TIF procedure with EsophyX® device; (**b**) the gastroesophageal valve: 24 months after the TIF procedure with EsophyX® device

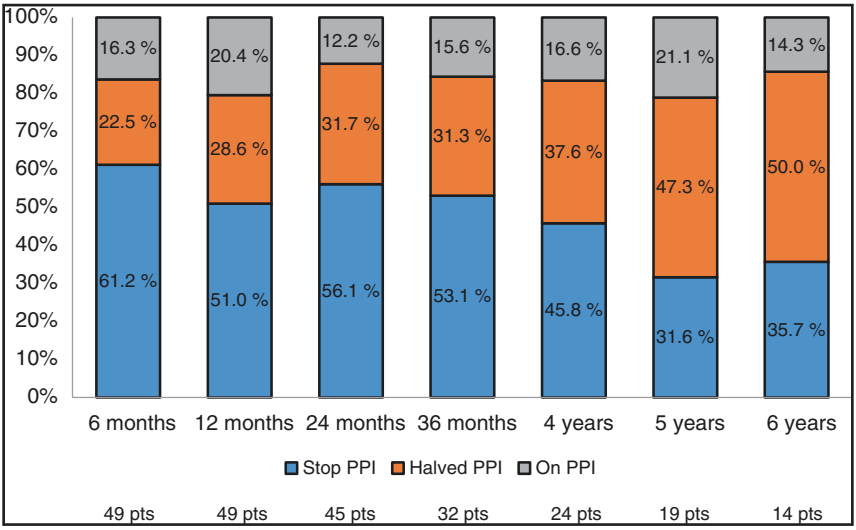

Fig. 7.8 Symptomatic responses 6 months and 1–6 years after TIF with EsophyX® device, classified according to proton pump inhibitor (PPI) use. Patients were grouped as complete responders (who completely stopped using PPI) or partial responders (who halved the previous PPI dose) and nonresponders (who still used the pre-TIF PPI dose): 12 months versus 6 months after TIF $P=0.8$; 24 versus 12 months $P=0.4$; 36 versus 24 months $P=0.7$; 4 years versus 36 months $P=1.0$; 5 versus 4 years $P=1.0$; 6 versus 5 years $P=1.0$

TIF more effective than PPI therapy in treating regurgitation and extraesophageal symptoms (97 % vs 50 % of patients, respectively; $P = 0.006$) [58]; the second one proved at intention-to-treat analysis TIF more effective than PPI in eliminating GERD symptoms (67 % vs 45 %, respectively; $P = 0.023$) [59]. These data show different outcomes and require additional randomized studies to clarify the efficacy of TIF in treating GERD. The third study compared 3- and 12-month results of TIF and Nissen fundoplication, showing TIF as effective and safe as Nissen fundoplication but with significantly lower hospital stay (2.9 ± 0.8 days vs 6.4 ± 0.7 days, respectively; $P < 0.0001$) [60].

Outcomes of TIF, with regard to the effects on PPI usage, are reported in Tables 7.1 and 7.2.

Table 7.1 Symptomatic responses after transoral incisionless fundoplication with the EsophyX® device

Follow-up		6 months	12 months	24 months	36 months	6 years
Cadière et al. [39]	2008	–	85 %	–	–	–
Cadière et al. [41]	2009	–	–	93 %	–	–
Testoni et al. [42]	2010	82 %	76 %	–	–	–
Velanovich et al. [44]	2010	79 %	–	–	–	–
Repici et al. [45]	2010	55 %	47 %	–	–	–
Demyttenaere et al. [43]	2010	–	53 %	–	–	–
Hoppo et al. [46]	2010	–	42 %	–	–	–
Barnes et al. [52]	2011	93 %	–	–	–	–
Bell et al. [47]	2011	75 %	–	–	–	–
Ihde et al. [48]	2011	76 %	–	–	–	–
Trad et al. [51]	2012	–	82 %	–	–	–
Testoni et al. [53]	2012	–	–	75 %	75 %	–
Petersen et al. [50]	2012	58 %	–	–	–	–
Bell et al. [55]	2012	86 %	–	–	–	–
Muls et al. [54]	2013	–	77 %	–	65 %	–
Bell et al. [61]	2013	–	82 %	–	–	–
Bell et al. [57]	2014	–	–	77–80 %	–	–
Trad et al. [58]	2015	93 %	–	–	–	–
Hunter et al. [59]	2015	–	72 %	–	–	–
Testoni et al. [56]	2015	84 %	80 %	88 %	84 %	86 %

Table 7.2 Symptomatic responses after transoral incisionless fundoplication with the MUSE™ system

Follow-up		6 months	12 months	24 months	36 months	6 years
Zacheri et al. [62]	2015	83 %	–	–	–	–
Roy-Shapira et al. [63]	2015	–	82 %	73 %	73 %	–

Unsuccessful outcomes after TIF were reported in three studies. Two series found worsening of distal esophageal acid exposure in 66.7 % of cases and persisting of GERD symptoms in 68 % of cases, respectively, in small series with a short follow-up (12 months). An open-label study comparing TIF with robot-assisted Nissen fundoplication in PPI-refractory GERD patients reported complete symptom remission and normalization of esophageal acid exposure time in 30 and 100 % of patients after TIF and 50 and 100 % after Nissen fundoplication [49]. These data suggest that in a challenging clinical setting such as PPI refractoriness, Nissen fundoplication seems more effective than TIF by EsophyX® device.

In case of failure of TIF, surgical fundoplication has been shown feasible, without technical difficulties or increased morbidity. Surgical revision after TIF failure was reported in from 8.1 to 18.0 % of cases [53, 54, 60, 64]. In two studies Nissen fundoplication induced complete disappearance of symptoms in all cases of TIF failure (respectively, 9 and 11 patients) [64, 65]. In our series, however, only one out of the four patients who underwent Nissen fundoplication for persisting GERD symptoms after TIF stopped acid-suppressive therapy: this finding may depend upon the particular subset of patients who underwent TIF in our series, who had only a mild impairment of the gastroesophageal junction and suffered from GERD-related symptoms that could have been generated by a number of complex mechanisms, including increased esophageal sensitivity to refluxate.

On the other hand, re-intervention after laparoscopic fundoplication has been reported in up to 14 % of cases, and TIF has been found effective after failed surgery [61].

Only two studies assessed so far the outcomes after TIF performed by MUSE™ technique (anterior fundoplication): a pilot study with a 5-year follow-up and a multicenter prospective study [62, 63]. The pilot study assessed GERD-related symptoms and PPI use up to 5 years after the procedure in 13 subjects: GERD-related symptom score at 6 months was normalized in 92 % of cases; PPI use was completely stopped or reduced by half in 77 % of cases (54 % off PPI completely) [63]. PPI therapy was abolished or reduced by half in 82 % of patients at 12 months and in 73 % at 36 months; this rate persisted unchanged up to 5 years. Another study assessed outcomes after TIF performed by MUSE™ technique (anterior fundoplication) in a multicenter, prospective international study enrolling 66 patients with a 6-month follow-up [62]. GERD-related symptom scores improved by more than 50 % in 73 % of patients and 64.6 % of them were no longer using daily PPI medication. Among patients who continued to take PPI, 56.5 % reduced by more than 50 % the dose. At 24-h pH recording, the total time with esophageal pH < 4.0 decreased significantly from baseline. There were no post-procedure side effects commonly seen after laparoscopic fundoplication as gas bloating, inability to belch or vomit, dysphagia, or diarrhea.

An important issue regarding all new interventional procedures introduced in clinical practice is the recognition of technique- or patient-related factors that could affect the outcomes.

In our series, from the technical point of view, the number of fasteners deployed and the rotational technique applied were associated with a good outcome; a larger number of fasteners raised the probability of being a responder about fourfold.

Another study reported the number of satisfactory fasteners as critical point for the success of the procedure, too. The rotational technique raised the probability of being a responder by one half, confirming other recent reports. Among patient-related factors affecting postoperative outcomes in our series, preoperative Hill grades III and IV, hiatal hernia larger than 2 cm, and ineffective esophageal motility were associated with a higher rate of unsuccessful results. The defective clearance of refluxate could induce an epithelial sensitization that might produce symptoms, even in the presence of low-volume gastroesophageal reflux. A univariate and multivariate analysis of preoperative factors influencing symptomatic outcomes of TIF by EsophyX was performed on data from 158 consecutive patients identified [57]. Predictors of successful outcomes for patients with typical symptoms have been found in the age ≥50 years, a GERD health-related quality of life score (GERD-HRQL) on PPIs ≥15, a reflux symptom index >13 on PPIs, and the gastroesophageal reflux symptom score ≥18 on PPIs. Age and GERD-HRQL remained significant predictors also at the multivariate analysis. For patients with atypical GERD symptoms only, a GERD-HRQL score ≥15 on PPIs was associated with successful outcomes.

7.5 Complications

The overall complication rate reported in studies so far available for TIF by EsophyX® ranges from 3 to 10 %. Major complications occurred rarely and were bleeding, mucosal tears or perforation requiring endoscopic intervention or surgery, pneumothorax, and mediastinal abscesses. The finding of free air in the abdomen immediately after the procedure is not always a sign of clinically relevant complications. Bleeding requiring transfusions has been reported in about 3–5 % of cases and can occur at the site of the helical retractor insertion. Mediastinal abscesses have been reported in less than 2 % of cases. No procedure-related deaths occurred. In the only study so far published on TIF by Medigus, minor side effects such as chest pain, sore throat, transient atelectasia, shoulder pain, and belching were reported in 5.5–22 % of patients; major complications were reported in 6.2 % of cases (4 out of 64 patients) and were pneumothorax (one case), pneumothorax and esophageal leak (one case), and bleeding (one case). Patients with pneumothorax and esophageal leak and with bleeding required intervention. All major complications occurred in the first 24 patients.

No late complications or long-lasting side effects occurred for both TIF techniques.

Conclusions

In the last years, TIF has been performed only in clinical trials including patients with typical gastroesophageal reflux symptoms responsive or partially responsive to PPI therapy, without hiatal hernia or with small hiatal hernia (<3 cm), who refused lifelong medical therapy, or were intolerant to PPIs or required high dosage of antisecretory maintenance therapy. Patients with grade C and D esophagitis, according to Los Angeles classification and Barrett's esophagus, were

excluded from these studies. In the majority of studies, TIF was done by EsophyX® device and was proven effective in the short term in approximately 75 % of patients, eliminating the daily dependence from PPIs in half PPI-responsive GERD patients and markedly reducing the overall PPI dose in the other cases. Similar results were obtained more recently for TIF done with Medigus endostapler, but in few studies.

Such results were confirmed in studies with a follow-up up to 3 years, although few, and in the only follow-up up to 6 years. Troublesome procedure-related persisting side effects were not reported in all the published studies.

Overall outcomes showed that TIF procedure can be an effective and safe alternative therapeutic option to surgery in a selected subset of patients, as were those recruited in the published studies. In available series with 3- to 6-year follow-up, post-TIF results were slightly inferior to those reported in patients operated by Nissen fundoplication, but similar to those with surgical posterior partial (Toupet) or anterior partial (Dor-Thal) fundoplication, without any of the surgery-related side effects such as dysphagia and gas bloat.

Currently, based on clinical results, TIF may be offered as an alternative to surgery in patients suffering from gastroesophageal reflux disease and grade A-B esophagitis, if present, with the sole limitation of the length and reducibility of an eventual hiatal hernia, which is at present the only limiting factor affecting the choice of the intervention. TIF may also be offered to patients who have some risk of developing persistent postsurgical side effects. To date, data supporting the efficacy of TIF in the treatment of severe grades of esophagitis or symptoms associated with oropharyngeal reflux are lacking.

However, as for all new procedures introduced in clinical practice, despite favorable short- and medium-term outcomes, questions still arise about the long-term efficacy of the techniques, mainly for the MUSE, in controlling symptoms and persistence over time of the newly created valve. Therefore, randomized controlled trials are warranted in order to establish the role of TIF in the management of GERD patients, which, among the two techniques, could be more effective and safe.

In addition, preoperative patient-related anatomo-functional findings and procedure-related technical aspects that can help select patients and predict a successful outcome need to be clarified.

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