# Transoral Incisionless Fundoplication

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**KEYWORDS**

• Esophagitis • Fundoplication • Gastroesophageal reflux • Hiatal hernia • Humans • Laparoscopy • Proton pump inhibitors • Treatment outcome reflux

**KEY POINTS**

- On the GERD spectrum, TIF may be a treatment option among patients with GERD with an intact and functioning crura, but would benefit from strengthening, tightening, and lengthening the LES complex. Therefore, patient selection is very important in determining which patients will likely have the best outcome.
- As an endoscopic procedure, TIF reduces EGJ distensibility, thereby decreasing tLESRs, and also creates a 3-cm high-pressure zone at the distal esophagus in the configuration of a flap valve.
- Level 1 evidence confirms both the safety and efficacy of TIF 2.0, especially in patients who have troublesome regurgitation despite PPI therapy.
- The concomitant laparoscopic hernia repair with TIF for those patients with hiatal hernia greater than 2 cm is now emerging as a potential strategy within laparoscopic antireflux surgery.
- Future potential applications that are currently being investigated include the use of TIF in (1) patients with Barrett's esophagus; (2) patients with achalasia after per-oral endoscopic myotomy; (3) bariatric patients before and after laparoscopic sleeve gastrectomy; and (4) patients after lung transplant.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) results from an incompetent barrier resisting the retrograde movement of gastric content. This mechanical defect can be restored with various techniques, one of which involves advancing and fixing the gastric fundus around the lower esophagus using a transoral longitudinal and rotational technique. The purpose of this article is to review the rationale, mechanisms of action,

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appropriate patient selection, technical aspects, clinical results, safety, and emerging application of the procedure known as transoral incisionless fundoplication (TIF 2.0).

## WHY TRANSORAL INCISIONLESS FUNDOPLICATION?

GERD is the most prevalent gastrointestinal disorder in the United States,[1] and the extent of anatomic alterations underlying the mechanism of GERD can be viewed as a spectrum from normal to a single anatomic alteration (eg, weak lower esophageal sphincter [LES]) to multiple anatomic alterations, such as weak LES, open diaphragmatic hiatus, and hiatal hernia (**Fig. 1**).[2,3] The degree of anatomic alterations also seem to correlate with the complications of GERD, namely degree of esophagitis, the presence of Barrett's metaplasia[4] dysplasia and its progression to esophageal adenocarcinoma. Thus, as GERD is a spectrum disorder, treatment should be individualized to the anatomic alterations of each patient. Although medical and surgical therapy have been the mainstay of treatment of GERD, there are currently several Food and Drug Administration (FDA)-approved devices available for endoscopic treatment of GERD, thus filling the therapeutic gap between medications and surgery. Endoscopic treatment options are now considered appropriate treatment in patients early in the GERD spectrum.

## HOW DOES IT WORK?

Pressure gradients between the abdominal stomach and thoracic esophagus would favor retrograde movement of gastric contents into the esophagus during much of human activity, were it not for a complex antireflux mechanism at the juncture of the esophagus, stomach, and diaphragm. One of the 2 primary components to this antireflux barrier is intrinsic to the esophagus and comprises the LES and esophagogastric junction (EGJ). The second component is the crural diaphragm, which in a normal individual acts in concert with the LES to open during swallowing and then contract, pinching the esophagus, to maximize the threshold preventing gastric reflux. The 2 components taken together constitute the high-pressure zone (HPZ) found during esophageal manometry, and high-resolution manometry demonstrates that both the crural diaphragm and the LES open synchronously during swallowing and belching.

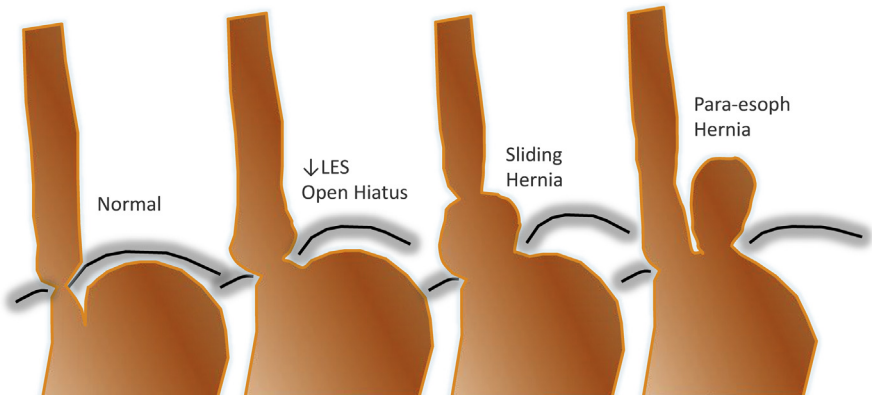


**Fig. 1.** Spectrum of anatomic defects among patients with gastroesophageal reflux disease. LES, lower esophageal sphincter.

Transient or permanent mechanical dysfunction of one or both of these components is a prerequisite for GERD. In early stages of GERD, transient opening of the HPZ occurs too frequently and is too often accompanied by reflux of gastric contents rather than merely air. Whether this occurs because of a neurologic reflex or transient shortening of the LES leading to loss of sphincteric competence has been a topic of debate; regardless, antireflux procedures, such as Nissen fundoplication have been found to decrease both the frequency of these transient events as well as the amount of gastric liquid reflux during these transient events. In more advanced stages of GERD, a chronic loss of LES length and pressure, and separation of crural diaphragm from the LES due to hiatal hernia, lead to more severe reflux.

Even though acid-reducing medication is the mainstay of treating GERD, medication does not decrease the frequency of reflux events, and persistent symptoms related to ongoing reflux often require a mechanical solution. Historically open or laparoscopic fundoplication procedures have been considered the "gold standard" intervention to restore the antireflux barrier because they enable restoration of both the crural component by hiatal hernia repair and the LES by creating a flap valve via fundoplication. However, both the level of invasiveness, and the gas-bloat side effects related to a supracompetent flap valve, have led to a search for alternative interventions.

In patients who have a largely intact crural sphincter (ie, absence or a very limited hiatal hernia, Hill grade 1 or 2), the potential for an endoluminal approach to restoring the LES exists. Conceptually this could entail decreasing the distensibility of the whole or just the bottom of the LES to prevent shortening and loss of LES competence during gastric distention, increasing the resting pressure of the LES, reinforcing the sling fibers at the gastroesophageal (GE) junction (**Fig. 2**), or locally altering vagal neuromodulation of transient LES openings.

Although early attempts at endoscopic fundoplication were unsuccessful and lacked durability, more robust devices and techniques designed to physically reconstruct a flap valve, namely the TIF procedure, have resulted in more successful and durable restoration of LES function, and have done so without the degree of side effects seen with a Nissen fundoplication. In its current technique iteration (TIF 2.0), this procedure is anatomically and physiologically similar to surgical fundoplication (**Fig. 3**). During the procedure, the gastric fundus is folded up and around the distal esophagus, which has been retracted below the diaphragm, and anchored with polypropylene fasteners. This results in tightening and reinforcing the sling fibers (see **Fig. 2**A, B) of the proximal stomach (the lower portion of the LES), accentuating the cardiac notch, steepening the angle of His, and reestablishing the flap valve mechanism. One can argue that, although both Nissen and TIF create a HPZ at the GE junction,[5] the TIF 2.0 procedure is actually creating a true flap valve.

The mechanism of action of the TIF procedure in many ways mirrors that of the Nissen laparoscopic antireflux surgery (LARS).[5] One paper, published by Rinsma and colleagues[6] characterizes such mechanisms. In their study involving 15 patients, they performed 90-minute postprandial combined with high-resolution manometry and impedance-pH monitoring followed by an ambulatory 24-hour pH-impedance monitoring. EGJ distensibility was evaluated using an endoscopic functional luminal imaging probe before and directly after the procedures. The patients were followed for 6 months. With regard to the stationary esophageal manometry and impedance-pH monitoring performed directly after the procedure, TIF 2.0 resulted in a marked reduction of both the number of transient LES relaxation episodes (tLESRs) (16.8 $\pm$ 1.5 versus 9.2 $\pm$ 1.3; $P<.01$) and the number of tLESRs associated with liquid-containing reflux after the procedure (from 11.1 $\pm$ 1.6 versus 5.6 $\pm$ 0.6; $P<.01$). TIF

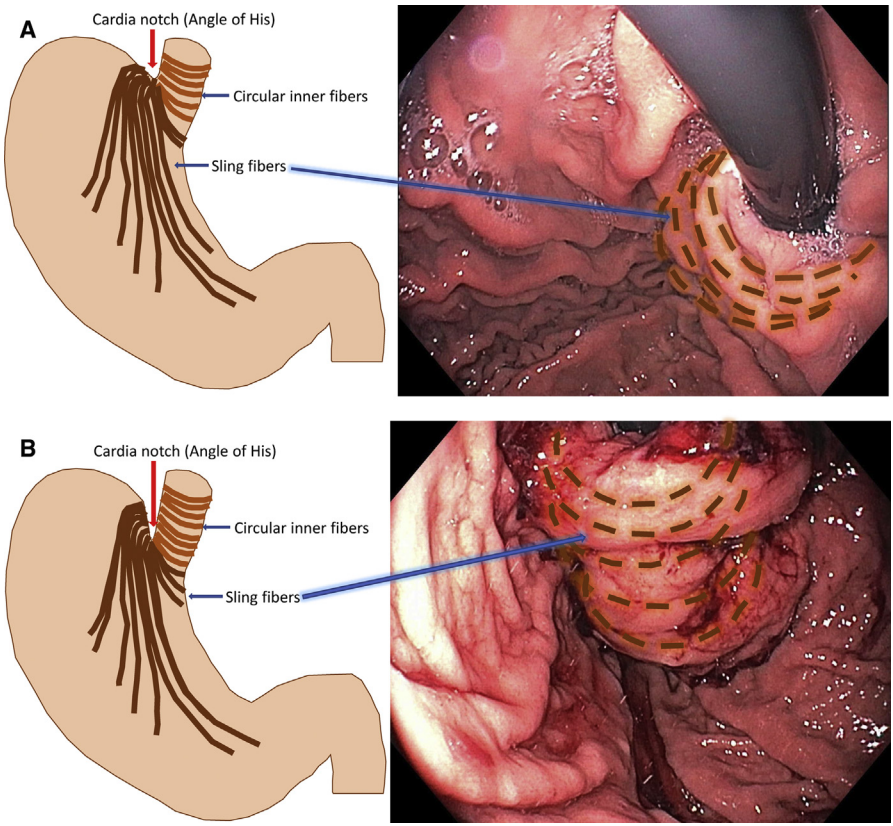


**Fig. 2.** Diagram and image of the muscle fibers in the distal esophagus (circular inner fibers) and proximal stomach (sling fibers) that make up the entirety of the lower esophageal sphincter. (*A*) Pre-TIF valve showing "flat" angle of His (Cardia Notch), short valve, and loose gastric sling fibers. (*B*) Post-TIF valve showing "steep" angle of His (Cardia Notch), tall valve, and tighter gastric sling fibers.

| Principles Of Antireflux Surgery | TIF 2.0 Procedure | Laparoscopic Fundoplication |
|---|---|---|
| Reduce hiatal hernia ≤2 cm | ✓ | ✓ |
| Repair hiatal hernia >2 cm and close crura | ✓[a] | ✓ |
| Elongate the intraabdominal esophagus | ✓ | ✓ |
| Fundoplication | ✓ | ✓ |
| • Approximate and tighten the fundus around the distal esophagus | ✓ | ✓ |
| • Recreate the dynamics of the angle of His | ✓ | ✓ |
| • Restore the distal high pressure zone | ✓ | ✓ |

**Fig. 3.** Applying the Principles of Antireflux Surgery to Laparoscopic Fundoplication and TIF 2.0. All of the principal elements are preserved in both. [a] As of June 22, 2017, EsophyX device indication was expanded to include patients with hiatal hernias larger than 2 cm, where a laparoscopic hiatal hernia repair (HHR) reduces the hernia to 2 cm or less. (*Courtesy of* EndoGastric Solutions, Redmond, WA; with permission.)

also led to a decrease in the number and proximal extent of reflux episodes and an improvement of acid exposure in the upright position; conversely, TIF had no effect on the number of gas reflux episodes, corroborating the low incidence of post-TIF gas-bloat symptoms. EGJ distensibility was reduced after the procedure ($2.4 \pm 0.3$ versus $1.6 \pm 0.2$ $mm^2$/mm Hg; $P<.05$). Also of note, the basal LES pressure in the fasted state was increased after TIF (from $13.9 \pm 1.0$ to $20.5 \pm 1.8$ mm Hg; $P<.01$). Thus, TIF reduces EGJ distensibility, thereby decreasing tLESRs, which is the main mechanism for upright refluxers. It also creates a 3-cm HPZ at the distal esophagus in the configuration of a flap valve, which should decrease both upright and supine reflux. However, because it is a 270° partial fundoplication, and the flap valve luminal diameter is controlled by the diameter of the device (preventing overtightening), gas can still escape from the stomach into the esophagus, minimizing the gas-bloat side effect.

## WHICH PATIENTS SHOULD CONSIDER TIF?

Patient selection for TIF is critical. First, the patient must have a clear indication for an antireflux procedure (see Rena Yadlapati and John E. Pandolfino's article, "Personalized Approach in the Work-up and Management of GERD," in this issue). One must then discern which patients are good candidates for TIF alone, and which patients are better served with a laparoscopic or combined approach (see the Concomitant Laparoscopic Hernia Repair and Transoral Incisionless Fundoplication section, below). We like to discuss with our patients that there are actually 2 "valves" that prevent reflux: the "inside valve" (LES) and the "outside valve" (crura). In addition, there are 3 components of the antireflux anatomy that we need to assess: (1) whether there is a hiatal hernia that needs to be reduced, (2) whether the right crura, which acts like a sling or noose around the GE junction[7,8] (see Robin A. Zachariah and colleagues' article, "Mechanism and Pathophysiology of GERD," in this issue), needs to be tightened, and (3) whether the LES needs to have a valve reconstruction. The axial or vertical length of the hiatal hernia can be assessed by an esophagram or upper endoscopy. Neither modality is perfect, as sliding hernias can often be missed. Even more tricky, however, is the assessment of the crural tightness (diaphragmatic hiatus). The Hill classification performed during a retroflex view is the most effective way to quantify the crural opening. However, this can often be misleading (ie, underestimating the Hill grade) for the following reasons: (1) insufficient time and insufflation during retroflex (**Fig. 4**) and (2) a fat pad can fill the open hiatus, creating a "stuffing" affect (**Fig. 5**). We recommend 60 seconds be spent in retroflex with active insufflation to determine the Hill classification. A Hill grade 1 or 2 is acceptable for TIF alone. However, if the hiatus is open more than 2 cm (or 2 scope diameters, ie, Hill 3), or there is an axial hernia length of more than 2 cm (Hill 4), the patient will most likely need a crural repair, which cannot be accomplished with TIF alone. We call this the $2 \times 2$ rule. In our experience, underestimation of the Hill grade is the most common reason for TIF failure. This cannot be overemphasized. In a paper describing salvage laparoscopic surgery among 5 patients who failed TIF, 3 of the 5 patients were found to have significant hiatal hernia that required repair at the time of revision.[9]

## HOW DO WE DO IT?

The TIF 2.0 procedure is performed using the disposable, single-use, EsophyX Z+ device (EndoGastric Solutions, Redmond, WA), designed to create full-thickness serosa-to-serosa plications and reconstruct valves approximately 3 cm in length, and 200° to 300° in circumference (**Fig. 6**). The device is comprised of an 18-mm-diameter frame

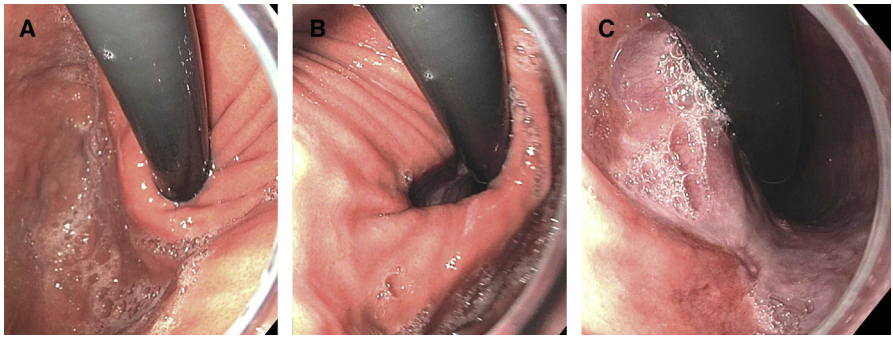


**Fig. 4.** The "60 seconds rule" for assessing the diaphragmatic hiatus in retroflexed position underscores the common mistake of underestimating the Hill grade. (*A*) Initially, after only a few seconds of inspection, assessment appears to be a Hill grade 1. (*B*) About 30 seconds later, with continuous $CO_2$ insufflation and scope rotation, the hiatus opens up to Hill grade 2, approximately 2 cm in diameter. (*C*) At close to 60 seconds, the hiatus opens even wider to approximately 3 cm in diameter.

through which a standard endoscope can be introduced (Fig. 7A); a handle with controls; tissue invaginator (Fig. 7B), consisting of side holes positioned at the distal end of the frame to which external suction can be applied; the tissue mold (Fig. 7C), which pushes tissue against the chassis of the device; a helical retractor (Fig. 7D), which is advanced into the tissue and allows for the retraction of the tissue between the tissue mold and the chassis; 2 stylets (Fig. 7E) that puncture the plicated tissue and tissue mold, and over which polypropylene H-shaped fasteners can be deployed; and a cartridge (Fig. 7F) that holds 20 fasteners.

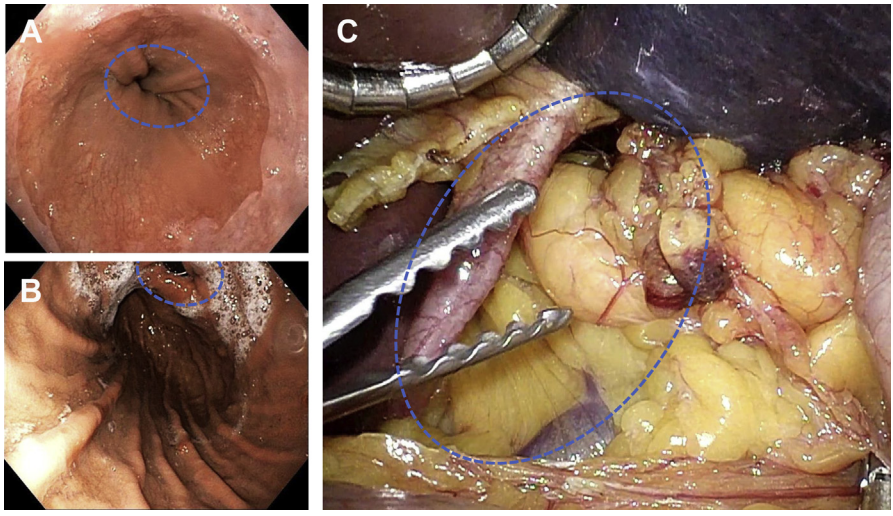


**Fig. 5.** One of the pitfalls for underestimating the Hill grade is the presence of a fat pad. (*A*) Antegrade view of the GE junction (*blue circle*) seems to be normal. (*B*) Retroflex view appears to be a Hill grade 2. (*C*) Concomitant laparoscopic view showing a 3 × 2-cm open hiatus that is "stuffed" with fat, which compresses the GE junction resulting in underestimation of an actual Hill grade 3 anatomy by endoscopy.

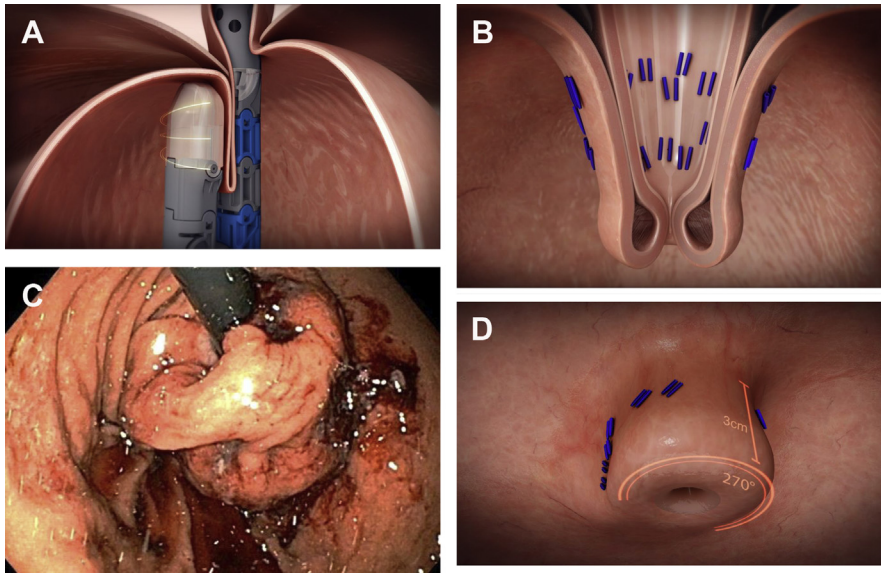


**Fig. 6.** The goal of TIF 2.0 is to create full-thickness serosa-to-serosa plications with the reconstruction of a valve that is 200° to 300° in circumference and 3 cm in length. (*A*) Traction of tissue into the EsophyX Z+ device results in the full 3-cm length neo valve reconstruction. (*B*) Full-thickness serosa-to-serosa plications cause fibroelastic tissue deposition and tissue adhesion for a durable valve. (*C*) The end results is a GE junction that is narrower, longer, and floppy. (*D*) Endoscopic image immediately after TIF showing a 4-cm length valve that is nearly circumferential. (*Courtesy of* EndoGastric Solutions, Redmond, WA; with permission.)

We perform the procedure under general anesthesia with muscle relaxation and positive pressure ventilation to aid in reducing any hernia, in the supine position to decrease pressure on the GE junction from the liver. Before the start of the procedure, it is helpful to first perform a diagnostic esophagogastroduodenoscopy examination to measure the length from the patient's incisors to the Z-line as well as the diaphragmatic pinch, note any anatomic abnormalities, and verify that the stomach is free of food contents. If there is any question about the compatibility of the endoscope, the Endoscopy Compatibility Tool can be used to verify that the diameter of the endoscope will be compatible with the EsophyX Z+.

The endoscope is then liberally coated with lubricant, and lubricant is also placed over the endoscope seal of the EsophyX Z+ device. The endoscope is then inserted through the seal and advanced until the endoscope tip extends approximately 10 to 15 cm beyond the distal tip of the device. Lubricant is then reapplied over the distal end of the endoscope and the distal two-thirds of the device. Predilation using an over-the-wire dilator (54 or 57 Fr) may be used to relax the hypopharynx and upper esophageal sphincter. The device is then placed in the patient's oral cavity, gently advanced under direct visualization, and advanced into the stomach. The device tissue mold will occasionally encounter resistance as it passes through the larynx and cricopharyngeus, and jaw thrust may aid safe passage. Sometimes having the anesthesiologist deflate the balloon of the endotracheal tube for just a few minutes will also help the device to pass through the hypopharynx. The stomach is insufflated (using an autoregulated $CO_2$ insufflator

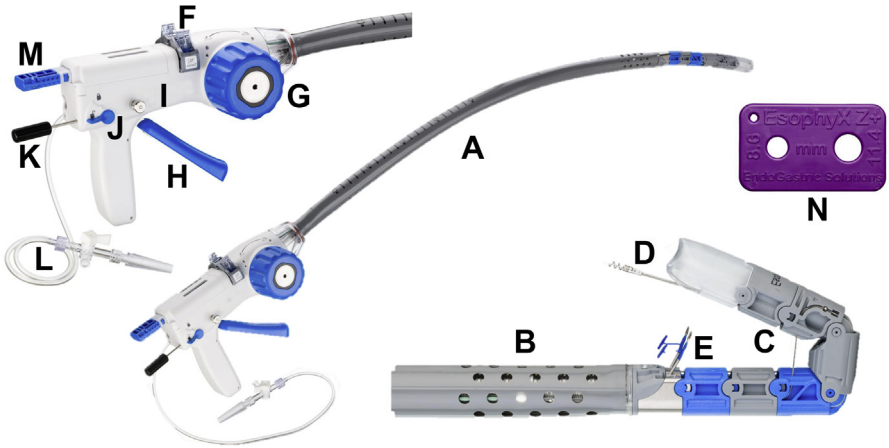


**Fig. 7.** The multiple parts and features of the EsophyX Z+ device. (A) Flexible shaft with measurement markings. (B) Invaginator suction ports that "couple" the device shaft to the tubular esophagus to aid in reducing a small hernia and in "pushing off the diaphragm." (C) Tissue mold that opens and closes to capture and rotate tissue for plication. (D) Helical retractor to retract tissue into the tissue mold to create valve length. (E) Stylets with H-shaped fasteners are "fired" from the shaft, through tissue, and into the receiving clear plastic chamber at the distal tip of the device. (F) Fastener cartridge containing 20 polypropylene fasteners that load 2 at a time. (G) Tissue mold knob that opens and closes the tissue mold. It has a ratchet mechanism that precludes backwards slippage of the wheel and a safety feature that precludes overtightening. (H) Fastener delivery trigger, which fires the stylets and fasteners across the tissue mold. (I) Fastener delivery trigger release, which must be depressed to release the trigger handle. (J) Helical retractor control lock, which, once in lock position, still allows the retractor to be pulled back, but does not allow slippage away from the device. (K) Helical retractor control, clockwise rotation of which allows insertion into tissue and counter-clockwise rotation to come off tissue. (L) Stop cock for invaginator, which connects suction to the invaginator ports. (M) Fastener pushers, which receive and push the fasteners down to the distal end of the device. (N) Endoscope compatibility tool, used to confirm that the endoscope will fit into the device. (*Courtesy of* EndoGastric Solutions, Redmond, WA; with permission.)

set to 15–18 mm Hg) through the working channel of the flexible endoscope, and the endoscope is positioned in retroflexion. Under direct visualization, the device is further advanced into the stomach until the second blue segment is seen entering the stomach, and then rotated to align the back of the tissue mold to the lesser curve of the stomach. The endoscope is retracted into the distal aspect of the chassis, and the tissue mold is closed. The endoscope is then re-advanced into the stomach through the side hole and placed back in retroflexion to visualize the EsophyX Z+ device and the GE junction (**Fig. 8**).

If there is a small hiatal hernia, the device can be withdrawn back into the distal esophagus, where suction is applied to engage the distal esophageal mucosa. The device can then be advanced to bring the herniated stomach back below the diaphragm.

Using the positions on a clock face, with 12 o'clock precisely on the lesser curve (**Fig. 9**), we usually begin at the posterior corner, which is toward the 11 o'clock position. If possible, we try to plant the helical retractor as close to 12 o'clock as possible (for both posterior and anterior corners), which allows for maximal folding of the fundus around the esophagus (**Fig. 10**); this has become known as the "Bell Roll."[10]

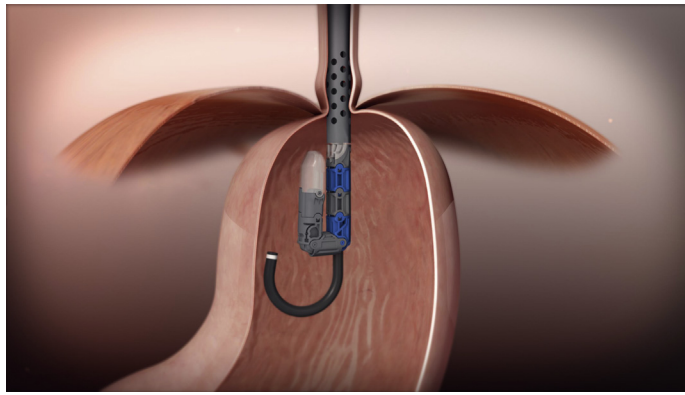

**Fig. 8.** The endoscope in position to provide light and visualization of the working end of the EsophyX Z+ device. The scope is first withdrawn from the distal tip back into the channel, the tissue mold is then closed, and the scope is re-advanced through the side port to assume this position. (*Courtesy of* EndoGastric Solutions, Redmond, WA; with permission.)

The helical retractor is now advanced until it is in contact with tissue just below the squamocolumnar junction, and the helical retractor control is rotated clockwise to engage tissue (Fig. 11). The mold and retractor are advanced by 1 cm, and the mold is opened slightly to release the retractor from the tissue mold. The entire device

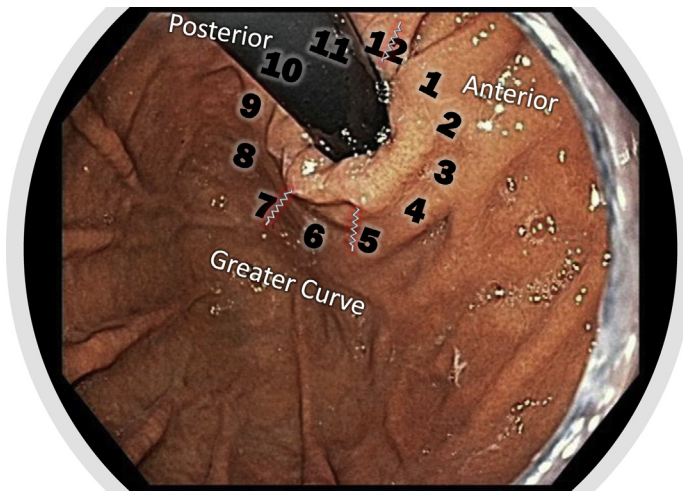


**Fig. 9.** Mapping of the TIF 2.0 protocol using standard landmarks for placement of the helical retractor and rotation toward the lesser curve. Using the positions on a clock face, with 12 o'clock precisely on the lesser curve we usually begin at the posterior corner, placing the retractor as close to 12 o'clock as possible, and rotating the tissue clockwise toward the lesser curve. After 3 plications in the posterior side, the device is rotated to the anterior side and 3 additional plications are placed with counter-clockwise wrapping of the fundus toward the lesser curve. Then the helix is secured at 5 o'clock and 2 plications are placed here (5 and 6 o'clock). The helix is then secured at 7 o'clock and 2 additional plications are placed here (7 and 8 o'clock). These last 4 plications on the greater curve do not involve any tissue rotation/wrapping.

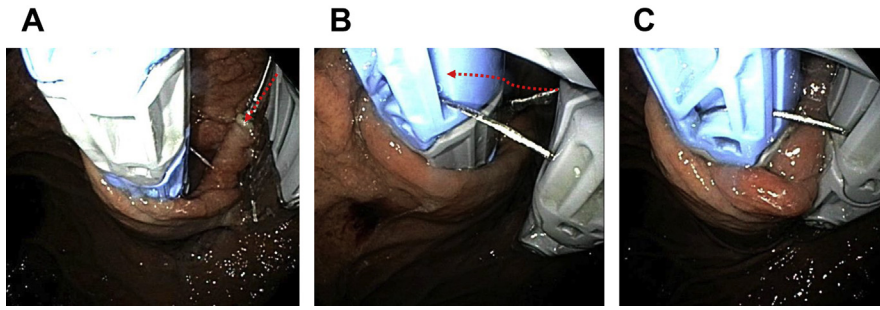


**Fig. 10.** The "Bell Roll" technique on the anterior corner. (*A*) With the helical retractor firmly secured at 12 o'clock, (*B*) the tissue mold is rotated back out to 6 o'clock, followed by de-sufflation and retraction of tissue; then (*C*) the tissue mold is rotated back toward the lesser curve, capturing the fundic tissue and wrapping it toward the back of the esophagus.

is then withdrawn to a level such that the proximal blue segment is above the GE junction (**Fig. 12**). This "sets" the device so that the 2 sharp stylets will exit the device approximately 1.5 cm proximal to blue segment.

While desufflating, the retractor is pulled down maximally (this excursion length will determine the length of the neo valve) (**Fig. 13**). With retraction, this tissue is pulled in between the tissue mold and the chassis. Once fully retracted (around 3 cm), rotation toward the lesser curve is started using a counter-clockwise motion with the handle. This will result in a clockwise rotation on the monitor. It is a combination of retraction and rotation that will optimize the wrap.

Once retraction and rotation is complete, there is a stepwise sequence that ensues, which is likened to a little "dance" called "lock, lock, suck; push off the diaphragm; fire" (**Fig. 14**). The first "lock" is to lock the helical retractor (see **Fig. 7**J). The second "lock" is to close and lock the tissue mold (see **Fig. 7**G). The "suck" is to have the assistant turn on the invaginator suction (see **Fig. 7**L) to couple the esophagus with the device (analogous to tight jeans or a wet suit, see **Fig. 14**B, C). At this point the

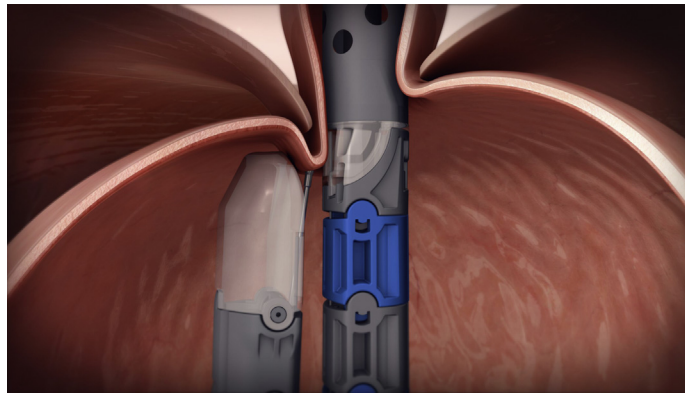

**Fig. 11.** Engaging the helical retractor. The helical retractor control is rotated clockwise to engage tissue, ideally right at the squamocolumnar junction where it tends to be most secure. (*Courtesy of* EndoGastric Solutions, Redmond, WA; with permission.)

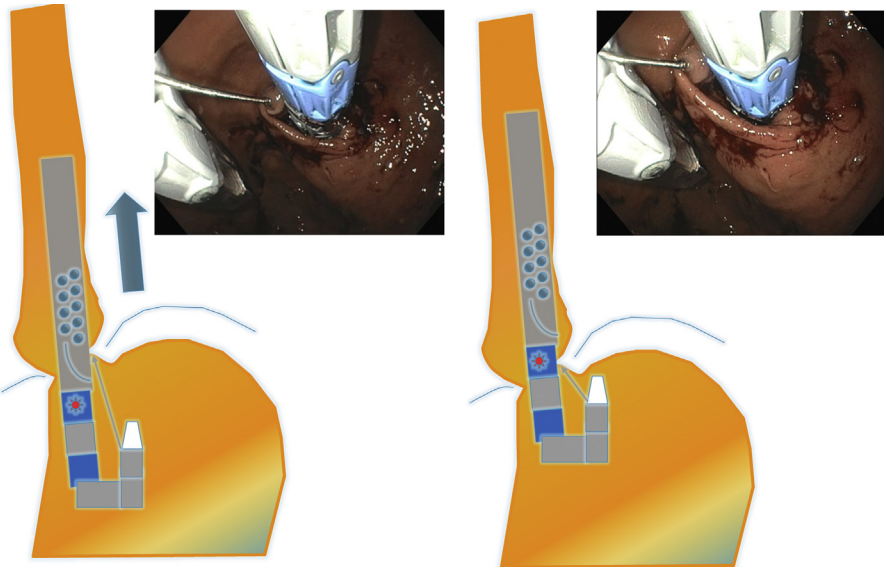

**Fig. 12.** "Set" the device. The entire device is then withdrawn to a level such that the proximal blue segment is above the GE junction. This "sets" the device so that the 2 sharp stylets will exit the device approximately 1.5 cm proximal to blue segment.

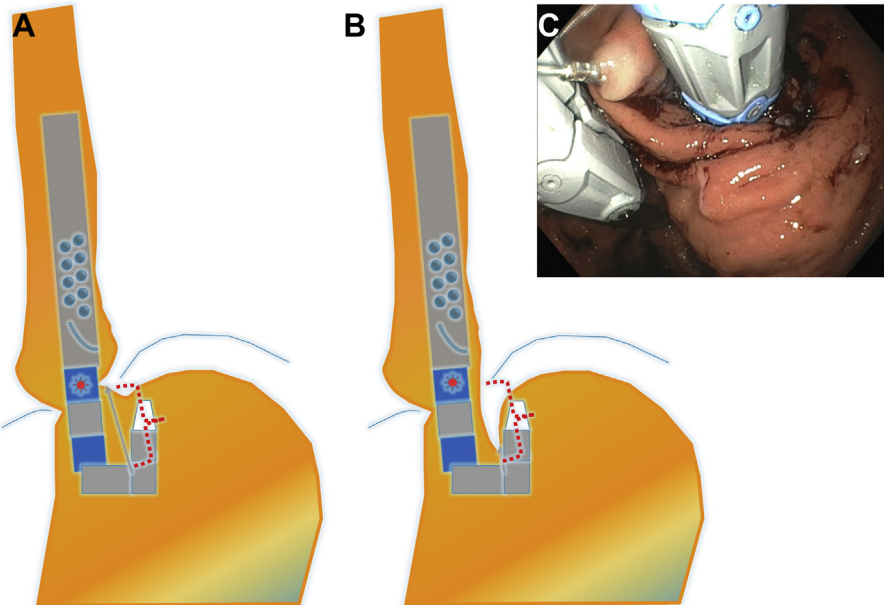


**Fig. 13.** "Pull on the retractor" to create the valve length. (*A*) While desufflating, the retractor is pulled down maximally (this excursion length will determine the length of the neo valve). (*B*) With retraction, this tissue is pulled in between the tissue mold and the chassis. (*C*) Once fully retracted (around 3 cm length, the helix wire is maximally shorten), begin rotation toward the lesser curve using a counter-clockwise motion with the handle. This will result in a clockwise rotation on the monitor. It is a combination of retraction and rotation that will optimize the wrap.

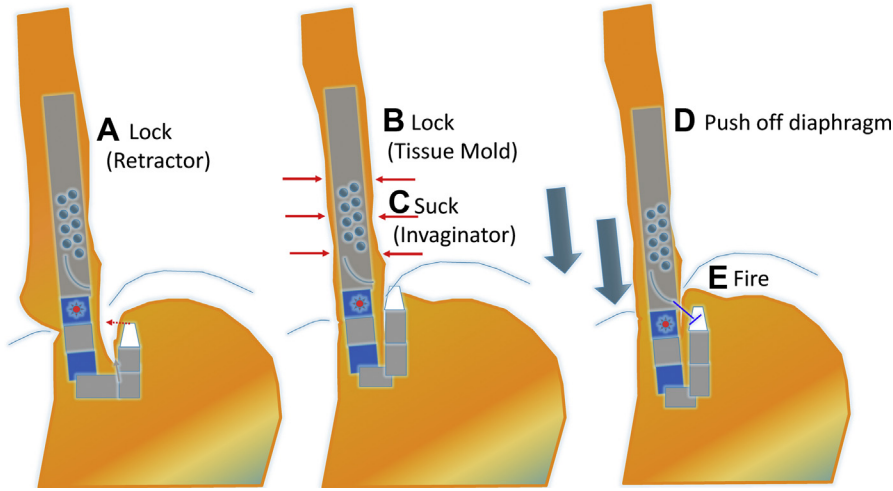


**Fig. 14.** "Lock, lock, suck, push off the diaphragm, fire" sequence. (A) "Lock"—first lock the helical retractor control lock. (B) "Lock"—then lock the tissue mold. (C) "Suck"—turn on the stop cock to apply suction to the invaginator ports. (D) "Push off the diaphragm"—with the device and esophagus now coupled via suction, push the device 0.5 to 1.0 cm distally to ensure that the stylet and fasteners do not penetrate through the diaphragm, but fire below the diaphragm. (E) "Fire"—depress the fastener delivery trigger release followed by squeezing the fastener delivery trigger. After this, one should reload the fasteners, release the suction, reinsufflate, and repeat as necessary.

stomach is reinsufflated. "Push off the diaphragm" means that the scope and device (as one construct) are re-advanced to the initial length of the GE junction (see Fig. 14D), which ensures that the stylets do not fire into and through the diaphragm muscles. Fasteners are loaded (if not done already), and finally "fire" (see Fig. 14E) by depressing the safety button (see Fig. 7I) and squeezing the trigger (see Fig. 7H) to deploy the double fasteners (see Fig. 7E).

At this time, the fasteners can be reloaded, and the invaginator turned off. The device is rotated out of the corner, and the retractor is unlocked and the tissue mold opened. This sequence is repeated for the second and third plications into the posterior corner. After 3 plications, the tissue mold is opened and the helical retractor removed. The device is then rotated to the anterior corner (Fig. 15), and an additional 3 plications are performed here.

Then, the device is positioned at the 5 o'clock and 7 o'clock positions (Fig. 16A–C). Here the main goal is retraction (no rotation at these positions) to gain additional length at the greater curve. These steps are repeated, taking 2 plications with the retractor at 5 o'clock (plicate at 5, 6) and another 2 plications with the retractor relocated to 7 o'clock (plicate at 7 and 8 o'clock).

After these 10 plications (3 posterior, 3 anterior, and 4 greater curve), which result in 20 fasteners deployed, whether further plications are necessary must be assessed. Typically, an additional 2 to 8 bites are performed to visual satisfaction (see Fig. 16D). As one becomes more proficient with the standard technique described here, there is room for "tailoring" the plications to the individual's anatomy. For example, in patients with previous failed Nissen fundoplication, one needs to consider where the previous fundoplication is intact and the areas of opportunity for TIF revision.

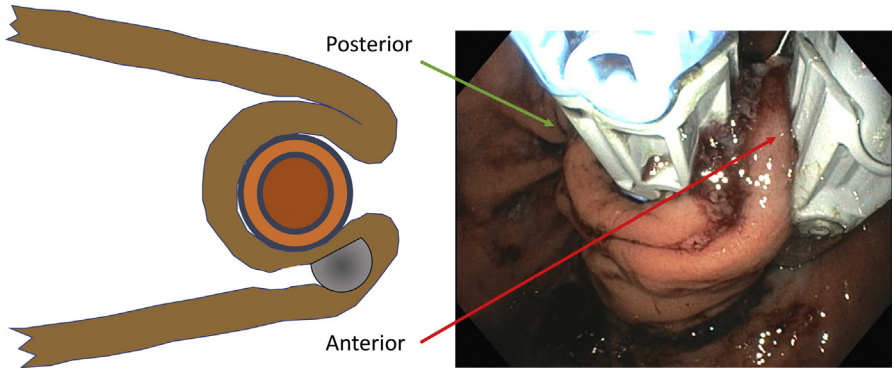


**Fig. 15.** After completing 3 plications in the posterior corner, the device is rotated to the anterior corner. The same sequences shown in Figs. 11–14 are now repeated in the anterior corner.

## HOW WELL DOES IT WORK?

The TIF technique has undergone significant evolution from a gastrogastric plication to an esophagogastric plication, with various degrees of roll and depth. In addition

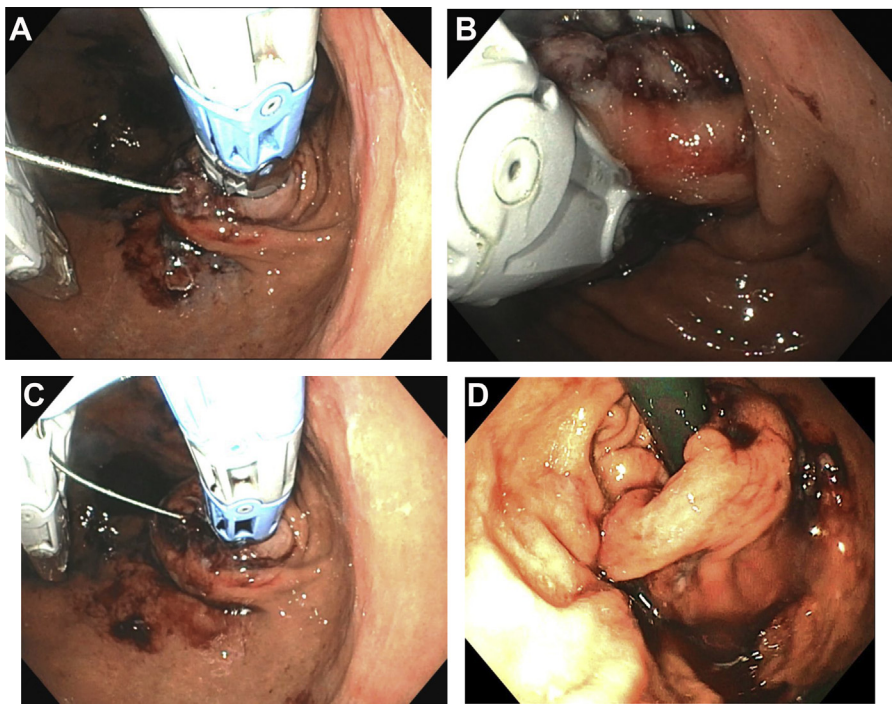


**Fig. 16.** (A) Position the device and helical retractor at the 5 o'clock and (C) 7 o'clock positions. (B) While desufflating, the retractor is pulled down maximally, (here there is no rotation into the corners), followed by same steps as in Figure 14. Here the main goal is retraction to gain additional length at the greater curve. Repeat these steps, taking 2 plications with the retractor at 5 o'clock (plicate at 5, 6) and another 2 plications with the retractor relocated to 7 o'clock (plicate at 7 and 8'oclock). (D) Completed Valve.

to technique modifications, the device itself has undergone several major iterations to improve ease of use, improve fastener delivery, and enable fastener delivery without having to visualize the stylet/fastener deployment. With improved ease of use, the proceduralist has been able to focus more on a standardized technique. With the ability to deploy fasteners without visualizing deployment enables a greater degree of rotational movement, which, at least on the anterior aspect of the fundoplication, can be significant. These enhancements have led to significantly better reproducibility and outcomes than the previous versions of EsophyX.

An additional aspect of evaluating outcomes concerns the relation of classic study design to patient-centric care. For most study designs, continued proton pump inhibitor (PPI) use in some form has been used as a measure of failure. However, most patients coming to antireflux interventions are not adequately controlled on medication (hence the decision to have an invasive procedure). A patient-centric approach would argue that a successful intervention would include taking a patient with persistent, uncontrolled symptoms on medication, to having controlled symptoms regardless of medication use.

There have been more than a dozen noncomparative studies evaluating the most current TIF 2.0 procedure.[11–22] There have also been multiple analyses of published studies, and rather than repeat the same we will highlight the level 1 data here.

There have been 3 recent randomized control clinical trials using TIF 2.0, which uses the most advanced technique, similar to LARS. The first, known as the TEMPO trial, consisted of 63 patients randomized to TIF (40 patients) versus high-dose PPI (23 patients).[23] The primary outcome was elimination of daily troublesome regurgitation or extraesophageal symptoms. Secondary outcomes were normalization of esophageal acid exposure, PPI use, and healing of esophagitis. At the 6-month follow-up, troublesome regurgitation was eliminated in 97% of patients who had undergone TIF versus 50% of patients on PPIs (relative risk [RR] = 1.9; 95% CI, 1.2-3.11; $P = .006$). Globally, 62% of patients who had undergone TIF experienced elimination of regurgitation and extraesophageal symptoms versus 5% of patients on PPIs (RR = 12.9; CI, 1.9–88.9; $P = .009$). Esophageal acid exposure was normalized in 54% of patients who had undergone TIF versus 52% of patients on PPIs (RR = 1.0; 95% CI, 0.6–1.7; $P = .914$). A total of 90% of patients who had undergone TIF were off PPIs. The authors concluded that, at the 6-month follow-up, TIF was more effective than maximum standard dose PPI therapy in eliminating troublesome regurgitation and extraesophageal symptoms of GERD. Of the 63 patients receiving TIF, 5 year follow-up data were available as follows: 60 were available at 1 year, 52 at 3 years, and 44 at 5 years.[21] Troublesome regurgitation was eliminated in 88% of patients at 1 year, 90% at 3 years, and 86% at 5 years. Resolution of troublesome atypical symptoms was achieved in 82% of patients at 1 year, 88% at 3 years, and 80% at 5 years. No serious adverse events occurred. There were 3 reoperations by the end of the 5-year follow-up (5%). At the 5-year follow-up, 34% of patients were on daily PPI therapy as compared with 100% of patients at screening. The total GERD-HRQL (health-related quality of life) score improved by decreasing from 22.2 to 6.8 at 5 years ($P<.001$). This paper concluded that most patients undergoing TIF 2.0 experienced a durable elimination of troublesome GERD symptoms with no severe adverse events (SAEs) or safety concerns, and that TIF 2.0 could be a cost-effective alternative to laparoscopic Nissen fundoplication.

The second clinical trial studying TIF 2.0 against PPIs was the RESPECT trial,[24] which was a prospective, sham-controlled trial to determine if TIF reduced troublesome regurgitation to a greater extent than PPIs in patients with GERD. A total of 696 patients with troublesome regurgitation despite daily PPI with 3 validated

GERD-specific symptom scales, on and off PPIs, were initially screened. Of these, 87 patients with GERD and hiatal hernias $\leq$2 cm were randomly assigned to groups that underwent TIF and then received 6 months of placebo, or sham surgery and 6 months of once- or twice-daily omeprazole (controls, $n = 42$). Patients were blinded to therapy during the follow-up period and reassessed at 2, 12, and 26 weeks. At 6 months, patients underwent 48-hour esophageal pH monitoring and esophagoduodenoscopy. By intention-to-treat analysis, TIF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) ($P = .023$). A larger proportion of controls had no response at 3 months (36%) than patients who received TIF (11%) ($P = .004$). Control of esophageal pH improved after TIF (mean 9.3% before and 6.3% after; $P<.001$), but not after sham surgery (mean 8.6% before and 8.9% after). Patients from both groups who completed the protocol had similar reduction in GERD symptom scores. The authors concluded that TIF was an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy, based on evaluation 6 months after the procedure.

The third clinical trial performed in a European study was a double-blind sham-controlled study in patients with GERD who were chronic users of PPIs.[25] Forty-four patients were randomized equally to 22 patients in each group. The primary effectiveness endpoint was the proportion of patients in clinical remission after a 6-month follow-up. Secondary outcomes were: PPI consumption, esophageal acid exposure, reduction in Quality of Life in Reflux and Dyspepsia and Gastrointestinal Symptom Rating Scale scores and healing of reflux esophagitis. Results showed that the time in remission after TIF procedure (197 days) was significantly longer compared with those submitted to the sham intervention (107 days) ($P<.001$). After 6 months, 13/22 (59%) of the patients with chronic GERD remained in clinical remission after TIF.

A recent meta-analysis[26] was conducted using data only from these 3 randomized studies that assessed the TIF 2.0 procedure compared with a control. The purpose of the meta-analysis was to determine the efficacy and long-term outcomes associated with performance of the TIF 2.0 procedure in patients with chronic long-term refractory GERD on optimized PPI therapy, including esophageal pH, PPI use, and quality of life. Results from this meta-analysis, including data from 233 patients, demonstrated that TIF subjects at 3 years had improved esophageal pH, a decreaseu in PPI use, and improved quality of life. Other recent publications are also showing favorable durability with long-term outcomes at 5 years[18,21] and even preliminary data at 10 years.[27]

## IS IT SAFE?

Two recent meta-analyses reported that the SAE rate is approximately 2% to 2.5%.[28,29] Huang and colleagues[29] reviewed 16 studies (4 randomized controlled trials [RCTs] and 12 prospective observational trials) reporting 19 SAEs in a total of 781 patients who underwent TIF (2.4%). Incorporating multiple versions of how the procedure has been done over the years (endoluminal fundoplication, TIF 1.0, and TIF 2.0), SAEs included 7 perforations, 5 cases of post-TIF bleeding, 4 cases of pneumothorax, 1 requiring intravenous antibiotics, and 1 involving severe epigastric pain. One death was reported 20 months after the TIF procedure, which was categorized as "probably not related" to the procedure. If, however, one were to exclusively examine the 4 RCTs that prospectively followed adverse events, there was only 1 SAE reported among 188 patients (0.5%), which was a pneumoperitoneum managed with needle decompression. Post-TIF dysphagia can occur transiently in 10% to 18% of patients,[25,30,31] bloating has been reported to occur in 18%,[25,31] and both seem to be self-limited. The overall safety of the procedure has been well established. Since

2008, there have been over 25,000 TIF 2.0 procedures performed, and the reported SAE rate is approximately 0.36% with no mortalities. Although uncommon, the reported SAE's include: esophageal perforation, pleural effusion, mucosal laceration or tear, bleeding, abscess, esophageal laceration, esophageal leak, stomach leak, pneumothorax, pneumoperitoneum, and mediastinitis. Details of these SAEs can be found in the Manufacturer and User Facility Device Experience (MAUDE) FDA database. In our experience, the following steps should be considered in maximizing safety: (1) make sure the procedure is indicated; (2) perform under general anesthesia along with a paralyzing agent; (3) antibiotic prophylaxis (eg, cefazolin 2 g); (4) consider predilation with a savory dilator (54 or 57 Fr) over a guidewire to expand the hypopharynx and the upper esophageal sphincter (not for distal esophagus); and (5) when inserting the device always maintain endoscopic visualization, consider jaw thrust and deflation of endotracheal cuff balloon, gentle left-right rocking motion of the device with forward movement, and stop pushing if force is too great or esophageal deviation is noted at the neck. Once the device is in the stomach, (6) make sure the stomach is well insufflated (using a $CO_2$ automatic insufflator) before withdrawing the scope into the device and re-advancing through the side port; (7) attempt to screw the helical retractor close to the Z-line (more secure anchor and less mucosal injury); (8) avoid placing fasteners sequentially on top of each other (potential for fistula or leak); (9) when "setting" the device, be mindful of the distance of the GE junction (ex. 40 cm) and visually inspect and avoid the tip of the tissue mold pressing up against the diaphragm; (10) make sure the stomach is well insufflated again before bringing the scope back into the device; and (11) when retracting the device from the esophagus, make sure the helical retractor is visible within the transparent channel, withdraw with a gentle left/right rocking motion, and capitalize on the fact that the scope is positioned in the transparent distal tip of the device—using this as a "window" to inspect the fasteners and any potential tears or breaks in the esophageal mucosa during withdrawal. Always perform a complete endoscopy after the procedure, washing any blood which may obscure a mucosal defect. Mucosal tears can be readily closed with endoscopic clips. Any bleeding encountered is most easily managed by closing the tissue mold over the area for a few minutes of tamponade pressure. Perforations may require endoscopic suturing, stenting, or rescue surgery. Once again, we would reiterate that TIF 2.0 is a very safe procedure—but care and caution should always be exercised to minimize complications.

## CONCOMITANT LAPAROSCOPIC HERNIA REPAIR AND TRANSORAL INCISIONLESS FUNDOPLICATION—DOES IT MAKE SENSE?

There continues to be an increased interest in performing TIF along with concomitant laparoscopic hernia repair (cTIF). For surgeons performing both LARS and TIF, the rationale for cTIF includes: (1) a trend moving away from Nissen fundoplication due to higher incidence of postoperative gas/bloat and dysphagia, coupled with established data that TIF produces much less gas/bloat and dysphagia,[32] and emerging data suggesting that cTIF also produces less gas/bloat than traditional LARS;[15,16,33] (2) the nonstandardization of the partial fundoplication (Dor or Toupet); and (3) the concern over future effects of stronger MRI machines on the magnetic sphincter augmentation device.[34]

The LOTUS trial brought to light, in a 5-year randomized, open, parallel-group trial in Europe, that although heartburn and regurgitation were better controlled in the LARS group compared with the esomeprazole group, the patients who underwent surgery had significantly more long-term dysphagia, bloating, and flatulence.[35] The

prevalence and severity of symptoms at 5 years in the esomeprazole (266 patients) and LARS groups (248 patients), respectively, were 16% and 8% for heartburn ($P = .14$), 13% and 2% for acid regurgitation ($P<.001$), 5% and 11% for dysphagia ($P<.001$), 28% and 40% for bloating ($P<.001$), and 40% and 57% for flatulence ($P<.001$). Experience and data such as these continue to prompt further investigation into procedural strategies that minimize postprocedure side effects while maximizing the therapeutic benefits of LARS.

From a surgical technical point of view, performing an anatomic repair of the hiatal defect alone avoids the more extensive LARS dissection, which may require the creation of a larger retroesophageal window, and the taking down of the short gastric vessels for complete fundic mobilization, which may increase the risk of bleeding and injury to the spleen, and necessitate reposition the bulk of the fundus in the retroesophageal space.

In addition, as mentioned earlier in discussing patient selection, most patients after careful inspection of the GE junction are found to have Hill 3 or above and would benefit from a laparoscopic hernia repair. At this point, if the patient is being evaluated by a gastroenterologist, there seems to be a greater comfort level for the patient who has already established a rapport with this physician, to then schedule a combined procedure with the same gastroenterologist along with the foregut surgeon. Although this is an interesting trend, we currently lack the RCTs needed to establish cTIF efficacy and side effects compared with the standard Nissen or partial fundoplication. However, existing nonrandomized data look promising.

Although the EsophyX device was FDA approved in 2007, the FDA further approved its use in 2017 in patients with hiatal hernias larger than 2 cm in conjunction with laparoscopic hernia repair. In 2011, Ihde and colleagues[15] published a retrospective community-based study evaluating the safety and symptomatic outcomes of a series of 42 patients who had either undergone TIF (24 patients) or cTIF (18 patients) based on the presence of a hiatal hernia 3 cm or larger. There were no long-term postoperative complications. GERD-HRQL scores indicated heartburn elimination in 63% of patients. The need for daily PPI therapy was eliminated in 76% of patients. Atypical symptom relief measured by the median reflux symptom index score reduction was significant (5 [0–47] versus 22 [2–42] on PPIs, $P<.001$).

In a recent 2-site community study, cTIF was performed in 99 patients with GERD and hiatal hernias between 2 and 5 cm.[33] These patients first underwent a hiatal hernia repair followed immediately by the TIF procedure during the same session. GERD-HRQL, RSI (Reflux Symptom Index), and GERSS (Gastroesophageal Reflux Symptom Score) questionnaires were administered before the procedure and mailed at 6 and 12 months. All patients were symptomatic on PPI medications before cTIF. At 12-month follow-up, median GERD-HRQL scores improved by 17 points, indicating that subjects had no bothersome symptoms. The median GERSS scores decreased from 25.0 at baseline to 1.0, and 90% of subjects reported having effective symptom control (score <18) at 12 months. Seventy-seven percent of subjects reported effective control of laryngopharyngeal reflux symptoms at 12 months with an RSI score of 13 or less. At 12 months, 74% of subjects reported that they were not using PPIs. All measures were statistically improved at $P<.05$. There were no adverse effects reported. They concluded that cTIF provides significant symptom control for heartburn and regurgitation with no long-term dysphagia or gas bloat normally associated with traditional LARS. Most patients reported durable symptom control and satisfaction with health condition at 12 months.

Although these 2 studies lacked objective esophageal acid exposure data, a more recent study had pre- and post-pH analyses on a subset of patients. In this study by

Idhe and colleagues,[16] 55 patients had cTIF, with 29 patients (53%) having matched preoperative and postoperative validated surveys and pH evaluations. The results showed no serious complications over a mean follow-up of 296 days. The mean GRD HRQL score improved from 33.7 (SD, 22.0) to 9.07 (SD, 13.95) ($P<.001$). The mean RSI score improved from 20.32 (SD, 13) to 8.07 (SD, 9.77) ($P<.001$). The mean pH score improved from 35.3 (SD, 2.27) to 10.9 (SD, 11.5) ($P<.001$). Twenty-two of the 29 patients were judged to have an intact hiatal repair with TIF (76%). Of the 22 patients with an intact hiatal repair and intact fundoplication, 21 (95%) had normalized pH exposure.

Although the emerging data are certainly noteworthy, what remains critically important is more definitive data from randomized control trials with objective outcomes comparing (1) hernia repair plus Nissen fundoplication versus hernia repair plus TIF and (2) hernia repair plus partial fundoplication versus hernia repair plus TIF. These RCTs are currently underway, and hopefully the optimal balance between therapeutic benefits and postprocedural side effects can be carefully weighted.

Not only is TIF now being done concomitantly with laparoscopic hernia repair, but it is also being used as salvage in patients with previous failed LARS. If the failure is with hernia recurrence, we have been performing cTIF for revision. If, however, the failure is with the fundoplication, TIF alone can be an excellent modality to revise the fundoplication without the need for surgery.

## WHAT'S NEXT?

With TIF now firmly established as an effective endoscopic antireflux procedure for select patients with GERD, there are many clinical "spaces" where TIF is being explored.

For example, we are now exploring the role of TIF in patients with Barrett's esophagus—including nondysplastic Barrett's—as well as in those patients with a previous history of Barrett's dysplasia who have now reached complete remission of intestinal metaplasia by endoscopic resection and/or ablation, but who are destined to lifelong use of PPIs.

In addition, TIF after per-oral endoscopic myotomy (POEM) is a very exciting area of exploration, because the benefits of POEM over laparoscopic Heller myotomy (LHM) with partial fundoplication for patients with achalasia may be outweighed by the incidence of post-POEM GERD. Recent meta-analyses show that POEM may have better results than LHM[36–39] for improvement of dysphagia, but the issue of post-POEM GERD being higher than post-LHM still needs to be addressed.[40] We need to keep in mind that LHM alone has an incidence of postoperative GERD of approximately 50%, whereas LHM in combination with a partial fundoplication reduces postoperative GERD to approximately 10%.[41] Therefore, most surgeons will automatically perform both operations together. If a substantial number of patients require antireflux surgery after POEM, then it could tip the balance back toward LHM plus partial fundoplication as the preferred first-line option. Fortunately, TIF may represent the endoscopic solution to post-POEM GERD.[42] In our experience of over 60 consecutive POEM procedures, only 3 patients were refractory to PPI medications and the TIF procedure was able to control GERD symptoms and esophagitis in all 3 patients.[43] Further studies examining both efficacy and durability of TIF after POEM are underway. The other consideration between POEM versus LHM plus fundoplication is—whereas the durability of the myotomy (with both POEM and LHM) should be very long, perhaps several decades—the durability of the partial fundoplication may be more limited, probably less than 10 years. At the point of fundoplication loosening, these patients would require either chronic PPI use, a revisional fundoplication, or

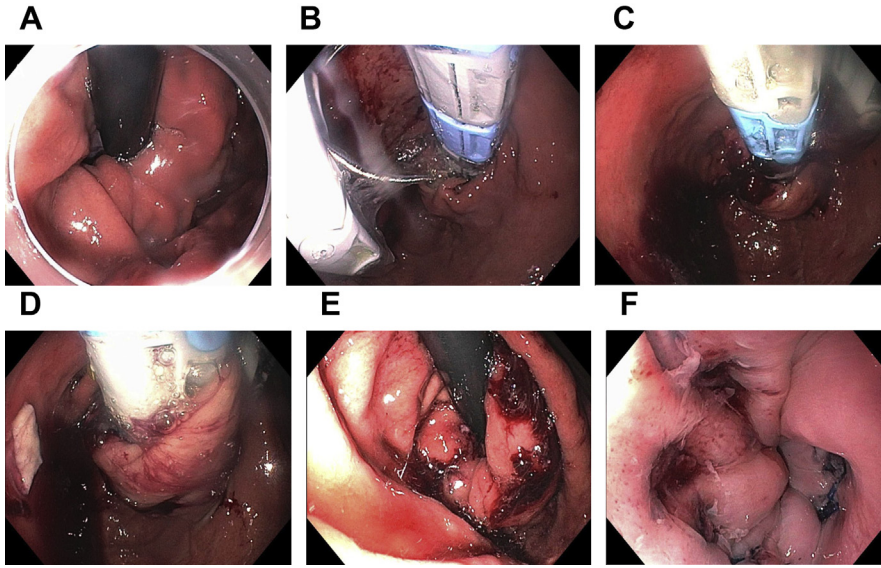


**Fig. 17.** (A) Pre-TIF Hill 2 Anatomy (B) Retractor secured to greater curve to create length of 3-4cm (C) Approaching lesser curve to create length of 1 to 1.5cm (D) Rotation into anterior corner (E) Completed 4 cm length flap valve (F) Well dispersed fasteners with highest along greater curve (left) and lower along lesser curve (right).

the TIF procedure. Ideally, a POEM with possible TIF in those patients refractory to PPIs will prove effective, as a repeat TIF is much easier to perform than the revision of a fundoplication. There may even be a subset of patients with achalasia who may benefit from concomitant POEM plus TIF in the same procedure. This strategy is being explored in type 1 achalasia patients with dilated and tortuous sigmoid esophagi who may benefit from a preemptive antireflux procedure (much like the LHM plus partial fundoplication strategy), which may also "straighten" the esophagus by retracting more of the esophagus below the diaphragm in creation of the neo valve.

TIF can be considered in obese patients before laparoscopic sleeve gastrectomy (SG), given the higher rate of GERD with SG compared with Roux-En-Y gastric bypass (RYGB).[44–47] Because TIF does not incorporate much of the gastric fundus into the fundoplication, an SG is still feasible after a TIF procedure. This strategy may decrease the number of patients going to RYGB due to preoperative GERD. TIF post-SG is possible, although it requires a sufficient gastric luminal diameter for the device to close (**Fig. 17**).

Finally, there is now a recognized association between lung transplant outcomes and GERD, with data supporting an association between GERD and allograft injury, encouraging a strategy of early diagnosis and aggressive reflux management in lung transplant recipients to improve transplant outcomes.[48,49] There are centers that are currently exploring the role of TIF in the management of these patients.

## SUMMARY

GERD is a spectrum disorder, and treatment should be individualized to the anatomic and physiologic alterations of each patient. TIF, as an endoscopic procedure, reduces EGJ distensibility, decreases tLESRs, and creates a 3-cm HPZ at the distal esophagus

in the configuration of a flap valve. The gas/bloat side effect is minimized with TIF as it produces a partial fundoplication with a controlled flap valve luminal diameter that allows for venting of the stomach. With proper patient selection, TIF has been shown to be a safe and effective treatment for patients with GERD with hernia less than 2 cm and Hill grade less than 3. The strategy of laparoscopic hernia repair with concomitant TIF is of increasing interest, as are other emerging applications for TIF, such as patients with GERD or Barrett's esophagus, in those after POEM, in those before SG, and even in recipients after lung transplant.

## CONFLICT-OF-INTEREST

Dr K.J. Chang has served as consultant for Apollo Endosurgery, Cook, Erbe, EndoGastric Solutions, Mauna Kea, Mederi, Medtronics, Olympus, Ovesco, and Pentax.

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