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TECHNICAL REPORT

**Alternative therapies for GERD: a way to personalized antireflux surgery**Erwin Rieder,<sup>1</sup> Martin Riegler,<sup>2</sup> Aleksandar P. Simić,<sup>3</sup> Ognjan M. Skrobić,<sup>3</sup> Luigi Bonavina,<sup>4</sup> Richard Gurski,<sup>5</sup> Matthias Paireder,<sup>1</sup> Donald O. Castell,<sup>6</sup> and Sebastian F. Schoppmann<sup>1</sup>

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**Gastroesophageal reflux disease (GERD) is a common disorder, known to affect about 20% of the Western population. Although conventional medical or surgical treatment has proven effective, there is certainly room for improvements. As only 10% of GERD patients are finally treated by antireflux surgery, a large therapeutic window exists. This treatment gap consists of patients who are not effectively treated with proton pump inhibitor but do not want to run the potential risks of conventional surgery. During the last two decades, several novel and intriguing options for the surgical treatment of GERD have been introduced and found their way into clinical use. The following summary will give an update of certain alternative therapeutic options to treat GERD or its pathological consequences.**

**Keywords:** GERD; fundoplication; radio frequency ablation; magnetic sphincter augmentation; endoscopic plication; electric sphincter augmentation

**Introduction**

Gastroesophageal reflux disease (GERD) is a common disorder, known to affect about 20% of the Western population.<sup>1</sup> Although symptomatic therapy with proton pump inhibitors (PPIs) or causative therapy by conventional antireflux surgery has been shown to be effective, there is certainly room for improvements. PPI therapy does treat some symptoms of GERD but not its cause. Even if these symptoms respond to medical therapy, PPIs have come under scrutiny due to eventual long-term adverse events.<sup>2</sup> Although several clinical studies have shown a cancer-protective effect of PPI, data remain contradictory.<sup>3</sup> As apparently only a very small proportion of GERD patients are finally treated by conventional antireflux surgery, a large therapeutic window of patients, who are not effectively treated with PPI but do not want to run the potential risks of conventional surgery, remains.

The last two decades have seen the development and clinical use of several novel and intriguing options to treat GERD and its consequences. These methods either aim to restore the esophageal cellular barrier after reflux-induced mucosal damage or aim to restore the physiological reflux barrier (i.e., the lower esophageal sphincter) itself. Radiofrequency ablation (RFA) of esophageal mucosa has become a mainstay within the treatment of reflux-induced esophageal mucosal dysplasia as well as early esophageal cancer, but the optimal time of either before or after potentially necessary antireflux surgery remains a matter of debate. Additionally, alternative endoscopic or surgical therapeutic options, such as endoscopic plication of the gastric fundus, magnetic sphincter augmentation, or even the electric sphincter augmentation, have been developed. These therapeutic options could challenge standard antireflux surgery but foremost might provide a less destructive option to treat

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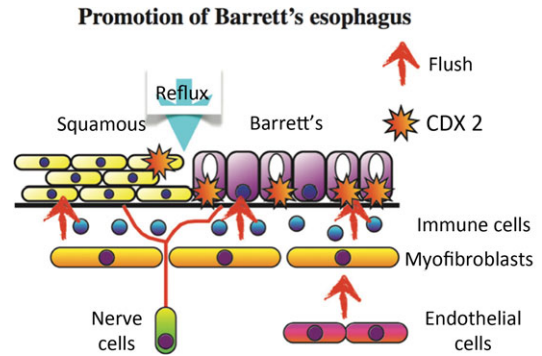
GERD, providing the opportunity of personalized surgical antireflux therapy.

## Reflux and mucosal integrity

GERD impairs the quality of life due to the symptoms and an increased cancer risk in those with columnar lined esophagus and Barrett's esophagus (BE) (0.5% per year).<sup>4,5</sup> GERD appears to develop as a progressive disease and also results from life style-induced dysfunction of the antireflux mechanism (i.e., the lower esophageal sphincter and the anchorage of the esophagus within the diaphragm).<sup>6</sup> As a consequence, reflux provokes an inflammatory response, which in turn loosens the epithelial integrity.<sup>7–9</sup> Electrophysiology, that is, transepithelial resistance and impedance, represents a well-accepted measure for the assessment of the integrity of the esophageal squamous epithelium and can be applied on esophageal biopsies *in vitro* and *in vivo* during esophageal impedance monitoring.<sup>7–10</sup>

Recent impedance studies have demonstrated that acid reflux impairs the esophageal resistance, that is, integrity of the epithelium.<sup>7–10</sup> The electron microscopic finding of enlarged intercellular spaces parallels these findings. Furthermore, electrical resistance is a good measure to monitor the recovery of the esophageal mucosa after RFA. RFA, used to eliminate BE with increased cancer risk (i.e., dysplasia and early cancer), eradicates the BE positive columnar lined esophagus with radiofrequency energy. Several weeks following RFA, neo-squamous epithelium reveals the ablated segments of the esophagus. Although the electrical resistance of the neo-squamous epithelium is significantly increased compared to Barrett's mucosa, it is significantly lower compared to normal squamous lined mucosa of the esophagus. Since patients receive high-dose PPI therapy after RFA, these resistance differences between normal and neo-squamous epithelium are suggested to be attributed to the lack of elimination of the reflux per se. Going in line with this notion, a recent study found that elimination of the reflux after effective fundoplication is more effective to restore the electrical resistance of the esophagus.<sup>11</sup>

Taken together, the above studies show that electrical resistance serves as a sensitive measure to monitor the integrity of the esophageal epithelium before and after medical or surgical therapy of GERD and



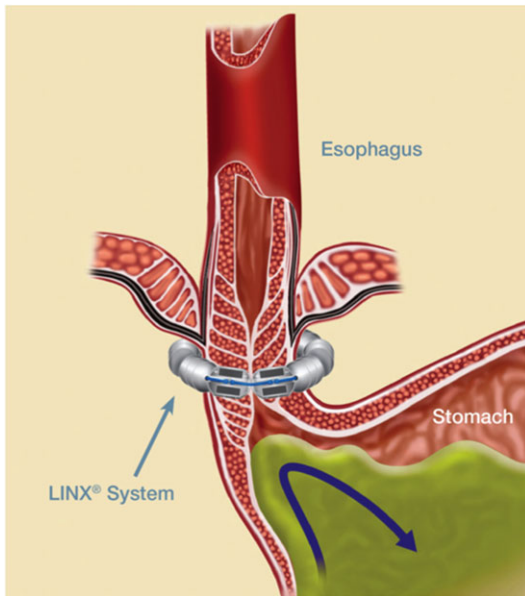
**Figure 1.** Gastroesophageal reflux activates an inflammatory response involving epithelial cells, nerve, immune cells, endothelial cells, and myofibroblasts. Acid and bile activate the release of proinflammatory mediators (substance P, neurotensin, and vasoactive intestinal peptide) from squamous epithelial cells and nerve cells, which in turn orchestrate the stimulation of immune cells (mast cells and leucocytes), myofibroblasts, and endothelial cells within the mucosa. As a consequence, these cells (mast cells, etc.) amplify and extend the mucosal inflammation by release of histamine, substance P, neurotensin, serotonin, prostaglandins, etc. Over time, this multi-mediator response involves the mucosa and submucosa of the esophagus, and mediates the perception of symptoms (heartburn, etc.). This results in the development of genetic changes, such as upregulation of gene transcription factors (e.g., CDX2), driving the formation of columnar lined esophagus ± intestinal metaplasia, dysplasia, and cancer.

BE.<sup>7–11</sup> Conceptually, GERD results from a reflux-induced orchestration of an inflammatory response, involving epithelial, nerve, inflammatory, and muscle cells within the esophageal mucosa<sup>4–6</sup> (Fig. 1).

## Shall we ablate patients before or after antireflux surgery?

Endoscopic RFA today represents a well-established, safe, and effective procedure for the treatment of BE<sup>12</sup> (Fig. 2). Choice of adjunct treatment to RFA emerges as an important clinical issue, due to the fact that recurrence of BE after complete eradication (CE) of intestinal metaplasia (IM) or dysplasia may occur. A systematic review and meta-analysis indicated that approximately 13% of RFA patients will have BE recurrence after previously achieved CE.<sup>13</sup>

Up to now, there are no randomized trials comparing the role of antireflux surgery (ARS) and PPIs on RFA outcomes. Several publications showed a possible protective role of ARS after successful RFA treatment. One of the studies revealed that patients



**Figure 2.** Schematic drawing of the LINX system.

with IM and dysplastic BE who were submitted to ARS after RFA have statistically lower incidence of persistent and recurrent BE opposed to those receiving PPI's on a 1-year follow-up.<sup>14</sup> In another study, which prospectively evaluated BE recurrence after RFA, ARS proved to be superior over the PPI regimen in patients with long BE ( $\geq 4$  cm), with significantly lower incidence on a 3-year follow-up.<sup>15</sup> Recent data that covered a 5-year follow-up of patients included in randomized Ablation of Intestinal Metaplasia Containing Dysplasia trial (AIM Dysplasia Trial) pointed out that recurrence of BE is most frequent in the first year following RFA.<sup>16</sup> Concerning the data available so far, we have to think of optimal prevention strategy in the early follow-up period and consider the ARS in selected group of patients.

Today, no data comparing the fundoplication prior or after the RFA are available. However, some technical difficulties when prior fundoplication existed have been shown, mostly reflected as inability of proper calibration and therefore optimal ablation.<sup>17</sup> One of the potential benefits of ARS in addition to RFA procedure might be in a challenging group of patients with major hiatal hernias and dilated distal esophagus, who mostly have long segments of BE. These patients can be treated by employing concomitant ARS and RFA.<sup>18</sup>

In this manner, after the hiatal hernia is reduced, esophagus encircled and pulled into the abdomen, esophageal lumen is narrowed, so that RFA electrodes apply more closely to the mucosa. Concomitant ARS and RFA was proven to be safe, not time-consuming, and it was performed in conjunction with the basic rules of RFA procedure, avoiding potential pitfall of choosing wrong balloon diameter.<sup>15</sup> To conclude, ARS as the addition to RFA of BE may play an important role in recurrence prevention, which, however, has to be demonstrated in sufficiently powered studies.

### Alternatives for surgical sphincter augmentation

The laparoscopic fundoplication is the current surgical gold standard for the treatment of GERD. A multicenter European trial comparing medical therapy with Nissen or Toupet fundoplication performed in selected centers by expert surgeons showed that 92% of medical patients and 85% of surgical patients remained in remission at 5 years of follow-up.<sup>19</sup> However, despite a remarkably low morbidity and mortality rates, fundoplication appears underused due to the perception of long-term side effects and fear of failure, which impacts referral patterns.<sup>20</sup> Gastroenterologists tend to limit their referrals for fundoplication only to patients with long-lasting severe disease and large hiatal hernias. A downward trend in the utilization of surgical fundoplication has been noted in the United States over the past decade.<sup>21–23</sup> Novel potentially less invasive options for sphincter augmentation will be discussed. Table 1 outlines some pros and cons of methods discussed.

### Do we go magnetic?

Magnetic sphincter augmentation (LINX<sup>®</sup> Reflux Management System) is a U.S. Food and Drug Administration (FDA)-approved device designed to provide a permanent solution to GERD by augmenting the lower esophageal sphincter (LES) barrier with a standardized laparoscopic procedure that does not alter gastric anatomy and does not deteriorate with time.

The LINX device is a dynamic implant that does not compress the esophagus and does not limit its range of motion upon swallowing, belching, and vomiting. For reflux to occur, the intragastric

**Table 1.** A short overview of current pros and cons when using alternative GERD therapies

	Pros	Cons
LINX	Does not limit belching and vomiting Direct postoperative dysphagia rate is reduced Limited dissection possible Reduced bloating rates	Limited in using MRI postoperative Foreign body at the EGJ No RCT data yet Cost
GerdX	Pure endoscopic procedure Easy procedure	Only for selected patients No long-term data Small amount of published data Contraindicated in (large) hiatal hernias
EsophyX	Pure endoscopic procedure Large amount of published data (including RCT) Easy procedure	Only for selected patients Questionable long-term data Contraindicated in (large) hiatal hernias
MUSE	Pure endoscopic procedure	Only for selected patients No direct vision Small amount of published data Technically demanding procedure Contraindicated in (large) hiatal hernias
EndoStim	Supposed to enhance the muscle function at the EGJ No risk for dysphagia Option for patients with severe IEM	Foreign body (abdominal wall and EGJ) Small amount of published data Mandatory reoperation after 7 years Unknown mechanism Cost
Stretta	Pure endoscopic procedure Low rate of adverse events Easy procedure	Data appear to be inconclusive

pressure must overcome the resistance to opening of both the patient's native LES pressure and the magnetic bonds of the device (Fig. 2). The LINX device is manufactured in different sizes and is capable of nearly doubling its diameter when all beads are separated. The Linx device, while augmenting the LES, allows for expansion to accommodate a swallowed bolus or the escape of elevated gastric pressure associated with belching or vomiting. The LINX device has recently received magnetic resonance imaging approval for scanning in systems up to 1.5 Tesla. The device is implanted with a standard laparoscopic approach under general anesthesia. After minimal dissection, the circumference of the esophagus is measured to determine the proper size of the LINX device to be implanted. The sizing tool is a laparoscopic instrument with a soft, circular curved tip actuated by coaxial tubes through a handset. The handset contains a numerical indicator that corresponds to the size range of the LINX device. Once the

appropriate Linx device has been selected, it is introduced through the posterior tunnel. The opposing ends are then brought to the anterior surface of the esophagus and connected together by engaging the two clasps. The decision to proceed with a posterior crural repair depends on the size of the hernia that is found intraoperatively.

A feasibility study included 44 patients implanted with the LINX device at four study centers in United States and Europe between February 2007 and October 2008.<sup>24–27</sup> In this study, patients served as their own control to assess the effect of treatment on esophageal acid exposure, symptoms, and use of PPI. The primary criteria for inclusion in the feasibility trial were age >18 and <85 years, typical reflux symptoms at least partially responsive to PPI therapy, abnormal esophageal acid exposure, and normal contractile amplitude and wave form in the esophageal body. All LINX devices were successfully implanted via a standard laparoscopic approach.

The median operative time was 40 (19–104) min and no intraoperative complications occurred. Thirty-three patients were followed at 5 years. The mean total GERD-HRQL score off PPI decreased from 25.7 at baseline to 2.9 at year 5 ( $P < 0.001$ ), and 94% (31 of 33) of patients had a greater than 50% reduction in the total score compared to baseline; 91% of patients reported of being satisfied with their current condition. Esophageal pH testing was completed in 20 patients at 5 years: 85% of patients achieved either normal esophageal acid exposure or had at least a 50% reduction from baseline. Normalization of esophageal pH was achieved in 70% of patients. Complete cessation of PPI or a reduction of 50% or more of the daily dose at 5 years was achieved by 88% and 94% of patients, respectively.

In Milan, Italy, 100 consecutive patients underwent LINX device implantation between 2007 and 2012. The median implant duration was 3 years, ranging from 378 days to 6 years. There was a significant reduction of acid exposure time and improvement of GERD-HRQL score; freedom from daily dependence on PPI was achieved in 85% of the patients.<sup>28</sup>

A recent analysis of the safety profile of the first 1000 worldwide implants in 82 hospitals showed 1.3% hospital readmission rate, 5.6% need of postoperative endoscopic dilations, and 3.4% reoperation rate.<sup>29</sup> Among the 36 patients who had the device removed, the most common symptoms were dysphagia and recurrence of reflux symptoms. In addition, 7% of patients enrolled in the U.S. multicenter single-arm trial had the device removed due to persistent dysphagia in four, vomiting in one, chest pain in one, and reflux in one.<sup>30</sup> A recent study focused on reoperations for LINX device removal and reported the long-term results of one-stage laparoscopic removal and fundoplication. Eleven out of 164 patients (6.7%) who underwent a LINX device implant were explanted at a later date, mostly between 12 and 14 months after the index operation. The main presenting symptom requiring device removal was recurrence of heartburn or regurgitation in 46%, dysphagia in 37%, and chest pain in 18%. In two patients (1.2%), full-thickness erosion of the esophageal wall with partial endoluminal penetration of the device occurred. Device removal was most commonly combined with partial fundoplication and there were no conversions to laparotomy.<sup>31</sup>



**Figure 3.** Image from the small diameter endoscope within the GerdX device, toward the esophagogastric junction.

In conclusion, long-term studies have now demonstrated the safety profile of magnetic sphincter augmentation and its favorable effect regarding long-term GERD control. Today, the LINX system appears to be a reasonable alternative option to treat selected patients with GERD, who are willing to receive a magnetic implant. However, as current studies lack blinding or randomization, further long-term data appear necessary.

### Is endoscopic plication a way?

The introduction of magnetic sphincter augmentation has certainly marked the beginning of a new era in the surgical treatment of GERD patients. However, even less invasive endoscopic options for GERD have been around for nearly two decades now.<sup>32</sup> Whereas some have not withstood clinical tests due to several reasons, the following short summary will describe three different available devices, which are still available and in clinical use. The general technical concept of all plication devices is the endolumenal creation of a serosa-to-serosa plication using either tags or staples to reinforce an insufficient “antireflux valve.”

Based on the no longer commercially available NDO surgical plicator, a significantly modified endoscopic full thickness plication device was introduced recently (GerdX, G Surg GmbH, Seon-Seebruck, Germany) and was found to improve



subjective as well as objective parameters at the 1-year follow-up.<sup>33</sup> This device is used with a small diameter endoscope, which is introduced into the stomach. Along with the device, it can be retroflexed to manipulate and retract the gastric cardia into the two arms of the plication tool and deploying sutures after gathering sufficient tissue. Multiple sutures are used to create an augmented antireflux valve (Fig. 3). Refinements of the device as well as technique are still under investigation.<sup>34</sup>

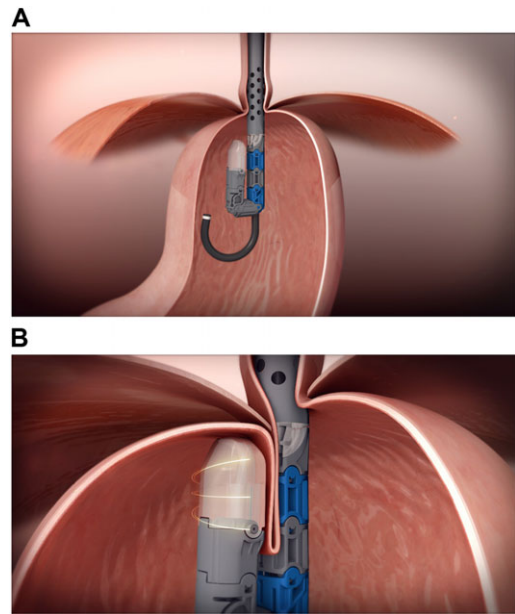
The majority of data are currently available on the transoral incisionless fundoplication (TIF) procedure using the EsophyX<sup>®</sup> device (EndoGastric Solutions, Redmond, WA). This device also uses a helical retractor and an additional integrated suction apparatus to grasp the distal esophagus, delivering multiple H-shape polypropylene fasteners to create a 2–3 cm, 270° full thickness esophagogastric fundoplication (Fig. 4A and B). A recently published systematic review, comparing the TIF procedure with a PPI/sham control group, found a significantly higher response rate to TIF.<sup>35</sup> However, no significant difference in the mean percentage of esophageal acid exposure time was observed. Additionally, response rate efficacy was found to decrease over time.

A completely different technology is used by the MUSE<sup>™</sup> (Medigus, Omer, Israel) endoscopic stapling system, which consists of built-in video camera, an endostapler, and an ultrasound transducer (Fig. 5). Under ultrasonic guidance, a stapler is fired at the level above the esophageal Z-line, which is repeated several times to form a sufficient fundoplication. Recently published data of a multicenter prospective study found nearly 70% of patients who remained off PPI after 4 years. The authors also reported a normalization of pH studies in 37% of patients after 6 months.<sup>36,37</sup>

To summarize, endoscopic plication could be an alternative or also initial therapy for highly selected patients and later surgical fundoplication appears not to be impaired.<sup>38</sup> Current data, however, also observed that long-term reflux control efficacy decreased with time and remains a matter of further research.

### How does electric sphincter stimulation work?

Electrical stimulation therapy (EST) of the lower esophageal sphincter (EndoStim<sup>®</sup>) is a novel treat-



**Figure 4.** Schematic pictures of the EsophyX<sup>®</sup> device inserted through the mouth and positioned at the esophagogastric junction (A) and creating a full-thickness tissue fold (B).

ment of GERD using neurostimulation. The technology is designed to restore the function of the LES, thereby reinforcing the barrier against reflux while preserving normal swallow ability. The treatment has been shown to be safe and effective in multicenter, international trials for more than 4 years, most notably improving/normalizing esophageal acid exposure.<sup>39–42</sup> Additionally, the procedure is reversible, which is attractive as it does not preclude another procedure in the future if it is needed.<sup>43</sup>

Two long-term international trials have been published, including 66 patients from 11 centers.<sup>39–42</sup> In all patients, GERD was verified at baseline by esophageal pH testing and validated symptom questionnaires. In a meta-analysis of the studies, GERD-health-related quality of life symptom scores improved significantly compared to both baseline on-PPI and baseline off-PPI scores.<sup>44</sup> Additionally, 89% of patients had discontinued regular PPI use at their last follow-up and 76% were no longer using any PPI. The effect is confirmed by a significant and sustained improvement in a 24-h distal esophageal acid exposure.

The sustained improvement in esophageal acid exposure over a 4-year duration, an objective measurement of GERD, indicates the stimulation has

a sustained effect on LES function. However, more remains to be learned about exactly which reflux mechanisms are affected by the neuromodulation.

One mechanism, identified in acute studies, is increased LES resting pressure resulting from stimulation. In acute studies, significant improvement of basal pressure was documented in all patients, with no impact on swallowing function ( $n = 15$ ). Importantly, no dysphagia or other gastrointestinal (GI) side effects were reported despite the increased tone.<sup>45,46</sup>

Initial data in patients with esophageal hypomotility or aperistalsis who received EndoStim therapy suggest that stimulation may increase peristaltic propulsion and reducing the duration of reflux episodes, although the mechanism of this observation remains unclear. Moreover, the stimulation does not cause new dysphagia in this challenging patient group.<sup>47</sup>

Finally, a significant effect on transient lower esophageal relaxations (tLESRs) has been reported in a group of patients evaluated with prolonged high-resolution manometry before and 3 months after LES stimulation. A significant reduction in the total number of tLESRs as well as the number of tLESRs associated with reflux episodes was observed, suggesting that the effect of LES stimulation on acid exposure and GERD symptoms is also mediated by improvement in tLESRs.<sup>48</sup>

In summary, more research is needed to fully understand the mechanism of EST at the neurohumoral level for GERD. However, preliminary evidence suggests positive therapeutic effect on tone, function, and transient LES relaxations.

### Use of the EndoStim device to treat PPI-resistant patients with significant motility disorder

Impaired esophageal motility (IEM) is repeatedly found in patients who receive functional esophageal testing for GERD, but its causation is not fully comprehended.<sup>49</sup> In the updated Chicago classification, version 3.0, IEM is defined as a distal contractile integral below 450 mmHg·s·cm in more than 50% of swallows, clarifying the discrepancy between week and failed swallows.<sup>50</sup> Especially after laparoscopic fundoplication, patients with IEM are likely to develop postoperative dysphagia and certainly are a specific challenge for antireflux surgery.<sup>51</sup>



**Figure 5.** The MUSE device.

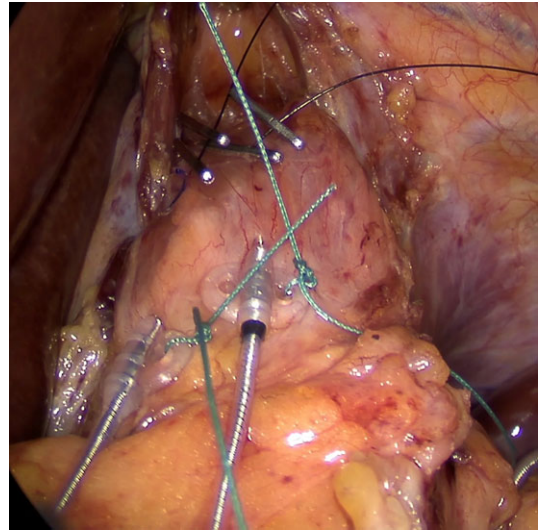
Electrical stimulation therapy of the lower esophageal sphincter (EST-LES) might be an appealing alternative surgical approach for this patient cohort. The LES stimulation device itself is an implanted pulse generator connected to a lead with two stimulation electrodes (Fig. 6), which are placed on the anterior side of the esophageal gastric junction.<sup>52</sup> As already mentioned, Rodriguez *et al.* could demonstrate in the first study in humans that EST-LES significantly increases LES pressure. There was neither an effect on LES relaxation in response to swallows nor did any patients report dysphagia.<sup>47</sup> The subsequent prospective trial in 25 GERD patients treated with EST-LES without hiatal repair showed an improvement in quality of life scores as well as a reduction of acid exposure of the distal esophagus. None of the patients complained about GI side effects of bloating, inability to belch, or dysphagia.<sup>53</sup> This absence of GI side effects was

maintained in the long-term 3-year results published recently. Interestingly, four patients decreased in esophageal acid exposure after a turn-off, but improved after re-engagement of the stimulation device.<sup>40</sup> In a multicenter trial including 42 patients, mild-to-moderate dysphagia was reported in only four patients and resolved without intervention. Seventeen patients also underwent hiatal repair, which included the patients with dysphagia. The short-term results of this trial proved the safety and efficacy of EST-LES in a multicenter setting.<sup>42</sup> The fact that there is no influence on the swallowing-induced sphincter relaxation appears appealing for the use of EST of the LES in patients with IEM. As surgical technique of EST-LES induces no or just minimal anatomical alteration, any mechanical reason for potential later dysphagia is lacking. Consequently, patients with IEM, eventually at risk for side effects after laparoscopic fundoplication, can be considered good candidates for lower esophageal sphincter stimulation. An ongoing prospective trial will provide further insight.

### Stretta therapy

The endoscopic radiofrequency procedure (Stretta<sup>®</sup>, Mederi Therapeutics, Norwalk, CT) was approved by the FDA as early as in 2000 to treat GERD. The Stretta catheter contains a balloon within a basket, which has needle electrodes to deliver radiofrequency energy. However, the physiological effect as well its outcome is still controversially discussed. The Stretta system uses radiofrequency energy delivered to the muscle at the gastroesophageal sphincter, which is supposed to induce fibrosis in the muscle tissue, leading to a less compliant distal esophagus. It is additionally hypothesized that low-power radiofrequency stimulation results in muscle proliferation and muscle thickening, which thereby increases the physiological barrier function. In a porcine model, it has been demonstrated that after Stretta collagen deposition and fibroblast reaction occur, indicating fibrotic reaction. This could lead to an increased lower esophageal pressure and/or a decreased rate of transient lower esophageal sphincter relaxation.

A recently published systematic review, including 2468 patients, revealed that the Stretta procedure significantly improved subjective and objective clinical endpoints, without significantly increasing the LES resting pressure. The adverse



**Figure 6.** Intraoperative situs after implantation of the stimulation leads on the anterior side of the esophageal gastric junction. Nylon threads are fixed with two 10-mm titanium clips and the silicone butterfly is fixed with a 3-0 multifilament thread (nonabsorbable). A posterior hiatal repair was done prior to placement of the electrodes.

event rate appeared to be less than 1%. Others state that randomized sham-controlled trials did not support the findings of the open-label trials as level I studies could not sufficiently demonstrate an improvement of objective parameters. However, currently published randomized trials did include only a small number of patients compared to a large cohort of nonrandomized patients treated by the Stretta procedure. Larger adequately powered trials could eventually answer these questions more sufficiently.

To summarize, several alternative therapeutic options to treat patients with GERD are available these days. This could not only lead to a more patient tailored treatment of GERD, but could especially be beneficial for patients within the therapeutic window of GERD.

### Competing interests

The authors declare no competing interests.

### References

1. Dent, J., H.B. El-Serag, M.A. Wllander, *et al.* 2005. Epidemiology of gastro-oesophageal reflux disease. A systematic review. *Gut* **54**: 710–717.



2. Johnson, D.A., P.O. Katz, D. Armstrong, *et al.* 2017. The safety of appropriate use of over-the-counter proton pump inhibitors: an evidence-based review and Delphi consensus. *Drugs* **77**: 547–561.
3. Dunbar, K.B., R.F. Souza & S.J. Spechler. 2015. The effect of PPI on Barrett's esophagus. *Gastroenterol. Clin. North Am.* **44**: 415–424.
4. Koch, O.O. & S.A. Antonious. 2016. Advances in diagnosing GERD. *Eur. Surg.* **48**: 203–208.
5. Riegler, M., I. Kristo, R. Asari, *et al.* 2017. Dietary sugar and Barrett's esophagus. *Eur. Surg.* **49**: 279–281.
6. Riegler, M., I. Kristo, M. Nikolic, *et al.* 2017. Update on the management of Barrett's esophagus in Austria. *Eur. Surg.* **49**: 282–287.
7. Tobey, N.A., C.M. Argote, X.C. Vanegas, *et al.* 2007. Electrical parameters and ion species for active transport in human esophageal stratified squamous epithelium and Barrett's specialized columnar epithelium. *Am. J. Physiol. Gastrointest. Liver Physiol.* **293**: G264–G270.
8. van Hoeij, F.B., P.W. Weijenberg, M.A. van den Bergh Weerman, *et al.* 2016. Mucosal integrity and sensitivity to acid in the proximal esophagus in patients with gastroesophageal reflux disease. *Am. J. Physiol.* **311**: G117–G122.
9. Kessing, B.F., A.J. Bredenoord, P.W. Weijenberg, *et al.* 2011. Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am. J. Gastroenterol.* **106**: 2093–2097.
10. Jovov, B., N.J. Shaheen, G.S. Orlando, *et al.* 2013. Defective barrier function in neosquamous epithelium. *Am. J. Gastroenterol.* **108**: 386–391.
11. Mauritz, F.A., N.F. Rinsma, E.L.W. van Heurn, *et al.* 2017. Esophageal mucosal integrity improves after laparoscopic antireflux surgery in children with gastroesophageal reflux disease. *Surg. Endosc.* **31**: 2910–2917.
12. Fleischer, D.E., B.F. Overholt, V.K. Sharma, *et al.* 2010. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* **42**: 781–789.
13. Orman, E.S., N. Li & N.J. Shaheen. 2013. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* **11**: 1245–1255.
14. O'Connell, K. & V. Velanovich. 2011. Effects of Nissen fundoplication on endoscopic endoluminal radiofrequency ablation of Barrett's esophagus. *Surg. Endosc.* **25**: 830–834.
15. Skrobić, O., A. Simić, N. Radovanović, *et al.* 2016. Significance of Nissen fundoplication after radiofrequency ablation for Barrett's esophagus. *Surg. Endosc.* **30**: 3802–3807.
16. Cotton, C.C., W.A. Wolf, B.F. Overholt, *et al.* 2017. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from ablation in intestinal metaplasia containing dysplasia trial. *Gastroenterology* **153**: 681–688.
17. Shaheen, N.J., H.P. Kim, W.J. Bulsiewicz, *et al.* 2013. Prior fundoplication does not improve safety or efficacy outcomes of radiofrequency ablation: results from the U.S. RFA registry. *J. Gastrointest. Surg.* **17**: 21–29.
18. Goers, T.A., P. Leão, M.A. Cassera, *et al.* 2011. Concomitant endoscopic radiofrequency ablation and laparoscopic reflux operative results in more effective and efficient treatment of Barrett esophagus. *J. Am. Coll. Surg.* **213**: 486–492.
19. Galmiche, J.P., J. Hatlebakk, S. Attwood, *et al.* 2011. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* **305**: 1969–1977.
20. Niebisch, S., F.J. Fleming, K.M. Galey, *et al.* 2012. Perioperative risk of laparoscopic fundoplication: safer than previously reported—analysis of the American College of Surgeons National Surgical Quality Improvement Program 2005 to 2009. *J. Am. Coll. Surg.* **215**: 61–69.
21. Finks, J.F., Y. Wei & J.D. Birkmeyer. 2006. The rise and fall of antireflux surgery in the United States. *Surg. Endosc.* **20**: 1698–1701.
22. Colavita, P.D., I. Belyansky, A.L. Walters, *et al.* 2013. Nationwide inpatient sample: have antireflux procedures undergone regionalization? *J. Gastrointest. Surg.* **17**: 6–13.
23. Khan, F., C. Maradey-Romero, S. Ganocy, *et al.* 2016. Utilization of surgical fundoplication for patients with gastroesophageal reflux disease in the USA has declined rapidly between 2009 and 2013. *Aliment. Pharmacol. Ther.* **43**: 1124–1131.
24. Bonavina, L., G. Saino, D. Bona, *et al.* 2008. Magnetic augmentation of the lower esophageal sphincter: results of a feasibility clinical trial. *J. Gastrointest. Surg.* **12**: 2133–2140.
25. Bonavina, L., T.R. DeMeester, P. Fockens, *et al.* 2010. Laparoscopic sphincter augmentation device eliminates reflux symptoms and normalizes esophageal acid exposure. *Ann. Surg.* **252**: 857–862.
26. Lipham, J.C., T.R. DeMeester, R.A. Ganz, *et al.* 2012. The Linx reflux management system: confirmed safety and efficacy now at 4 years. *Surg. Endosc.* **26**: 2944–2949.
27. Saino, G., L. Bonavina, J. Lipham, *et al.* 2015. Magnetic sphincter augmentation for gastroesophageal reflux at 5 years: final results of a pilot study show long-term acid reduction and symptom improvement. *J. Laparoendosc. Adv. Surg. Tech. A* **25**: 787–792.
28. Bonavina, L., G. Saino, D. Bona, *et al.* 2013. One hundred consecutive patients treated with magnetic sphincter augmentation for gastroesophageal reflux disease: 6 years of clinical experience from a single center. *J. Am. Coll. Surg.* **217**: 577–585.
29. Lipham, J.C., P.A. Taiganides, B.E. Louie, *et al.* 2015. Safety analysis of first 1000 patients treated with magnetic sphincter augmentation for gastroesophageal reflux disease. *Dis. Esophagus* **28**: 305–311.
30. Ganz, R.A., S.A. Edmundowicz, P.A. Taiganides, *et al.* 2016. Long-term outcomes of patients receiving a magnetic sphincter augmentation device for gastroesophageal reflux. *Clin. Gastroenterol. Hepatol.* **14**: 671–677.
31. Asti, E., S. Siboni, V. Lazzari, *et al.* 2017. Removal of the magnetic sphincter device. Surgical technique and results of a single-center cohort study. *Ann. Surg.* **265**: 941–945.
32. Filipi, C.J., G.A. Lehman, R.I. Rothstein, *et al.* 2001. Transoral, flexible endoscopic suturing for treatment of GERD: a multicenter trial. *Gastrointest. Endosc.* **53**: 416–422.

33. Koch, O.O., A. Kaindlstorfer, S.A. Antoniou, *et al.* 2013. Subjective and objective data on esophageal manometry and impedance pH monitoring 1 year after endoscopic full-thickness plication for the treatment of GERD by using multiple plication implants. *Gastrointest. Endosc.* **77**: 7–14.
34. Weitzendorfer, M., G.O. Spaun, S.A. Antoniou, *et al.* 2017. Interim report of a prospective trial on the clinical efficiency of a new full-thickness endoscopic plication device for patients with GERD: impact of changed suture material. *Surg. Laparosc. Endosc. Percutan. Tech.* **27**: 163–169.
35. Huang, X., S. Chen, H. Zhao, *et al.* 2017. Efficacy of transoral incisionless fundoplication for the treatment of GERD: a systematic review with meta-analysis. *Surg. Endosc.* **31**: 1032–1044.
36. Zacherl, J., A. Roy-Shapira, L. Bonavina, *et al.* 2015. Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. *Surg. Endosc.* **29**: 220–229.
37. Kim, H.J., C.I. Kwon, W.R. Kessler, *et al.* 2016. Long-term follow up results of endoscopic treatment of gastroesophageal reflux disease with the MUSE endoscopic stapling device. *Surg. Endosc.* **30**: 3402–3408.
38. Bell, R.C., R.R. Kurian & K.D. Freeman. 2015. Laparoscopic anti-reflux revision surgery after transoral incisionless fundoplication is safe and effective. *Surg. Endosc.* **29**: 1746–1752.
39. Rodriguez, L., P. Rodriguez, B. Gomez, *et al.* 2016. Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES) is successful in treating GERD—long-term 4 year results. *Gastroenterology* **150**: S476.
40. Rodriguez, L., P. Rodriguez, B. Gómez, *et al.* 2016. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: long-term 3 year results. *Surg. Endosc.* **30**: 2666–2672.
41. Siersema, P.D., A.J. Bredenoord, J.M. Conchillo, *et al.* 2017. Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES) for refractory GERD and two year results of an international multicenter trial. *Gastroenterology* **152**: S470.
42. Kappelle, W., A. Bredenoord, J. Conchillo, *et al.* 2015. Electrical stimulation therapy of the lower esophageal sphincter for refractory gastro-esophageal reflux disease—interim results of an international multicenter trial. *Aliment. Pharmacol. Ther.* **42**: 614–625.
43. Rodriguez, L., P. Rodriguez, B. Gomez, *et al.* 2013. Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. *Endoscopy* **45**: 595–604.
44. Attwood, S.E., G.I. Leontiadis, L. Rodriguez, *et al.* 2015. Global clinical experience with EndoStim lower esophageal sphincter stimulation therapy: an individual patient data meta-analysis of the open label clinical trials. *UEG J.* **3**: A295.
45. Rodriguez, L., P. Rodriguez, M. Neto, *et al.* 2012. Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease. *Neurogastroenterol. Motil.* **24**: 446–450.
46. Banerjee, R., N. Pratap, R. Kalpala, *et al.* 2014. Effect of electrical stimulation of the lower esophageal sphincter using endoscopically implanted temporary stimulation leads in patients with reflux disease. *Surg. Endosc.* **28**: 1003–1009.
47. Ramirez, M., C. Zubieta, F. Ciotola, *et al.* 2016. Electrical stimulation of the LES—an emerging therapy for GERD patients with failed esophageal peristalsis. *UEG J.* **4**: A24.
48. Rinsma, N.F., B.F. Kessing, N.D. Bouvy, *et al.* 2016. Effect of electrical stimulation therapy of the lower esophageal sphincter on postprandial reflux mechanisms in GERD patients. *Gastroenterology* **150**: S478.
49. Felix, V.N., K. DeVault, R. Penagini, *et al.* 2013. Causes and treatments of achalasia, and primary disorders of the esophageal body. *Ann. N.Y. Acad. Sci.* **1300**: 236–249.
50. Kahrilas, P.J., A.J. Bredenoord, M. Fox, *et al.* 2015. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol. Motil.* **27**: 160–174.
51. Novitsky, Y.W., J. Wong, K.W. Kercher, *et al.* 2007. Severely disordered esophageal peristalsis is not a contraindication to laparoscopic Nissen fundoplication. *Surg. Endosc.* **21**: 950–954.
52. Eypasch, E. 2014. Electrical stimulation of the lower oesophageal sphincter: an emerging therapy for treatment of GORD. *Eur. Surg.* **46**: 57–64.
53. Rodriguez, L., P. Rodriguez, B. Gomez, *et al.* 2013. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial. *Surg. Endosc.* **27**: 1083–1092.