

# Endoscopic treatment of gastro-oesophageal reflux disease

## *Il trattamento endoscopico della malattia da reflusso gastro-esofageo*

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### Key words

Reflux disease • Endoscopic treatment • Endoluminal management

### Parole chiave

*Reflusso gastro-esofageo • Trattamento endoscopico • Terapia endoluminale*

### Summary

Gastro-oesophageal reflux disease is a common chronic disorder which has a severe effect on the patient's quality of life. In view of the high cost of medical therapy and the limitations of surgery, a variety of endoscopic techniques have been developed for the treatment of this condition, and these have shown apparently encouraging results, at least in the short term. However, several inconsistencies have emerged between the efficacy of endoscopic treatment in improving symptoms and quality of life and a lack of improvement of objective parameters. Controlled studies are urgently needed in order to clarify the potential of endoscopic therapy. Currently, the use of endoscopic treatment should be limited to clinical trials.

### Riassunto

*La malattia da reflusso gastroesofageo è un disordine frequente di tipo cronico recidivante con notevole impatto sulla qualità di vita dei pazienti. Dati i costi elevati della terapia farmacologica ed i limiti della terapia chirurgica, è stato sviluppato un certo numero di trattamenti endoscopici che hanno dimostrato risultati incoraggianti nel breve termine. Ciononostante, sono emerse alcune incongruenze tra efficacia clinica e mancanza di miglioramento dei parametri funzionali (esposizione acida esofagea, ecc.); pertanto vi è urgenza di studi clinici controllati che chiariscano il vero potenziale di questo tipo di trattamento. Al momento, la terapia endoscopica del reflusso deve essere valutata nell'ambito di trials clinici.*

## Background

Gastro-oesophageal reflux disease (GERD) is a common medical condition that typically requires lifelong medical treatment or surgery for the management of patients with frequent symptoms. The current standard of management in patients with regular symptoms is to begin treatment with a proton-pump inhibitor (PPI). Although extremely effective, about 10% of patients are intolerant to these drugs and another 15% of patients have persistent GERD symptoms unresponsive to PPIs. Furthermore, these prescription medications are expensive and frequently an inconvenience for the prescribing physician, due to increasing scrutiny and restrictions. On the other hand, surgical treatment of GERD has its own share of problems. Although more appealing in the last 10 years, following the development of the minimally invasive laparoscopic approach, which overcomes a possible psychological barrier for patients, there is an ever-increasing recognition of the complications of fundoplication<sup>1,2</sup> as well as the high rate of recidivism to medical therapy that occurs in 20-62% of patients within 1-10 years after "curative" surgical intervention<sup>3</sup>.

These factors have all fueled the recent excitement about endoscopic treatment for GERD as an alternative to more conventional approaches. The concept of "one-time" endoscopic intervention that obviates the need for daily medication or surgery is attractive to both clinicians and patients.

## Procedures and mechanisms of action

Several endoscopic anti-reflux procedures aimed at creating an anti-reflux barrier and reducing or eliminating the need for chronic medical therapy or fundoplication have been introduced and validated as feasible, safe and effective. Today, it is possible to manage GERD patients with a multi-option approach of medical, endoscopic or surgical therapies according to the size of the hiatal hernia, the lower oesophageal pressure profile and their clinical response to single-modality therapy.

To date, there have been basically three approaches to endoluminal treatment for GERD:

1. radiofrequency energy ablation delivered to the lower oesophageal sphincter (LES);
2. endoscopic gastroplasty plication of the gastric

folds immediately distal to the oesophago-gastric junction;

3. endoscopic implantation of a bulking agent or polymer in the region of the LES.

#### RADIOFREQUENCY ENERGY ABLATION

The technique of radiofrequency energy ablation (STRETTA™ procedure) is performed using a radiofrequency delivery catheter. The catheter consists of a flexible balloon-basket assembly with 4 electrode needle sheaths. RF is delivered at different levels starting 1 cm above the squamo-columnar junction. Each application lasts 60 seconds for a total of 22 sets of needle deployments with 4 antegrade levels at the junction and two rings of cardia lesions made in pull back (Fig. 1). The procedure is easily carried out either under conscious sedation or general anaesthesia on an outpatient basis<sup>4-10</sup>.

Potential mechanisms of action of the Stretta procedure include: 1) a mechanical effect due to scarring of the oesophago-gastric junction secondary to collagen deposition, with increase of LES pressure and decrease of LES distensibility, and 2) a neuromodulation effect due to selective neurolysis of vagal afferents leading to reduced elicitation of transient LES relaxations (tLESRs). The supposed influence of RF energy on sensory nerves with reported reduced sensitivity to noxious stimuli might be explained by a number of possible effects such as reduction of inflammation of the distal part of the oesophagus due to a reduction in reflux, improved barrier of the oesophageal mucosa (tight junctions) due to a decreasing in reflux or influence on sensory nerves that mediate heartburn<sup>4-10</sup>.

#### ENDOLUMINAL GASTROPLASTY

Endoluminal gastroplasty involves the plication of the gastric folds immediately distal to the oesophago-

gastric junction with two sets of sutures applied endoscopically with the EndoCinch™ suturing device inserted into the oesophagus through an overtube. The major effect is intuitively that of mechanically restoring the anti-reflux barrier function, though some data suggest a decrease in oesophageal sensitivity to acid as part of the mechanism responsible for the reduction of reflux symptoms<sup>11-14</sup>. Another technique of endoluminal gastroplasty can be performed with the full-thickness Plicator™ method, which creates layered sutures of the stomach wall in the cardiac region. An accessory endoscope is angled to enable the cardiac region to be observed. The arm of the device is opened and a tissue retractor is rotated and implanted in the gastric wall fully retracting the tissue into the arms that are closed and pre-tied stitches applied. Suturing and fixation are performed simultaneously<sup>15-17</sup>.

#### IMPLANT TECHNIQUES

Finally, implant techniques consist of injecting a non-absorbable co-polymer (Enteryx™) into the muscle or deep submucosa of the LES where it solidifies into a sponge-like permanent implant and prevents or reduces gastric acid reflux into the oesophagus<sup>18-21</sup>. This technique is no longer commercially available since it has been withdrawn from the market due to safety issues (five deaths attributable to the procedure). The Gatekeeper™ technique, which consisted in the endoscopic implantation of self expanding hydrogel prostheses into the submucosal layer of oesophagogastric junction<sup>22,23</sup> underwent the same fate.

#### Outcomes

With over 10,000 patients treated to date, the Stretta procedure is the most widely applied endoluminal

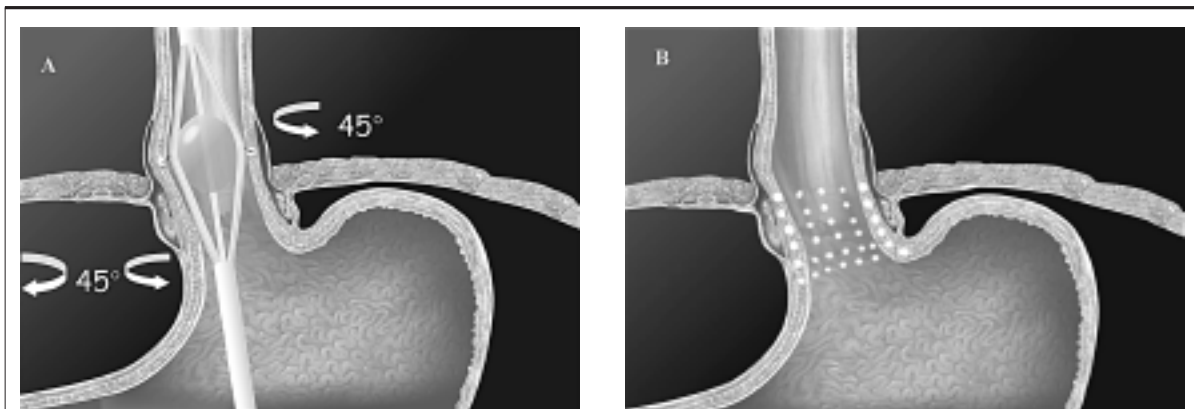


Fig. 1. Schematic picture of the Stretta procedure. Delivery catheter in situ with needles into the muscle layer of the LES (A); sites of RF energy lesions (B).

**Table I.** Negative outcome of endoscopic therapy in Italy <sup>26</sup>.

Procedure	N. cases	Early (< 72 hrs)	Late	Severe
Endocinch	69	Bleeding 2 Odynophagia 1 Fever 1	None	Bleeding 1 Intubation 1
Enteryx	48	Retrosternal pain 12 Fever 7 Dysphagia 1	None	
Stretta	48	Retrosternal pain 11 Fever 7 Dysphagia 1	Gastroparesis 1	
Gatekeeper	13	None	None	

anti-reflux technique. Controlled data demonstrate that RF energy delivery produces a significant improvement in GERD symptomatology and quality of life as well as reducing the use of anti-reflux medication, with negligible morbidity <sup>4-10 24 25</sup>. Stretta has been tested in a double-blind, sham-controlled, randomized trial, showing pH improvement and normalization of acid exposure in nearly half the treated patients, as well as less need for medication <sup>8</sup>. Durability of these results has been demonstrated at  $\geq 4$  years, in multi-centre patient study on 560 cases <sup>26</sup>. Stretta is the only effective endoluminal-endoscopic therapy that does not preclude other treatment should the need arise. Moreover, it has an excellent safety profile, with a very low complication rate  $< 0.07\%$ . A recent cost analysis, based on US health service data, showed that endoscopic therapy appeared to offer an economic advantage for patients requiring a PPI twice daily, and this advantage was sustained for 2.5 years <sup>27</sup>.

Endoscopic gastroplication is a safe and minimally invasive endoscopic treatment for GERD with reasonable short-term results <sup>12 13</sup>. In contrast, long-term outcome is disappointing, probably due to suture loss

in the majority of patients <sup>28-30</sup>. Therefore, technical improvements to ensure suture durability are mandatory before endoscopic suturing can evolve as a therapeutic option.

### Discussion

Endoscopic anti-reflux procedures have led to convincing results in only two-thirds of patients, with a medium follow-up of 6 to 12 months. There are a number of inconsistencies between the efficacy of treatment in terms of improvement of symptoms and quality of life, and the lack of improvement of objective parameters such as LES pressure and oesophageal acid exposure. Possible explanations for this are the heterogeneity of patients with GERD, the variability over time of gastro-oesophageal reflux, the limitations of the investigation methods used to assess physio-pathological parameters, the incomplete knowledge concerning the mechanism of action of different devices, and, finally, the possible placebo effect in these studies, very few of which are "controlled". These endoscopic therapies still suffer

**Table II.** Score comparison between Stretta treatment (RF) and endoluminal gastroplication (ELGP).

	1	2	3	4	5
N. patients and trials				RF/ELGP	
Safety			ELGP	RF	
Short-term			RF/ELGP		
Long-term	ELGP		RF		
Reversibility	RF	ELGP			
Difficulty		RF		ELGP	

1 bad; 2 poor; 3 good; 4 very good; 5 excellent

from a number of methodological flaws and there is potential room for improvement both in efficacy and duration of the therapeutic effect. It is imperative that the endpoints for forthcoming high-quality studies use validated measures to evaluate outcomes. Clearly, the marketplace (our patients) continues to look for alternatives beyond daily use of prescription medications or surgical procedures for GERD<sup>31-33</sup>.

Safety issues should also be given careful consideration: in the preliminary studies on therapy using radiofrequency and suturing devices, a number of adverse events were reported. Of course this can occur with any new device. The introduction of some technical and methodological changes have since reduced the risk of adverse effects with these techniques, but it still persists, especially when compared with the relative safety of medical therapy<sup>34,35</sup>. Intensive post-marketing surveillance, device registries, and long-term clinical follow-up studies will be able to document safety and durability. The effect of retreatment for relapses or suboptimal initial treatment response should also be defined.

Cost-effectiveness will be a critical factor in the determination of the ultimate place for these interventions. If the technology is safe and effective, the evaluation of the cost over time will allow for the appropriate comparisons with other standard (medical, surgical) and even other endoscopic approaches. No data substantiate that these procedures are equivalent to or better than medical therapy. Given the excellent efficacy and side-effect profile of PPIs, until such data do exist, using endoscopic methods interchangeably with medical management in the PPI-responsive patient, based solely on patient preference, seems imprudent. On the basis of evidence to date, these endoscopic interventions should be offered only to those patients who respond to medical therapy.

While we wait for higher-quality and longer-term data on these procedures, is it possible to forecast a potential role for these devices in the management of GERD? Although data are sparse, subjects who suffer symptoms or complications of volume reflux and are not surgical candidates may be reasonable candidates for these procedures. Another group who might be reasonable candidates are those with GERD symptoms on medical therapy with very poor oesophageal motility. While such patients are sometimes rejected by surgeons for fear of persistent dysphagia following the procedure, one of the procedures which is reversible by severing endoscopic su-

tures might be an effective and conservative alternative. Finally, elderly patients not responding to medical therapy but are not surgical candidates are a reasonable group to consider. The life expectancy of these patients is such that the lack of long-term outcome data, in these procedures, becomes irrelevant. Finally, it is conceivable, albeit premature, to envision these endoscopic therapies serving a role in the management of anti-reflux surgical failures. Furthermore, this approach may also have an ultimate role in the management of extra-oesophageal GERD complications where aggressive medical therapies, and even surgical interventions, are not universally effective.

## Conclusions

To date, the efficacy of endoluminal treatment for GERD is not supported by a high level of evidence. Only one randomised controlled trial has been published<sup>8</sup> in full, reporting the beneficial effects of radiofrequency energy delivery *vs.* a sham procedure in terms of symptom relief and quality of life, but without a statistically significant reduction in oesophageal acid exposure.

The target population for endoscopic therapy of GERD is represented by PPI-dependent reflux patients in the absence of a large hiatal hernia or severe oesophagitis. The largest clinical experience with Endocinch plication and RF energy delivery suggests that these procedures are safe and can be performed on an outpatient basis. However, prolonged follow-up is required and detailed registries of all complications should be developed for every new endoscopic procedure.

For the time being, endoscopic anti-reflux procedures should be performed in a controlled environment, preferably in reference centres. Integration of new endoscopic GERD therapies into routine clinical practice requires more information from carefully performed and analysed trials. Future studies should improve targeting of which patients benefit, further elucidate the relevant underlying pathophysiological mechanism, and provide detailed comparisons to alternative treatments.

Endoscopists should carefully balance the potential of these new devices and the specific clinical situation with the appeal of marketing and of being at the technological cutting edge.

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