RATIONALE AND DEVELOPMENT OF ENDOOLUMINAL THERAPY IN GORD

Gastro-oesophageal reflux disease (GORD) is a common chronic disorder that has severe impact on quality of life. Moreover, GORD may also cause reflux oesophagitis and sometimes severe complications, such as ulceration, strictures, Barrett’s mucosa, and adenocarcinoma of the oesophagus. Surveys revealed that up to 15–20% of adults experience heartburn on a weekly basis and therefore the cost of drugs prescribed for the treatment of GORD represents a heavy economic burden for society. Although proton pump inhibitors (PPIs) are extremely effective in healing oesophagitis and improving typical reflux symptoms, they also have shortcomings and limitations. Firstly, they do not restore the normal antireflux barrier at the gastro-oesophageal junction and there is frequently a rebound acid hypersecretion after cessation of drug intake which both contribute to the high relapse rate observed after discontinuation of PPI therapy. Additionally, even though PPIs are usually extremely well tolerated drugs they can interact with Helicobacter pylori infection and occasionally be responsible for some rare side effects or drug interferences. In contrast with short term administration of H2 antagonists, PPIs are less potent in reducing nocturnal acid secretion. Finally, a challenging problem remains the treatment of the approximately 10–20% of patients with proven GORD who have only a partial or no response to high doses of PPIs.

Laparoscopic fundoplication is often proposed as an alternative and more definitive option, especially in young patients, because it is intended to cure the disorder and the laparoscopic approach makes surgery more acceptable. Despite the high success rate of surgery in resolving typical reflux symptoms, substantial morbidity and some mortality exist. Complications such as dysphagia, inability to belch, diarrhoea, and flatulence may develop in up to 30% of patients. Recent publications tempered the enthusiasm for antireflux surgery. Spechler et al reported that 62% of patients who underwent open antireflux surgery as part of a controlled study were still taking acid suppressive drug after 10 years. Similar data were reported in patients who underwent this procedure in routine clinical practice. Medical therapy was required for control of heartburn in approximately one third of patients after laparoscopic fundoplication and new onset of symptoms was common after surgery. Thus in spite of well established short term efficacy, surgery is not an ideal solution.

During the past few years, a number of endoscopic procedures aimed at improvement of the barrier function of the lower oesophageal sphincter (LOS) have emerged. In general, these new endoscopic techniques use three different approaches to improve gastro-oesophageal barrier function: the gastro-oesophageal junction can be tightened by creation of plications, by delivery of radiofrequency energy at the cardia, or by injecting inert material into the muscle layer.

Endoscopic gastroplication (Endocinch) was the first endoscopic antireflux procedure to become commercially available. It soon gained a level of acceptance. In a number of publications in the 1990s, the techniques of endoscopic suturing and of endoscopic knotting were developed and refined by Swain and colleagues. A device based on Swain’s studies was developed and commercialised by BARD, and approved for use by the Food and Drug Administration. Meanwhile, other types of suturing devices, at present still under evaluation, have been proposed by Wilson-Cook (Flexible Endoscopic Suturing Device) and by NDO (Full-Thickness Plicator).

The second endoscopic procedure to obtain Food and Drug Administration approval was the Stretta procedure. Treatment by radiofrequency waves is traditionally used to obtain nerve ablation and collagen remodelling. Classical applications are ablation of accessory conductive bundles in patients with cardiac arrhythmias, remodelling of the palate in people who snore, or treatment of prostate hypertrophy. Application of radiofrequency energy to the LOS in a porcine model was found to augment lower oesophageal sphincter pressure and to increase the gastric yield pressure.

Endoscopic submucosal injections at the level of the cardia, using bovine collagen or Teflon, have been attempted in the past, with encouraging but transient results in terms of symptoms.
and LOS pressure improvements. However, the results were short lived as Teflon particles migrated from the injection site and collagen was biodegraded, and animal collagen was no longer considered safe. Promising results were also obtained by injecting small glass particles.\textsuperscript{17} The development of a biocompatible non-biodegradable polymer (Ethylene-Vinyl-Alcohol) that solidifies in contact with water and does not migrate seemed to provide a more ideal approach to improving the gastro-oesophageal barrier.\textsuperscript{18} However, other injection techniques have also been developed, such as placement of several prostheses (Gatekeeper).\textsuperscript{19}

In theory, all of these new antireflux procedures could provide an attractive alternative to long term maintenance therapy with PPIs or surgery. Accordingly, many recent reports describing these various endoscopic techniques show symptomatically successful outcomes. The aim of the present review is to provide a critical examination of the current literature.

\textbf{PATIENT SELECTION AND TECHNIQUES OF ENDOOLUMINAL THERAPY}

In most series, patients were recruited among chronic PPI dependent GORD patients (that is, the group of patients who need continuous PPI therapy for the relief of their symptoms and maintenance of healing of oesophagitis). Exclusion criteria were the presence of moderate or high grade erosive oesophagitis, a large hiatal hernia (3 cm or more), Barrett’s mucosa, and sometimes also severe oesophageal hypomotility and obesity.\textsuperscript{20–22}

In theory, all of these techniques could provide an attractive alternative to long term maintenance therapy with PPIs or surgery. Accordingly, many recent reports describing these various endoscopic techniques show symptomatically successful outcomes. The aim of the present review is to provide a critical examination of the current literature.

Figure 1  Schematic overview of the Endocinch procedure (reproduced with permission from Bard).
is injected into the muscle of the cardia under fluoroscopic control (known as Enteryx) mixed with radiopaque tantalum, which is a biodegradable polymer (an ethylene-vinyl-alcohol copolymer). The mucosal layer is kept at a temperature below 45˚C to induce a local controlled rise in temperature (up to 85˚C). The mucosal layer is kept at a temperature below 45˚C with a continuous flow of cold water. The catheter is connected to a radiofrequency generator which controls the temperature on both sides of the needle insertion sites and stops energy delivery when a defined safety threshold temperature is reached. By rotating and moving about the catheter, a total of approximately 50–60 lesions can be created in the gastro-oesophageal area.

The Stretta procedure (fig 3), developed by Curon Medical, has become a standardised method for the delivery of radiofrequency energy at the gastro-oesophageal junction. A dedicated catheter is used. The latter is equipped with a balloon which, when inflated up to a diameter of 3 cm, deploys four needle electrodes that penetrate into the muscular layer of the oesophagus. Each needle creates a lesion in the muscle layer of the target tissue through induction of a local controlled rise in temperature (up to 85˚C). The mucosal layer is kept at a temperature below 45˚C with a continuous flow of cold water. The catheter is connected to a radiofrequency generator which controls the temperature on both sides of the needle insertion sites and stops energy delivery when a defined safety threshold temperature is reached. By rotating and moving about the catheter, a total of approximately 50–60 lesions can be created in the gastro-oesophageal area.

The Stretta catheter is passed over a guidewire through the patient’s mouth into the oesophagus and positioned above the z line. Four needle electrodes are deployed starting 1 cm above the z line. Radiofrequency energy is delivered for 90 seconds. The catheter is rotated 45˚ and a second application is delivered. Both treatments are repeated 0.5 cm above the z line, at the z line, and 0.5 cm below the z line. Additional treatments are performed by advancing the catheter into the cardia and pulling back the balloon when inflated with 22 and 25 ml of air, until resistance is met at the gastro-oesophageal junction. Three applications (initial, 45˚ to the left, and 45˚ to the right) are performed at each level.

The Enteryx procedure (fig 4) uses a biocompatible non-biodegradable polymer (an ethylene-vinyl-alcohol copolymer known as Enteryx) mixed with radiopaque tantalum, which is injected into the muscle of the cardia under fluoroscopic control. Once the polymer comes in contact with water, it is transformed into a foamy particle. As this chemical reaction generates heat, injections must always be performed relatively slowly. It is important to avoid injecting in the submucosal layer or transmurally. Dark colouration of the mucosa is indicative of submucosal injection, and transmural injections can be diagnosed by fluoroscopy. The optimal treatment result consists of a ring-like filling around the gastro-oesophageal junction. In most cases however several injections are necessary, resulting in circumferentially distributed patches of injected material.

The Gatekeeper system (fig 5) consists of placing several dry hydrogel cylinder-shaped prostheses in the submucosal layer. Each prosthesis absorbs fluids and gradually swells, reaching up to 15 mm in length and 6 mm in diameter. A specially designed overtube is used for prosthesis placement. A region of the distal oesophageal mucosa is sucked into an opening of the overtube and physiological saline is injected. Saline creates an artificial chamber into which the prostheses are placed. Implantation of several prostheses above the z line reduces the diameter of the gastro-oesophageal junction.

CLINICAL OUTCOME OF GORD AFTER ENDOLUMINAL THERAPY

In comparison with the long and difficult process of drug development and approval, these new endoscopic antireflux techniques received rapid approval from regulatory agencies, despite the absence of well designed large scale clinical studies establishing efficacy. Table 1 summarises the results for the different procedures. Except for the Stretta procedure,
the efficacy of which has now been confirmed in one sham controlled randomised trial,\(^2\) all of the other procedures have only been evaluated in open label setting, with consequent relatively low levels of evidence concerning their clinical effectiveness.

For the Endocinch endoscopic gastroplication device, the available literature consists mainly of small single centre case series with a brief follow up. Unfortunately, no central registry, aimed at evaluating results and adverse events, was implemented for this procedure. A US multicentre study provides the largest series of patients (64 patients) published in a full paper.\(^{21}\) During a six month follow up, the frequency and intensity of heartburn and regurgitation were significantly improved at three and six months. Sixty four per cent of patients were no longer taking any acid suppressive drugs six months after the procedure. However, there was no significant change in oesophageal acid exposure (9.6% of time pH <4 v 8.5%; NS) and the number of reflux episodes during prolonged pH monitoring (158 v 117; NS). Park and Swain published their combined experience in 142 patients as an abstract only.\(^{26}\) All patients received two vertical plications in a procedure which lasted, on average, 30 minutes. After a follow up of up to five years, a significant improvement in pH monitoring (8.4% to 2.7% of the time; \(p<0.05\)), an increase in LOS pressure (5 to 8 mm Hg; \(p<0.05\)) and lengthening of the LOS (2 to 3 cm; \(p<0.05\)) were observed. A reduction or stop of PPI use occurred in 84% of patients. Arts et al also reported significant improvement in pH monitoring one year after endoscopic gastroplication in 20 patients refractory to medical therapy.\(^{27}\) Velanovich et al published a case control study comparing the outcomes of Endocinch with those of classical Nissen fundoplication, with 27 patients in each arm. Satisfaction rate was higher in the surgical group (26 v 21; \(p<0.01\)). Median symptom scores improved similarly in both groups. These data suggest that endoscopic gastroplication has the potential to provide an alternative to laparoscopic fundoplication in selected patients, but up to 25% of patients will have inadequate

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**Figure 4** Overview of the Enteryx procedure. (A) Foamy particles of biopolymer after solidification in water. (B) Ring-like aspect of biopolymer after injection at the lower oesophageal sphincter. (C) Histological feature of the reaction induced by biopolymer injection (reproduced with permission from Boston Scientific).

**Figure 5** Schematic overview of the Gatekeeper system (reproduced with permission from Medtronic).
improvement.29 Furthermore, it has been reported that
laparoscopic Nissen fundoplication is technically feasible
after failed gastroplication.29

These mostly single centre studies may suggest that
endoscopic gastroplication offers at least short term possiblities
for GORD treatment. However, many questions remain
to be answered before this approach can be recommended
in routine clinical practice. The long term effect was only
evaluated in very small series and showed rather disappointing
results.30 31 Information on long term outcome in the US
multicentre trial and single centre trials would be extremely
valuable, and a systematic and complete registration of
procedures, results, and potential complications is needed.
More studies need to address the optimal location and
number of plications. It is also clear that a subgroup of
patients does not respond to this treatment for reasons which
have yet to be determined. Finally, the exact role of
endoscopic gastroplication relative to maintenance medical
therapy, classical surgery, and other endoscopic antireflux
procedures requires additional large and well conducted
studies.

Up to now there has been only one multicentre trial
performed with the Full-Thickness Plicator. Sixty four
patients were treated, and after six months there was a
significant improvement in symptoms and acid control, with
normalisation of 24 hour pH monitoring in 31% of patients.24

Several groups have reported their experience with the
Stretta procedure (table 1). A US non-randomised, prospec-
tive, multicentre study included 118 patients.22 At 12 months,
the study showed significant improvement of symptoms and
acid control, with 50% treatment response was more likely in patients with

discontinued PPIs, and 12.3% reduced PPI dosage by at least
50%. Treatment response was more likely in patients with
residual implant volume of at least 5 ml. GORD symptom
scores significantly improved at 12 months compared with
baseline (p<0.001). There were significant reductions in
median supine, upright, and total per cent time of oesopha-
geal exposure to pH <4. Oesophagitis grades were
initially were crossed over to active treatment after six
months, and they also experienced significant symptom
benefit six months later (fig 6). However, in this sham
controlled study, improvement in pH monitoring after
radiofrequency energy delivery was well below that reported
in previous series and did not reach statistical significance
compared with sham procedures at six months. Furthermore,
there were no differences at six months in daily drug use
after a medication withdrawal protocol was applied.
Although this study does argue against a major placebo
effect in the published Stretta case series, it raises a number
of questions regarding the mechanism of action and exact
role of this approach in GORD management.

Experience with the Enteryx procedure is at present more
limited. Eighty five patients were enrolled in a multicentre
trial.25 At 12 months, 80.3% of 81 evaluable patients were
treatment responders. Of the responders, 87.7% completely
discontinued PPIs, and 12.3% reduced PPI dosage by at least
50%. Treatment response was more likely in patients with
residual implant volume of at least 5 ml. GORD symptom
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| Table 1 Outcome of symptoms and acid exposure after endoscopic therapy in gastro-
| oesophageal reflux disease: summary of uncontrolled studies |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| | Symptoms | pH <4%time |
| | Pre | Post | Pre | Post | No of patients |
| Endocinch | | | | | |
| Park et al20 | 5 | 1* | 8.5 | 3.7* | 142 |
| Filipi et al20 | 62.7 | 17* | 9.6 | 8.5 | 64 |
| Mahmoud et al20 | 79 | 27* | 11.1 | 9.3* | 21 |
| Arts et al20 | 11.6 | 7.1* | 17.0 | 9.8* | 20 |
| Enteryx | | | | | |
| Johnson et al20 | 25.5 | 8.5* | 9.0 | 6.4* | 85 |
| Stretta | | | | | |
| Triadafilopoulos et al21 | 27 | 9* | 10.2 | 6.4* | 94 |
| DilBaise et al21 | 21.5 | 7* | 9.5 | 6.2* | 18 |
| Tam et al21 | 19.9 | 6* | 10.6 | 6.3* | 15 |
| Meier et al21 | 17 | 7* | 25 | 1 | |
| Houston et al21 | 3.7† | 5.1†* | 8.4 | 4.4* | 41 |
| Wollsen et al22 | 26% | 77%* | | | 558 |

*Significant difference.
†QOLRAD score.
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unchanged. The Enteryx procedure also uses a centralised registry which is likely to provide results and complications on a large group of patients in the future.

The Gatekeeper system was evaluated in one open trial. Sixty patients were treated and after six months 75% of the prostheses were still present in the submucosa. Evaluation after six months showed a significant improvement in symptoms. Twenty four hour pHi monitoring improved after six months but this was not statistically significant.19

COMPlications AND Adverse Effects OF EndOLUMINAL TherAPIES

Because most patients who are candidates for these endoluminal therapies are primarily individuals with a good quality of life while on PPIs, the number and severity of adverse events for any therapeutic intervention has to be very low. For the Stretta and Enteryx procedures, central registries have been organised by the manufacturers, thus providing comprehensive data on complications and morbidity of these techniques. Unfortunately, such data are missing for the Endocinch device.

Of all the endoscopic antireflux procedures, endoluminal gastroplication is the most challenging to the endoscopist skills. Visibility is sometimes impaired by the capsule, especially when bleeding occurs, and this most likely explains the occurrence of some complications, such as creation of a split oesophageal lumen when the sutures are placed more than 90° from each other. However, the procedure is reversible by simply cutting the wire with endoscopic scissors. The use of an overtube is also responsible for some possibly severe lesions, including oesophageal lacerations and bleeding. Suction of the full wall thickness into the capsule and subsequent passage of the needle can cause a transmural perforation but this is usually self contained and can be managed conservatively. Other reported side effects include transient throat ache, vomiting, abdominal pain, transient hypoxaemia, and self limited gastric bleeding. In the absence of a central registry, we do not have a clear view on the frequency of these side effects.

The first generation of the Full-Thickness Plicator caused severe complications, such as haemothorax, haemopneumothorax, and gastric perforation. The device was modified and these severe complications did not occur.24 Post-marketing experience for the Stretta procedure has supported a generally favourable safety profile. However, during the first six months of use, a number of serious complications were reported, including oesophageal perforation in four patients and two deaths due to aspiration pneumonia.25 Other reported complications were mucosal injury, bleeding, pleural effusion, and atrial fibrillation.

The incidence of adverse events submitted to the medical device reporting system of the Food and Drug Administration has declined sharply over the past three years due to adjustments of the technique, proper training, and increasing experience of the operators. The overall serious complication rate is estimated to be 0.24%, and continues downward since the initial experience. Most patients only report some epigastric pain for up to three days after the procedure, and almost all patients are able to go to work after two to three days.

The Enteryx procedure was also found to be generally safe but complications are possible. Almost all patients report transient retrosternal pain, which usually disappears after two to three days. Transmural injection of the material is possible and may lead to the development of a pleural effusion. Submucosal injections are more frequent and create long lasting mucosal ulcerations due to a progressive erosion of the material into the lumen. Ulcers can persist for more than four weeks after injection. In the pilot trial, 6/15 patients had lost more than 50% of the originally injected material at a second follow up.26 Important inflammation and acute fever are not unusual after the procedure. Dysphagia due to narrowing of the lumen by the polymer has been reported in up to 20% of patients.26 Once the inflammation or the ulcers are cured, dysphagia usually resolves spontaneously but in some patients oesophageal dilatation has been required.

The Gatekeeper system caused in one perforation and in one patient persistent nausea in the first trial. Removal of the prosthesis was feasible and the nausea disappeared.19

WHAT Are THE UNDERLYING MECHANISMS OF ACTION OF EndOLUMINAL TherAPIES IN GORD?

Although pH data are not always convincing, most trials showed a small, sometimes significant, reduction in oesophageal acid exposure or of any other relevant pH variable (table 1), at least in patients who satisfactorily respond to these new therapeutic modalities. It is possible, but certainly unexpected, that this reduction is enough to reduce symptoms but will not be sufficient to heal erosive oesophagitis or alter the evolution of Barrett’s mucosa. Alternatively, the fact that acid exposure does not normalise, despite good subjective response, may suggest an important placebo effect; however, the Stretta sham study argues against this hypothesis. It is also conceivable that narrowing of the gastro-oesophageal junction leads to a decrease mainly in the volume of the refluxate, which is not fully detectable by pH monitoring, but which may yield important symptomatic benefit.

Several theoretical considerations are available to explain why these new endoluminal techniques reduce acid exposure and improve symptoms of GORD. The most logical explanation would be an increase in LOS pressure. Although positive results were obtained in animal studies,26 28 29 basal LOS pressures remained usually unchanged after the Stretta and Endocinch procedures.21 22 Only the Enteryx procedure was reported to induce a modest increase in LOS pressure after relaxation.30 Postprandial pressure was increased after the Stretta procedure but unchanged after the Enteryx.31 The Endocinch and Enteryx procedures were reported to significantly increase the length of the LOS but it is unclear whether this is sufficient to constitute an antireflux effect.20 21 These changes are far from impressive and do not seem sufficient to explain the symptomatic benefit and improvement in pH monitoring.

It is well established that transient LOS relaxations (tLOSRs) are the most important underlying pathophysiological event in mild to moderate GORD. A number of observations suggest that these therapies reduce the occurrence of tLOSRs.20 41 By changing the compliance of the gastro-oesophageal region, due to plications, heating with fibrosis, or the presence of implants, the threshold for triggering a transient relaxation could be increased. As radiofrequency energy induces nerve ablation (for example, the use of radiofrequency energy in the treatment of arrhythmias), the Stretta procedure could also interfere with the efferent or afferent nerves responsible for triggering the tLOSRs.

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Neurolysis could potentially also induce reduced acid sensitivity at the gastro-oesophageal junction. To investigate the sensitivity before and after a Stretta procedure, we performed a Bernstein oesophageal acid perfusion test. Six months after the Stretta was performed, we found a significant increase in time elapsed before symptom occurrence during HCl infusion, 5 cm above the z line, suggesting that radiofrequency energy delivery reduces oesophageal acid sensitivity over time. It is unclear whether this is related to or contributes to the clinical improvement after the procedure. Whether the change in oesophageal acid sensitivity reflects a direct effect on acid sensitive receptors located at sensory nerve endings of the squamous layer or whether this occurs secondary to a reduction in oesophageal acid exposure (with restoration of tight junctions and decreased mucosal permeability) warrants further investigations.

CONCLUSIONS AND RESEARCH AGENDA

Although PPIs remain the cornerstone of GORD treatment, they have some limitations. As surgical fundoplication is also not an ideal solution, there may be room for one or more of the endoscopic antireflux therapies outlined above. The most encouraging aspects of endoscopic antireflux treatments are their ability to be performed on an outpatient basis, combined with the high proportions of patients able to discontinue medical therapy, which have been reported in many studies, thereby reducing socioeconomic costs. Overall, the apparent clinical efficacy may be partly attributable to a placebo effect although a sham controlled study with radiofrequency ablation argues against this playing a major role. In contrast, the reduction in acid exposure has generally been unimpressive and normalisation is obtained only in a minority of patients. Alternatively, other potential beneficial effects such as reduction of the volume of the refluxate or an effect on non-acid reflux cannot be excluded at present. In the absence of reliable predictors of response or failure, and in the absence of well controlled studies comparing endoluminal antireflux therapies to standard clinical approaches, it seems premature to implement these in a routine clinical setting. It is clear that further large scale and well controlled studies are required for these novel therapeutic modalities, and it is our opinion that all patients should at present be included in research or follow up protocols. Finally, it should be emphasised that the period of follow up is limited and does not exceed 12 months in most of the published studies. This is rather short given the chronic nature of GORD in most patients.

The safety of the procedures seems encouraging but again detailed and prolonged follow up is required. Early experience suggests that these procedures do not interfere with subsequent antireflux surgery in case of failure but more systematic data are needed. With the Stretta procedure, severe complications have been observed during the early phase, but an extensive database of all treated patients now seems reassuring. Furthermore, it is unfortunate that a detailed registry does not exist for each of these procedures.

The underlying mechanism(s) of these new therapies deserve many more mechanistic studies. Indeed, in addition to a decrease in the rate of LOSRs, other beneficial potential effects, such as changes in oesophageal sensitivity, may develop after radiofrequency energy application.

For the time being, endoscopic antireflux procedures should be done in a controlled environment, preferably in reference centres. Comparative studies of these techniques, including economic aspects, are needed in order to determine their place in future clinical practice.

Summary

- To date, the efficacy of endoluminal therapy for GORD is not supported by a high level of evidence. Only one randomised controlled trial has been published in full, showing a benefit of radiofrequency energy delivery versus 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 GORD 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 radiofrequency 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.
- The underlying mechanisms of these new therapies deserve many more mechanistic studies. Indeed, in addition to a decrease in the rate of LOSRs, other beneficial potential effects, such as changes in oesophageal sensitivity, may develop after radiofrequency energy application.
- For the time being, endoscopic antireflux procedures should be done in a controlled environment, preferably in reference centres. Comparative studies of these techniques, including economic aspects, are needed in order to determine their place in future clinical practice.

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