Recent Advances in the Invasive Treatment of Gastroesophageal Reflux Disease

Chih-Lang Lin, Rong-Nan Chien, Kuan-Meen Fang, Cho-Li Yen, Jia-Jang Chang, Tsung-Shih Lee, Ching-Jung Liu, and Li-Wei Chen

Division of Gastroenterology, Department of Internal Medicine,
Chang-Gung Memorial Hospital and University, Keelung, Taiwan

Abstract

The term gastroesophageal reflux disease (GERD) describes any symptomatic condition or histopathologic alternation resulting from episodes of gastroesophageal reflux. It usually manifests as heartburn, regurgitation, or dysphagia, and predisposes to development of esophagitis, stricture, Barrett's metaplasia, esophageal adenocarcinoma, and a substantial decreased in the quality of life. Conventional pharmacotherapy (proton pump inhibitor；PPI) is effective, but is associated with a high relapse after discontinuing medication. Laparoscopic Nissen fundoplication is an alternative management regimen for young, healthy patients with severe disease. However, extreme caution is advised in regard to its significant morbidity, high reoperation rate, and an approximate 0.2% mortality rate. Recently, a number of endoscopic or endoluminal approaches have been developed aimed at impro-ving the function of the esophagogastric junction to prevent gastroesophageal reflux and may be ca-tegorized into injection bulking, endoluminal plication, and radiofrequency Stretta procedures. The procedural mechanisms, associated benefits and cost advantages are of interest to researchers. In the present study, we discuss the mechanisms, benefits, and outcomes of each individual option. To date, no standard therapy guideline has been recommended since the appearance of these new endosco-pic procedures. According to limited preliminary data, a new guideline can be established for clinical practice. (J Intern Med Taiwan 2004; 15: 237-248)

Key Words：Gastroesophageal reflux disease therapy, Endoscopic or endoluminal approaches, Injection bulking, Endoluminal plication, Radiofrequency delivery procedure.

Introduction

The term gastroesophageal reflux disease (GERD), first described by Winkelstein in 1935 1, describes any symptomatic condition or histopatho-
logic alternation resulting from episodes of gastroesophageal reflux 2. It usually manifests as heartburn, regurgitation, or dysphagia, and predisposes to the

development of esophagitis, stricture, Barrett's metaplasia, and esophageal adenocarcinoma, in addition to a substantial decrease in the quality of life.

Based on the most common symptom of heartburn, it affects more than 60 million American adults on a regular basis, including more than 25 million adults who experience heartburn at least once a week 3. However, no conclusive data is available for Eastern countries, including epidemiological data, although a gradually increasing prevalence and rising therapy costs are without doubt a growing concern. Therefore, recent advances in the treatment of GERD are in need of further clarification and evaluation.

Diagnosis

Endoscopic findings for the diagnosis of GERD included normal studies, reflux erosive esophagitis, ulcers, and Barrett's esophagus 4. A 24-hour pH meter examination was then used for identifying normal endoscopic symptomatic patients (pH < 4 and > 3.5% recording time 5, or a high value Demeester score 6). If the patients complained of typical manifestations of GERD without any abnormalities of endoscopy or the 24-hour pH meter, a Bernstein test was applied in documenting this disease 7.

Conventional management

1.Lifestyle modification

Simple lifestyle modifications are the first methods employed by patients, and, because of their low cost and simplicity, they should be continued even when more potent therapies are initiated. Most of these methods were the main therapeutic modalities before the late 1970s and include elevation of the head in bed, wearing of loose fitting clothing, avoidance of meals before bedtime, weight loss, and abstinence of smoking, alcohol, coffee, and fat 8-9 (Table 1). Because of the minimal published data available related to the efficacy of these nonpharmacologic therapies for GERD 10, it is unlikely that they will suffice, except in mild cases of GERD disease.

2.Pharmacological treatment

Pharmacological treatment can relieve symptoms, avoid complications, and heal esophageal mucosa. Proton pump inhibitor (PPI), a potent acid-suppressive drug, is currently the most important and successful medical therapy. Long-term safety and efficacy of standard PPI doses are supported by European studies with patient follow-up over a decade 11.

Most patients with GERD can be adequately managed by treatment with a PPI; however, symptom relapse is common after cessation of treatment, and thus many patients must commit to lifelong therapy. The rate of relapse reaches 100% in patients with extremely low lower esophageal sphincter (LES) pressures 12 or 33% in two years 13. This high rate of relapse is not surprising because medication suppresses

acid production and thus the symptoms of the di-sease are treated and not the underlying disease itself.

3.Laparoscopic Nissen fundoplication

Laparoscopic Nissen fundoplication, until recently, is the single alternative to lifelong treatment for a young, healthy patient with severe disease, in whom there is a lifelong need for medical therapy because of persistent reflux symptoms despite PPI drug use 14. Compared with open Nissen fundoplication, it has been demonstrated as effective with fewer complications and a similar rate of patient satisfaction 15-18. Nevertheless, only a small number of patients undergo surgical fundoplication, because both physicians and patients are cautious in regard to the surgical procedure, which, although effective, has significant morbidity (up to 5%, including flatulence, bloating, and dysphagia), a high reoperation rate (up to 13%, because of complications and/or recurrent reflux), and an approximate 0.2% mortality rate 19. In addition, long-term comparative analysis has shown that medical treatment is still required post antireflux surgery 20.

Owing to the above limitations, a number of endoscopic or endoluminal approaches have been recently developed, aimed at improving the function of the esophagogastric junction in order to prevent ga-stro-esophageal reflux.

New endoscopic or endoluminal approaches

New endoscopic or endoluminal approaches may be categorized into injection bulking, endoluminal plication, and radiofrequency energy delivery.

1.Injection bulking

The use of biocompatible materials as tissue augmenting factors is an established procedure in urological and plastic surgery. In the early phase, in order to impede the reflux in GERD disease, endoscopic submucosal injections at the level of esophagocardiac junction by bovine collagen in 1988 21 or polytef (polytetrafluoroethylene) in 1996 22 have been attempted, with encouraging albeit transient results in terms of improvements in symptoms and LES pressure. The improvements have been of short duration because collagen is biodegradable, and polytef particles tend to migrate from the injection site.

In fact, injection bulking utilizes a combination effect of the retained material and consequent tissue response of bulking agents at the esophagocardia junction to impede reflux in GERD disease. Therefore, the ideal implant should be biologically and chemically inert, nonmigrating, durable, and should induce a negligible foreign-body reaction. Recently, because of advancements in chemical engineering, polymethylmethacrylate (PMMA) in 2001 23, ethylene vinyl alcohol with tantalum in 2002 (Enteryx Polymer, Enteric Medical Technologies, Inc., Palo Alto, Calif. and Boston Scientific International, Cedex, France) 24 , and hydro gel prosthesis in 2003

(Gatekeeper Reflux Repair System; Medtronic, Minneapolis, MN) 25 were applied for new bulking agents. However, just Enteryx Polymer is approved by the Food and Drug Administration (FDA) for treatment of GERD in April 2003 and others remain investigational at the time of this writing.

(1).Polymethylmethacrylate (PMMA)

A gelatinous implant containing polymethylmethacrylate (PMMA) beads was successfully used to augment the diminished thickness of the chorium in patients with skin defects and wrinkles. Endoscopic submucosal implantation of PMMA was carried out in 10 patients with GERD who were either refractory to or dependent on PPI 23. Five to six injections at different sites with a volume of 24 to 39 mL (mean, 31.77 mL) were performed in 10 to 30 minutes. At 5 to 11 months of follow-up (mean, 7.2 months), endoscopic ultrasonography (EUS) demonstrated the continuing presence of PMMA particles at all sites in all 10 patients, with a significant decrease in the symptom severity score, mean total time with an esophageal pH less than 4, and a mean Demeester score was noted. Seven of 10 patients took no medication after PMMA implantation. There were no serious procedural related complications.

(2).Ethylene vinyl alcohol with tantalum (Enteryx Polymer)

Enteryx has been used for embolization of arteriovenous malformations 26. Enteryx Polymer reported in 114 patients who have a relapse in symptoms post discontinuation of PPI therapy 24,27-29. Implantation with 4 to 8 mL of Enteryx in 1 to 6 injections along the muscle layer or deep submucosal layer of the cardia was performed in a forward and side-viewing endoscope suite equipped for fluoroscopy. The average procedure time and mean complete injection time were 33.8 ± 10.0 minutes (mean ± SD)and 24.6 ± 9.8 minutes. At 4 to 12 months of follow-up, Enteryx implantation in the muscle of the cardia was feasible and safe, except 19 treated patients in Johnson DA. Study 27-28 underwent retreatment between 1 and 3 months. There were statistical improvements in reducing the heartburn score, off PPI therapy, raising the quality of life score, and diminishing the 24-hour PH exposure time (Demeester score), but no change or worse in endoscopic esoph-agitis. In the aspect of the resting lower esophageal sphincter pressure, increasing in 13 of 15 cases at month 1 and sustaining at a median follow-up of 6 months (range, 4-12 months) were only found in Deviere J. study 24. There were no major adverse events that were considered serious, life threatening, or requiring surgical intervention or hospitalization.

2.Endoluminal plication

Originally, Swain et al. 30 developed an endoscopic sewing machine 30, an endoscopic knot tying technique 31 and an endoscopic suture-cutting device 32, with which it is possible to pass a suture through the muscularis propria. These endoscopic

antireflux procedures have been performed on human cadavers and in beagle dogs 33, swine 34, baboons 35, and human patients 36-37.

Later, endoluminal plication developed into EndoCinch, ESD, full-thickness application, and endoscopic ultrasonography guided transgastric gastropexy and hiatal hernia repair. Among them, EndoCinch and full-thickness application became FDA-approved devices for use as therapy in patients with GERD.

(1).The EndoCinch (Bard, Billerica, Mass.)

This system includes a suturing capsule attached to an endoscope, a knot pusher, and a suture cutter. A minimum of 2 plications are placed for each procedure. To perform the EndoCinch procedure 38, an oroesophageal overtube (19.7-mm outside diameter, 30-cm length) is placed to facilitate passage of the suturing device. The suture capsule is attached to the tip of a 9-mm outside diameter endoscope and loaded with a tilt-tagged suture. After positioning the suture capsule over the selected site, suction through the external vacuum line is applied. Tissue is suctioned into the capsule cavity, and the suture placed by the needle driver. Suction is released and the tissue is withdrawn from the capsule. The procedure is repeated on an adjacent site. Drawing two adjacent sutured sites together creates a plication. Sutures are cinched together with a ceramic plug and ring assembly. Additional sutures are deployed in either a linear or circumferential configuration.

A multicenter trial in 2001 evaluated 79 EndoCinch procedures for the treatment of GERD in 64 patients 39, and another one year prospective follow-up study in 2003 evaluated 26 procedures in 24 patients 40. Additions, some other available data 37, 41-58 are uncontrolled, of short duration, commonly retrospective in nature, mostly available only in abstract form, and often measure physiologic outcomes or selected clinic outcomes alone. They all revealed significant improvements in regurgitation symptoms, heartburn severity, 24-hour pH meter monitoring, Demeester score, discontinuance of medication, and quality of life. However, there were no significant

differences in the changes of endoscopic findings and LES manometry. All transient post-procedure complaints resolved within 72 hours, and only one patient had a self-contained suture perforation that was successfully treated with antibiotics.

(2).Endoscopic suturing device; ESD (Wilson-Cook Medical, Winston-Salem, N.C.)

The ESD system is single-use and includes a sew-rite device, two quick-load sutures, a loading wire, four vacuum caps, one tie-rite knot device, two knot-loaders, one external accessory channel, one seal cap, one pair of scissors, and one vacuum cap remover. The endoscope is inserted with the external accessory channel (EAC) attached, and the operative site is determined. The sew-right device is inserted into the EAC and advanced until viewed endoscopically. Tissue is aspirated into the vacuum

cap, and while maintaining suction, a lever is activated to deploy the needle to which the suture is attached. When the lever is released, the needle retracts, placing the suture. Suction is then discontinued, releasing the tissue. These steps are repeated for a second suture placement, followed by the knot tying process and the cutting of excess suture material 38.

There is no peer-reviewed data on the Wilson-Cook ESD for treatment of GERD at the time of this study.

(3).The Full-Thickness Plicator (Ndo Surgical, Inc, Mansfield, Mass.)

The device consists of a reusable instrument and a single-use, suture-based implant. In addition, a proprietary endoscopic tissue retractor and standard overtube are used to perform the full-thickness endoscopic plication procedure. To perform the endoscopic plication procedure 59, a standard upper endoscope is passed into the stomach. After inspection of the stomach, a savary spring-tipped metal guidewire (Wilson-Cook Medical, Inc., Salem,NC) is passed through the endoscope. The endoscope is removed, and a 54F savary dilator and specially designed overtube (60F) are passed over the guidewire. The dilator and guidewire are removed, and the EPS and endoscope assembly are passed into the stomach. The overtube is retracted so that its distal end is proximal to the gastroesophageal junction, and the stomach is distended with air. The endoscope is advanced and retroflexed so that the instrument may be visualized, retroflexed, and properly positioned. The endosco-pic tissue retractor then is inserted within 1 to 2cm of the GE junction and advanced up to the level of the serosa. After this, the full thickness of the gastric wall is retracted, and the instrument arms are closed. The implant then is deployed to secure the full-thickness plication, and the tissue retractor is disengaged from the gastric wall. The arms are opened, and the instrument is disengaged from the implant. After closing the arms and straightening the instrument and the endoscope, both are removed, followed by the overtube.

A pilot study in 2003 59 enrolling seven men and a multicenter trial in 2004 60 enrolling 64 patients

evaluated the full-thickness placation procedure for GERD therapy. Significant improvements in GERD symptoms, heartburn score, health-related quality of life, 24-hour pH meter monitoring, Demeester score, and discontinuance of medication were well documented. However, no noteworthy change was observed in the mean LES resting pressure at manometry or mean distal esophageal amplitude of contraction at manometry for baseline vs. three-month follow-up 60. The mild adverse reactions occurred after the plication procedure resolved spontaneously. Six patients with serious adverse events including two cases of respiratory distress post overtube, one case of spontaneous pneumothorax, one case of pneumoperitonium, and one case of gastric perforation all successfully recovered after medical or surgical

ma-nagement.

(4).Endoscopic ultrasonography guided transgastric gastropexy and hiatal hernia repair

A new method for stitching under flexible endoscopic sonography control was first described by Fritscher-Ravens et al. in 2002 61. However, this year, a porcine model study in 22 pigs was published for endoscopic ultrasonography guided transgastric gastropexy and hiatal hernia repair 62. Through the ability to visualize and manipulate structures outside the wall of the gut by endoscopic sonography support, they examined the feasibility of performing endoluminal GERD surgery by placing stitches between the median arcuate ligament (MAL) and the lower
esophagus sphincter to form a posterior gastropexy (Hill repair) in 18 animals. This procedure was based on the surgical antireflux repair developed by Lucius Hill 63. It significantly increased lower esophageal sphincter pressure in pigs. Median lower esophageal sphincter pressure, determined manometrically, was 11 mm Hg before surgery and 21 mm Hg after stitch placement ($p = 0.0002$). Furthermore, the hiatal hernia ‘repair’ was performed by stitching between the left crura and the right crura of the diaphragm.

Owing to a lack of human clinical trials and a comprehensive experiment design, future clinical
studies are needed to assess whether an endoscopic sonography-assisted antireflux procedure offers advantages over conventional laparoscopic or current endoluminal flexible endoscopic antireflux procedures.

3.Radiofrequency energy delivery (RFe; Stretta device)

Radiofrequency energy has been shown capable of ablating aberrant nerve pathways, as in Wolf-Parkinson-White syndrome 64, tightening lax tissue, as in damaged joints 65, shrinking the prostate in benign prostatic hypertrophy 66, shrinking liver tumors 67, and volumetric reduction of the palate in snoring and sleep apnea 68.

However, radiofrequency energy for the treatment of GERD is delivered by Stretta (Curon Medical Inc., Sunnyvale, Calif.), which is an endoscopically mediated endoluminal device and is FDA-approved. Stretta treatments 69 are typically done during a sedated EGD. The investigator confirmed the endoscopic eligibility criteria, measured the distance to the gastroesophageal junction (the squamocolumnar junction), withdrew the endoscope, and introduced the radiofrequency delivery catheter orally. The catheter consisted of a flexible balloon-basket assembly with 4 electrode needle sheaths. The investigator then inflated the balloon 2 cm proximal to the squamocolumnar junction, deployed the electrode needles (22 gauge; 5.5-mm length), and delivered radiofrequency energy for 90 seconds. The needles were then

withdrawn, the balloon was deflated, the catheter was rotated 45^0 and the procedure was repeated. This process was serially repeated every 0.5 cm, covering an area 2 cm above and 1.5 cm below the squamocolumnar junction (used as the approximate location of the gastroesophageal junction) plus 6 sets in the cardia, for a total of 22 sets of needle deployments.

Two potential mechanisms of action have been proposed for Stretta treatment of EGJ in GERD patients: scarring of the EGJ and neurolysis in the region of EGJ. Scarring or collagen deposition can mimic the effect that radiofrequency energy application has on joint capsules and can potentially 'tighten' the EGJ, limiting the occurrence and/or volume of gastroesophageal reflux on that basis. Neurolysis in the region of the EGJ can potentially destroy sensory or motor nerve endings. The destruction of chemosensitive or mechanosensitive nerve endings can potentially reduce the sensitivity of the esophagus to noxious stimuli. Destruction of vagal afferents in the region of the gastric cardiac can potentially reduce elicitation of transient lower esophageal relaxations (tLESRs), thereby reducing the number of reflux events attributable to that reflex 70.

In all human and animal trials 71-75, including a randomized sham-controlled trial 69, a significant reduction in the severity of heartburn is revealed, including a significant improvement in the quality of life score with no significant change in the severity of esophagitis and low esophageal sphincter pressure. However, affection of the 24-hour pH meter is variable because of significant, averaging improvements of 3.7% in the uncontrolled trial and no change in the sham-controlled trial.

A review of the FDA Manufacturer And User Facility Device Experience database (MAUDE) from November 27, 2001 identified two deaths occurring three and seven days after the Stretta procedure, attributed to vomiting and aspiration, and four esophageal perforations requiring surgery. The current role of Stretta in clinical practice (circa January 2003) is as follows. Clear indications for Stretta treatment are nil because of the paucity of controlled data available, the limited follow-up currently available on treated patients, and the confusing nature of the data that are available. This opinion is in sharp disagreement with the FDA 510(k) summary statement on Stretta concluding that "the risk-benefit profile (of Stretta) is substantially equivalent to that of fundoplication surgery." Because there are no clear indications for the procedure, it is the opinion of this author that all Stretta treatments rendered at this time should be done in the setting of clinical trials. A possible indication for Stretta treatment is in the management of a patient with endoscopy-negative or low-grade esophagitis with unsatisfactory heartburn resolution despite PPI therapy. Both

uncontrolled and sham-controlled trials suggest that such individuals will benefit in terms of a reduction in heartburn severity despite reduced PPI usage.
Contraindications for Stretta treatment are circumstances in which there has been no demonstration of clinical efficacy: high-grade (LA C or D) esophagitis, Barrett's metaplasia, management of extraesophageal manifestations of GERD, or management of any GERD symptom other than heartburn 70.
Efficiency Comparison and Application
Improvement of symptomatic severity, quality of life, 24-hour pH meter regurgitation, Demeester
score, and discontinuance of medication can be significantly approached from injection bulking, endoluminal plication, and radiofrequency energy deli-very (Table 2). However, in low esophageal sphincter pressure retrieving, just endoscopic ultrasonography guided transgastric gastropexy and Enteryx Polymer injection can ameliorate the effects. Endoscopic ultrasonography guided hiatal hernia repair may be the other choice for hiatal hernia management other than operation. Because these endoscopic approaches are invasive, serious complications can occur, especially after radiofrequency energy delivery. Therefore, a possible indication for Stretta treatment is in the
management of a patient with endoscopy-negative or low-grade esophagitis with unsatisfactory heartburn resolution despite PPI therapy.
Consequently, if failure or easy relapse occurs in the midst of lifestyle modification management and pharmacotherapy, an algorithm for GERD therapy can be useful in schematically presenting a decision tree of how to decide which patients should take the endoscopic approach (Fig. 1). If obvious hiatal
hernia is found by endoscopy study with refractory GERD, either Laparoscopic Nissen fundoplication or endoscopic ultrasonography hiatal hernia repair can be administered. If GERD persists with apparent low esophageal sphincter pressure, we can perform endoscopic ultrasonography guided transgastric gastropexy and Enteryx Polymer injection to restore pressure. After correction of structural hiatal hernia and low esophageal sphincter pressure with persisting GERD symptoms, all recent updated methods, including injection bulking, endoluminal plication, and radiofrequency energy delivery can be accomplished. Selecting by the conditions of FDA-approved maneuvers and serious complications, the EndoCinch sewing procedure and full-thickness placation should be performed. When there are no abnormalities found during endoscopy, manometry, and 24-hour pH meter, except for GERD symptoms (especially heartburn), the Bernstein test should be applied in order to confirm this disease. Radiofrequency energy deli-very is perhaps the other therapeutic choice for lower esophageal muscle hypersensitivity owing particular to

the neurolysis effect.

In conclusion, these procedural mechanisms, benefits, and cost efficacy are of interest to researchers. However, in many cases, there is a lack of data in randomized controlled trials, and only preliminary or pilot clinical studies are available. Comparative, longer-term efficacy and safety data are needed. Because this is a rapidly evolving area, practitioners should continue to monitor the medical literature for subsequent data about the efficacy, safety, and economic aspects of such technologies.

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Table 1. Lifestyle modifications that can improve GERD symptoms

Sleeping with the head of the bed elevated
Sleeping on the left side
Avoiding late meals/avoiding recumbent position 3 hours after meals
Avoiding high-fat meals
Eating smaller meals
Using saliva-stimulating agents (i.e., hard candies, chewing gum)
Wearing of loose-fitting clothing
Abstaining from smoking, alcohol, coffee, chocolate
Losing weight

Table 2. Comparison of various new endoscopic or endoluminal approaches available

	PMMA**	enteryx	EndoCinch	Full thickness application	RFe** delivery	EUS** guide-approach
Symptom improvement	+	+	+	+	+	nil
Life quality improvement	+	+	+	+	+ *	nil
24-hour pH meter /Demeester score improvement	+	nil	+	+	+/(-)[(a)]	nil
LES pressure –manometry	nil	+/-	-	-	-	+
Hiatal hernia repair	-	-	-	-	-	+
Medication Discontinuance	+	+	+	+	+	nil
Serious complications	-	-	-	-	+	-

- * specific for heartburn sensitivity
- [(a)] improvement –3.7% in the uncontrolled trial and no change in the sham-controlled trial
- nil means no data at the time of this study

**: PMMA: Polymethylmethacrylate
RFe: Radiofrequency
EUS: Endoscopic ultrasonography

Fig.1. Algorithm for GERD therapy in patients who are failure or easy relapse of lifestyle modification management and pharmacotherapy.

胃食道逆流疾病侵入性治療之最新進展

林志郎　簡榮南　方昆敏　嚴卓立　張家昌　李宗實　劉競榮　陳立偉

基隆長庚醫院　內科部肝膽胃腸科

摘　　要

胃食道逆流疾病（gastroesophageal reflux disease; GERD）是指“由胃食道逆流所產生之症狀或食道組織病理的變化”。常見的臨床表現包含胸口灼熱感、反胃、或吞嚥困難，且易引起食道炎、食道狹窄、及巴瑞特氏（Barrett's）化生，甚至導致癌症而造成嚴重的生活品質下降。傳統的氫離子幫浦阻斷劑(proton pump inhibitor; PPI)在治療上是相當有效的，但是停藥後常見較高的復發率。對於年輕健康但有嚴重症狀的病人，Nissen 腹腔鏡胃基底褶疊整型術則是另一種治療的選擇，然而，它明顯的罹病率、較高的再手術率、及大約 0.2%的死亡率是非常需要注意考慮的。近來，已發展了一些新的內視鏡治療法來改善胃食道接合點的功能，以防止胃食道逆流的發生，包括有充填注射術（injection bulking）、內視鏡褶疊術（endoluminal plication）、及射頻電燒灼術（radiofrequency Stretta procedures）。令研究者感興趣的則是這些新技術的機轉、療效、及經濟效益。本篇文章的主要目的是探討其各種治療，並針對其機轉、療效、和成果來作綜合討論。然而這些新的內視鏡治療法出現迄今，仍無標準的指導方針可供依循。因此我們根據有限的初步資料，期望重新建立一套治療的指導方針，以供日後醫師和患者選擇治療法之最佳參考。