



Future opportunities and developments for endoscopic gastroesophageal reflux disease therapy

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The current techniques of endotherapy for gastroesophageal reflux disease (GERD) have been described elsewhere in this issue. Endotherapy for GERD is still in its infancy with the ideal methods yet to be identified. This article presents issues that need to be addressed for optimization of an endoscopic approach, including a discussion of the anatomy that is critical to targeting endotherapy and current and needed methods for the successful alteration of this critical anatomy. In addition, this article assesses effectiveness of GERD therapies and speculates on future directions in endotherapy for GERD.

Anatomy

Central to a discussion of GERD endotherapy is an understanding of the critical related anatomy. This article does not present a comprehensive discussion of the anatomic pathophysiology of GERD but attempts to focus on the key elements of the distal esophageal and proximal gastric anatomy—the lower esophageal sphincter (LES), the esophagogastric (EG) junction, and the cardia. The squamo-columnar (SC) junction is a key visual landmark during GERD endotherapy and is normally within the midpoint of the endoluminally viewed LES, at or just below the level of the diaphragm. The esophageal visual component of the LES is estimated to be approximately 2 cm long. This component of the LES can be identified within a minimally distended esophagus by the prominent mucosal cushions typically present (Fig. 1A,B). The endoscopically viewed or endolumi-

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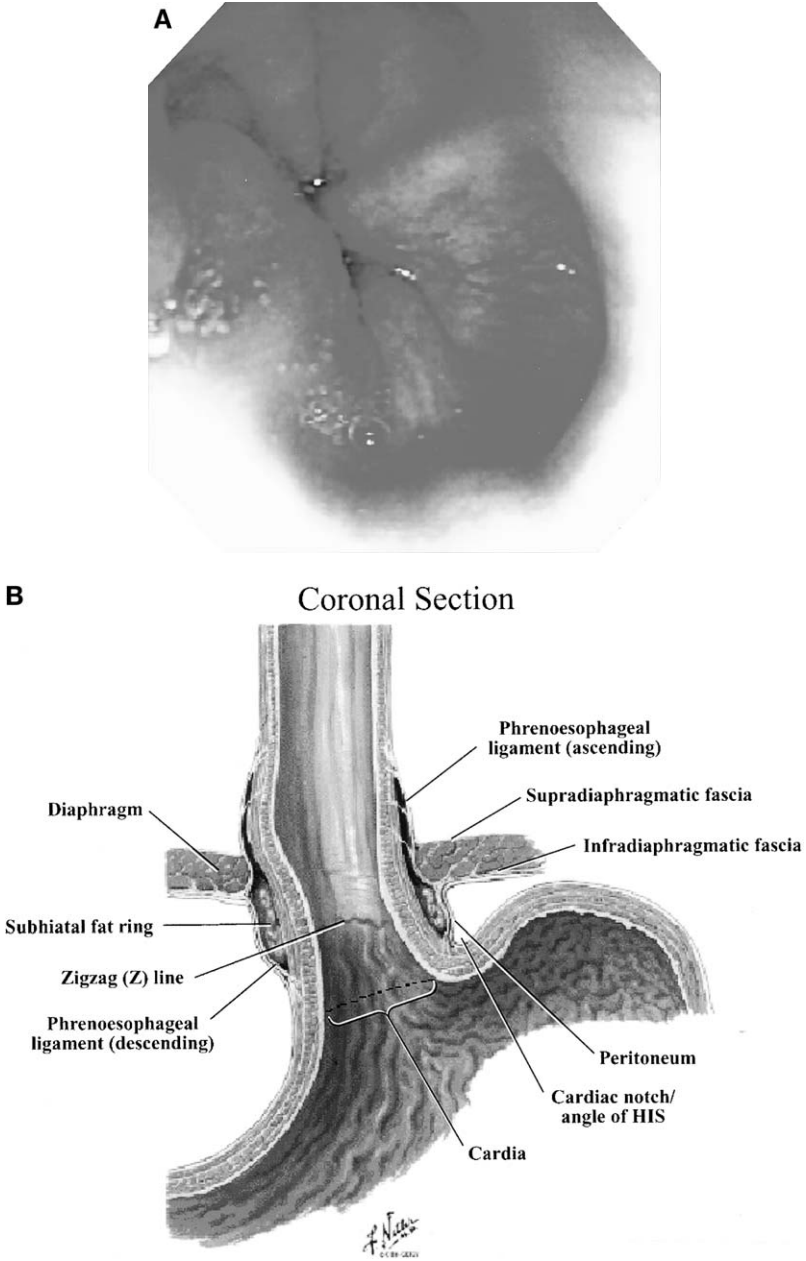


Fig. 1. (A) Squamocolumnar junction with prominent distal esophageal mucosal cushions estimating the esophageal endoluminal area of the lower esophageal sphincter (LES). (B) Anatomic depiction of the LES, including esophageal and gastric cardiac components. (See also Color Plate 12.) (Copyright 1995, Ciba-Geigy Corporation, with permission.)

nal” LES extends into the cardia for a distance of 1 to 2 cm as well. The EG junction is used to describe the “mural muscular junction” between esophagus and stomach that is at or immediately distal to the SC junction. Localization of the EG junction is best defined by manometry and is approximately at the level of the extrinsic crural segment of the LES. It is visually earmarked as the border between the fine linear mucosal vessels within the distal esophagus and the upper extend of the gastric rugal folds (Fig. 2). The cardia is composed of a semicircular or horseshoe-shaped collar, spanning the anterior wall, greater curve, and posterior wall of the uppermost stomach, with the angle of His created by this collar of tissue at the point of the greater curve. This semicircular or horseshoe-shaped area of the cardia is open to the lesser curve. The cardia is normally closely approximated to the endoscope on retroflexed view (Fig. 3) [1].

Lieberman-Meffert et al [2] described an intriguing concept of the oblique gastroesophageal ring (GER), which may be relevant to endotherapy. The GER is defined as the area of maximal muscular thickness at the EG junction and was found in cadaveric studies to be caused by the increased mass of the inner muscle coat. These inner muscle bundles were found to form short transverse “clasps” rather than rings on the lesser curvature, with openings facing the greater curvature. Conversely, on the greater curvature, the inner muscle bundles formed long oblique gastric fiber loops or “slings.” The GER was found to be proximal to the angle of His, distal to the SC junction, and below the lower leaflet of the phrenoesophageal membrane. It was asymmetrical, with its thickest component on the greater curvature. A follow-up study strengthened their hypothesis that the

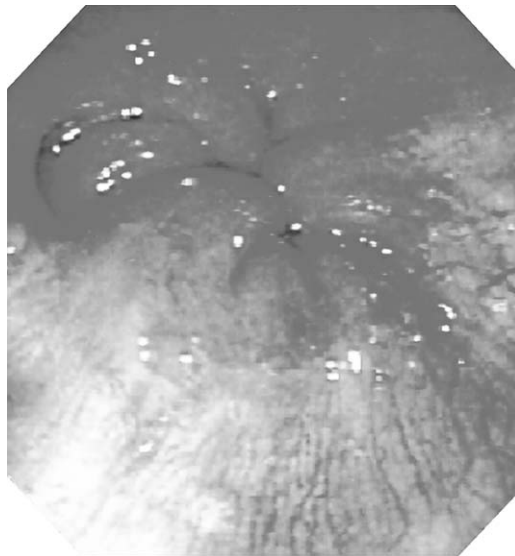


Fig. 2. Esophagogastric junctional area visually noted as the border between the linear mucosal distal esophageal vessels and the upper ends of the rugal folds. (See also Color Plate 13.)



Fig. 3. Retroflexed view of the cardia demonstrating the collar of tissue that comprises the angle of His and the open area within the lesser curvature. (See also Color Plate 14.)

area of greatest manometric pressure corresponds to the GER. Support for this was that the high-pressure zone is of similar length to this muscular thickening and the greatest pressure, like the greatest thickening, is on the greater curvature side [3]. In effect, the asymmetric muscular thickening was mirrored by the three-dimensional manometric measurements. There may be some limitation to this reasoning as it may mainly apply to the resting state [2]. The GER concept supports the targeting of endotherapy within the cardia and, more so, suggests specific sites to be primarily manipulated.

Korn et al [4] investigated the relationship of a dilated “patulous cardia” with LES dysfunction. Two distinct muscular units were described forming clasp and sling fiber functions altered by the increased diameter of the cardia. Normally, the “oblique sling fibers” on the greater curvature side of the cardia “descend and advance medially” to meet the transverse-oriented clasp fibers of the lesser curvature side of the cardia. With chronic dilatation of the cardia, the oblique fibers lengthen, losing some of their strength, and their orientation changes, thus decreasing the overlap pressure zone. This patulous or dilated appearance to the cardia is noticeable during endoscopy on retroflexion (Fig. 4). In patients with GERD with dilated cardias, there was a direct correlation between the severity of GERD and increased perimeter of the cardia. Dilatation of the cardia was not proposed as the origin of GERD, however, but as the “point of no return” at which the LES becomes mechanically defective. The open area of laxity, which corresponds to the lesser curve, is a critical anatomic target for endoscopic suture plication.

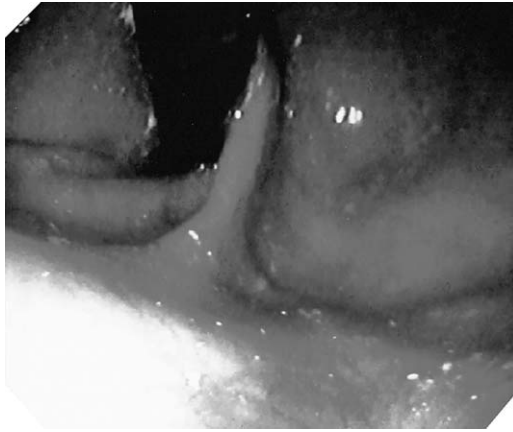


Fig. 4. Patulous cardia of a patient with gastroesophageal reflux disease. (See also Color Plate 15.)

The acute angle of entry of the esophagus into the stomach has been hypothesized to act as a “flap valve”[5]. Its anatomic advantage is compromised with deep inspiration when the angle of His becomes less acute. This is compensated by the right crus of the diaphragm occluding the esophageal lumen during deep inspiration. The horseshoe collar of cardial tissue comprising the angle of His is another critical target for endotherapy that is intended to accentuate this angle. One more anatomic factor believed to maintain the gastroesophageal barrier and targeted as well for endotherapy is the intra-abdominal length of the LES. Lower pressures needed to act as a barrier have been shown to correspond with a longer LES length, especially the cardial component, and conversely shorter lengths have been shown to have greater reflux as measured by 24-hour pH recordings.

There are other factors affecting the LES competence and resultant GERD, such as the resting pressure, transient relaxations (tLESRs), and hiatal hernia. Endoscopic treatment is at present crudely limited to altering some of the anatomic and mechanical factors involved in the pathophysiology of GERD.

The technical challenges

Like surgery, endoscopic treatment is intended to increase the esophagogastric pressure gradient. Radiofrequency energy treatment of the LES and the EG junction neural complex also has been shown to decrease tLESRs [6,7]. The fundamental issues for therapeutic intervention include whether to target the esophageal or gastric side of the EG junction, what tissue depth to target, and which of the previously described anatomic factors should be altered. The goal of endoscopically altering this anatomy can be accomplished in several ways: tightening the open end of the cardial horseshoe (lengthening the LES) within the lesser curve, creating a barrier (“speed bump”) within the lesser curve at the level of the cardia (bulking), accentuating the angle of His, and lengthening the

angle of His. At present, aside from coagulative ablation of the LES, there are no other endoscopic interventions designed to directly alter the LES itself.

Earlier techniques applied within the cardia did not directly alter the LES but rather the mucosa and submucosa and attempted to create a barrier by either bulking or stimulating contraction and fibrosis (stricture). The failure of fibrosis of the gastric cardia to result in sustained clinical improvement is not unexpected because this region readily replaces damaged tissues with normal tissue. The same tissue remodeling and healing readily sheds foreign materials implanted into the submucosa [8]. Induction of an esophageal stricture similar to that obtained during variceal sclerotherapy, which may involve the muscularis propria, may be long lasting, however. The obvious drawback for scarification within the distal esophagus is the potential for inducing dysphagia. These earlier methods of bulking and scarification introduced the notion that alteration of the cardiac/His anatomy could improve GERD symptoms and predicted that other methods, such as suturing, might be effective in this area.

The EndoCinch system (Bard Interventional Products, Billerica, MA) described in this issue can be used to tighten the lax cardia and close the semicircular or horseshoe collar described previously. The NDO system (NDO Surgical, Inc., Mansfield, MA) under pilot clinical testing, described in chapter 8, tightens the collar of cardiac tissue and accentuates the angle of His by creating a large full-thickness plication anteriorly within the cardia. The gastric stapler discussed in chapter 9 simulates a surgical fundoplication by creating a functional nipple valve circumferentially along the length of the LES. The Stretta[®] procedure described in chapters 10 and 11 tightens the LES with scarification by direct tissue injury and decreases tLESRs by an undetermined mechanism. Finally, injection therapy, described in chapters 12 through 15, serves to bulk the LES, thereby increasing tone and perhaps functionally lengthening the cardiac component of the LES.

Mechanical methods

The mucosa and submucosa are markedly different from the serosa histologically, especially in their response to trauma [9]. Serosal surfaces easily fuse whereas mucosal surfaces do not. Endoscopic sutures using everted plications predominantly join mucosa and submucosa, whereas inverted plications join serosal surfaces (Fig. 5A,B). Different endoscopic methods with different mechanical requirements are required to create either everted or inverted plications. In both types of plications, serosa-to-serosa apposition can ultimately be achieved by using transmural sutures. Eventually, a fusion between the serosal surfaces occurs with the greatest amount of anatomic and histologic alteration from the inverted plication.

In the absence of serosal fusion between joined stitches, a tissue reaction, which includes fibrosis, must be induced. This effect is most important to everted plications created by current endoscopic suturing devices where the sutures may be restricted to the submucosa or, at best, the muscularis propria, with the serosal surfaces in short or no contact. Mucosal and submucosal folds in this setting

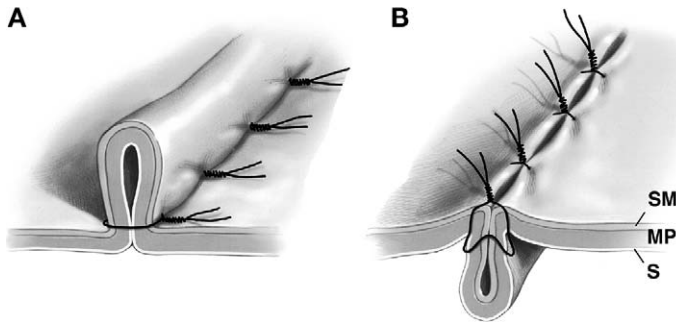


Fig. 5. (A) Everted plication dominated by mucosal and submucosal apposition. (B) Inverted plication with full-thickness apposition of serosal surfaces. (Copyright 2002, Mayo Clinic.)

predictably will not fuse. The current authors have learned historically and their animal studies that fibrosis is short-lived within the mucosa and submucosa [10]. Fibrosis begins to have more presence at the level of the muscularis propria, as long as there is direct injury to this gut wall layer.

The type of suture and the tension are also important issues relevant to successful (ie, durable) endoscopic suturing. Different suture materials induce predictable tissue reactions. In addition, endoscopic suturing, even transmurally, may lack a significant injury to trigger a healing response compared with that induced by a transmural incision. Whether a suture material that causes a more exuberant inflammatory reaction (eg, silk) should be used to compensate for the absence of full-thickness tissue damage is still unknown. Prolene (Ethicon, Somerville, NJ), one of the suture materials currently in use, is permanent and offers little frictional resistance, which is an advantage in endoscopy. A disadvantage, however, is that it may induce mild tissue reactions.

Suture tension is essential when apposing any tissue [11]. A tight “knot” may tear the tissue or induce ischemia. The current authors’ study found that the inflammatory reaction and fibrosis caused by a stitch were associated with the amount of ischemia created by the loop of the suture. A loose knot does not juxtapose the tissue adequately, which impairs healing and avoids any suture tension–induced tissue ischemia. Suture (knot) tension is classically operator dependent and strongly relies on the touch of the knot by the surgeon’s finger. Endoscopic extracorporeal knot tying or “cinching” does not offer as fine a tactile feedback. Suture materials also influence knot integrity and suture tension. The most desirable tension in endoscopically manipulated suture has yet to be defined. Replacing the suture with a mechanical closure device, such as a rivet or clip, carries similar problems caused by the amount of squeeze exerted by the deployed device.

The transmural techniques, such as the NDO plication system and the Boston Scientific Microvvasive gastric stapler, are attractive in that serosa-to-serosa apposition is readily obtained and therefore seem to offer durability despite the challenges regarding tissue ischemia and inflammation-related fibrosis. Sixto et al

[12] presented an abstract at DDW 2002 (Digestive Disease Week) describing transmural clip placement at the angle of His in a porcine model. The long-term effects of transmural fixation devices have yet to be fully determined. One of the baboons in a gastric stapler trial died 6 days postoperatively from a mediastinal abscess [13]. Presumably, this was an immediate postprocedure complication, but it raises concern for leakage or fistulization by transmurally placed and permanent materials. Other possible major complications with transmural methods are vagal nerve injury in those cases that include the distal esophagus; with methods involving the cardia, damage to the short gastric vessels, with subsequent hemorrhage, and diaphragmatic or lung injury in patients with a hiatal hernia are possible.

The ideal endoscopic mechanical methodology may be to incorporate assessment of the three-dimensional pressure image of the LES, its perimeter measurement, and the length and angle of the “sling” force component among other factors to evaluate individual patient candidacy and tailor the treatment approach. The development of therapies is somewhat limited by the lack of an isolated animal model study that simulates human reflux patterns and the technical challenges.

Injection methods

Injection therapies offer the easiest and most appealing endoscopic method, with potentially minimal procedural risks. The depth of an implantation and the type of implanted material are major factors determining success and durability of symptom control. Past experience in humans and animals questions the durability of any submucosally placed materials. Experience with submucosally injected materials within the urogenital tract for control of urinary incontinence indicates that long-term success depends on the use of implanted particles that must be at least within a size range, roughly 80 to 100 μm , to avoid dissipation or eventual extrusion [14]. Of the most current injectable materials being reported, polymethylmethacrylate, a particulate of 100 μm , is placed submucosally, whereas the ethylene-vinyl-alcohol copolymer is intended to be placed in the LES, which is even more appealing for durability [15,16]. The use of a soft expansile polymer appears to defy some of the observations made with other implanted materials. Potential complications of injection and implantation treatment include sloughing from injection into the superficial submucosa or implantation of large materials (eg, the hydrogel prosthesis) [17] and extramural injection with indiscriminant extravasation of foreign substances.

Optimization of endotherapy

From previous studies, it is clear that much variability exists in complication and success rates. It has been suggested that the anesthesia experience significantly affected the procedure duration of endoluminal gastroplication [18]. The ideal endotherapy would provide consistent results with minimal risk for com-

plications and be performed by the community endoscopist. A therapy could be titrated to affect symptom control, allowing subsequent procedures and thereby increasing tolerance for error with the procedure. Reversibility is always desirable for both the patient and physician. Direct visualization throughout the procedure is advantageous. Avoidance of over-tubes simplifies any technique, reduces sedation demands, and eliminates potential complications from passage of large tubes. Procedures that do not preclude a future surgical fundoplication are also desirable [19].

Measurements of effectiveness

Various methods have been used to determine success rates for GERD interventions. Subjective assessments have included general and GERD-related quality of life questionnaires, diverse symptom scoring systems, cessation of medications, and the need for subsequent surgery. Objective assessments have included manometry, 24-hour pH studies, and yield pressures. The results from techniques available thus far have favored the subjective determinants of effectiveness and have been confusing. The use of yield pressure, *in vivo* or *ex vivo*, is intriguing but its value is uncertain. *Ex vivo* measurements are affected by fixation of the tissue and the lack of appropriate neural feedback and its associated response. *In vivo* measurements may be useful in the animal model, but human correlation is uncertain.

There is a need for subjective and objective measurements. Subjective measurements should be validated and responsive to changes induced by the endoscopic intervention. One new instrument is the Reflux Symptom Questionnaire (RSQ and RSQ-1W) that Dhillon and others at the Mayo Clinic (2003) have developed and validated as accurate and responsive to changes in patients with GERD. For objective measurements, the value of manometry assesses effectiveness by demonstrating change. As a measurable LES length increases by some form of endotherapy, the pressure required to maintain a barrier decreases. Manometry does not measure the influence of angle-of-His changes, however. The gold standard for objective measurement is 24-hour pH monitoring. It is reasonable to perform this preprocedure and at follow-up intervals to assess effect and durability. Other measures that might be developed include the use of endoscopic ultrasound to identify and even quantify tissue changes within the cardia, distal esophagus, and even the LES itself in response to an endotherapy. The use of three-dimensional ultrasound reconstruction or an alternative imaging with spatial reconstruction may offer better methods to assess the immediate and long-term impact of therapies.

The best assessment of outcomes for endoscopic therapy depends on careful matching of patient groups and the use of sham-controlled treatment arms. Furthermore, treatment methods need to be matched with appropriate patient groups based on the methodology, anatomy, and patient-specific pathophysiology. Patients with normal manometry and angles of His may not be candidates for

endoscopic treatment at all or perhaps should be treated with a technique that simply attempts to lengthen the intra-abdominal segment of the LES. Patients with hiatal hernias might benefit from a mechanical and transmural approach.

What's ahead

Endotherapy has significant potential for effective control of GERD. This field is still evolving and should evolve into therapy that controls the disease and not just the symptoms. This potential for success has been described elsewhere in this issue. Newer methods and materials offer the greatest potential for the most durable results. These methods should take advantage of what is known about tissue responses to implanted materials, suture materials, and suture depth. New injection materials should be and are being developed that are inert, site stable, and can be augmented by repeated therapy. Mechanical methods are dependent on transmural tissue apposition for lasting benefit or else direct manipulation of the LES. These methods are challenged by the need for simplicity of application. The suture may remain a mainstay in this arena but is likely to face competition with alternative methods of tissue apposition, such as clips, both permanent and bioabsorbable, and other adaptations taken from laparoscopic instrumentation for tissue apposition. Injection and mechanical methods will survive and assemble themselves into a menu of options, using single and combination therapies. Choices will be based on several issues: the anatomy at hand, the need for a bridge to surgery, augmentation of therapy for the refractory patient or patient with complications, patient preference, and the need for repeated therapy. The forces of nature that control tissue response to intervention will almost certainly limit the benefits of endotherapy. Economic modeling of cost benefits comparing long-term drug therapy and surgery should direct efforts at establishing techniques that provide a minimal expected duration of disease control vis-à-vis these traditional alternative therapies. Large hiatal hernias will remain problematic for all methods. The use of anatomically targeted endotherapy in patients with Barrett esophagus must be carefully studied and defined. More is ahead for endotherapy; it will be exciting to monitor this evolution.

References

- [1] Boyce HW. Endoscopic definitions of esophagogastric junction regional anatomy. *Gastrointest Endosc* 2000;51:586–92.
- [2] Liebermann-Meffert D, Allgower M, Schmid P, et al. Muscular equivalent of the lower esophageal sphincter. *Gastroenterology* 1979;76:31–8.
- [3] Stein HJ, Liebermann-Meffert D, DeMeester TR, et al. Three-dimensional pressure image and muscular structure of the human lower esophageal sphincter. *Surgery* 1995;117:692–8.
- [4] Korn O, Csendes A, Burdiles P, et al. Anatomic dilatation of the cardia and competence of the lower esophageal sphincter: A clinical and experimental Study. *J Gastrointest Surg* 2000;4:398–406.
- [5] Jamieson GG, Duranceau A. Normal defense mechanisms of the esophagus. In: Jamieson GG, Duranceau A, editors. *Gastroesophageal reflux*. Philadelphia: WB Saunders; 1988. p. 5–12.

- [6] Mittal RK. Pathophysiology of gastroesophageal reflux disease. In: Castell DO, Richter JE, editors. *The esophagus*. Philadelphia: Lipponcott, Williams & Wilkins; 1999. p. 397–406.
- [7] Tam WC, Schoeman MN, Zhang Q, et al. Delivery of radiofrequency energy to the lower esophageal sphincter and gastric cardia inhibits transient LES relaxations and gastroesophageal reflux in patients with reflux disease [abstract]. *Gastroenterology* 2001;120:77.
- [8] O’Conner KW, Lehman GA. Endoscopic placement of collagen at the lower esophageal sphincter to inhibit gastroesophageal reflux: a pilot study of 10 intractable patients. *Gastrointest Endosc* 1988;34:106–12.
- [9] Thornton FJ, Barbul A. Healing in the gastrointestinal tract. *Surg Clin N Am* 1997;77:549–75.
- [10] Feitoza AB, Gostout CJ, Burgart LJ, et al. Understanding endoluminal gastroplications: a histopathologic analysis of intraluminal suture placements [abstract]. *Gastrointest Endosc* 2002;55:255.
- [11] Kadiramanathan SS, Shelton JC, Hepworth CC, et al. A comparison of the strength of knots tied by hand and at laparoscopy. *J Am Coll Surg* 1996;182:46–54.
- [12] Sixto R, Kortenbach J, McBrayer S, et al. A flexible endoscopic clip device for treatment of gastroesophageal reflux disease [abstract]. *Gastrointest Endosc* 2002;55:16.
- [13] Mason RJ, DeMeester TR, Schurr MO, et al. Per oral endoscopic fundoplication: the introduction of a new era [abstract]. *Gastrointest Endosc* 2001;53:74.
- [14] Malizia AA, Reiman HM, Myers RP, et al. Migration and granulomatous reaction after periurethral injection of Polytef (Teflon). *JAMA* 1984;251:3277–81.
- [15] Deviere J, Pastorelli A, Louis H, et al. Endoscopic implantation of a biopolymer in the lower esophageal sphincter for gastroesophageal reflux: a pilot study. *Gastrointest Endosc* 2002;55:335–41.
- [16] Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implantation of Plexiglass (PMMA) microspheres for the treatment of GERD. *Gastrointest Endosc* 2001;53:423–6.
- [17] Lehman GA, Watkins JL, Hieston K, et al. Endoscopic gastroesophageal reflux disease (GERD) therapy with Gatekeeper system. Initiation of a multicenter prospective randomized trial [abstract]. *Gastrointest Endosc* 2002;55:261.
- [18] Liu JJ, Knapp RM, Carr-Locke DL. The impact of anesthesiologists experience on endoluminal gastroplication [abstract]. *Gastrointest Endosc* 2002;55:119.
- [19] Park P-O, Kjellin T, Kadiramanathan S, et al. Results of endoscopic gastroplasty for gastroesophageal reflux disease [abstract]. *Gastrointest Endosc* 2001;53:115.