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Novel therapies for gastroesophageal reflux disease

Laura Flores, BA[a], Crystal Krause, PhD[b], Bhavani Pokala, MD[b], Salim Hosein, MD[c], Priscila Rodrigues Armijo, MD[b], Tripurari Mishra, MD[d], Shanu Kothari, MD[d], Dmitry Oleynikov, MD[e,*]

Introduction

Physiology and pathogenesis of gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is defined by "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung."[1,2] Other definitions, such as those from The Brazilian consensus, are more comprehensive, adding that GERD is a chronic disorder and citing the importance of including detailed characteristics of the chronic and progressive nature of the disease in the definition.[2] GERD is marked by esophageal and extraesophageal symptoms including heartburn, regurgitation, dysphagia, wheezing, and sleep disturbances, among a spectrum of other symptoms. Atypical symptoms of GERD include asthma, chronic cough, and noncardiac chest pain. Of the atypical presentations, asthma seems to be the most highly associated pulmonary manifestation of GERD.[3] In fact, an estimated 50%-80% of asthmatics in the United States are also suspected to have GERD.[3] It is similarly possible to have GERD without objective symptoms. A population-based study out of Sweden reported that as many as 36.8% of patients with erosive esophagitis presented with no symptoms at all.[13] GERD ranges in severity from mild, nonerosive reflux

From the [a]Center for Advanced Surgical Technology, University of Nebraska Medical Center MD-PhD Scholars Program, University of Nebraska Medical Center, Omaha, NE; [b]Department of Surgery, Center for Advanced Surgical Technology, University of Nebraska Medical Center, Omaha, NE; [c]Section of Minimally Invasive and Bariatric Surgery, Center for Advanced Surgical Technology, University of Nebraska Medical Center, Omaha, NE; [d]Section of Minimally Invasive and Bariatric Surgery, Gundersen Health System, La Crosse, WI; and [e]Section of Gastrointestinal, Minimally Invasive, and Bariatric Surgery, Department of Surgery, Center for Advanced Surgical Technology, University of Nebraska Medical Center, Omaha, NE

* Address reprint requests to Dmitry Oleynikov, MD, Section of Minimally Invasive and Bariatric Surgery, Department of General Surgery, University of Nebraska Medical Center, Omaha, NE 68198-6246.

E-mail address: doleynik@icloud.com (D. Oleynikov).

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disease to erosive esophagitis. Mucosal damage, as seen in erosive esophagitis and Barrett's esophagus, is a potential hallmark of GERD, however, a majority of symptomatic patients do not have mucosal erosion, as is the case in nonerosive reflux disease (NERD).[4]

The pathophysiology of GERD is multifactorial and complex. The symptoms and/or mucosal damage apparent in GERD are thought to result from incompetent antireflux mechanisms, imbalances in acid production, and structural abnormalities in the stomach, esophagus, or surrounding anatomy. The combination of abnormal physiologic relationships between the stomach and esophagus, abnormal acid production, delayed gastric emptying, and irregular esophageal motor function may each contribute to the development of GERD and hint at a multifactorial pathogenesis. Further, ingestion of caustic agents, disorders in mucosal integrity, hypersensitivity, and genetics may also play a role in the development and progression of GERD.

Lower esophageal sphincter dysfunction

The lower esophageal sphincter (LES), a 3-4 cm segment of smooth muscle responsible for preventing gastroesophageal reflux and is often implicated in GERD pathophysiology. GERD occurs when LES pressure is lower than intragastric pressure, and a defective LES is found in more than 70% of GERD patients.[14] LES pressure, which is determined by myogenic and neurogenic factors, is variable among individuals and fluctuates throughout the day. The LES functions in combination with the crus of the diaphragm and appropriate abdominal pressure, as an antireflux barrier commonly known as the esophagogastric junction. Working synergistically through complex neuromuscular mechanisms, the LES and surrounding anatomy are able to maintain tonicity and undergo contraction at appropriate times.[15] The diaphragmatic crus is also an important contributor to the esophagogastric junction through maintenance of pressure. In a study of 231 patients, those with GERD had significantly greater crural diaphragm-LES separation, indicating a strong association between abnormal anatomy and GERD.[16] When combined with the architecture of the gastroesophageal flap value, the function of the antireflux barrier is maintained.[17]

Relaxation of the LES is necessary in primary and secondary peristalsis, when ingesting the contents of the esophagus into the stomach, and tonicity is required to prevent reflux. However, an incompetent LES relaxes when it should not, allowing acid and stomach contents to reflux retrograde through the esophagus and into the oral cavity. This malfunction in the esophagogastric junction, and subsequent reflux events can be due to a multitude of reasons, including – transient lower esophageal sphincter relaxations, shorter LES length, low LES pressure, neuromuscular malfunction, or anatomical problems such as large hiatal hernia.

Transient lower esophageal sphincter relaxations are a well-studied mechanism by which GERD occurs. Transient LES relaxations are a normal occurrence in a well-functioning LES, and act as a physiologic response to gastric distension. They are predominantly mediated by vagal nerve impulses and neurotransmitter release, with potential contribution by pharyngeal stimulation.[18] When transient LES relaxations become more frequent and obsruct the surrounding structures that are fundamental to normal LES function, they become pathologic. Transient LES relaxations have been shown to account for nearly one third of reflux episodes in patients with GERD.[19] Furthermore, even in patients with a normal resting LES pressure, transient lower esophageal sphincter relaxations are thought to contribute to 40% of reflux cases.[20] These findings indicate that transient LES relaxations play an important role in the pathophysiology of GERD.

Improper acid production

Acid, bile, and pepsin play a major role in the pathogenesis of GERD, as well as in the progression to more serious GERD complications such as Barret's esophagus and esophageal cancers. Gastric juice is comprised of acid, bile, and digestive enzymes that are necessary in the digestion of food and subsequent uptake of nutrients further in the digestive tract. This material is highly acidic at a pH of 1.5-3.5, and therefore can injure most epithelium, without proper buffering mechanisms.

There are specific disease states, such as Zollinger-Ellison disease, which are characterized by hypersecretion of gastric acids. These hypersecretory states are certainly associated with severe reflux disease. Outside of these rare diseases, studies have shown that gastric acid secretion is similar between patients with and without GERD, suggesting abnormal or excessive acid secretion is not the primary mechanism of GERD itself.[21] A recent study that monitored gastric acid secretion by 24-hour intragastric pH, concluded that mild erosive esophagitis can occur in the presence of normal, and even deceased acid secretion, echoing the sentiment that excess acid production is likely not the main culprit.[22]

Anatomical abnormalities

Hiatal hernia. The presence of hiatal hernia, the protrusion of part of the stomach through the esophageal opening of the diaphragm, disrupts most of the natural anatomical antireflux mechanisms, and is a well-recognized cause of GERD.[23] Many studies have demonstrated a high percentage of GERD among hiatal hernia patients, citing the close relationship between them.[24,25] A study by Schlottmann et al, found that both the presence and size of hiatal hernia were associated with more frequent GERD symptoms. Furthermore, on high resolution manometry, larger hernia size was associated with weaker LES pressure and decreased esophageal peristalsis.[24] An additional study exploring the use of hiatal hernia subsequent to sleeve gastrectomy, found that there was a significant decrease in GERD in those who underwent hiatal hernia repair at the same time as their sleeve gastrectomy, compared to those who did not.[26] These findings are congruent with the message that hiatal hernia is an important contributor to the development of GERD, and its repair helps alleviate GERD symptoms.

Sleeve gastrectomy. Sleeve gastrectomy has increased in popularity among the bariatric community due to its robust weight loss effects and simple surgical technique when compared to other bariatric procedures.[27] Despite its popularity, attention has turned to the development of de novo GERD following sleeve gastrectomy, which is reported to occur in up to 73% of patients.[28,29] The proposed mechanisms of de novo GERD development are varied, ranging from the dismantling of the anatomical reflux barrier to technical variation during surgery. The final shape of the sleeve is often cited as a factor favoring the development of GERD.[27]

Data in recent literature is mixed on whether sleeve gastrectomy negatively impacts GERD symptoms. A majority of studies are retrospective, with very limited data emerging from randomized controlled trials. A report by Sheppard et al, explored the incidence of GERD after either sleeve gastrectomy or Roux-en Y gastric bypass, and found that GERD symptoms were significantly increased in the sleeve patients. These patients also required more proton pump inhibitor treatment than their Roux-en Y counterparts.[30] Conversely, in a prospective evaluation of nearly 400 patients, Daes et al, documented a 94% resolution of GERD symptoms following sleeve gastrectomy.[31] The authors emphasize the importance of surgical technique in the resolution of symptoms.

Obesity. The implications of obesity as a direct cause of GERD are debated in the literature. Many studies have investigated a potential relationship between increasing (body mass index [BMI]) and GERD symptoms, concluding that those with obesity have higher incidences of LES dysfunction, transient LES relaxations and abnormal peristalsis.[32-34] A study by Pandolfino et al, found a relationship between increasing BMI and GERD prevalence, with those of higher BMI having an elevated risk of GERD, however the authors note that there is no direct relationship between increased pressure and abnormal acid levels in the esophagus.[16] Some studies report that morbidly obese patients with GERD have higher incidence of LES incompetence and transient LES relaxations than obese patients without GERD.[35] Although obesity is an important consideration in GERD patients from an epidemiologic standpoint, a direct pathogenesis between the 2 is harder to elucidate. Visceral fat, organomegaly, and elasticity of the core muscles may have each been implicated to play an important role in the relationship between obesity and GERD, however little evidence exists to validate these claims.[27]

Studies have also suggested there may be a link between increased adiposity, leading to increased estrogen levels in circulation, and GERD. An early study published in JAMA, surveyed more than 65,000 individuals in Norway, and found a dose-response association between increasing BMI and reflux symptoms in both sexes, however the association was significantly stronger in women.[36] Moreover, this association was greater in premenopausal women and women on hormone therapies, when compared to postmenopausal women. From these findings, the authors suggest that adipose derived estrogens may play an important role in the pathophysiology of GERD in populations with obesity, given their significant relationships.

In addition to proposed hormonal changes, individuals with obesity may experience alteration of the transdiaphragmatic pressure gradient due to compression by abdominal and visceral adipose tissue. El-Serag et al, found that BMI was weakly correlated with increased intragastric pressure, which was responsible for an increase in the gastroesophageal pressure gradient.[37] The increased gastric pressure causes stress and disruption of the LES, potentiating GERD symptoms. Additionally, the increased pressure may predispose individuals to hiatal hernia, which have been previously mentioned as a major culprit in GERD pathophysiology.[23]

Diagnosis

Definition

The definition of GERD incorporates the symptoms and/or mucosal damage resulting from reflux of gastric contents into the esophagus over a lengthy period of time.[38] Typically, if reflux symptoms are present more than twice a week for a few weeks, the diagnosis of GERD is made. GERD is also referred to as acid indigestion, acid reflux, acid regurgitation, heartburn, or reflux. However, an important detail is that reflux symptoms must be present repeatedly over time in order to classify as GERD. The diagnosis of gastroesophageal reflux disease is highly prevalent in the United States, affecting nearly 20% of the population and accounting for more than 9 million ambulatory care visits.[5] GERD is characterized by heartburn, regurgitation, and dysphagia, in anywhere from 20% to 80% of patients. Atypical presentation of GERD includes symptoms such as bloating, cough, globus sensation, and hoarseness, and can often be misdiagnosed as other gastrointestinal diseases and disorders.

Among its treatment options, pharmacology is usually the first line, with an estimated cost of $10 billion annually, representing 50% of the cost estimated for the management of this disease.[39] This common use is reflected in the 18% of the population currently taking proton pump inhibitors (PPI).[5] Due to the well-documented harms of long-term antireflux pharmacologic therapy, antireflux surgery has become the most definitive and beneficial option for these patients. Surgical candidacy involves several factors, including staging of the disease, esophageal testing, and patient symptoms. GERD is often associated with other disorders and diseases, such as gastroparesis, eosinophilic esophagitis, and esophageal dysmotility, which must also be taken into account when performing esophageal testing, classification, and imaging in a potential GERD patient.

Classification

GERD can be further subclassified into 2 main groups – NERD or erosive esophagitis. Each classification is defined by hallmark findings, and potentially represents a disease with a distinct course. NERD is categorized by the presence of typical symptoms of GERD, such as heartburn sensation, in the absence of visible esophageal injury. More simply, NERD encompasses the symptoms of GERD without mucosal damage. A diagnosis of NERD can be made with positive pH testing and negative mucosal injury on endoscopic evaluation. NERD is estimated to be present in 50%-70% of all patients reporting heartburn symptoms.[40] Conversely, erosive esophagitis is a category of GERD characterized by severe mucosal injury secondary to refluxed acid contents.

Despite the name, the morphologic and histologic changes seen in erosive esophagitis are unrelated to inflammation, and rather resemble ulceration and erosion.[41]

There is debate in the literature as for theories of progression. Some researchers believe there exist a spectrum between NERD and erosive esophagitis, with NERD being on the mild end of the spectrum and esophagitis being on the severe end. These researchers suggest NERD will inevitably progress to erosive esophagitis, with long-term studies suggesting a 94% progression rate from NERD to erosive esophagitis over long-term follow-up.[42] This suggestion has been challenged by literature suggesting that NERD and erosive esophagitis respond to therapy differently, affect unique populations, and have separate hallmarks of disease.[40] Additionally, a handful of studies have found low rates of progression from NERD to erosive esophagitis (2%-17%) in long-term patient cohorts, pointing to 2 distinct pathological processes.[43] An additional categorization schema with 3 separate categories, NERD, erosive esophagitis, and Barrett's esophagus, has been proposed as well.[44] This framework suggests interplay between genetics and environment will determine the distinct category of GERD a patient will progress to throughout the course of their disease.

The degree of symptom overlap between NERD and erosive esophagitis makes it very difficult to assess and diagnose GERD from subjective information alone, and thus an evaluation including subjective and objective measures must be completed.

Endoscopic technique to visualize mucosal disease

Due to the wide range of asymptomatic and symptomatic presentations of GERD, definitive diagnosis should be made objectively, rather than on patient presentation alone. Objective measures include esophagogastroduodenoscopy (EGD), pH testing, esophageal manometry, and X-ray of the upper gastrointestinal system. EGD is the gold standard to directly visualize mucosal disease, or damage to the mucosa caused by GERD, and it can be used to examine the inside of the esophagus and stomach, as well as collect biopsies of tissue. This is an outpatient procedure that takes approximately 30-60 minutes, and is often used in patients who present with dysphagia, are unresponsive to acid-suppression therapy, and patients at high risk for Barrett's esophagus.[45] The current recommendations for screening endoscopy is for male patients with long-term diagnosis of GERD (>5 years), with 2 of more preexisting risk factors, such as age older than 50 years, smoking, or increased BMI.[46]

EGD visualizes the mucosa of the esophagus and allows for evaluation of the degree of reflux severity. The Los Angeles classification of esophagitis is used to categorize the disease into grades A to D. Grade A represents a low extension and quantity of mucosal breakage, whereas grade D represents very severe damage. The diagnosis of Barrett esophagus is based on the grade of dysplasia from the normal squamous epithelium of the esophagus to the specialized columnar-lined epithelium.[46]

Nonetheless, due to the diverse presentation of GERD, including no mucosal damage, a normal endoscopy does not rule out GERD, illustrating an important limitation of the examination. Still, despite the low sensitivity for the diagnosis of GERD, EGD is the most appropriate examination to evaluate complications of GERD such as severe mucosal damage, Barrett's esophagus, esophageal strictures, and the presence of hiatal hernias.[5]

Sampling and biopsy interpretation

Biopsy specimens obtained via EGD are an important component of the evaluation for patients with GERD, due to the direct visualization of histologic change. Biopsies are generally minimal risk, with only a slight risk of minor complications such as bleeding and pain. Bleeding complications following endoscopic biopsy have been reported to range between 0.03% and 0.14%, signaling an exceptionally safe procedure.[47]

Endoscopic mucosal biopsies are routinely performed and very safe, with low incidence of minor complications.[47] Tissue is obtained for histologic examination or monitoring of disease

progression via either "hot" biopsy, requiring electrocoagulation, or a "cold" biopsy, using standard forceps. Because esophagitis is only present in approximately 20% of GERD patients who undergo EGD, and due to the low prevalence of Barrett esophagus, estimated in 1.6% of the population, biopsy recommendations are sparse.[46,47] The current recommendation is to perform a biopsy only in patients who present with irregularities in the mucosa, if suspicions of pathology are corroborated by clinical signs. Routine biopsy is discouraged in patients without macroscopic abnormalities, and if Barrett's esophagus is ruled out, no additional screening is necessary.[48]

In order to make a correct diagnosis and subsequent treatment choice for esophageal disease, it is essential to have appropriate communication with the pathology team. Although biopsy provides histologic findings, the biopsy team should provide adequate clinical information and together with biopsy, confirm the diagnosis.

Despite the feasibility and safety of EGD, new, noninvasive technology has emerged as an even safer, cheaper, and faster alternative to aid in the diagnosis of GERD. These tests require only a sample of saliva or sputum.[6] The office-based test focuses on pepsin, which is a key biomarker of the esophageal damage present in GERD. Pepsin is ordinarily found only in the stomach, so its presence in the saliva indicates that it may reflux stomach contents that have traveled upward. In a study of 250 patients with GERD symptoms, the pepsin test had a sensitivity of 73% and a specificity of 88.3% for diagnosing GERD.[6] Furthermore, pepsin tests following a meal had an even more robust ability to detect GERD. The literature is mixed, however, with other studies finding pepsin in participants without GERD as well, and pointing to a pepsin test as only one piece of a comprehensive GERD evaluation.[49]

Epidemiology and risk factors

Prevalence

GERD prevalence exhibits a wide range of geographic variability. A systematic review of GERD prevalence worldwide reported GERD in the USA to be between 18% and 27%.[50] GERD prevalence in Europe and the Middle East was reported to be slightly lower on average, at 8.8%-25.9% and 8.7%-33.1%, respectively. Australasian GERD rates were reported at 11.6%, and East Asia had the lowest reported GERD, ranging between 2.5% and 7.8%.[50]

The analysis of trends in the geographic prevalence of GERD show a statistically significant increase in GERD worldwide since 1995 through the calculation of prevalence rate ratios from more than 30 published studies.[50] All reported geographic areas (North America, South America, Europe, East Asia, Middle East, and Australasia) had a significant increase in the prevalence of GERD.

The demographic prevalence of GERD is also highly variable. Some studies have found no association between sex and symptoms of GERD in North America and in Europe, and that in South America and in the Middle East, women were approximately 40% more likely to report GERD symptoms than men.[51] Increasing age as a risk factor for GERD symptoms is also controversial, as some studies have found no association with age and increased incidence and prevalence of GERD, while other studies have shown a correlation.[52] In the United States, GERD is reported to have similar prevalence among different racial groups when controlled for age, sex, medications, BMI, and family history of GERD.[53]

Obesity and diet

Obesity is a major risk factor for symptomatic GERD, with the condition having an odds ratio of 1.73 for GERD.[51] Conversely, reductions in body mass and specifically, a decrease in waist circumference, have been shown to result in GERD symptom improvement.[54] The association of obesity with GERD can be further exacerbated by certain dietary factors. Although specific foods

do not directly cause GERD, certain foods, and eating behaviors can trigger a reflux response. Certain refluxogenic foods (foods high in fat, spicy or sour, citrus, onions, tomatoes, and chocolate), coffee, beverages, and products containing peppermint, carbonated beverages, and alcohol) can aggravate GERD symptoms through a variety of mechanisms, including decreasing the tension of the LES, delaying stomach evacuation, stimulating sensory receptors in the esophagus, or increasing gastric juice.[55] There is a correlation between consumption of fewer meals per day and increased GERD symptoms as well as an association between large meals and increased GERD symptoms.[55,56]

Smoking

Smoking can lead to GERD by reducing the resting pressure of the LES.[57] Tobacco smoking is also associated with a prolonged acid clearance time, which is likely due to reduced salivary secretion and bicarbonate concentration.[58] Esophageal pressure was reported to have normalized relatively quickly after smoking was stopped, and the effects of tobacco on acid clearance diminished after smoking cessation as well.[59] Smoking cessation was not associated with decreased GERD symptoms in overweight or obese individuals, indicating that tobacco use may have a smaller role in GERD or it could be a more important risk factor in normal weight individuals.[59]

Concomitant diseases

GERD symptoms can manifest in a number of different diseases and conditions that have an impact on the esophagus or esophageal function. Patients with diabetes mellitus can have an increased incidence of esophageal dysfunction, including reduced esophageal contraction amplitude, reduced LES pressure, and the time of esophageal transit has been reported to be delayed in approximately 35% of patients with diabetes.[52,60] The pathophysiology of GERD in diabetes mellitus is not well understood, but is thought to be attributable to autonomic neuropathy and the effect of vagal nerve damage on gastric emptying.[52]

Asthma and the relationship to GERD has been well-studied, but estimates of the prevalence of GERD in individuals with asthma are highly variable, ranging anywhere between 30% and 90%.[61] One systematic review found that the average prevalence of reflux symptoms in adults with asthma was 59%, and the prevalence of asthma in individuals with GERD is 1.2-fold higher than in the population without asthma.[61]

Connective tissue disorders (including scleroderma, systemic lupus erythematosus, dermatomyositis, and others) affect a wide range of organ systems, and often detrimentally impact the skin and gastrointestinal tract. These patients can develop GERD and the associated complications due to esophageal dysfunction, and the first choice for management in these conditions is medication. There is debate as to whether or not surgery is an appropriate intervention because of the esophageal involvement in the connective tissue disorder. A study conducted by Patti et al. showed that, in patients with connective tissue disorders and GERD, esophageal function was preserved and peristalsis was similar to the control group. However, in patients with end-stage lung disease and connective tissue disorder, peristalsis was present in only 50% of the patients, suggesting that surgical treatment of GERD may be a viable option for some of these patients where medical therapy is not effective.[62]

Therapeutic management of GERD

The main endoscopic therapies currently available and approved by the US Food and Drug Administration (FDA) for GERD are transoral incisionless fundoplication (TIF) (EsophyX; EndoGastric Solutions, Redmond, WA), Medigus Ultrasonic Surgical Endostapler (MUSE, Medigus, Omer, Israel), and radiofrequency (RF) ablation (Stretta; Mederi Therapeutics, Norwalk, CT).

Transoral incisionless fundoplication

GERD affects up to one third of the adult population of the US and approximately 20% of the population worldwide.[63] The estimated cost of therapy is $15-20 billion annually with more than $10 billion spent on the medical management of reflux disease.[64] GERD is associated with serious health risks including esophagitis, esophageal stricture, Barrett's, and adenocarcinoma of the esophagus. Although there are many causes of GERD, often many at play at the same time, which been discussed earlier in this text, current therapeutic options are likewise myriad.

Treatment options vary by symptomology, individual patient characteristics, and preferences. Interventions may range from simpler things like weight loss, smoking cessation, limiting alcohol, and adding acid reducing medications to arguably more aggressive therapies like antireflux surgery. Not to be overlooked, however, advances in endoscopic technology have allowed for an alternate "middle ground."

Medical management of GERD with histamine blocker or PPI therapy has proven to be an effective means of durable symptom relief and numerous studies have demonstrated long-term safety and low toxicity. However, long-term use of PPI therapy is not without its risks, which include bone demineralization with the risk of fractures, and increased risk of *Clostridium difficile* associated diarrhea, B_{12} deficiency, pneumonia, dementia, drug interactions, and hypergastrinemia, to name a few.[65] Up to one fifth of patients have refractory symptoms despite maximal medical therapy and in those who do respond to therapy, the effectiveness of PPI treatment decreases over time.[66] The above, coupled with the need for potentially lifelong therapy and high costs, make this not an ideal intervention for all patients.

Laparoscopic antireflux surgery (ARS) is considered the gold standard intervention for GERD and can be used as a primary intervention in cases where patients fail medical therapy or for complications related to GERD. What surgical options have in common is that they augment LES pressure, decrease LES compliance, and, where necessary such as with a hiatal hernia, restore functional anatomy. Long-term outcomes are excellent overall with good patient satisfaction. However, these are not benign procedures and there are inherent surgical and anesthetic risks, in addition to risks of dysphagia, need for dilations, and an approximately 2.3% reoperative rate.[67]

It is therefore no surprise that endoscopic interventions aimed to reproduce the mechanisms affected by ARS, while being considered "less invasive," have gained interest and popularity over the past 2 decades, as endoscopic technology has continued to evolve. At present in the United States, the 3 most popular endoscopic therapeutic interventions discussed below, can be grouped into 2 categories based on mechanism of action: use of TIF and nonablative RF energy.

TIF aims to reconstruct the LES anatomy and help restore the LESs function as a reflux barrier. Two of the most popular devices in use in the United States are the EsophyX and Medigus Ultrasonic Surgical Endostapler, discussed below. Both devices can be used in the setting of a small (<2 cm) hiatal hernia and can in fact be used to reduce the herniated GE junction to an intra-abdominal, subdiaphragmatic position in this setting.

Indications and contraindications

As with other endoscopic reflux therapies, the ideal patients for TIF are those with minimal anatomic change at the gastroesophageal junction and moderate-to-severe GERD symptoms that are responsive to PPI therapy. Additionally, patients must be candidates for general anesthesia. TIF should not be performed in patients with significant hiatal hernias (>2 cm), severe esophagitis, esophageal dysmotility, or in the setting of esophageal varices. Also, TIF is not recommended for acid control in patients with Barrett's esophagus because normalization of esophageal pH has not been consistently demonstrated. Finally, TIF is contraindicated in children (age <18 years) and in patients with a BMI greater than 35 kg/m^2.

The Stretta system has been approved for use since 2000, and is considered an appropriate procedure for adult patients with GERD who want to discontinue antisecretory therapy, but

refuse laparoscopic fundoplication.[68] Potential candidates for the use of RF ablation are those who experience side effects, have poor compliance, or whose GERD symptoms are not well controlled with medical therapy. Candidate criteria also include individuals with typical GERD symptoms (heartburn and or regurgitation), low-grade erosive esophagitis (Los Angeles grade A or B), and have a negative endoscopy with abnormal esophageal acid exposure.[69] RF ablation should not be used for individuals with hernias larger than 3 cm or who exhibit an LES pressure less than 5 mm Hg.[69]

EsophyX

This was developed by Endogastric Solutions (Redwood City, WA) and approved for use by the FDA in 2007. It is an endoscopic device used to facilitate creation of a 2-3 cm, 270° esophagogastric fundoplication. The device has a channel allowing placement of an endoscope for direct visualization (Fig 1). It is inserted orally and advanced into the stomach. The device consists of a helical retractor used to engage and retract the gastroesophageal junction, a tissue mold that engages the fundus, suction, and tissue fasteners (Fig 2). Although the initial TIF procedure created a plication at the level of the gastroesophageal junction, the current TIF 2.0 technique generates a physiologic valve via fasteners placed on the far posterior and anterior sides of the lesser curvature, with additional fasteners placed 1-3 cm proximal to the gastroesophageal junction. The permanent, polypropylene "H-shaped" fasteners allow full thickness serosa to serosa fusion and reconstruct an anatomic valve similar to traditional partial circumference fundoplication (Fig 2).

The procedure, under general anesthesia, is usually accomplished in less than an hour and requires a surgeon to operate the device, while an assistant operates the endoscope. It routinely performed as an outpatient procedure and patients can return to routine activities including work, within a few days, making TIF an attractive option for the treatment of GERD.

Medigus ultrasonic surgical endostapler (MUSE)

Similar to the Esophyx device, the MUSE system is an endoscopic device delivered transorally, allowing for the creation of an anterior partial fundoplication to reinforce and/or reconstruct the LES. The MUSE system is a single-use disposable device and incorporates a forward viewing, flexible miniature camera similar to a gastroscope to guide insertion and positioning. It then employs ultrasound energy emitted from the end of the device to guide optimal tissue compression by an adjustable screw deployed between the anvil and stapling cartridge and finally, staples to secure the fundoplication (Fig 3). The system uses 5 standard surgical staples, instead of fasteners, in 3 staggered rows to attach the fundus of the stomach to the esophagus. Like EsophyX, the procedure takes approximataly hour to complete, but requires a single operator. The procedure allows for the reduction of small hiatal hernias and the creation of a durable 270° partial anterior fundoplication, between 1 and 3 cm long (Fig 4). Proponents of this system tout improved safety with the ability of ultrasound guidance to measure tissue thickness prior to staple firing, given direct visualization of the space between fundus and esophagus is not otherwise possible.

Stretta

The Stretta system utilizes RF ablation to deliver low-power, low-temperature energy to the LES and gastric cardia, which leads to tissue remodeling in the affected areas. This can result in improved functioning of the LES and a decrease in LES relaxation events that can exacerbate reflux symptoms. The Stretta system consists of the flexible Stretta catheter and a control module (Fig 5). The catheter has a 20 F soft bougie tip and balloon, with the widest inflation area

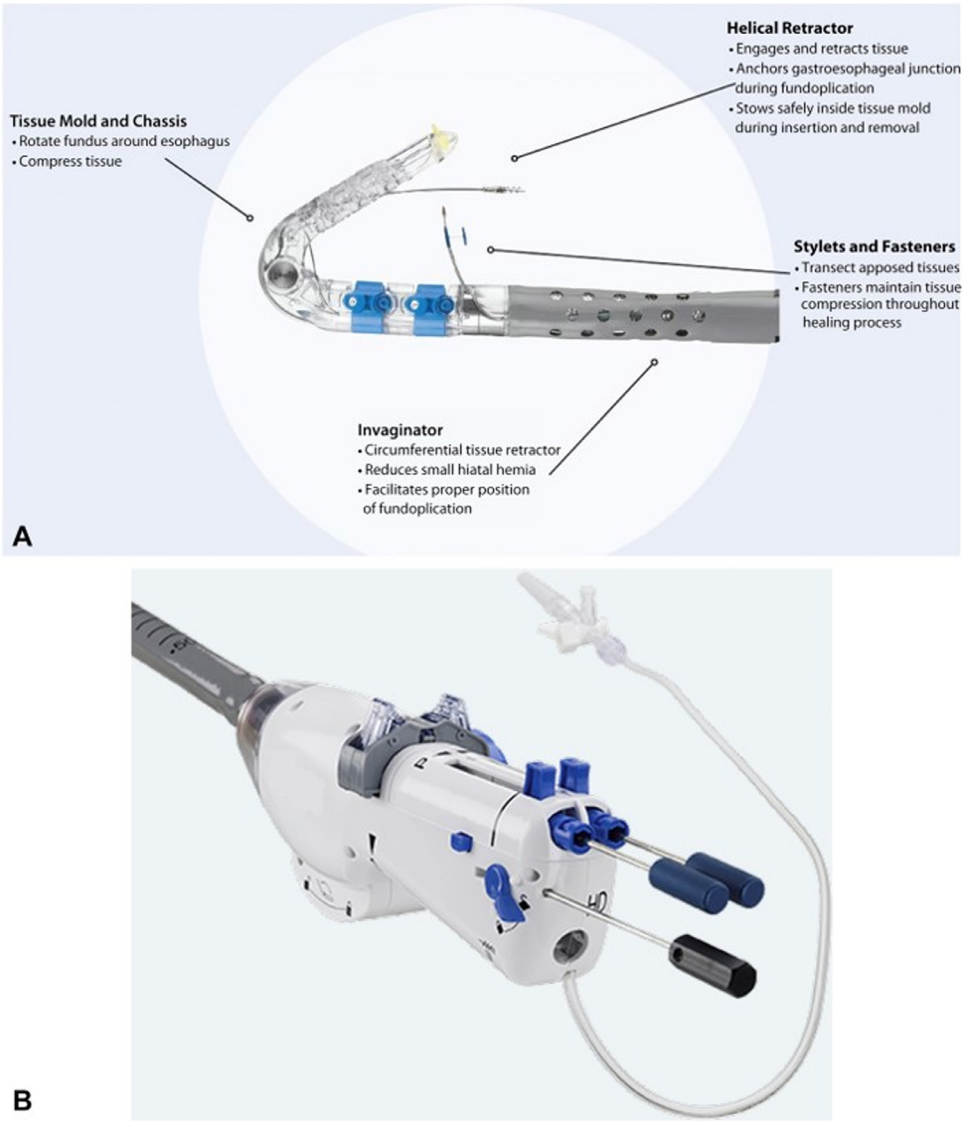

Fig. 1. EsophyX_2 HD device. (A) Tip and (B) control body (EndoGastric Solutions, Redmond, Wash). Adapted with permission, from Thosani et al, 2017.[99]

having 4 needle electrodes that can be extended into the lower esophageal muscle tissue.[69] The catheter functions to irrigate and aspirate water from the esophageal lumen, while the control module generator provides energy to the needles, heating the muscle tissue to between 65 and 85°C. During the RF ablation, temperatures are monitored by the system and cooling to the mucosa is provided by the catheter irrigation.[69]

Stretta procedures are generally performed by endoscopy with sedation on an outpatient basis, with preoperative preparation similar to other upper endoscopies. The Stretta catheter is inserted and used to locate the squamocolumnar junction (Z-line), and the catheter is positioned 1-2 cm above. Simultaneous irrigation and aspiration of cooled water through the catheter is

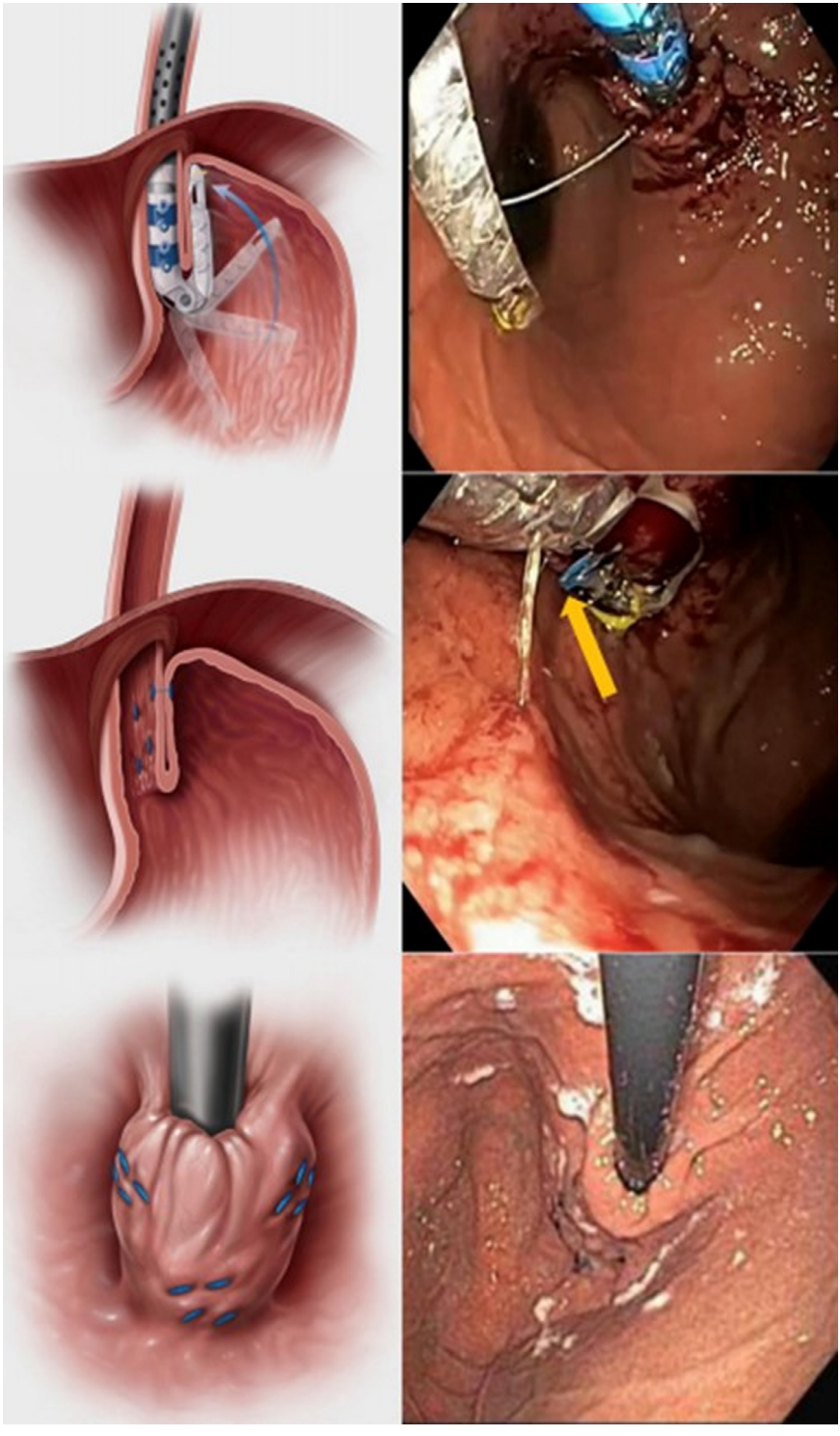

Fig. 2. TIF 2.0 procedure using the EsophyX device. Adapted with permission, from Thosani et al, 2017.[99]

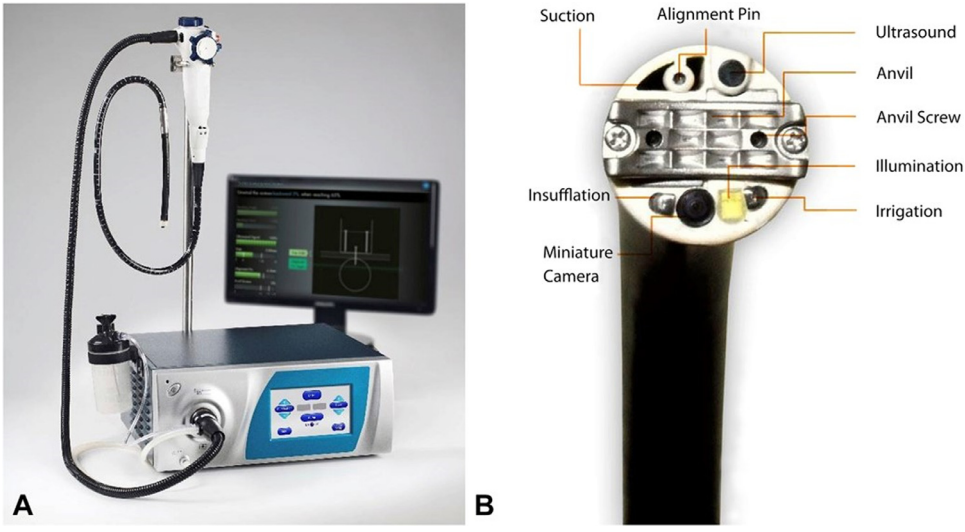

Fig. 3. MUS System for GERD Treatment. (A) MUSE console and (B) tip of the endoscope. Adapted with permission, from Thosani et al, 2017.[99]

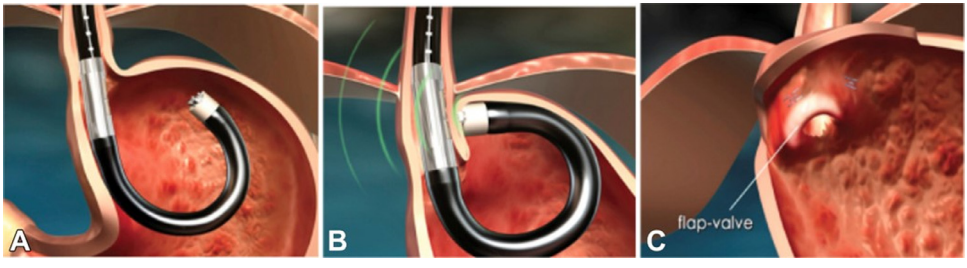

Fig. 4. MUSE procedure. (A) retroflexion. (B) stapling. C, recreated gastroesophageal junction. Adapted with permission, from Thosani et al, 2017.[99]

initiated, the catheter balloon is inflated, and the needle electrodes are deployed into the muscle of the gastroesophageal junction. RF energy is delivered using the control module, and irrigation/aspiration is performed at the same time as the RF ablation. This treatment is repeated until a concentric ring is formed 1 cm above the Z-line. Patients are generally instructed to continue any antireflux medications for 3 weeks after completion of the procedure.[69]

Outcomes

The TIF procedure has been extensively studied over the past 2 decades since its original introduction in terms of both efficacy and safety, and as alluded to above, has undergone evolutionary changes making it more effective and better able to replicate the antireflux valve created in ARS. Data discussed in the following text is applicable to TIF procedures in general and how they compare to medical and surgical therapeutic options. As far as the individual EsophyX and MUSE device systems are concerned, a recent single-center study from Italy found no statistically significant difference between the 2 when used for TIF at 6- and 12-month follow-up.[70]

Since the introduction of TIF in clinical practice, numerous studies have reported on its outcomes. A systematic literature search of the available evidence revealed more than 60 reports on TIF. A meta-analysis from 2018 looking at feasibility, efficacy, and tolerability identified 32

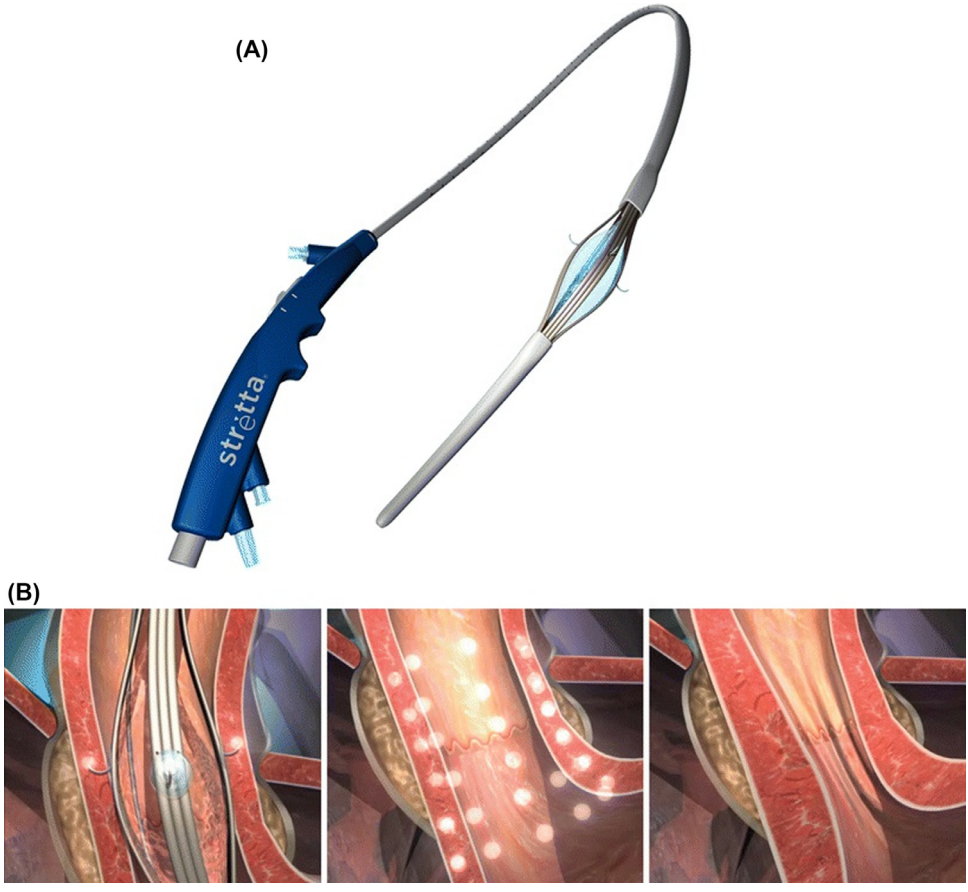

Fig. 5. (A) The Stretta device. (B) The Stretta device delivers low-power radiofrequency energy to the Lower esophageal sphincter and gastroesophageal junction via endoscopic balloon-mounted needles. Adapted with permission, from Wilson et al, 2014.[100]

studies involving 1475 patients. The authors reported a procedural success rate of 99% with a 2% complication rate and statistically significant improvements in GERD Health Related Quality of Life (HRQL) scores and Reflux Symptom Index. Furthermore, DeMeester scores improved on average by 10 points and 89% of patients were able to discontinue PPI therapy.[71] However, a major limitation of this and similar studies on TIF are the lack of long-term outcomes data. The majority of studies report on 6-month to 6-year outcomes and there are a limited number of randomized controlled trials.

In sham-control trials, TIF has demonstrated significant improvement in esophageal acid exposure time and has been shown to be similar to that of patients on PPIs. Patients after-TIF also have been found to have a reduction in the total number of reflux episodes compared with those on PPIs, with a mean difference of −29.07 (95% confidence interval: −39.17 to −18.98, $p < 0.00001$), although the incidence of acid reflux episodes reveals no significant differences between TIF and PPI treatment groups.[72]

A single-institution retrospective review of 28 patients with a median follow-up of 14 months demonstrated 64% of patients were able to remain off PPI therapy altogether and another 18% required only occasional use of medications, compared to 89% of patients with ineffective symptom control on daily PPI therapy preprocedure. More than, 86% of patients reported GERD-HRQL scores improved by at least 50% while 65% reported normalization. From a baseline of 92% of

patients unsatisfied with their current health condition preprocedure, this figure decreased to 11% postprocedure.[73] In addition, a 6-month weighted average patient satisfaction, based on 10 observational studies, approaches 70%.[72]

Severe adverse events have been reported in 16 studies (4 RCTs and 12 prospective observational trials).[71] An incidence rate of 2.4% has been reported, based on severe adverse events occurring in 19 out of 781 patients who underwent TIF. Reported severe adverse events included perforations (7), bleeding (5), pneumothorax (4), infection requiring intravenous antibiotics (1), and severe epigastric pain (1). One death was reported 20 months after the TIF procedure, although causality was not defined.

One area of concern is that a failed TIF may increase the surgical risk of subsequent ARS, given scar tissue formation and the presence of permanent fasteners or staples. Three studies have demonstrated that fundoplication after TIF can be accomplished safely and effectively.[68] We have personal experience converting a failed TIF procedure to a surgical fundoplication and found the use of the robotic platform with concomitant intraoperative upper endoscopy particularly useful when identifying and removing H-fasteners and ensuring complete take-down of the failed wrap before proceeding with reconstruction.

Another area of concern and controversy, as alluded to earlier, is the lack of homogenous long-term data. A meta-analysis that examined long-term outcomes after the procedure reported by observational studies found the effectiveness of the procedure diminished over time reaching a maximum level just over 70% at 6 months and just under 40% 6 years later in terms of symptom control. Although most of the patients resumed PPI treatment during the long-term follow-up, PPI doses were reduced compared with their baseline.[72] Contrary to this, the TEMPO trial, a randomized multicenter trial with a cross-over arm, published in 2018, demonstrated TIF 2.0 to have sustained long-term GERD symptom control, extending to 5 years postprocedure. Of 63 patients who underwent TIF with a 70% 5-year follow-up rate, at 5 years they found GERD-HQRL scores decreased from 22.2 to 6.8, 66% of patients remained off PPI therapy entirely, and troublesome regurgitation and atypical symptoms remained absent in 86% and 80% of patients, respectively.[74] Yet another study evaluating 50 patients at 6-year follow up found that more than 80% of TIF patients either stopped or halved PPI therapy, with significantly improved impedence monitoring (fewer total and acid reflux episodes) at 2 years and improved GERD quality of life scores at 6 years.[70]

The most recent Society of American gastrointestinal and Endoscopic Surgery guidelines on the treatment of GERD indicate that ARS is superior in terms of effectiveness on GERD outcomes, compared to PPIs and TIF.[75]

In a trial of 50 consecutive patients who received Stretta, at a 2-year follow-up, PPI use had decreased from 99.5% to 54%, heartburn and regurgitation scores improved significantly, and quality of life reported improvement as well.[76] A recent systematic reviews found that Stretta treatment decreased the incidence of erosive esophagitis, improved health-related quality of life, and reduced PPI use, but it did not significantly affect LES basal pressure.[77] A study with 10-year follow-up results of Stretta showed that more than 70% of patients achieved normalization of GERD health-related quality of life and more than 50% reduced or eliminated PPI use, and the most common side-effect was short-term chest pain.[78] The Stretta procedure was less effective in improving heartburn, regurgitation, and chest pain when compared to laparoscopic Toupet fundoplication in a 3-year follow-up study.[79]

One of the concerns for the use of this procedure is that the mechanism of action is not fully understood. It is thought that Stretta is effective in the relief of GERD symptoms through some or a combination of: decreased compliance in the distal esophagus, mechanical scarring of the esophageal wall, or disruption in the vagal innervation of the distal esophagus.[80]

Conclusions

TIF has a demonstrable safety track record and is a viable therapeutic option for patients with chronic GERD unwilling to proceed with surgery or to take life-long medications. Although

numerous studies clearly demonstrate effectiveness in the short term, fewer studies report on long-term outcomes and reported outcomes are contradictory. Although the procedure in its current form may not yet be perfect, it has undergone evolutionary changes and endoluminal therapies for GERD will likely continue to evolve and improve, meaning surgeons should continue to familiarize themselves with and keep abreast of evolving technologies in an ever-more minimally invasive surgical world.

Surgical treatment of GERD

Fundoplication

The primary goal of ARS is to re-establish a mechanical barrier to acid reflux. To this end, all procedures are comprised of 4 key steps: hiatal hernia reduction, tension-free restoration of intra-abdominal esophagus, reapproximation of the diaphragmatic crura, and performance of a fundoplication. Compared to open, the laparoscopic approach offers several benefits including shorter length of stay, decreased perioperative morbidity and cost.

Clinical indications

The most common indications for ARS are failure of medical management, patients experiencing complications of medical therapy, atypical symptoms, patients with large hiatal hernias, or patients who wish to discontinue medical therapy. Existing literature suggests that individuals who demonstrate typical GERD symptoms that are exacerbated in the supine position have a better prognosis compared to those with extraesophageal symptoms. Patients with pathologic pH monitoring are 5 times more likely to have success with ARS compared to those with normal pH testing. Similarly, those patients who have had a good clinical response to medical therapy are 3 times more likely to respond to surgical treatment.[81]

A total fundoplication is generally performed in the presence of normal esophageal motility. If preoperative manometry is indicative of an esophageal motility disorder, a partial fundoplication is preferred.[7] A literature review comprised of 32 studies comparing outcomes of partial and total posterior fundoplication in patients with abnormal esophageal motility found patients who underwent Nissen fundoplication to have higher rates of dysphagia and postoperative gas-bloat.[82] Another study comparing the efficacy of Toupet vs Nissen fundoplication found partial posterior wraps to have lower dysphagia rates with little difference in control of GERD at long-term follow-up.[83] Given these findings, we generally elect to perform a posterior Toupet fundoplication in the setting of esophageal motility disorder. A review of 9 randomized clinical trials published by Fein et al reported that anterior fundoplication is associated with an increased risk of recurrent GERD symptoms compared to posterior partial or total fundoplications.[84] In our practice, an anterior Dor fundoplication is typically reserved for patients undergoing Heller myotomy.

Contraindications

In general, patients carrying diagnosis of high-grade esophageal dysplasia or cancer are not candidates for ARS. If esophageal pathology is unable to be successfully treated with endoscopic ablation or resection, ARS could then be considered. For patients with morbid obesity, several weight-related factors including increased intra-abdominal pressure, reduced esophageal clearance, increased transient relaxation of the LES, and distortion of the gastroesophageal junction contribute to GERD development. In this patient cohort, counseling regarding benefit of roux-en-y gastric bypass should be discussed as anatomic modifications including creation of a small gastric pouch, exclusion of the gastric fundus and most of the body which contain acid-producing parietal cells, and formation of the roux-en-y configuration results in decreased GER. The benefits of this operation on GERD have also been shown to be independent of weight loss.[85]

We start by placing the patient on the surgical table in the supine position with both arms tucked. The primary surgeon stands to the patient's right with the assistant on the left. An orogastric tube is placed for gastric decompression. The video monitor is positioned at the head of the bed to ensure adequate visualization for both the primary surgeon and assistant.

The abdomen is accessed and insufflated using a Veress needle at Palmer's point. Next, an 11 mm optical trocar is placed 2 cm to the left of midline, approximately 10 cm below the xiphoid. Three additional working ports are then placed under direct visualization. This includes an 11 mm port in the left upper quadrant just inferior to the rib cage, another 11 mm lateral to this in the left upper quadrant, and a 5 mm in the right upper quadrant entering through the falciform ligament. A 5 mm epigastric incision is then made to accommodate the Nathanson liver retractor. The primary surgeon operates through the 2 most cephalad ports while the assistant drives the camera using the caudal 11 mm port and retracts using the left lateral port. It is imperative that ports are placed high and to the left of midline in order to ensure proper triangulation at the hiatus.

We begin the dissection by dividing the short gastric vessels and entering the lesser sac. Early ligation of the short gastrics facilitates mobilization of the gastric fundus. Next, we continue our dissection cephald toward the left phrenoesophageal membrane which is then divided to expose the left crus. We then turn our attention to the right crus. The gastrohepatic ligament is opened and the right phrenoesophageal membrane is divided exposing the right crus. A medial plane between the right crus and esophagus is developed allowing for visualization of the crural decussation. Care is taken to identify and protect the anterior and posterior vagi during this mobilization.

The esophagus is then elevated to facilitate posterior dissection allowing for full mobilization of the esophagus and creation of a large retroesophageal window. A penrose drain is placed around the esophagus for ease of retraction. Mediastinal mobilization of the esophagus is performed until adequate length of intra-abdominal esophagus, typically 3-4 cm, is attained. The hiatus is then closed using permanent sutures ensuring straight orientation of the esophagus. Our preference is to use a 2-0 nonabsorbable V-lock suture to reapproximate the crura posteriorly. We do not routinely use bougies given the risk of esophageal and/or gastric perforation. Next, we turn our attention to the creation of the fundoplication.

Total fundoplication

A Nissen fundoplication is a 360° (total) wrap of the fundus around the posterior aspect of the esophagus. The 2 most cephalad sutures are used to approximate the fundus to the right and left crus. Additional sutures are used to secure the fundus to the esophagus. A temporary stay suture may be helpful when creating the 360° wrap and can be removed after placement of the crural sutures.

Partial fundoplication

The Toupet fundoplication is similar to a Nissen as it is also a posterior wrap. The partial fundoplication is positioned between 180° and 270°, however, A Dor fundoplication is a partial anterior wrap that does not require disruption of the posterior attachments to the esophagus. The angle of His is recreated by suturing the medial fundus to the left crus and esophagus on the left. The fundus is then folded over the esophagus anteriorly and secured to the right crus and then the esophagus.

Intraoperative evaluation of fundoplication

Regardless of which type of fundoplication is created, we recommend evaluation with intraoperative EGD. It is important to verify that the esophagus is not kinked or twisted. The LES sphincter should open easily with insufflation. Careful inspection of the fundoplication during retroflexion should be performed routinely to ensure that there is no redundant stomach above the wrap.

Complications and outcomes

The prevalence of gastric or esophageal injury in patients undergoing ARS is approximately 1%.[86-88] These complications most frequently occur in the reoperative setting with formation of scar tissue and distortion of anatomic landmarks. In primary cases, esophageal or gastric injury can occur with rough tissue handling and can also be inflicted when passing a bougie into the stomach. Typically, these injuries can be repaired with hand-sewn or stapled wedge resection if identified intraoperatively. If these injuries are not discovered until the postoperative period, they may require reoperation vs observation or stenting for small contained perforations.

Occurring in approximately 2% of cases, capnothorax is one of the most commonly reported intraoperative complications of LARS.[89] Violation of the pleural space allows carbon dioxide to enter the intrathoracic cavity. A sudden rise in end tidal CO_2 is suggestive of this process. When recognized by the anesthesia provider, inspection of the pleura should be performed by the surgical team. Once the site of pleural violation is identified, it can be reapproximated with sutures or an endoloop. Postoperative chest radiography should be performed as patients may benefit from supplemental oxygen therapy to facilitate resolution. Since there is no underlying lung injury, no further intervention is typically required.

The most commonly reported solid-organ injury resulting from ARS involves the spleen. Splenic bleeding occurs in approximately 2.3% of cases, with splenic infarction, lacerations, and subcapsular hematomas occurring more infrequently. Splenic parenchymal injuries typically occur with mobilization of the gastric fundus and greater curvature.[88] Avoiding excessive traction on the splenogastric ligament can help to prevent this complication. In general, splenic bleeding can usually be controlled with pressure and topical hemostatic agents. Partial splenic infarction can potentially result from inadvertent coagulation of the superior pole branch of the main splenic artery during transection of the short gastrics.[90] Typically, this does not result in any clinically significant sequela. Lacerations and subcapsular hematomas of the left lateral liver can occur with manual retraction and, therefore, the use of a fixed retractor can be protective.

Postoperative management

Patients undergoing ARS are routinely admitted to the surgical floor for postoperative care. An enhanced recovery pathway is employed. On the day of operation, patients are started on a clear liquid diet. Ambulation and use of incentive spirometry is encouraged. On the first postoperative day, patients are typically given a full liquid diet. Patients able to maintain hydration on full liquids, and whose pain is controlled with oral pain medications, are discharged home. Dietary instructions regarding the slow reintroduction of soft foods are provided. In general, the diet is advanced to moist foods with soft textures for 2 weeks postoperatively. Breads, raw vegetables, and tough cuts of meat can prompt dysphagia. Medications are typically switched to liquid forms when available, or are crushed or opened during initial postoperative period. We routinely prescribe simethicone with meals in order to prevent gas-bloat. Most patients are able to tolerate a regular diet in approximately 4-6 weeks postoperatively.

Clinical outcomes

Laparoscopic ARS is a safe approach with mortality rate being far less than 1%.[83] Reported morbidity rates range from 4.7% to 8.3%. However, the majority of complications experienced such as urinary retention, wound infection, and ileus are minor and not specific to ARS procedures.[86,91-93] Although the vast majority of ARS patients have resolution of transient discomfort or dysphagia if kept on a soft, bland diet for 4-6 weeks, there are several bothersome side effects that may persist, including dysphagia, gas-bloat syndrome, and GERD-like symptoms.

Most patients undergoing primary ARS report mild, transient dysphagia that resolves in 2-4 weeks. The most common etiology of early postoperative dysphagia is tissue edema involving the wrap at the esophageal hiatus. Less frequently, dysphagia is due to esophageal or gastric hematoma formation adjacent to sutures. In either case, additional intervention is typically not indicated as patients are usually able to tolerate liquids with significant improvement over the next few days. Patients reporting severe dysphagia with inability to tolerate liquids should be studied with an UGI series in order to rule-out anatomic abnormalities, including an early hiatal

hernia or obstruction at the gastroesophageal junction. For this group, further evaluation consisting of Upper Gastrointestinal (UGI) series and endoscopy is necessary. In many cases, prolonged dysphagia is due to an overly tight wrap which can be treated with endoscopic dilation. If slippage or reherniation has occurred, reoperation is necessary.

Gas-bloat syndrome occurs when the fundoplication prevents elimination of swallowed air, resulting in gastric, and enteric gas accumulation. Belching allows for venting of swallowed air and occurs with transient LES relaxation. This vagal-mediated mechanism is blunted following ARS and therefore patients are unable to belch to expel air.[94] Patients may experience epigastric pain, abdominal distension, nausea with the inability to belch or vomit, early satiety, and increased flatus. Interestingly, a study investigating gas-related symptoms following Nissen and Toupet fundoplications determined that preoperative air swallowing and belching was not predictive of postoperative bloating, and proposed that gastrointestinal hypersensitivity to gaseous distension as an additional factor contributing to gas-bloat.[95] Management of gas-bloat syndrome typically consists of conservative measures such as dietary restriction and patient education regarding aerophagia. We have had success with implementation of routine dietary and behavioral interventions including avoidance of chewing gum, straws, and consumption of carbonated beverages. In our experience, patients also benefit from scheduled simethicone taken with meals in the early postoperative period. For patients experiencing severe bloating in the immediate postoperative period, abdominal x-rays should be obtained to assess for gastric distension or air-fluid levels. Placement of a nasogastric tube for 24-hours of decompression can be helpful. Ultimately, the majority of gas-bloat cases are self-limiting. For those patients enduring severe and persistent symptoms, endoscopic dilation can be considered.

There are several causes for failure of ARS. Anatomic causes include herniated or slipped wrap, disrupted wrap, paraesophageal hernia, overly tight wrap, or a wrap that was erroneously performed on the stomach. Of this list, herniated wrap is the most prevalent. Once diagnosed, reoperation is indicated. Esophageal dysmotility present prior to the index operation or resulting from an obstructive wrap is also possible. Similarly, presence of gastroparesis either presents preoperatively or resulting from iatrogenic vagal nerve injury, could also exacerbate GERD. In the absence of motility or anatomic complications, patients with GERD recurrence can be treated with a trial of medical therapy or revisional fundoplication.

Postoperative follow-up

We routinely follow our patients for 12 months postoperatively. At this time, an UGI series is performed to assess each patient's outcome. Postoperative symptom score questionnaires are also utilized. Patients with recurrence, persistence, or development of new "GERD-like" symptoms in the long-term setting require further evaluation. The UGI series is used to assess reflux, dysmotility, and anatomic complications. HREM, pH testing, and gastric emptying studies may also be indicated.

Linx

GERD is one of the most common diseases afflicting the developed world. The pathophysiology behind the disease is commonly attributed to the failure of the LES. There are 2 mechanisms that contribute to the antireflux function of the LES, which includes the intrinsic sphincter and the crural pinch.[96] Both mechanisms are each thought to have a 50% contribution to the function of the LES.[96] Failure of either mechanism can lead to episodes of reflux into the esophagus causing further damage to esophageal mucosa and LES sphincter muscle worsening GERD pathology.

Initial treatment modalities include diet modifications, weight loss, sucralfates, PPI therapy, and histamine-2 blockers. Surgery is reserved for patients who do not have good control of symptoms on medications or patients who are intolerant of these medications, those with breakthrough symptoms on escalating doses, or those who desire for freedom from daily pharmaceutical intervention and their side effects. Nissen fundoplication has become the established operation for GERD since it was first published by Nissen in 1956.[97] However, outcomes after Nissen

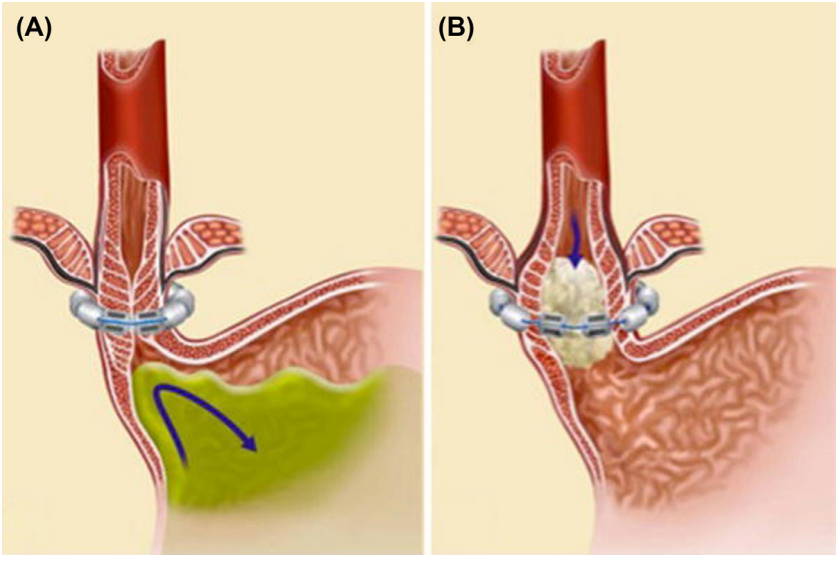

Fig. 6. Magnetic sphincter augmentation (MSA) with the LINX Reflux Management System. (A) MSA at rest in the closed position. It is noncompressive and controls reflux by resisting sphincter opening due to gastric challenges (ie, magnetic force>gastric pressure). (B) MSA in the open position. The beads' magnetic attraction is overcome by bolus pressures, which allows the device to open (ie, the bolus pressure >magnetic attraction). This is transient, though; as the swallow pressure drops, the device will be drawn closed by the magnetic attraction. Adapted with permission, from Wilson et al, 2014.[100]

fundoplication have been quite variable with the highest success rates (90%), seen in higher volume centers. Furthermore, there are postoperative quality of life issues such as increased bloating, flatulence, and dysphagia. This has led most referring physicians to only consider antireflux surgery in patients with end-stage disease or larger hiatal hernias with poorly controlled GERD.

The LINX Reflux Management System (Torax Medical, Inc., Shoreview, MN) was initially developed to address this "therapy gap" between patients who had good control of symptoms with medications and those that required a Nissen fundoplication.[8] The LINX device involves magnetic sphincter augmentation (MSA) of the LES and was approved in 2012 by the US FDA for use in patients with GERD. The LINX device is a ring of magnets that are connected by titanium wires that is placed laparoscopically around the LES. It reinforces the intrinsic sphincter of the LES but does not cause the supraphysiologic valve pressures seen with Nissen fundoplication, preserving patients' ability to eructate and emesis (Fig 6).[9] The original trial assessing safety and efficacy of MSA had strict inclusion criteria and patients were ineligible if they had hiatal hernias larger than 3 cm as determined by endoscopy, a BMI greater than 35 kg/m^2, esophageal dysmotility or anatomic abnormality, esophagitis grade C or D, Barrett's esophagus, prior electrical implant, esophageal varices, or prior antireflux procedure.[10] However, after the initial trial, the eligibility criteria have been extended as surgeons are placing MSA devices in patients with higher BMIs, and those with larger hiatal hernias or with prior electrical implants.[9] Currently, the only absolute contraindication to MSA placement is allergy to titanium, stainless steel, or ferrous material, which can be tested by giving patient a trial device to wear 3-4 days prior to surgery.[9]

Preoperative evaluation

The preoperative evaluation for MSA placement is similar to the evaluation for Nissen fundoplication. It begins with a thorough history and physical examination. The GERD-Health Related

Quality of Life (GERD-HRQL) questionnaire should be given to document the subjective component of patients' symptoms. Further diagnostic evaluation includes EGD, a pH study, esophagogram, and motility study.[9] A preoperative diet should be considered in patients with higher BMIs to assist with liver exposure/retraction for the surgery. Patients should be counseled on the importance of hourly intake of food while awake during the initial 4-6 postoperative weeks which minimizes scarring or stricture around the device and can decrease dysphagia rates and need for endoscopic dilation. The most common postoperative complaint after MSA placement is dysphagia.

Surgical technique

MSA is performed laparoscopically under general anesthesia. Preoperative antibiotics should be given since there will be a magnetic prosthetic implant. The positioning can be either lithotomy or supine based on surgeon preference. A total of 4 trocars are typically placed and a liver retractor is used to perform the surgery. The initial trocar can be placed supraumbilical using either the Hasson or Veress needle technique. Next, a liver retractor is placed in the epigastric region and a port can be placed in the left subcostal region approximately at the midclavicular line. One port should be placed in the right subcostal region close the right anterior axillary line to accommodate the angle for the measuring device. Finally, another subcostal port should be placed in the left anterior axillary line to aid in retraction if needed.

The dissection is started by dividing the pars flaccida. The hepatic branch of the vagus nerve should be preserved to act as a landmark for appropriate placement of the device on the LES. The phrenoesophageal ligament is divided anteriorly and the dissection is carried anteriorly over to the left crus, taking care to preserve the anterior vagus nerve. Next, the dissection can be performed from the right crus heading toward the decussation and toward the left crus avoiding any injury to the posterior vagus nerve. Once the esophagus is dissected circumferentially, a penrose can be placed around the esophagus to retract caudally while the dissection is performed to achieve 2-3 cm of intra-abdominal esophageal length.

The hernia sac, if present, must be completely reduced. Resection of the hernia sac is optional but ideally should be performed while preserving the vagus nerves. Short gastric vessels do not need to be divided while performing this dissection. Once the esophagus is completely mobilized, a small window should be created between the posterior vagus and esophagus where the device is placed. Once the esophageal dissection is completed, the hiatal hernia should be repaired per the surgeon's preference to restore the crural pinch. Next, a sizing device can be inserted from the patient's right subcostal port. When using the sizing device, care should be taken to avoid pushing on the esophagus as this may give a false measure regarding the true diameter. The goal is to have approximate size of the esophagus without impingement, which often translates to 3 beads above the mark where the magnet detaches in the sizing device. The size options that are available currently are 13-17 bead devices. Once a size has been determined, the MSA device can be inserted through a port and placed around the esophagus through the posterior vagus window (Fig 7). Once the device is clasped together, gentle traction on the sutures ensures that clasping mechanism has been fully engaged and the sutures are removed.

Complications and outcomes

The outcomes of MSA are similar to Nissen fundoplication, with more than 90% of patients reporting satisfaction with the surgery and 80%-90% reporting being free from daily PPI use.[9-11] The most common postoperative complication is dysphagia, which often improves over the first 6 months. Dysphagia and regurgitation were noted in 11% and 2%, respectively, of patients at 1-year follow-up.[10] Nineteen percent of patients underwent esophageal dilation in the initial study.[10] However, rates of dilation have improved significantly, with a rate of 6.5% in more recent

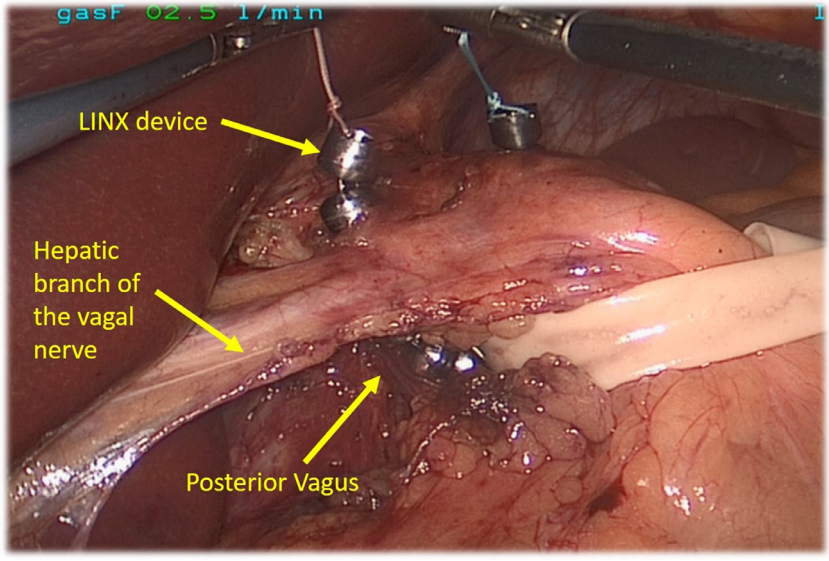

Fig. 7. Intraoperative placement of MSA device through the posterior vagus window.

Table 1
Comparison of Nissen fundoplication versus magnetic sphincter augmentation (MSA). Reprinted with permission from Aolfi et al, 2018.[12]

Symptoms	Nissen	MSA
Ability to eructate	65.9%	95.2%
Ability to emesis	49.5%	93.5%
Bloating and flatulence	53.4%	26.7%
Postoperative dysphagia	33.9%	47.1%
Off PPI	81.5%	81.4%
MRI	No restrictions	Limited to 1.5 Tesla MRI
LES	Supraphysiologic valve	Restores to baseline
Foreign body	No	Yes

MSA = magnetic sphincter augmentation; LES = lower esophageal sphincter; MRI = magnetic resonance imaging; PPI = proton pump inhibitor.

reports.[8,98] The removal rates have been 0.5%-1.7%, most commonly for persistent dysphagia.[11,12] The rates of erosion in 2 systematic reviews were noted to be 1 of 686 (0.15%) and 1 of 415 (0.2%).[11,12]

When comparing these complications to the well-established treatment option of Nissen fundoplication, the outcomes are comparable, but MSA patients often require more endoscopic dilations than patients who have undergone Nissen fundoplication.[12] A systematic review, published by Aiolfi et al, reported an esophageal dilation rate of 9.3% after MSA as compared to the 6.6% rate after laparoscopic Nissen fundoplication.[12] A systematic review by Skubleny et al reported an esophageal dilation rate of 3.3% after laparoscopic Nissen fundoplication compared to 23.4% in MSA patients.[11] However, MSA patients have improved outcomes with respect to eructation, emesis, bloating, and flatulence.[11] Studies with longer term follow-up are needed before determining the duration of symptom relief from MSA compared to Nissen fundoplication (Table 1).

Postoperative management

Patients can often be discharged the same day after MSA surgery with reinforcement of the dietary recommendations as outlined previously. Cessation of PPI therapy can be initiated imme-

diately after surgery. Patients should be seen in the postoperative period to evaluate the degree of symptom relief and severity of dysphagia. Steroids can be considered for refractory management of persistent dysphagia after surgery. Dysphagia rates continue to decrease each month after surgery with very low rates of persistent dysphagia 6 months after MSA. Any dilation should be postponed until 3 months from MSA. Of note, patients need to avoid MRI with a magnetic force stronger than 1.5 Tesla as this can damage the MSA device.

Conclusions

MSA adds another tool to the armamentarium of surgeons for the treatment of GERD. MSA is noted to be just as effective in patients with GERD as the Nissen fundoplication but with a more favorable side effect profile at the expense of a higher postoperative dysphagia rate.

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