DEMEESTER FESTSCHRIFT

A Controversy That Has Been Tough to Swallow: Is the Treatment of Achalasia Now Digested?

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Abstract Esophageal achalasia is a rare neurodegenerative disease of the esophagus and the lower esophageal sphincter that presents within a spectrum of disease severity related to progressive pathological changes, most commonly resulting in dysphagia. The pathophysiology of achalasia is still incompletely understood, but recent evidence suggests that degeneration of the postganglionic inhibitory nerves of the myenteric plexus could be due to an infectious or autoimmune mechanism, and nitric oxide is the neurotransmitter affected. Current treatment of achalasia is directed at palliation of symptoms. Therapies include pharmacological therapy, endoscopic injection of botulinum toxin, endoscopic dilation, and surgery. Until the late 1980s, endoscopic dilation was the first line of therapy. The advent of safe and effective minimally invasive surgical techniques in the early 1990s paved the way for the introduction of laparoscopic myotomy. This review will discuss the most up-to-date information regarding the pathophysiology, diagnosis, and treatment of achalasia, including a historical perspective. The laparoscopic Heller myotomy with partial fundoplication performed at an experienced center is currently the first line of therapy because it offers a low complication rate, the most durable symptom relief, and the lowest incidence of postoperative gastroesophageal reflux.

Introduction

Esophageal achalasia is a rare neurodegenerative disease of the esophagus and lower esophageal sphincter (LES) that leads to dysphagia and other associated symptoms. The incidence of achalasia in western populations is one to three per 100,000 people.[1,2] Patients with achalasia present to the gastroenterologist within a spectrum of disease severity

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related to the progressive pathological changes affecting the esophagus, such as grades of esophageal dilation, and associated conditions, such as esophageal diverticulum.[3] Because achalasia is rare and the spectrum of disease severity is wide, few randomized controlled clinical trials have properly delineated the best treatment strategy. The safety, effectiveness, and durability of current treatment options, including pharmacologic, endoscopic, and surgical therapy, varied widely. Until the late 1980s, endoscopic dilation was considered first-line therapy;[4] but after minimally invasive surgical techniques were introduced toward the end of the last century, expert opinion shifted. Currently, most experts agree that first-line therapy should be laparoscopic myotomy with partial fundoplication, performed by an experienced surgeon, and that endoscopic methods should be reserved as an alternative to surgery for patients who are poor surgical candidates, refuse an operation, and possibly patients for whom surgery fails.[5–13]
In this paper, we review the current understanding of the pathophysiology of achalasia, standard and emerging diagnostic tools, and outline the various treatment options before and after the development of minimally invasive

surgical techniques, with an emphasis on symptom relief and complications.

Pathophysiology

Achalasia, though rare, is possibly the most studied and best described motility disorder of the esophagus, yet its pathogenesis remains incompletely understood. It is a neurodegenerative disorder affecting the function of the muscle of the esophageal body and LES, as well as the vagal trunks and dorsal vagal nuclei.[14] The pathogenesis stems from an idiopathic and irreversible loss of postganglionic inhibitory neurons in Auerbach's myenteric plexus.[15] The resulting imbalance toward cholinergic stimulation[15,16] causes loss of LES relaxation and failure of the esophageal body peristalsis after swallowing, giving the condition the name achalasia, a Greek word meaning "failure to relax".

There are no well described effects of achalasia outside the abnormalities seen in the esophagus, LES, and the vagus nerves.[17] Whether the failure of esophageal body peristalsis is secondary to the obstruction caused by nonrelaxing LES or is a primary defect of the esophageal body is also still debated. Achalasia can present at any age, but incidence increases during the second and third decades of life. There is no evidence that the disease has a predilection for a particular race or gender.

Despite considerable investigation, the cause of ganglion cell degeneration in achalasia is still unknown. Possible associations have been described with class II human leukocyte antigen DQw1, implicating an autoimmune mechanism[16] or an inflammatory reaction due to a viral infection such herpes, measles, poliomyelitis, varicella zoster, and human papilloma virus.[14,18,19] Supporting an immune-mediated response to a virus in a genetically susceptible population are data that from Boeckxstaens et al.[20] who produced clonal proliferation of cytotoxic T cells taken directly from the gastroesophageal junction (GEJ) of patients with achalasia in response to herpes virus-1 (HSV-1). As suggested by this evidence, a smoldering HSV-1 infection could cause a myenteric plexitis and eventual self-mediated neuronal destruction in a genetically susceptible patient. Whether the mechanism of neuronal destruction is an autoimmune or infectious process and which virus(es) can lead to neuronal destruction is still unclear.

There is mounting evidence that the main downstream effect of neuronal destruction is an alteration in the neurotransmitter nitric oxide (NO) pathway. NO is the dominant small molecule mediating relaxation of the LES.[21] NO activity decreases due to loss of the inhibitory neurons that release NO and thus decreased relaxation of the LES.[22] These inhibitory neurons are thought to be severely impaired, while interestingly, their cholinergic counterparts are less affected.[23] In humans, this pattern was shown by comparing the response of the LES in patients with achalasia with that in healthy controls, after intravenous injection of several well-defined pharmacologic stimuli. The LES of achalasia patients was more sensitive than that of healthy controls to methacholine and pentagastrin. Edrophonium increased the LES pressure in achalasia patients but had no significant effect on control patients, whereas atropine increased the LES pressure in both groups.[23] Furthermore, nitric oxide synthase (NOS) knock-out mice display consistently higher resting LES pressure and failure of relaxation of the LES in response to swallowing,[24] which is a similar manometric pattern to that of many patients with achalasia. Finally, GEJ biopsies from patients with achalasia display a complete absence of NOS containing neurons.[25]

Ultimately, degeneration of the myenteric plexus produces a functional defect causing loss of esophageal body peristalsis and failure of relaxation of the LES in response to swallowing. These abnormalities in motility produce the slowed transit of solids and liquids, resulting in the dysphagia that is most often the primary, but not the sole complaint, of patients. Swallowed material pools above the LES, causing irritation of the esophageal mucosa and regurgitation, and may contribute to dilation of the esophagus proximal to this outflow obstruction. In addition to dysphagia and esophageal mucosal changes, this pattern of dysmotility reliably produces manometric and radiologic findings that are required for the diagnosis of achalasia.[26–29]

Diagnosis

The most common presenting symptom of achalasia is dysphagia, which can often become so debilitating that profound weight loss occurs. However, the primary symptom of achalasia in up to 40% of patients may be regurgitation of undigested food, unexplained chest pain, "heartburn" mimicking reflux, cough, or recurrent pneumonia. The standard current workup of a patient suspected of having esophageal achalasia consists of a barium esophagram, esophageal manometry, and upper endoscopy.[30]

The *barium esophagram* can be a window into the static structure and the dynamic function of the esophagus. The mechanical outflow obstruction created by the LES leads to dilatation of the esophageal body that narrows sharply to form a classic "bird's beak" appearance seen on esophagram. Retained food is often seen in the esophagus and transit of barium past the LES is slow. Radiographic findings suggestive of achalasia have a specificity of about 75%.[17,31] As the disease progresses, often dilation worsens and the esophagus can take on a sigmoidal shape with
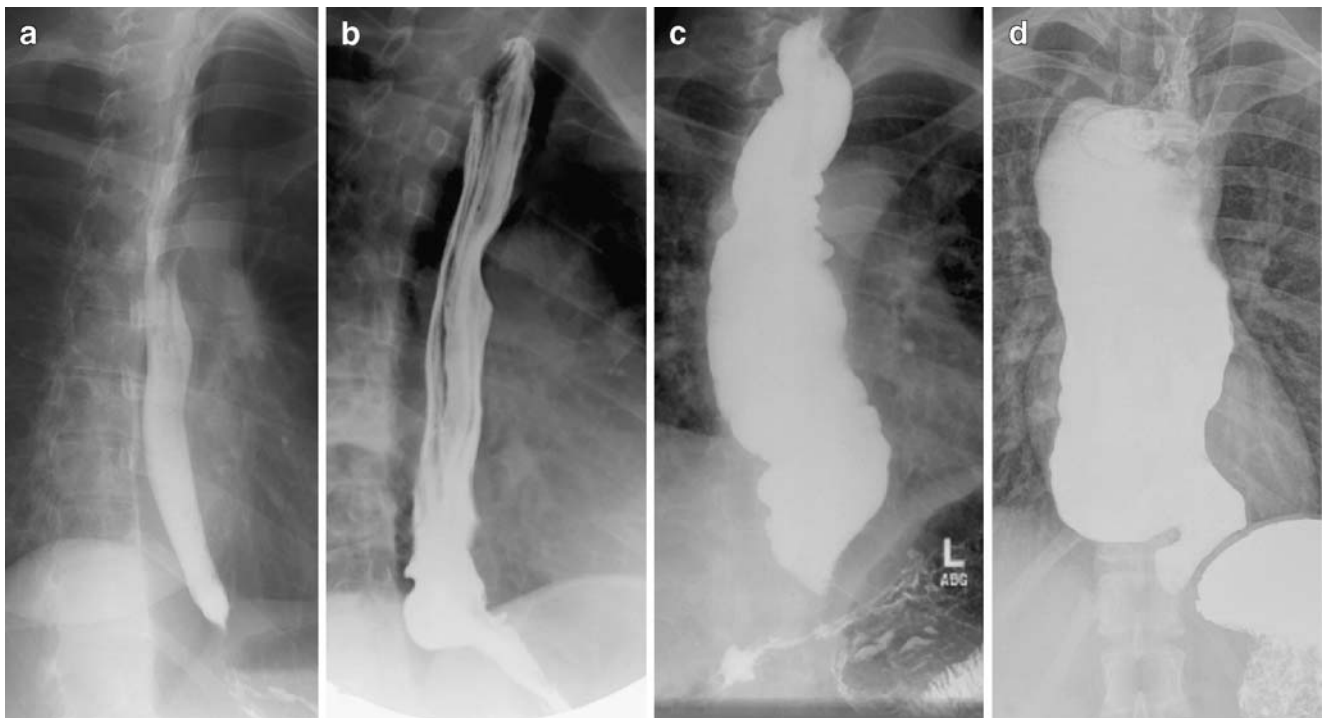
Figure 1 Examples of progressive dilation of the esophagus in different patients with achalasia. **a** Normal diameter esophagus leading to a bird's beak at the LES. **b** Minimal esophageal dilation (from 4 to 7 cm). **c** Progressive esophageal dilation (from 7 to 10 cm) with preserved esophageal axis. **d** Greater dilation (>10 cm) and initial sigmoidal course of the distal esophagus.

various degrees of dilation (Fig. 1). A sigmoid esophagus is defined as dilation of the distal esophagus to more than 10 cm in diameter and/or one that takes a tortuous course through the chest towards the GEJ. Another sign of longstanding esophageal outflow obstruction is the development of esophageal pulsion diverticula that produces external compression on the esophagus (Fig. 2).

Standard stationary esophageal manometry is currently the gold standard for diagnosing achalasia. Manometry is important for differentiating achalasia from other esophageal motility disorders such as diffuse esophageal spasm, hypertensive LES, or nutcracker esophagus.[32] Findings on manometry that suggest the diagnosis are (1) absence of peristalsis of the distal two thirds of the esophageal body and (2) incomplete LES relaxation in response to deglutition.[33] The LES is hypertensive in approximately 50% of cases,[34] but it can also be normo or hypotensive; consequently, elevated resting LES pressure is not required for the diagnosis of achalasia.[33] The diagnosis does require the finding of an aperistaltic esophagus;[33,35] although aperistalsis of the esophageal body is not a finding specific to achalasia, as it can be seen in diabetes, gastroesophageal reflux disease, and collagen vascular diseases.

Manometric diagnosis of achalasia may be a challenge in a small subset of patients with variants of the disease such as vigorous achalasia. Vigorous achalasia is thought to be an early stage of the disease.[36,37] LES pressure and the amplitude of the simultaneous aperistaltic contractions are significantly higher in vigorous achalasia than in "classic" achalasia, and the repetitive ("mirror image") waves are more frequent.[38]

Newer techniques such as high-resolution manometry (HRM) and multichannel intraluminal impedance monitoring can be used to study esophageal function and have helped clinicians further classify patients with achalasia and

Figure 2 A barium esophagram showing a normal caliber esophagus with a large epiphrenic diverticula in a patient with achalasia.

possibly guide treatment.[39,40] High-resolution manometry records the pressure generated by the entire length of the esophagus and reports this information as a topographical plot. These data allow for more accurate definition of the contractile elements of deglutition as they are traced from the pharynx to the stomach.[41,42] In a recent study evaluating 213 patients with achalasia, HRM was used to classify the disease into three subtypes based on the function of the contractile elements: In type I (classic) achalasia (21.2% of patients), there was no distal esophageal pressurization to greater than 30 mmHg in greater than or equal to eight of the ten test swallows; in type II achalasia (with compression; 49.5% of patients), at least two test swallows were associated with an esophageal pressurization to greater than 30 mmHg; and in type III, patients (spastic; 29.3% of patients) had two or more spastic contractions with or without periods of compartmentalized pressurization.[42] Using logistic regression, the investigators related these subtypes to treatment response and showed that patients with type II achalasia were the least likely to report poor symptom improvement or require further therapy within 12 months of the initial treatment. Symptom relief was obtained in 71% of type II patients after endoscopic injection of botulinum toxin (EBTI), 91% after endoscopic dilation (ED), and 100% after Heller myotomy. Type I patients had a good response to therapy 56% of the time, whereas type III patients had a good response only 29% of the time.[42]

Multichannel intraluminal impedance pH monitoring entails positioning a series of electrodes inside the esophagus and measuring the resistance to flow of electricity between these electrodes.[43] If the esophageal lumen is filled with air, the impedance is high relative to a lumen filled with fluid. This test can also follow the dynamic impedance of a food bolus after deglutition, and during the same swallow, manometry results can be recorded. Achalasia results in a dilated and fluid-filled esophageal lumen with slowed transit of food boluses, so measuring the intraluminal impedance adds to the information about the amplitude and progression of muscle contractions gained from manometry.[35,43]

Patients being evaluated for achalasia often describe the sensation of gastroesophageal reflux (GER) or heartburn, either in addition to or in place of dysphagia. Most achalasia patients likely do not have actual reflux of gastric contents through the GEJ, but rather they experience this sensation as a direct result of fermentation of retained food in the distal esophagus and regurgitation. Fermentation is the breakdown of carbohydrates into acids or alcohol under the right conditions, and this can take place in the esophagus of a patient with esophageal outflow obstruction. Crookes et al.[44] showed that chewed samples incubated in vitro with saliva but never exposed to gastric acid slowly ferment. The pH of these samples gradually drops to around 4, but usually not below that. They also showed that achalasia patients can have pH tracings that mimic this gradually decreasing pH, or they can have sharp dips in pH more characteristic of actual reflux events. Therefore, to make the diagnosis of reflux in a patient with achalasia, the pH must drop below 3 or the tracing must display sudden sharp drops in pH; otherwise, the decreasing pH is likely a product of retained food fermenting in the distal esophagus. This is an important diagnostic distinction because it is the unusual patient who has both achalasia and GER. Crookes et al. looked at 20 patients before surgery for achalasia and found that five (20%) had abnormally high esophageal acid exposure. Of those five patients, only one (5%) had sudden pH drops characteristic of GER.[44] Evidence is lacking, but theoretically, these patients might be at a higher risk for postprocedure reflux, and should be counseled accordingly.[45]

Diagnostic upper endoscopy must be performed in all patients suspected having achalasia, although it may be normal in up to 44% of cases.[17] It is an indispensable part of the workup because primary, idiopathic achalasia must be differentiated from secondary, or pseudoachalasia. Endoscopy is required for this discrimination because manometric findings in pseudoachalasia can be indistinguishable from those in primary achalasia.[46] Pseudoachalasia can develop as a result of a parasitic infection by the leishmanial forms of *Trypanosoma cruzi* (Chagas' achalasia), which occurs most often in South Africa and South America,[47,48] or in cases of a malignant disease of the distal esophagus and the gastric cardia or peri-esophageal tumors.[47–49] Pseudoachalasia has also been associated with mesenchymal tumors, secondary amyloidosis, peripheral neuropathy, or neurological disorders resulting from brain tumors, lymphoma, and encephalitis.[31,50,51] Further causes include iatrogenic conditions such as an incorrectly constructed or tight fundoplication during antireflux procedures (ARPs) and placement of laparoscopic adjustable gastric banding for the treatment of morbid obesity (Fig. 3).[31,50,51] Although rare, esophageal and gastric malignancies may occur in patients with long-standing achalasia,[38,52] so a retroflexed view of the GEJ with routine distal esophageal and cardia biopsies should be obtained to ensure that all mucosal abnormalities are identified. Furthermore, some authors have recommended endoscopic ultrasound and/or a computed tomography scan in older patients and patients with advanced disease to uncover small, submucosal lesions, which might otherwise go undetected by other diagnostic tests.[53]

Nonspecific findings on chest X-ray may include mediastinal widening, presence of an air-fluid level in the midesophagus, absence of a gastric air bubble, and abnormal pulmonary markings due to chronic aspiration.

Figure 3 A barium esophagram in a patient with a gastric band causing pseudoachalasia. The esophagus is dilated and empties barium slowly.

After treatment, timed barium swallow (TBS) is an additional tool to evaluate esophageal emptying and correlate it with patient symptoms. During TBS, the patient is instructed to drink 150 ml of barium as quickly as comfortable within a time interval of 30 to 45 s. Spot films of the esophagus are taken 1 and 5 min after ingestion of the barium. The area of the barium column is measured on timed digital images. Esophageal emptying is then calculated by comparing the area of the residual barium column on the 1- and 5-min images.[54] Oezcelik et al.[55] evaluated the TBS of 30 patients at 3 and 6 months after myotomy to access esophageal emptying. They correlated the TBS results with patient reported symptom relief and found that esophageal emptying as measured by standard means did not change significantly after myotomy, but initial esophageal clearance improved dramatically (by 81%) and this correlated well with symptom improvement.

In summary, the diagnosis of achalasia is often suggested by history, barium esophagram, and upper endoscopy. Stationary esophageal manometry is currently the gold standard. Because achalasia represents a spectrum of disease, manometric findings can vary and the addition of HRM, impedance manometry, and pH-impedance can further classify the pathological state and may assist the clinician during these diagnostic dilemmas. Twenty-four hour pH monitoring can identify the unusual patient with GER prior to treatment.

Treatment

Several treatment options for esophageal achalasia are available. The overall health of the patient, coupled with the patient's expectations for symptom relief, must be considered to ensure a proper treatment plan. Treatment strategies attempt to relieve the obstructive nature of the LES at rest and after swallowing, to allow a more normal transit of liquids and solids, while taking great care not to induce GER. Currently, there is no available treatment to correct the dysmotility of the esophagus and LES created by the disease. Treatment options consist of pharmacologic therapy, endoscopic therapy, and surgery.

Pharmacologic Therapy

The goal of pharmacological therapy, the only noninvasive treatment for achalasia, is to lower the resting LES pressure. Because drug absorption is impaired due to the poor esophageal emptying, sublingual medications are preferred. Sublingual calcium channel blockers (nifedipine) and sublingual isorbide dinitrates (nitrates) are the two most common medications used.[56,57] Less commonly used medications include anticholinergics, beta-blockers, beta-adrenergic agonists (carbuterol, terbutaline, cimetropium bromide), nitroglycerine, and theophylline (aminophylline).[58–61]

In collected outcomes for 229 patients treated with pharmacologic therapy, we found that symptoms improved in 61% of patients after use of nifedipine and 70% of patients after use of nitrates.[116–123] Manometry was used to document LES pressure before and after drug therapy in all trials in different subsets of patients. A transient decrease in LES pressure was documented in 46% of patients when manometry was performed. This transient effect seemed to be better after nitrate use than after nifedipine use, as measured by the transient mean decrease in LES pressure (baseline pressure−posttherapy pressure)×100, which was 66% after nitrates but only 38% after nifedipine. Nitrates also seemed better than nifedipine with regard to the time to maximum effect (25 vs 9 min), but the duration of effect was longer for nifedipine (40 vs 30 min).

The short clinical response and common presence of side effects such as headache, dizziness, tachycardia, hypotension, nausea, and ankle edema were limiting problems with pharmacological therapy. It should be considered only for patients who decline or are considered too frail for endoscopic or surgical treatment options.

Endoscopic Therapy

Achalasia was first described in the literature in 1672 by Sir Thomas William, and the first described treatment for achalasia (then called "cardiospasm") was performed in London, by Thomas Willis. Of note, other notable accomplishments of Thomas Willis include numbering the cranial nerves and identifying the vascular arcade of the brain that is now called the Circle of Willis. In 1674, he described treatment of cardiospasm by forceful passage of a

piece of whalebone padded with a sponge through the LES.[62] With the advent of modern endoscopic techniques, endoscopic dilation was first-line therapy for achalasia until the advent of minimally invasive surgery in the 1980s.[63] Endoscopic treatments are directed at relieving the obstruction caused by the LES and now include endoscopic botulinum toxin injection (EBTI), described in 1991,[64] or endoscopic dilation (ED) of the LES.

EBTI decreases tonic and swallow-induced LES pressure by inhibiting acetylcholine release from the inhibitory cholinergic presynaptic nerve innervating the LES.[65] As reported in a recent systematic review,[66] EBTI relieves symptoms in 79% of patients surveyed up to 1 month after treatment, but unfortunately, the symptom relief declines to 70% at 3 months, 53% at 6 months, and 41% after 12 months.[66] Due to this progressive return of dysphagia, almost half (47%) of the patients undergoing EBTI required repeat injection.[66] Relief of dysphagia was found to be somewhat better if a second injection was planned at a 1-month interval after the first, but again, symptom relief was not durable and symptoms returned in 66% of patients at 2 years.[67] Primary failure of EBTI can also be due to antibody formation that causes resistance to the acetylcholine injection in 26% of patients.[68–70] In addition to these primary failures, EBTI leads to fibrosis of the mucosa and muscle layers that could make the myotomy, during a future surgical therapy, considerably more challenging.[71,72]

The other mode of endoscopic therapy is ED, and the current method of choice for dilation is a controlled pneumatic dilation.[63,73–75] Other older dilation methods have gradually been abandoned as they were associated with a higher perforation rate.[66] During controlled pneumatic dilation, a balloon is placed across the LES under direct endoscopic or fluoroscopic visualization. The balloon is inflated for 1 to 3 min, to a pressure of 300 mmHg (10–12 psi). To obtain an acceptable therapeutic effect, dilation to a diameter of at least 3.0 up to 4.0 cm must be performed.

The goal of ED is similar to the goal of any surgical therapy, as they both attempt to produce a controlled division of the esophageal muscle while leaving the mucosa intact. Review of the literature shows that dilator size, the amount of pressure applied, and duration of dilation were inconsistent between endoscopists and symptom relief seems to be dependent on these variables. ED is a relatively safe procedure and the most serious complication of the currently used methods of ED is perforation of the esophagus, which was seen in 1.6% of patients in a review of 1,065 patients, but the perforation rate can be as high as 12% using older dilation techniques.[66] Symptom relief has been related to the ability of the procedure to decrease the resting LES pressure by more than 10 mmHg, or produce a reduction of ≥50% of LES pretreatment pressure.[76]

A recent Cochrane Review, published in 2008, comprised of six randomized controlled trials including 178 patients, looked at symptom recurrence after ED vs EBTI at 1, 6, and 12 months after treatment. This review found that 30% of patients undergoing ED experienced symptom recurrence and treatment failure at 12 months vs 74% of EBTI patients.[77]

A recent systematic review and meta-analysis of 105 articles reporting on 7,855 patients treated for achalasia showed that symptom relief after ED was obtained in 85% of patients at 1 month and declined with time to 68% at 12 months and 58% at 1.5 years (Table 1).[66] Symptom relief was better for ED than for EBTI (68% vs 41%, odds ratio (OR) 3.4; 95% confidence interval (CI) 1.2–9.8; $P=$ 0.02), and the need for further procedures was lower after ED than after EBTI (25% vs 47%; OR 2.6; 95% CI 1.05–6.5; $P=$0.04).[66]

In addition to dysphagia recurrence, patients undergoing ED can experience the onset of GER, with 33% of patients reporting symptomatic GER at 4 years.[78–80] When 24-h pH monitoring was used as a proxy, more than 30% of patients had an increase in episodes and duration of reflux.[44,81]

In summary, published evidence shows that ED is consistently more durable than EBTI, but that after ED, symptoms recur in 42% of patients and about 30% of all of the patients treated with ED require further therapy. Prior to any surgical intervention, knowledge of the patient's history of previous endoscopic therapies at the GEJ is important to the surgeon because some experts propose that ED and EBTI lead to fibrosis of the mucosa and muscular layers of

Table 1 Symptom Improvement After Initial Treatment of Achalasia by Therapeutic Endoscopy (Adapted from Campos et al.[66])

Treatment	Number of studies	Number of patients	Symptom improvement at (numbers are mean[a] % and range)				
			≤1months	3months	6months	≥12months	≥36months
Endoscopic injection of botulinum toxin	9	315	78.7 (64–93)	70.0 (55–83)	53.3 (44–57)	40.6 (10–55)	n/a
Endoscopic pneumatic balloon dilation	15	1,065	84.8 (56–97)	n/a	73.8 (51–97)	68.2 (38–90)	58.4 (33–70)

n/a data were not recorded for these time points in the studies used to compile the systematic review and meta-analysis

[a] Weighted averages of the sample prevalence in each of the studies, with weights equal to the number of patients

the esophagus. Less predictable symptom relief has been reported in patients who have been previously treated with endoscopic therapy,[72,82] which could be due to the greater technical difficulty of doing the operation in these patients. To avoid mucosal perforation in these cases, the location of the GEJ and the proper dissection planes must be identified during the myotomy.

Surgical Therapy

The initial attempts to treat achalasia with an operation in the early twentieth century combined several modifications of gastroesophageal junction reconstructions (cardioplasties) to esophageal resections.[83] Those techniques failed due to high operative morbidity and excessive postoperative gastroesophageal reflux and led to the development of distal esophageal myotomy. The first successful surgical myotomy of the lower esophagus and lower esophageal sphincter was reported in 1913, by the German surgeon Ernest Heller.[84] His original technique used anterior and posterior myotomies extending for 8 cm or more along the distal esophagus and GEJ through a left thoracoabdominal approach. Although this technique was successful in improving dysphagia, excessive gastroesophageal reflux resulted. In 1918, the Dutch surgeon Zaaijer[85] described a modification of Heller's original technique to a single, anterior cardiomyotomy that has remained the myotomy of choice until now. Based on Heller's original idea, many surgeons performed the distal esophageal and LES myotomy through a left thoracotomy[86] as a way to perform an appropriate myotomy while attempting to preserve the natural anatomical antireflux components of the gastroesophageal junction, such as the His angle and the phrenoesophageal membrane, thereby possibly preventing postoperative GER. Both the transabdominal and transthoracic techniques have been used since.

The end of the last century witnessed the shift from open surgery in the chest and abdomen towards thoracoscopic and laparoscopic surgery. The myotomies performed through both approaches have evolved in parallel[87,88] into minimally invasive procedures through the chest and abdomen. The first laparoscopic Heller myotomy was described by Shimi et al. in 1991.[89]

One advantage of the transabdominal operation is that it makes it easier to create a fundoplication because better exposure of the structures of the GEJ can be obtained. Thoracoscopic myotomy is also more technically challenging the transabdominal, because the myotomy must be performed perpendicular to the course of the esophagus. Finally, as discussed below, the thoracoscopic approach is associated with a higher incidence of postoperative GER, making the laparoscopic operation the preferred approach performed at most experienced centers.[87,90,91]

A 2009 systematic review and meta-analysis of the surgical options summarized 64 articles, including 4,871 patients (Table 2).[66] Regression analysis confirmed that the laparoscopic approach yielded similar symptom relief to the open thoracic operation (89% vs 83%; OR 1.3; 95% CI 0.8–2.0; P=0.3) and the open abdominal operation (89% vs 84%; OR 1.1; 95% CI 0.5–2.5; P=0.8), but better relief than then the thoracoscopic operation (89% vs 78%; OR 1.9; 95% CI 1.1–3.7; P=0.048) and also ED (89% vs 56%; OR 5.9; 95% CI 3.7–9.3; P=<0.01).[66]

In a recently published study of over 400 consecutive patients, Zaninotto et al. reported their experience with laparoscopic Heller myotomy and Dor fundoplication. Similar to results previously reported by other authors,[92,93] the best predictor of a dysphagia relief was preoperative LES pressure >30 mmHg.[94]

Some authors have debated the need to perform an ARP after the myotomy.[95–97] The 2009 systematic review and meta-analysis also evaluated the development of postoperative GER and found that adding an antireflux procedure after laparoscopic myotomy dramatically decreased the incidence of GER symptoms from 31% down to 9% (OR 4.3; 95% CI 1.9–9.7; P=0.001) without altering the resolu-

Table 2 Results (Symptom Improvement and Postoperative GER) After Surgical Treatment for Achalasia (Adapted from Campos et al.[66])

Treatment	Months follow-up (range)	Number of studies	Number of patients	Mean symptom improvement[a] % (range)		Mean prevalence[a] of GER (range)	
				No ARP	With ARP	No ARP	With ARP
Transthoracic myotomy	102.0 (57–172)	13	842	85.1 (66–97)	80.2 (66–97)	29.2 (4–66)	13.6 (0–28)
Thoracoscopic myotomy	36.4 (12–72)	8	211	77.6 (31–94)	n/a	28.3 (15–60)	n/a
Transabdominal myotomy	87.4 (8–190)	10	732	64.4 (57–66)	89.7 (73–100)	28.5 (21–64)	7.5 (0–15)
Laparoscopic myotomy	35.4 (8–83)	39	3,086	89.9 (86–100)	90.3 (77–100)	31.5 (11–60)	8.8 (0–44)

ARP antireflux procedure, *n/a* data not collected for at that time points in the studies used to compile the meta-analysis, *GER* postprocedure gastroesophageal reflux symptoms

[a] Weighted averages of the sample prevalence in each of the studies, with weights equal to the number of patients

tion of dysphagia (90% vs 90%; OR 1.6; 95% CI 0.74–3.3; $P=0.23$).[66] When measured by 24-h pH monitoring, the incidence of GER after laparoscopic myotomy without fundoplication was 42% vs 15% after laparoscopic myotomy with fundoplication (OR 4.2; 95% CI 1.5–12.8; $P=0.01$). The addition of an ARP seems crucial for satisfactory outcome in the treatment of achalasia, and the addition of a fundoplication does not increase morbidity.[98–100]

Selecting the proper treatment course for a given patient requires analysis of the rates of complication of all of the treatment options. With pneumatic balloon dilation, currently the accepted standard, the perforation rate is 1.6%.[66] Systematic review of the results of 3,086 patients who had laparoscopic myotomy found that complications were reported in 6% and death in 0.1%.[66] Intraoperative perforation of the esophageal or gastric mucosa was reported in about 7%.[66] Most of those injuries were repaired during the index operation, and only 19 patients, or 0.7%, experienced symptoms from perforation postoperatively. When overall complication rates reported after laparoscopic myotomy are compared with ED, differences are possibly related to an innate more invasive nature of the laparoscopic surgery, but differences in baseline patient characteristics and severity of the disease likely have an impact on the results of each method reported. A 2001 decision analysis for the treatment of achalasia evaluated four strategies for the initial management of achalasia: (1) laparoscopic Heller myotomy and partial fundoplication, (2) pneumatic dilatation, (3) botulinum toxin injection, and (4) thoracoscopic Heller myotomy[101]. According to the analysis, laparoscopic myotomy with fundoplication was the proper first treatment strategy unless the patient's risk of operative mortality was higher than 0.7%.

Surgical Technique

Laparoscopic Myotomy

Laparoscopic myotomy has proven over time to be the approach that consistently produces the most durable symptom relief.[99,100] The operation begins with trocar placement similar to that for any laparoscopic operation taking place at the GEJ.[100] The gastrohepatic ligament and the phrenoesophageal membrane are opened to expose the esophagus. The anterior vagus nerve is carefully identified and preserved as the dissection is carried out in clockwise fashion around the anterior esophagus. The anterior fat pad covering the GEJ may be removed to facilitate the myotomy.

In most cases, posterior esophageal dissection is not needed. Leaving the posterior attachments intact also provides an anchor to help keep the GEJ in the proper anatomic location. A posterior dissection is only performed

in patients who have large concomitant hiatal hernias so that the hernia can be reduced into the abdominal cavity and the crura can be repaired properly.

The myotomy is begun by bluntly dividing the longitudinal muscle fibers of the esophagus with graspers (Fig. 4), scissors, or the hook. The myotomy is carried cephalad for at about 6 cm and through the longitudinal and circular muscle fibers down to the esophageal submucosa and extended 2 cm in the caudal direction from the GEJ on the anterior stomach to ensure complete division of the sling fibers, making the total length of the myotomy about 8 cm (Fig. 5). A gastric extension that is too short is one important cause of failure of the myotomy to relieve dysphagia. The gastric extension is also the part of the myotomy where the most mucosal perforations occur because the plane between the submucosa and the muscularis is not as pronounced in this location. Any mucosal perforation should be primarily repaired with interrupted absorbable suture.

Antireflux Procedure

After the myotomy is completed, an antireflux procedure is performed to prevent postoperative GER by recreating the His angle and keeping the GEJ inside the abdominal cavity. A 360° Nissen fundoplication has been used in selected series;[98,102,103] however, a Nissen fundoplication may hinder esophageal clearance, resulting in progressive postoperative dilatation of the aperistaltic esophagus and recurrent dysphagia. Although a few centers with significant experience in esophageal surgery still advocate a Nissen fundoplication after myotomy,[103] most do not recommend it due to reported reoperation rates as high as 29%.[10,32,86,104–108]
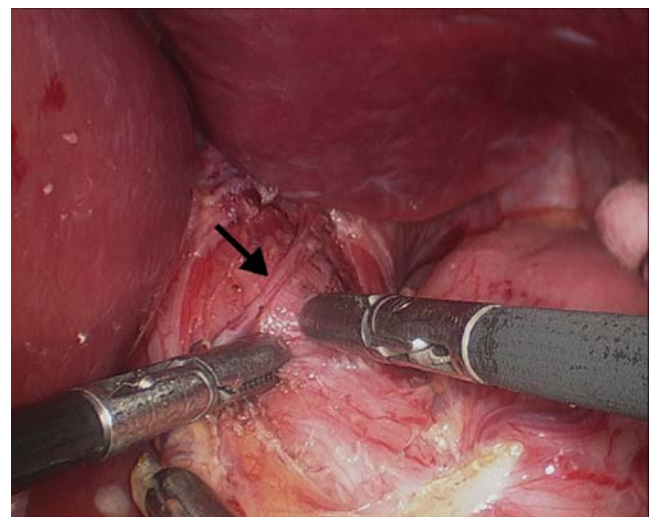

Figure 4 The anterior vagus nerve (*arrow*) is identified and preserved. Then two graspers are used to begin the myotomy just above the GEJ.
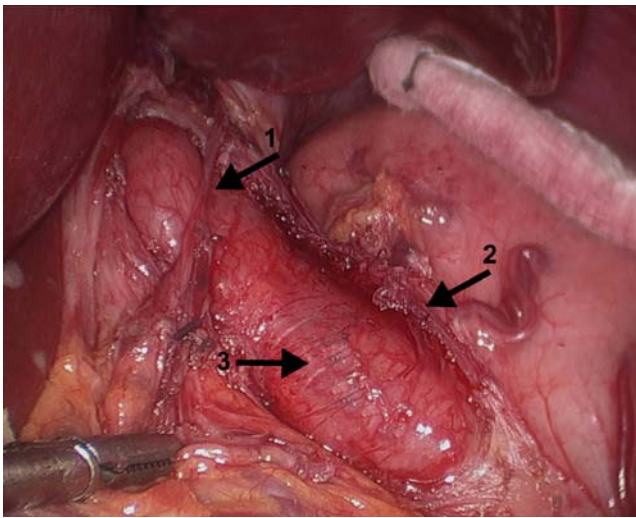
Figure 5 A completed 8-cm myotomy is shown. *Arrow 1* points to the anterior vagus nerve. *Arrow 2* points to the left edge of the myotomy. *Arrow 3* points to the exposed esophageal submucosa.

Two partial fundoplications have been used with equipoise, a posterior fundoplication (Toupet fundoplication) and an anterior fundoplication (Dor fundoplication). The *Toupet fundoplication* seems to provide an appropriate antireflux barrier. The theoretical advantages of the Toupet fundoplication are that due to its anatomical configuration, (1) it keeps the edges of the myotomy pulled apart, thus preventing scarring and recurrent dysphagia, and (2) that it can be performed just after the lower esophagus has been pulled downward and straightened, thus improving passage through the cardia and again minimizing postoperative
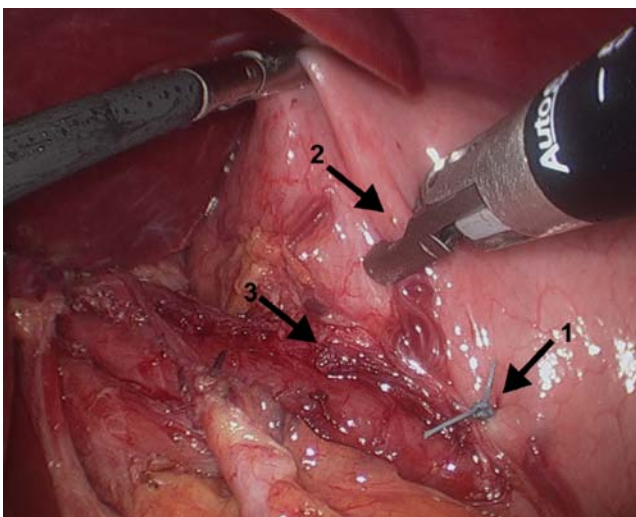
dysphagia.[109] The drawbacks of the Toupet fundoplication are the need for circumferential dissection of the gastro-esophageal junction and the possibility that diverticula will develop at the site of the myotomy years after surgery because the fundoplication does not cover the myotomy site.[110]

Proponents of the *Dor fundoplication* argue that the procedure is faster because the posterior esophageal attachments may be left in place.[109] Another advantage is that a properly constructed Dor fundoplication can prevent post operative reapproximation of the myotomy.[111] Furthermore, covering the myotomy with the fundoplication may seal inadvertent mucosal injury and prevent future development of diverticulae at the site of the myotomy. The Dor fundoplication is described in detail elsewhere,[100] and it is described briefly below.

Dor Fundoplication

The creation of the fundoplication begins with a complete mobilization of the fundus of the stomach, including division of the short gastric vessels all the way to the His angle. This dissection is required to permit the creation of the proper geometry of the fundoplication. Two vertical rows of sutures secure the gastric fundus to the left and right edges of the myotomy to create the fundoplication. Initially, the inferior edge of the left side of the esophageal myotomy is sutured to the medial gastric fundus. Then
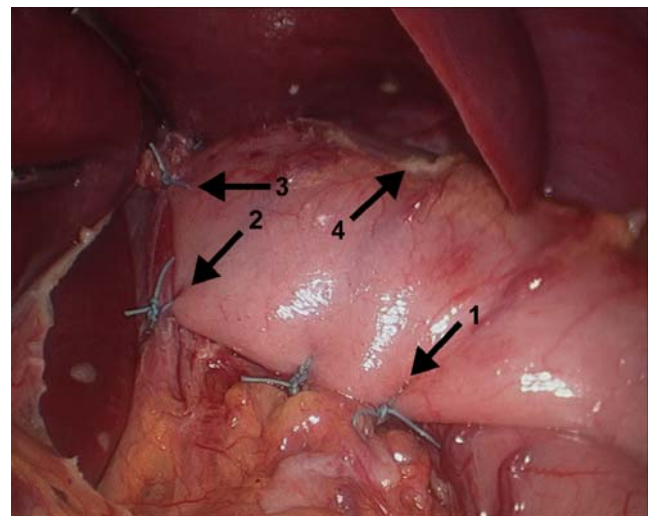

Figure 6 The creation of a Dor fundoplication. The first suture from the anterior portion of the fundus to the left edge of the myotomy (*arrow 1*). The second suture will anchor the fundoplication and part of the myotomy in the abdomen by apposing the fundus (*arrow 2*) to the left crus (not shown) and then to left edge of the myotomy (*arrow 3*).

Figure 7 The completed Dor fundoplication. *Arrows 1 and 2* show the suture line that anchors the fundoplication to the right edge of the myotomy. *Arrow 2* incorporates the fundus, the right crus to the right edge of the myotomy. *Arrow 3* points the suture that secures the fundoplication to the diaphragm. *Arrow 4* points to the divided short gastric vessels that are brought into an anterior position as the fundoplication is created. This reinforces the need for a complete mobilization of the gastric fundus for the proper configuration of the fundoplication.

(Fig. 6), a stitch is placed from a superior portion of the gastric fundus to the left diaphragmatic crus and then the left side of the myotomy about 2 to 3 cm cephalad of the first suture. Two to 3 cm cephalad to the previous suture, a suture secures the left side of the myotomy to the gastric fundus without incorporating the crus. Attention to the geometric arrangement of the fundus produced during this step is important because the reconstructions of the His angle, in addition to having an intra-abdominal GEJ, are what provide the major antireflux barriers. A final suture, again on the left and cephalad to the last, brings the fundus to the left edge of the myotomy, this time just below the myotomy apex.[100]

A suture line is then created down the right edge of the myotomy. The first suture secures the superior right edge of the myotomy to a bite of gastric fundus. The suture line is continued caudally down the right myotomy edge. The second suture incorporates the right diaphragmatic crus to the fundus and the myotomy edge. Two final sutures on the right side bring the fundus to the inferior edge of the myotomy, and the exposed mucosal surface should now be completely covered by the fundus at this point. One or two sutures should then be placed to secure the superior aspect of the fundus to the anterior esophageal hiatus to prevent anterior herniation of the fundoplication into the chest (Fig. 7).

Persistent postoperative dysphagia can be the result of the following technical factors: (1) the myotomy is too short distally, (2) the myotomy is too short proximally, or (3) the fundoplication has been constructed incorrectly. Some patients may develop recurrent dysphagia after a symptom-free interval. This type of failure may be due to gastroesophageal reflux and the development of peptic stricture, healing, and fibrosis of the distal portion of the myotomy.[112]

Treatment of advanced stages of achalasia is somewhat controversial when the esophagus has dilated severely and its course in the chest becomes sigmoidal. Some authors have proposed that the gross pathology of the esophagus is so advanced that it will not respond to myotomy and fundoplication and therefore requires esophageal resection. However, recent studies suggest that these patients may have good outcomes after myotomy and fundoplication, although studies with long-term follow-up are still lacking.[113–115] Esophagectomy may need to be contemplated in selected cases.

Summary

Achalasia is a debilitating motility disorder of the esophageal body and LES. The standard diagnostic workup includes a barium esophagram, esophageal manometry, and diagnostic upper endoscopy. The diagnosis cannot be made without the finding of an aperistaltic esophagus on manometry. Impedance testing and high-resolution manometry may prove to be useful adjuncts in the future because patient characteristics are highly variable at the time of presentation. Achalasia can be treated with pharmacologic therapy, EBTI or ED, or surgery. The treatment course should be selected based on the patient's age, overall state of health, and expectations for recovery. Pharmacologic and EBTI therapy can reduce dysphagia, but unfortunately, symptom relief is often not durable. ED provides a longer interval of symptom relief than EBTI, but dysphagia commonly returns and often requires further intervention. ED was considered first-line therapy for achalasia until the late 1980s, when minimally invasive surgery was introduced. Most centers have since adopted the laparoscopic Heller myotomy with a partial fundoplication as the procedure of choice for treating achalasia. This operation provides durable symptom relief with a low rate of complications and infrequent development of postoperative GER.

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