Achalasia: History

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Introduction

Esophageal achalasia is a primary esophageal motility disorder characterized by the absence of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax in response to swallowing. These abnormalities lead to impaired emptying of food from the esophagus into the stomach with resulting food stasis. Most patients experience severe dysphagia and regurgitation that can lead to aspiration and respiratory problems [1].

The pathophysiology of achalasia involves the selective degeneration of inhibitory neurons of the esophageal plexuses, which are needed for peristalsis of the smooth muscle of the esophageal body, as well as relaxation of the tonic LES. The most common form of achalasia is idiopathic, situation in which the etiology of the degenerative process remains unknown. A similar clinical picture can be present in patients with local or distant cancer (pseudoachalasia) or in patients with Chagas' disease, both characterized by the destruction of the plexuses either by infiltrating tumors or circulating autoantibodies or still by *Trypanosoma cruzi* infection [2].

First Treatments

The first reference to achalasia was in 1679 by the English doctor Thomas Willis (Fig. 1.1) who not only described the disability but also reported a successful treatment. He dilated the esophagus by using a sponge at the end of a whale bone, improving patient's symptoms [3, 4].

There are virtually no reports of achalasia and its treatment in the eighteenth century but at the end of the nineteenth and at the beginning of the twentieth century, coinciding with important improvements in surgical conditions with the advent of aseptic surgery, anesthetics with procedures under mechanical ventilation, as well as better understanding of the pathophysiology [3].

In 1887, over 2 centuries after the remarkable description by Willis, J. C. Russell also in England, placed an inflatable rubber balloon covered with silk at the end of a bougie and blew up the balloon to dilate the stricture [5]. H. Plummer, in 1908, opened the cardia using olive-tipped bougies over a swallowed string. Later he used a hydrostatic dilator to effectively

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M. G. Patti et al. (eds.), *Foregut Surgery*, https://doi.org/10.1007/978-3-030-27592-1_1

relieve symptoms by rupturing the constricting circular muscle fibers. The satisfactory results obtained with dilatation by pneumatic or hydrostatic balloon gave rise to the idea of proceeding to surgical dilation, which could be done under direct vision and not blind [6].

In 1904, Mikulicz, by an abdominal incision, inserted a rubber sheath forceps through a gastrostomy opening and dilated the cardia from below (Fig. 1.2). Barrow, in 1915, used the technique of digital dilation, invaginating the anterior wall of the stomach avoiding the opening of the organ. This technique was later adopted by Kümmel in 1921. Anschütz (1921) dilated the cardia with a balloon but opened the abdomen to correctly place it.

Also procedures to reduce the size of the dilated esophagus such as those of Ressinger (1907) and Meyer (1911) or shortening of the organ by invagination as proposed by Tuffier (1921) and Freeman (1923) gave poor results [6].

Fig. 1.1 Thomas Willis (1621–1675)

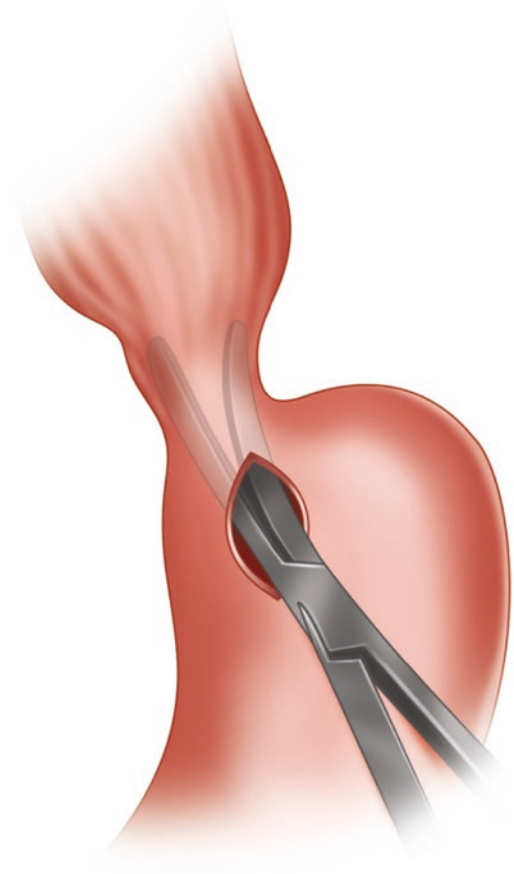

Fig. 1.2 Mikulicz's technique

Operations on the Cardia

Cardioplasties/Cardiectomies

With the observation that the point of obstruction to the progression of food was located in the cardia and with the improvement of the conditions in which the operations were performed, several procedures began to appear for the treatment of achalasia. Cardioplasty began with the operation of Wendel (1909), inspired by the Heineke-Mikulicz pyloroplasty. It consisted of a longitudinal incision of all layers of the wall at the esophagogastric junction and closure of the opening in a transverse direction (Fig. 1.3).

Another type of cardioplasty used by many surgeons was that described by Heyrowsky

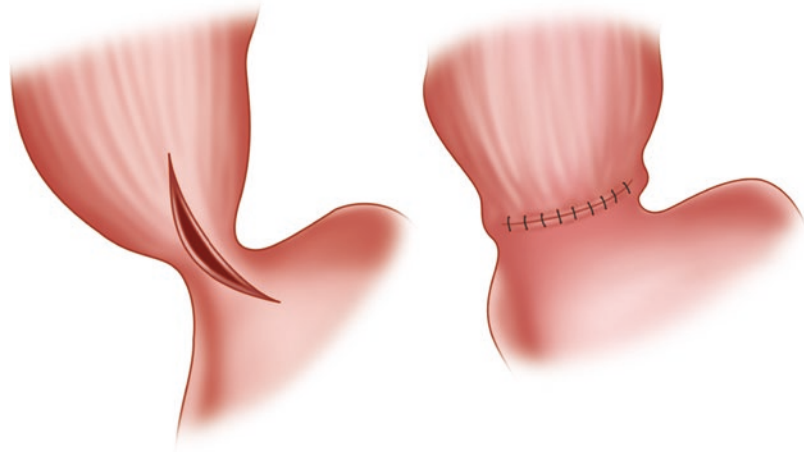

Fig. 1.3 Wendel's technique: It consisted of a longitudinal incision of all layers of the wall at the esophagogastric junction and closure of the opening in a transverse direction

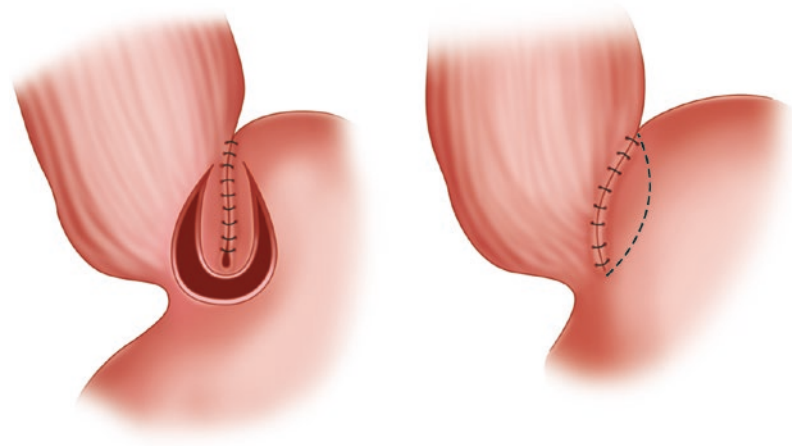

Fig. 1.4 The Backer-Gröndhal technique: the longitudinal incision was replaced by a curved incision passing through the esophagogastric junction

(1913), which consisted of an anastomosis of the lateral wall of the distal esophagus with the gastric fundus. This, however, was associated with retention of food between the lateral esophagogastric anastomosis and the cardiac orifice. The most widespread variant to correct such problem was described by Backer-Gröndhal (1916), in which the longitudinal incision was replaced by a curved incision passing through the esophagogastric junction (Fig. 1.4) [6].

The immediate result of the cardioplasty was satisfactory from the clinical point of view, with improvement or even disappearance of the regurgitation and dysphagia. However, long-term follow-up of the patients operated showed reflux esophagitis, which was particularly severe because of the lack of peristalsis to clear acid refluxed from the stomach, with a long contact time with the esophageal mucosa [6].

Authors such as Thal (1965), Frejat (1974), and Guarner and Gaviño (1983) proposed the association of various cardioplasty with a fundoplication or developed procedures that created valvular mechanisms in the gastro esophageal area. Serra Dória et al. (1968), aiming to solve the problem of reflux esophagitis in megaesophagus operated patients, associated Gröndhal's cardioplasty with the subtotal gastrectomy with Roux-en-Y transit reconstitution [7] adapting the Holt and Large operation for stenosis.

Authors such as Bier (1920), Radlinski (1936), and Wangensteen (1951) proposed resection of

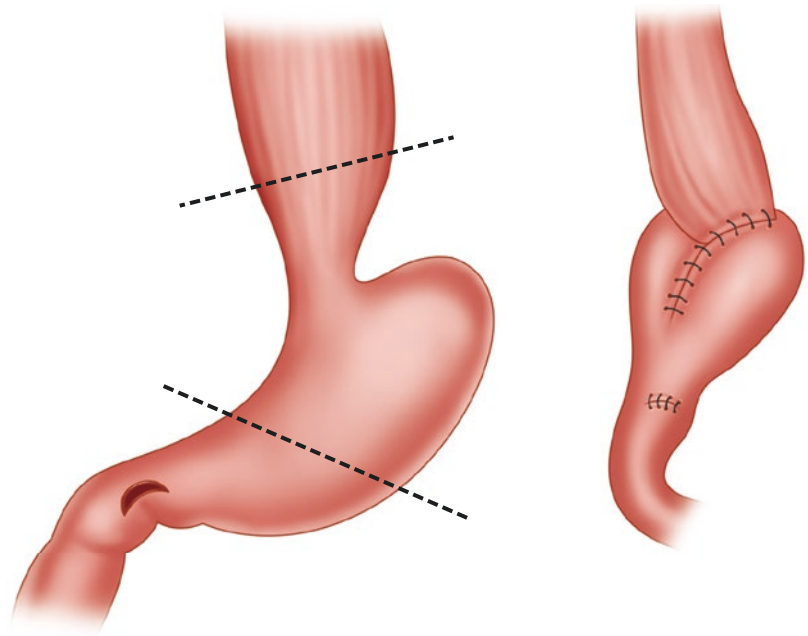

Fig. 1.5 Resection of the cardia and esophagogastrostomy

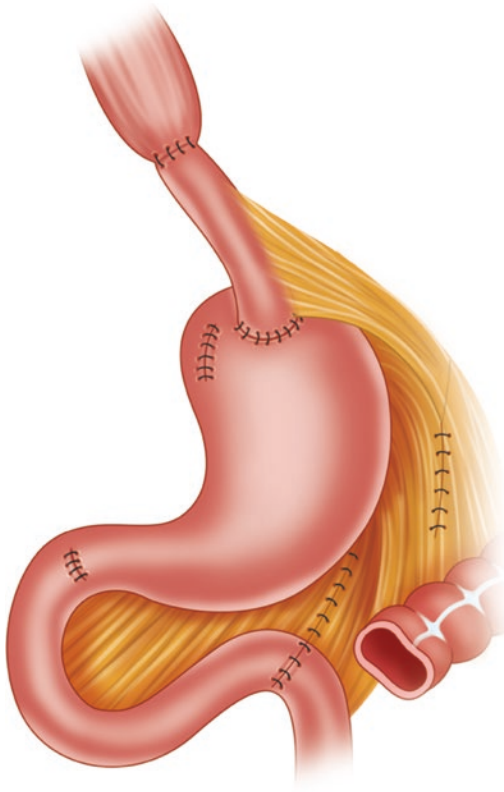

Fig. 1.6 Merendino technique: resection of the esophagogastric junction with intestinal interposition

the cardia and esophagogastrostomy as a therapeutic modality for this disease, with encouraging initial results but with the disadvantages of a high-risk resection and anastomosis for that time (Fig. 1.5). Others, like Merendino and Dillard (1955), adopted the resection of the esophagogastric junction with intestinal interposition (Fig.1.6) [8, 9].

Myotomy

In 1913, Ernst Heller (Fig. 1.7) introduced an operation consisting of a posterior and anterior myotomy, extending from 2 cm above the constrictions down over the cardia (Fig. 1.8). Despite the simplicity of execution and its efficacy, the cardiomyotomy was not immediately accepted as a solution for the surgical treatment of achalasia, and surgeons, mainly in Germany where Heller worked, continued to prefer cardioplasty [10]. Several modifications of Heller's original technique were proposed. The first of these is credited to Girard (1915) and consisted of closing the incision transversely as in Heineke-Mikulicz pyloroplasty. Groenveldt, in the Netherlands, proposed performing only one incision in the

Fig. 1.7 Ernst Heller (1877–1964)

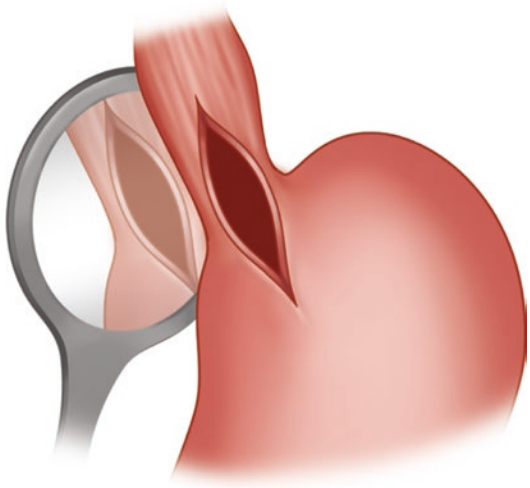

Fig. 1.8 Heller's technique: posterior and anterior myotomy, extending from 2 cm above the constrictions down over the cardia

anterior wall of the esophagus, obtaining results equivalent to those of the double incision of Heller (Fig. 1.9).

Although the incidence of postoperative reflux esophagitis is lower with cardiomyotomy than

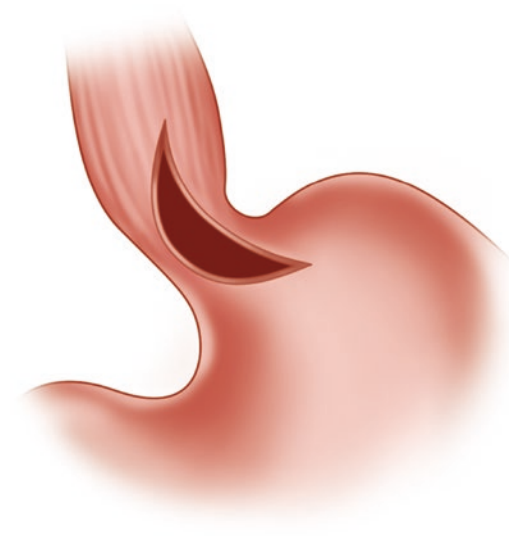

Fig. 1.9 De Bruine Groenveldt's technique: performing only one incision in the anterior wall of the esophagus

with classic cardioplasties, the number of patients presenting with this complication was still significant, which led surgeons to complement the myotomy with some antireflux procedure.

Lortat-Jacob (1953) was the first to emphasize the accentuation of the angle of His for the prevention of reflux in patients who underwent a cardiomyotomy, recommending the fixation of the gastric fundus to the left border of the esophagus. Dor et al. (1962) from Marseille described a partial fundoplication technique covering the area of the myotomy. Toupet (1963) described an analogous operation, which differs from Dor's operation by performing a fixation of the gastric fundus on the posterolateral side of the esophagus and not on the anterior face associated with its fixation to the diaphragm.

Jekler and Lhotka (1967) modified Dor's technique, adding to it the fixation of the gastric fundus to the esophagus, 1–2 cm above the superior commissure, in order to further accentuate the angle of His (Fig. 1.10). Pinotti et al. (1974) developed a posterolateral anterior procedure enveloping the esophagus in about two-thirds of its circumference [11].

In 1991, Cuschieri's group from the University of Dundee, United Kingdom, reported the first laparoscopic Heller myotomy (LHM) [12], which

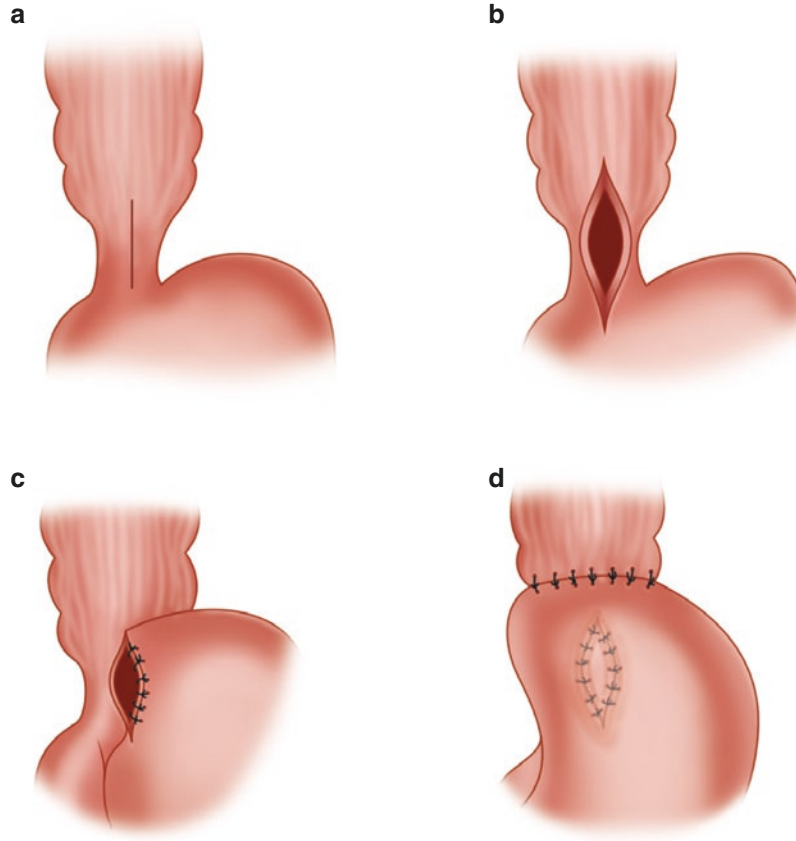

Fig. 1.10 Jekler and Lhotka's technique: fixation of the gastric fundus to the esophagus, one to two cm above the superior commissure, in order to further accentuate the angle of His. (**a**) Myotomy. (**b**) Esophagostomy. (**c**) Fixation of the gastric fundus to the esophagus. (**d**) Tranversal closure of the anastomosis

brought improvements due to the advantages of this surgical access route such as shorter hospitalization time, early mobilization, and absence of extensive abdominal scarring.

In 1992, Pellegrini et al. from the University of California, San Francisco, described the results of 17 patients who underwent a left thoracoscopic myotomy with excellent relief of dysphagia [13]. However, the thoracoscopic approach had significant drawbacks such the need for a double lumen endotracheal intubation to exclude the left lung, the need for a chest tube, and the inability to add a fundoplication to prevent reflux. The same group later compared the results for thoracoscopic myotomy versus laparoscopic myotomy with a Dor fundoplication. Similar results were found in regards to resolution of dysphagia, but with remarkable superiority of laparoscopy considering regarding the incidence of postoperative reflux (from 60% to 17%) [14].

LHM for esophageal achalasia continues to present excellent results today, as demonstrated by Zaninotto et al. [15] that studied more than 400 patients who underwent LHM and Dor fundoplication and reported a 90% success rate at a median follow-up of 30 months. A recent European multicenter randomized trial [16] showed a success rate of 84% after 5 years of LHM, and another randomized trial [17] found that at a follow-up of 5 years, only 8% of the patients after LHM had recurrence of symptoms.

More recently, achalasia surgery has been performed in the robotic-assisted way [18]. Advantages of robotic-assisted surgery include improved visibility of the operative field with three-dimensional imaging, increased degrees of freedom of surgical movements, and improved ergonomics. Retrospective studies [19–21] have shown that with this technique there are lower rates of esophageal mucosa perforations, with success rates similar to conventional LHM. On

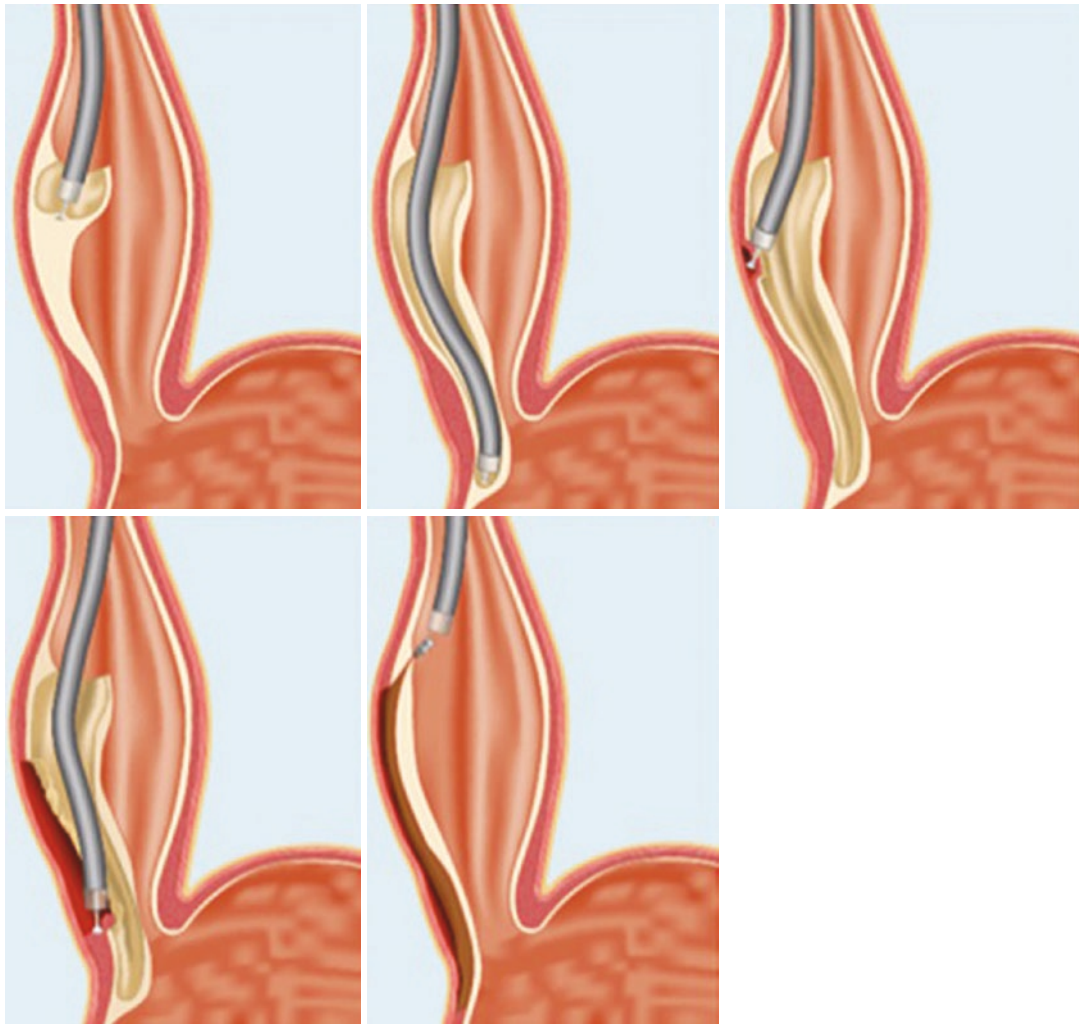

Fig. 1.11 POEM technique. (Reprinted with permission ©Georg Thieme Verlag KG [24])

the other hand, a multicenter retrospective analysis of a large administrative database including 2116 laparoscopic myotomies and 149 robotic myotomies showed comparable results between both groups, but increased costs in the robotic cohort [22].

Already described by Ortega in 1980 [23], per-oral endoscopic myotomy (POEM) was rediscovered and fairly widespread by Inoue et al. in 2010 [24]. It is a procedure similar to that of Heller but performed according to precepts of the natural orifice transluminal endoscopic surgery (NOTES), with good immediate results (Fig.1.11).

With the current literature data, we observed again that although both LHM and POEM present good results in the resolution of dysphagia, reflux-disease incidence appears to be also significantly more frequent after POEM than after LHM with fundoplication [25].

Esophagectomy

In the same year of 1913 that Heller performed his first myotomy, two surgeons described different ways to perform an esophagectomy: Torek, a German surgeon, performed in New York a transthoracic esopha-

gectomy, and Von Arch, a German surgeon in Munich, a transmediastinal esophagectomy [26]. Pinotti (1977) [27] added the transection of the diaphragm for a better exposure of the mediastinum, a technique useful to treat the advanced megaesophagus.

Orringer (1982) [28, 29] proposed esophagectomy as definitive treatment for esophageal neuromotor dysfunction, with good results obtained in 22 patients operated mostly by transmediastinal route with a follow-up of 25 months [29].

Even today, an esophagectomy is still a complex procedure linked to high morbidity and mortality, as recently shown by a meta-analysis (27.1% morbidity rate and 2.1% mortality rate) [30]. Thus, an esophagectomy should be a last resort and should be reserved to patients who have been symptomatic for a long time and who have failed other treatment modalities such as PD, LHM, and POEM.

Pharmacological Treatment

Pharmacologic agents include smooth muscle relaxants, such as long-lasting nitrates and calcium channel blockers, and 5′-phosphodiesterase inhibitors. Since achalasia is a disease characterized by impaired release of nitric oxide (NO) from inhibitory neurons, the rationale for the use of these agents consists in the enhancement of the residual neural inhibitory function in the esophageal wall [31].

The first drug used to treat dysphagia by decreasing LES pressure in the 1940s was nitroglycerin. In the early 1980s, nifedipine, a calcium channel blocker, was used as well in the treatment of achalasia [32]. These drugs act by blocking the action of calcium that is necessary for the contraction of the esophageal smooth muscle cells. However, both types of drugs do not improve LES relaxation or esophageal motility.

More recently, the use of sildenafil, a 5′-phosphodiesterase inhibitor, has been proposed [33]. This agent has an inhibitory action on the 5′-phosphodiesterase that inactivates the NO-stimulated cGMP, thus increasing the intracellular levels of cGMP and therefore promoting the relaxation of the smooth muscular cells.

All these medications, however, are associated with poor clinical results and several side effects, and their use is currently reserved for patients with advanced age or significant comorbidities [34, 35].

Endoscopic Management

Pneumatic Dilatation

Although it has been used since the description of the disease, forced dilatation of the esophagus to treat achalasia showed great progress in the 1980s when it began to be guided by endoscopy.

Pneumatic dilatation (PD) using controlled pneumatic pressure devices (30, 35, and 40 mm in diameter) is the most effective non-surgical treatment for achalasia. The clinical response in terms of dysphagia relief to a single PD session is 85% at 1 month, 66% at 12 months, 50% at 5 years, and 25% at 10 years [36].

Literature data showed dysphagia relief with PD comparable to LHM. There is, however, a need for multiple PD sessions in a considerable number of cases. Boeckxstaens et al. [37] published the results of a European multicenter trial comparing the results of PD to the outcome of LHM and Dor fundoplication. After 2 years, therapeutic success was similar between the two groups, obtained in 86% of PD patients and 90% of LHM patients. In 2016, Moonen and colleagues [16] reported the results of the 5-year follow-up. In the full analysis, there was no significant difference in the success rate between PD (82%) and LHM (84%). Redilatation was performed in 25% of PD patients. Esophageal perforation is the most serious complication after PD, with an overall rate reported in the literature around 2%.Esophageal reflux occurs in a higher rate as compared to LHM [38].

Endoscopic Botulinum Toxin Injection

Described in 1993, endoscopic botulinum toxin injection (EBTI) has since been used to treat achalasia [39]. The toxin acts by decreasing LES pressure through the inhibition of the release of acetylcholine in the cholinergic synapses.

Table 1.1 Treatment algorithm for naïve achalasia based on Chicago Classification

Type I or II achalasia		Type III achalasia	
Pneumatic dilation	Heller myotomy	POEM	POEM
Less morbidity/cost	Equal to PD in RCT	Highly effective in short-term RCT	Only procedure to adequately cut the length of the spasms
Expect repeated dilations over year	Effective across all ages/genders	Minimal pain	Avoids chest operation
Equal to HM in RCT	Preferred with megaesophagus, diverticulum, or hiatal hernia	Lots of GERD (>50%)	Superior to PD and HM
Older women may do best	More GERD	Insurance issues	Insurance issues
Minimal GERD			

HM Heller myotom, *RCT* randomized controlled trial, *GERD* gastroesophageal reflux disease, *PD* pneumatic dilatation, *POEM* per-oral endoscopic myotomy

The effect of EBTI progressively diminishes over time, with more than 60% of patients experiencing recurrent symptoms after 1 year [40]. EBTI needs to be repeated in most patients to achieve some benefits that, however, are of short duration due to the regeneration of the axons and the development of antibodies. In a meta-analysis published in 2009, Campos et al. confirmed the decreasing efficacy overtime of the EBTI [38]. Among patients who were treated with EBTI, symptoms relief was present in 70% after 3 months, 53% after 6 months, and 41% after 12 months, and almost 50% of patients required a second EBTI.

Thus, currently EBTI should be only considered in patients with advanced age or significant comorbidities who are not candidates for LHM or POEM.

Current Situation

After all this historical evolution, it is currently accepted that all achalasia patients in good clinical condition should undergo PD, LHM or POEM (Table 1.1). Pharmacological therapy (smooth muscle relaxants, such as long-lasting nitrates and calcium channel blockers, and 5′-phosphodiesterase inhibitors) and/or endoscopic Botox injection (EBTI) should be considered only in patients with advanced age or significant comorbidities who are not candidates for LHM or POEM. Patients who have failed initial treatment should be referred for pneumatic dilatation. If symptoms persist, it is reasonable to consider POEM for those who underwent LHM initially and LHM for those who underwent POEM first. Esophagectomy should be reserved for patients who have failed all these previous interventions [41].

Conflict of Interest The authors have no conflicts of interest to declare.

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