Developments in the management of esophageal dysfunction

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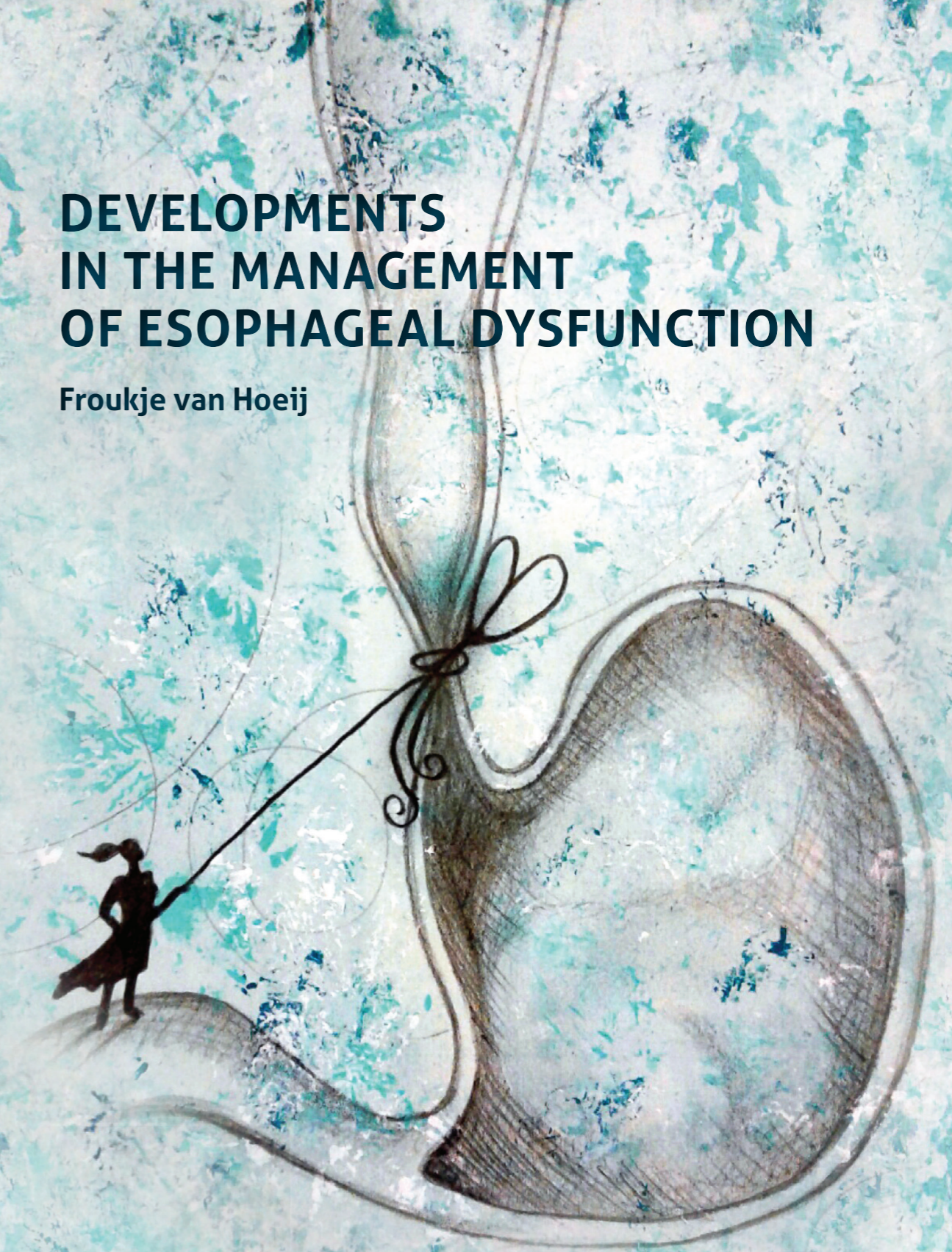
DEVELOPMENTS IN THE MANAGEMENT
OF ESOPHAGEAL DYSFUNCTION

Froukje Bernieke van Hoeij

DEVELOPMENTS IN THE MANAGEMENT
OF ESOPHAGEAL DYSFUNCTION

ACADEMISCH PROEFSCHRIFT

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE

GENERAL INTRODUCTION

Figure 1. Esophageal anatomy. *Used with permission from Rogier Trompert Medical art.*

The esophagus is a tubular organ made up of different layers (fig 1). The inner layer, the mucosa or epithelium, is surrounded by two muscle layers: the circular muscle and the longitudinal muscle.[1] In between those muscle layers are two networks of nerves, the submucosal plexus and the myenteric plexus. The sensory nerves receive (pain) signals from the esophagus, while the motor nerves send signals to regulate muscle contractions.[2]

The esophagus facilitates food bolus passage from the mouth cavity towards the stomach. This passage is enabled by a peristaltic contraction wave propagating the bolus forward, followed by a relaxation of the lower esophageal sphincter (LES) to let the bolus pass into the stomach.[3] During multiple subsequent swallows, the LES will remain relaxed. When there is no bolus passage, the LES will remain in its natural contracted state.[4]

The LES is a thickened region of the circular muscle layer, acting together with the crural diaphragm. Together they form the junction between the esophagus and stomach.[4] The tonic resting pressure of the esophagogastric junction (EGJ) is higher than the intra-

abdominal pressure, to prevent reflux of stomach contents towards the esophagus. During acute abdominal pressure increase (coughing, sneezing, etc), as a reflex, the striated muscle of the crural diaphragm will contract, creating a pressure increase. The peristaltic movements and LES contraction and relaxation are called: the motor function or motility of the esophagus.[3, 4] Esophageal dysfunction occurs when the esophageal peristalsis and/or the action of the EGJ is disturbed.

A variety of disorders is caused by esophageal dysfunction, and this thesis covers three of them: gastroesophageal reflux disease (GERD), achalasia and esophagogastric junction (EGJ) outflow obstruction. All three diseases can cause various symptoms, including chest pain, regurgitation and/or dysphagia.[5, 6] Due to the overlap in symptoms, it remains challenging and often requires multiple diagnostics to distinguish these three diseases. Our major goal was to uncover the pathogenesis and improve treatment strategies of these diseases. Therefore, in part I of this thesis, we aimed to improve our understanding of 1) symptom generation in GERD, 2) the role of manometry in diagnosing GERD. And in part II of this thesis we evaluated 3) efficacy and safety of achalasia treatments, and 4) the long-term management of achalasia and EGJ outflow obstruction.

PART I GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is one of the most common diseases in Western countries.[7] It is diagnosed when reflux of stomach content causes troublesome symptoms and/or complications. It is a multifactorial disease, partially caused by overweight, hiatus hernia, smoking, alcohol and a low LES pressure, but also by increased esophageal sensitivity to acid.[8, 9] Due to chronic reflux, the mucosal layer of the esophagus can become progressively damaged, eventually enabling the refluxed stomach content to reach the sensory nerves, causing pain.[9] The exact role of sensitivity to acid and the integrity of the mucosa in symptom generation in GERD, however, are not completely understood (**Chapter 2**).

Diagnosis

Gastroesophageal reflux disease can cause a variety of symptoms. Typical GERD symptoms are regurgitation and heartburn, but it can also cause chest pain, cough and dysphagia.[10] During upper endoscopy, reflux-induced esophagitis is seen in a minority of patients. At least half of the patients however, have no esophagitis but so-called non-erosive reflux disease.[11] The gold standard for diagnosing GERD is a 24-hour pH-impedance measurement.[12] Ambulatory pH-impedance measures the acidity and frequency of reflux, and the correlation between reflux symptoms and (acidic) reflux.[12, 13] Gastroesophageal reflux disease is also associated with ineffective esophageal motility and a low LES pressure on high-resolution manometry (HRM), but it is unknown whether it is possible to diagnose GERD with HRM alone, without using other diagnostic tools (**Chapter 3**).

Management

Initial therapy is based on lifestyle interventions (weight loss, head of bed elevation and cessation of tobacco, alcohol and foods that potentially aggravate reflux symptoms).[11] When necessary, acid secretion-inhibiting medication is added, of which proton pump inhibitors (PPIs) are the most effective.[14] In patients with PPI-refractory GERD, anti-reflux surgery is considered.[11, 15] During surgery an anti-reflux barrier is created by wrapping the fundus of the stomach totally (Nissen fundoplication) or partially (Toupet fundoplication) around the distal part of the esophagus.[11]

PART II Achalasia AND RELATED DISORDERS

Esophageal achalasia is a chronic and benign motility disorder of the esophagus. There is absent or abnormal peristalsis in the esophagus, in combination with a non-relaxing lower esophageal sphincter (LES).[16, 17] This causes slowly progressive dysphagia to liquids and solids, regurgitation of undigested food and chest pain.[17, 18] In achalasia, the motility abnormalities in the esophagus result from progressive degeneration of neurons in the myenteric plexus.[19] The underlying etiology is not completely elucidated, but the most widely accepted theory is an autoimmune response triggered by an unknown viral infection in genetically susceptible persons.[20, 21]

Achalasia is a very rare disease with a prevalence of 10 per 100.000 individuals.[22] The most common age of onset is 30 – 60 years and the life expectancy of achalasia patients is normal.[22, 23] Epidemiological knowledge on achalasia is scarce, and the cost of long-term treatment and follow-up is largely unknown (Chapter 4).

Diagnosis

In patients with achalasia, during upper endoscopy, a dilated, atonic esophagus is seen, with retained fluid and a very tight LES. High-resolution manometry (HRM) is the gold standard for diagnosing esophageal motility disorders.[24] A catheter with pressure sensors measures the esophageal motor function throughout the whole esophagus and LES continuously.[25] In achalasia, a continuously high pressure in the lower esophageal sphincter is measured, with absence or impairment of swallow-associated relaxation.[16, 26] Achalasia subtypes are differentiated by absent contractility (type I), panesophageal pressurization (type II) or spastic contractions (type III).[27] Timed barium esophagography is a contrast radiography to evaluate structural and functional abnormalities of the esophagus, and EGJ.[28] In achalasia, aperistalsis, a dilated esophagus and narrowing of the esophagogastric junction, with poor esophageal emptying of the barium into the stomach, can be seen.[28, 29] In late stages a severely dilated, tortuous or sigmoid shaped esophagus is sometimes seen.[23]

Management

The most often used treatments for achalasia are pneumatic dilation, Heller myotomy and peroral endoscopic myotomy (POEM).[18] Other options are botulinum toxin injections and stent placement. Medications have fallen out of use due to lack of effect.[16, 17, 30] All these therapies have their own advantages and disadvantages and success of different therapies appears to be dependent on individual patient characteristics.[18]

In pneumatic dilation for achalasia treatment, the non-relaxing lower esophageal sphincter is dilated forcefully with a balloon to restore the esophageal clearance.[16] During upper endoscopy, a guidewire is placed in the stomach, via the esophagus and the LES. Next, a balloon is placed over the guidewire in the lower esophageal sphincter (fig 2).[31] This balloon is inflated for one or two minutes, stretching the sphincter. Often, this treatment has to be repeated. Different balloon sizes, inflation pressures and number of dilations can be performed, all leading to different success rates.[32] It is unknown which treatment protocol for pneumatic dilation is the most efficient and safe (**Chapter 5**).

Botulinum toxin injections can also be used in achalasia and related spastic esophageal motility disorders.[33] Botulinum toxin inhibits acetylcholine release from cholinergic neurons, preventing neuromuscular conduction, thus relaxing the smooth muscles.[34] Botox injections are not regularly used however, because of the short-lived effect, despite the fact that botox is regarded the safest treatment option, especially in older patients or patients with comorbidities or not fit for surgery.[35] In isolated cases severe side-effects have been reported and there are still insufficient data from large cohorts, to confirm that this is in fact the safest treatment for achalasia (**Chapter 6**).
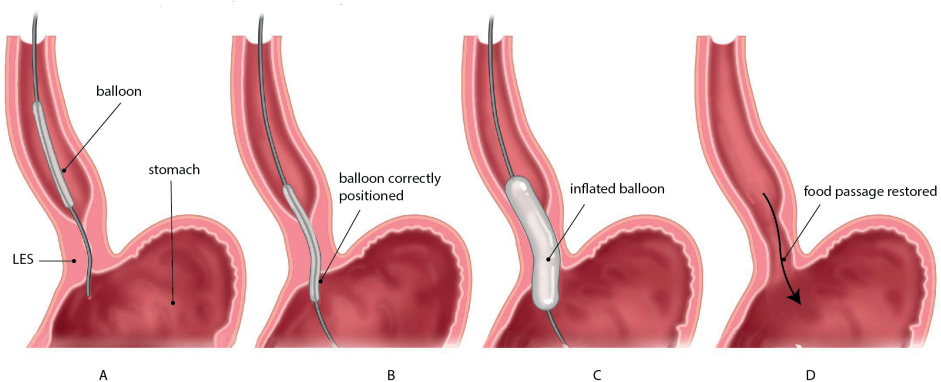
Figure 2. Pneumatic dilation of the lower esophageal sphincter. Used with permission from Ron Slagter.

A surgical (Heller) myotomy and peroral endoscopic myotomy (POEM) are regarded the most permanent and effective treatment options for achalasia.[18] In both procedures, the lower esophageal sphincter is cut to enable food passage. In the Heller myotomy this is done via the abdomen.[36] POEM was invented in 2010 and studies show that it is a very safe and effective treatment.[37, 38] Figure 3 shows the steps of the POEM: first a submucosal bleb is created (A), next a tunnel is made between the mucosal layer and the muscle layers (B and C).
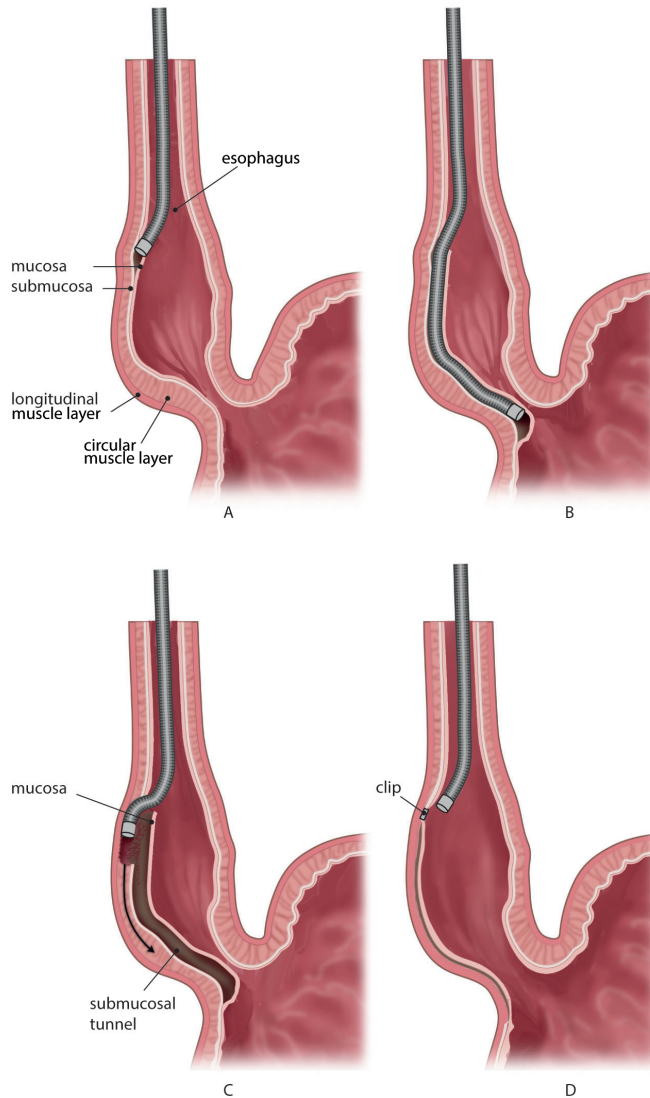
Figure 3. Peroral endoscopic myotomy (POEM). Used with permission from Ron Slagter.

Then, the LES muscle layers are cut (D and E) and last, the entrance of the tunnel is closed with clips (F).[37] Gastroesophageal reflux is a very common finding after POEM.[39] Reflux can cause erosive esophagitis, which is associated with peptic strictures, Barrett's esophagus and a higher risk of esophageal carcinoma.[40] It is important but very challenging to identify patients with reflux esophagitis, because they often have no symptoms (**Chapter 7**). Furthermore, because POEM is a relatively new treatment, there are no guidelines yet on how to treat patients with persisting or recurrent achalasia symptoms after POEM (**Chapter 8**).

When to re-treat patients

Achalasia is a chronic disease, which cannot be cured. All treatments are symptomatic, therefore often multiple treatments are needed.[18] After initial treatment, symptoms of achalasia do not correlate very well with esophageal emptying and pressure in the lower esophageal sphincter.[41] This creates a subgroup of patients with few symptoms but significant stasis, which could develop esophageal dilation and mega-esophagus at the long term.[23] If this would be the case, pre-emptive treatment of asymptomatic patients with poor esophageal emptying should be considered. There is no consensus however, on follow-up of these patients, whether or not to pre-emptively treat these patients, and whether these patients will experience earlier symptom recurrence than patients without stasis (**Chapter 9**).

EGJ outflow obstruction

EGJ outflow obstruction is a disease very similar to achalasia. This disease is characterized by a non-relaxing lower esophageal sphincter, as in achalasia.[26, 42] The difference with achalasia, is that there is normal peristalsis in EGJ outflow obstruction.[26] Patients experience dysphagia and sometimes regurgitation or chest pain, due to the non-relaxing LES.[42] The clinical relevance of this disease is largely unknown and choice of treatment remains therefore very challenging (**Chapter 10**).[42, 43]

OUTLINE

The main focus of this thesis is the diagnosis and management of esophageal dysfunction, specifically gastroesophageal reflux disease (GERD), achalasia and esophagogastric junction (EGJ) outflow obstruction. To optimize the management of these disorders, we aimed to evaluate 1) symptom generation in GERD, 2) the role of manometry in diagnosing GERD, 3) efficacy and safety of achalasia treatments and 4) the optimal long-term management of achalasia and EGJ outflow obstruction.

The first part of this thesis focuses on diagnosis of GERD. In **chapter 2** the role of acid sensitivity and mucosal integrity in GERD is studied. In **chapter 3** functional abnormalities in GERD are evaluated using high-resolution manometry.

The second part of this thesis focuses on epidemiology and treatment of achalasia and related disorders. In **chapter 4** the epidemiology and cost of achalasia in the Netherlands is described. **Chapter 5** is a meta-analysis, aiming to find the optimal pneumatic dilation protocol. In **chapter 6** side-effects and complications of esophageal botulinum toxin injections are described. In **chapter 7** a prediction model is presented for the most common side-effect of peroral endoscopic myotomy (POEM), being reflux esophagitis. In **chapter 8** we examined treatment options for patients with recurrent symptoms after POEM. **Chapter 9** describes how to manage patients with persisting esophageal stasis after achalasia treatment. In **chapter 10** patients with EGJ outflow obstruction are described, aiming to find the best management options for these patients. **Chapter 11** is the general discussion, in which different diagnostic options for GERD, and treatment options for achalasia, and EGJ outflow obstruction, are compared.
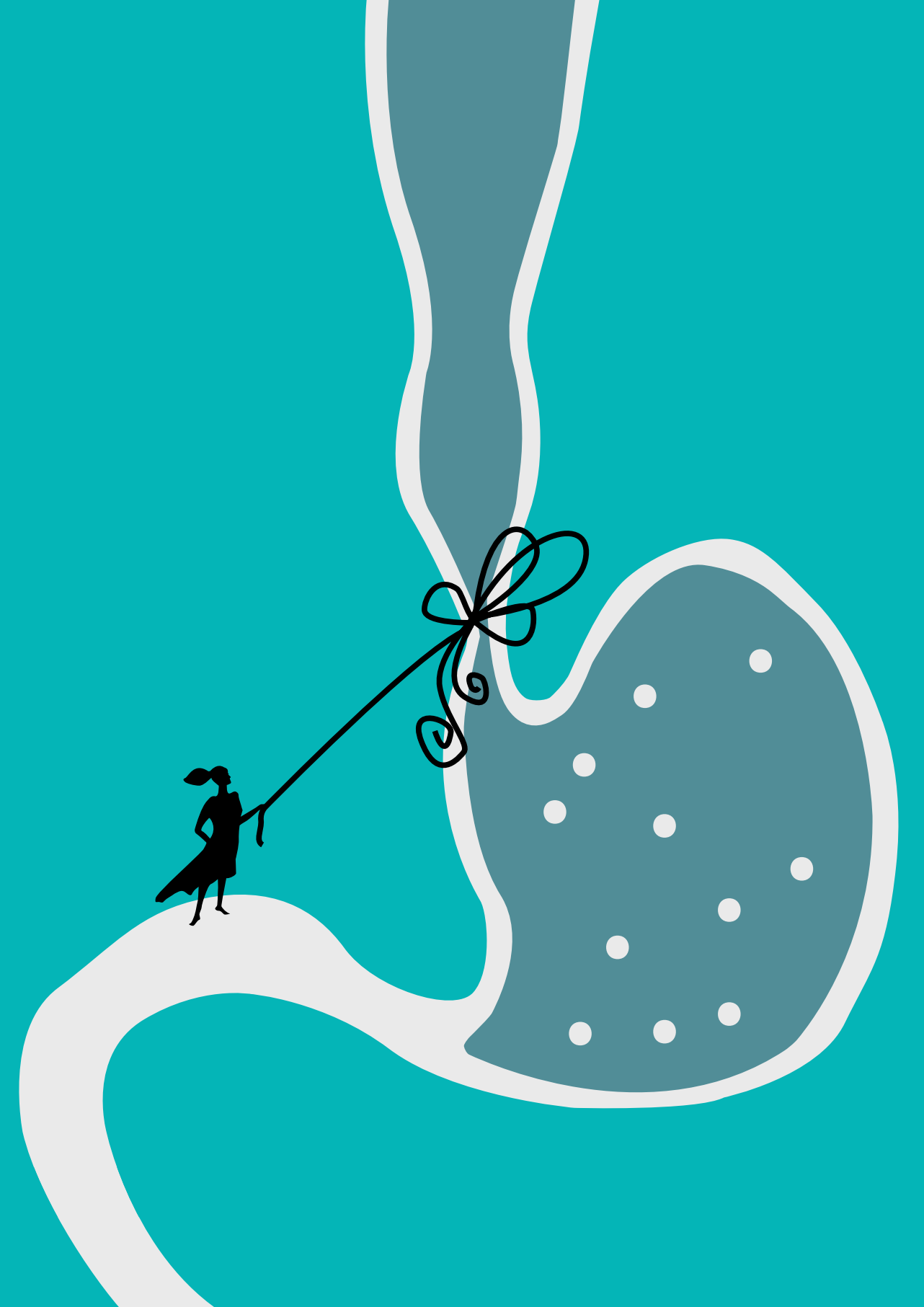
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PART

GASTROESOPHAGEAL REFLUX DISEASE

CHAPTER 2

MUCOSAL INTEGRITY AND SENSITIVITY TO ACID IN THE PROXIMAL ESOPHAGUS IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

Background

Acid reflux episodes that extend to the proximal esophagus are more likely to be perceived. This suggests that the proximal esophagus is more sensitive to acid than the distal esophagus, which could be caused by impaired mucosal integrity in the proximal esophagus. Our aim was to explore sensitivity to acid and mucosal integrity in different segments of the esophagus.

Methods

A prospective observational study, including 12 patients with gastroesophageal reflux disease. After stopping acid secretion-inhibiting medication, two procedures were performed: an acid perfusion test and an upper endoscopy with electrical tissue impedance spectroscopy and esophageal biopsies. Proximal and distal sensitivity to acid and tissue impedance were measured in vivo, and mucosal permeability and epithelial intercellular spaces at different esophageal levels were measured in vitro.

Results

Mean lag time to heartburn perception was much shorter after proximal acid perfusion (0.8 minutes) than after distal acid perfusion (3.9 minutes); $p = 0.02$. Median in vivo tissue impedance was significantly lower in the distal esophagus (4563 $\Omega \cdot m$) compared to the proximal esophagus (8170 $\Omega \cdot m$); $p = 0.002$. Transepithelial permeability, as measured by the median fluorescein flux was significantly higher in the distal (2051 nmol/cm^2/h) than in the proximal segment (368 nmol/cm^2/h); $p = 0.033$. Intercellular space ratio and maximum heartburn intensity were not significantly different between the proximal and distal esophagus.

Conclusion

In GERD patients off acid secretion-inhibiting medication, acid exposure in the proximal segment of the esophagus provokes symptoms earlier than acid exposure in the distal esophagus, whereas mucosal integrity is impaired more in the distal esophagus. These findings indicate that the enhanced sensitivity to proximal reflux episodes is not explained by increased mucosal permeability.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common chronic disorders, with a prevalence of 10-20% in the western world.[1] GERD is diagnosed when it is proven that reflux of gastric content is causing typical symptoms and/or esophageal mucosal damage.[2] Typical reflux symptoms are heartburn and regurgitation.[3]

In healthy subjects, gastroesophageal reflux occurs several times a day without causing symptoms.[4] Whereas a subset of GERD patients exhibit excessive esophageal acid exposure, most GERD patients do not have excessive reflux but are more sensitive to reflux than healthy subjects. They perceive reflux episodes more readily, even in the absence of esophageal erosions.[5] It is hypothesized that this enhanced esophageal sensitivity for reflux in GERD patients is caused by impaired mucosal integrity.[6] In a healthy esophagus, the squamous epithelium forms an effective barrier against gastric contents. In GERD patients however, an impaired mucosal barrier has been repetitively demonstrated, even in the absence of visible erosions.[7, 8] One of the hypotheses is that impaired mucosal integrity enables the refluxed material to reach the chemosensitive nociceptors easier and faster, resulting in reduced thresholds for pain elicitation.[6, 7]

GERD patients more often have reflux episodes reaching the proximal part of the esophagus than asymptomatic controls.[4, 9, 10] In both controls and GERD patients, proximal reflux generates symptoms more readily than reflux that only reaches the distal esophagus.[10-12] Even during proton pump inhibitor (PPI) treatment, which leads to reflux that is less acidic, proximal reflux episodes are more often associated with symptoms.[13, 14] Based on this evidence, the proximal segment of the esophagus seems to be more sensitive to exposure to gastric content than the distal segment. In the current study we aim to investigate the underlying mechanisms through which gastroesophageal reflux causes symptoms.

Our hypothesis was that the higher acid sensitivity of the proximal part of the esophagus of GERD patients, as compared to the distal esophagus, is due to a more pronounced impairment in mucosal integrity in the proximal part. If this would be the case, then future therapy could be directed at protection of the mucosa. For this reason, we evaluated the acid sensitivity and the mucosal integrity of the proximal and distal segments separately in patients with GERD.

METHODS
Study subjects

This prospective, observational study was conducted in the Academic Medical Center, Amsterdam, the Netherlands. We included patients > 18 years old, with heartburn lasting

more than 12 months, and gastroesophageal reflux disease confirmed by a positive symptom association probability (SAP) > 95% between reflux-specific symptoms and acidic reflux episodes on ambulatory pH-impedance measurement.[15] Patients were recruited at the outpatient clinic of the Motility Center of our hospital. None of the patients had peptic ulcer disease, Barrett's esophagus, history of gastrointestinal cancer or history of upper gastrointestinal tract surgery. All patients gave written informed consent and the study was approved by the Medical Ethics Committee of our hospital.

Sample size

We based our sample size on a previous pilot study by Niemantsverdriet et al. with a similar protocol in healthy volunteers.[12] In their study in 12 subjects they found significantly higher pain scores after proximal esophageal acid perfusion (mean 6.5) compared to distal esophageal perfusion (mean 3.6). When using the measured mean pain scores with the combined standard deviation of 3.1 and a paired 2-sided t-test with a significance level of 5% and a power of 80%, the sample size required to measure a difference in our patient group was 11. To ensure enough power, we included 12 patients.

Study protocol

Patients on PPIs, H_2-receptor antagonists or prokinetic drugs underwent a 10-day pharmacological washout before upper endoscopy because these drugs can mask the effect of acid reflux on esophageal mucosa and can reverse the presence of dilated intercellular spaces (DIS) in the mucosa.[16] For the reduction of severe symptoms, patients were allowed to take rescue medication in the form of antacids. After 7 days of pharmacological washout, patients were asked to fill out the reflux disease questionnaire (RDQ) before an acid perfusion test was performed. Three days later, an upper endoscopy was performed. The RDQ is a 12-item questionnaire assessing the current severity and frequency of 3 GERD-related symptom domains (heartburn, regurgitation and epigastric pain). Each domain is assessed by four questions, all rated on a 5-point Likert scale. The mean RDQ scores thus range from 0 to 5. This questionnaire was translated into Dutch and validated.[17]

Acid perfusion test – Acid sensitivity

Patients underwent an acid perfusion test, according to a previously described protocol.[18, 19] A water-perfused manometry catheter was transnasally placed in the esophagus, with 2 infusion channels at 3 and 18 cm above the lower esophageal sphincter (LES). Through these channels, we perfused hydrochloric acid solution (0.1 N HCl, pH 1) or normal saline (0.9% NaCl, pH 6.5). After a 5-min adaptation period, each segment of the esophagus was perfused for 10 minutes with either a HCl or NaCl solution first and then with the other solution, at a rate of 2.5 ml/min. The sequence of the 4 perfusion periods was randomly assigned and patients were blinded to the nature of the infused solution. During HCl infusion via the proximal channel, bicarbonate (1.4% $NaHCO_3^-$) was infused through

the distal channel, to neutralize the acid in the distal segment. Simultaneous pH monitoring with a catheter with pH electrodes at the infusion sites, ensured that a pH < 4 was achieved at the HCl infusion site and a pH > 4 at the other segment.[12]

During the test, subjects were asked to score the symptom intensity every 2 minutes on a horizontal 100-mm visual analogue scale (VAS) with the extremes labelled 'no pain' and 'worst possible pain'. Furthermore, they were asked to report the first sensation of heartburn, discomfort and pain. When subjects experienced pain, acid infusion was discontinued immediately. The lag time from the start of acid infusion to initial discomfort and the maximum VAS score during acid perfusion were noted. Combining both parameters, the perfusion sensitivity score (PSS) was calculated as (total acid perfusion time - lag time to perception) · maximum VAS.[20]

Upper endoscopy

In each patient, after 10 days of pharmacological washout, an upper endoscopy was performed by one and the same gastroenterologist. After routine inspection of the esophagus, stomach and proximal duodenum, Electrical Tissue Impedance Spectroscopy (ETIS) measurements were performed at 3 cm and 18 cm proximal to the Z-line. Additionally, at each level 5 large mucosal biopsies were obtained with a jumbo biopsy forceps.[21] These biopsies were used to investigate the mucosal permeability in Ussing chambers, and to measure dilation of intercellular spaces using transmission electron microscopy. All biopsies were taken from macroscopically unaffected mucosa.

Electrical tissue impedance spectroscopy – *in vivo* mucosal integrity

Electrical tissue impedance spectroscopy (ETIS) measurements were performed at two levels, in a 4-quadrant fashion, using a dedicated probe (diameter 3.2 mm).[22] The probe with 4 electrodes on the tip (Medical Engineering Section, Royal Hallamshire Hospital, Sheffield, UK) was passed through the working channel of the endoscope and pushed against the esophageal wall with a minimum angle of 30° and with a force that just caused a blanching of the mucosa. Two electrodes on the tip injected an alternating current with a peak magnitude of 20 μA, and the other 2 electrodes measured the potential difference.[22] The impedance was calculated as previously described.[23]

Ussing Chambers – *in vitro* mucosal integrity

To evaluate the hypothesis that sensitivity is related to increased permeability to small molecules, transepithelial mucosal resistance and permeability was analyzed in Ussing chambers. Therefore, 4 mucosal biopsies from both the distal and proximal esophageal segments were immediately immersed in ice-cold oxygenated Meyler buffer. Within 15 minutes, the specimens were mounted in biopsy holders (aperture diameter 2 mm, square area 0.0314 cm^2) in Ussing chambers. Biopsies were kept at 37 °C, in Meyler buffer and continuously gassed with carbogen (95% O_2 - 5% CO_2) (Figure 2.1).

After a 15-minute acclimatization period, the luminal bathing solution was replaced with a modified Meyler buffer containing fluorescein (376 Da, 0.5 mg/ml). The transepithelial flux of fluorescent molecules was measured by sampling the bath at the basolateral side of the biopsy after 0, 15, 30, 45 and 60 minutes. The volume in the basolateral bath was kept constant by adding Meyler buffer. The fluorescein concentration in the samples was measured with a fluorescence plate reader (BioTek Synergy, BioTek, Winooski, VT, USA). Luminal to basolateral fluorescein flux was expressed as $nmol/cm^2/h$.

Furthermore, two sets of electrodes (World Precision Instruments, Berlin, Germany) were used to measure the voltage deflection induced by a bipolar constant current of 20 µA. The transepithelial electrical resistance (TEER) was measured after 0, 15, 30, 45 and 60 minutes throughout the measurement.

Transmission Electron Microscopy – *in vitro* mucosal integrity

Intercellular space between epithelial cells in the basal epithelial layers is considered a measure of mucosal integrity.[8, 16] Two mucosal biopsies, taken at 3 cm and 18 cm above the LES, were immediately immersed in Karnovsky fixative and stored at 4° Celsius for 48 hours. Then tissues were post-fixed with 1% osmiumtetroxide, block-stained with 1% uranyl acetate, dehydrated in dimethoxypropane and embedded in epoxy resin LX-112. With
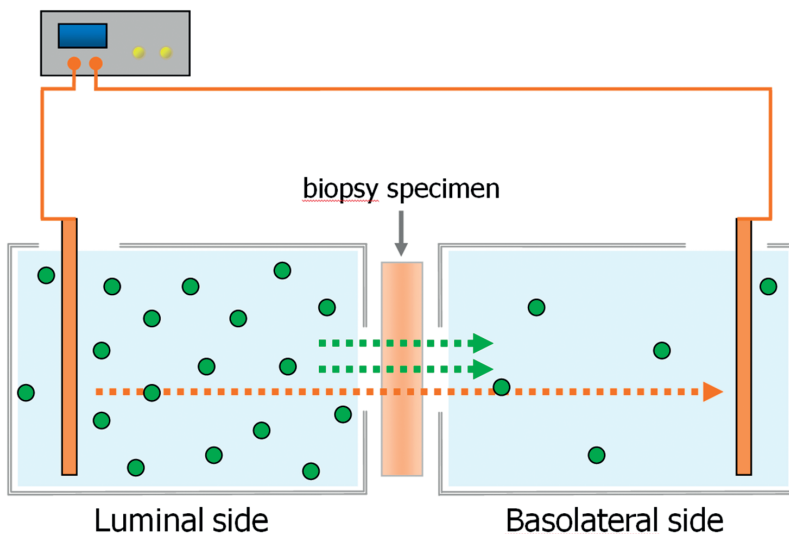
Figure 1. Ussing Chambers. The biopsy specimen is placed in between the two chambers filled with Meyler buffer. The luminal bathing solution contains fluorescein. The transepithelial flux of fluorescent molecules was measured by sampling the basolateral bath. Also, two sets of electrodes connected to a dual voltage clamp were used to measure the voltage deflection induced by a bipolar constant current of 20 µA, also called the transepithelial electrical resistance.

a Philips CM10 transmission electron microscope (FEI Technai G2 Spirit), the laboratory technician, blinded to the origing of the biopsy, took 10 random photographs of each biopsy at the basal layer (magnification 4600x), using a digital transmission EM camera (Morada 10-12, Soft Imaging System, RvC, Soest, NL). Dedicated software was used (Qwin, Leica Microsystems, Wetzlar, Germany) to calculate the intercellular space ratio by dividing the intercellular space surface by the total cell surface (Figure 2.2).[22]

Statistical analyses

We performed all analyses using SPSS Statistics version 22.0 and Graph Pad Prism version 5.0. Normally distributed data are described as number and percentage or mean with range when appropriate. Not normally distributed data are described as median with interquartile range (IQR) or range when appropriate. Lag time to initial heartburn perception was analyzed using survival curves and the log rank (Mantel-Cox) test. Symptom intensity, perfusion sensitivity scores, and intercellular space ratio were compared using the Wilcoxon signed rank test (paired samples). The multiple related measurements obtained for each individual subject with the ETIS probe and with the Ussing experiments were analyzed by calculating a median of the multiple measurements, followed by the Wilcoxon signed rank test (paired samples). A p-value < 0.05 was considered significant.

RESULTS

Subject characteristics

We included 12 GERD patients (8 females), with a mean age of 49 years (range 28 - 66 years). The mean RDQ score was 3.4 out of 5. Seventy-five percent of patients reported
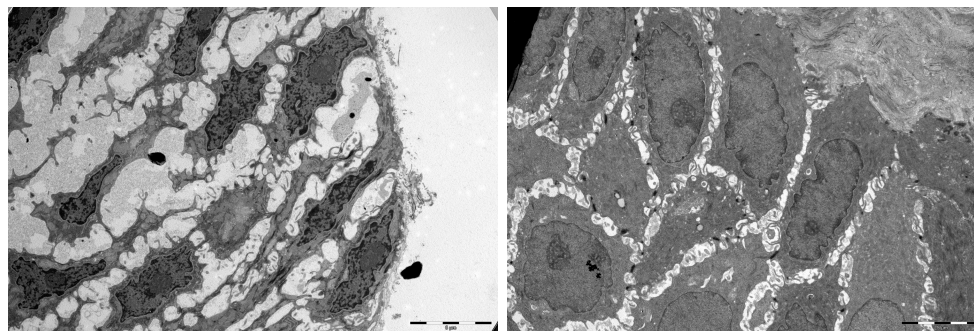
Figure 2. Two electron microscopy pictures of esophageal mucosal biopsies. In the left picture, dilated intercellular spaces (DIS) can be seen, in the right picture, normal intercellular spaces are shown. The basal layer is in both pictures visible on the right.

that they had daily heartburn and regurgitation. Median (IQR) acid exposure time, as measured with 24-hour pH-impedance monitoring off PPI, was 9.7% (8.4 - 14.3%). Median number of reflux events was 134 (IQR 93 - 162). All patients had a symptom association probability (SAP) > 95% for acidic reflux episodes. All patients used PPIs and discontinued PPI use.

Esophageal acid sensitivity

In all patients, the esophageal acid sensitivity test was successfully performed (Figure 2.3). Two out of 12 patients (17%) did not experience heartburn during the test. The lag time to heartburn perception was shorter after proximal acid perfusion (mean 0.8 minutes, 95% CI 0.1 - 1.5) compared to distal acid perfusion (mean 3.9 minutes, 95% CI 2.4 - 5.4); log rank p = 0.02. Maximum heartburn intensity was similar during proximal (median VAS (IQR) 4.0 (1.3 - 7.1)) and distal (median VAS (IQR) 3.5 (1.8 - 6.9); p = 0.638) acid perfusion. There was a trend towards a higher perfusion sensitivity score in the proximal (median (IQR) 40 (11 - 59)) compared to the distal segment (median (IQR) 25 (5 - 41)), p = 0.059.
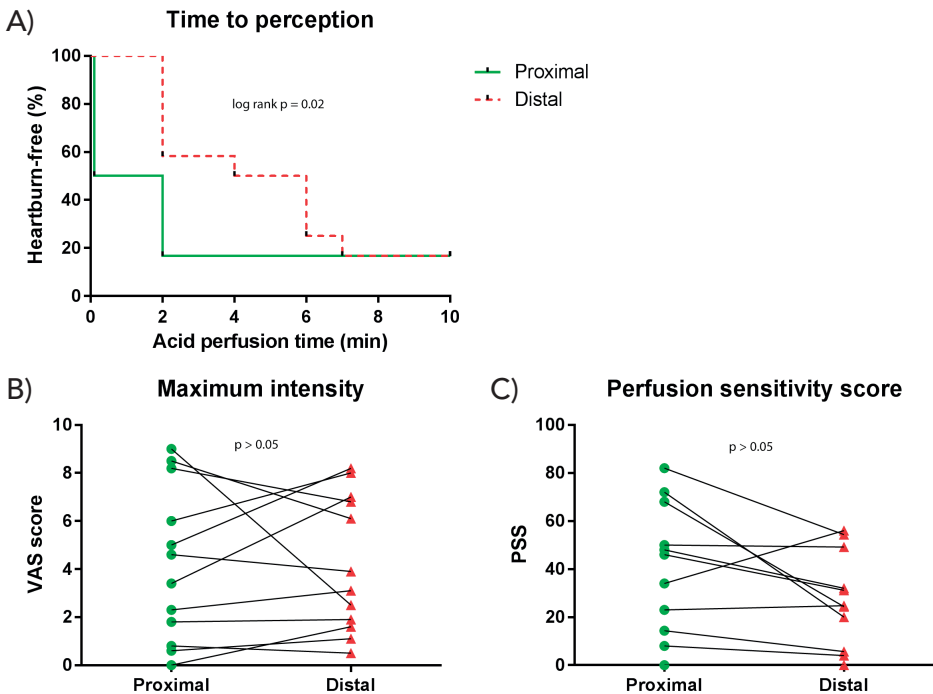
Figure 3. Parameters of acid perception in the proximal and distal esophageal segment of gastroesophageal reflux disease patients, A) Lag time to initial heartburn perception, B) Maximum symptom intensity and C) Perfusion sensitivity score. VAS, visual analogue scale; PSS, perfusion sensitivity score.

Esophageal mucosal integrity and intercellular spaces

Extracellular in vivo tissue impedance (ETIS) and in vitro fluorescein flux were significantly different between the proximal and distal esophagus (Figure 2.4). The tissue impedance was significantly lower in the distal esophagus (median (IQR) 4563 $\Omega \cdot m$ (3640 - 5429)) compared to the proximal esophagus (8170 $\Omega \cdot m$ (7353 - 10110); p = 0.002). Transepithelial permeability, measured by the fluorescein flux, was significantly higher in the distal than in the proximal segment (median (IQR) 2051 (1201 - 3708) nmol/cm^2/h and 368 (0 - 1389) nmol/cm^2/h; p = 0.033. Both are signs of a more impaired mucosal integrity at the level of the distal esophagus. Transepithelial electrical resistance (TEER) was comparable in the proximal and distal esophagus (median (IQR) 133 (92 - 149) Ω/cm^2 and 108 (83 - 146) Ω/cm^2 respectively; p = 0.11).

Intercellular space ratio was not significantly different between the proximal (median (IQR) 0.17 (0.12 - 0.23) and distal esophagus 0.14 (0.10 - 0.26); p = 0.833). In four samples the basal membrane could not be identified in the specimen, hampering orientation and therefore these biopsies were not used for assessment of intercellular space ratio.
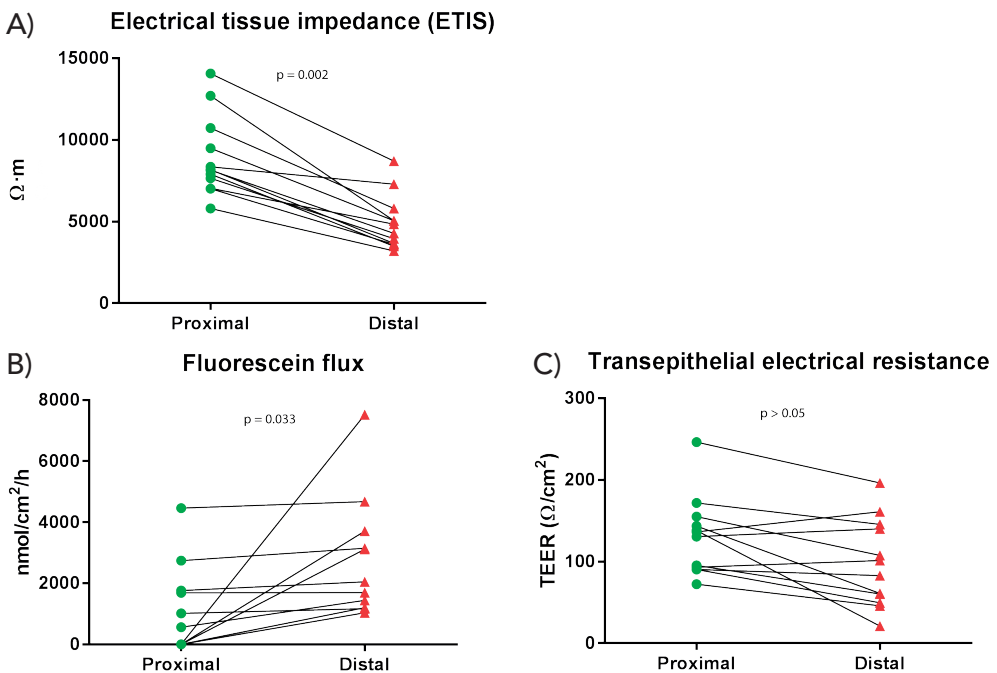
Figure 4. Mucosal integrity represented by A) Extracellular impedance in vivo measured by the ETIS probe, B) Transepithelial fluorescein flux in vitro measured in Ussing chambers and C) Transepithelial electrical resistance in Ussing chambers. ETIS, electrical tissue impedance spectroscopy; TEER, transepithelial electrical resistance.

DISCUSSION

In the present study we demonstrated that in GERD patients the threshold for induction of heartburn by intraesophageal acid perfusion was lower in the proximal than in the distal segment of the esophagus, while mucosal integrity was more impaired in the distal than in the proximal esophageal segment.

Several previous studies have shown that reflux reaching the proximal esophagus is more likely to provoke symptoms than distal reflux, in both GERD patients and controls.[10-12, 24] In addition, it has been found that GERD patients have a higher proximal esophageal acid exposure and longer duration of proximal reflux events than healthy controls[4, 9, 10] and that PPI-refractory GERD is associated with more proximal reflux episodes.[13, 14, 25] Understanding of the mechanisms that underlie the enhanced proximal sensitivity could lead to improvement of GERD treatment. The current study was the first combining the measurement of acid sensitivity and mucosal integrity in the proximal and distal segment separately, in an attempt to explain the underlying mechanism of enhanced sensitivity of proximal reflux.

We hypothesized that GERD patients would be more sensitive to proximal than distal acid perfusion due to more pronounced mucosal integrity changes in the proximal esophagus. Although we confirmed the presence of increased sensitivity to acid at the proximal segment, the mucosa was actually more impaired distally.

From our results, we conclude that the enhanced perception of proximal reflux that is frequently present in patients with GERD cannot be attributed to increased mucosal permeability in the proximal esophagus. Moreover, we think that the enhanced proximal sensitivity is not likely to be due to a larger reflux volume or a lower pH-drop, causing a stronger trigger for exposed nociceptors, as previously suggested.[24, 26] Our results demonstrate that infusion of small volumes of acid in the proximal esophagus lead to faster perception than infusion of similar volumes of acid in the distal esophagus. In our opinion, this makes it less likely that a larger reflux volume is underlying the faster perception of acid in the proximal esophagus. However, it should be noticed that in our study the proximal acid infusion area (3 to 18 centimeters above the LES) is larger than the distal infusion area (3 centimeters above the LES), even though we buffered the distal area during proximal acid infusion. This means that a larger exposed esophageal area or delayed acid clearance can still be a possible explanation for increased sensitivity in the proximal esophagus, but this is also the case in the esophagus after a reflux episode.[27] The results of a recent study suggest that the mucosal afferent nerves are located more superficially than in the distal esophagus. This feature also can be a possible explanation for the observed enhanced sensitivity to acid of the proximal esophagus.[28]

In the current study, we confirmed that, in patients with GERD, mucosal integrity in the distal esophagus is impaired. Only one previous study compared this to the mucosal integrity of the proximal esophagus, in healthy volunteers.[28] We found that the mucosal integrity in the distal esophagus was lower than in the proximal esophagus, which is consistent with their results of a lower baseline impedance and a trend towards a lower TEER in the distal than the proximal esophagus.[28] It is tempting to explain the isolated distal mucosal impairment by the fact that the distal segment is exposed to acid reflux more frequently and for longer periods of time than the proximal segment.[7, 29, 30] However, Farré and co-workers observed that a 30-minute perfusion of acidic or weakly acidic solutions in healthy subjects provoked dilatation of the intercellular spaces not only in the distal but also in the proximal esophagus.[30] Perfusion of a neutral solution did not provoke dilated intercellular spaces.[30] In two other studies, in vitro acid exposure also provoked a significant decrease in transepithelial electrical resistance (TEER) in biopsies of both GERD patients and healthy subjects.[7, 29] When biopsies were pretreated with alginate solution, the drop in TEER was no longer significant.[7] Infusion with both acid and bile salts induced changes that were similar to those induced by acid alone. These findings support the hypothesis that enhanced mucosal permeability in the distal esophagus is provoked by reflux of stomach contents.

Our patients were allowed to take rescue medication in the form of antacids. It is possible that this may have reduced the abnormalities in mucosal permeability. However, no conclusive literature was found regarding the effect of antacids on esophageal mucosal healing. Moreover, prohibiting antacids could introduce selection bias and raise ethical concerns. Based on these methodological objections and the pharmacodynamics, we chose to allow antacid use.[31]

In conclusion, the findings of this study show that, in GERD patients, acid exposure in the proximal esophagus provokes symptoms earlier than acid exposure in the distal esophagus, whereas mucosal integrity is impaired more in the distal esophagus. These observations indicate that the enhanced sensitivity to proximal reflux episodes, characteristic of GERD, cannot be explained by increased permeability of the mucosa in the proximal esophagus.

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CHAPTER

3

PREDICTIVE VALUE OF ROUTINE ESOPHAGEAL HIGH-RESOLUTION MANOMETRY FOR GASTROESOPHAGEAL REFLUX DISEASE

Froukje B van Hoeij, André JPM Smout, Albert J Bredenoord

ABSTRACT

Background

Using conventional manometry, gastroesophageal reflux disease (GERD) was associated with a reduced lower esophageal sphincter (LES) pressure and impaired peristalsis. However, with a large overlap between GERD patients and controls, these findings are of limited clinical relevance. It is uncertain whether the more detailed information of high-resolution manometry (HRM) can discriminate GERD patients. Therefore, we aimed to determine to which extent HRM findings can predict GERD.

Methods

HRM measurements in 69 patients with GERD and 40 healthy subjects were compared and the predictive value of HRM for the diagnosis of GERD was explored.

Results

GERD patients had a significantly lower contraction amplitude (55 vs 64 mmHg; *p*=0.045) and basal LES pressure (10 vs 13.2 mmHg; *p*=0.034) than healthy controls. GERD patients more often had a hiatal hernia than healthy subjects (30% vs 7%; *p*=0.005). Patients with reflux esophagitis had a lower DCI than patients without reflux esophagitis (558 vs 782 mmHg·cm·s; *p*=0.045). No significant difference was seen in CFV, DL, number of peristaltic breaks, residual LES pressure and LES length. On multivariate logistic regression analysis, both EGJ type I (OR 4.971; 95%CI 1.33-18.59; *p*=0.017) and mean wave amplitude (OR 0.95; 95%CI 0.90-0.98; *p*=0.013) were found to be independent predictors of GERD. However, the sensitivity and specificity of these findings were low.

Conclusions

Hiatal hernia, low contraction amplitude and LES pressure are associated with GERD, but do not predict the disease with sufficient accuracy. Routine esophageal HRM can therefore not be used to distinguish GERD patients from healthy subjects.

INTRODUCTION

Impairment of esophageal motility is a common finding in patients with gastroesophageal reflux disease (GERD).[1-3] Using conventional manometry, reduced lower esophageal sphincter (LES) pressure, low peristaltic amplitude and/or impaired peristalsis in the esophageal body are often seen in GERD patients.[3-5] A low LES pressure might facilitate the occurrence of gastroesophageal reflux, while abnormal esophageal peristalsis and lower distal contractions may contribute to impaired esophageal clearance of refluxate.[2, 6, 7] It remains somewhat controversial whether these motility changes are cause or consequence of GERD.[1, 2, 6] In several previous studies, conventional manometry was found unable to serve as a tool for diagnosing GERD.[8-11]

High-resolution manometry (HRM) provides a more detailed assessment of the pressure pattern of the esophageal musculature contractions and the LES function than conventional manometry.[12, 13] This more accurate measurement suggests a better possibility to measure differences in esophageal motor function between GERD patients and healthy persons and perhaps an ability to predict reflux disease.

Until now, few studies have used HRM to characterize esophageal smooth muscle contraction and LES pressure in subjects with GERD. These small studies mostly focused on only one or two parameters and have yielded contradictory results.[14-18] Hypotensive LES, short LES length, ineffective esophageal peristalsis and a longer transition zone have been described in patients with reflux disease.[14-18] Some studies suggest an increasing prevalence of esophageal motility abnormalities with increasing severity of GERD, from non-erosive reflux disease to erosive reflux disease and Barrett's esophagus.[3, 19, 20] However, other studies found no differences in HRM parameters in subjects with GERD compared to healthy subjects.[15, 16]

A comprehensive evaluation of all manometric parameters in the GERD population is essential for a clear judgment of the predictive value of HRM. Therefore, we considered it worthwhile to reevaluate the potential relationship between abnormal HRM findings and pathologic acid exposure. The aim of our study was to evaluate all manometric parameters to explore whether they are different in GERD patients from those in controls and to determine to what extent HRM variables are able to predict GERD.

MATERIALS AND METHODS
Subjects

Routine esophageal HRM was performed in 69 GERD patients (age 52, range 19-80, 34 males) and 40 healthy volunteers (age 35, range 25-64, 23 males). The included

GERD patients all had reflux symptoms of heartburn, regurgitation or chest pain, and a pathological acid exposure. Pathological acid exposure was defined as pH < 4 in > 6% of time over the 24-hour monitoring period, according to previously described criteria.[21] Healthy subjects were individuals without symptoms of GERD who were recruited through advertisement among hospital personnel and students. They did not use medication that could affect upper gastrointestinal motility or gastric acid secretion. Exclusion criteria were the presence of concomitant other esophageal disorders such as achalasia, rumination syndrome, eosinophilic esophagitis, a history of esophageal or gastric surgery and continuation of PPIs during pH-impedance measurement.

High-resolution manometry protocol

Esophageal routine HRM study was performed after a 4-h fasting period and discontinuation of medication that could affect esophageal peristalsis for 3 days. Measurements were performed according to a standardized protocol in our center.[22] A 4.2-mm outer diameter solid-state manometric assembly (Given imaging, Los Angeles, CA, USA) with 36 circumferential sensors spaced at 1-cm intervals was used. Before measuring, the transducers were calibrated at 0 and 300 mmHg. After placing the catheter transnasally and fixing it to the nose, measuring was performed in a supine position. After an adaptation period, ten water swallows of 5 mL were administered. Subsequently, the patient was asked not to swallow for 30 seconds, in order to measure a landmark recording for computer analysis.

Data analysis

Manometric data were analyzed using Manoview software (Given imaging, Los Angeles, CA, USA), customized for processing manometric data into isocontour pressure plots. First, data were corrected for thermal sensitivity of the pressure-sensing elements, using the thermal compensation function of Manoview. Next, the markers for the upper esophageal sphincter (UES) and the LES were manually placed (both recognizable as high-pressure zones). Subsequently, the gastric marker was placed in the low-pressure zone below the LES.

The 10 wet swallows were individually analyzed, according to the Chicago Classification, version 2.[13] The distal contractile integral (DCI) was calculated as the product of intensity and length (mmHg·s·cm) of the contraction in the 20-mmHg isobaric contour pressure level. The contractile deceleration point (CDP) was determined as the deceleration point on the 30-mmHg isobaric contour of the distal contraction. The contractile front velocity (CFV) was measured as the best fit slope of the 30-mmHg isobaric contour from the CDP to the top of the distal contraction. The distal latency (DL) was calculated as the time between the UES relaxation and the CDP. All outcome variables were measured in all 10 wet swallows. For each outcome variable the software calculated the median over all 10 swallows.
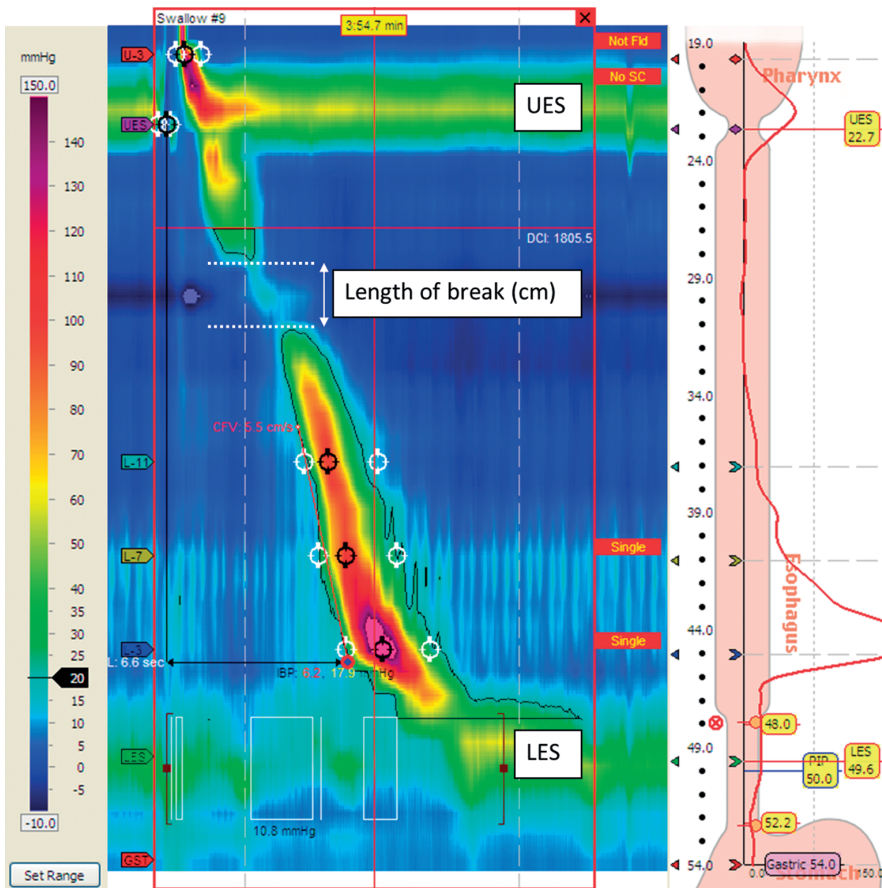
Figure 1. Example of a measurement of the length of breaks in high-resolution manometry analysis, with the locations of the upper (UES) and lower esophageal sphincter (LES).

In addition to these parameters, the number and length of peristaltic breaks was assessed. Breaks are pressure troughs between smooth muscle contraction segments, measured in centimeters, using the 30-mmHg isobaric contour thresholds (Figure 3.1). Moreover, the esophagogastric junction (EGJ) morphology was analyzed as described by Pandolfino and co-workers.[23] EGJ type I is defined as no separation between the LES and the crural diaphragm (CD) at inspiration, in EGJ type II there is a LES-CD separation of 1-2 cm at inspiration and in EGJ type III the LES-CD separation is > 2 cm at inspiration.[23]

Statistical methods

All parameters were summarized using the mean values per patient. Further statistical analysis was performed using SPSS Software for Windows (version 21.0; IBM statistics,

IBM corporation, Chicago, IL, USA). The medians of not-normally distributed variables were compared using the Mann-Whitney U test. The unpaired Student t-test was used to compare means between normally distributed variables. Proportions were compared using the Pearson Chi-square test. Differences were considered significant when $p <$ 0.05. A multivariate logistic regression analysis was performed to identify independent predictors of GERD. Finally, a receiver operating characteristic (ROC) curve was plotted to further evaluate the ability of HRM markers to predict GERD.

RESULTS

Baseline demographic data

High-resolution manometry was successfully performed in all 69 GERD patients and 40 healthy subjects. The presenting symptoms in the GERD patients were regurgitation (n=55), heartburn (n=46) and retrosternal pain (n=30). Out of 69 GERD patients, 28 patients (41%) had a hiatal hernia and 20 patients (29%) had reflux esophagitis during upper endoscopy. Moreover, 62 patients (90%) had a positive symptom association between reflux symptoms and reflux episodes.

Markers of LES pressure

Comparison of HRM parameters between patients with reflux disease and healthy subjects is summarized in Table 3.1. GERD patients showed a lower basal LES pressure (10 mmHg [6.4-14.8], (mean [IQR]) compared to controls (13.2 mmHg [9-19.5]; p=0.034). However, a large overlap was seen between the groups (Figure 3.2). No statistically significant differences were seen in residual LES pressure during swallow-associated relaxation (IRP4) or length of the LES. Control patients had significantly more often no hiatal hernia (93% EGJ type I) compared to GERD patients (70% EGJ type I; p=0.005) and GERD patients had significantly greater LES-CD separation (13% vs 0% EGJ type III; p=0.017).

Contraction wave parameters

The mean contraction wave amplitude was significantly lower in GERD patients (55 mmHg [38-75]) compared to controls (64 mmHg [50-88]; p=0.045) (Table 3.1). Again, a large overlap was seen between the groups (Figure 3.2). Fragmented contractions tended to occur more often in GERD patients (42%) than in healthy subjects (28%), however this difference was not significant (Figure 3.3). Also, no statistically significant differences were seen in distal contractile integral (DCI), contractile front velocity (CFV) and distal latency (DL).

Correlation between HRM and endoscopy parameters

We analyzed outcomes of upper gastro-intestinal endoscopy of all GERD patients. Of 3 patients, no data on endoscopy could be retrieved. Of the remaining 66 GERD patients,
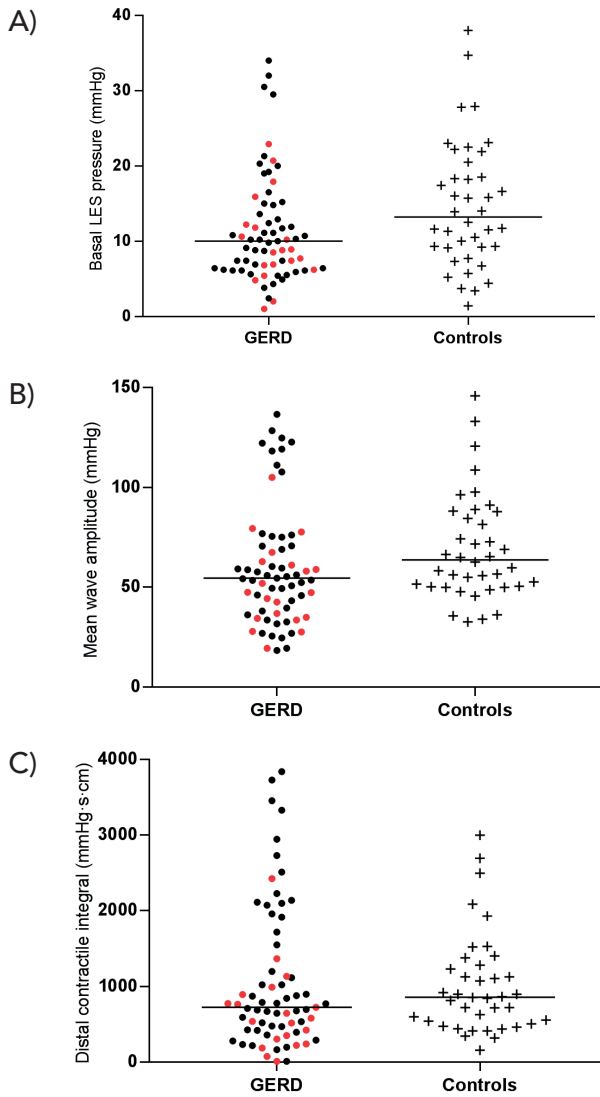
Figure 2. A) basal LES pressure, B) wave amplitude and C) DCI values in GERD patients compared with controls. The black horizontal lines represent the median values. Red dots represent GERD patients with reflux esophagitis, black dots are patients without reflux esophagitis. *DCI is significantly lower in GERD patients with reflux esophagitis than controls. No significant difference in DCI is seen between all GERD patients and controls.

data are shown in Table 3.2. No significant difference was seen in HRM parameters between patients with or without hiatal hernia on endoscopy. Patients with reflux esophagitis had a significantly lower DCI than patients without reflux esophagitis (558 vs 782 mmHg·cm·s; p=0.045). No other statistically significant difference was measured in HRM parameters
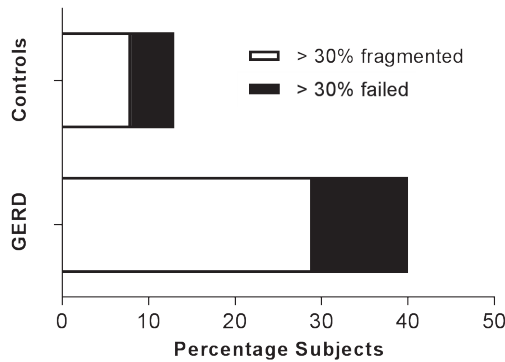
Figure 3. Prevalence of > 30% fragmented and > 30% failed contractions in GERD patients compared with controls. The percentage of subjects in the GERD group with > 30% fragmented contractions was not significantly higher than in the control group.

between patients with or without reflux esophagitis. If we compared patients with reflux esophagitis with healthy controls, a decreased LES pressure (8.7 vs 13.2 mmHg; p=0.024), decreased mean wave amplitude (47.4 vs 63.7 mmHg; p=0.006) and decreased DCI (558 vs 858 mmHg·cm·s; p=0.017) was found in reflux esophagitis patients.

Multivariate logistic regression analysis

We included the manometric variables that were significantly different between GERD patients and controls, i.e. basal LES pressure (LESp), wave amplitude and presence of EGJ type I, in the logistic regression model. We excluded the DCI due to collinearity (correlation coefficient 0.9) between DCI and wave amplitude and because DCI was only significantly different between patients with reflux esophagitis and healthy subjects. Both mean wave amplitude (OR 0.95; 95%CI 0.90-0.98; p=0.013) and EGJ type I (OR 4.971; 95%CI 1.33-18.59; p=0.017) were found to be a statistically significant independent predictor of GERD.

Sensitivity and specificity of HRM to detect GERD

The LESp, contraction wave amplitude and EGJ type I were used in receiver operating characteristic (ROC) analysis (Figure 3.4). The optimal cut-off point was estimated as the point with the highest combined sensitivity and specificity. The best cut-off point of the mean wave amplitude was ≤61.8 mmHg to diagnose GERD, with a very low sensitivity of 66.7% and specificity of 52.5%. The best cut-off point of the LESp was ≤11.2 mmHg, with also a low sensitivity of 63.8% and specificity of 62.5% to diagnose GERD. The absence of EGJ type I had a sensitivity of 30.4% and a specificity of 92.5%. In addition, the combined diagnostic characteristics of the three parameters to identify GERD were calculated, this combined predictive value was not higher than the three parameters alone (sensitivity
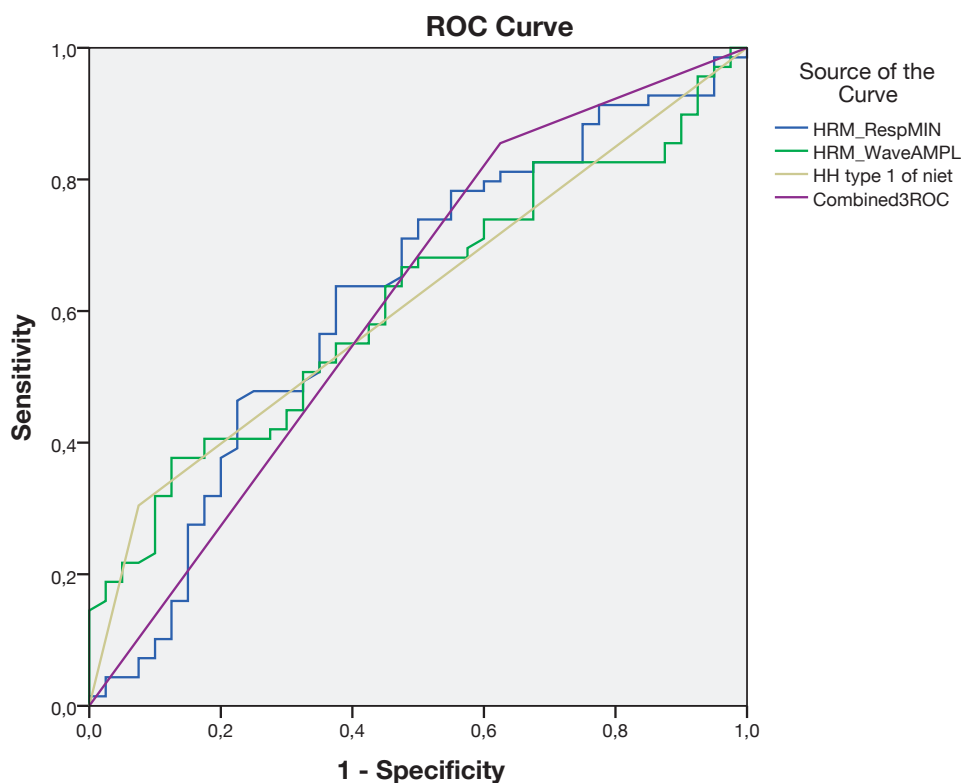
Figure 4. ROC curve of the basal LES pressure, mean wave amplitude and presence of EGJ type I to detect GERD on HRM. All three parameters had a low diagnostic value to predict GERD. The combination of the three markers showed a sensitivity of 53.6%, specificity of 72.5%, positive predictive value of 77.1% and a negative predictive value of 47.5%.

53.6%, specificity 72.5%, PPV 77.1% and NPV 47.5%). Moreover, the usage of DCI revealed no higher diagnostic value than the usage of amplitude.

DISCUSSION

In pathophysiological studies, a dysfunctional anti-reflux barrier and impaired esophageal clearance have been shown to contribute to GERD.[24-26] LES hypotension and hiatal hernia are mechanisms contributing to a dysfunctional anti-reflux barrier, while peristaltic defects lead to impaired reflux clearance and thus to prolonged esophageal acid exposure.[24, 26] These findings however, were mainly observed with conventional manometry. It has never been shown possible to diagnose GERD based on these nonspecific manometric alterations on conventional manometry.

High-resolution manometry (HRM) allows a more accurate measurement of the esophageal motility pattern,[12, 27] suggesting a possibility to measure differences between GERD patients and controls and perhaps to use HRM as a tool to predict GERD. Therefore, the aim of the current study was to calculate the predictive value of HRM parameters that were found to be different between GERD patients and healthy subjects. In addition to previous studies evaluating this, we assessed both individual and combined HRM parameters and added a multivariate analysis and ROC analysis.

In our study, on univariate analysis, only three HRM parameters differed significantly between GERD patients and healthy individuals: basal LES pressure, contraction wave amplitude and type of EGJ morphology. DCI was significantly lower in patients with reflux esophagitis compared to healthy subjects. However, these parameters showed a large overlap between the two groups, and thus had a very low predictive value for GERD. In a multivariate analysis, EGJ morphology and contraction wave amplitude were found to be independent predictors of GERD. However, with an odds ratio of approximately 1, contraction amplitude also had a very low predictive value. In all other LES markers or peristalsis parameters also a large overlap was seen between patients with reflux disease and control subjects. Moreover, no good correlation was found between endoscopic findings and HRM markers in patients with reflux disease.

Our finding of a lower basal LES pressure in GERD patients, compared to healthy individuals is concordant with several other studies.[5, 15, 28-30] Kumar et al. stated that the basal LES pressure is an independent predictor of GERD.[15] In addition, LES length has been found to be shorter in GERD patients than in controls.[28] Our finding of a lower contraction wave amplitude in GERD patients than in controls is also concordant with previous studies.[14, 15] Association of fragmented peristalsis with impaired bolus clearance, and thus prolonged acid exposure has been suggested earlier.[24, 31] Our group of GERD patients was older than the group of control patients, however, this difference was not statistically significant and a large age range was present in both groups. To our knowledge, only two studies have been performed assessing the effect of age on HRM parameters.[32, 33] In these studies, it was concluded that younger patient was not correlating with a difference in basal LES pressure, contraction wave amplitude or risk of hiatal hernia.

As mentioned above, the basal LES pressure, wave amplitude and EGJ morphology lack diagnostic value to predict reflux disease with HRM. Even if we combine the parameters, the sensitivity and specificity remain very low. This is mainly due to a large variation in basal LES pressure and wave amplitude among patients with reflux disease, resulting in a large overlap between GERD patients and controls. Subgroup analysis suggests an increasing prevalence of esophageal motility abnormalities with increasing severity of GERD, from non-erosive reflux disease via erosive reflux disease to Barrett's esophagus.[3, 6] For this

ANALYSIS OF HIGH-RESOLUTION MANOMETRY IN GERD PATIENTS

reason, no obvious cut-off point can be determined for LES pressures or wave amplitudes to allow HRM as a diagnostic test for GERD.

An alternative explanation for the low predictive value of HRM, is the multifactorial pathophysiology of reflux disease. GERD is caused by a combination of increased esophageal acid exposure (due to decreased LES pressure and impaired esophageal peristalsis), hypersensitivity of the esophagus, an impaired mucosal barrier function and supposedly even psychological factors.[34] HRM is able to detect only a limited part of these causative factors, which is insufficient to adequately identify reflux disease. Even the most complex and complete analysis of esophageal function will not suffice to reliably diagnose GERD.

In summary, in our cohort, a low mean contraction wave amplitude, a low basal LES pressure and a hiatal hernia were more prevalent in GERD. The predictive value of these HRM findings to detect GERD patients is very low however. This can be explained by the notion that hypomotility is only one out of many contributing factors to GERD and that even HRM does not provide a complete picture of all motility factors involved. In conformity with previous studies, our results indicate that it is not possible to identify GERD patients with HRM.

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PART II

ACHALASIA AND RELATED DISORDERS

CHAPTER

INCIDENCE AND COSTS OF ACHALASIA IN THE NETHERLANDS

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ABSTRACT

Background

Recent reports show increasing incidence of achalasia in some populations. The aim of this study was to estimate incidence, prevalence and healthcare costs of achalasia in a large cohort in the Netherlands.

Methods

Data were obtained from the largest Dutch healthcare insurance company (± 4.4 million insured). Adult achalasia patients were identified between 2006 and 2014 when having an achalasia diagnosis code registered. A total of 907 achalasia patients were identified and included in our database, along with 9068 control patients (non-achalasia patients), matched by age and gender.

Results

The mean incidence over the nine-year period was 2.2 per 100,000 persons and the mean prevalence was 15.3 per 100,000 persons. Mean age of achalasia patients was 54 (range 18-98) years. Male to female ratio was 1:1. Socio-economic status distribution was similar in achalasia patients and controls. Prior to the diagnosis, 74% of achalasia patients received proton pump inhibitors and 26% received anti-emetic medication. The first year after diagnosis median total direct medical costs of achalasia patients were € 2,283,- (IQR 969-3044) per year. Patients above the 90th percentile of € 4,717,- were significantly older than other patients below the 90th percentile (mean age 63 versus 57); *p* = 0.005.

Conclusions

In this large study that used a database comprising about 25% of all inhabitants of the Netherlands, it is confirmed that achalasia affects individuals of both genders and all ages. The costs associated with diagnosis and treatment of new cases of achalasia increase with increasing age.

INTRODUCTION

Esophageal achalasia is a motility disorder of the esophagus caused by degeneration of the myenteric plexus.[1] The loss of neurons evokes abnormal or absent peristalsis and impaired relaxation of the lower esophageal sphincter, generating symptoms of difficult food passage, reflux symptoms and chest pain.[1, 2] The underlying etiology is generally thought to be an autoimmune response triggered by a viral infection in genetically susceptible subjects.[1, 3]

Epidemiological knowledge on achalasia is scarce, and the majority of data is derived from retrospective studies (Table 4.1).[4, 5] Achalasia affects women and men equally and has no racial predisposition. It can manifest at any age, although there is a peak incidence around age 30 to 60 years.[4] A large dispersion in reported incidence rates is seen.[5-10] Older studies in developing countries have calculated incidence rates as low as 0.03 or 0.27 per 100,000 persons per year.[11, 12] Recent studies show an increasing incidence of achalasia in some populations, of up to 4.6 per 100,000 persons per year.[5, 6] This large dispersion and slight increase is also seen in reported prevalence rates, ranging from 8.7 to 32.6 per 100,000 individuals per year.[5, 9, 10]

We used a national healthcare database to study the incidence and prevalence, as well as the age and sex distribution of achalasia in the Netherlands. We also compared socio-economic status between achalasia patients and individuals without achalasia to identify whether this is a risk factor for achalasia. Secondary aims were to calculate the healthcare costs of achalasia patients and to identify risk factors for high costs. Achalasia is a chronic disease often leading to multiple treatments.[1, 2] Long-term treatment and follow-up costs are largely unknown. Giving insight in these costs or finding risk factors for high costs could be the roadmap to cost reduction.

METHODS

Settings and design

We conducted a nationwide study of newly diagnosed adult achalasia patients in the Netherlands from 2006 to 2014. Data were obtained from the "Zilveren Kruis", the largest Dutch healthcare insurance company with approximately 4.4 million insured throughout the Netherlands. The approximately 4.4 million insured are equally distributed throughout the country and a good representation of the 17 million residents of the Netherlands.[13] Health insurance is compulsory in the Netherlands (99.2% of all residents is insured) and all claims are routinely recorded for each of the insured in the Zilveren Kruis Health Database. Because of the financial importance of correctly paying claims there is intensive automated monitoring. In addition, each claim is corresponding with a diagnosis code,

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Table 1. Published studies reporting incidence and prevalence of achalasia

	Region	Years	Case identification	Mean age at diagnosis	Incidence		Prevalence
					Average	Per year	
Samo S et al. [5]	Chicago, USA	2004 - 2014	Hospital based	56	0.77 - 1.35 * / 1.41 - 4.60	1.07 * / 2.92	4.68 - 14.42 * / 15.64 - 32.58
Tebaibia A et al. [12]	Algeria	1990 - 2014	Endoscopy	43	0.04 - 0.27	0.27	3.2
Duffield JA et al. [6]	South Australia	2004 - 2013	CBS	62	2.3 - 2.8	2.5	-
Kim E et al. [17]	Korea	2007 - 2011	ICD code	53	-	0.39	6.29
Sadowski DC et al. [10]	Canada	1995 - 2008	ICD or procedure code	53	1.5 - 1.7	1.63	2.5 - 10.82
Gennaro N et al. [8]	Veneto, Italy	2001 - 2005	ICD code, case notes	-	1.3 - 1.8	1.59	-
Farrukh A et al. [22]	South Asians in Leicester, UK	1986 - 2005	ICD code, case notes	54	0.5 - 1.7	0.89	-
Birgisson S et al. [9]	Iceland	1952 - 2002	ICD code, case notes	45	0.5 - 0.7	0.55	8.7
Ho KY et al. [23]	Singapore	1989 - 1996	Manometry, case notes	43	-	0.3	1.8
Howard PJ et al. [7]	Edinburgh, Scotland	1986 - 1991	Registry, endoscopy and manometry	44	-	0.8	-
Stein CM et al. [11]	Zimbabwe	1974 - 1983	-	-	-	0.03	-
Arber N et al. [24]	Israel	1973 - 1983	ICD code, case notes	-	0.8 - 1.1	0.95	7.9 - 12.6
Mayberry JF et al. [16]	Nottingham, England	1966 - 1983	ICD code, case notes	-	-	0.51	8.0
Galen EA et al. [25]	Virginia, USA	1975 - 1980	-	-	-	0.6	-
Mayberry JF et al. [26]	Cardiff, Wales	1926 - 1977	-	-	-	0.4	-
Earlam RJ et al. [27]	Rochester, USA	1925 - 1964	Gastroenterologist estimations	-	-	0.6	-

* ICD = International classification of diseases. - Missing data. Incidence and prevalence rates are presented per 100,000 persons per year. This table is adapted and updated from Duffield et al.[6] and Samo et al.[5]

making the case identification rate highly reliable. This automatically makes the database accurate and valid in calculating incidence, prevalence and costs of diseases. Diagnosis codes are based on the International Classification of Diseases, tenth revision (ICD-10). Data were provided anonymously and in accordance with the Dutch privacy legislation. This study was approved by the Medical Ethics Committee of the Academic Medical Center Amsterdam (W16_380 # 16.446).

Patients

Adult achalasia patients were identified between 2006 and 2014 when an achalasia diagnosis code (ICD-10 code K22.0) was registered by an internist or a gastroenterologist. A total of 907 achalasia patients were identified and included in our database, along with 9068 control patients matched by age and gender. Control patients are healthy or non-healthy patients without achalasia, insured at the same insurance company. The database includes background information (age, gender and ZIP code) of all patients. For each year they were insured by Zilveren Kruis, all health care claim data were available. Of each claim; the type, date, costs and corresponding diagnosis were available. The registration includes all the care of general practitioner, hospital care; type of consultations, diagnostics, delivered medication, surgical procedures, referrals, outpatient services and hospitalizations. The same measures were available for all (non-achalasia) control patients (ratio 1:10).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY, USA). Summary statistics were generated for background information of achalasia patients and control patients separately. Proportions were described as number and percentage. Normally distributed variables were described as mean ± standard deviation (SD). ZIP codes were matched with corresponding socio-economic status (SES), based on data from the Netherlands Institute for Social Research (SCP).[14] A SES-score of 1 = very high SES, 2 = high SES, 3 = average SES, 4 = low SES and 5 = very low SES. Differences in background information were tested with an unpaired Student's t-test for numerical data and with a Chi-square test for proportions.

Annual incidence and prevalence rates of achalasia were estimated. The annual incidence rate is the total number of new cases per year divided by the total number of insured people in the corresponding population during the same year, multiplied by 100.000. The annual prevalence rate is the total number of known cases divided by the total number of people in the corresponding population, multiplied by 100.000. The mean incidence and prevalence for the time period 2006 to 2014 were also calculated.

For all achalasia patients together, median annual achalasia-related direct costs per person were calculated. For these analyses, only costs of healthcare claims corresponding with an achalasia diagnosis were used.

RESULTS

Population characteristics

We included all newly diagnosed achalasia patients (n=907) and approximately 10 control patients (n=9068) for each achalasia patient, matched by age and gender. Background characteristics of the total population are described in Table 4.2. Mean age in the total population was 54 (± 18) years, with 49.5% female patients. The majority of patients and controls (62%) was insured at our insurance company during the complete study duration of 9 years, with a mean duration of 7.4 years. Among achalasia patients these numbers were even higher: 65% was insured at our company during the complete study duration, with a mean duration of 7.8 years. Mean age of achalasia patients was 54 (± 19) years with a large range (18 - 98 years) in age distribution (Figure 4.1). Male to female ratio in achalasia patients was 1:1 (49.5% female and 50.5% male). Age and gender distribution were consistent over the years. Socio-economic status distribution was comparable between achalasia patients and controls (Table 4.2). A large number of achalasia patients (74%) received anti acidic medication such as a proton pump inhibitor the years before the diagnosis of achalasia. A smaller group (26%) received anti-emetic drugs that stimulate gastric motility such as metoclopramide or domperidone.

Incidence of achalasia

During the study period, annual incidence ranged from 1.7 to 4.2 per 100,000 persons per year (Figure 4.2). Mean incidence over the nine year period was 2.2 per 100,000 persons.

Table 2. Background characteristics of achalasia patients and control patients

	Achalasia patients (n = 907)	Control patients (n = 9068)	p-value
Age	53.6 (18.5)	53.9 (18.4)	-
Gender (female)	449 (49.5%)	4489 (49.5%)	-
Socio-economic status *			
1	171 (19%)	1570 (18%)	
2	160 (18%)	1344 (15%)	
3	150 (17%)	1583 (18%)	0.286
4	173 (19%)	1725 (20%)	
5	247 (27%)	2512 (29%)	

* Socio-economic status: 1 = very high, 2 = high, 3 = average, 4 = low, 5 = very low. - p-value not stated while control patients and achalasia patients were matched by age and gender. Data are presented as mean (SD) or number (%).
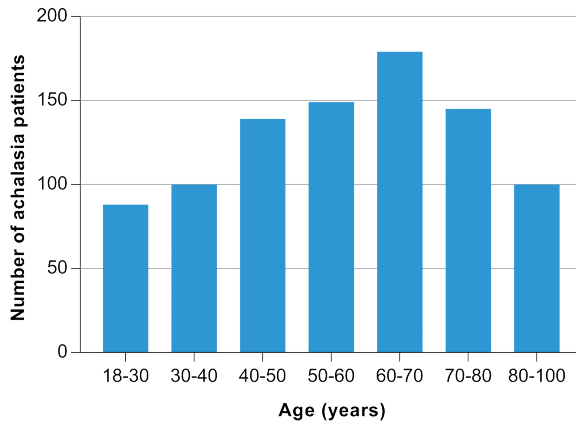
Figure 1. Age distribution of achalasia patients

Figure 2. Incidence of achalasia over time. The continuous line represents the incidence per 100,000 persons per year. The straight dotted line represents a linear trend line.

A slight increase in the incidence of achalasia between 2006 and 2014 was observed, although this rise was not statistically significant. Annual prevalence remained fairly stable during the study period, ranging from 14.5 to 16.8 per 100,000 persons (Figure 4.3), with a mean prevalence of 15.3 per 100,000 persons.

Costs of achalasia

The first year after diagnosis, the median total direct medical costs of achalasia patients were € 2,283,- (IQR 969 - 3044) per year. The 90th percentile of high costs was € 4717,-.

Patients above the 90th percentile were significantly older (63 years ± 18) than patients below the 90th percentile of high costs (57 years ± 19) $p = 0.005$. They were significantly more often treated with "complex treatment followed by more than two nights hospital admission" (36% versus 1%) $p < 0.001$, which could be either a Heller myotomy or a peroral endoscopic myotomy. There was no statistically significant difference in sex distribution between patients above the 90th percentile (62% female) and patients below the 90th percentile (49% female), $p = 0.101$.

In the years following the year of diagnosis, median total direct medical costs of achalasia patients were € 279,- (IQR 0 - 334) per year. Approximately 38% of the patients had no costs at all years following the year of diagnosis. The 90th percentile of high costs was € 816,-. Patients above the 90th percentile significantly more often had outpatient clinic visits, diagnostic measurements and retreatments compared to other patients. Again, they were somewhat older (59 years ± 18) than patients below the 90th percentile of high costs (57 years ± 18), although this difference was not significant $p = 0.076$. There was no statistically significant difference in sex distribution between patients above (53% female) and below (47% female) the 90th percentile of costs, $p = 0.096$.

DISCUSSION

This large study describes the current epidemiology of achalasia in the Netherlands based on a database comprising about 25% of all inhabitants of the Netherlands. Between 2006 and 2014, a slight rise in the incidence of achalasia was observed while the prevalence
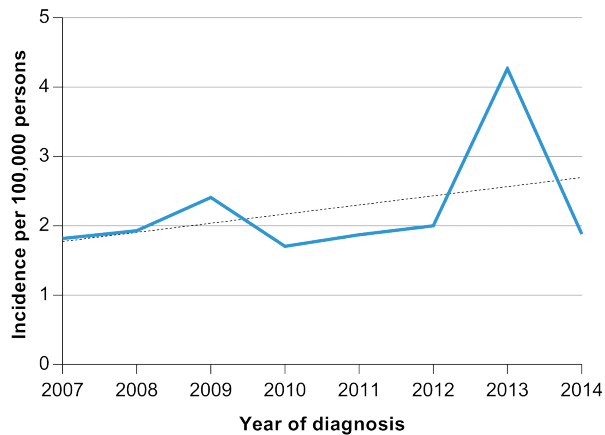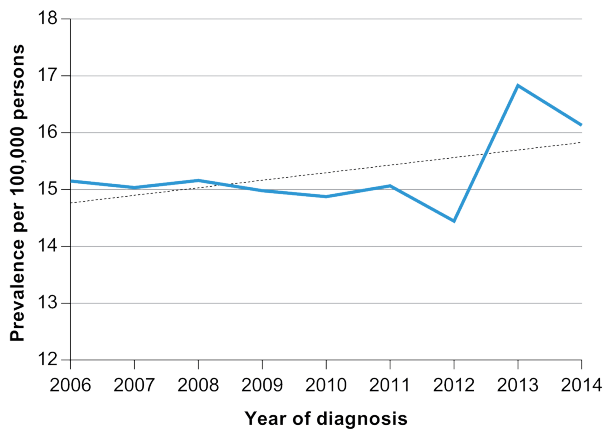

Figure 3. Prevalence of achalasia over time. The continuous line represents the prevalence per 100,000 persons per year. The straight dotted line represents a linear trend line.

remained consistent. Our study confirms that achalasia is a disease that affects individuals of both genders and all ages. The costs associated with diagnosis and treatment of new cases of achalasia increase with increasing age.

We estimated a mean incidence of 2.2 per 100,000 persons. As expected, this number was very similar to recently published incidence rates from other Western countries.[5, 6] True incidence and prevalence depend on the completeness of case finding. Using a health insurance database minimizes the risk for over- and under detection because all Dutch residents are compulsory insured and all claims are routinely recorded in combination with a diagnosis. As a result, 99.2% of the population is covered by medical insurance according to the Netherlands Institute for Social Research. This ensures reliable data on incidence and costs. In general, the health insurance database is a good representation of the total Dutch population.[13] It covers a predefined population, which, in contrary to defining a geographic area around a tertiary referral center, minimizes the risk of selection bias. Furthermore, our database comprises a consistent population with the majority being insured during the complete study duration, diminishing the risk of bias caused by people switching to other health insurance instances. Yet, we could overestimate the incidence the first years of our database due to unknown achalasia claims in the years prior to our database. On the other hand, we do not know what portion of achalasia patients goes undetected due to missed achalasia diagnoses. Furthermore, it is unknown how many achalasia patients are missed due to having no health care claims during the nine-year period. Last, we do not know to what extent our incidence rate is influenced by the age-distribution in our population. The mean age in our total cohort of achalasia patients was 53 years, while achalasia can manifest already at young age, with the age of onset spreading from the first to the ninth decade of life. We only included adult patients, thereby missing the new cases during childhood.

The slight increase in incidence between 2006 and 2014 is most likely caused by improved diagnostic pathways of esophageal motility disorders, more acquaintance and attentiveness for achalasia, and improved data storage. It is likely that the introduction of high-resolution manometry has contributed to a reduction in the number of missed achalasia diagnoses. Apart from this continuous rise, both the incidence and prevalence show a small peak in 2013. This is probably caused by a switch to a new declaration system in the Netherlands in 2012, creating a backlog in the next year. Furthermore, our study confirmed that incidence and prevalence of achalasia increased with increasing age, which has repeatedly been described previously.[6, 8, 15-17] This higher incidence with increasing age suggests an environmental risk factor as a necessary cause of achalasia, which matches the hypothesis that achalasia could be caused by an auto-immune reaction to a viral infection in genetically susceptible subjects.[3]

Our prevalence of 15 per 100,000 persons was somewhat higher than the most recently reported prevalence rates in Western countries, ranging between 4.7 to 10.8 per 100,000 persons per year.[5, 10, 17] As previously stated, our prevalence is the total number of patients with health-insurance claims linked to achalasia diagnosis codes each year. When known achalasia patients had no claims during a year following the diagnosis, we still added these patients to the prevalence calculation, while achalasia is a chronic disease. Probably, previous studies did not have the opportunity to add these patients to the prevalence calculation, which could explain our higher prevalence rates as compared to previous studies. Although we agree that our prevalence is dependent on the completeness of case finding, and achalasia patients without health care claims during 2006 - 2014 will be missed.

Median total direct medical costs of achalasia patients were € 2,283,- in the first year after diagnosis. Previously, costs for pneumatic dilatation and Heller myotomy have been estimated to be approximately € 2,000,- and € 7,000,- respectively.[18-20] The European Achalasia trial calculated total costs of € 3,259,- for PD and € 6,720,- for Heller.[21] They however had the opportunity to add costs of personnel, complications and subsequent treatment, which explains their higher costs. Furthermore, in the Netherlands, most achalasia patients are treated with pneumatic dilatation, which also explains our relatively low median costs per year. As stated above, we only calculated the direct costs, linked to an achalasia diagnosis code. Therefore we lack information on, for example, costs of complications of achalasia treatment that are not linked to an achalasia diagnosis code but for example to a subsequent peritonitis code. We found that patients with higher costs in the first year after diagnosis were significantly older and more often treated with complex treatment.

In summary, incidence rates of achalasia seem to be increasing. We found that the incidence and prevalence rates are markedly higher than previously reported. Notably, achalasia can manifest at all ages in both genders equally. Diagnostic and treatment costs are higher in older patients.

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CHAPTER 5

EFFICACY AND SAFETY OF PNEUMATIC DILATION IN ACHALASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

One of the most used treatments for achalasia is pneumatic dilation of the lower esophageal sphincter to improve esophageal emptying. Multiple treatment protocols have been described with a varying balloon size, number of dilations, inflation pressure and duration. We aimed to identify the most efficient and safe treatment protocol.

Methods

We performed a systematic review and meta-analysis of studies on pneumatic dilation in patients with primary achalasia. Clinical remission was defined as an Eckardt score ≤ 3 or adequate symptom reduction measured with a similar validated questionnaire. We compared the clinical remission rates and occurrence of complications between different treatment protocols.

Results

We included 10 studies with 643 patients. After 6 months, dilation with a 30-mm or 35-mm balloon gave comparable mean success rates (81% and 79% respectively), whereas a series of dilations up to 40 mm had a higher success rate of 90%. Elective additional dilation in patients with insufficient symptom resolution was somewhat more effective than performing a predefined series of dilations: 86% versus 75% after 12 months. Perforations occurred most often during initial dilations, and significantly more often using a 35-mm balloon than a 30-mm balloon (3.2 versus 1.0%); p=0.027. A subsequent 35-mm dilation was safer than an initial dilation with 35 mm (0.97% versus 9.3% perforations), p=0.0017.

Conclusions

The most efficient and safe method of dilating achalasia patients is a graded approach starting with a 30-mm dilation, followed by an elective 35-mm dilation and 40-mm when there is insufficient symptom relief.

INTRODUCTION

Achalasia is a primary motor disease of the esophagus, manometrically characterized by loss of peristalsis and a non-relaxing lower esophageal sphincter (LES).[2] The classic presentation is progressive dysphagia to both solids and liquids, often accompanied by regurgitation of undigested food and chest pain.[3, 4] On radiography, poor esophageal emptying and a very narrow LES is seen, and histopathology shows loss of neural cells in the myenteric plexus of the esophagus.[5]

Unfortunately, there is no curative treatment that can target the neurodegenerative process. Therefore, all treatments are symptomatic, aiming to improve esophageal emptying by means of LES tone reduction.[2] Currently, the most common and effective interventions are surgical Heller myotomy, per-oral endoscopic myotomy (POEM) and pneumatic dilation (PD).[6] Many different techniques and treatment protocols have been described for pneumatic dilation.[7] In general, a noncompliant polyethelene balloon (Rigiflex, Boston Scientific, Natick, MA, USA) is positioned across the LES under fluoroscopic guidance, aided by radiopaque markers on the balloon catheter, and the balloon is inflated with a handheld manometer.[2] Various balloon sizes, number of dilation sessions, inflation pressures and inflation durations can be used.[7] Consequently, the reported series are heterogeneous with respect to the treatment protocol. Reported treatment success rates vary from 52% to 99%.[8, 9] The current American College of Gastroenterology (ACG) guideline for PD in achalasia patients recommends a graded approach using a 30-mm balloon, followed by a 35-mm balloon, and thereafter a 40-mm balloon in non-responding patients.[4]

Due to the chronic and progressive character of the disease, many achalasia patients have to undergo several treatments during their life.[6] Therefore, it is important to identify the most efficient and safe way of performing pneumatic dilations. In this systematic review we compare the clinical remission rates and occurrence of complications associated with different dilation protocols in untreated patients with primary achalasia. We describe the effect of different balloon diameters, and the effect of a predefined series of dilations versus elective additional dilation sessions based on insufficient symptom resolution. Additionally, we examine which treatment protocol has the lowest risk of complications; specifically perforation, post procedural retrosternal pain and reflux symptoms.

METHODS

Literature search and screening

To identify studies describing the efficacy of pneumatic dilation in achalasia patients, we searched Pubmed, Embase and Cochrane. We performed our search on December 8th 2016, using the following terms (including synonyms): 'esophageal achalasia', 'pneumatic

dilation' and 'size' or 'effect'. The exact search is displayed in supplement 1, and Figure 5.1 shows a summary of our literature search, screening and selection. During title and abstract screening, we used the following inclusion criteria: adult patients with primary achalasia; treatment with pneumatic dilation and article type: no reviews, commentaries, meta-analyses or case reports. Next, we more accurately screened the full text of the remaining articles using stricter inclusion criteria: no previous treatments; use of Rigiflex balloon and full description of the procedure; use of Eckardt score or a similar validated questionnaire and full text availability. Publications that did not meet the above-mentioned criteria were excluded from further analysis.

Critical appraisal and article selection

Of the remaining articles, we determined the relevance and validity during critical appraisal (table 1). We noted the number of included patients, the study design, the level
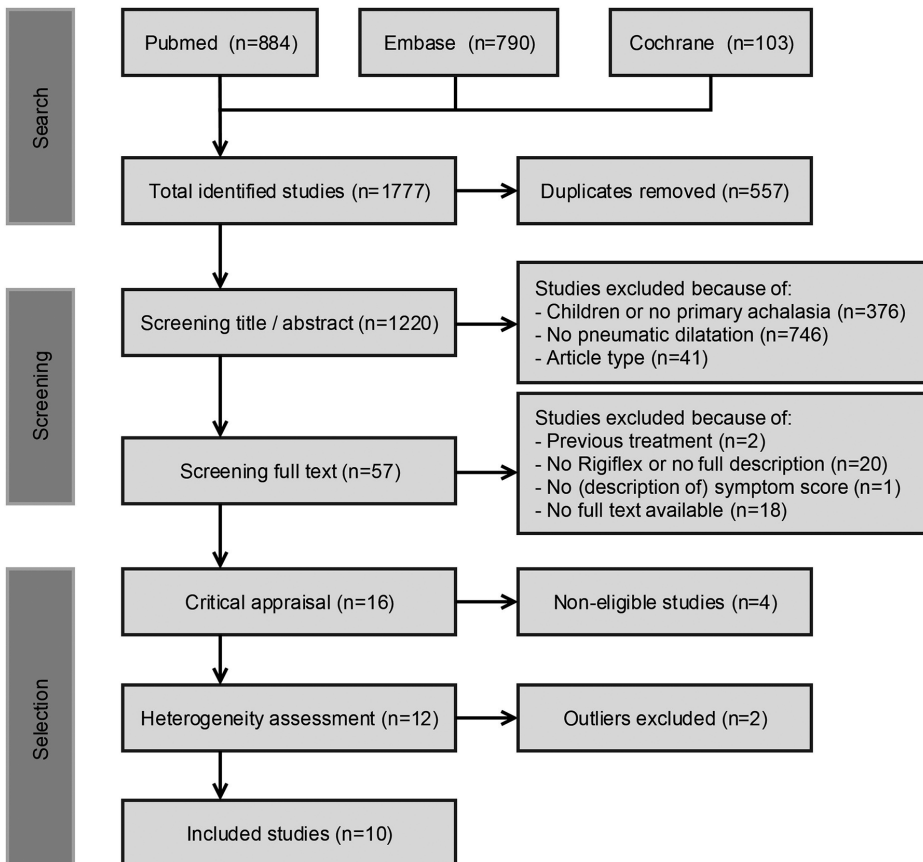
Figure 1. Flowchart of literature search, screening and selection.

of evidence[1] and the inclusion period of the patients. The relevance of the articles was assessed by critically appraising the patient group, intervention and outcome. The validity of the articles was assessed using the following criteria: (1) comparability: all patients were included at a comparable point in the course of their disease; (2) intervention description: a full description of each procedure is included; (3) analysis: all patients were analyzed in the group to which they were classified; (4) total follow-up duration; (5) percentage of patients lost to follow-up; and (6) equality: all patients were treated with the same dilation technique.

Data extraction

The primary outcome was the percentage of patients in clinical remission, as defined by an Eckardt score ≤ 3. The only other remission criterion that was considered valid was being completely symptom-free or having > 50% symptom reduction on a similar validated questionnaire comparable to the Eckardt score. For each study, we noted the number of patients, the description of the symptom score, the definition of clinical remission and the clinical remission rates after 6 and 12 months. Furthermore, we noted the treatment characteristics: balloon size, number of dilation sessions, inflation pressure, inflation duration and usage of predefined series of dilations versus elective additional dilations only in patients with recurrent symptoms. Secondary outcomes were number and type of complications: perforation, post-procedural pain and reflux symptoms.

Statistical analyses

After extracting all data from all articles, the total number of treated patients, the number of patients in remission after 6 and 12 months and the 95% confidence interval were imported in Comprehensive Meta-Analysis software (version 3, Biostat, Englewood, NJ). The inconsistency between studies was assessed and quantified by calculating the heterogeneity (I^2) and the between-study variance (τ^2).[10] Studies yielding extreme effects that appeared to be outlying were tested and excluded when significantly influencing the heterogeneity. Next, a random-effects analysis was performed creating a Forest plot to compare the remission rates between dilation up to 30, 35 and 40 mm. The same analysis was performed to compare the remission rate between articles using a predefined treatment protocol versus additional dilation only in patients with recurrent symptoms. The number of perforations was compared between different groups using a two-tailed Fisher's exact test in GraphPad Prism software (version 7, San Diego, California). A p-value < 0.05 was regarded significant.

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RESULTS

Literature search, screening and selection

The search yielded 1777 records: Pubmed 884, Embase 790 and Cochrane 103. After removing 557 duplicates, 1220 unique studies were identified. Of these, 1163 studies were excluded during title and abstract screening and another 41 articles during full text screening (Figure 1). The remaining 16 articles were critically appraised. Four studies were excluded during critical appraisal, and two other studies were excluded because the reported success rates were outliers that caused significant heterogeneity. Finally, 10 articles were found eligible and included in our systematic review.

Critical appraisal and heterogeneity assessment

The four excluded studies during critical appraisal are visible in Table 5.1. Two of the four excluded studies were excluded because of an inconsistent treatment protocol: both Ding et al. (1995)[11] and Yamashita et al. (2013)[12] dilated some of their patients initially with a 30-mm and others with a 35-mm balloon without distinguishing between these patients in the results. Furthermore, Ding et al. did not describe their final success rate after follow-up or their outcome measurement. A third study, by Ahmed et al. (2008)[13], was excluded because no definition of clinical remission was specified. The fourth study to be discarded was that of Muehldorfer et al. (1996)[14] because it included a heterogeneous group of treated and untreated patients without stating the previous treatment or making a distinction in treatment results between these patients.

The two excluded outlier studies during heterogeneity assessment were Khan et al. (1998) and Khan et al. (2005)[9, 15]. These studies yielded extreme results that appeared to be outlying. The percentage of total inconsistency across studies due to true heterogeneity (I^2) was 79% including these studies and dropped to 64% without these studies. Moreover, the between-study variance (τ^2) dropped from 0.64 to 0.25 when excluding these studies. Based on this, both studies were considered outliers significantly influencing the true heterogeneity between studies and therefore excluded from further analyses.

Comparing efficacy between different balloon sizes

A total of 10 studies with 643 patients were included and subdivided into three groups; dilation up to 30, 35 and 40mm. Dilation with 30 mm and 35 mm showed comparable mean remission rates after 6 months (81% and 79%) whereas dilation up to 40 mm had a higher remission rate of 90%. After 12 months, the success rates decreased in all groups to77%, 70% and 87% respectively. The results are shown in Table 5.2 and Figure 5.2.

Dilation up to 30 mm led to a mean clinical remission rate of 81% after 6 months and 77% after 12 months (Figure 5.2). Four articles were included in this subgroup, with a mean follow-up time of 28 months and a total of 180 patients at 12 months follow-up. Chuah et

Table 1. Critical appraisal

Author (year)	Study characteristics				Relevance			Validity					
	Nr of patients	Study design	Level of evidence[1]	Inclusion period	A	B	C	1	2	3	4	5	6
Ghoshal (2001)	10	RCT	1b	1997 - 2000	●	●	●	●	●	●	●	●	●
Moonen (2015)	96	RC	2b	2003 - 2008	●	●	●	●	●	●	◉	◉	●
Maris (2010)	82	RC	2b	1997 - 2007	●	●	●	●	●	●	◉	◉	●
Smeets (2015)	26	RCT	1b	-	●	●	●	●	●	●	◉	◉	●
Allescher (2001)	13	RCT	1b	1994 -1996	●	●	●	●	●	●	●	●	●
Mikaeli (2004)	262	RCT	1b	1993 - 2003	●	●	◉	●	●	●	●	●	●
Khan (2005)	300	RC	2b	1987 - 2003	●	●	◉	●	●	●	●	●	●
Tanaka (2010)	55	PC	2b	2002 - 2007	●	●	◉	●	●	●	●	●	●
Chuah (2008)	33	RC	2b	1998 - 2004	●	●	◉	●	●	●	◉	●	●
Vaezi (1999)	24	RCT	1b	1995 - 1997	●	●	◉	●	●	●	◉	◉	●
Khan (1998)	81	RCT	1b	1989 - 1994	●	●	◉	●	●	●	○	●	●
Dobrucali (2004)	42	RC	3	-	●	●	◉	●	●	●	●	○	●
Ding (1995)	15	RC	2b	1989 - 1995	◉	●	○	●	●	◉	●	●	◉
Muehldorfer (1996)	25	RCT	1b	-	○	●	◉	●	●	●	◉	-	○
Ahmed (2008)	32	RC	2b	2000 - 2005	●	●	○	●	●	◉	◉	●	●
Yamashita (2013)	25	RC	4	2005 - 2011	●	●	◉	●	◉	◉	●	●	○

Grey color represents studies excluded based on critical appraisal

RCT : randomized controlled trial

RC : retrospective cohort

PC : prospective cohort

- : not specified

Level of evidence : according to Oxford Centre[9]

A: Domain

● ; untreated achalasia patients

◉ ; previous bougie dilation

○ ; previous treatment other than bougie

B: Intervention

● ; pneumodilation with Rigiflex balloon

◉ ; variable initial balloon size was used

○ ; different inflation protocol in a subgroup

C: Outcome (remission)

● ; Eckardt score ≤ 3 or symptom free

◉ ; <50% of baseline symptoms

○ ; any decline on symptom score

1: Comparability

● ; all patients included at comparable disease point

◉ ; not all patients included at a comparable point

2: Intervention description

● ; full description of each procedure

◉ ; no full procedure description

3: Analysis

● ; patients analyzed in classified group

◉ ; no separate analysis per patient group

4: Total follow-up

● ; > 2 years of follow up

◉ ; 1 - 2 years of follow up

○ ; <1 year of follow up

5: Lost to follow up

● ; < 10%

◉ ; 10 - 20%

○ ; > 20%

6: Equality

● ; same dilation technique in all patients

◉ ; variable initial balloon size was used

○ ; different inflation protocol in a subgroup

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al. (2008)[16] and Tanaka et al. (2010)[17] treated the patients with one 30-mm dilation. These two studies show very different success rates, ranging from 75 to 91% after 6 months and from 73 to 81% after 12 months. In the study by Tanaka et al. (2010)[17] the lowest efficacy rates were found and also the lowest inflation pressure was used (table 3). Ghoshal et al. (2001)[18] and Maris et al. (2010)[19] both initially dilated with 30 mm, and repeated dilation with 30 mm when symptoms recurred. Their success rates were 80% – 83% after 6 months and 78% – 80% after 12 months. Maris et al. (2010)[19] offered their patients up to 3 dilations with a 30-mm balloon, based on symptom recurrence. All of these studies used an inflation time of 60 seconds, with inflation pressures varying between 3 and 15 psi.

Dilation protocols up to 35 mm resulted in a comparable mean clinical remission rate: 79% after 6 months and 70% after 12 months (Figure 5.2). Three studies are included in this group. The total number of included patients at 12 months is 92 patients, with a mean follow-up of 28 months. Hence, not all patients were dilated with a 35-mm balloon, depending on the treatment protocol. Overall, 55% of patients received a 35-mm dilation. Vaezi et al. (1999)[20] and Dobrucali et al. (2004)[21] used a comparable dilation protocol, namely 30 mm followed by 35 mm within a few weeks in patients with insufficient symptom relief. When necessary, Dobrucali et al. (2004)[21] repeated the 35-mm dilation one extra time. They had the highest success rate of 88% on the 6-month interval, although this decreased to only 54% after five years of follow-up. In the last study, by Smeets et al. (2015)[22], a considerably lower success rate of 73% after 6 months was attained, even though all patients underwent two dilations (30 mm followed by 35 mm within a few weeks) and the duration of balloon
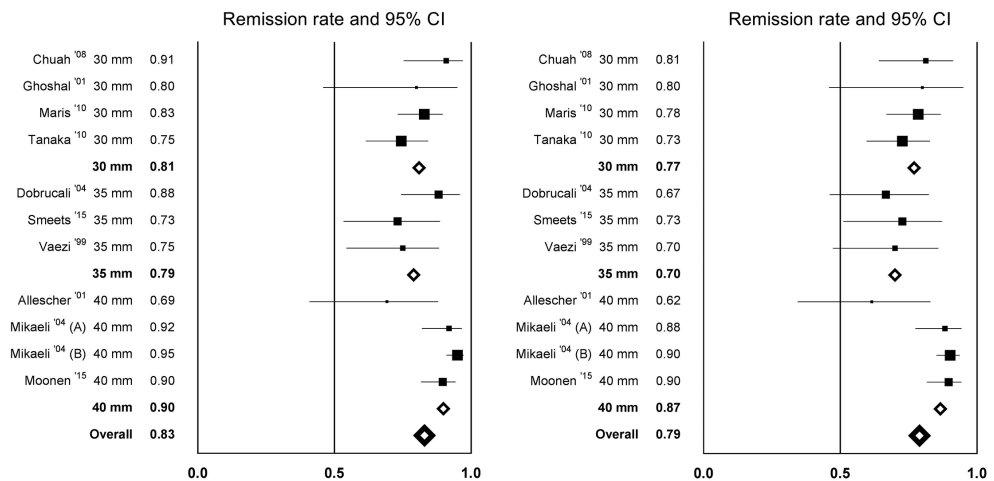
Figure 2. Remission rates per article after 6 months (left) and 12 months (right) of follow-up, comparing dilation up to 30 mm, 35 mm and 40 mm.

Table 2. Summary of dilation protocols and efficacy

Author (year)	Number of patients per dilation session			Treatment protocol	Time in-between (wks)	Remission rates			Total FU (mos)	Prespecified protocol
	1st	2nd	3rd			6 mos (%)	12 mos (%)	End of study (%)		
Chuah (2008)	33	-	-	30	8	91	81	-	12	Yes
Tanaka (2010)	55	-	-	30	1	75	73	73	74	Yes
Ghoshal (2001)	10	4	-	30 - 30	-	80	80	-	12	No
Maris (2010)	82	14	2	30 - 30 - 30	4 - 80	83	78	-	12	No
Dobrucali (2004)	42	18	4	30 - 35 - 35	6 - 8	88	67	54	60	No
Smeets (2015)	26	26	-	30 + 35	1	73	73	-	12	Yes
Vaezi (1999)	24	7	-	30 - 35	14	75	70	-	12	No
Allescher (2001)	13	9	-	35 - 40	4 - 200	69	62	45	48	No
Mikaeli (2004)*	A:62 B:200	A:18 B:56	A:3 B:8	A: 35 - 40 - 40 B: 30 - 35 - 40	4 - 192	A:92 B:95	A:88 B:90	A:70 B:89	60	No
Moonen (2015)	96	96	24	30 + 35 - 40	4	90	90	82	120	No

-: not applicable. wks: weeks. mos: months. FU: follow-up. * Two different dilation protocols were used, which are separately represented.

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inflation was longer (180 s). However, they used a low inflation pressure of 5 psi, whereas the other studies used a pressure of 10-15 psi (Table 5.3).

The average success rate of dilation up to 40 mm was considerably higher than dilation to 30 or 35 mm: 90% after 6 months and 87% after 12 months (Figure 5.2). The total number of included patients at 6 and 12 months was 371 and 348 respectively, with a mean follow-up of 76 months. Three studies are included in this group. Again, not all patients but only the minority with insufficient effect of 35-mm dilation (16%) received a 40-mm dilation. Mikaeli et al. (2004)[7] used two different treatment protocols: 35 – 40 – 40 mm dilation (group A) and 30 – 35 – 40 mm dilation (group B), and will therefore be described as two different studies. Moonen et al. (2016)[23] used the same balloon sizes as in group B of Mikaeli. These two studies showed the highest success rates attained with dilation up to 40 mm, both after 6 months (95% and 90%) and after 12 months (both 90%). Allescher et al. (2001)[24] described the lowest success rates at the 6-month (69%) and 12-month interval (62%), using 35 – 40 mm as gradation protocol. All studies using dilation up to 40 mm used inflation pressures of 8-10 psi for 60 seconds (table 3).

Comparing efficacy between different dilation protocols
We also compared studies that followed a predefined series of dilations (3 studies) with studies that performed elective additional dilations in patients that had persisting

Table 3. Perforation rates per study

Author (year)	Treatment protocol	Perforation n (%)	Initial/ Subsequent	Inflation time (s)	Inflation pressure (psi)
Perforation					
Chuah (2008)	30	1/33 (3%)	Initial	60 + 30	12 + 12
Dobrucali (2004)	**30**- 35 - 35	1/42 (2.3%)	Initial	60	15
Vaezi (1999)	**30**- 35	1/24 (4.2%)	Initial	60	9-15
Moonen (2016)*	**30** + 35 - 40	3/96 (3.1%)	Initial	60 + 60	5 + 8
		2/96 (2%)	Subsequent		
Moonen (2016)*	35	4/13 (32%)	Initial	60 + 60	5 + 8
Mikaeli (2004)*	**35**- 40 - 40	3/62 (5%)	Initial	10	10
No perforation					
Tanaka (2010)	30	0/55	-	60+ 60+ 60	3-4 + 4-5 + 5-7
Ghoshal (2001)	30- 30	0/10	-	60	10-15
Maris (2010)	30 - 30 - 30	0/82	-	60-180	9
Smeets (2015)	30 + 35	0/26	-	180	5
Allescher (2001)	35 - 40	-	-	120	8-10
Mikaeli (2004)*	30 - 35 - 40	0/200	-	10	10

- : not specified. n: number. s: seconds. psi: pound-force per square inch. * Two different dilation protocols are used, which are presented separately. Bold numbers represent the dilation where a perforation occurred.

or recurrent symptoms (7 studies). The second group had a higher remission rate after 6 months (88%) and 12 months of follow-up (86%), when compared to the group that underwent dilations according to a predefined protocol (78% and 75%). The additional dilation group however, had a wider range of final success rates (Figure 5.3). Regarding the studies performing a predefined series of dilations, 2 out of 3 only dilated up to 30 mm: Chuah et al. (2008)[16] and Tanaka et al. (2010)[17], and one study dilated up to 35 mm: Smeets et al. (2015)[22]. This partially explains the lower remission rates in the predefined treatment group when compared to the elective additional dilation group.

Complications

All studies except one reported the occurrence of complications such as perforations (table 3). In 7/10 studies a perforation occurred in one or more patients. The risk for perforation using a 30-mm balloon was very low (6/588, 1.0%) and, interestingly, all of these perforations occurred during the initial dilation. When only initial dilations were considered the chance of perforation with a 35-mm balloon was significantly higher (7/75, 9.3%) than with a 30-mm balloon (6/568, 1.1%); $p < 0.001$. In one study[23] a high perforation rate during initial balloon dilation of 35 mm was encountered (4/13 patients, 32%), prompting a change of protocol into starting with a 30-mm balloon.

When all dilations (initial and subsequent dilations together) were considered, the chance of perforation using a 35-mm balloon was significantly higher (9/282 patients, 3.2%) than using a 30-mm balloon (6/588 patients, 1.0%); $p < 0.001$. But, when only looking at 35-mm dilations, a subsequent dilation was evidently safer than an initial dilation (0.97% versus 9.3% perforations), $p = 0.008$. Surprisingly, none of the 62 dilations with 40-mm balloons caused a perforation.

There is little data available on other side effects. After dilation up to 30 mm, two studies described chest pain after the procedure in 2/10 (20%) and 7/81 (8.6%) patients. This pain occurred directly after dilation and reduced within 48 hours. Symptoms suggestive of gastroesophageal reflux were reported by 6.9% of patients that received a dilation up to 35 mm. After 40-mm dilation no side effects were specified.

DISCUSSION

In this large systematic review and meta-analysis, we compared different pneumatic dilation treatment protocols in patients with primary achalasia. Regarding efficacy, we found that elective additional dilation with 40-mm increases the success rate after an initial 30-mm and 35-mm dilation and that, in general, elective additional dilation is slightly more successful than following a predefined dilation protocol. Regarding safety, we found that perforations occurred significantly more often when the first dilation was performed

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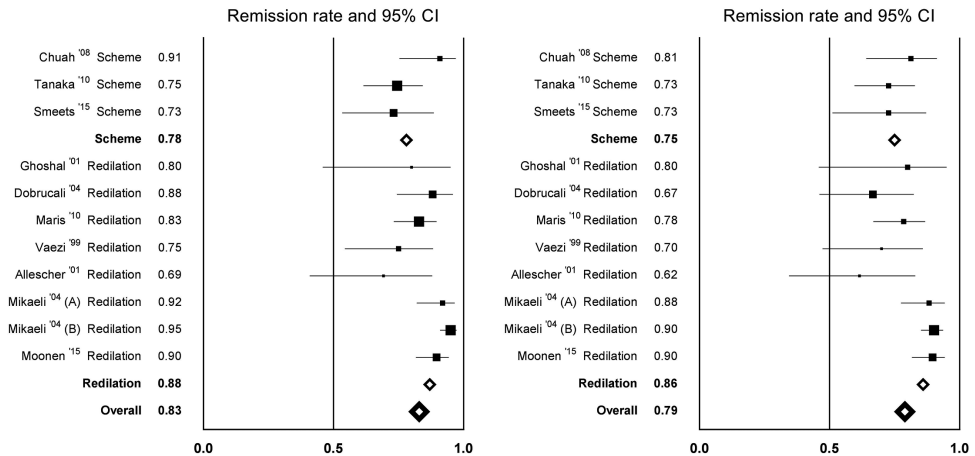
Figure 3. Remission rates per article after 6 months (left) and 12 months (right) of follow-up, comparing studies that used a predefined dilation protocol ('Scheme') with studies in which additional dilations were performed when symptom recurrence occurred ('Redilation').

using a 35-mm balloon than when the first dilation was performed with a 30-mm balloon. A subsequent 35-mm dilation was significantly safer than initial dilation with a 35-mm balloon. No perforations were described in patients undergoing a 40-mm dilation.

We conclude that the safest and most efficient dilation method for patients with primary achalasia is to start with a 30-mm balloon, followed by an elective 35-mm and an elective 40-mm balloon dilation in patients with insufficient symptom relief. It is surprising that we could not find a higher efficacy of 35 mm after 30 mm. Numerous previous studies did report additional benefit of a 35-mm dilation after a 30-mm dilation in a subgroup of patients.[7, 20, 21] Our relatively low efficacy of dilation up to 35 mm could be caused by the smaller sample size in this group, as compared to the number of patients dilated with a 30-mm or 40-mm balloon.

Although we did not find additional benefit from a 35-mm balloon dilation after initial 30-mm dilation, dilation up to 40 mm gave higher remission rates than 30 and 35 mm (90% versus 77-81% after 6 months). It is hard to distinguish whether the additional benefit of a 40-mm dilatation is caused by the larger balloon size or by the higher number of dilations, because it was always performed in a series of two or three dilations. It is most likely a combination of the two. A previous large study calculated that a series of three dilations was significantly more successful higher than one or two dilations.[25] Furthermore, a cumulatively rising efficacy per larger balloon diameter has been reported, with the highest efficacy of a graded series dilations up to 40-mm.[4] This is in line with our findings and also with the recommendation of the current ACG guideline for achalasia: a graded series

of balloon dilations, starting with 30-mm and using a larger diameter in patients whom continue to be symptomatic, up to 40 mm.[4] On the other hand, in patients after previous Heller myotomy, it has been described that patients with insufficient symptom relief after a 35-mm dilation will not experience any improvement from a 40-mm dilation.[26]

Clearly, the use of a larger balloon can only be justified when the benefits outweigh the risks. For 35 and 40-mm there seems to be a certain benefit. Unfortunately, there also seems to be an undeniable increase of perforation risk. As expected, perforations occurred significantly more often during 35-mm dilations than during 30-mm dilations, even when not only looking at initial dilations (3.8% versus 0.6%, $p< 0.001$). The dilation protocol used by Moonen et al. (2016)[23] starting with a 35-mm balloon and inflating it twice for 60 seconds resulted in a high perforation rate, despite the fact that low inflation pressures (5 and 8 psi) were used. This suggests that the size of the balloon plays a role.[23] The majority of the perforations in our review occurred during the initial dilation, and more often with 35 mm than 30 mm. This again stresses the importance of a graded approach. Surprisingly, no perforation occurred with the usage of 40-mm balloon, although the number of studies using this balloon size was small. It must be considered that all studies used a graded approach with 40 mm as the final step, which is also in line with the hypothesis of a graded approach being safer.

We have no direct indication that a high inflation pressure is more likely to cause perforations. When looking at table 3, it seems that in studies associated with a high perforation rate more often pressures ≥ 10 psi were used and studies without perforation more often used 5 – 10 psi, although this is not a significant difference. Theoretically, once the balloon is completely filled with air and the waist of the tight LES has gone, it should not make a difference whether the pressure in the balloon is high or low as the diameter will be the same. However, the data suggests inflation pressure also seems to influence the success rates of PD to a certain degree. Our results indicate that a lower inflation pressure (< 10 psi) is more likely to give a lower final success rate than using higher pressure.[8, 17, 27, 28] On the other hand, clinical experience tells us that even low pressures of 5-8 psi are enough to completely open the balloon and entirely eliminate shouldering. Two studies with a low success rate compared to studies with similar protocols used low inflation pressures between 3 and 7 psi.[8, 27] The other two studies allowed intermediate pressures between 9 and 10 psi.[8, 28] The recommendation of the current ACG guideline is 8 – 15 psi for 15 – 60 seconds.[4] The characteristics of the patients also need to be taken into account. For example, one study described perforation in a short Taiwanese patient with a very low body mass.[16] In children often the same balloon sizes are used as in adults and perforations occur more often with larger balloons.[29]

In almost all studies, the remission rates eventually decrease with time, which suggests that pneumatic dilation is for many patients a temporary solution for their achalasia

symptoms. The higher efficacy of additional dilation in patients with symptom recurrence, rather than following a predefined treatment protocol, also suggests a temporary effect.[9] The mechanism of effect of pneumatic dilation is not completely understood.[30] A previous study showed only stretching of the LES and no muscular disruption on endoscopic ultrasound after pneumatic dilation.[30] Hypothetically, regeneration of the muscle fiber cells could cause the temporary effect. Another reason could be the progressive neurodegenerative character of achalasia, that can cause symptom increase. Unfortunately, there is no data to support these hypotheses.

In conclusion, in untreated achalasia patients, an initial 30-mm balloon dilation followed by an elective 35-mm and 40-mm balloon dilation in patients with persisting or recurrent symptoms results in the optimal therapeutic efficacy with acceptable perforation risks. Although using a 35-mm balloon in the first dilation session increases the risk of perforation, dilation to 35 and 40 mm is relatively safe when it is preceded by a 30-mm dilation.

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CHAPTER | 6

COMPLICATIONS OF BOTULINUM TOXIN INJECTIONS FOR TREATMENT OF ESOPHAGEAL MOTILITY DISORDERS

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ABSTRACT

Background

In achalasia and spastic esophageal motility disorders, botulinum toxin (botox) injection is considered an effective and low-risk procedure for short-term symptom relief. It is mainly offered to medically high-risk patients. However, no analysis of risks of botox injections has been performed. We therefore aimed to determine the incidence and risk factors of procedure-related complications after esophageal botox injections.

Methods

We analysed the records of all patients undergoing botox injection therapy for esophageal motility disorders at four university hospitals in Europe and North America between 2008 and 2014. Complications were assigned grades according to the Clavien-Dindo classification.

Results

In 386 patients, 661 botox treatments were performed. Main indications were achalasia (51%) and distal esophageal spasm (DES) (30%). In total, 52 (7.9%) mild complications (Clavien-Dindo grade I) were reported by 48 patients, the majority consisting of chest pain or heartburn (29 procedures) or epigastric pain (5 procedures). No ulceration, perforation, pneumothorax or abscess were reported. One patient died after developing acute mediastinitis (Clavien-Dindo grade V) following injections in the body of the esophagus. In univariate logistic regression, younger age was associated with an increased risk of complications (OR 1.43, 95%CI 1.03-1.96). Treatment for DES, injections into the esophageal body, more injections per procedure, more previous treatments and larger amount of injected botulinum toxin were no risk factors for complications.

Conclusions

Esophageal botox injection seems particularly appropriate for high-risk patients due to low complication rate. However, it should not be considered completely safe, as it is associated with rare side-effects that cannot be predicted.

INTRODUCTION

Botulinum toxin (botox) injection in the esophageal body or lower esophageal sphincter (LES) is considered an effective and low-risk procedure for the short-term relief of symptoms in achalasia and spastic esophageal motility disorders.[1, 2] In achalasia patients with advanced age, significant comorbidities or high risk of surgery-related complications, botox injection is often the treatment of choice, since it is considered the safest therapy for this disease.[2-5] It has comparable short-term efficacy, but fewer significant adverse effects than myotomy or dilatation.[3, 6] In spastic esophageal motor disorders, botox injection is superior to sham treatment, but the overall efficacy is lower than in achalasia.[1] However, recently, a fatal mediastinitis following esophageal botulinum toxin injection has been reported,[7] raising the question whether this treatment is really as safe as we think.

Esophageal injection of botulinum toxin was first described in 1993 in a patient with therapy-resistant achalasia.[8] Botulinum toxin, a purified neurotoxin complex, inhibits acetylcholine release from cholinergic neurons, preventing neuromuscular conduction. The following chemical denervation is intended to relax the esophageal smooth muscles, therefore reducing dysphagia and retrosternal pain.[9] In achalasia, it is recommended to inject a total dose of 80 to 100 U divided in four or five equally distributed doses, through an endoscopic needle. In spastic esophageal motor disorders, botox is injected at several levels close to the lower esophageal sphincter and in the distal esophageal body.[1] It is important to avoid submucosal injection or injection outside the esophageal wall.[10] On average, it is reported that symptom relief occurs in 70%-90% of patients within 30 days after the procedure. However, >50% of patients require repeat treatment within 6-24 months.[11]

The most common complications of esophageal botox injections are mild, and related to the injection procedure or the decreased LES pressure. Occurrence of transitory chest pain and gastro-esophageal reflux has been reported after 0 to 30% of procedures.[5, 11-14] Until now, no serious adverse events have been reported in secondary or pre-appraised publications.[6] However, a number of case reports has been published on severe complications after esophageal botox injections.[7, 15-25] We found case reports on a pneumothorax[15], anaphylactic reaction[16], acute urinary retention[17], formation of a sinus tract between distal esophagus and fundus[18], gastroparesis[19, 20], peri-esophageal adhesion and inflammation[21, 22], subdiaphragmatic abscess with sepsis[19] and perforation with mediastinitis[23],[24]. To our knowledge, only two fatal complications have been reported: an arrhythmia followed by acute heart block[25] and a mediastinitis leading to haemorrhagic shock and death.[7] However, the pathogenesis and the association between botox treatment and some of these complications is uncertain.

Until now, no systematic analysis of the risks and complications of esophageal botulinum toxin injections has been conducted. The primary aim of this study was therefore to

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determine the incidence of procedure-related complications and mortality after esophageal botulinum toxin injections in a large, multi-center cohort of patients. The secondary aim was to identify risk factors for complications for botulinum toxin treatment.

MATERIALS AND METHODS

Subjects

We included all patients that underwent esophageal botulinum toxin injections for esophageal motility disorders in four tertiary referral hospitals in Europe and North America between 2008 and 2014. We collected demographic characteristics (age and gender), indication for treatment and the place and amount of injected botulinum toxin. In addition, we determined the number, type and severity of procedure-related complications. Predefined criteria for complications were: all symptoms or findings not present before botox treatment, and reported in patient records in relation to the botox treatment, even when not leading to pharmaceutical treatment or intervention. Complications were assigned grades according to the Clavien-Dindo classification.[26] Finally, we tried to identify risk factors for complications of botulinum toxin injections.

Endoscopic Botulinum toxin injection

Endoscopic botulinum toxin (Botox; Allergan Pharmaceuticals, Los Angeles, CA, USA) injections were performed according to the same standardized protocol in each center, based on a previously described procedure.[10] In achalasia, 100 Units of botulinum toxin is dissolved in 4 ml of normal saline (0.9% NaCl). A sclerotherapy needle is used to inject 4 aliquots of 1 ml of botox intrasphincterically in each quadrant of the LES. In spastic esophageal motility disorders, 100 Units of botulinum toxin is dissolved in 4 to 10 ml of 0.9% normal saline. Eight to ten separate injections, each with 10 to 12.5 Units of botox are injected distributed through the esophageal body or into muscular rings. In one center, the protocol also allowed to inject 200 Units of botulinum toxin in patients with achalasia type III or distal esophageal spasm.

Statistical analysis

We performed all analyses using SPSS Statistics version 20.0 (IBM corporation, Chicago, IL, USA). Normally distributed data are described as number and percentage or mean with range when appropriate. Not normally distributed data are described as median with interquartile range (IQR) or total range when appropriate. Univariate binary logistic regression was used to evaluate demographic variables and intervention characteristics for risk of complication. Results are described as odds ratio (OR) and 95% confidence interval (95% CI). When appropriate, also the p-value is given.

RESULTS

Subjects

In total, 661 botox injection sessions were performed in 386 patients (284 male, mean age 63 years, range 18-98). The main indications were achalasia (196 patients; 51%), distal esophageal spasm (114 patients; 30%), nutcracker or jackhammer esophagus (28 patients; 7%) and EGJ outflow obstruction (26 patients; 6.7%) (Table 6.1). Other indications for esophageal botox treatment were suspected achalasia not qualifying for all criteria (8 patients; 2.1%), dysphagia without known etiology (6 patients; 1.6%), a muscular ring (4 patients; 1.0%) and dysphagia after Nissen fundoplication (3 patients; 0.8%). All patients treated for suspected achalasia showed some features of ineffective, weak or frequent failed peristalsis in combination with one or more features suggesting (beginning) achalasia, however not meeting achalasia criteria. For example a high-normal LES pressure, intermittent incomplete LES relaxation or stasis on barium esophagography were seen. Patients with dysphagia after Nissen fundoplication were treated with botox injections in the lower esophageal sphincter because it was not certain in these patients whether the symptoms were the result of the operation or because of an initially missed achalasia. In the 196 patients with achalasia, the distribution based on manometric subtype was: type I in 17 (9%) patients, type II in 24 (12%) patients, type III in 40 (21%) patients and not specified type of achalasia (diagnosed with conventional manometry) in 114 (58%) patients.

Esophageal botox injections

Injections were delivered to the LES (279 procedures; 43%), the body of the esophagus (211 procedures; 32%), a combination of both (152 procedures; 23%) or occasionally directly into a constriction (15 procedures; 2%) (Table 6.2). A median of 100 U (IQR 100-100, range 60-200 U) of botulinum toxin was injected per treatment. In the vast majority of patients (604 patients; 92%) 100 U were injected. Botulinum toxin was equally distributed over

Table 1. Indication for 661 botulinum toxin injections in 386 patients.

Diagnosis	Number (%)
Achalasia	196 (50.8%)
DES	114 (29.5%)
EGJ outflow obstruction	26 (6.7%)
Jackhammer	14 (3.6%)
Nutcracker	14 (3.6%)
Other*	22 (5.7%)
Total	386

* Suspected achalasia (8x), unknown etiology for dysphagia (6x), muscular ring (4x), postnissen dysphagia (3x). DES: Distal esophageal spasm, EGJ: esophagogastric junction

a median of 5 injections (IQR 4-8, range 2-16 injections). The median number of received treatments per patient was 1 treatment (IQR 1-2, range 1-33 treatments). In total, 127 patients (33%) underwent more than 1 treatment.

Complications

A total of 52 (7.9%) mild complications (Clavien-Dindo grade I) were reported by 48 patients, consisting of chest pain or heartburn in 29 procedures, epigastric pain in 5 procedures, vertigo, nausea or vomiting in 4 procedures, acute urinary retention requiring bladder catheterization in 1 procedure and other mild complications of fatigue, sore throat, dyspnoea or vomiting in 9 procedures. (Table 6.3) No complications of ulceration, perforation, pneumothorax, abscess or heart block were reported. One 64-year old patient died after developing acute mediastinitis (Clavien-Dindo grade V) following injections of a total of 100 U botulinum toxin in the body of the esophagus for treatment of distal esophageal spasm. Within one week he developed a mediastinitis with an abscess between the esophagus and aorta, for which he was treated with intravenous antibiotics and subsequently with surgical drainage of the abscess. After initial symptom relief his condition suddenly deteriorated three weeks later. During thoracotomy he died of a ruptured infectious aneurysm of the aorta. Early treatment failure was reported after 85 (25%) procedures. In four patients, the procedure was aborted prematurely. In two patients early termination was due to restlessness, in one patient due to concern for perforation and in one patient due to stasis of food. The distribution of complications is different per diagnosis. Out of 195 treatments for achalasia, 26 (13.3%) procedures led to a complication. Among 141 treatments for spastic disorders (diffuse esophageal spasm, Jackhammer or Nutcracker esophagus), after 23 (16.3%) procedures a complication was reported. After treatment for EGJ outflow obstruction a complication occurred in 2 (8.3%) out of 24 procedures. Treatment for other indications only led to a complication in 1 (4.5%) out of 22 procedures. The type of complication per diagnosis is shown in Figure 6.1.

Risk factors for complications

In univariate logistic regression, younger age was associated with a higher risk of complications (OR 1.43, 95% CI 1.03-1.96, p= 0.031). However, there is a large overlap

Table 2. Botox injection site in 657 procedures in 382 patients.

Injection site	Number (%)
LES*	279 (43%)
Esophagus	211 (32%)
LES and esophagus	152 (23%)
Constriction	15 (2%)
Total	657

* LES: Lower esophageal sphincter. In total 657 procedures, because 4 procedures were aborted.

Table 3. Reported complications following 657 botulinum toxin injections in 382 patients.

Complication	Number (%)
Chest pain / heartburn	29 (4.4%)
Epigastric pain / bloating	5 (0.8%)
Vertigo / nausea / vomiting	4 (0.6%)
Acute mediastinitis (fatal)	1 (0.15%)
Acute urinary retention	1 (0.15%)
Other *	9 (1.4%)
Total	52 (7.9%)

* Fatigue (3x), sore throat (4x), difficulty breathing (2x)
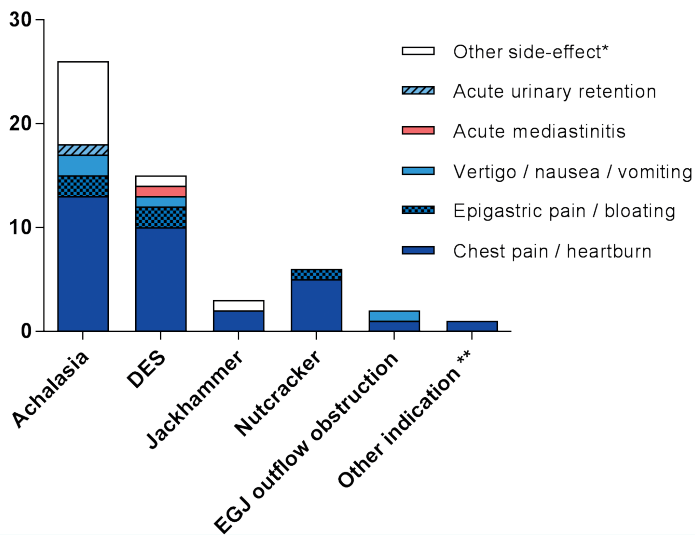
Figure 1. Distribution of 52 complications according to diagnosis. *Fatigue, sore throat or difficulty breathing. **Suspected achalasia, unknown etiology for dysphagia, muscular ring, postnissen dysphagia

in age between patients with complications (mean age 57 years, SD ± 12) and patients without complications (median age 63 years, SD ± 12) making age not a likely true risk factor for complications. Younger patients did not have a higher prevalence of one specific complication. Treatment for distal esophageal spasm had a similar risk of complications as treatment for other indications (OR 0.635, 95% CI 0.34-1.20). Furthermore, injections into the esophageal body had a similar risk of complications as injections into the LES (OR 1.321, 95% CI 0.59-2.95).

More injections per procedure (OR 1.046, 95% CI 0.55-1.98) and more injected botulinum toxin (OR 1.002, 95% CI 0.99-1.01, p=0.754), were no risk factors for complications. Also,

more previous treatments was not a risk factor for complications (OR 0.912, 95% CI 0.79-1.05). Finally, a lower number of procedures per center was not a risk factor for complications (OR 1.055, 95% CI 0.82-1.37). Two centers performed less than 70 procedures in total and two centers performed over 240 procedures in total. The complication rate is similar between the four centers.

DISCUSSION

This study was designed to investigate the occurrence of procedure-related complications after esophageal botox injections. To our knowledge, this is the largest multi-center cohort of patients studied after esophageal botox injections. We found that (1) mild complications occurred after 7.9% of procedures; (2) the most common complications were transient chest pain and reflux symptoms; (3) one fatal complication occurred, leading to a mortality rate of 0.15%; and (4) complications did not occur more often in a specific group of patients.

A 7.9% incidence of mild complications is in accordance with previously reported risk rates in smaller controlled studies, in which the most common mild side effects were also transitory chest pain or heartburn in 0-30% of patients.[5, 11-14] Nonetheless, the retrospective design of our study may have resulted in an underestimation of minor adverse effects in some patients. Chest pain and heartburn are most likely related to the injection procedure and decreased LES pressure.[21] Up to 75% of patients show an objective reduction in LES pressure after intrasphincteric botox injections, enabling gastro-esophageal reflux.[2, 11] However, in a double-blind controlled trial comparing botox and placebo injections, also in the placebo group 25% of patients reported mild transitory chest pain.[27]

Our very low incidence of severe complications is also comparable to previous studies. In two large secondary publications, no serious adverse effects of esophageal botox injections were reported.[6, 13] In our study, one severe complication of a perforation and subsequent mediastinitis occurred.[7] Transmural inflammation, fibrosis and/or perforation are known risks of esophageal injections.[28] Several case reports and at least one prospective study in achalasia high-risk patients have reported esophageal wall inflammation and mediastinal adhesions after botox therapy.[19, 21-24] In one of these case reports, the perforation was caused by usage of a less suitable needle.[23] However, in the other cases, no apparent cause for inflammation was found. Mediastinitis and pericarditis have also been described as a complication after esophageal sclerotherapy.[29, 30] The occurrence of peri-esophageal inflammation is a rare, but dangerous complication, not easily distinguished from 'regular' retrosternal pain, while fever is not always present.

Because of the thinner muscle layers we expected a higher complication rate after injections in the body of the esophagus compared to the lower esophageal sphincter. Moreover,

we expected a higher chance of complications after a larger number of previous botox treatments, because of the known risk of inflammation and fibrosis following subsequent botox injections.[28] We could not demonstrate any of these associations in our cohort of patients. Probably our number complications was too small to determine an association between procedure characteristics and the occurrence of complications.

Compared to other treatment options for achalasia, intrasphincteric botox injections still have the lowest complication and mortality rate. The risk of perforation is higher in both pneumatic dilatation and myotomy, 2 - 5.2% and 0.37% respectively.[3, 6] Moreover, the risk of other postoperative complications in myotomy is higher. Although botox therapy is not completely safe, it remains the safest option for high-risk achalasia patients, and the benefits are outweighing the risks. Botox shows a high remission rate in 75 - 90% of patients after 6 months.[4, 5, 11] Yet, > 50% of patients require repeat treatment in 6-24 months.[11]

We conclude that esophageal botulinum toxin injection is a welcome option in the management of esophageal motility disorders and seems particularly appropriate for medically high-risk achalasia patients due to low risks. However, it is associated with rare side effects that cannot be predicted.

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6

CHAPTER | 7

PREDICTION OF PRESENCE OF REFLUX ESOPHAGITIS AFTER POEM IN ACHALASIA

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ABSTRACT

Background

Gastroesophageal reflux is common after treatment with peroral endoscopic myotomy (POEM) in achalasia. Reflux can cause erosive esophagitis, which is associated with development of Barrett's esophagus, peptic sstrictures and an increased risk of esophageal carcinoma. The aim of this study was to construct a novel, broadly applicable prediction model for presence of reflux esophagitis after POEM.

Methods

The derivation cohort consisted of achalasia patients treated with POEM and no other treatments. Based on literature and backward elimination, possible predictors that could prevent invasive tests after POEM were selected. The endpoint was significant reflux esophagitis, defined as Los Angeles grade B to D esophagitis, in patients not using anti-reflux medication. The model's discriminative performance and the model fit were estimated.

Results

Of 151 patients, 39 patients (26%) had significant reflux esophagitis after POEM. Selected risk factors were initial achalasia subtype 3, a high body-mass index (BMI), alcohol intake, and a high GERDQ score after POEM. The prediction model had an overall discriminative accuracy of 73% (AUC-ROC). The optimal cut-off for identifying patients without reflux esophagitis is a predicted risk of ≤ 20%, with a negative predictive value of 87%. These patients will have only one or none of the four risk factors.

Conclusions

Type III Achalasia, high BMI (> 25 kg/m^2), alcohol intake (> 2 units/day), and GERDQ (> 8) are risk factors for significant reflux esophagitis after POEM. In patients with two or more of these risk factors we advise empiric PPI treatment and an early upper endoscopy. In patients with one or no risk factors, the chance of significant reflux esophagitis is very low and follow-up endoscopy or PPI may not be required.

INTRODUCTION

With no curative therapy for achalasia available, all treatment options are symptomatic, aiming to improve esophageal emptying.[1] During peroral endoscopic myotomy (POEM), this is achieved by cutting the muscle fibers of the lower esophageal sphincter (LES).[2, 3] The LES disruption however, results in a risk of increased reflux of gastric contents into the esophagus.[3, 4] This can lead to reflux esophagitis[5], which is associated with development of peptic strictures, Barrett's esophagus and a higher risk of esophageal carcinoma.[6]

After POEM, the risk of reflux esophagitis seems to be higher than after other achalasia treatments.[4, 7] We recently reported that reflux esophagitis occurred in 48% of patients after POEM, including 8% with grade C or D reflux esophagitis.[8] As POEM is a relatively novel treatment, there are no international guidelines yet on how to monitor and treat these patients. In large series, anti-reflux medication is usually given during the first weeks or months after POEM and thereafter only in patients with symptoms, and an upper endoscopy is performed one year after the POEM.[8]

Unfortunately, among patients without achalasia, there is an inconsistent relationship between reflux symptoms and actual occurrence of increased reflux or presence of erosive esophagitis.[9, 10] Therefore, repeat endoscopies are necessary to identify patients with reflux esophagitis and to monitor their response to anti-reflux treatment. If a low risk for reflux esophagitis can be predicted, endoscopy would probably not be necessary, while patients with a high predicted risk can be treated empirically and monitored more strictly.

Therefore, the aim of this study was to construct a novel, broadly applicable prediction model for presence of significant reflux esophagitis after POEM.

METHODS

Patient population

All achalasia patients treated with POEM between 2011 and 2017 were identified in Northwestern University Hospital in Chicago, IL, United States of America and the Academic Medical Center in Amsterdam, the Netherlands. These two hospitals have been performing POEM for over five years, and all patients are treated and followed-up according to standard protocols.[2] Patients with diagnoses other than achalasia, incomplete follow-up after POEM and/or other achalasia treatments besides POEM were excluded. Since this was a retrospective study, the need for formal medical ethical assessment was waived by the institutional review board of the Academic Medical Center Amsterdam (reference number W17_306 # 17.359). Informed consent was obtained from patients

with achalasia that underwent POEM at Northwestern and the protocol was approved by the Northwestern University Institutional Review Board.

Data collection

Follow-up investigations had to be performed within 6 months to 2 years after POEM. First, demographic data was collected (gender, age at time of POEM, body-mass index (BMI) before and after POEM, units of alcohol consumed per week, current smoking habits and pack years). Furthermore, the outcome of the GERDQ questionnaire before and after POEM and clinical findings before and after POEM were collected (endoscopy, manometry and barium esophagography). These data are further specified under the subheading diagnostic measurements. Last, the total length of myotomy, the length of the esophageal part of the myotomy and the length of full-thickness myotomy were noted. The study endpoint was defined as significant reflux esophagitis: Los Angeles (LA) grade B, C or D reflux esophagitis during follow-up after POEM, after stopping any anti-reflux medication for at least 7 days.[11] LA grade A reflux esophagitis was left out because this is also often encountered in healthy subjects and is of uncertain clinical relevance.[12-14]

Diagnostic measurements

BMI, pack-years and GERDQ score

Body-mass index was calculated as body weight (kg) divided by square body length (m^2). Pack-years were computed as the average number of packs (20 cigarettes) per day multiplied by the duration of smoking in years.[15] Alcohol use was based on patient history and categorized in: rare: 0-1 units per week, light: 2-3 units per week, moderate: 4-14 units per week, heavy: >14 units per week.[16] The validated 6-item GERDQ score was used to measure frequency of heartburn and regurgitation and the impact of these symptoms on the person's daily life.[17, 18] The maximum score is 18 points and a score > 8 indicates a high probability of gastroesophageal reflux disease (GERD).[17]

Upper endoscopy

Diagnostic upper gastrointestinal endoscopy was performed before POEM and during follow-up after POEM. The presence or absence of esophagitis and a hiatal hernia were reported. The Los Angeles classification was used to describe the severity of reflux esophagitis.[11] This classification describes four grades of reflux esophagitis: grade A: erosions are limited to the mucosal folds and < 5 mm, grade B: erosions are limited to the mucosal folds but > 5 mm, grade C: erosions extend between mucosal folds but no more than 75% esophageal circumference and grade D: erosions extend over more than 75% of the esophageal circumference.[11]

Esophageal high-resolution manometry (HRM)

Esophageal HRM was performed at the time of diagnosis and during follow-up after POEM, using a solid-state HRM catheter (Given imaging, Los Angeles, CA, USA), according to

standard protocols.[19, 20] Manoview software (Given Imaging, Los Angeles, CA, USA) was used to analyze the measurements. The basal LES resting pressure was calculated as the median LES pressure related to the gastric pressure during a period of no swallowing. The 4-s integrated relaxation pressure (IRP-4) of the LES was calculated as the median LES pressure related to the gastric pressure during the 4 seconds of lowest LES pressure within a timeframe of 10 seconds after a wet swallow.[21] Achalasia subtypes were determined according to Pandolfino et al.[19] and the Chicago Classification.[22]

Timed barium esophagography

Timed barium esophagography was performed at the time of diagnosis and during follow-up after POEM.[23] After fasting for at least eight hours, patients were standing upright while drinking 100-250 mL of a barium sulfate suspension. At 0, 1, 2 and 5 minutes after ingestion, esophageal radiographs were taken. The maximal width of the esophagus during drinking and the height of the barium column after 5 minutes were measured in centimeters.[24]

Ambulatory pH-impedance measurement

In some patients an ambulatory 24-hour pH-impedance measurement was performed during follow-up after POEM. A catheter with impedance sensors was placed transnasally with a pH sensor 5 cm above the LES.[25] Acid exposure time (AET) was measured as the percentage of time the pH was below 4 in the esophagus. Abnormal AET was defined as > 6%.[25]

Selection of predictors

General factors promoting reflux are high age, male gender, high body-mass index, smoking, alcohol intake and certain medications,[26, 27] hiatus hernia, low LES pressure, increased distensibility of the esophagogastric junction and reduced esophageal clearance.[28-30] A risk factor unique for achalasia is the contraction pattern associated with the different achalasia subtypes. We chose to only include readily available non-invasive risk factors, to avoid additional invasive tests after POEM. The following six possible predictors not needing invasive tests after POEM were selected: age, gender, BMI (kg/m^2) after POEM, current alcohol intake (units per week), initial achalasia subtype (categorized in type 3 or no type 3) and GERDQ score after POEM.[26-28]

Statistical analyses

Statistical analyses were performed using SPSS version 23.0 (Armonk, NY, USA) and R version 3.3.3 (R Studio Inc, Boston, MA, USA). Continuous variables were described as mean and standard deviation (SD) or as median and interquartile range (IQR), depending on the distribution, and proportions as number and percentage (%). Statistical difference in proportions between groups was compared using two-tailed Fisher's exact test. Statistical difference in continuous variables between groups was compared using Students t-test

or Mann-Whitney U test, depending on distribution of variables. A *p*-value < 0.05 was considered statistically significant.

The prediction model was developed using a derivation cohort of two hospitals. Based on the number of events, we used multiple regression backward elimination to reach the appropriate number of events per variable (1 variable per 10 events).[31] After selecting the final set of variables, missing values of these variables were imputed using single stochastic imputation based on fourteen variables including the outcome variable. Of continuous variables, linearity in the logit was checked by restricted cubic spline. Next, a shrinkage factor, derived from a bootstrap validation with 100 bootstrap samples, was applied to correct for optimism.

The probability of significant reflux esophagitis was calculated for different patient groups, using the log odds of the outcome, derived from the regression equation. After this, to quantify the models' discriminative performance, we calculated the Nagelkerke's R^2. A ROC curve was composed to estimate the overall discriminative accuracy using the area under the curve (AUC-ROC). The Hosmer and Lemeshow test was used to test the fit of the model (calibration). A nomogram was made to enable calculation of the probability of significant reflux esophagitis for each patient individually. Based on positive and negative predictive values optimal cut-off values were chosen to identify patients with a low or high risk of reflux esophagitis.

RESULTS

Population characteristics

A total of 403 achalasia patients treated with POEM more than 6 months ago were identified: 189 patients from the Academic Medical Center in Amsterdam and 214 patients from Northwestern Memorial Hospital in Chicago. Of these patients, 252 patients were excluded because of additional treatments prior to or subsequent to POEM or incomplete follow-up. The final derivation cohort consisted of 151 achalasia patients treated with POEM: 71 patients from Amsterdam and 80 patients from Chicago.

The baseline characteristics and findings on manometry, upper endoscopy, barium esophagography and questionnaires before and after POEM are presented in table 7.1. The cohorts between the two hospitals were generally similar, but there were several differences. The BMI before POEM was higher in the Chicago cohort than in Amsterdam. Furthermore, a shorter-length myotomy was performed in Chicago than in Amsterdam, which could not be explained by achalasia subgroup distribution differences, as this was similar in both centers. Furthermore, in Amsterdam the myotomy was often partially full-thickness, whereas in Chicago it was attempted to preserve the longitudinal layer, although

Table 1. Baseline characteristics of the derivation cohort

		Full cohort n = 151	Amsterdam n = 71	Chicago n = 80
Demographic findings	Age (years)	49 ± 16	49 ± 14	48 ± 17
	Gender (male)	95 (63%)	39 (55%)	56 (70%)
	BMI before POEM (kg/m^2)	24 (21 – 28)	23 (21 – 27)	25 (22 – 29) *
	BMI after POEM (kg/m^2)	26 (24 – 29)	25 (23 – 28)	27 (25 – 32)
	Alcohol (current use) [a]	92 (62%)	41 (59%)	51 (64%)
	Alcohol (units per week) [a]	2 (0 – 4)	2 (0 – 7)	2 (0 – 4)
	Smoking (current use) [a]	17 (11%)	9 (13%)	8 (10%)
	Smoking (packyears) [a]	0 (0 – 4)	0 (0 – 15)	0 (0 – 1)
Diagnostics before POEM	Achalasia subtype 1	39 (26%)	12 (17%)	27 (34%)
	2	85 (56%)	46 (65%)	39 (49%)
	3	27 (18%)	13 (18%)	14 (17%)
	LES resting pressure (mmHg) [a]	39 ± 16	33.4 ± 14.3	44.2 ± 16.7 *
	IRP 4-s (mmHg) [a]	31 ± 13	28.2 ± 10.7	33.5 ± 14.1
	Barium column after 5 minutes (cm) [b]	8 (5 – 12)	7 (4 – 9)	10 (6 – 16) *
	Maximum esophageal width (cm) [b]	3.5 (3 – 5)	3.3 (2 – 5)	3.6 (3 – 5)
	GERDQ score (abnormal; > 8) [a]	58 (68%)	39 (65%)	19 (76%)
	Esophagitis (present) [a]	18 (13%)	3 (4%)	2 (3%)
	Hiatus hernia (present) [a]	10 (7%)	5 (7%)	5 (6.3%)
POEM	Total length myotomy (cm)	11 (10 – 13)	12 (11 – 14)	10 (9 – 11) *
	Length esophageal myotomy (cm)	7 (6 – 9)	9 (7 – 10)	6 (6 – 8) *
	Length gastric myotomy (cm)	4 (3 – 4)	4 (3 – 4)	4 (3 – 4)
	Length full-thickness myotomy (cm)	2 (2 – 6)	8 (3 – 10)	2 (0 – 2) *
Diagnostics after POEM	LES resting pressure (mmHg) [b]	16 ± 8	14.4 ± 7.7	17.1 ± 7.7
	IRP 4-s (mmHg) [b]	12 ± 6	11.2 ± 6.7	12.6 ± 5.4
	Barium column after 5 minutes (cm) [a]	2 (0 – 4)	2 (0 – 3)	2 (0 – 5.5)
	GERDQ score (abnormal; > 8) [a]	47 (31%)	24 (34%)	23 (29%)
	PPI use (current use) [a]	56 (37%)	19 (17%)	36 (45%)
	Abnormal esophageal AET (%) [b]	38 (47%)	29 (52%)	9 (36%)
	No reflux esophagitis	72 (48%)	35 (49%)	37 (47%)
	LA Grade A reflux esophagitis	40 (26%)	19 (27%)	21 (26%)
	LA Grade B reflux esophagitis	27 (18%)	10 (14%)	17 (21%)
	LA Grade C or D reflux esophagitis	12 (8%)	7 (10%)	5 (7%)

* $p < 0.05$, [a] 1 – 5 % missing data, [b] 5 – 15 % missing data, BMI = body-mass index, GERDQ = gastroesophageal reflux disease questionnaire, IRP 4-s = 4 second integrated relaxation pressure, LA = Los Angeles classification, LES = lower esophageal sphincter, PPI = proton pump inhibitor, POEM = peroral endoscopic myotomy, AET = acid exposure time

there was often splaying of the muscle fibers, resulting in partial full thickness myotomy. Therefore, we based the prediction model on both groups combined, instead of using one population as derivation cohort and the other population as validation cohort.

Reflux symptoms and esophagitis after treatment

During follow-up 6 months to 2 years after POEM, 47 patients (31%) had abnormal GERDQ scores. More patients had an abnormal GERDQ score before POEM (58 patients; 68%) than after POEM. Reflux symptoms after treatment were not always related to the presence of reflux esophagitis: 62% (29/47) of patients with a high GERDQ score (> 8) had no or mild esophagitis and, vice versa, 20% (21/104) of patients with a normal GERDQ score (≤ 8) had significant reflux esophagitis.

Before treatment, none of the patients had reflux esophagitis. During follow-up 79 patients (52%) developed reflux esophagitis. The majority of these (40 patients; 27%) had LA grade A reflux esophagitis, 27 patients (18%) had LA grade B reflux esophagitis and the remainder (12 patients; 8%) had LA grade C or D reflux esophagitis. These frequencies were similar in the two centers. Only a minority of patients (81 patients) was tested with 24-hour pH-impedance measurement during follow-up. Of these patients, 38 patients (47%) had an abnormally high AET.

When comparing patients with significant reflux esophagitis (LA grade B, C or D) versus patients with absent or mild reflux esophagitis, the most striking difference was a significantly higher body-mass index in patients with significant reflux esophagitis (table 7.2). After POEM, patients with significant reflux esophagitis had a significantly higher BMI. Furthermore, significantly more patients with significant reflux esophagitis had an abnormal GERDQ score (46% versus 26%; p = 0.027). Several typical reflux predictors like age, gender and LES pressure were not significantly different between the two groups.

Prediction model development

We identified 39 patients (26%) with significant reflux esophagitis after POEM, enabling inclusion of four variables in our prediction model. Using backward elimination, two of the selected variables were sequentially excluded based on the smallest contribution to the model fit: first, age was removed (OR 1.006, p = 0.720, df1) and next, gender was removed (OR 1.562, p = 0.349, df1). The eligible predictors that were included in the final model were: initial achalasia subtype, BMI during follow-up, alcohol intake and GERDQ score after POEM. Missing values were achalasia subtype in one patient (0.7%), BMI in eight patients (5.3%), alcohol intake in two patients (1.3%) and GERDQ in ten patients (6.6%). These values were imputed with single stochastic imputation based on fourteen other variables. Using multivariate logistic regression, the odds ratio of the four predictors was calculated (table 7.3). BMI after POEM was a better predictor (OR 1.12, p = 0.005) than the other variables: alcohol intake (OR 1.09, p = 0.054), GERDQ after POEM (OR 1.19, p = 0.07) and initial achalasia subtype (OR 1.4, p = 0.40).

Table 2. Comparison of patients with and without reflux esophagitis LA grade B to D

	Variable	Absent or mild reflux esophagitis (LA grade A reflux esophagitis) n = 112	Significant Reflux esophagitis (LA grade B to D) n = 39
Demographic findings	Age (years)	48 ± 16	51 ± 16
	Gender (male)	68 (61%)	27 (69%)
	BMI before POEM (kg/m^2)	24 (21 – 26)	27 (23 – 32) *
	BMI after POEM (kg/m^2)	26 (23 – 28)	28 (25 – 33) *
	Alcohol (current use) [a]	65 (61%)	27 (71%)
	Alcohol (units per week) [a]	1 (0 – 4)	4 (1 – 7)
	Smoking (current use) [a]	11 (10%)	6 (16%)
	Smoking (packyears) [a]	0 (0 – 1)	0 (0 – 15)
	Achalasia subtype (type 3)	17 (15%)	10 (26%)
Before POEM	LES resting pressure (mmHg) [a]	39 ± 17	39 ± 16
	IRP 4-s (mmHg) [a]	31 ± 14	31 ± 11
	Barium column after 5 minutes (cm) [b]	8.5 (5 – 12)	7.2 (4 – 13)
	Maximum esophageal width (cm) [b]	3.6 (3 – 5)	3 (2 – 4)
	GERDQ score (abnormal; > 8) [a]	44 (66%)	14 (78%)
	Esophagitis (present) [a]	3 (3%)	2 (5%)
	Hiatus hernia (present) [a]	7 (6%)	3 (8%)
POEM	Total length myotomy (cm)	11 (10 – 13)	11 (10 – 12)
	Length esophageal myotomy (cm)	7 (6 – 9)	7 (6 – 10)
	Length gastric myotomy (cm)	4 (3 – 4)	4 (3 – 4)
	Length full-thickness myotomy (cm)	2 (1 – 6)	2 (2 – 8)
After POEM	LES resting pressure (mmHg) [b]	16 ± 7	15 ± 9
	IRP 4-s (mmHg) [b]	12 ± 6	11 ± 6
	Barium column after 5 minutes (cm) [a]	2.2 (0 – 5)	0.0 (0 – 3)
	GERDQ score (abnormal; > 8) [a]	29 (26%)	18 (46%) *
	PPI use (current use) [a]	38 (34%)	17 (44%)
	Abnormal esophageal AET (%) [b]	29 (44%)	9 (60%)

* $p < 0.05$, [a] 1 – 5 % missing data, [b] 5 – 15 % missing data, BMI = body-mass index, GERDQ = gastroesophageal reflux disease questionnaire, IRP 4-s = 4 second integrated relaxation pressure, LA = Los Angeles classification, LES = lower esophageal sphincter, PPI = proton pump inhibitor, POEM = peroral endoscopic myotomy, AET = acid exposure time

Table 3. Outcomes of multivariable logistic regression analysis to predict significant reflux esophagitis after POEM

Variable	Odds Ratio (95% CI)	Standard error	p-value
Initial achalasia subtype (type 3)	1.415 (0.528 - 3.792)	0.503	0.400
BMI after POEM (kg/m^2)	1.120 (1.028 - 1.220)	0.044	0.005
Alcohol (units per week)	1.091 (0.994 - 1.197)	0.047	0.054
GERDQ score after POEM	1.188 (0.986 - 1.431)	0.095	0.070

Significant reflux esophagitis = Los Angeles grade B to D reflux esophagitis

7

Prediction model performance

After correction for optimism by shrinkage of the model, the median predicted probability of significant reflux esophagitis was 22% (IQR 14 - 31%). Regarding patients with significant reflux esophagitis, the median predicted probability by the model was 31% (IQR 22 - 44%). Regarding patients with absent or mild reflux esophagitis, the median predicted probability by the model was 18% (IQR 5 - 28%). Nagelkerke's R^2 showed that
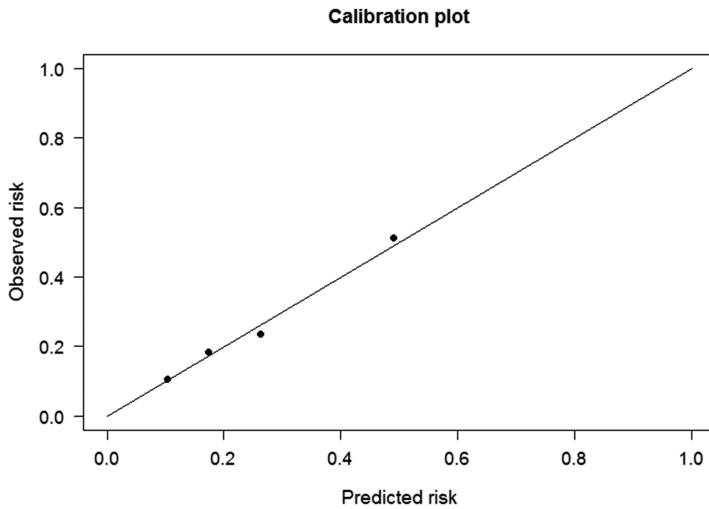
Calibration plot

Figure 1. Calibration plot of the prediction model
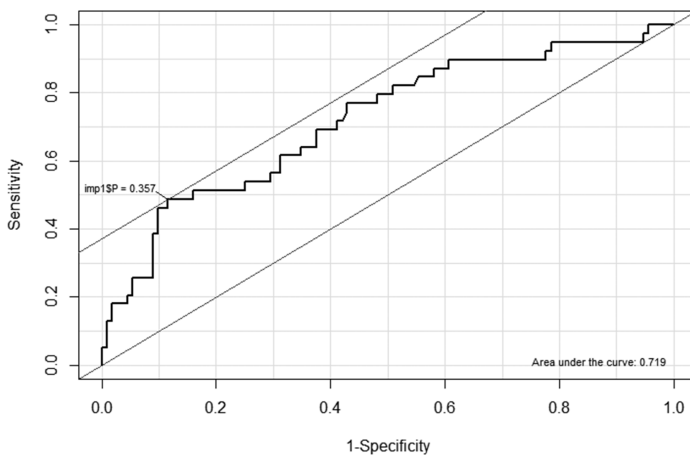
Figure 2. ROC curve of the prediction model

the prediction model explained 20.1% of the variance in outcome. The Hosmer and Lemeshow test showed moderate calibration of the model with at most 7.3% absolute difference between the actually observed risks and predicted risks (Chi-square 2.34, df2, p = 0.31) (figure 7.1). Furthermore, the area under the ROC curve showed that the overall discriminative accuracy of the model is 73% (figure 7.2).

A nomogram was made to enable calculation of the probability of reflux esophagitis for each patient individually (figure 7.3). The model showed a good ability in identifying patients with a low chance of reflux esophagitis, with an optimal cut-off value at a predicted risk of ≤ 20%. This group represented 46% of all cases. This gave a high negative predictive value of 87%, a sensitivity and specificity of 77% and 55% respectively, and a positive predictive value of 37%. The model showed moderate to low ability in identifying patients with a high risk for significant reflux esophagitis. The cut-off value of a predicted probability of ≥ 40% (this group represents 15% of all cases) gave a positive predictive value of 57%, with a sensitivity and specificity of 33% and 91% respectively and a negative predictive value of 80% (table 4).

The model development and performance did not substantially change if patients with LA-A esophagitis were excluded from the analysis, i.e. patients with no esophagitis were compared with LA B-D esophagitis, or if they were included within the reflux esophagitis cohort, i.e. patients with no esophagitis were compared with LA A-D.

DISCUSSION

In this study, a prediction model was developed to predict significant reflux esophagitis in achalasia patients after treatment with POEM. Previous studies have shown that developing

Table 4. Classification accuracy of the prediction model

Predicted probability of significant reflux esophagitis ≤ 20%	n = 151
Positive predictive value	37 %
Negative predictive value	87 %
Sensitivity	77 %
Specificity	55 %
Predicted probability of significant reflux esophagitis ≥ 40%	**n = 151**
Positive predictive value	57 %
Negative predictive value	80 %
Sensitivity	33 %
Specificity	91 %

Significant reflux esophagitis = Los Angeles grade B to D reflux esophagitis
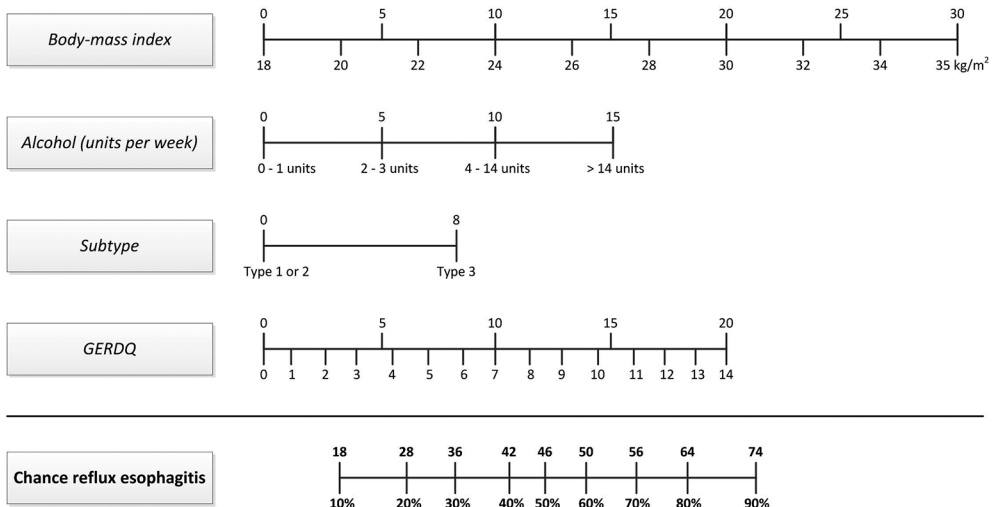
Figure 3. Nomogram of the prediction model

significant reflux esophagitis after POEM is common.[7, 8] Timely identification of patients with esophagitis could prompt treatment and thus prevent development of complications of longstanding esophagitis such as strictures, Barrett's metaplasia and cancer. On the other hand, patients without any risk of esophagitis may not need a follow-up endoscopy at all. We therefore developed a prediction model that allows identification of patients with a low risk for esophagitis. Our model is based on a large international cohort, is easily applicable using only readily available data after POEM and enables a risk calculation for individual patients.

Patients with a low risk of reflux esophagitis can be identified by the model with sufficient accuracy, when using the cut-off value of a predicted risk of ≤ 20%. These patients can be easily identified, because they will have no or only one risk factor. The risk factors are as follows: BMI > 25 kg/m^2, alcohol > 2 units/day, GERDQ > 8 and type 3 achalasia. For patients with only one or no risk factor, we suggest no follow-up endoscopy or PPI treatment, unless when having symptoms. This group represents 46% of all cases. Unfortunately, the model has insufficient accuracy in distinguishing patients with a high risk of reflux esophagitis from those with a moderate risk. Predicted probabilities between 20% and 40% poorly discriminate between reflux esophagitis or no reflux esophagitis, and a predicted probability above 40% only has a moderate discriminative value. We therefore advise for patients with a predicted probability of reflux esophagitis > 20% (two or more risk factors present) PPI treatment and an early follow-up endoscopy after temporal cessation of PPI, and continue PPI for indefinite time in case of significant reflux esophagitis.

The endpoint of significant reflux esophagitis (LA grade B to D) was chosen because this is an objective and clinically very relevant outcome, as it is associated with a higher risk of stricture development, Barrett's metaplasia and esophageal carcinoma. Reflux symptom scores are a less reliable outcome than visible reflux esophagitis during upper endoscopy,[9, 10] because reflux esophagitis does not correlate well with reflux symptoms.[7] A previous study also aiming to find predictors for reflux esophagitis after POEM, selected the DeMeester score as outcome and could, aside from female sex, not find predictors for a high DeMeester score.[4] However, the DeMeester score is based on esophageal acid exposure and in achalasia esophageal acid exposure may not equate to gastro-esophageal reflux, but instead can also be caused by acidification of food remnants or stasis of ingested acidic foods. In another recent study, approximately half of the patients had reflux esophagitis after POEM while only one third had a pathologic DeMeester score.[7] We therefore chose the endpoint of significant reflux esophagitis, defined as Los Angeles grade B to D reflux esophagitis. We left grade A esophagitis out because this has uncertain clinical relevance as it is may be present in healthy asymptomatic subjects.[12-14]

It was challenging to predict significant reflux esophagitis without using invasive parameters. However, a prediction model is only of additional value when not including invasive parameters, because otherwise performing an upper endoscopy would often be a better option. We found BMI as significant predictor of reflux esophagitis, which is also a known risk factor for esophagitis in non-achalasia patients.[26-28] Furthermore, achalasia subtype 3 gave a higher odds for significant reflux esophagitis than achalasia subtype 1 and 2. This can possibly be explained by the longer proximal myotomy in these patients, disrupting the proximal muscle layers, facilitating stasis of reflux.[32] On the other hand this finding is surprising because often remnants of peristalsis are seen in patients with type 3, which could facilitate reflux clearance.[33] The role of the achalasia subtype in reflux is not completely understood. Age and gender were not significant predictors. Although discrepancies were observed in this and previous studies between the presence of reflux symptoms and reflux esophagitis, the GERDQ score was a moderately good predictor of reflux esophagitis.[9]

Based on previous studies, the risk for reflux seems to be higher after POEM than after pneumodilation or Heller myotomy.[7, 8] This can partly be explained by the antireflux wrap during Heller myotomy and the less severe disruption of the LES-muscles during pneumodilation.[7, 34] One could argue to not perform a POEM but rather a pneumodilation or surgical myotomy in patients with a high risk for reflux after POEM, or to counsel patients with a high BMI and alcohol usage before POEM. Our prediction model however, only includes postoperative parameters making this decision impossible to make. We therefore focused on determining a postoperative management for patients after POEM. We tried to identify the optimal cut-off value to avoid unnecessary treatment with PPIs on one hand

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and missing patients with reflux esophagitis on the other hand. One could argue however, that unnecessary PPI treatment is preferable over missing esophagitis. PPIs have only few side effects, most of which are not dangerous and only occurring during chronic use.[35]

While our study demonstrated a potentially clinically-beneficial prediction model for reflux esophagitis after POEM, our study does carry several limitations. Our model development method, including backward elimination and use of categorized variables may be subject to selection bias and associated overfitting or loss of predictive ability, respectively. We prevented however, other possible causes of overfitting by imputing our few missing data, and performing shrinkage of the model, which prevents loss of data and overfitting, respectively.[36] Additionally, we unfortunately did not have the opportunity to externally validate our model in a different population. Since there were too many differences between the two populations we had to assemble them. Additional studies are necessary to externally validate our prediction model, or to optimize it with additional predictors.

In conclusion, this prediction model identifies achalasia patients with a low risk of significant reflux esophagitis (LA grade B to D) after POEM. It predicts a clinically relevant outcome using non-invasive predictors and is based on a large international cohort. The following risk factors were identified: type 3 achalasia, high BMI (> 25 kg/m^2), alcohol intake (> 2 units/day) and reflux symptoms (GERDQ > 8). Patients with less than two risk factors are not at risk for reflux esophagitis and do not need PPI treatment or follow up endoscopy. In patients with two or more risk factors, we suggest performing an early follow-up endoscopy after temporal cessation of PPI and continuing PPI for indefinite time in case of significant reflux esophagitis.

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CHAPTER | 8

MANAGEMENT OF RECURRENT SYMPTOMS AFTER PER-ORAL ENDOSCOPIC MYOTOMY IN ACHALASIA

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ABSTRACT

Background

Peroral endoscopic myotomy (POEM) has been rapidly gaining ground as a treatment for achalasia. Although POEM is a safe and effective treatment, a subset of patients has persistent or recurrent symptoms after POEM. This study aimed to examine the efficacy of different retreatments after failed POEM.

Methods

POEM was performed on 441 achalasia patients at three tertiary care hospitals between 2010 and 2015. A review of prospectively collected data was conducted. All achalasia patients with significant persistent or recurrent symptoms within 3 years after POEM, defined as an Eckardt symptom score > 3, were included.

Results

43/441 (9.8%) patients had persistent or recurrent symptoms after POEM, of which 34 (8%) patients received one or more retreatments. Retreatment with laparoscopic Heller myotomy and re-POEM showed a modest efficacy of 45% and 63% respectively, whereas pneumatic dilatation showed a poor efficacy of only 0 - 20%, depending on the size of the balloon. Male patients were more likely to have retreatment failure than female patients (p = 0.038).

Conclusions

In achalasia patients with persistent or recurrent symptoms after failed POEM, retreatment with laparoscopic Heller myotomy or re-POEM has a higher efficacy than retreatment with pneumatic dilatations. Failure of retreatment occurred more often in male patients.

INTRODUCTION

Achalasia is a rare esophageal motility disorder, characterized by absent peristalsis and incomplete relaxation of the lower esophageal sphincter (LES), resulting in troublesome food passage. Consequently, patients suffer from dysphagia, retrosternal pain, regurgitation and weight loss.[1] Achalasia is induced by progressive degeneration of neurons in the esophageal myenteric plexus. The underlying cause of this degeneration is unknown.[2] Treatment therefore aims at symptom relief by dilating or dissecting (myotomy) the muscle fibers of the LES, removing the barrier that prevents esophageal emptying. In the past, the main treatment modalities were endoscopic pneumatic dilatation, laparoscopic Heller myotomy (LHM) and endoscopic botulinum toxin injections.[3]

Recently peroral endoscopic myotomy (POEM) was introduced as a new treatment for achalasia.[3, 4] POEM is a minimally invasive endoscopic technique to perform a myotomy, successfully implemented within the context of NOTES (Natural Orifice Transluminal Endoscopic Surgery). During the first reported endoscopic myotomy in 1980, the muscle layer of the LES was dissected directly through the mucosal layer.[5] This procedure was not considered safe and thus not implemented.[6] Submucosal tunneling as a safe alternative was first described[7] and performed on animals in 2007.[8] In 2010, the technique was refined and first performed in a series of human patients by Inoue et al.[4] The POEM procedure nowadays consists of creating a submucosal tunnel, followed by a partial myotomy of the circular muscle layer or a full myotomy of the circular and longitudinal muscle layer, and ending with closure of the small mucosal opening in the mid-esophagus.[4]

Several open-label case series demonstrate that POEM is a safe therapy with a short-term success in 82% to 100% of patients, regardless of age or previous therapy for achalasia.[6, 9, 10] Although long-term follow up results of randomized controlled trials are yet unknown, POEM is rapidly gaining ground and more and more centers are implementing the technique as a routine treatment for achalasia.

Although POEM is thus a safe and effective treatment for achalasia, failure of POEM treatment with recurrent or persistent symptoms does occur.[11] A possible explanation for suboptimal results of POEM is the learning curve, as suggested by two studies showing that POEM failure more often occurred within the first 10 to 20 cases in a center.[11, 12] Other possible explanations are an incomplete myotomy or scarring of the myotomy.[11, 13] It is currently not known how these patients should be managed.

This study therefore aimed to investigate the efficacy of different treatments for achalasia patients suffering from persistent or recurrent symptoms after POEM. Moreover, we tried to identify predictors of success of subsequent treatments after failed POEM.

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METHODS

Study subjects

All achalasia patients with recurrent or persistent symptoms at any moment after POEM were identified in three tertiary care hospitals between 2010 and 2015. The hospitals are situated in the USA, the Netherlands and Germany. These three hospitals have been performing POEM for over four years in randomized controlled trials, and all patients are treated according to standard protocols and entered into prospective databases.[4] All patients were included in randomized controlled trials, except one that was treated while the trials were already running. Therefore, in the vast majority, treatment was allocated by the computer. In these trials, in case of symptom recurrence, re-treatment was chosen according to trial protocols. We retrospectively studied these data. We considered symptoms of dysphagia after POEM to be significant when patients presented with an Eckardt symptom score > 3. We excluded patients who underwent POEM for another indication than achalasia. The need for formal medical ethical assessment was waived by the institutional review board of the Academic Medical Center Amsterdam (reference number W14_320 # 14.17.0384).

Data collection

All data were prospectively collected during randomized controlled trials. The principles of the Declaration of Helsinki were followed. We enrolled all patients with recurrent or persisting symptoms after POEM (Eckardt > 3). We collected information on demographic characteristics (age, gender, weight and hospital) and clinical findings at time of diagnosis: onset and type of symptoms, Eckardt symptom score, diagnostic procedures (indicated below) and previous treatments before POEM. Next we collected information on the POEM procedure itself: date and duration of the procedure, length of the tunnel and myotomy, perioperative events (pneumoperitoneum, bleeding and difficult closure) and adverse events. Finally we collected clinical findings during symptom relapse after POEM: onset and type of symptoms, Eckardt symptom score, diagnostic procedures (indicated below) and date, type and efficacy of retreatments after POEM. Retreatment success after failed POEM was defined as an Eckardt ≤ 3 for at least six months after retreatment. Failed retreatment was defined as an Eckardt > 3 at any moment after retreatment. If patients developed recurrent symptoms after a temporarily symptom-free period, regardless the duration of this period, they were also identified as failures.

8.3.3 Diagnostic measurements

Eckardt symptom score

At the time of diagnosis, one and two years after POEM and during symptom relapse after POEM, all patients filled out the Eckardt score.[14] This is a validated questionnaire for achalasia symptoms, containing 4 items. The Eckardt score is the sum of the symptom scores for dysphagia (0 = never, 1 = occasional, 2 = daily and 3 = during each meal),

regurgitation (0 = never, 1 = occasional, 2 = daily and 3 = during each meal), chest pain (0 = never, 1 = occasional, 2 = daily and 3 = during each meal) and weight loss (0 = no weight loss, 1 = <5 kg, 2 = 5-10 kg and 3 = >10 kg). The maximum score, indicating the worst symptoms, is 12. A score > 3 is considered a high score, needing treatment.[14, 15]

Esophageal high-resolution manometry (HRM)

Esophageal HRM was performed in all patients at the time of diagnosis, one and two years after POEM and when necessary also during symptom relapse after POEM. A solid-state HRM catheter (Given imaging, Los Angeles, CA, USA) with 36 circumferential pressure sensors was used. The manometry was performed after a 4-hour fasting state, according to standard protocols.[16, 17] Manoview software (Given Imaging, Los Angeles, CA, USA) was used to analyze the measurements. For the present study we analyzed the 4-s integrated relaxation pressure (IRP-4) of the LES, which is calculated as the median LES pressure related to the gastric pressure during the 4 seconds of lowest LES pressure within a timeframe of 10 seconds after a wet swallow.[18] Achalasia subtypes were determined according to Pandolfino et al.[16] and the Chicago Classification.[19]

Timed barium esophagography

In a subset of patients, timed barium esophagography was performed before POEM, one and two years after POEM and during symptomatic relapse after POEM.[20] After fasting at least eight hours, patients were standing upright while drinking 100-250 mL of a barium sulfate suspension. At 0, 1, 2 and 5 minutes after ingestion, esophageal radiographs were taken. The height of the barium column after 5 minutes and the maximal width of the esophagus were measured in centimeters. The barium column height after 5 minutes was used as a parameter for esophageal emptying.[21]

Esophagogastroduodenoscopy

Upper gastrointestinal endoscopy was performed in all patients before POEM and one and two years after POEM. When necessary it was also performed during symptom relapse. A high-resolution endoscope was used. After inspection of the esophagus, stomach and first part of the duodenum, a retrospective inspection of the fundus was performed. During endoscopy, the presence or absence of esophagitis, a dilated esophagus and stasis of food in the esophagus were always reported.

Statistical analysis

All statistical analyses were performed using SPSS version 23.0 (Armonk, NY, USA). Normally distributed variables were described as mean and range. Not normally distributed variables were described as median and interquartile range (IQR). Proportions were described as number and percentage (%). Statistical difference in proportions between groups was compared using two-tailed Fisher's exact test. Univariate binary logistic regression was

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used to identify predictors of retreatment success after POEM failure. Due to a small number of events we did not perform a multivariate logistic regression analysis. A *p*-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

From a cohort of 441 patients that underwent POEM, excluding technically failed procedures, we identified 43 patients (9.8%; 14 females) with achalasia and an Eckardt score of > 3 at any moment after POEM. Twenty-four patients were included in Germany, 10 patients in the Netherlands and 9 patients in the USA. All POEMs were performed in between august 2010 and January 2015, and follow up was recorded up to august 2015. In Table 8.1 we have summarized the patient characteristics and diagnostic findings before POEM. At the time of POEM, mean age was 42 years (range 17 - 84 years) and median symptom duration was 3 months (range 1 month - 27 years). Subtype distribution of achalasia as assessed before any treatment was: type I in 19 patients (44%); type II in 15 patients (35%); type III in 5 patients (12%) and unspecified type in 4 patients (9%).

Table 1. Patient characteristics and diagnostic measurements of patients with POEM failure

	Before POEM (n = 43)	During symptom relapse after POEM (n = 43)
Male [a]	29 (67%)	-
Age (years) [b]	42 (17 - 84)	-
Achalasia subtype [a]		-
Type 1	19 (44%)	
Type 2	15 (35%)	
Type 3	5 (12%)	
Unspecified type	4 (9%)	
Eckardt score [b]	8 (4 - 11)	5 (4 - 6)
Type of symptoms [a]		
Dysphagia	43 (100%)	40 (93%)
Regurgitation	28 (65%)	23 (53%)
Retrosternal pain	23 (54%)	22 (51%)
Weight loss	2 (5%)	2 (5%)
IRP-4 (mmHg) [c]	21 (16 - 31)	12.5 (11 - 18)
Stasis (cm) [c]	4.8 (1.4 - 6.6)	4.7 (3.0 - 6.4)
Max width (cm) [c]	3.3 (2.5 - 4.6)	3.7 (2.8 - 4.3)

-: similar to situation before POEM, IRP-4: Integrated 4-s relaxation pressure of the lower esophageal sphincter on manometry, Stasis: stasis after 5 minutes on barium esophagography, Max width: maximum width of the esophagus on timed barium esophagography. Data are expressed as a number (%), b mean (range) or c median (IQR).

Before POEM, most patients had either received no previous treatment (22 patients; 51%) or endoscopic dilatations (17 patients; 40%). Only a few patients had received botox injections (2%), or a combination of pneumodilatation with other treatments (7%) (Table 8.2).

Median duration of POEM was 101 minutes (IQR 87 - 127). The median (IQR) length of the submucosal tunnel was 16 cm (13 - 17), and the median (IQR) length of the myotomy was 11 cm (9 - 12), of which 8 cm (6 - 10) esophageal myotomy and 3 cm (2 - 3) gastric myotomy. The following perioperative events were reported: a pneumoperitoneum in 26% of procedures, a perioperative bleeding coagulated with endoscopic coagulation forceps in 9% of procedures, a combination of a pneumoperitoneum and bleeding in 4.5% and a difficult closure in 2.5% of procedures respectively. No adverse events occurred after POEM.

Symptoms after POEM

Median duration of follow-up was 39 months (range 6 - 59 months) after POEM. The median (IQR) relapse time of symptoms was 6 months (range 0 - 36 months) after POEM. Sixteen patients (37%) never had any symptom relief or had recurrent symptoms within 3 months after POEM. The remaining 27 patients (63%) had symptom recurrence after initially good response to POEM. As expected, symptom recurrence was often reported during the follow-up moments one and two years after POEM. Dysphagia was the main symptom in all 43 patients and the majority also had regurgitation (28 patients; 65%). Median Eckardt score measured after symptom relapse after POEM was 5 (IQR 4 - 6).

Diagnostic testing after POEM

During endoscopy, which was performed in 41 patients (95%) during symptom relapse after POEM, esophageal stasis was seen in 28 patients (68%) and esophagitis was seen in five patients (12%), of which four had LA grade A reflux esophagitis and one had LA grade B reflux esophagitis. In 32 patients (75%) an HRM was performed after symptom relapse. Median IRP-4 was 12.5 mmHg (IQR 11.4 - 18.0 mmHg). In 24 patients (56%)

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Table 2. Previous treatments before initial POEM

Previous treatment	Number of patients (%)
None	22 (51 %)
Dilatation *	17 (40 %)
Botox	1 (2 %)
Pneumodilatation and Heller myotomy	2 (5 %)
Pneumodilatation and Botox	1 (2 %)
Total	43 (100%)

* Pneumodilatation 15x, Savary dilatation 2x

barium esophagography was performed after symptom relapse. In these patients, median (IQR) stasis after 2 and 5 minutes was 4.9 (3.9 - 7.0) and 4.7 cm (3.0 - 6.4) respectively, and median diameter of the distal esophagus was 3.7 cm (IQR 2.8 - 4.3).

8.4.4 Efficacy of initial retreatment after POEM

The majority of patients (34 patients; 79%) received one or more subsequent treatments after POEM (Figure 8.1). The other 9 patients refused treatment, chose to start a modified diet or were lost to follow up. None of the patients required a feeding tube. Efficacy of retreatment varied considerably for the choice of treatment.

In 15 patients the initial retreatment was a series of pneumodilatations up to 35 mm (two cases were not started with 30 mm but immediately treated with 35 mm), which was effective in only 22% of the patients. In 8 patients the initial treatment after POEM was a re-POEM, which was effective in 63% of cases. A laparoscopic Heller myotomy (LHM) was
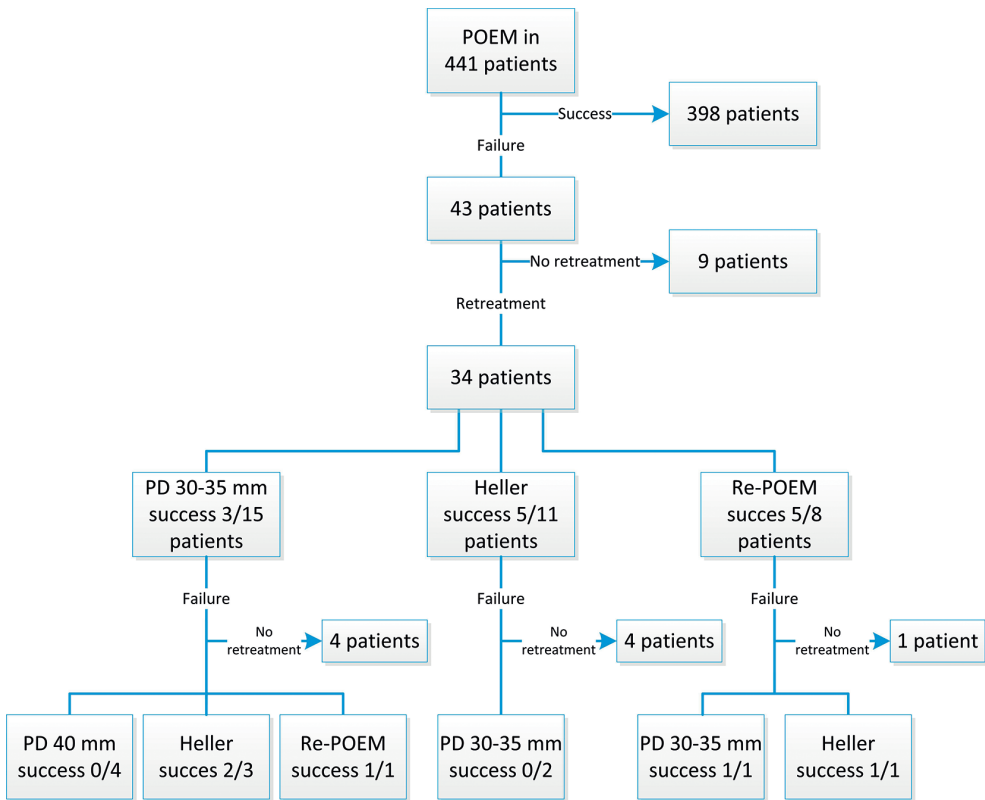
Figure 8.1. Flowchart of patient selection and type of retreatment. PD: Pneumatic dilatation, LHM: Laparoscopic Heller myotomy, POEM: Peroral endoscopic myotomy.

performed as initial retreatment after POEM in 11 patients, which was effective in 45% of cases (Table 8.3). Success percentages between initial retreatment options were compared using a two-tailed Fisher's exact test. Although re-POEM seemed more effective (63%) than pneumatic dilatations (20%) after failed POEM, this difference did not reach statistical significance ($p = 0.071$), likely due to small sample sizes. Also LHM was not significantly more effective (45%) than pneumatic dilatations (20%; $p = 0.218$), as was the case between re-POEM (63%) and LHM (45%; $p = 0.65$).

8.4.5 Efficacy of secondary retreatment after POEM

After the first retreatment, some patients were treated again because of persistent treatment failure (Figure 8.1). When dilatation up to 35 mm was not effective, an additional dilatation up to 40 mm was also not effective (0/4 patients), while LHM after failed pneumodilatation succeeded in 2 out of 3 patients. One patient underwent a re-POEM after failed pneumodilatations, which was successful. After failed LHM after failed POEM, 2 patients underwent pneumatic dilatation which also failed in both patients. After failed re-POEM, one patient underwent a successful LHM and one patient a successful pneumatic dilatation. When taking all retreatments into account, in 17 patients (50%) the final retreatment was effective for at least six months, in the other 17 patients retreatment was only effective for a short time or was never effective at all. No adverse events were reported.

Predictors of retreatment success after POEM

On univariate logistic regression, patients that failed on retreatment after POEM were more often male patients (14/17), as compared to cases with good outcome of retreatment (8/17); (OR 5.25, 95% CI 1.09 - 25.2, $p = 0.038$). Table 8.4 shows that, using univariate logistic regression, we could not find other possible predictors of retreatment success after POEM. Achalasia subtype, age, previous treatments before POEM, symptom duration and findings on HRM or barium esophagography were not predictors of retreatment success.

Table 3. Efficacy of initial re-treatment after failed POEM

Treatment	Successful in	
PD up to 35 mm	3 out of 15 treated patients	20%
PD of 40 mm (after 35 mm)	0 out of 4 treated patients	0%
Re-POEM	5 out of 8 treated patients	63%
LHM	5 out of 11 treated patients	45%

PD: Pneumatic dilatation, POEM: Peroral endoscopic myotomy, LHM: Laparoscopic Heller myotomy

Table 4. Possible predictors of good retreatment efficacy after failed POEM

	Factor	Odds ratio *	95% Confidence interval	p-value
Baseline characteristics	Female gender	5.25	1.09 - 25.2	0.03
	Age	0.97	0.93 - 1.02	0.24
	Achalasia subtype	1.00	-	-
Before initial POEM	Stasis (cm)	0.88	0.58 - 1.32	0.52
	Max width (cm)	1.00	-	-
	IRP-4 (mmHg)	1.04	0.96 - 1.13	0.36
	Symptom duration (months)	0.97	0.92 - 1.01	0.14
	Previous treatment (yes)	0.49	0.13 - 1.92	0.31
After initial POEM	Stasis (cm)	1.19	0.72 - 1.97	0.49
	Max width (cm)	1.29	0.54 - 3.06	0.56
	IRP-4 (mmHg)	1.05	0.91 - 1.21	0.55
	Time to symptom relapse (months)	1.04	0.96 - 1.13	0.37

-: 95% CI and *P*-value not stated, not significant. POEM: Peroral endoscopic myotomy, IRP-4: Integrated 4-s relaxation pressure of the lower esophageal sphincter on manometry, Stasis: stasis after 5 minutes on barium esophagography, Max width: maximum width of the esophagus on timed barium esophagography.
* Odds ratio resulting from univariate binary logistic regression analysis

DISCUSSION

Although many reports show that POEM is a very effective treatment for achalasia, treatment failure does occur. We describe the management of achalasia patients with recurrent or persistent achalasia symptoms after POEM. In our cohort, laparoscopic Heller myotomy (LHM) and re-POEM showed a moderate efficacy after POEM failure, whereas pneumodilatation showed a rather poor efficacy. After failure on 35-mm diameter pneumodilatation, 40-mm diameter balloon dilatations were not effective either. The chance of failure of retreatment was higher for male patients.

Management of POEM failure has not been studied extensively before. A small subgroup analysis was reported by Werner et al.[11] They retreated 13 patients after POEM failure, 5 of whom finally achieved good symptom relief. Pneumodilatation failed in all cases, whereas LHM led to symptom relief in 63% and re-POEM in 56% of patients. This is in accordance with our findings of a modest efficacy of LHM (45%) and re-POEM (63%), and a poor efficacy of pneumodilatations (22%) after failed POEM. An international registry of 46 patients showed an even higher clinical success of re-POEM in 85% of patients.[22] A smaller study in which fifteen patients underwent a re-POEM reported therapeutic success in all patients.[23] Based on this limited evidence, it seems that after failed POEM, re-POEM or LHM are better treatment options than pneumatic dilatations. It should

be taken into account however, that re-POEM is technically more demanding due to post-operative fibrosis.[23]

Reasons for POEM failure have not been studied extensively. Two studies suggested that the learning curve influences POEM treatment outcome.[11, 12] In one study, 8 POEM failures were identified within the first 10 cases in each center.[11] The other study more extensively studied the learning curve in POEM.[12] The 2 POEM failures that occurred in 22 cases were case numbers 1 and 3 and the Eckardt score after 1 year was negatively correlated to the case number. A likely mechanistic explanation for POEM failure is an incomplete myotomy, which is supported by two previous studies that both doubt the durability of POEM.[11, 13] One study observed an increase in LES pressure in all failed cases after 8 and 11 months, compared to LES pressure at 3 months after POEM.[11] The other study, in 112 patients after POEM, also reported a slight increase in IRP-4 within one year after POEM, although this was not statistically significant.[13] In our group of patients with symptoms after POEM, no significant correlation was seen between IRP-4 height and duration of the symptom-free period. The median IRP-4 during symptom relapse was 13 mmHg, resulting in a few patients with a normal IRP during symptom relapse. Two of these patients had a very wide esophagus, wider than 6 centimeters, explaining the symptoms due to poor emptying. In the other patients we hypothesize that the symptoms are caused by an incomplete myotomy, especially when having early treatment failure, or formation of fibrotic tissue around the LES, probably resulting in less distensibility of the LES but not a high IRP. We have described similar achalasia patients with low IRP but stasis on barium esophagogram recently.[24]

Possibly, we can learn from experience gained in treatment of cases of failed LHM. Failed LHM and subsequent retreatment efficacy have been studied more extensively than failed POEM. After failed LHM, pneumatic dilatation is reasonably effective (56 - 76%)[25-27] and redo-LHM or POEM seem to yield better results (75 - 85%).[28-31] We cannot explain why the efficacy of pneumodilatation after POEM failure is poor, compared to the modest efficacy of pneumatic dilatation after LHM failure. In their review, Patti et al.[32] listed possible causes for recurrent symptoms after LHM. Two of these causes might also apply to failed POEM: 1) scarring of the myotomy, due to too limited incision or to previous treatments with botox or pneumodilatation; 2) postoperative gastroesophageal reflux. Both occur mostly after a symptom-free interval. Gastroesophageal reflux following POEM occurs in 20 - 46% of patients, leading to erosive lesions in 36.8% of patients.[6, 11] When achalasia symptoms persist or recur after POEM, one should be aware of the possibility that they are caused by reflux, to prevent an erroneous diagnosis of POEM failure. In the present study, we ruled out GERD as cause of the symptoms by means of endoscopy, or we treated it empirically before diagnosing failure of POEM. Also, presence of significant stasis at the barium esophagogram studies suggests that it was not reflux but stasis that caused recurrent symptoms in our patients with recurrent symptoms after POEM.

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In the present study, we identified female gender as a predictor of retreatment success after POEM failure. This is in accordance with the observation made by Werner et al[11], who reported that in their cohort all patients with persistent symptoms after POEM were men. Young men have also been shown to have a greater failure risk after pneumatic dilatation.[33, 34] We have no explanation for the fact that men apparently have a greater failure rate of (certain types of) achalasia treatment. To our knowledge, no other studies investigated predictors for retreatment success after POEM failure.

In conclusion, re-POEM and LHM are the most effective retreatments after POEM failure while the efficacy of retreatment with pneumodilatations is poor. Failure of retreatment occurs more often in male patients.

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CHAPTER | 9

ESOPHAGEAL STASIS IN ACHALASIA PATIENTS WITHOUT SYMPTOMS AFTER TREATMENT DOES NOT PREDICT SYMPTOM RECURRENCE

Froukje B van Hoeij, André JPM Smout and Albert J Bredenoord

ABSTRACT

Background

After achalasia treatment, a subset of patients has poor esophageal emptying without having symptoms. There is no consensus on whether or not to pre-emptively treat these patients. We hypothesized that, if left untreated, these patients will experience earlier symptom recurrence than patients without stasis.

Methods

99 treated achalasia patients who were in clinical remission (Eckardt ≤ 3) at 3 months after treatment were divided into two groups, based on presence or absence of esophageal stasis on a timed barium esophagogram performed after 3 months.

Results

Two years after initial treatment, patients with stasis after treatment still had a wider esophagus (3 cm; IQR 2.2-3.8) and more stasis (3.5 cm; IQR 1.9-5.6) than patients without stasis (1.8 cm wide and 0 cm stasis; both $p < 0.001$). In patients with stasis, the esophageal diameter had increased from 2.5 to 3.0 cm within two years of follow-up. The symptoms, need for and time to retreatment were comparable between the two groups. Quality of life and reflux symptoms were also comparable between the two groups.

Conclusions

Although patients with stasis initially had a wider esophagus and two years after treatment also had a higher degree of stasis and a more dilated esophagus, compared to patients without stasis, they did not have a higher chance of requiring retreatment. We conclude that stasis in symptom-free achalasia patients after treatment does not predict treatment failure within two years and can therefore not serve as a sole reason for retreatment.

INTRODUCTION

Achalasia is a neurodegenerative disease affecting myenteric neurons in the esophageal wall, leading to diminished motility of the esophagus. This impairs food transit through the esophagus, causing dysphagia, regurgitation, chest pain and weight loss.[1] Diagnosis is made by manometry, supported by symptom assessment, timed barium esophagography and endoscopy. Manometric criteria to diagnose achalasia are loss of peristalsis and impaired relaxation of the lower esophageal sphincter (LES).[2] On timed barium esophagography (TBE) the barium column height, which is a measure of esophageal emptying, and width of the esophagus are measured.[3]

Hitherto there is no curative treatment for achalasia, but there are several symptomatic therapies to improve esophageal clearance, by dilating or incising the LES. The preferred treatment options are pneumatic dilatation with a balloon, laparoscopic Heller myotomy or peroral endoscopic myotomy (POEM).[4] There is clear consensus that treatment is necessary when achalasia is confirmed by symptoms, manometry and timed barium esophagography.[5]

The treatment goal is to relieve symptoms and improve esophageal emptying.[5] Symptoms however, show a poor correlation with esophageal emptying,[6-10] creating a subset of patients with good symptom resolution, despite poor esophageal emptying.[11] In general, treatment is considered to have been successful when the patient has become asymptomatic, regardless of the persisting stasis of barium on TBE.[12] It is unclear whether this is justifiable, considering the fact that long-term complications of chronic stasis can be esophageal squamous carcinoma and a dilated esophagus or mega-esophagus, defining end-stage achalasia.[13] These data support the need to perform additional measurements besides symptom-assessment, to better evaluate esophageal emptying.[5, 10]

In contrast to symptom assessment, timed barium esophagography is very useful to evaluate esophageal emptying reliably.[14, 15] Several observational studies have shown that stasis[16], no decrease of barium column height[11, 17] and widening of the esophagus[18] on TBE after treatment, are good predictors of persisting symptoms and thus need for retreatment in symptomatic patients.[11, 16-18] These data support the use of esophagography in addition to symptom-assessment, even in symptom-free patients, as is recommended by the guideline of the American College of Gastroenterology.[5, 10] There are no data however, to support retreatment of asymptomatic patients with stasis on TBE.[5]

We hypothesize that asymptomatic patients with persisting stasis after treatment, if left untreated, have a higher chance of symptom recurrence and thus need for retreatment than patients without stasis, despite the absence of symptoms. Furthermore, patients with few symptoms but significant stasis could develop esophageal dilation and mega-esophagus

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at the long term. If this would be the case, pre-emptive treatment of asymptomatic patients with poor esophageal emptying should be considered. To test this hypothesis, we compared symptoms and retreatment rates between asymptomatic patients with and without stasis after treatment.

METHODS

Patient population

For the current study, patient data were collected systematically as patients were treated and followed-up according to standardized protocols in our center. All patients had been diagnosed with symptomatic manometry-confirmed idiopathic achalasia, were 18-80 years old, and had no previous surgery of esophagus or stomach, pregnancy, esophageal malignancies, Barrett's esophagus, eosinophilic esophagitis or esophageal strictures. Follow-up was performed according to standardized protocols (questionnaires and diagnostic investigations 3 months, 1 year and 2 years after initial treatment). At each follow-up visit a timed barium esophagography and a manometry were performed and the patient filled out questionnaires regarding the Eckardt symptom score, general quality of life and gastroesophageal reflux symptoms. The need for formal medical ethical assessment was waived by the institutional review board of the Academic Medical Center Amsterdam (reference number W16_198 # 16.231).

Study design

We retrospectively reviewed these prospectively collected data. Inclusion criteria for the current study were: adult achalasia patients who were in clinical remission the first 3 months after treatment (either pneumodilation, laparoscopic Heller myotomy or peroral endoscopic myotomy) and who completed all investigations at all follow-up moments. Clinical remission was defined as an Eckardt symptom score ≤ 3.

We divided the patients into two groups: |1| clinical remission with stasis on TBE and |2| clinical remission without stasis, three months after treatment. Stasis was defined as a barium column height > 0 cm in the esophagus 5 minutes after swallowing the barium suspension. Patients received additional retreatment when having an Eckardt score > 3 in combination with an elevated IRP and/or stasis on TBE and after exclusion of other possible causes for the symptoms, according to trial protocols.

Our primary endpoints were the proportion of patients (%) that received additional retreatment after 2 years and time to retreatment (months). Secondary endpoints were the Eckardt symptom score, height of the barium column on TBE after 5 minutes (cm), maximum width of the esophagus on TBE (cm), proportion of patients with inadequate

LES relaxation on manometry (mmHg), quality of life and reflux symptom score 2 years after treatment.

Materials and methods

Timed barium esophagography

After drinking 100-200 mL low-density barium sulphate suspension, upright frontal photos of the esophagus were obtained at 1, 2, and 5 minutes after ingestion, according to a standardized procedure.[3] The height of the barium column above the distal tapered esophagus and the maximum width of the distal esophagus were measured in centimeters. The barium column height after 5 minutes was used as a measure of esophageal emptying.[15]

Esophageal manometry

A manometry catheter was transnasally placed in the esophagus and stomach. The catheter measured the esophageal pressure pattern throughout the whole esophagus, while the patient drank 10 sips of 5 mL of water according to a standardized procedure.[19] Dedicated software (Manoview, Given Imaging, Los Angeles, CA, USA) was used to analyze the measurement. Manometric criteria to diagnose achalasia are loss of peristalsis and impaired relaxation of the lower esophageal sphincter (LES), defined by an integrated relaxation pressure (IRP) of the LES > 15 mmHg.[2] Based on contractility pattern, achalasia was classified in three subtypes: classic achalasia with absent contractility (type 1), achalasia with panesophageal pressurization (type 2) or spastic achalasia (type 3).[20] A subgroup of our patients was measured using conventional manometry. The catheter placement was exactly the same, but different software was used for analysis (Medical Measurement Systems, Enschede, the Netherlands). Manometric criteria to diagnose achalasia are aperistalsis and incomplete LES relaxation, defined by a relaxation resting pressure of the LES > 8 mmHg.[21] Criteria for identifying achalasia subtypes were validated for conventional manometry.[22]

Eckardt symptom score

The severity of typical achalasia symptoms was measured using the Eckardt symptom score, assessed by a physician.[23] The Eckardt score is the sum of the four symptom scores for dysphagia, regurgitation, chest pain (0 = never, 1 = occasional, 2 = daily and 3 = during each meal) and weight loss (0 = no weight loss, 1 = <5 kg, 2 = 5-10 kg and 3 = >10 kg). The maximum score, indicating the worst symptoms, is 12. A score > 3 is considered a high score, needing treatment.[10, 23]

Gastroesophageal Reflux Disease Questionnaire (GERDQ)

The current frequency of gastro-esophageal reflux symptoms (heartburn and regurgitation) and the impact of these symptoms on the person's daily life were measured with the GERDQ, a validated 6-item self-assessment questionnaire.[24] It consists of questions on frequency

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of heartburn, regurgitation, dyspepsia, nausea, insomnia and medication intake. For each question a score 0 – 3 is given (0 = 0 days, 1 = 1 day, 2 = 2-3 days, 3 = 4-7 days), with a maximum of 18 for the complete questionnaire. A score < 8 means a low probability of GERD.[24, 25] The questionnaire has a good diagnostic validity in symptomatic patients.[25]

Short Form-36 Health Survey (SF-36)

The generic quality of life was measured using the SF-36, a 36-item self-assessment questionnaire.[26] The SF-36 consists of eight scores on eight different domains: bodily pain, emotional role functioning, general health perception, mental health, physical functioning, physical role functioning, social role functioning and vitality. Each score is calculated on a 0 – 100 scale, with 0 indicating the worst health status and 100 a perfect health status.[26] We used a validated Dutch version of the SF-36. Item discriminant validity and internal consistency reliability are high across all eight scales.[27]

Treatment methods

POEM was performed under general anesthesia, using carbon dioxide insufflation, according to a previously described standardized protocol.[28] Laparoscopic Heller myotomy was performed including an anterior fundoplication, according to a standardized protocol.[29] Pneumatic dilatation was performed with a Rigiflex balloon. During the first dilatation, a 30 mm balloon was used, followed by a 35 mm balloon after two weeks.[30] When no symptom resolution (Eckardt < 3) was achieved, a 40 mm balloon dilatation was performed. In case of symptom recurrence after more than 1 year, again a dilatation with a 35 mm and 40 mm balloon were performed with two weeks in between.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY, USA). Summary statistics were generated for sociodemographic and clinical characteristics in each group. Proportions were described as number and percentage. Normally distributed variables were described as mean, standard deviation (SD) and range. Not normally distributed variables were described as median and interquartile range (IQR). Baseline comparability of numerical variables between groups was tested with an unpaired t-test or Mann-Whitney U test, depending on the distribution of data. Comparability of proportions was tested with the two-tailed Fisher's exact test.

The proportion of patients requiring additional treatment of their achalasia within two years was calculated in each group, with a corresponding 95% confidence interval obtained by bootstrapping, using the simple sampling method with 1000 samples, to estimate the precision of the statistical inference for the target population. Time to retreatment was compared between the groups with log-rank tests on Kaplan-Meier estimates. Correlation between Eckardt score and barium column height was calculated with Spearman's rank

test. Changes of Eckardt scores and barium column height within groups during follow-up were tested with Wilcoxon Signed-Rank test. A corresponding 95% confidence interval was calculated via bootstrapping, using the same method and number of bootstraps as mentioned above.

RESULTS

Baseline patient characteristics

After exclusion of five patients with incomplete follow-up, we included 99 achalasia patients (58 male), with an Eckardt score ≤ 3 after treatment taking place between 2003 and 2014. Reasons for incomplete follow-up were unwillingness to travel a long distance (n = 2), pregnancy prohibiting TBE investigation (n = 1) and loss to follow-up for unknown reasons (n =2).

The mean age of these patients during treatment was 51 years (± 14, range 19 – 80). The distribution of achalasia subtypes was 30% type I, 53% type 2 and 17% type 3. Patients were treated with pneumatic dilatations (n = 41), POEM (n = 30) or laparoscopic Heller myotomy (n = 24). Only four patients had received more than one treatment: pneumodilations and POEM, Heller myotomy and POEM, pneumodilations and Heller myotomy and a combination of all three treatments. Gender, age, achalasia subtypes and treatment allocation were equally distributed among the groups with and without stasis on TBE after 3 months (Table 9.1). Before initial treatment, there was no difference in Eckardt score, number of patients with inadequate LES relaxation, barium column height and maximum esophageal width between the groups. After three months, the median height of the barium column at 5 min was 4.4 cm (IQR 2.6 – 6.2) in the group with stasis. There was a difference in median diameter of the distal esophagus between the groups; patients without stasis had a smaller median diameter (2 cm (IQR 1.7 – 2.3)) than patients with stasis (2.5 cm (IQR 2 – 3.9)), $p < 0.001$. The median Eckardt score (1 (IQR 0 – 2) versus 1 (IQR 1 – 2)) and the number of patients with inadequate LES relaxation (6 (11%) versus 7 patients (15%)) after treatment were not different between the two groups. The correlation between Eckardt score and barium column height was very poor, with a correlation coefficient of r = 0.19, $p = 0.06$.

Two years after treatment

Two years after initial treatment the proportion of patients that received additional retreatment was identical in the two groups. In the no-stasis group, 10/53 (19%) patients (95% CI 11 – 32%) received additional treatment, compared with 8/46 (17%) patients (95% CI 9 – 31%) in the stasis group (Relative Risk 0.905; 95% CI 0.32 – 2.53; $p = 1.00$) (table 9.2). Also, the median time to additional treatment was comparable between the two

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Time to retreatment
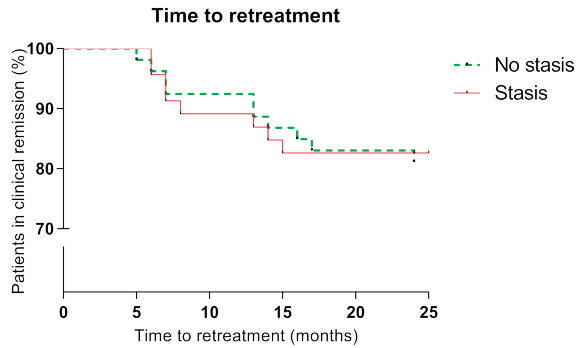
Figure 1. Time to retreatment. Survival curve showing the time to symptom recurrence requiring additional retreatment in patients with and without stasis after initial treatment.

Table 1. Patient characteristics and diagnostic measurements before treatment

	No stasis after 3 months (n = 53)	Stasis after 3 months (n = 46)	p-value
Male [a]	28 (53%)	30 (65%)	0.23
Age (years) [b]	53 (± 14)	48 (± 14)	0.97
Achalasia subtype [a]			
Type 1	13 (25%)	17 (37%)	0.40
Type 2	30 (57%)	22 (48%)	
Type 3	10 (19%)	7 (15%)	
Treatment allocation [a]			
PD	22 (42%)	20 (44%)	0.11
LHM	17 (32%)	7 (15%)	
POEM	14 (26%)	19 (41%)	
Eckardt score [c]	8 (6 – 9)	7 (5 – 9)	0.38
Stasis after 5 min (cm) [c]	7.9 (5.0 – 11.5)	7.3 (5.0 – 12.2)	0.84
Inadequate LES relaxation [a]	52 (98%)	43 (96%)	0.59
Maximum esophageal diameter (cm) [c]	3.1 (2.6 – 3.9)	3.8 (3.0 – 4.8)	0.13

PD: pneumatic dilatations, LES: lower esophageal sphincter, LHM: laparoscopic Heller myotomy, POEM: peroral endoscopic myotomy. Stasis after 5 minutes and maximum esophageal diameter are measured on timed barium esophagography. Inadequate LES relaxation is measured as IRP-4 on high resolution manometry and as relaxation resting pressure on conventional manometry. Data are expressed as a number (%), b mean (SD) or c median (IQR).

groups. Patients with stasis after treatment required new treatment after a median of 8 months (95% CI 5.1 – 10.9) and patients without stasis after a median of 13 months (95% CI 4.7 – 21.3); p = 0.893 (Figure 9.1). In total, a high percentage of patients (82%) remained in clinical remission.

There was still a difference in stasis on barium esophagography between the two groups. The stasis group had a median column height of 3.5 cm (IQR 1.9 – 5.6), while the no-stasis group still had good esophageal emptying after 2 years (0 cm (IQR 0 – 0, range 0 - 9), p < 0.001). Also, the difference in median diameter of the distal esophagus had become larger, compared to directly after treatment. The no-stasis group had a smaller median esophageal diameter (1.8 cm (IQR 1.5 – 2.7)) than the stasis group (3.0 cm (IQR 2.2 – 3.8)), p < 0.001 (Figure 9.2).

The median Eckardt score was comparable sbetween the two groups, with a very poor correlation between Eckardt score and barium column height: r = 0.12, p = 0.25. The stasis group had a statistically significant lower general health perception (67 out of 100) than the no-stasis group (77 out of 100); p = 0.025 two years after initial treatment. On the other seven domains no difference in quality of life was found between the two groups. There was also no difference in reflux symptom score after two years between patients with or without stasis (Table 9.3).

Table 2. Follow-up and diagnostic measurements 2 years after treatment

	No stasis after 3 months (n = 53)	Stasis after 3 months (n = 46)	p-value
Stasis after 5 minutes (cm)	0.0 (0.0 – 0.0)	3.5 (1.9 – 5.6)	< .001
Inadequate LES relaxation	8 (16%)	7 (17%)	1.00
Maximum esophageal diameter (cm)	1.8 (1.5 – 2.7)	3.0 (2.2 – 3.8)	< .001
Patients that received retreatment	10 (19%)	8 (17%)	1.00

Inadequate LES relaxation is measured as IRP-4 on high resolution manometry and as relaxation resting pressure on conventional manometry. Data are expressed as median (IQR) or number (%).

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Maximum esophageal diameter
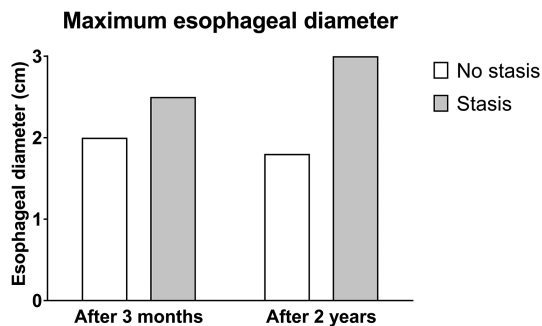
Figure 2. Maximum esophageal diameter. Changes in (median) maximum esophageal diameter between 3 months and 2 years after initial treatment, in patients with and without stasis after initial treatment.

Changes in Eckardt score and barium column height between 3 months and 2 years after treatment were calculated. In both patient groups, a significant increase of the Eckardt score was measured after 2 years of follow-up. In both groups, the median Eckardt score had increased with + 1 point (95% CI 0 – 1), $p < 0.001$. In the stasis group there was no significant change in barium column height between 3 months and 2 years.

DISCUSSION

In a group of achalasia patients that were in clinical remission after treatment, we aimed to compare long-term symptom recurrence and need for additional treatment between patients with and without stasis after treatment. We hypothesized that, if left untreated, patients with stasis would have a higher chance of symptom recurrence and retreatment.

A high percentage of patients (82%) remained in clinical remission for two years. We did not find, however, that asymptomatic patients with persisting stasis after treatment more often had symptom recurrence needing retreatment than patients without stasis. We therefore conclude that stasis does not predict symptom recurrence and the need for retreatment within two years after treatment.

In contrast to our results, other studies did show that, even in symptom-free patients, timed barium esophagography is useful to identify patients at risk of persistent symptoms needing retreatment.[10, 15] Vaezi et al.[15] found that 90% of patients with poor esophageal emptying but complete symptom relief, failed within one year of treatment.[15] However,

Table 3. Patient-reported outcome measures after 2 years

	No stasis after 3 months (n = 53)	Stasis after 3 months (n = 46)	p-value
Eckardt score	2 (1 – 3)	2 (1 – 3)	0.21
GERDQ	6 (6 – 8)	7 (6 – 9)	0.61
SF-36			
Bodily pain	84 (72 – 100)	72 (62 – 84)	0.10
General health perception	77 (47 – 87)	67 (57 – 87)	**0.025**
Mental health	84 (72 – 92)	80 (68 – 88)	0.29
Physical functioning	95 (80 – 100)	100 (90 – 100)	0.87
Role emotional	100 (100 – 100)	100 (100 – 100)	0.14
Role physical	100 (100 – 100)	100 (75 – 100)	0.67
Social functioning	100 (75 – 100)	100 (88 – 100)	0.98
Vitality	75 (60 – 80)	70 (60 – 80)	0.78

GERDQ : gastro-esophageal reflux disease questionnaire, SF-36: short form generic quality of life questionnaire. Data are expressed as median (IQR).

their patients were significantly older and often were only treated with pneumodilation to 30 mm, which may explain the high secondary failure rate. Other studies in symptomatic patients concluded that a smaller decrease in barium column height or width predicts persistence of symptoms, leading to additional treatment.[17, 18, 31] In these observational studies barium column height was measured after 1 or 2 minutes, while we measured barium height after 5 minutes. Their patients were thus experiencing more symptoms during less longstanding stasis, compared to our patients. We think this can explain our lower symptom rates. Although both our patient groups had low symptom scores two years after initial treatment, the general health perception was significantly lower in the stasis group than the no-stasis group. We are not sure about the validity and clinical relevance of this finding, while on the other seven quality of life domains no difference was found between the two groups and these patients had a low Eckardt score and GERDQ score. Possibly, the patients with stasis had to eat slower, or avoid certain types of food, which could contribute to poorer general health perception.

Our results show that patients with stasis had a more dilated esophageal lumen after initial treatment than patients without stasis. The stasis remained present during the first two years after treatment and dilation even became more pronounced, which is a concern and warrants further investigation. It is known that long-lasting stasis can lead to dilation of the esophagus, which can develop into megaesophagus ultimately requiring esophagectomy.[13] Progression towards megaesophagus takes years however, therefore longer follow-up time is needed to evaluate this. Esophageal stasis and widening is also thought to be associated with long-term complications such as dysplasia and ultimately squamous cell carcinoma.[32] These complications of long-lasting stasis were not assessed in our study, and thus we cannot draw conclusions with respect to the risks associated with accepting esophageal widening.

In our cohort, patients received additional treatment per protocol when they had an Eckardt score > 3, regardless of other diagnostic testing. It turned out that patients with stasis on TBE after initial treatment did not have a higher Eckardt score than patients without stasis. There are conflicting results regarding this finding in previous studies. Several studies have shown that the correlation between symptoms and esophageal emptying is relatively poor.[6-10] This is in line with our results, as patients with and without stasis had similar Eckardt scores, and a very poor correlation between Eckardt score and barium column height. One factor that could explain this lack of symptoms in patients with stasis is diminished esophageal mechanosensitivity and chemosensitivity in more advanced disease, which might theoretically be caused by both motor and sensory nerve loss.[33] There are also some observational studies however, that did find a significant association between symptom improvement and barium column height after treatment.[11, 17, 18, 31] An observational study found that a detailed history is more sensitive than the Eckardt score

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to detect deterioration in esophageal emptying.[7] A few studies have shown that a high IRP on manometry after treatment is a good predictor of treatment failure,[34, 35] and that improvement of IRP was associated with symptom relief and improved emptying on TBE.[35] Rohof et al. found that esophageal stasis on TBE is a better predictor of treatment failure than LES relaxation pressure on manometry.[16] These findings altogether support the need to perform additional measurements besides symptom assessment, to better evaluate esophageal emptying, even in asymptomatic patients.[5, 10]

In conclusion, we identified a subgroup of achalasia patients who have mild to no symptoms after treatment but who nevertheless have poor esophageal emptying on TBE. Although after 2 years these patients show more stasis and esophageal widening than patients without stasis, their symptoms did not prompt more additional treatment than patients with complete or near-complete esophageal emptying. More long-term data would be of value to evaluate whether these patients would nevertheless benefit from pre-emptive treatment as their esophageal luminal dilation does seem to increase.

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CHAPTER | 10

CHARACTERIZATION OF IDIOPATHIC ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

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ABSTRACT

Background

Esophagogastric junction (EGJ) outflow obstruction is a manometric diagnosis, characterized by an elevated relaxation pressure (IRP4) of the lower esophageal sphincter (LES) and intact or weak peristalsis. The etiology and preferred treatment remain unknown. We describe a large patient cohort in detail, for a better understanding of this rare disorder.

Methods

We included 47 patients, diagnosed with EGJ outflow obstruction on high-resolution manometry (HRM) between 2012 and December 2014.

Results

Idiopathic EGJ outflow obstruction was diagnosed in 34 patients (age 57, M:F 7:26). The majority (91%) of patients presented with retrosternal pain or dysphagia. The median (IQR) for various HRM parameters was; IRP4 18.9 mmHg (18-23), intrabolus pressure (IBP) 8.3 mmHg (5-12) and basal LES pressure 27.5 mmHg (22-33). Peristaltic breaks were seen in 88% and elevated IBP_{max} in 74% of patients. No patients had stasis, difficult LES passage or esophageal dilation on endoscopy. Only 7/25 patients (28%) had stasis on barium esophagography. In 26 patients (82%) no treatment was required: 18 had symptoms judged unrelated to outflow obstruction, 5 had spontaneous symptom relief, 3 declined therapy. Eight patients were treated: 5 received botox injections with a good but short-lived effect, 3 received pneumatic dilatation, of which 1 was successful. Three patients were diagnosed with achalasia on a subsequent manometry.

Conclusions

Primary EGJ outflow obstruction has an unclear clinical significance. A substantial part of patients has unrelated symptoms, spontaneous symptom relief or no stasis. Treated patients showed a beneficial response to botox injections. A small proportion develops achalasia at follow-up.

INTRODUCTION

Esophagogastric junction (EGJ) outflow obstruction is a diagnosis made by high-resolution manometry (HRM), characterized by incomplete relaxation of the esophagogastric junction in combination with preserved peristalsis.[1, 2] Patients often present with symptoms of dysphagia, chest pain or a combination of both.[1, 3] The etiology of this disease has not been completely clarified yet. The elevated relaxation pressure can be caused by impaired relaxation of the crural diaphragm or lower esophageal sphincter (LES) or by a mechanical obstruction, for example a neoplasm or stricture.[4-7] It is also frequently considered as a variant of achalasia or as an early-stage achalasia.[1, 2, 7]

The diagnosis is defined by an elevated 4-s integrated relaxation pressure (IRP4), in combination with preserved or weak peristalsis on HRM, such that the criteria for achalasia are not met.[2] Often it is accompanied by an elevated intrabolus pressure (IBP), which is considered a logical consequence of impaired relaxation and thus validating the determination of impaired EGJ relaxation.[1, 7] In addition to endoscopy and HRM, various other diagnostics are recommended to identify underlying causes for incomplete relaxation. Most often suggested are a CT scan and/or endoscopic ultrasound to exclude infiltrative or inflammatory causes.[7, 8]

Distinguishing secondary outflow obstruction (for example caused by a mechanical obstruction) is important, because patients with mechanical obstruction need different therapy than patients with primary or idiopathic EGJ outflow obstruction. The finding of an EGJ outflow obstruction in the absence of a mechanical etiology is accompanied by clinical uncertainty. Some of these patients seem to have an early stage of achalasia, while others have no obstructive symptoms whatsoever and the elevated IRP only seems to be a coincidental finding without any relevance or clinical implications. However, if symptoms are correlating to the EGJ outflow obstruction, or if stasis is seen on barium esophagography, therapy is usually directed towards lowering LES pressure. Generally, conventional achalasia therapy is given, consisting of endoscopic dilation or intrasphincteric botulinum toxin injection.[5] Sometimes even a myotomy is performed.[1]

Since little is known this far on this condition, the aim of our study was to describe a large cohort of patients with primary EGJ outflow obstruction in detail and to investigate whether HRM parameters or the presence of stasis could differentiate between those patients with symptomatic EGJ outflow obstruction as a potential early achalasia stadium and those patients for whom the high IRP is a coincidental finding without clinical relevance.

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METHODS

Patients

We included all patients from the outpatient clinic of our tertiary referral hospital, diagnosed with EGJ outflow obstruction between January 2012 and December 2014.

All patients underwent a routine high-resolution manometry. An EGJ outflow obstruction was defined as a combination of preserved peristalsis and incomplete EGJ relaxation.[2] More precisely, the preserved peristalsis was defined as some instances of intact peristalsis or weak peristalsis with small breaks. The incomplete EGJ relaxation was measured by an integrated relaxation pressure (IRP4) of 15 mmHg or higher. All electronic patient records were reviewed in detail for medical history and endoscopic records. Based on these findings, patients were divided into two groups: patients with secondary outflow obstruction, caused by a mechanical etiology, and patients with primary or idiopathic outflow obstruction. Patients with secondary EGJ outflow obstruction were excluded from further analyses. Subsequently, electronic patient records of patients with primary outflow obstruction were reviewed in detail for barium esophagography records and follow-up data on symptoms, diagnosis, investigations, treatment and treatment effect.

Esophageal manometry

A solid-state manometry catheter (Given imaging, Los Angeles, CA, USA), with 36 circumferential sensors, was used to perform esophageal HRM measurements. Recording was performed according to a standardized protocol in our center.[9] After a 4-hour fasting period, the manometry catheter was placed transnasally and positioned adequately to record from hypopharynx to stomach. The patient was placed in supine position and asked to swallow ten boluses of 5-mL of water. Subsequently, the patient was asked not to swallow for 30 seconds in order to measure a baseline recording for positioning of markers of the upper and lower esophageal sphincter and measuring the basal LES pressure.

HRM analyses

Esophageal HRM measurements were analyzed using ManoView Analysis software 3.0 (Given imaging, Los Angeles, CA, USA). Analyses were performed according to a previously described method.[10] After thermal compensation, markers for upper and lower esophageal sphincter and gastric pressure were manually placed in the baseline segment. The basal LES pressure during the baseline recording was automatically calculated by the software. Next, the ten swallows were evaluated separately. If necessary, the contractile deceleration point marker and the slope of the contractile front velocity were manually corrected. Following this, distal latency, distal contractile integral, average intrabolus pressure, maximum intrabolus pressure and IRP4 were automatically calculated by the software. In Figure 10.1, we display a contour pressure plot depicting how the software calculated the intrabolus pressure during LES relaxation (IBP_{LESR}) and the maximum intrabolus pressure
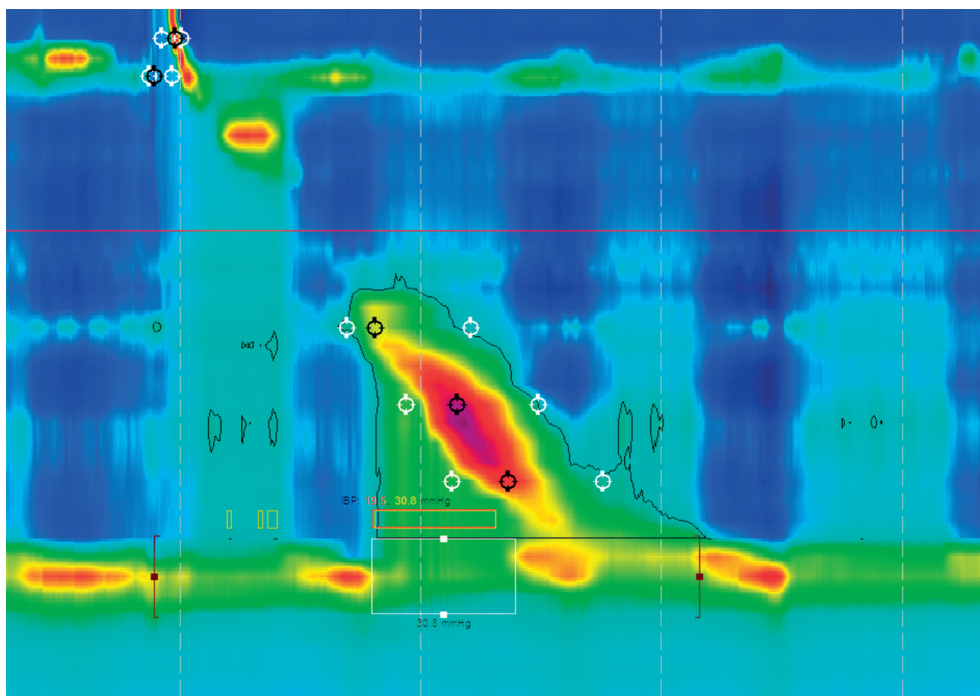
Figure 1. This plot is an example of an EGJ outflow obstruction with accompanying elevated IBP. The IBP$_{LESR}$ is displayed and calculated within the red boxes in the IBP region. It is the average pressure in the IBP region during LES relaxation, relative to the gastric pressure. The IBP$_{max}$ is displayed and calculated within the yellow boxes in the IBP region. It is the mean of the maximum pressure in the IBP region, measured within a noncontinuous duration of 3 second width.

(IBP$_{max}$). The IBP$_{LESR}$ is the average IBP during LES relaxation. The IBP$_{max}$ is the mean of the maximum IBP pressure.

Statistical analysis

Statistical analyses were performed using SPSS version 20 (SPSS, Inc, Chicago, IL, USA). Continuous data were expressed as median (interquartile range (IQR)). Patient groups were compared using the Mann-Whitney U-test. Proportions were compared using the Chi square test. We considered $p<0.05$ statistically significant.

RESULTS

Primary and secondary EGJ outflow obstruction

A total of 1142 esophageal high-resolution manometric studies were performed in our hospital in three years' time. EGJ outflow obstruction was diagnosed in 47 patients. In 13

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(28%) of these patients (mean age 56 years, range 42-72, M:F 7:6), a mechanical obstruction was found to be the underlying etiology of the outflow obstruction. In 12 patients this was diagnosed during upper endoscopy, in one patient during barium esophagography. Causes were intrathoracic stomach (2x), paraesophageal hernia, Schatzki ring, esophageal cancer, esophageal metastasis, vascular compression, mitochondrial myopathy, gastric band (2x), fundoplication and previous atresia operation. These patients were excluded from further analyses. Patients without underlying mechanical etiology were considered having primary or idiopathic EGJ outflow obstruction.

Patient characteristics

Primary or idiopathic EGJ outflow obstruction was diagnosed in 34 patients (mean age 57 years, range 22-81, M:F 7:27). Symptoms of these patients are summarized in Table 10.1. Median duration of symptoms was 12 months (IQR 6-74 months). The majority of patients presented with dysphagia or retrosternal pain as dominant symptom. Only three patients presented with solely non-achalasia symptoms (cough, globus or dyspepsia). Five patients (15%) were on opiates for chronic back- or joint pain.

HRM characteristics

The various HRM parameters for these patients are summarized in Table 10.2. All patients had an elevated IRP4, with a median (IQR) of 18.9 mmHg (18-23). The intrabolus pressure during LES relaxation was elevated in 50% of patients, with a median (IQR) of 8.3 mmHg (5-12). The maximum intrabolus pressure was elevated in 74% of patients, with a median (IQR) of 18.3 mmHg (14-24). Median (IQR) basal LES pressure was 27.5 mmHg (22-33), distal contractile integral 1019 mmHg·s·cm (569-1749), and distal latency 6.0 s (5.2-7.1). Peristaltic breaks were seen in 88% of patients, with a median length of 2.4 cm. A significantly lower basal LES pressure was found in patients with dysphagia as a dominant symptom (26.4 mmHg) versus patients with other dominant symptoms (36.4 mmHg; $p<0.05$). No other differences in HRM parameters, stasis or treatment effect were seen between patients with and without dysphagia as dominant symptom. No statistically significant differences in symptoms, HRM parameters or treatment effect were found between patients with or without elevated intrabolus pressure.

Table 1. Presenting symptoms in all 35 patients diagnosed with primary EGJ outflow obstruction

Symptom	Number (%) of patients
Retrosternal pain	24 (71%)
Dysphagia	23 (68%)
Regurgitation	12 (35%)
Weight loss	11 (32%)
Other complaints *	5 (15%)

* Cough, dyspepsia (3x), globus

Upper endoscopy and timed barium esophagography

None of the patients with primary EGJ outflow obstruction had stasis of food or luminal dilation on upper endoscopy. Only one patient had difficult LES passage on upper endoscopy, this patient was diagnosed with achalasia on a HRM 18 months later. In 25 patients a timed barium esophagography was performed, which showed a dilated esophagus in 3 patients (12%) and stasis in 7 patients (28%). Patients with stasis were significantly older (70 years, ± 5) than patients without stasis (54 years, ±16; *p*=0.018). No statistically significant differences in symptoms, HRM parameters or treatment effect were found between patients with or without stasis on barium swallow.

Treatment

In 26 patients (76%) with primary EGJ outflow obstruction, treatment was not required. The reasons for withholding therapy are summarized in Table 10.3: 13 patients had symptoms judged not to be correlated to an outflow obstruction, 5 patients were found to have another explanation for dysphagia such as reflux esophagitis, 5 patients had spontaneous symptom relief and 3 patients declined therapy. The remaining eight patients (24%) had typical achalasia symptoms with dysphagia as dominant symptom in all, followed

Table 2. High-resolution manometry parameters in all 35 patients diagnosed with primary EGJ outflow obstruction

HRM parameter	Median (IQR)
IRP4 (mmHg)	18.9 (18-23)
IBP (mmHg)	8.3 (5-12)
IBP$_{max}$ (mmHg)	18.3 (14-24)
Basal LES pressure (mmHg)	27.5 (22-33)
DCI (mmHg·s·cm)	1019 (569-1749)
DL (s)	6.0 (5.2-7.1)

Data are presented as median (IQR). IRP4: integrated 4-sec relaxation pressure, IBP: average intrabolus pressure during LES relaxation, IBP$_{max}$: maximum intrabolus pressure, DCI: distal contractile integral, DL: distal latency.

Table 3. Reasons for no treatment for primary EGJ outflow obstruction in 26 patients

Reason	Number of patients (%)
Continuous retrosternal pain, deemed not related to obstruction	8 (31%)
Other explanation for symptoms*	5 (19%)
Non-obstructive symptoms**	5 (19%)
Spontaneous symptom relief	5 (19%)
Mild symptoms, patient declined therapy	3 (12%)

* Reflux esophagitis (2x), esophageal hypersensitivity, weak peristalsis, proximal dysphagia and stasis after cervical botox treatment. ** Cough, dyspepsia (3x), globus

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by retrosternal pain and regurgitation in six patients and weight loss in three patients (Table 10.1). For this reason they were treated with conventional achalasia therapy. Five patients received intrasphincteric botox injections which resulted in a good but short-lived effect in all. Pneumatic dilatation was effective in one patient and unsuccessful in two other patients. The eight patients in whom treatment was deemed necessary did not have a statistically significant higher IRP4, higher IBP or more often stasis or dilation on barium swallow or other abnormal findings in additional diagnostics. They were treated based on their typical achalasia symptoms which were judged to be caused by the EGJ outflow obstruction and the absence of an alternative explanation for their symptoms.

Follow-up

Three of the eight treated patients were diagnosed with achalasia during follow-up on the basis of a subsequent manometry after 11 and 18 months respectively. One of these patients had no stasis or dilatation on previous barium esophagography. In the other patient, no previous esophagography was performed.

Of the other five treated patients, three patients that received botox injections were symptom-free for 6 to 10 months hitherto. One of them redeveloped retrosternal pain and infrequent mild dysphagia, but did not yet receive additional treatment. Two patients that received pneumatic dilatation continued to have symptoms of retrosternal pain, without effect of calcium channel blockers.

DISCUSSION

In this study we describe a cohort of patients with primary, idiopathic EGJ outflow obstruction in detail. This is the largest series and most comprehensive description of this group of patients thus far. We investigate whether HRM parameters or the presence of stasis could differentiate between those patients with symptomatic EGJ outflow obstruction as a potential early achalasia stadium and those patients in whom the high IRP is a coincidental finding without clinical relevance.

The group of patients with primary EGJ outflow obstruction was found to be very heterogeneous. Only a minority (24%) of patients with primary outflow obstruction had typical and severe achalasia symptoms, most likely caused by outflow obstruction. They received conventional achalasia therapy, resulting in a good effect in 75% after the first treatment. The other patients presented with a variety of symptoms such as retrosternal pain not related to eating or other non-obstructive symptoms and sometimes these symptoms disappeared spontaneously.

Based on additional HRM characteristics or barium esophagography findings, it was not possible to distinguish patients with typical achalasia symptoms from patients without

symptoms judged to be caused by EGJ outflow obstruction. The decision to treat the patients in our series was mainly based on the nature and severity of their symptoms and the absence of a different explanation for their symptoms. In some previous studies, different additional diagnostics are recommended in order to discriminate clinically important EGJ outflow obstruction with impaired bolus transit from incidental findings, for example EndoFLIP or impedance measurement. But this is expert opinion and not based on data.[7, 11]

Although the numbers are very small, botulinum toxin injections had a good effect in all five treated patients, while pneumatic dilatation only had effect in 1 out of 3 patients. A previous study of Scherer et al.[1] studied the clinical response to conventional achalasia therapies in nine patients with functional EGJ outflow obstruction. They found a poor treatment response to either conventional treatment in six patients. In their study Heller myotomy was found to be effective in all three treated patients. However, in that study, only a symptom relief persisting for more than one year was regarded as a positive response.[1] Another study evaluating botulinum toxin injections in patients with EGJ outflow obstruction, revealed symptomatic relief in 73% at 1 month.[3] It was found that chest pain, younger age and contraction amplitudes >180mmHg independently predicted short-term response to botox. The use of botox is limited by its variable and transient effect.[3] No other data is available on treatment effect for primary EGJ outflow obstruction. In our cohort, a minority of patients had spontaneous symptom relief. For this reason, it seems justifiable to wait a short time before treating.

Three of our patients with primary EGJ outflow obstruction developed a full-blown achalasia during follow-up. These patients had no impaired peristalsis on previous HRM and no abnormalities on previous barium esophagography. All patients were seen recently and there are thus no data on long-term follow-up on these subjects, leading to incomplete knowledge of long-term treatment effect and development of achalasia. One previous study recommends the rapid swallow test to distinguish achalasia from EGJ outflow obstruction, because it evokes peristalsis and LES relaxation in healthy individuals or functional outflow obstruction, while in patients with esophageal spasm and achalasia, this response will be incomplete or absent.[5, 12]

The presence of an elevated IRP in the absence of an elevated IBP is an indistinct finding. We added an example pressure contour plot of such a swallow (Figure 10.2). Apart from a true primary EGJ outflow obstruction, there are alternative mechanisms that can contribute to an elevated IRP. First of all, the use of the 95% confidence interval to determine the normal upper value of the IRP, causes 5% of normal subjects to have a high IRP.[10] Potentially also, crural contractions due to discomfort with the test, can cause an elevated IRP.[13] In the current study, we can not rule out the presence of these mechanisms causing a high IRP in the absence of a true outflow obstruction. These limitations of the IRP are resulting in an ambiguous clinical validity of EGJ outflow obstruction as a diagnosis.

In conclusion, primary, idiopathic EGJ outflow obstruction is a manometric diagnosis with unclear clinical significance. A substantial part of patients has no symptoms that can be explained by outflow obstruction and symptoms disappear spontaneously in some. Patients with symptoms compatible with outflow obstruction showed a beneficial response to treatment with botox injections. Prospective long-term studies should be performed to determine the optimal management for this disorder and to identify predictors of clinically important outflow obstruction and achalasia development.
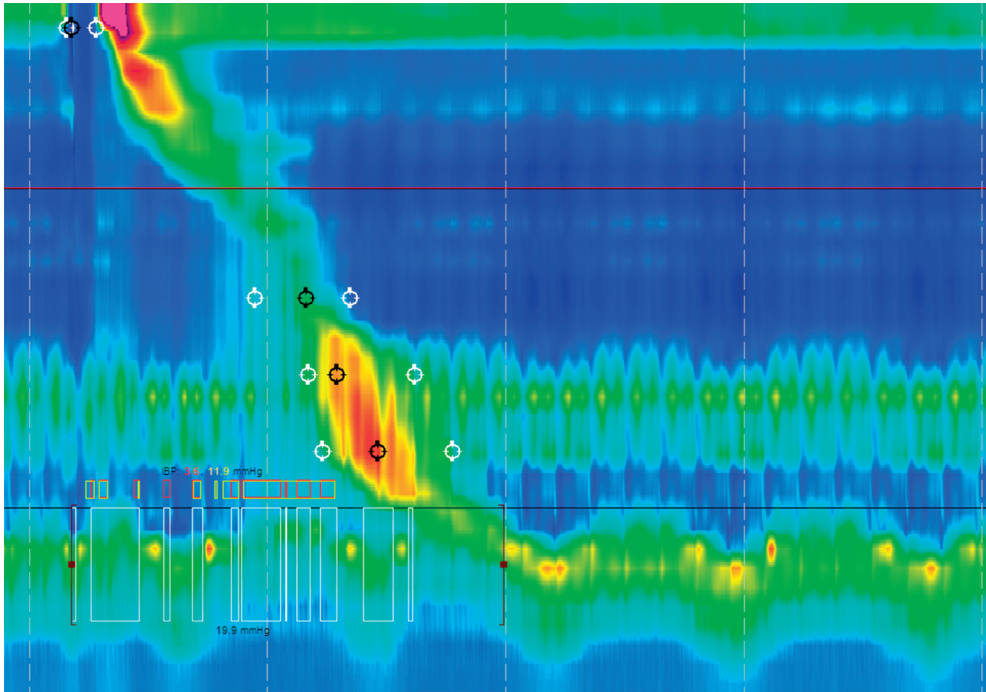
Figure 2. This plot is an example of an EGJ outflow obstruction without elevated IBP. It is indistinct whether an elevated IRP in the absence of a high IBP is clinically relevant, or caused by a limitation of the IRP measurement.

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CHAPTER | 11

GENERAL DISCUSSION

The studies in this thesis evaluated the pathogenesis, diagnostic pathways and treatment strategies for esophageal dysfunction. We evaluated 1) symptom generation in gastroesophageal reflux disease (GERD), 2) the role of high-resolution manometry (HRM) in the diagnosis of GERD, 3) efficacy and safety of achalasia treatments, and 4) the long-term management of achalasia and esophagogastric junction (EGJ) outflow obstruction. We believe that our findings add to the knowledge of these diseases. This general discussion elaborates on the consequences our findings may have for optimizing the diagnostic and treatment strategies for esophageal dysfunction.

WHAT CAUSES SYMPTOMS IN GERD?

The first aim of this thesis was to improve our understanding of symptom generation in GERD. Better understanding of the etiology behind symptoms in patients with GERD could be the roadmap to new therapeutic targets. Most GERD patients are more sensitive to reflux than healthy subjects, even in the absence of visible erosions.[1, 2] Several studies report that hypersensitivity to acid in the distal esophagus is strongly associated with (microscopically) impaired mucosal integrity of the distal esophagus.[3, 4] Impaired mucosal integrity enables reflux to reach the nociceptors and cause heartburn more easily.[2] We were urged to further investigate this mechanism by two situations of discrepancy between mucosal damage and symptom severity. First, patients with Barrett's esophagus, thus severe mucosal damage, have no enhanced reflux perception.[5] Secondly, the increased reflux sensitivity in GERD patients seems to be even worse for reflux reaching the proximal part of the esophagus.[6] We hypothesized that this was caused by a microscopic damage of the mucosa in the proximal esophagus.

To evaluate our hypothesis that reflux sensitivity is related with microscopic lesions of the mucosa in the proximal esophagus, in **chapter 2** both symptom severity and mucosal damage in the proximal as well as the distal esophagus were measured in GERD patients. After a 7-day discontinuation of anti-reflux medication, we observed more mucosal damage in the distal esophagus, while acid perfusion in the proximal esophagus caused earlier pain. We concluded that the hypersensitivity in the proximal esophagus cannot be explained by microscopic mucosal damage. Although our hypothesis was not confirmed, our study demonstrated that a larger reflux volume is not likely causing the earlier perception of proximal reflux, as the infused acid volume was similar in the proximal and distal esophagus. Other previously suggested underlying mechanisms for enhanced proximal sensitivity are delayed acid clearance or a larger exposed esophageal area.[7, 8] In our study, the proximal acid infusion area was larger than the distal infusion area, as is the case in a 'normal' reflux episode. This implies that a larger exposed esophageal area can still be a possible explanation for enhanced proximal sensitivity.

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Possibly, we can learn from previously found factors that are related with reflux sensitivity to all types of reflux episodes, not only proximal extending reflux episodes, in GERD patients. Known factors contributing to increased esophageal sensitivity are central sensitization, upregulation of acid sensitive receptors, and specific components (gas and acidity) within the refluxate.[4, 9-12] It has also been demonstrated that psychological stress can shorten the time to acid perception during an acid perfusion test.[13] Another study found that proximal hypersensitivity could be caused by more superficially positioned nociceptors in the proximal esophagus.[14] Although the underlying mechanisms for reflux symptoms are not yet completely understood, it would be interesting to further investigate the role of the more superficially located nociceptors in reflux hypersensitivity. If this causal relation is confirmed, the effect of topical protection of the mucosa or neuromodulators should be investigated as promising new therapeutic options.[15, 16] This is of particular interest in GERD patients with proton pump inhibitor (PPI)-refractory symptoms and hypersensitivity to acid.[17, 18] As the majority of GERD patients shows a good response to PPI treatment, this will remain the main therapy. More so because PPIs are safe, very effective, cheap and widely available.[19]

THE ROLE OF HIGH-RESOLUTION MANOMETRY IN GERD

The second aim of this thesis, was to evaluate the role of high-resolution manometry (HRM) in diagnosing GERD. Endoscopy is the first diagnostic step for suspected GERD, but during endoscopy only patients with visible reflux complications like erosions or peptic strictures can be diagnosed.[20] The gold standard for diagnosing GERD, is a 24-hour pH-impedance measurement.[21] However, before performing a pH-impedance measurement, an HRM has to be performed to exclude other esophageal disorders with comparable symptoms and to determine the correct position for the pH-sensor during pH-impedance measurement. Given the overlap in symptoms between GERD and esophageal motility disorders, and given that HRM is one of the first diagnostic steps in these patients, it would be helpful to be able to distinguish (a subgroup of) GERD patients using solely HRM.

In **chapter 3** we describe that it was not possible to diagnose GERD with HRM. Patients with GERD have a lower LES pressure, lower contraction amplitude and more often a hiatal hernia, but these findings are also often found in healthy subjects, making it impossible to diagnose GERD with HRM alone. This conclusion is not surprising, as GERD is a multifactorial disease, not only caused by functional abnormalities that are measurable with HRM, but also by patient characteristics like age, gender, weight, sensitivity to acid and components of the refluxate.[22] Although HRM is thus able to precisely measure contributing factors to GERD such as hiatus hernia, hypotensive LES and ineffective or absent peristalsis, the precise relation between these motility abnormalities and the severity of reflux disease

remains unclear. More precisely, we do not know whether motility abnormalities initiate GERD, or inversely, whether reflux initiates motility abnormalities.[23, 24] A prospective study comparing HRM findings in GERD patients before and after successful treatment can give insight in the relationship between motility abnormalities and GERD severity. Also, a study evaluating the ability of HRM to predict the severity of GERD would be of value to determine the clinical value of HRM in GERD.

We concluded that pH-impedance measurement additional to HRM is necessary to diagnose GERD in patients who do not have visible abnormalities during endoscopy. Yet, there are two important functions of HRM in GERD patients. First, in patients with medication-refractory GERD that need a surgical anti-reflux intervention, HRM can assess the esophageal peristalsis. Sufficient es0phageal peristalsis is necessary to prevent dysphagia after anti-reflux surgery.[25] Secondly, HRM can be used to diagnose achalasia, EGJ outflow obstruction or other motility disorders in patients with suspected GERD. Occasionally, patients with achalasia are misdiagnosed as GERD, due to the overlap in symptoms.[26] Therefore, an HRM should always be performed in patients with suspected GERD and no good effect of adequate treatment.

In EGJ outflow obstruction, HRM is the gold standard for diagnosis and assessment of treatment effect.[27] EGJ outflow obstruction is a relatively new diagnosis, defined by the following manometric criteria: normal peristalsis and a non-relaxing lower esophageal sphincter.[27] There is no well-defined treatment strategy for this disease, and the role of HRM in choice of treatment is yet unclear.[27, 28] Therefore, in **chapter 10**, we studied a group of patients with EGJ outflow obstruction, aiming to find the most effective treatment options. A subgroup of patients had no obstructive symptoms, spontaneous symptom relief and/or no delayed esophageal emptying. In these patients the clinical relevance of the HRM diagnosis is unclear. On the contrary, a minority of patients (9%) developed achalasia within a year after the diagnosis of EGJ outflow obstruction. Using HRM, we could not distinguish these forthcoming achalasia patients. Therefore, HRM is necessary in diagnosing EGJ outflow obstruction, but not always sufficient to determine a definitive therapy and management. Future studies should focus on comparing diagnostic findings between patients with beginning achalasia and patients with spontaneous symptom relief, in order to enable differentiation of these patients, and to further characterize different underlying etiologies of EGJ outflow obstruction.

In addition to endoscopy and HRM, use of other diagnostic tools like barium esophagography to establish esophageal emptying, a CT scan or endoscopic ultrasound to identify underlying causes for incomplete relaxation are recommended.[29, 30] Also, the endoscopic functional luminal imaging probe (EndoFLIP), a new diagnostic measurement tool, is rapidly gaining ground for diagnosing esophageal dysfunction.[31] EndoFLIP is a balloon that

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measures the distensibility (stiffness) of the esophageal wall and esophagogastric junction. Recent studies showed that EndoFLIP is equivalent to HRM in diagnosing achalasia, with a sensitivity of 100% for detecting achalasia and 95% for detecting other major motility disorders.[32] EndoFLIP can detect an abnormal response to esophageal distension, which enhances the functional evaluation of non-obstructive dysphagia.[32] Therefore, possibly in EGJ outflow obstruction, EndoFLIP can serve as a tool to distinguish forthcoming achalasia patients from coincidental findings of a high EGJ pressure, and to guide treatment choice in EGJ outflow obstruction. In **chapter 10** we recommend a waiting period before starting treatment, to exclude patients with spontaneous symptom relief, or a coincidental finding. In 'true' functional EGJ outflow obstruction with delayed emptying (and without underlying mechanical or inflammatory cause), we saw good efficacy of botulinum toxin injections and a moderate efficacy of pneumatic dilations. Other studies reported good efficacy of botox and peroral endoscopic myotomy (POEM), and conflicting efficacy of pneumatic dilations, although the treated number of patients was very small.[33] Additional therapeutic trials directly comparing treatment efficacy of different treatment options in EGJ outflow obstruction may provide insight in the optimal treatment for these patients.

EFFICACY AND SAFETY OF ACHALASIA TREATMENTS

The third aim of this thesis was to analyze the efficacy and safety of different achalasia treatments. The therapeutic management of achalasia is a challenging and important task. With no curative therapy for achalasia available, all treatments are symptomatic, aiming to improve esophageal emptying.[34] Due to the chronic and progressive character of the disease, many achalasia patients have to undergo several treatments during their life.[35] Therefore, it is important to identify the most effective and safe method of all achalasia treatments.

For identification of effectiveness and safety of methods, we needed more fundamental information on incidence and prevalence of achalasia. In **chapter 4** therefore, we assembled information on incidence, prevalence and cost of achalasia in the Netherlands. For the past nine years, the incidence of achalasia was 2.2 per 100.000 persons (approximately 375 new achalasia patients each year in the Netherlands) and the prevalence was 15 per 100.000 persons. Initial costs were higher for treatment requiring overnight hospital stay (POEM and/or Heller myotomy), while follow-up costs were higher for patients needing retreatment. In general, retreatment rate is highest for botulinum toxin injections, followed by pneumatic dilations, whereas POEM and Heller have lower retreatment rates.[36-38] Two previous studies and one randomized controlled trial (RCT) concluded that, on the long term, pneumatic dilation is superior to Heller myotomy in cost-effectiveness.[39-41] There are no long-term data available on cost-effectiveness of POEM yet because the procedure was first described in 2010.

When trying to analyze the efficacy and safety of treatments, results of RCTs are of particular interest. A randomized controlled trial is the only suitable way to accurately compare efficacy and safety between treatments. Hitherto, one large RCT was performed, comparing Heller myotomy with pneumatic dilations.[36, 42] Two RCTs are currently running, comparing POEM with Heller myotomy, and POEM with pneumatic dilations.[43, 44] When combining (preliminary) results of these trials, pneumatic dilations and Heller myotomy have comparable success rates after at least 5 years follow-up, although pneumatic dilations have to be performed repeatedly (table 12.1).[36] Peroral endoscopic myotomy seems to have better short-term efficacy than pneumatic dilations and comparable efficacy to Heller myotomy, although no long-term results longer than 5 years are yet available to assure this.[42, 43] Two dominant guidelines recommend graded pneumatic dilation or a laparoscopic Heller myotomy with partial fundoplication as the initial preferred treatment of achalasia.[45, 46] Peroral endoscopic myotomy is not yet included in the guidelines, but has also become an initial preferred treatment.[47] With **chapter 5, chapter 6**, **chapter 7** and **chapter 8** we aimed to increase knowledge on the efficacy and safety of treatment of achalasia with botulinum toxin injections, pneumatic dilations or POEM.

Although botulinum toxin injections are regarded the safest treatment option in achalasia, a number of case reports on severe complications have been published.[48-51] We performed a comprehensive evaluation of a large cohort for a clear judgment on safety. In **chapter 6**, we confirmed that botulinum toxin (botox) is indeed a safe therapy for achalasia, with only 7.9% chance of mild side effects like chest pain or heartburn, even in elderly patients with comorbidities. The very rare severe side effects (0.2% mediastinitis) however, cannot be predicted. Compared to other achalasia treatments, botox has the lowest morbidity and mortality rate.[37, 52] It therefore remains the safest option for high-risk achalasia patients. Nevertheless, botox has a very short-lived effect and it needs to be repeated every few months.[53, 54] It is therefore not a viable treatment option in young and healthy patients. Those patients should be offered another treatment with a longer duration of effect.[34]

Pneumatic dilation and POEM are alternative therapies. In **chapter 5** we aimed to establish the optimal treatment protocol for pneumatic dilation. Pneumatic dilation can be performed in many different ways, using different balloon sizes, inflation pressures, inflation durations and number of dilations. According to our meta-analysis, the optimal

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Table 1. Efficacy of achalasia treatments, results from randomized controlled trials. POEM = peroral endoscopic myotomy

	Pneumodilation	Heller myotomy	POEM
1-year efficacy [42,43]	70-90%	93%	92%
5-year efficacy [36]	82%	84%	-

protocol was a graded approach, starting with a 30-mm balloon, and offering a 35-mm and 40-mm balloon in patients with insufficient symptom relief. Reported efficacy of all different methods for dilation varied between 50% and 90%.[55, 56] When using our recommended treatment protocol (30 – 35 – 40 mm), a consequent success rate of around 90% was seen after one year. Furthermore, the risk of perforation is significantly lower when a graded approach followed.

In **chapter 8** we found that POEM has a good short-term efficacy in almost 90% of patients. We furthermore identified efficacy of different treatments after failed POEM, which will be discussed later. In **chapter 7** we established that the risk of reflux esophagitis was approximately 50% after POEM. This is in concordance with previous literature.[43, 57] Based on our results, patients with a high BMI, alcohol intake, achalasia type 3 and reflux symptoms are especially at risk for reflux esophagitis after POEM. We suggest that these patients are treated empirically with proton pump inhibitors and offered an early endoscopy for evaluation of reflux esophagitis. Additional studies are necessary to externally validate this prediction model, or to optimize it with additional predictors.

Summarizing, botox is the safest treatment for achalasia, but demands regular retreatment within a few months and is therefore only suitable for elderly high-risk patients. Pneumatic dilation, Heller myotomy and POEM seem to have comparable efficacy in untreated achalasia patients, especially when using our optimal scheme for pneumatic dilation. Pneumatic dilation however, is less cost-effective than Heller myotomy, and probably also POEM. All three treatments are safe, although POEM increased the risk for reflux esophagitis compared with pneumatic dilation and Heller, while pneumatic dilation increases the risk for esophageal perforation compared with Heller or POEM. More randomized controlled trials are necessary to find risk factors for complications and treatment failure. Furthermore, additional research should be focusing on new treatment options not disrupting the lower esophageal sphincter, for example esophageal stents.[58] In the future, maybe, curative treatment options for achalasia will become available. Possibly we can learn from investigations regarding tissue remodeling in other diseases. For example, nerve regeneration using stem cell transplantation, which is already performed in peripheral nerve injury with promising results.[59, 60]

LONG-TERM MANAGEMENT OF ACHALASIA

Achalasia is a chronic disease. Given the fact that all treatment options are symptomatic, the majority of patients needs multiple achalasia treatments in their life. If we know risk factors for complications and treatment failure, we can develop an individual treatment choice for patients. Therefore, our fourth aim was to identify risk factors for complications (**chapter 7**) and to study patients with recurrent symptoms after initial achalasia treatment (**chapter 8** and **chapter 9**).

POEM has rapidly gained ground as one of the three preferred treatments for achalasia.[38] As POEM is a relatively novel treatment, there are no international guidelines yet on how to monitor and manage these patients after treatment.[45, 46] We, therefore, tried to optimize the follow-up after POEM in chapter 7 and chapter 8. In chapter 7 we showed that the most common complication after treatment with POEM is reflux esophagitis. From our study it appears that the risk of reflux esophagitis after POEM is higher in patients with a high BMI, alcohol consumption, type 3 achalasia, and GERD symptoms. Also in previous studies, a greater BMI, greater use of alcohol and existing reflux symptoms were reported as risk factors for reflux esophagitis.[22] We concluded that, for patients with a very high risk for reflux esophagitis after POEM, other initial treatment such as Heller myotomy or pneumodilation should be considered. Furthermore, if high risk patients undergo a POEM, they should be monitored very strictly and when necessary treated with PPI. In addition, in chapter 8 we tried to find the best management for patients with recurrent symptoms after POEM. We found that the best re-treatment after failed POEM is a re-POEM or a Heller myotomy. These treatments have better efficacy than pneumatic dilations. A randomized controlled trial comparing re-POEM and Heller myotomy after failed POEM would be of value to identify the optimal treatment for these patients.

In addition to this, in chapter 9 we aimed to determine a management strategy for asymptomatic patients with persisting esophageal stasis after achalasia treatment. After two years, these patients had a more dilated esophageal lumen than patients that had no stasis after treatment. It is of concern that the stasis remained present during the first two years after treatment and dilation became more pronounced. It is known that long-lasting stasis and dilation can develop into megaesophagus and a higher risk of esophageal carcinoma.[61, 62] Yet, the patients with persisting stasis did not have a higher chance of symptom recurrence prompting earlier need for re-treatment. Long-term data are needed to evaluate whether these patients would benefit from pre-emptive treatment as their esophageal luminal dilation increases again after treatment.

Not only treatment protocols, but also diagnostic methods to assess efficacy after treatment can be further improved. For instance, EndoFLIP can serve as an alternative or complimentary method to HRM in assessing treatment efficacy in achalasia.[32, 63] EndoFLIP can guide the need for a subsequent pneumatic dilation in individual patients.[64] Furthermore, it can be used intraoperatively during POEM to prevent incomplete myotomy and, at the same time, enable a shorter myotomy without reducing the clinical outcome.[65] It has been suggested that EndoFLIP will make manometry unnecessary in the future.[66] In any case, although EndoFLIP is a more invasive and more expensive measurement than HRM, it appears to improve diagnosis and assessment of treatment efficacy.

In the near future, the goal in achalasia treatment is a patient-tailored treatment. From previous literature, a few subgroups of achalasia patients have a clear preferred treatment.

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Several studies reported that success rates of all treatments are highest in patients with type 2 achalasia, and lowest in patients with (spastic) type 3 achalasia.[67-69] In patients with type 3 achalasia, POEM is the preferred therapy, because the myotomy can also cut the spastic segment besides the non-relaxing LES.[70] Furthermore, in young, male patients, a Heller myotomy has been reported to be more effective than pneumatic dilation.[71, 72] Last, in elderly patients, or patients who are somehow unfit or unwilling to undergo surgery or pneumatic dilation, botulinum toxin injections are the preferred treatment. Apart from these subgroups that have a clearly preferred treatment, a large group of patients has equal expected efficacy of different treatments. Individual patient characteristics that determine the success of different treatments should be further investigated. With this information, in the future, most likely an individual treatment choice for each achalasia patient will become available.

The ultimate goal in achalasia research is to prevent or cure achalasia, instead of performing symptomatic treatment. The most widely accepted theory on the etiology of achalasia is an infectious agent causing a neurodegenerative response directly or via an autoimmune reaction, in genetically susceptible subjects. This theory is based on a higher prevalence of autoimmune diseases, antineural autoantibodies and T-cell infiltrates within the myenteric plexus in achalasia patients.[73, 74] Furthermore, there are several reports on Guillain-Barré or varicella zoster preceding the onset of achalasia and increased titers of herpes viruses in achalasia patients.[75] If we could identify the responsible genes and/or infectious agent, this could be the roadmap to preventing achalasia. Also, promising curative treatment options from other fields, like nerve regeneration using stem cell transplantation, as mentioned before, should be further investigated in the future.

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CHAPTER | 12

SUMMARY

The goal of this thesis was to further elucidate the pathogenesis and improve diagnostic and treatment strategies for esophageal dysfunction, specifically gastroesophageal reflux disease (GERD), achalasia, and esophago-gastric junction (EGJ) outflow obstruction.

PART I: GASTRO-ESOPHAGEAL REFLUX DISEASE

In **Chapter 2** it is described how we studied symptom generation in 12 GERD patients off anti-acidic medication. Most GERD patients are more sensitive to reflux than healthy subjects, even in the absence of visible erosions in the esophagus.[1, 2] Heartburn in these patients is strongly associated with (microscopically) impaired mucosal integrity.[3, 4] We aimed to evaluate why, in these patients, reflux reaching the proximal esophagus generates worse heartburn than reflux in the distal esophagus. In this prospective observational study, we performed an acid perfusion test and an upper endoscopy with impedance spectroscopy and biopsies. Sensitivity to acid and mucosal integrity were measured in the proximal and distal part of the esophagus separately. Acid exposure in the proximal part of the esophagus provoked symptoms earlier than in the distal esophagus, while mucosal integrity is impaired more in the distal esophagus. This indicates that the enhanced sensitivity to proximal reflux is not explained by increased mucosal permeability.

In **Chapter 3** we studied the role of high-resolution manometry (HRM) in diagnosing GERD. If GERD causes abnormalities on HRM, it would be possible to diagnose GERD with HRM alone. Patients with GERD have a significantly lower contraction amplitude, lower basal LES pressure and more often a hiatal hernia than healthy controls. These findings were nonspecific however, and also often found in asymptomatic persons. There was a large overlap between all characteristics on HRM, making it impossible to reliably distinguish GERD patients from healthy subjects. This confirms that functional abnormalities are not the only factors contributing to GERD and that it is not possible to diagnose GERD with sufficient accuracy, using routine esophageal HRM.

PART II: ACHALASIA AND RELATED DISORDERS

In **Chapter 4** the current epidemiology of achalasia in the Netherlands is described, based on a large healthcare insurance database. The mean incidence of achalasia was 2.2 per 100.000 persons and the prevalence 15 per 100.000 persons. The mean age of achalasia patients was 54 years, with both genders equally affected. There was no difference in socio-economic status between achalasia patients and controls. Prior to the diagnosis, achalasia patients often used proton pump inhibitors and anti-emetic medication. The costs associated with diagnosis and treatment of new cases with achalasia increased with increasing age.

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Chapter 5 is a systematic review and meta-analysis which aimed to evaluate which treatment scheme of pneumatic dilation is the most effective in achalasia. Pneumatic dilation is one of the most often used treatments in achalasia. There are different treatment schemes using different balloon sizes, numbers of dilations and inflation duration and pressure. Our meta-analysis confirms that a graded dilation scheme of a 30-mm balloon dilation, followed by 35 mm and 40 mm in patients with insufficient symptom relief gives the best results with acceptable perforation risks. Employing a scheme of elective additional dilation in case of symptom recurrence was more effective than using a predefined series of dilations.

Chapter 6 confirms that esophageal botulinum toxin injections are a very safe treatment for achalasia and similar spastic motility disorders. During 661 treatment sessions, mild complications occurred in only 7.9% of cases, mainly consisting of chest pain, heartburn or epigastric pain. No ulceration, perforation, pneumothorax or abscess was reported. One patient died after developing acute mediastinitis (0.2%). This study shows that esophageal botox injection have a very low complication rate, however they are associated with rare side effects that cannot be predicted.

In **Chapter 7** we present a prediction model for the most common side-effect of POEM: reflux esophagitis. The risk of developing reflux esophagitis is approximately 50%, but it only generates symptoms in a minority of patients. Timely identification of these patients is therefore very challenging, but also very important to prevent further complications, like peptic strictures and esophageal carcinoma. The prediction model identifies patients with significant reflux esophagitis (Los Angeles grade B – D), using the following risk factors: type 3 achalasia, high body-mass index (> 25 kg/m^2), alcohol intake (> 2 units/day) and reflux symptoms (GERDQ score > 8). In patients with only one or none of these risk factors we advise no follow-up endoscopy or treatment, while in patients with two or more risk factors we advise an early upper endoscopy, and in the meantime empiric proton pump inhibitor (PPI) treatment.

In **Chapter 8** we describe management options for achalasia patients with persisting or recurrent symptoms of achalasia after peroral endoscopic myotomy (POEM). Only 9.8% of patients had persistent or recurrent achalasia symptoms, and 8% received additional treatment. Retreatment with laparoscopic Heller myotomy and a re-POEM showed a moderate efficacy (45% and 63% respectively), while pneumatic dilation had a poor efficacy of 20%. Male patients were more likely to have failure of additional treatment after ineffective POEM. We conclude that after ineffective POEM, a Heller myotomy or a re-POEM are the best treatment options.

Chapter 9 is a cohort study which aimed to evaluate how to manage patients with persisting stasis after achalasia treatment. A group of 99 patients in clinical remission was

divided in two groups 3 months after treatment: (1) clinical remission with stasis on barium esophagography and (2) clinical remission without stasis. After two years, patients with stasis still had a wider esophagus (3 vs 1.8 cm, $p < 0.001$) and more stasis (3.5 vs 0 cm, $p < 0.001$) than patients without stasis. In patients with stasis, the esophageal diameter had increased from 2.5 to 3 cm within two years. Nevertheless, symptoms, quality of life, need for and time to retreatment, were similar in the two groups. Even though patients with stasis after treatment will have a wider esophagus and more stasis after two years, this does not predict need for additional treatment within two years.

In **Chapter 10** we studied a disease, very similar to achalasia, but only detectable on manometry. Idiopathic esophagogastric junction (EGJ) outflow obstruction is characterized by a non-relaxing lower esophageal sphincter, but intact peristalsis. The disease has an unclear clinical significance. A cohort of 34 patients was included, of which 74% had an elevated intrabolus pressure, and only 30% had stasis on barium esophagography. A substantial part of patients had unrelated symptoms, spontaneous symptom relief, or no stasis on barium esophagography. Only 12% of patients required treatment, of which botox injections showed the best efficacy.

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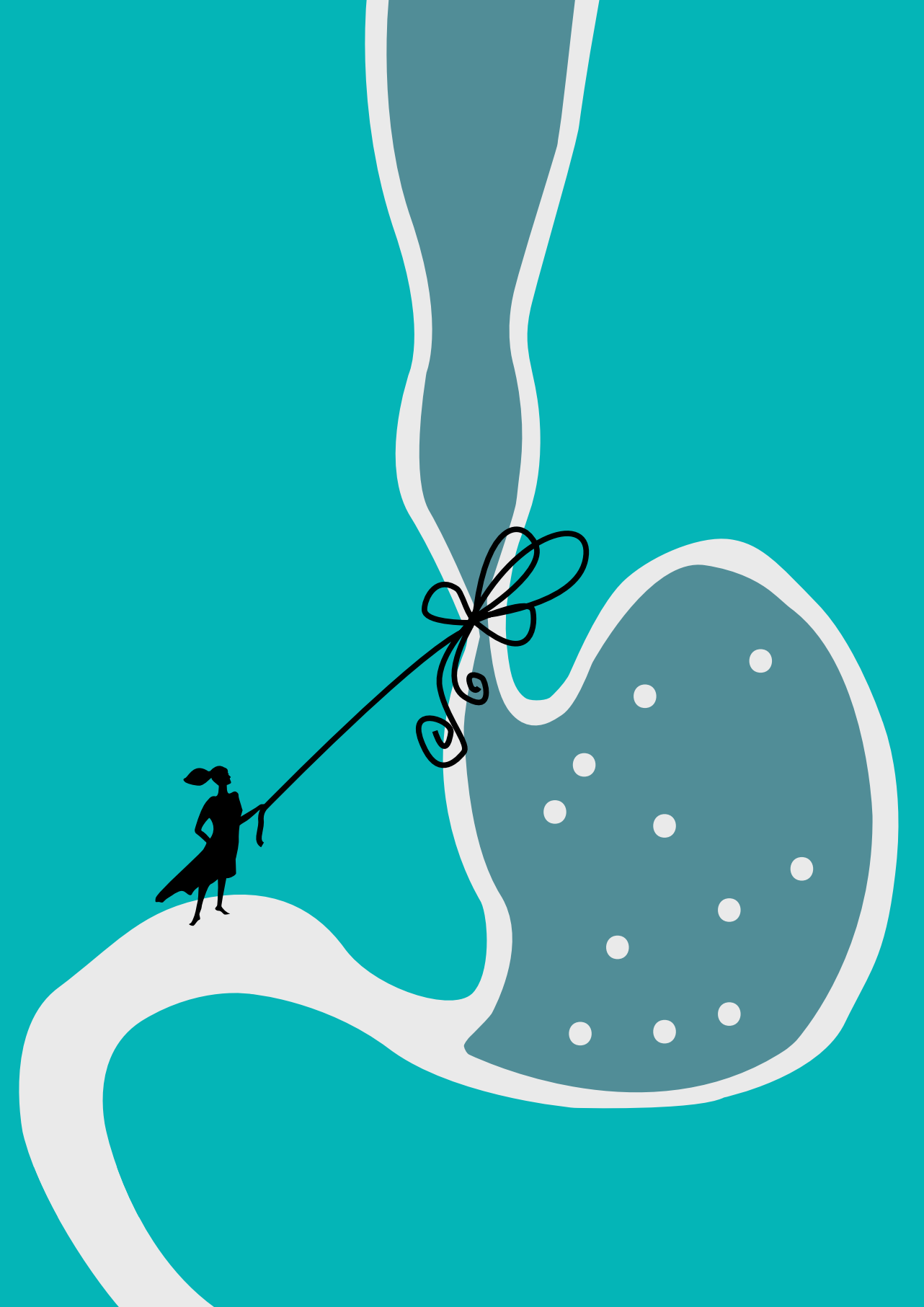
APPENDIX

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NEDERLANDSE SAMENVATTING

Het doel van deze thesis was de pathogenese, diagnose en behandeling van slokdarmdysfunctie te bestuderen en verbeteren. Om precies te zijn van gastro-oesofageale refluxziekte, achalasie en esophagogastric junction (EGJ) outflow obstruction.

Deel I: Gastro-oesofageale refluxziekte

In **Hoofdstuk 2** is beschreven hoe we het ontstaan van symptomen hebben bestudeerd bij 12 patiënten met refluxziekte, na het staken van anti-reflux medicatie. De meeste patiënten met refluxziekte zijn gevoeliger voor reflux dan gezonde personen, zelfs als ze geen zichtbare refluxschade (erosies) in hun slokdarm hebben. Zuurbranden is bij deze patiënten geassocieerd met microscopische schade aan het slijmvlies, waardoor het slijmvlies doorlaatbaarder wordt. We hebben onderzocht waarom, bij deze patiënten, reflux die het bovenste deel van de slokdarm bereikt, erger zuurbranden veroorzaakt dan reflux in het onderste deel van de slokdarm. In deze prospectieve observationele studie, hebben we een zuurperfusietest verricht en een endoscopie van de slokdarm met impedantie meting (weerstand) en biopten. Zuurgevoeligheid en doorlaatbaarheid van het weefsel werden zowel in het bovenste als onderste deel van de slokdarm gemeten. Zuurperfusie in het bovenste deel van de slokdarm gaf eerder klachten dan in het onderste deel, terwijl het slijmvlies doorlaatbaarder was in het onderste deel van de slokdarm. Dit wijst erop dat de verhoogde gevoeligheid voor reflux in het bovenste deel van de slokdarm niet verklaard wordt door toegenomen doorlaatbaarheid van het slijmvlies in dat deel van de slokdarm.

In **hoofdstuk 3** hebben we bestudeerd wat de rol is van hoge-resolutie manometrie (HRM) in de diagnose refluxziekte. Als refluxziekte meetbare afwijkingen op HRM veroorzaakt is het misschien mogelijk om refluxziekte met HRM te diagnosticeren. Patiënten met refluxziekte hebben een significant lagere contractie-amplitude van slokdarmperistaltiek, een lagere basale druk in de onderste slokdarmsfincter en vaker een middenrifsbreuk (hiatus hernia). Deze bevindingen waren echter niet specifiek, en waren ook vaak aanwezig bij gezonde personen. Er was een grote overlap tussen patiënten en gezonde personen bij deze HRM-bevindingen, waardoor het onmogelijk was hen te onderscheiden met HRM. Dit bevestigt dat functionele afwijkingen niet de enige bijdragende factoren aan refluxziekte zijn en dat het niet mogelijk is om refluxziekte met voldoende zekerheid te diagn0sticeren met HRM.

Deel II: Achalasie en verwante ziekten

In **hoofdstuk 4** worden de huidige gegevens betreffende het voorkomen van achalasie in Nederland beschreven, gebaseerd op een grote database van zorgverzekeraar Zilveren Kruis Achmea. De gemiddelde incidentie van achalasie is 2,2 per 100.000 personen en de prevalentie 15 per 100.000 personen. De gemiddelde leeftijd van achalasie patiënten was 54 jaar, met evenveel mannen als vrouwen. Er was geen verschil in socio-

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economische status tussen achalasie patiënten en gezonde controles. Voorafgaand aan de diagnose gebruiken achalasie-patiënten vaak protonpompremmers en medicatie tegen misselijkheid. De kosten geassocieerd met diagnose en behandeling van nieuwe achalasie patiënten zijn hoger bij hogere leeftijd.

Hoofdstuk 5 is een systematic review en meta-analyse met als doel om het meest effectieve behandelprotocol van pneumodilataties (ballon-oprekkingen) voor achalasie te achterhalen. Pneumodilatatie is één van de meest gebruikte achalasiebehandelingen. Er zijn veel verschillende manieren van uitvoering, waarbij de ballonmaat, aantal dilataties en opblaasdruk en/of –tijd kan verschillen. Onze meta-analyse bevestigt dat een gegradeerd dilatatieschema van een 30-mm ballon dilatatie, gevolgd door een 35 mm en 40 mm dilatatie bij patiënten met blijvende klachten, de beste resultaten geeft, met een acceptabel risico op perforatie. Een schema volgen van electieve herdilatatie bij patiënten met blijvende klachten heeft een beter effect dan het volgen van een vooropgesteld schema van een serie dilataties.

Hoofdstuk 6 bevestigt dat botox-injecties in de slokdarm een veilige behandeling voor achalasie en vergelijkbare spastische slokdarmziekten zijn. Tijdens 661 behandelingen traden milde bijwerkingen slechts op in 7,9% van de gevallen: met name pijn op de borst, zuurbranden of maagpijn. Geen ulceratie, perforatie, klaplong of abces werd gerapporteerd. Één patiënt (0,2%) overleed na het ontwikkelen van een acute mediastinitis. Deze studie laat zien dat botox injecties in de slokdarm een erg lage kans hebben op complicaties, alhoewel er zeldzame complicaties zijn gerapporteerd die niet voorspeld kunnen worden.

In hoofdstuk 7 presenteren we een predictiemodel voor de meest voorkomende complicatie van POEM: reflux-oesofagitis. Het risico op reflux-oesofagitis is ongeveer 50%, maar het veroorzaakt slechts in een minderheid van de gevallen symptomen. Tijdige identificatie van deze patiënten is daarom lastig, maar ook erg belangrijk om verdere complicaties zoals peptische stricturen of slokdarmcarcinoom te voorkomen. Het predictiemodel identificeert patiënten met significante reflux oesofagitis (Los Angeles grade B – D), met gebruik van de volgende risicofactoren: type 3 achalasie, hoge body-mass index (> 25 kg/m^2), alcohol inname (> 2 eenheden/dag) en refluxsymptomen (GERDQ score > 8). In patiënten met slechts 1 of geen van deze risicofactoren adviseren we geen follow-up endoscopie of anti-refluxbehandeling, terwijl we voor patiënten met twee of meer risicofactoren, een vroegtijdige endoscopie adviseren, en in de tussentijd preventieve behandeling met een protonpompremmer.

In hoofdstuk 8 beschrijven we behandelopties voor achalasie-patiënten met blijvende of terugkerende achalasie-symptomen na perorale endoscopische myotomie (POEM). Slechts 9,8% van de patiënten had blijvende of terugkerende klachten na POEM, en 8% kreeg

hiervoor een herbehandeling. Herbehandeling met laparoscopische Heller myotomie en een her-POEM hadden een matige effectiviteit (respectievelijk 45% en 63%), terwijl pneumodilataties een slechte effectiviteit (20%) hadden. Bij mannelijke patiënten was de kans groter dat de herbehandeling na een ineffectieve POEM ook geen goed effect had. We concluderen dat na een ineffectieve POEM, een Heller myotomie of een her-POEM de beste behandelopties zijn.

Hoofdstuk 9 is een cohortstudie waarin we hebben onderzocht hoe we achalasiepatiënten met blijvende klachten na behandeling moeten (her)behandelen. Een groep van 99 patiënten in klinische remissie werd, 3 maanden na behandeling, onderverdeeld in twee groepen: (1) klinische remissie met stase op bariumslikfoto en (2) klinische remissie zonder stase. Na twee jaar hadden patiënten met stase nog steeds een wijdere slikdarm en meer stase dan patiënten zonder stase. In patiënten met stase was de slokdarmdiameter in twee jaar tijd toegenomen van 2,5 naar 3 cm. Desalniettemin waren symptomen, kwaliteit van leven, noodzaak tot en tijd tot herbehandeling gelijk in de twee groepen. Alhoewel patiënten met stase na behandeling dus een grotere kans hebben op een wijdere slokdarm en meer stase na twee jaar, hebben ze geen grotere kans op herbehandeling binnen twee jaar tijd.

In hoofdstuk 10 hebben we een ziekte bestudeerd die vergelijkbaar is met achalasie, maar alleen met HRM kan worden vastgesteld. Esophagogastric junction (EGJ) outflow obstruction wordt gekarakteriseerd door een niet-relaxerende onderste slokdarmsfincter, maar intacte slokdarmperistaltiek. De ziekte heeft een onduidelijke klinische betekenis. Een cohort van 34 patiënten werd geïncludeerd, waarvan 74% een verhoogde intrabolusdruk had, en maar 30% stase op bariumslikfoto. Een substantieel deel van de patiënten had ongerelateerde symptomen, spontane afname van symptomen, of geen stase op de slikfoto. Slechts 12% van de patiënten had behandeling nodig, waarvan botox-injecties het beste effect gaven.

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Herregods TV, **van Hoeij FB**, Bredenoord AJ and Smout AJ. Subtle lower esophageal sphincter relaxation abnormalities in patients with unexplained esophageal dysphagia. *Neurogastroenterology and Motility*. 2017 Aug; doi: 10.1111/nmo.13188

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PHD PORTFOLIO

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Period: April 2014 – July 2017
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Co-supervisor: A.J. Bredenoord

	Year	ECTS
General courses (Graduate school, AMC)		
Clinical Data Management	2016	0.3
Scientific Writing in English	2015	1.5
Oral Presentation in English	2015	0.8
Basic course Legislation and Organization for		
Clinical Researchers (BROK)	2014	1.0
Practical Biostatistics	2014	1.1
Evidence Based Searching	2014	0.3
Project Management	2014	0.6
Specific courses (UvA)		
Master Evidence Based Practice; Clinical Epidemiology	2014-2016	98.0
Seminars, workshops and master classes		
Biweekly seminars in gastroenterology	2014-2017	1.5
Biweekly clinical motility meeting	2014-2017	1.5
Gutclub meetings	2014-2017	1.5
AG&M PhD-retraite	2016	0.5
Oral Presentations		
Stasis in symptom-free achalasia patients after treatment	2017	0.5
Voorjaarscongres NVGE, Veldhoven, Nederland		
Mucosal integrity and acid sensitivity in GERD	2016	0.5
UEGW, Wenen, Oostenrijk		
POEM and Achalasia	2016	0.5
Klinische les AMC, Amsterdam, Nederland		
Management of recurrent symptoms after POEM	2016	0.5
AG&M PhD-retraite, Garderen, Nederland		
Oral Presentations		
Achalasia and the POEMA trial	2016	0.5
Boston Scientific Symposium, Utrecht, Nederland		
Mucosal integrity and acid sensitivity in GERD	2016	0.5
Management of recurrent symptoms after POEM	2016	0.5
Voorjaarscongres NVGE, Veldhoven, Nederland		
Complications of esophageal botox injections	2015	0.5
Voorjaarscongres NVGE, Veldhoven, Nederland		
Poster Presentations		
Stasis in symptom-free achalasia patients after treatment	2017	0.5
DDW, Chicago, USA		

PhD portfolio (continued)

	Year	ECTS
Poster Presentations (continued)		
Mucosal integrity and acid sensitivity in GERD	2016	0.5
DDW, San Diego, USA		
Management of recurrent symptoms after POEM (2x)	2016	1.0
UEGW, Wenen, Oostenrijk & DDW, San Diego, USA		
Complications of esophageal botox injections	2015	0.5
Characterizing idiopathic EGJ outflow obstruction	2015	0.5
DDW, Washington, USA		
(Inter)national conferences		
Digestive Disease week	2015-2017	1.5
Amsterdam Live Endoscopy	2015-2017	1.5
NVGE Voorjaarscongres	2015-2016	1.0
United European Gastroenterology Week	2016	0.5
Boston Scientific Symposium	2016	0.5
Teaching		
Lecturing: Elective gastroenterology course 2nd year	2015-2017	1.5
Tutoring: Bachelor thesis 3rd year medical student	2016	1.0
Parameters of esteem		
AMC Lustrumbeurs	2017	
NVGE travel grant	2017	
UEGW travel grant	2016	

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ABOUT THE AUTHOR

Froukje was born in Utrecht on December 20, 1988. She graduated from the Christelijk Gymnasium Utrecht in June 2007 and started Medical School at Utrecht University in the same year. She went abroad for two internships: Infectiology in Cape Town and Tropical Medicine in Ghana. During her clinical rotations she became more and more interested in Gastroenterology, especially after an elective internship in the St Antonius Hospital in Nieuwegein in 2012. Her enthusiasm for research was enhanced in 2013 when she performed a scientific internship in the same hospital, under supervision of prof. Bas Weusten. She obtained her Medical Degree and started in 2014 as a PhD student in the Academic Medical Center in Amsterdam at the Department of Gastroenterology and Hepatology under supervision of prof. André Smout and dr. Arjan Bredenoord. Her three-year clinical research focused on diagnosis and treatment of esophageal motility disorders, resulting in this thesis. During her PhD she also worked at the motility outpatient clinic, and she performed a research fellowship in the Northwestern University hospital in Chicago under supervision of prof. John Pandolfino. In addition, she obtained a Master degree in Clinical Epidemiology at the University of Amsterdam in 2016. In January 2018 she will start her specialist training for Gastroenterology and Hepatology at the University Medical Center Utrecht.

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