Achalasia

Breaking down barriers

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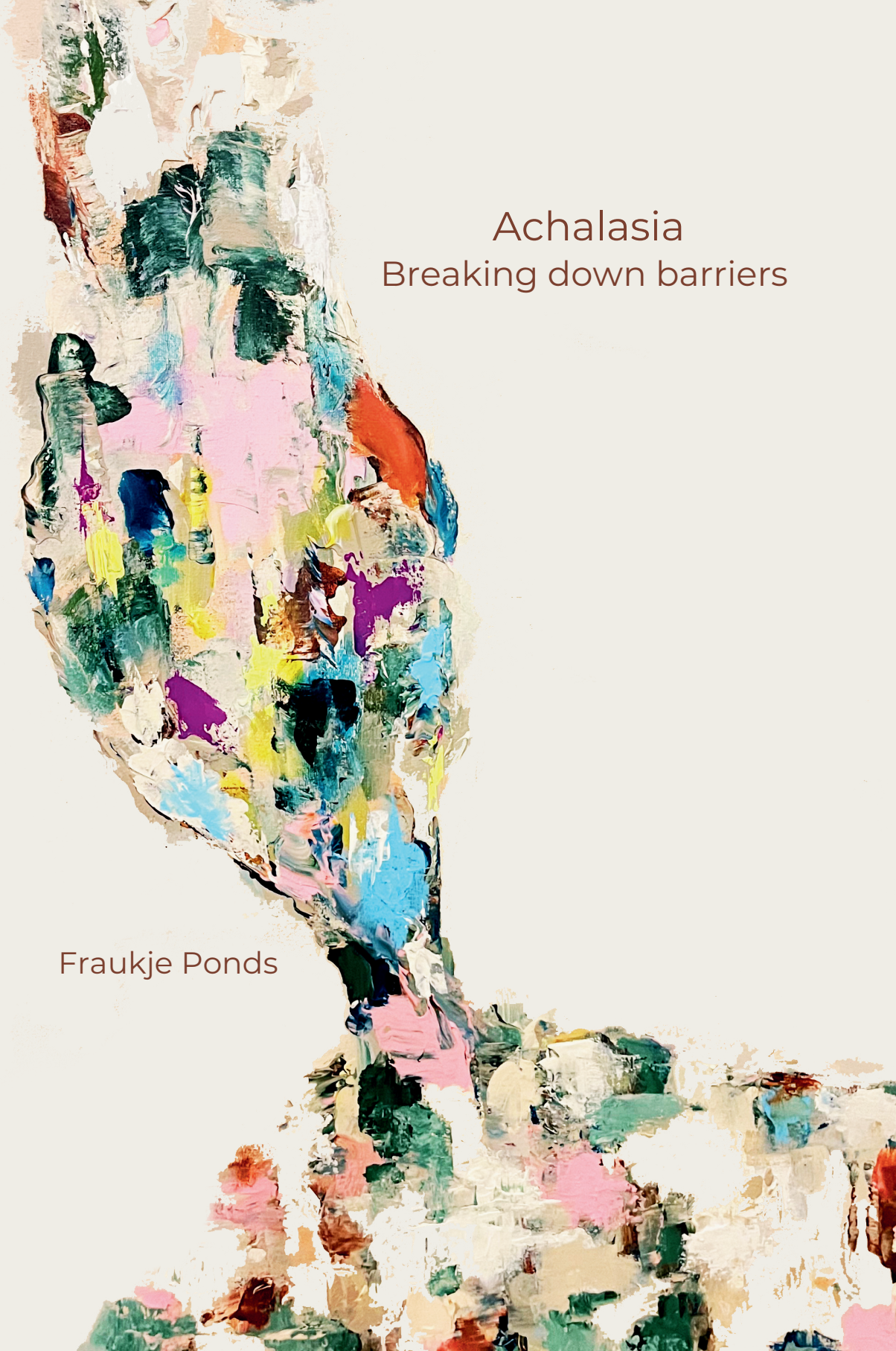

Fraukje Ponds

Achalasia

Breaking down barriers

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Faculteit der Geneeskunde

Voor papa en mama

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General introduction and outline of thesis

1

GENERAL INTRODUCTION

Esophagus

Anatomy

The esophagus is a muscular tubular organ, connecting the oropharynx with the stomach. It consists of two sphincters, the upper (UES) and lower esophageal sphincter (LES), with in between the esophageal body. The esophagus consists of four layers; starting from the inside with the mucosa, submucosa and two outer muscle layers: the circular and longitudinal muscles (**figure 1**).[1] The proximal esophagus contains striated muscles that gradually change to smooth muscles in the distal esophagus. There are two intersecting enteric nerve networks between the layers, the submucosal and the myenteric plexus (**figure 1**).[2] The submucosal plexus is located in the submucosa and contains neurons involved in pain perception and mucosal secretion.[3,4] The myenteric plexus is located between the circular and longitudinal muscle layers and innervates both, controlled by the vagal nerve of the central nervous system.[3,4] The plexus contains afferent sensory neurons with tension- and mechanoreceptors and efferent motor neurons, both excitatory and inhibitory, to regulate muscle contractions.[3,4]

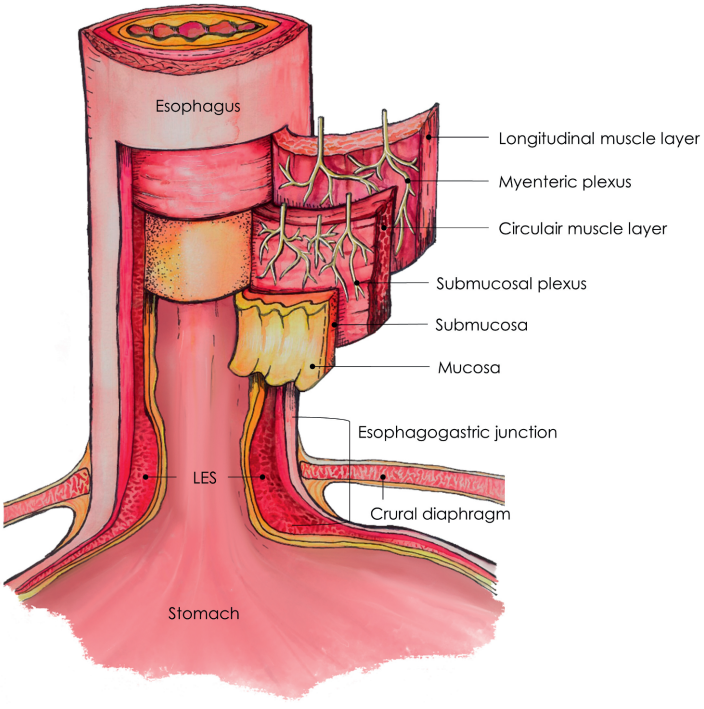

Figure 1. Anatomic overview of the esophagus and esophagogastric junction.
Image created by L. Langenberg.

Physiology

The function of the esophagus is two-fold, transportation of food and mucus from the oropharynx towards the stomach and preventing reflux of stomach content across the LES, except during belching or vomiting.[5] To facilitate bolus passage, relaxation of both esophageal sphincters is necessary combined with peristalsis of the esophageal body by the circular muscle layer. Peristalsis is the net result of coordinated esophageal muscle contraction and relaxation, mediated by the vagal nerve combined with excitatory and inhibitory neurons of the myenteric plexus.[6,7] Once a solid or liquid bolus has entered the esophagus, peristaltic contractions of the striated muscles lead to aboral propagation of the bolus. The striated muscles are directly excited by the release from acetylcholine at the motor end plates, innervated by neurons of the vagal nerve located in the nucleus ambiguous.[4,6] Peristalsis is continued by the smooth muscles and proceeds with inhibition to delay contractions to promote filling and transport through the esophagus.[1,4] This deglutitive inhibition is activated by inhibitory neurons of the myenteric plexus that release nitric oxide, innervated by neurons of the vagal nerve located in the dorsal motor nucleus, and relax the smooth muscles.[4,6] Smooth muscle contractions follow deglutitive inhibition, by sequential activation of the excitatory neurons located in the myenteric plexus that release acetylcholine.[1,4] This excitatory activation is initiated by the vagal nerve and as a response to esophageal distension.[8] The interaction between muscle inhibition and excitation is essential for sufficient esophageal peristalsis. Eventually, peristaltic waves transport the food bolus to the distal part of the esophagus where esophageal emptying is preceded by LES relaxation.

The LES is a specialized thickened region of the circular muscle layer, 2-3 cm in length (**figure 1**).[5] Together with the crural diaphragm and gastric sling fibers it forms the esophagogastric junction (EGJ), a high-pressure zone against the pressure gradient between stomach and esophagus (**figure 1**).[9] The LES is considered the internal sphincter of the EGJ, generating a tonic resting pressure of 15-30 mmHg above intragastric pressure mediated by acetylcholine release of neurons in the myenteric plexus.[5,10] The crural diaphragm, considered the external sphincter, contracts during activities that further increase intra-abdominal pressure, such as inspiration and coughing.[9] The synergy of the two sphincters creates a sufficient high-pressure zone across the EGJ preventing reflux of gastric content into the esophagus. Conversely, a decrease of the high-pressure zone is necessary for passage of ingested food across the EGJ into the stomach. This is achieved by reducing the LES tone. Relaxation of the LES is triggered by swallowing and esophageal distension, mediated by the vagal inhibitory pathway.[11] Efferent nerve fibers of the vagal nerve, originated in the dorsal motor nucleus, innervate inhibitory neurons of the myenteric plexus that

release nitric oxide or vasoactive intestinal polypeptide at the motor end plate of the smooth muscles of the LES, causing relaxation.[6,11]

The combined action of esophageal peristalsis and EGJ function is called esophageal motility and its dysfunction is referred to as esophageal motility disorders. Dysfunction occurs when peristalsis of the esophageal body fails and/or the EGJ function is disturbed. There is a variety of esophageal motility disorders, with mild to severe dysfunction leading to e.g. absent contractility, distal esophageal spasm or EGJ outflow obstruction.[12] This thesis covers the most well-defined and characterized esophageal motility disorder, achalasia.

Esophageal motility disorder: Achalasia

Achalasia is a rare, chronic motility disorder of the esophagus. It is characterized by absent or severely abnormal peristalsis of the esophageal body and impaired relaxation of the LES, caused by functional loss of neurons in the myenteric plexus.[1,13] This hampers normal esophageal emptying leading to food stasis in the esophagus that cause symptoms of progressive dysphagia for solids and liquids, regurgitation of undigested food, chest pain, respiratory symptoms (nocturnal cough, aspiration) and weight loss.[1,5,14] The annual incidence is estimated on 1-2.2 cases per 100,000 individuals, with a prevalence rate of 10-15.7 per 100,000 individuals.[15–17] There is no gender preference or specific age of onset.

Advances in diagnostic testing and treatment during the last decade changed clinical management of this disease leading to new insights and challenges. The focus of this thesis lies on the diagnosis, treatment and follow-up of achalasia. The goal is to improve the diagnostic management (**part I**), evaluate the efficacy of current and new treatments (**part II**) and enhance strategies for long-term follow-up (**part III**) of this disease.

Pathophysiology

The neuronal loss in the myenteric plexus of achalasia patients starts with a preferential degeneration of the inhibitory neurons leading to a misbalance between excitatory and inhibitory control of the esophagus and LES, with eventually a complete destruction of all myenteric neurons.[1,8] The unopposed excitatory stimulation results in impaired relaxation of the LES, loss of deglutitive inhibition causing hypercontractility and rapidly propagating contractions of the esophageal body, with in the end progression to aperistalsis in absence of both inhibitory and excitatory neurons.[1,13] The pathophysiology of the neuronal loss is incompletely elucidated, but accumulating evidence suggests an aberrant auto-immune response, both cell- and antibody-mediated, causing severe inflammation of the myenteric plexus with eventually fibrosis and aganglionosis.[6,8] Examinations of esophageal resection specimen and biopsies

of patients with achalasia, reveal infiltration of T-cell lymphocytes and evidence of compliment activation within myenteric neurons.[13,18–21] In addition, increased anti-neuronal antibodies are detected in the serum of patients with achalasia, especially in patients with a genetic predisposition.[22–25] The specificity of these antibodies are however questionable and could present an epiphenomenon, a non-specific reaction to inflammation rather than the cause.[6,22] All these findings suggest that achalasia is an immune-mediated disease, however the antigen that triggers the cell- and antibody-mediated response that is functionally limited to the esophagus remains to be identified.[8] In general, it is suggested that auto-immune diseases develop in genetically predisposed patients where environmental factors, e.g. an infection or toxin, initiate an immune response against the foreign pathogen but cross-react with a self-protein resulting in ongoing inflammation and tissue damage.[26] For achalasia, indolent viruses, like herpes, measles or human papillomavirus are postulated as potential antigens.[8,27–30] Especially herpes simplex virus 1 (HSV-1) seems a potential candidate as evidenced by proliferation and cytokine activation of isolated esophageal oligoclonal T cells of achalasia patients on exposure of HSV-1 antigens.[30,31] In addition, HSV-1 is a neurotrophic virus with a predilection for squamous epithelium.[13] Summarizing the current evidence, the general hypothesis is that achalasia is an auto-immune disorder targeting esophageal myenteric neurons by a cell- and antibody mediated response triggered by a viral infection, in genetically predisposed patients.

Diagnosis

Patients with achalasia typically present with symptoms of progressive dysphagia for solids and liquids, regurgitation of undigested food, chest pain and weight loss, objectively evaluated by the Eckardt symptom score that assesses the severity of these four symptoms.[1,5,14] These symptoms are however not disease-specific which explains the diagnostic delay and erroneous diagnosis of especially gastroesophageal reflux disease in some of these patients. Consequently, diagnosing achalasia requires a careful evaluation of symptoms with appropriate use and interpretation of diagnostic tests.[1,14]

The first step in the diagnostic approach to patients suspected of achalasia is an esophagogastroduodenoscopy to rule out mechanical obstruction (strictures, rings or malignancy) or severe inflammation (gastroesophageal reflux, eosinophilic esophagitis). Esophagogastroduodenoscopy has no role in diagnosing achalasia, only in advanced cases a dilated, tortuous esophagus, with retained saliva and food, and increased resistance passing the EGJ can be observed.[13,32,33] The gold standard to diagnose achalasia and other esophageal motility disorders is by high-resolution manometry (HRM).[12,32,33] HRM uses a catheter with closely spaced pressure sensors that measures motor activity

of the esophagus and EGJ continuously, and displays the results as pressure topography plots. Esophageal motility is evaluated based on the analysis of ten single swallows with 5 mL of water.[12,34] Manometric criteria to diagnose achalasia are incomplete LES relaxation, reflected by a high integrated relaxation pressure (>15 mmHg) and absent peristalsis upon deglutition.[12] Based on pressure topography plots, three achalasia subtypes can be differentiated according to esophageal contractile patterns; type I: absent contractility, type II: panesophageal pressurization and type III: spastic contractions.[12] This heterogeneity seems a reflection of the variability in the degeneration and dysfunction of inhibitory neurons. In type III achalasia spastic contractions are observed as a result of increased preservation of excitatory neurons.[8] A preserved but decreased function of both inhibitory and excitatory neurons in type II achalasia results in panesophageal pressurization and absent contractility in type I achalasia is caused by nearly complete aganglionosis.[8] Studies reveal that treatment outcome is different per subtype, with a higher treatment efficacy in type II achalasia (90-95%) compared to type I (55-85%) and III (30-85%).[36,37] This suggest that achalasia subtypes should be carefully assessed to optimize treatment strategy for each individual patient.

Despite the increased accuracy of HRM, providing objective criteria for esophageal motility disorders as achalasia, this diagnostic test is not flawless. As achalasia is a slowly progressive disease, with gradual transition from normal peristalsis and LES relaxation to absent peristalsis and LES dysrelaxation, at intermittent time points these abnormalities not always meet all diagnostic criteria.[35] In **chapter 2** a subgroup of patients is further characterized to assess if achalasia can be present in case of absent peristalsis but manometrically normal LES relaxation.

Besides upper endoscopy and HRM, radiological examinations play a role in the diagnostic management of achalasia. Standard or timed barium esophagogram is considered a valuable and complementary diagnostic test, but has limited yield in the diagnosing achalasia or other esophageal motility disorders.[33,39] The additional value of the barium esophagogram is the information on the contour of the esophagus, structural abnormalities and esophageal stasis. In achalasia, a dilated esophagus with a narrowed EGJ, stasis of barium with poor esophageal emptying to the stomach and aperistalsis are often observed.[40] The timed barium esophagogram is the preferred examination as it uses set time intervals after barium ingestion which improves objective assessment of esophageal emptying.[33,40] Post-treatment, timed barium esophagogram seems also useful as an objective parameter to assess treatment outcome by improved esophageal emptying in addition to symptom evaluation.[41,42] A major disadvantage of radiography is however the exposure to a significant

degree of ionizing radiation. With the advancement of HRM, provocative tests are introduced to add information on integrity of deglutitive inhibition and esophageal contractility reserve in addition to single swallows to increase the diagnostic sensitivity for esophageal motility disorders.[43–46] With a rapid drinking challenge, consecutively drinking 200 mL of water, EGJ obstruction can be assessed.[45–48] In untreated achalasia, the rapid drinking challenge initiates sustained pressurization in the esophageal body with a high-pressure gradient across the EGJ, a reflection of impaired esophageal emptying and stasis.[45,46] **Chapter 3** evaluates if a rapid drinking challenge during HRM can assess esophageal stasis in achalasia patients comparable to stasis on a timed barium esophagogram.

Although achalasia is a well-characterized motility disorder and idiopathic in nature, other disorders can manifest with similar symptoms, manometric and radiological features. This condition, in which clinical and manometric signs of idiopathic achalasia are mimicked by another abnormality, is referred to as pseudoachalasia. There is a diversity of underlying causes, e.g. obstruction by a tight fundoplication, gastric banding or a para-esophageal hernia, but in 70% of the cases a primary or secondary malignancy is involved.[49,50] Early recognition of especially malignancy-associated pseudoachalasia is important to prevent inappropriate therapeutic interventions and a delay in adequate treatment. Risk factors that discriminate achalasia from malignancy-associated pseudoachalasia are therefore warranted and determined in **chapter 4**.

Treatment

As the pathophysiology of achalasia remains unknown, treatment is focused on symptom relief, primarily by disruption of the LES facilitating adequate esophageal clearance. Secondly, treatment can reduce the risk of esophageal dilatation which seems to be associated with a poor outcome.[51,52] Treatment consist of pharmacological, endoscopic and surgical options.

Nitrates and calcium channel blockers are the two most used oral pharmacological drugs for the treatment of achalasia.[53–56] Both are smooth-muscle relaxants and attempt to transiently reduce the LES pressure. Studies do not show convincing evidence of the therapeutic effect of the smooth-muscle relaxants and side effects (hypotension, headache) are a limiting factor in their use.[53–56] Botulinum toxin injections are a different and more widely used pharmacological treatment for achalasia.[57,58] Botulinum toxin is endoscopically injected in the LES where it blocks acetylcholine release from the excitatory neurons in the myenteric plexus causing LES relaxation.[59] It is an effective treatment with a very low complication rate but the response fades within 6-12 months.[58,60] Consequently, pharmacological therapy should not be used

as a first-line treatment and only reserved for older patients or patients with a lot of comorbidities, not fit for more invasive procedures.

Endoscopic pneumodilation is worldwide the most performed treatment for achalasia. The LES tears after forcefully dilating the LES with a balloon, restoring esophageal clearance. A non-compliant cylindric balloon is used that is positioned at the EGJ often under fluoroscopic guidance. The procedure starts with a guidewire placement by upper endoscopy, followed by inserting a deflated balloon over the guidewire, correctly positioned at the EGJ by slightly inflating the balloon and ends with complete inflation of the balloon for one to two minutes distending the LES (**figure 2**).[61] There are different balloon sizes (diameters 30, 35 and 40 mm) and the procedure can be repeated in case of recurrent symptoms. The procedure is minimally invasive and the long-term therapeutic success rate is 50-85%.[61–65] The variation in success rates depends on the dilation strategy (balloon size, number of dilations performed), patient selection and definition of treatment failure. Esophageal perforation is the most serious complication, occurring in 1-3% of endoscopic pneumodilations performed by experienced endoscopists.[61,66,67]

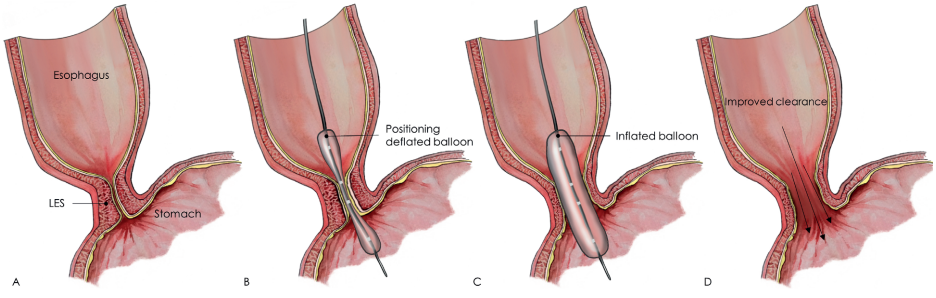

Figure 2. Steps of the pneumodilation. A: Starting point with impaired LES relaxation. B: Positioning deflated balloon under fluoroscopic guidance at the LES. C: Complete inflation of the balloon to tear the LES. D: End point with an open LES and improved clearance. Images created by L. Langenberg.

The surgical treatment for achalasia is known as Heller's myotomy. This is a laparoscopic procedure that divides the circular muscle layer, starting at the gastric cardia progressing proximally across the LES. The length of the myotomy is limited by the part of the esophagus that can be safely accessed from below the diaphragm.[35] The surgical myotomy causes an increased propensity for gastroesophageal reflux and is therefore combined with a partial fundoplication. Compared to botulinum toxin injections and pneumodilation, laparoscopic Heller's myotomy offers a more permanent solution for achalasia with success rates of 80-90%.[61,62,66] This technique is however considerably

more invasive and can be associated with severe complications like transmural perforation, bleeding or infection and is therefore often considered as treatment for pneumodilation non-responders, but is can also be performed as first-line treatment.[66]

A relatively new endoscopic technique, developed in the last decade, for the treatment of achalasia is the peroral endoscopic myotomy (POEM).[68] With this technique the myotomy of the LES is performed endoscopically. It starts with a mucosal incision in the proximal or mid esophagus (**A**), creating a submucosal tunnel between mucosa and the muscle layer (**B**), followed by a myotomy, dividing the circular muscle layer from the proximal or mid esophagus across the LES to the cardia (**C-D**, **figure 3**).[68] The mucosal incision is closed by clips (**E**). Case series and prospective studies reveal favorable safety and high short-term efficacy rates (80-97% ≥12 months) which has led to increased adoption of POEM worldwide.[69–72] However, data comparing POEM with current treatment options in randomized trials are lacking. **Chapter 5** describes the first multicenter randomized clinical trial comparing the effects of POEM versus pneumodilation as the initial treatment of treatment-naive patients with idiopathic achalasia.

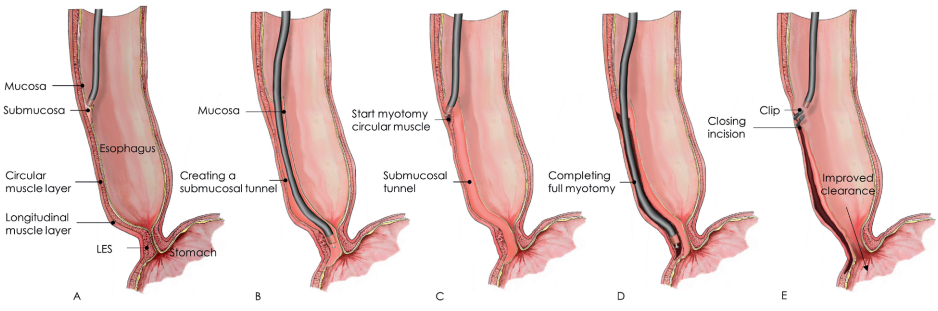

Figure 3. Steps of the POEM procedure. A: Mucosal incision proximal esophagus. B: Submucosal tunnel between mucosa and circular muscle layers. C-D: Myotomy of the circular muscle layer from proximal esophagus till the cardia. E. Closing mucosal incision by clips. Images created by L. Langenberg.

A major advantage of the POEM technique is the possibility to create a longer proximal myotomy. Especially in type III achalasia and other spastic disorders like distal esophageal spasm (DES), characterized by premature and rapidly propagated esophageal contractions, POEM may be a promising long-term treatment option.[73–75] In **chapter 6** challenges arising with the treatment of DES by POEM are addressed.

Long-term follow-up

Achalasia is a chronic and incurable disease. Follow-up of achalasia patients is important for symptom control but also to identify complications or treatment-related side effects. Current guidelines do not strictly advice standardized follow-up visits to evaluate treatment efficacy or complications, except in case of persistent or recurrent symptoms.[32,33,76] Lack of a universal definition of failure after any treatment, deficient long-term follow-up studies and the variable correlation between symptoms and objective outcome measures post-treatment, complicate the development of a standardized follow-up.[33,76] Besides ineffective initial treatment, there are a variety of potential causes that can generate symptoms post-treatment e.g. esophageal fibrosis, tight fundoplication after myotomy, aperistalsis or gastroesophageal reflux. Comprehensive evaluation of these symptoms with objective testing is necessary to discriminate the underlying cause and start adequate treatment. Since failed treatment and esophageal fibrosis are the most common causes of persistent or recurrent symptoms, evaluation starts with the assessment of esophageal clearance by timed barium esophagogram, HRM and/or impedance planimetry to measure EGJ distensibility.[32,33,76]

In addition to ineffective treatment, symptoms can also be attributed to treatment-related side effects. One of the major side effects of achalasia treatment is gastroesophageal reflux. The goal of achalasia treatment is symptom relief, achieved by disruption of the LES, compromising the barrier function of the EGJ against reflux of gastric content. Gastroesophageal reflux can cause mucosal damage, leading to reflux symptoms, reflux esophagitis and even Barrett's esophagus. Post-treatment, the prevalence of presumed reflux-related complications is variable, ranging from 5-60%.[61,66,77–81] This variability is in part related to the type of treatment, with higher occurrence rates after laparoscopic or endoscopic myotomy (20-60%) compared to pneumodilation (5-25%), the definition and assessment of gastroesophageal reflux.[61,66,77–81] In addition, reflux symptoms like heartburn, chest pain and regurgitation are also indicative of achalasia. Studies further showed a considerable discordance between reflux symptoms, esophageal acid exposure as measured by pH monitoring and presence of esophagitis during endoscopy.[82–86] Despite these observations the current treatment strategy for gastroesophageal reflux post achalasia treatment is acid suppression by proton pump inhibitors, which has variable efficacy. The advancement of POEM, with a high post-procedural prevalence of reflux symptoms and esophagitis, further underlines the urgency for a better understanding of this problem.[77,79] In **chapter 7** mechanisms underlying reflux symptoms in treated achalasia patients are studied by analyzing esophageal function, acid exposure, acidification patterns, symptom perception and mucosal status.

A long-term complication of achalasia is the development of esophageal carcinoma. Compared to the general population achalasia patients have an increased relative risk to develop squamous cell carcinoma (10-50 fold increased risk) or adenocarcinoma (0.5-10 fold increased risk).[87–93] Impaired esophageal clearance, leading to stasis of food and gastric content, increases bacterial growth, chemical irritation and mucosal inflammation resulting in dysplastic changes of esophageal epithelial cells eventually progressing to esophageal squamous cell carcinoma.[94] Development of esophageal adenocarcinoma is related to increased acid exposure, a consequence of achalasia treatment by reducing LES pressure, that may lead to esophagitis, Barrett's esophagus and ultimately adenocarcinoma.[91,92] The type of treatment seems not to influence the risk of cancer.[92,95] Despite the increased cancer risk, guidelines advise against regular endoscopic follow-up.[32,33,76] This is based on the observed controversy in studies on the exact cancer risk caused by difference in study design (retrospective versus prospective), length of follow-up and number of included patients.[96] Furthermore there are limited data on the yield of endoscopic cancer screening and its cost-effectiveness in patients with achalasia. With the introduction of high-resolution endoscopy and chromoendoscopy with Lugol staining the sensitivity to detect precursor lesions may have been significantly improved.[97,98] Studies that evaluate the efficacy of endoscopic cancer screening with the current techniques in longstanding achalasia are warranted. In **chapter 8** the use of Lugol staining for the detection of precursor lesions for esophageal carcinoma in achalasia is evaluated.

Outline thesis

The goal of this thesis is to break down barriers in the management of achalasia both literally and metaphorically by improving diagnostic management, evaluating the efficacy of current and new treatments and enhancing strategies for long-term follow-up of achalasia.

Part I - diagnostic management

The first part of this thesis focusses on improving diagnostic testing in achalasia patients. **Chapter 2** aims to oppose the observation, that a subgroup of patients with typical achalasia symptoms, but not meeting all diagnostic HRM criteria are not diagnosed with achalasia. **Chapter 3** examines a new provocative test during HRM in order to observe esophageal stasis comparable to timed barium esophagogram pre- and post-treatment. **Chapter 4** attempts to identify risk factors that discriminate achalasia from malignancy-associated pseudoachalasia to prevent delay in appropriate treatment.

Part II - treatment

The second part covers the treatment of achalasia, highlighting a relative new treatment, the POEM procedure. **Chapter 5** describes a randomized controlled trial comparing POEM versus pneumodilation as the initial treatment for achalasia, evaluating the effect on symptoms, LES pressure, esophageal emptying and gastroesophageal reflux. In **chapter 6** the additional value of POEM for spastic motility disorders is reported.

Part III - long-term follow-up

The final part of this thesis focuses on the follow-up protocol, discussing treatment-related side effects and long-term complications. Gastroesophageal reflux is one of the most observed side effects of achalasia treatment. **Chapter 7** describes the mechanisms underlying reflux symptoms post-treatment by analyzing esophageal function, acid exposure, acidification patterns, symptom perception and mucosal status. Compared to the general population achalasia patients have an increased risk to develop esophageal cancer. In **chapter 8** the need and effectiveness of endoscopic screening for detecting esophageal carcinoma in longstanding achalasia is evaluated.

The general discussion, **chapter 9**, describes the main findings of the studies presented in this thesis with their implications for the current management of achalasia. Furthermore, future perspectives on unraveling the pathophysiology, optimizing diagnostic strategies, patient-tailored treatment and improvement of long-term management are discussed.

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Part I
Diagnostic management

Esophagogastric junction distensibility identifies achalasia subgroup with manometrically normal esophagogastric junction relaxation

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2

ABSTRACT

Background

Manometric criteria to diagnose achalasia are absent peristalsis and incomplete relaxation of the esophagogastric junction (EGJ), determined by an IRP >15 mmHg. However, EGJ relaxation seems normal in a subgroup of patients with typical symptoms of achalasia, no endoscopic abnormalities, stasis on timed barium esophagogram (TBE) and absent peristalsis on HRM. The aim of our study was to further characterize these patients by measuring EGJ distensibility and assessing the effect of achalasia treatment.

Methods

Impedance planimetry (EndoFLIP) was used to measure EGJ distensibility and compared to previous established data of 15 healthy subjects. In case the EGJ distensibility was impaired achalasia treatment followed. Eckardt score, HRM, TBE and EGJ distensibility measurements were repeated >3 months after treatment.

Results

We included 13 patients (5 male; age 19-59 years) with typical symptoms of achalasia, Eckardt score of 7 (5-7). HRM showed absent peristalsis with low basal EGJ pressure of 10 (5.8-12.9) mmHg and IRP of 9.3 (6.1-12) mmHg. Esophageal stasis was 4.6 (2.7-6.9) cm after 5 min. EGJ distensibility was significantly reduced in patients compared to healthy subjects (0.8 (0.7-1.2) mm^2/mmHg vs 6.3 (3.8-8.7) mm^2/mmHg). Treatment significantly improved the Eckardt score (7 (5-7) to 2 (1-3.5)) and EGJ distensibility (0.8 (0.7-1.2) mm^2/mmHg to 3.5 (1.5-6.1) mm^2/mmHg).

Conclusion

A subgroup of patients with clinical and radiological features of achalasia but manometrically normal EGJ relaxation has an impaired EGJ distensibility and responds favorably to achalasia treatment. Our data suggest that this condition can be considered as achalasia and treated as such.

INTRODUCTION

Achalasia is a rare motility disorder of the esophagus characterized by loss of peristalsis in the esophageal body and impaired relaxation of the esophagogastric junction (EGJ). Patients typically present with dysphagia, regurgitation of food, chest pain and weight loss.[1] In the diagnostic approach to patients suspected of achalasia, endoscopy is the first investigation that is performed to exclude other causes of the symptoms. In 60% of the patients with achalasia endoscopy shows a dilated esophagus and a pinpoint stenosis of the EGJ.[2] Furthermore, a timed barium esophagogram (TBE) typically shows a dilated esophageal body, a bird beak sign at the EGJ and stasis of contrast.[3] Both endoscopy and radiology have a reasonable sensitivity to diagnose achalasia, especially in advanced cases.[2] However in the early stage of the disease both tests can be completely normal. Therefore, the gold standard to diagnose achalasia is esophageal manometry. A manometric diagnosis of achalasia is made when absent peristalsis and incomplete relaxation of the EGJ are measured.[4] Currently, high-resolution manometry (HRM) is the common standard to diagnose motility disorders. HRM replaced conventional manometry because of its superior diagnostic performance and its user-friendliness.[5,6] Impaired EGJ relaxation is defined with HRM as the presence of an integrated relaxation pressure (IRP) >15 mmHg.[7] Despite the increased accuracy of diagnosing esophageal motility disorders by HRM, we identified a subgroup of patients with typical symptoms and radiological findings of achalasia, no abnormalities during endoscopy, absent peristalsis on HRM but with a normal EGJ relaxation reflected by an IRP <15mmHg. According to the Chicago Classification this subgroup cannot be classified as achalasia.[7] However, manometry only provides surrogate measures of the EGJ opening and cannot measure resistance to flow across the EGJ which is mainly determined by its distensibility in response to increased intraluminal pressure.[8–10] Measuring the distensibility of the EGJ gives a more direct view of the EGJ function compared to the IRP. Previous studies showed that in treatment naïve achalasia patients with manometrically incomplete EGJ relaxation, the EGJ distensibility is clearly impaired compared to healthy subjects.[10–16] Therefore we hypothesized that in this subgroup of patients the EGJ distensibility is reduced which explains the discrepancy between the clinical and radiological features and the apparently normal EGJ relaxation on HRM. The aim of this study was to further characterize this subgroup of patients with clinical and radiological features of achalasia but manometrically normal EGJ relaxation by assessing distensibility measurements of the EGJ. Additionally, we looked at the effect of achalasia treatment in these patients.

MATERIALS AND METHODS

Subjects

For this cohort study we included patients that presented at the outpatient clinic of our center between 2011 and 2014 with typical symptoms suggestive of achalasia and stasis on a barium swallow in whom HRM showed aperistalsis but an IRP <15 mmHg. All patients previously underwent an upper endoscopy that showed no obstruction. This study was evaluated by the local Medical Ethical Committee and approved (W15_048#15.0059). The principles of the Declaration of Helsinki were followed and written informed consent obtained of all included patients.

Study protocol

Patients that fulfilled the inclusion criteria were studied with TBE and EGJ distensibility measurements. Symptoms were assessed using the Eckardt score. In case EGJ distensibility was impaired achalasia treatment followed. Three months after treatment patients were evaluated again with the Eckardt score, HRM, TBE and EGJ distensibility measurements. At initial presentation, EGJ distensibility measurements were performed on the same day as HRM and TBE or within a week of the previous measurements. At 3 months follow-up all measurements were performed the same day.

Esophageal high-resolution manometry

Manometric studies were carried out using a solid-state HRM catheter with 36 circumferential sensors spaced at 1-cm intervals (Given Imaging, Los Angeles, CA, USA). The catheter was placed transnasally and positioned to record from hypopharynx to the stomach with at least three intragastric transducers. According to a standardized protocol, patients received 10 water boluses of 5 mL in supine position with an interval of 20 seconds followed by a period of 30 seconds not swallowing to create a recording period for baseline EGJ pressure measurement. HRM studies were analyzed using dedicated software (Manoview, Given Imaging, Los Angeles, CA, USA). Thermal compensation was applied before analysis.[6] Esophageal motility was assessed according to the Chicago Classification and the following key esophageal pressure topography metrics were measured: integrated relaxation pressure (IRP), expiratory basal EGJ pressure, peristaltic integrity using the 20-mmHg isobaric contour, intrabolus pressure pattern, distal contractile integral and distal latency.[7] EGJ pressures were referenced to gastric pressure, whereas esophageal contractions parameters were referenced to atmospheric pressure.[6] The upper limit of normal for the IRP was defined as <15 mmHg.[7] Based on the esophageal pressure topography metrics esophageal contraction and pressurization patterns were defined which was utilized to diagnose achalasia and discriminated achalasia subtypes: type I 100% failed peristalsis; type II 100%

failed peristalsis with panesophageal pressurization in ≥20% of the swallows; type III no normal peristalsis with premature, spastic contractions in ≥20% of the swallows.[7] Besides evaluating HRM according to the Chicago classification, we assessed EGJ relaxation as a percentage relative to EGJ basal pressure in this study by measuring the percentual pressure drop from the expiratory basal EGJ pressure to the median IRP of the 10 evaluated swallows. A drop in pressure of ≥ 50% was considered as normal EGJ relaxation.

Timed barium esophagogram

TBE was performed to assess esophageal emptying. Patients were instructed to ingest a maximal tolerable amount of low density barium sulphate suspension (200 mL) in an upright, slightly left posterior oblique position during a time window of 30-45 seconds without regurgitation or aspiration. After ingestion of the barium suspension radiographs were taken at 0, 1, 2 and 5 minutes to determine esophageal stasis.[3] The distance from the tapered distal esophagus to the top of the barium column and the maximal esophageal diameter were measured. Height of the barium column at 5 minutes was used to determine completeness of emptying.[17]

EGJ distensibility assessed by EndoFLIP

For the measurement of EGJ distensibility the commercial available Endo functional luminal imaging probe (EndoFLIP) was used (Crospon Ltd, Galway, Ireland). EndoFLIP uses impedance planimetry to measure cross sectional areas (CSAs) in the alimentary tract, as previously described.[18] The EndoFLIP consisted of a 240 cm long, 3 mm outer diameter catheter with distally an infinitely complaint bag of 14 cm which could be filled with a specially formulated conductive solution. Inside the bag 17 electrodes were placed with a 4 mm interval over an 8 cm segment. A constant current of 100 A was generated between two adjacent electrodes at a frequency of 5 kHz. With the use of impedance planimetry, CSAs were determined for the 16 cross-sections of the bag during volumetric distension. The minimal to maximal measured range for CSA was 10-490 mm^2. A pressure sensor located on the catheter measured intrabag pressure during volumetric distension, allowing assessment of EGJ distensibility. The catheter was precalibrated by the manufacturer. The deflated catheter was inserted through an anesthetized nostril without sedation. The center of the bag was positioned at the EGJ based on manometry reading and inflated by the following distension protocol; 20, 30, 40 and 50 mL volume. During each step of volumetric distension, intrabag pressures and CSAs were measured at 10 Hz, during 30 seconds. Measurements were repeated in case of migration of the bag or disturbance by esophageal peristalsis. EGJ distensibility was determined by dividing the median minimal CSA, reflecting the EGJ, by the median intrabag pressure at a given volume distension during the 30s recording

period. EGJ distensibility was expressed in mm^2/mmHg. Data from 15 previous studied asymptomatic healthy subjects were used as a control group for EGJ distensibility.[11] The cutoff for a normal EGJ distensibility was determined at 2.9 mm^2/mmHg by a volume distension of 50 mL.[11] Baseline and post-treatment EGJ distensibility measurements were analyzed in a blinded fashion.

Symptom scores

To assess the symptoms of the patients, the Eckardt score was used. This score reflects the sum of symptom scores for dysphagia, regurgitation and chest pain (0=absent, 1=occasionally, 2=daily, 3=each meal) with additionally the score of weight loss (0=no weight loss, 1=<5 kg, 2=5-10 kg, 3=>10 kg).[19] The score ranges between 0-12 with higher scores indicating more severe symptoms. After treatment, an Eckardt score of 3 or less was considered as treatment success.

Data analysis and statistics

Data are presented as median (interquartile range, IQR). Statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, United States). Data of patients and healthy controls were compared using the Mann-Whitney U-test in case of continuous data and the Chi-square test for categorical data. Paired continuous data were tested by the Wilcoxon signed rank test. Differences were considered statistically significant when P<.05. All reported P-values are 2 tailed.

RESULTS

Clinic characteristics and initial presentation

In total 13 patients were included (5 male, age 19-59 years). This was 5.2% of all patients newly diagnosed with achalasia between 2011-2014 in our center. Patients presented with typical symptoms of achalasia with a median Eckardt score of 7 (5-7). The duration of symptoms before consultation was 24 (12-35) months. Endoscopy showed no causes that could explain the symptoms. TBE displayed incomplete emptying of the esophagus in all patients with stasis of 4.6 (2.7-6.9) cm after 5 minutes and an esophageal diameter of 2.4 (2.1-2.9) cm. The HRM that followed showed absent peristalsis with an IRP of 9.3 (6.1-12.0) mmHg and a basal EGJ pressure of 10 (5.8-12.9) mmHg (**figure 1**). Nine patients had failed peristalsis (achalasia type I), 2 patients had failed peristalsis and pan-esophageal pressurization (achalasia type II) and 2 patients had premature, spastic contractions (achalasia type III). When expressing EGJ relaxation as the percentage of relaxation from the basal EGJ pressure the mean degree of relaxation was 11± 4.8%, 92% of the patients had an EGJ relaxation of less than 50%.

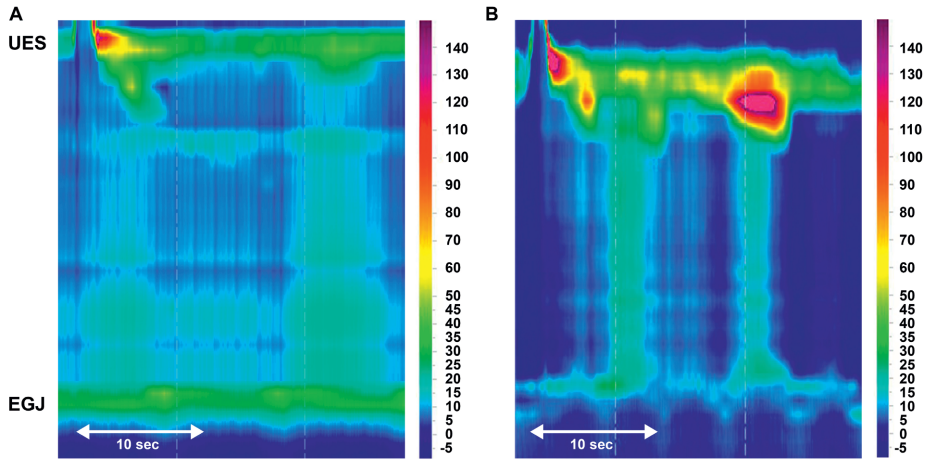

Figure 1. High-resolution manometry (HRM) of typical and atypical achalasia. (A) HRM of a typical achalasia patient with absent peristalsis and impaired relaxation of the EGJ (IRP >15 mmHg) compared to the (B) HRM of a patient with clinical and radiological features of achalasia who showed absent peristalsis but an apparent normal EGJ relaxation (IRP <15 mmHg).

EGJ distensibility

All measurements showed an hourglass shape of the EndoFLIP bag during volume distension. In healthy subjects the hourglass shape was less pronounced compared to the patients (**figure 2**). There was no difference in age and gender between patients (5 male, age 19-59 year) and healthy subjects (8 male, age 23-57 years (*P*=.5/*P*=.9)). As shown in **figure 3**, minimal EGJ CSA was lower in patients than in healthy subjects, except for the 20 mL distension volume. At higher distension volumes the EGJ distensibility was significantly lower in the patients than in the healthy subjects (30 mL: 1.1 (0.8-1.3) mm^2/mmHg vs 2.3 (1.6-4.3) mm^2/mmHg, *P*<.001; 40 mL: 0.9 (0.6-1.3) mm^2/mmHg vs 4.9 (3.5-6.9) mm^2/mmHg, *P*<.001; 50 mL: 0.8 (0.7-1.2) mm^2/mmHg vs 6.3 (3.8-8.7) mm^2/mmHg, *P*<.001). All patients exhibited EGJ distensibility below the cutoff value set for normality at a volume distension of 50 mL (**figure 5**).

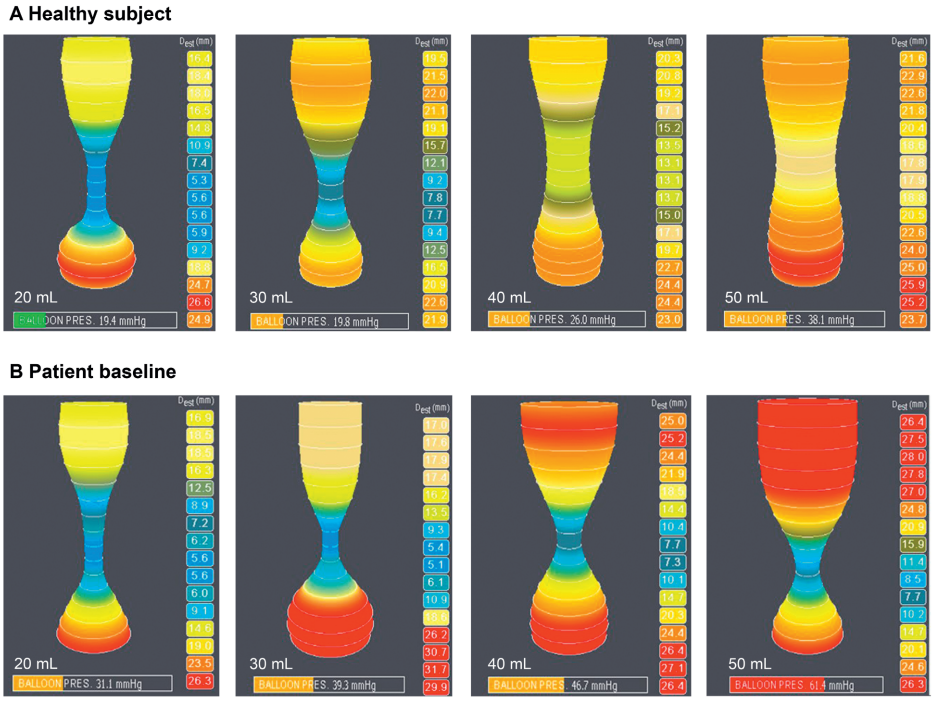

Figure 2. Examples of EndoFLIP measurement during all distension volumes in a healthy subject (A) and a patient at baseline (B). Values in the right panel represent the diameter of the bag. In the healthy subject the EGJ opening is wider than in the patient. At all distension volumes the intrabag pressure (displayed in bottom panel) is lower in the healthy subject than in the patient.

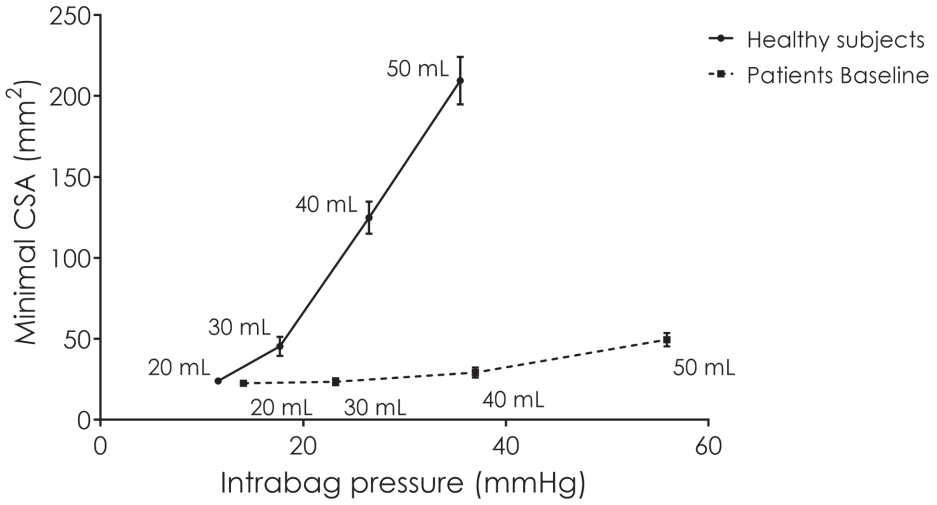

Figure 3. Cross sectional area (CSA) and intrabag pressure during EndoFLIP measurements. The narrowest CSA, reflecting the EGJ (mm^2) plotted against intrabag pressure (mmHg) for healthy subjects (n=15) and patients at baseline (n=13) at all distension volumes. Data are in median (IQR). At distension volumes of 30, 40 and 50 mL patients at baseline have a smaller CSA with a higher intrabag pressure compared to healthy subjects.

Effect of treatment

All included patients had an impaired EGJ distensibility and therefore underwent achalasia treatment depending on patient preference. One patient underwent botulinum toxin injections, 9 patients were treated with pneumodilation and 2 patients were treated with Heller myotomy. One patient underwent Heller myotomy three months after initial pneumodilations because of early recurrence of symptoms. For pneumodilation a standard protocol of two pneumodilations within 1-2 weeks with a Rigiflex balloon of 30 and subsequently 35 mm was performed. In case of persistent symptoms a pneumodilation with a 40 mm Rigiflex balloon followed within 2 weeks. This was performed in 2 patients. All procedures were performed without complications. Post-treatment, the Eckardt score was significantly reduced from 7 (5-7) to 2 (1-3.5) (P<.001). Three patients still experienced symptoms after treatment, which was reflected by an Eckardt score above 3. In 7 (n=5 pneumodilation, n=2 Heller myotomy) of the 13 patients the EGJ distensibility measurements, HRM and TBE were repeated at 3-months follow-up. The other patients declined to undergo the investigations again. EGJ distensibility showed a significant increase at a distension volume of 50 mL compared to baseline EGJ distensibility (**figure 4**). At a distension volume of 30 and 40 mL EGJ distensibility was also significantly increased after treatment (30 mL: 1.0 (0.7-1.2) mm^2/mmHg vs 2.2 (1.4-3.0) mm^2/mmHg, 40 mL: 0.7 (0.4-1.0) mm^2/mmHg vs 3.2 (1.8-4.1) mm^2/mmHg, both P<.05).

In 4 of the 7 patients EGJ distensibility reached values within the normal range. But compared to healthy subjects the distensibility in all 7 patients was still significantly lower at a volume distension of 50 mL (3.5 (1.5-6.1) mm^2/mmHg vs 6.3 (3.8-8.7) mm^2/mmHg, *P*<.05) (**figure 5**)). The 3 patients in whom EGJ distensibility remained impaired were also still symptomatic with an Eckardt score above 3, although lower than before treatment. The initial treatment of these patients had been pneumodilation. Treatment did not change basal EGJ pressure significantly (10 (5.0-13.2) mmHg vs 7.9 (3.8-11.5) mmHg, *P*=.34), nor did it change EGJ relaxation (IRP 9.3 (5.3-13.2) mmHg vs 8.3 (4.6-13.2) mmHg, *P*=.31) (**figure 4**). Esophageal emptying during TBE was slightly improved after treatment (5.8 (4-6.5) cm vs 4.2 (3.3-6.8) cm, *P*=.7). In two of the three symptomatic patients with impaired distensibility, TBE showed increased stasis at 5 minutes. The esophageal diameter was not significantly different after treatment (2.4 (1.8-2.9) cm vs 1.8 (1.5-3.2) cm, *P*=.7).

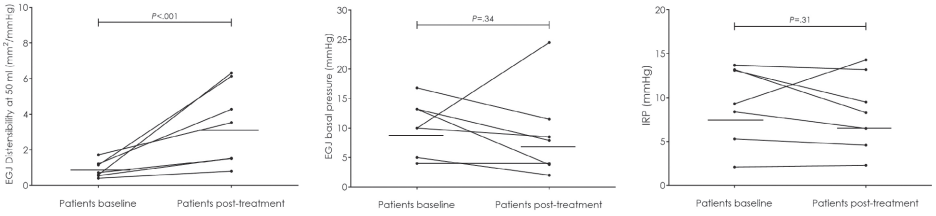

Figure 4. Esophagogastric junction (EGJ) distensibility at a volume distension of 50 mL, EGJ basal pressure and integrated relaxation pressure (IRP) of patients at baseline and post-treatment (n=7). Data are in median (IQR). After treatment EGJ distensibility was increased significantly (*P*<.001). Treatment did not significantly change EGJ basal pressure or EGJ relaxation.

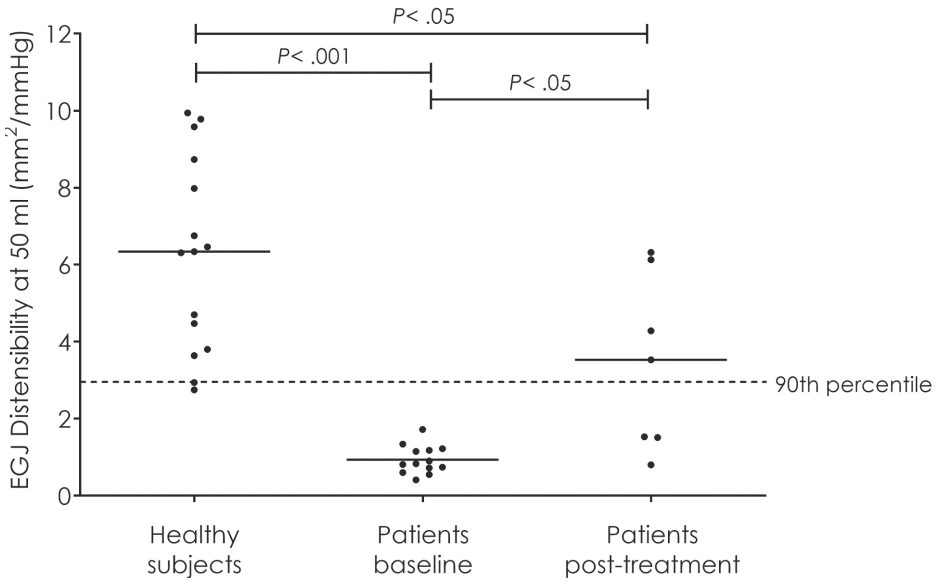

Figure 5. EGJ distensibility at the maximum volume distension of 50 mL in healthy subjects (n=15), patients at baseline (n=13) and patients post-treatment (n=7). Data are in median (IQR). The cutoff for normality was determined at the 90th percentile of healthy subjects at a value of 2.9 mm^2/mmHg. Healthy subjects had a significantly higher EGJ distensibility compared to patients at baseline and post-treatment (*P*<.001; *P*<.05). Treatment significantly improved the EGJ distensibility of patients (*P*<.05). At baseline none of the patients had an EGJ distensibility within the normal range and after treatment this was 4 of the 7 patients. The 3 patients with a low distensibility after treatment were all symptomatic.

DISCUSSION

This study shows that a subgroup of patients with clinical and radiological features of achalasia but manometrically normal EGJ relaxation has an impaired EGJ distensibility at EndoFLIP measurements. The impaired EGJ distensibility, which is also seen in achalasia patients with manometric dysrelaxation of the EGJ,[10–16] explains the discrepancy between the clinical and radiological features of achalasia and the apparently normal EGJ relaxation on HRM. This finding supports our hypothesis that these patients actually suffer from achalasia. The observation that achalasia treatment is effective in these patients provides further support to this concept. We therefore conclude that the diagnosis of achalasia can sometimes also be made in patients with an IRP lower than 15 mmHg.

The physiology of the EGJ is complex and its function depends on the interaction between LES, crural diaphragm, sling fibers of the proximal stomach and phrenoesophageal ligament.[20] Effective esophageal bolus transport is not only determined by productive peristaltic contractions of the esophageal body but also by the distensibility of the EGJ in response to

intraluminal pressure.[8–10] Therefore, optimal evaluation of the EGJ function is established by measuring the resistance to flow across the EGJ. Introducing HRM as a replacement of conventional manometry has led to more accuracy in evaluating the UES and EGJ due to closely placed, circumferential pressure sensors.[5,6] However, HRM still provides a surrogate measure of EGJ opening because EGJ relaxation is measured passively.[10] Thereby an occlusive pressure of the esophagus against the catheter is necessary to assess relaxation of the EGJ. During HRM a low to normal basal EGJ pressure (10 (5.8-12.9) mmHg) was observed in all patients. This low to normal basal EGJ pressure causes an apparent normal EGJ relaxation because it is not possible to have a relaxation pressure or IRP above 15 mmHg when the resting pressure is persistently below 15 mmHg. In previous studies, using conventional manometry, complete LES relaxation was also seen in patients with low to normal baseline LES pressure who furthermore had aperistalsis and clinical and radiological features of achalasia.[21,22] Increased EGJ pressure influences the resistance to flow across the EGJ but impaired esophageal emptying in patients with failed peristalsis is mainly determined by EGJ distensibility, even when EGJ pressure is low or absent.[10,11] Studies evaluating the efficacy of achalasia treatment confirmed this by showing a low EGJ pressure with apparently normal relaxation during manometry in patients with poor response.[10,11] However, all these patients still had an impaired EGJ distensibilty and reduced esophageal emptying, similar to our subgroup of patients.[10,11] Measuring EGJ distensibility seems therefore a valuable diagnostic tool to diagnose or exclude achalasia in case HRM is not conclusive. Compared to healthy subjects, EGJ distensibility of our patients was clearly impaired with similar low values to that seen in treatment naïve achalasia patients with manometric dysrelaxation of the EGJ (0.7-1.0 mm^2/mmHg at a distension volume of 50 mL).[10–16] This confirmed our hypothesis that this subgroup should be diagnosed and treated as achalasia.

Besides the basal EGJ pressure Lin *et al* showed that the IRP is dependent on the pattern and timing of distal esophageal contractility.[23] The study revealed that in the absence of any distal esophageal contractility and low intraesophageal pressure, the IRP is mainly dependent on the LES potentially leading to normal values despite still causing bolus obstruction.[23] Based on a classification and regression tree model Lin and co-workers determined IRP cutoffs based on contractile patterns. The data demonstrated that for achalasia type I, in absence of esophageal contractions, the IRP cutoff for EGJ relaxation was lower (>10 mmHg).[23] For achalasia type III the IRP threshold was higher (>17 mmHg) due to premature, spastic esophageal contractions.[23] In our study, 70% of our patients showed esophageal contractile patterns compatible with type I achalasia, 15% type II and 15% type III. Of the patients with achalasia type I, 5 of the 9 patients still had an IRP below the new suggested cutoff of 10 mmHg. The low IRP identified

in our patients could only be partly explained by the pattern of esophageal contractility and is probably mainly caused by the low EGJ basal pressure.

Although transnasal passage seemed well tolerable for the majority of our patients, distensibility measurements are still invasive, expensive and not widely available. Another method to evaluate EGJ function would be to express manometric EGJ relaxation as a percentage relative to the EGJ basal pressure, as has been proposed by investigators using conventional manometry. This would allow correction for low EGJ basal pressure. In our patient group relaxation of the EGJ was only 11±4.8% and in 92% of the patients the EGJ relaxation was less than 50%. A disadvantage of this technique is that relaxation would be considered normal when the EGJ pressure drops significantly but still remains at a high level, for example, a relaxation from 40 to 17 mmHg would be considered normal if 50% would be taken as a cutoff for normality. To prevent this shortcoming the residual or nadir pressure was introduced to assess EGJ relaxation, which is currently determined by the IRP in HRM. However, in case of low EGJ basal pressure, evaluating EGJ relaxation as a percentage drop in LES pressure could be helpful.

The latest version of the Chicago Classification proposed to consider the diagnosis of achalasia if there is a borderline median IRP with evidence of esophageal pressurization (≥ 20% of the swallows).[7] Two of the 13 patients with an apparent normal EGJ relaxation, IRP of 10.6 mmHg and 13.7 mmHg respectively, showed panesophageal pressurization in ≥ 20% of the swallows at time of the initial HRM. EGJ distensibility was in both patients impaired and thereby confirms the proposal of the recent Chicago Classification to consider the diagnosis of achalasia in these patients. In addition, TBE showed incomplete emptying of the esophagus that is concordant to the findings during HRM and EGJ distensibility measurements. Measuring EGJ distensibility may not be necessary to confirm the diagnosis of achalasia in patients with panesophageal pressurization despite a low IRP. Studies of Lin et al and Agrawal et al also show the limitations of strict conformation to the manometric feature of incomplete EGJ relaxation for the diagnosis of achalasia.[23,24] As mentioned previously Lin and co-workers showed that the IRP is dependent on esophageal contraction patterns and suggest a lower IRP cutoff for EGJ relaxation (>10 mmHg) for patients with achalasia type I due to absent contractions. The study of Agrawal et al demonstrated that with conventional manometry 60-80% of the achalasia patients have absent or incomplete LES relaxation with wet swallows. Overall, these studies further support our observation that the diagnosis of achalasia can also be made in patients with manometrically normal EGJ relaxation.

Previous studies with conventional manometry have also described apparent complete LES relaxation in patients with clinical and radiological features of achalasia.[9,21,22,25,26] It was suggested that this subgroup represents an early stage of achalasia. Two studies showed that these patients were younger and had a shorter duration of symptoms compared to patients with typical achalasia.[25,26] Contrary to these findings, we observed that age (42 (30-50) years) and duration of symptoms (24 (12-35) months) were comparable to typical achalasia patients in our outpatient clinic. Other studies also did not find differences in clinical characteristics between the subgroup and typical achalasia.[9,21,22] Treatment of the low LES nadir pressure achalasia patients was successful in 80-100% of the patients, which is in line with our findings.[21,22] All patients in our study had reduced symptoms after treatment but in 23% the Eckardt score was still above 3. Follow-up measurements by EndoFLIP and TBE confirmed that EGJ distensibility of these patients was not in the normal range and esophageal emptying was still impaired. The 3 patients with poor response all underwent pneumodilation as the initial treatment. The limited effect of pneumodilation may be explained by the fact that two patients were classified as type I and III achalasia. Previous studies described that both subtypes are predictors of treatment failure.[27,28] The other patient was relatively young, 33 years. Age ≤40 years is also a known risk factor for failure after pneumodilation.[29]

The relatively small number of patients included in this study and the limited number of patients that underwent follow-up measurements after treatment are possible limitations of our study. This could be the reason that after treatment no significant differences were observed between IRP, basal EGJ pressure and stasis during TBE. However, the outcomes of the measurements were quite consistent and no apparent disparity between patients was observed. More long-term data would be of value to evaluate the response to achalasia treatment in this subgroup for a longer follow-up as this is a chronic disease.

In conclusion, impaired EGJ distensibility is present in a subgroup of patients with clinical and radiological features of achalasia but manometrically normal EGJ relaxation. The observed impaired EGJ distensibility in these patients is similar to that seen in classical achalasia, as described in previous studies and the response to achalasia treatment is equally favorable.

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Rapid drinking challenge during high-resolution manometry is complementary to timed barium esophagogram for diagnosis and follow-up of achalasia

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3

ABSTRACT

Background

Esophageal stasis is a hallmark of achalasia. Timed barium esophagogram (TBE) is used to measure stasis but exposes patients to ionizing radiation. It is suggested that esophageal stasis can be objectified on high-resolution manometry (HRM) as well using a rapid drinking challenge test (RDC). We aimed to assess esophageal stasis in achalasia by a RDC during HRM and compare this to TBE.

Methods

Thirty healthy subjects (15 male, age 40 (IQR 34-49)) and 90 achalasia patients (53 male, age 47 (36-59), 30 untreated/30 treated symptomatic/30 treated asymptomatic) were prospectively included to undergo HRM with RDC and TBE. RDC was performed by drinking 200 ml of water. Response to RDC was measured by basal and relaxation pressure in the esophagogastric junction (EGJ) and esophageal pressurization during the last 5 seconds.

Results

EGJ basal and relaxation pressure during RDC were higher in achalasia compared to healthy subjects (overall $P<.01$). Esophageal body pressurization was significantly higher in untreated (43 (33-35 mmHg)) and symptomatic treated patients (25 (16-32) mmHg) compared to healthy subjects (6 (3-7) mmHg) and asymptomatic treated patients (11 (8-15) mmHg, overall $P<.01$). A strong correlation was observed between esophageal pressurization during RDC and barium column height at 5 minutes on TBE ($r=0.75$, $P<.01$), comparable to the standard predictor of esophageal stasis, IRP ($r=0.66$, $P<.01$).

Conclusion

The RDC can reliably predict esophageal stasis in achalasia and adequately measure treatment response to a degree comparable to TBE. We propose to add this simple test to each HRM study in achalasia patients.

INTRODUCTION

Achalasia is an esophageal motility disorder caused by functional loss of neurons in the myenteric plexus leading to aperistalsis of the esophageal body and impaired relaxation of the esophagogastric junction (EGJ). The subsequent stasis of food and liquid results in typical symptoms of dysphagia, regurgitation, chest pain and weight loss.[1] In the diagnostic approach and follow-up of achalasia three diagnostic modalities are central: endoscopy, esophageal manometry and the timed barium esophagogram (TBE). Each modality has it unique attribute, but there is significant overlap in the acquired information and in many patient all tests are performed.[2] Endoscopy is the initial investigation performed to rule out obstruction, it is required before definite treatment for achalasia is performed. Radiographic examination of the esophagus can be diagnostic for achalasia but the gold standard to confirm diagnosis is esophageal manometry, showing absent peristalsis and incomplete relaxation of the EGJ.[3] The additional value of TBE is the information it gives on the contour of the esophagus and esophageal stasis, one of the hallmarks of achalasia. Previous studies showed that evaluating esophageal emptying by TBE is a useful metric to assess treatment outcome and identify patients at risk for recurrence of symptoms.[4–6] It even proved to be a better predictor of treatment success than EGJ pressure measured by manometry.[5] However, a major disadvantage of TBE is the exposure to a significant degree of ionizing radiation.

With the introduction of high-resolution manometry (HRM), new metrics to evaluate esophageal motility were introduced, leading to a new classification of esophageal motility disorders known as the Chicago classification.[7–9] HRM has largely replaced conventional manometry because of its superior diagnostic performance.[10] The increased accuracy and details provided by HRM also increased the value of esophageal manometry in the assessment of treatment outcome. It was shown that a normalized integrated relaxation pressure (IRP) is associated with symptom improvement.[11] However, esophageal stasis on TBE still is considered an important outcome measure which not always correlates with HRM metrics.[2,11] Esophageal stasis can also be assessed with HRM, by looking at the intrabolus pressure after standard 5-ml water swallows, as well as by performing provocative tests. Assessing provocative tests during HRM adds information on integrity of deglutitive inhibition and esophageal body contraction reserve in addition to the single swallows.[12–17] Two variants have been used: a short rapid drinking test, called multiple rapid swallows (MRS), with 5-10 rapid swallows of 2 ml to assess the inhibitory mechanism and peristaltic reserve[12,13,18,19], and a rapid drinking challenge test (RDC) with 100-200 ml free drinking to assess EGJ obstruction.[2,14,15,20] Studies by Marin et al and Ang et al showed that a RDC in newly diagnosed achalasia patients initiates sustained pressurization of the entire esophageal body and a high-pressure gradient

across a non-relaxed EGJ.[14,15] We hypothesized that the pressurization during RDC reflects intrabolus pressure related to retention of large liquid volumes and is indicative of esophageal stasis on TBE. Analyzing esophageal stasis by HRM could help to reduce the exposure to ionizing radiation by TBE. The aim of our study was therefore to assess esophageal stasis in achalasia patients using a rapid drinking challenge test during HRM and to compare this to the TBE protocol.

MATERIALS AND METHODS

Study subjects and inclusion criteria

Adult achalasia patients undergoing a HRM in the period January 2013 till October 2016 were prospectively included for this study. Patients were allocated to three different subgroups: untreated newly diagnosed patients; treated symptomatic patients and treated asymptomatic patients. The definition of symptomatic or asymptomatic treated patients was based on the Eckardt symptom score.[21] Effective treatment was defined as an Eckardt score ≤3. Treated asymptomatic patients were included after a post-treatment interval of at least 1 year. Inclusion of treated symptomatic patients was based on recurrent symptoms and independent of time or type of treatment. In addition, 30 healthy volunteers without a history of upper gastrointestinal complaints or surgery, that were previously studied to develop normal values for HRM, were included to function as a control group.[22] Subjects who used medication that could affect upper gastrointestinal motility were excluded. Healthy subjects only underwent measurements with HRM. The study was evaluated by the Medical Ethical Committee of the Academic Medical Center and the need for formal medical assessment was waived (Amsterdam, the Netherlands; internal reference number W15_053#15.0064; February 2015). The study with healthy subjects to assess normal values for HRM was previously approved by the Medical Ethical Committee of the Academic Medical Center (Amsterdam, the Netherlands; internal reference number MEC 212_017).[22]

Study protocol

Study subjects, healthy subjects and achalasia patients, that fulfilled the inclusion criteria first underwent a HRM measurement. A TBE was carried subsequently at the same day in all achalasia patients but not in healthy subjects. Clinical data were collected and symptoms were assessed using the Eckardt score. This score reflects the sum of symptom scores for dysphagia, regurgitation and chest pain (0=absent, 1=occasionally, 2=daily, 3=each meal) with additionally the score of weight loss (0=no weight loss, 1=<5 kg, 2=5-10 kg, 3=>10 kg).[21] In treated achalasia patients data on the type of treatment (pneumodilation, Heller myotomy or peroral endoscopic myotomy), treatment date and time until recurrent symptoms were assessed.

High-resolution manometry and analysis

Manometric studies were performed using a solid-state HRM catheter with 36 circumferential pressure sensors spaced at 1-cm intervals (Medtronic, Minneapolis, MN, USA). Patients and healthy subjects were instructed to fast at least 6 hours before the manometry was carried out. Before placement of the catheter, the pressure sensors were calibrated from 0-300 mmHg. The catheter was placed transnasally and positioned to record from hypopharynx to the stomach. At least three pressure sensors were placed intragastrically. Following a standardized protocol, all study subjects received ten 5-ml water swallows in supine position (10°-20°) with an interval of 20 seconds after a 5-minute baseline recording for adaptation. This was followed by a period of 30 seconds not swallowing to measure EGJ baseline pressure. The HRM data were analyzed using dedicated software (Manoview, Medtronic, Minneapolis, MN, USA). Thermal compensation was applied before analysis.[7] Esophageal motility was assessed according to Chicago classification version 3.0 and the following key esophageal pressure topography metrics were measured: EGJ basal pressure at end-expiration, the 4-s integrated relaxation pressure (IRP), distal contractile integral (DCI), distal latency (DL), peristaltic integrity using the 20-mmHg isobaric contour and intrabolus pressure pattern with ≥30 mmHg isobaric contour.[9] EGJ pressures were referenced to gastric pressure, whereas esophageal contraction metrics were referenced to atmospheric pressure.[7] Achalasia was defined as an IRP >15 mmHg without peristalsis.[9] Esophageal contraction and pressurization patterns were used to allocated achalasia patients into 3 different subtypes: type I 100% failed peristalsis; type II 100% failed peristalsis with panesophageal pressurization in ≥20% of the swallows; type III no normal peristalsis with premature, spastic contractions in ≥20% of the swallows.[9] Treated patients with an IRP <15 mmHg were not categorized in achalasia subtypes but received a manometric diagnosis of a motility disorder without EGJ outflow obstruction according to the Chicago classification version 3.0.[9]

Rapid drinking challenge

At the end of the HRM measurement the rapid drinking challenge test (RDC) was performed. Study subjects were in semirecumbent (30°- 45°) position and were instructed to drink rapidly 200 ml of water using a straw. In case a first attempt was unsuccessful due to dysphagia, pain or regurgitation a second RDC was performed after a break of 5 minutes. Analysis of an incomplete RDC was performed till the moment the patient stopped drinking. The time and number of swallows required to drink 200 ml of water was assessed. Esophageal body pressurization during RDC was analyzed using the isobaric contour. The maximal esophageal body pressurization during the last 5 seconds of the RDC was assessed by narrowing the isobaric contour till the moment it started to disappear (**figure 1**). Measurement of the esophageal body pressurization was at

a fixed level for all study subjects, 1-2 cm below the UES, at the transition zone, till the proximal margin of the LES, 1-2 cm above the LES. To accurately validate esophageal stasis during RDC and compare it with the outcome of TBE only the last 5 seconds were evaluated. EGJ basal pressure during complete RDC was measured using the smart mouse function (**figure 1**). The EGJ relaxation pressure during complete RDC was measured by the IRP window (IRP-RDC). During a 20-second period after completion of the RDC contractile response and basal EGJ pressure were evaluated. For the assessment of the contractile response of the esophageal body to the water load, the topographic metrics for single swallows of the Chicago classification version 3.0 were used.[9] An after-contraction was considered normal when the swallow had DCI >450 mmHg·s·cm and a normal DL (>4.5 s), and pressurization was absent. EGJ pressures were referenced to gastric pressure, all other pressures were referenced to atmospheric pressure.

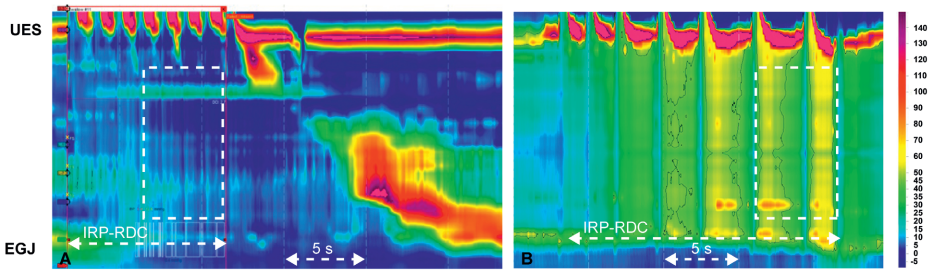

Figure 1. Rapid drinking challenge during HRM in a healthy subject (A) and an untreated achalasia patient (B). For each study subject duration of RDC, number of swallows, EGJ function (EGJ basal pressure and IRP-RDC) during complete RDC (white arrow) and esophageal body pressurization during the last 5 seconds (white box) was measured. The IRP-RDC was measured by the IRP window for single swallows. Esophageal body pressurization was assessed by the isobaric contour, see panel B. In the healthy subject complete inhibition of peristaltic activity and EGJ relaxation (IRP-RDC 6.3 mmHg) is observed during the RDC, which is followed by an after-contraction. The RDC of the achalasia patient shows a non-relaxing high-pressure EGJ (IRP-RDC 24.7 mmHg) and progressive esophageal body pressurization of 45 mmHg.

Timed barium esophagogram

Esophageal emptying and the width of the esophagus was evaluated by timed barium esophagogram (TBE). Achalasia patients were instructed to ingest a maximal tolerable amount of low density barium sulfate suspension (200 ml) during a time window of 30-60 seconds without regurgitation or aspiration. Patients were instructed to stand in an upright, slightly left posterior oblique position. After ingestion of the barium suspension radiographs were taken at 0, 1, 2 and 5 minutes to determine esophageal stasis.[23] The distance in centimeters from the tapered distal esophagus, starting at the EGJ, to the

top of the barium column was measured to determine the barium height.[23] The maximal esophageal diameter during TBE was measured to assess the esophageal width. The barium column height at 5 minutes was used to evaluate completeness of emptying.[4] Esophageal emptying was considered complete if 1 cm or less stasis was observed after 5 minutes.

Statistical analysis

Continuous data are presented as median (interquartile range, IQR) according to distribution. Categorical data are presented in percentages. Comparison of the outcome of continuous data measured by HRM, RDC and TBE between groups was performed using the Kruskal-Wallis test. *Post-hoc* analysis was performed using Mann-Whitney U-test with Bonferroni correction for multiple testing. For categorical data Chi-square test or Chi-square test for trend were used for analysis. Correlation between outcome parameters of RDC (esophageal pressurization, EGJ basal and relaxation pressure), HRM (IRP) and TBE (esophageal stasis and width) were analyzed by linear regression analysis (Spearman's rank). For esophageal pressurization during the RDC and the IRP-RDC a cut-off for normality was determined by the 90th percentile in healthy subjects. Optimal diagnostic thresholds for both parameters were also obtained by receiver operator characteristic (ROC) curves with the data of untreated achalasia patients and healthy subjects. The optimal cut-off value was defined as the cut-off corresponding to the point of the ROC curve closest to the sensitivity=1, specificity=1 optimum. According to obtained cut-off values contingency tables were created and data were compared by Chi-square test or Fisher's exact test. Differences were considered statistically significant when P<.05 (P<.001after Bonferrroni correction). All reported P-values are 2-tailed. Statistical analysis was performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY, United States).

RESULTS

Patient characteristics

Measurement results gathered from 30 healthy subjects (15 (50%) male, median age 40 (IQR 34-49)) and 90 achalasia patients (53 (59%) male, age 47 (36-59)) were analyzed in this study. The achalasia patients were allocated to different three subgroups: 30 untreated patients (19 (63%) male, age 46 (33-54)), 30 treated patients with recurrent symptoms (17 (57%) male, age 47 (35-64)) and 30 treated patients without symptoms (17 (57%) male, age 50 (41-61)). The follow-up after treatment in symptomatic patients was 18 (11-36) months and 12 (12-12) months in asymptomatic patients. In **table 1** the patient characteristics are shown.

High-resolution manometry

Data on HRM parameters are presented in table 1. The integrated relaxation pressure (IRP) was significantly higher in the group of untreated (33 (26-37)

mmHg) and symptomatic treated patients (19 (15-24) mmHg) compared to healthy subjects (9 (6-12) mmHg) and asymptomatic patients (8 (7-11) mmHg); *P*<.001). Similar findings were observed for EGJ basal pressure. Four (12%) healthy subjects showed a minor motility disorder on HRM; one had ineffective esophageal motility and the other three showed fragmented peristalsis. In treated asymptomatic patients, two (8%) patients had an IRP >15 mmHg with failed contractions and were classified as type I achalasia. The other patients all had an IRP <15 mmHg and were classified as absent contractility (n=24, 80%) or fragmented peristalsis (n=4, 12%). All three achalasia subtypes were observed in both untreated and symptomatic treated achalasia patients, see **table 1**. In both groups, the majority of patients was classified as type I or II.

Timed barium esophagogram

Untreated and symptomatic treated achalasia patients showed significantly decreased esophageal emptying on TBE, reflected by increased esophageal stasis (7 (5.5-9) cm; 3.5 (1.9-5.5) cm) and a wider esophagus (2.9 (2.5-3.8) cm; 2.8 (2.1-3.6) cm) compared to effectively treated achalasia (stasis 0 (0-1) cm; diameter 2.1 (1.8-2.5) cm; *P*<.01), see **table 1**.

Table 1. Patient characteristics

	Healthy subjects	**Untreated**	**Treated with symptoms**	**Treated without symptoms**	***P*-value**
Age (years)	40 (34-49)	46 (33-54)	47 (35-64)	50 (41-61)	.12
Gender male (n (%))	15 (50%)	19 (63%)	17 (57%)	17 (57%)	.8
Eckardt score		7 (5-9)^#	4 (4-5)#	2 (1-2)	<.01
Type of treatment (n (%))	-				-
Pneumodilation			21 (70%)	12 (40%)	
Heller myotomy			1 (3%)	-	
POEM			3 (10%)	15 (50%)	
Pneumodilation and Heller			5 (17%)	1 (3%)	
Pneumodilation and POEM		-	-	2 (7%)	
Achalasia subtype					.15
Type I		7 (23%)	13 (43%)		
Type II		18 (60%)	14 (47%)		
Type III		5 (17%)	3 (10%)		
Basal pressure EGJ HRM (mmHg)	17 (10-22)	34 (25-45)*^#	16 (11-22)#	9 (7-14)	<.01
IRP HRM (mmHg)	9 (6-12)	33 (26-37)*^#	19 (15-24)*#	8 (7-11)	<.01
Barium column height TBE at 5 min (cm)	-	7 (5.5-9)^#	3.5 (1.9-5.5)#	0 (0-1)	<.01
Maximal esophageal diameter TBE (cm)	-	2.9 (2.5-3.8)#	2.8 (2.1-3.6)#	2.1 (1.8-2.5)	<.01

***** *P*<.001 vs healthy subjects; ^ *P*<.001 vs treated with symptoms; # *P*<.001 vs treated without symptoms (*P*<.0011 after Bonferroni correction). Data are presented as median (IQR) or number (n (%)).

Rapid drinking challenge

In **table 2** the outcome of the RDC is presented. Overall, four untreated achalasia patients (3.3% of all study subjects) did not succeed to complete the RDC due to regurgitation. The duration of the RDC was most prolonged in untreated achalasia patients (21 (17-31) s) and significantly longer compared to healthy subjects (15 (12-19) s; *P*<.001). No difference was observed in the number of swallows during the RDC. All healthy subjects showed complete inhibition of the esophageal body, with low pressurization and a sustained EGJ relaxation. Basal and relaxation (IRP-RDC) EGJ pressure during the complete RDC were significantly higher in all achalasia patients compared to healthy subjects. Within achalasia subgroups, EGJ basal pressure was significantly more increased in untreated patients (24 (19-33) mmHg) compared to the two treated groups (treated symptomatic 14 (10-23) mmHg; treated asymptomatic 14 (10-17) mmHg; *P*<.001). The EGJ relaxation pressure (IRP-RDC) was significantly higher in both untreated as treated symptomatic achalasia patients (24 (16-28) mmHg; 14 (10-20) mmHg) compared to treated asymptomatic patients (9 (5-12) mmHg; *P*<.001). In all achalasia patients the esophageal body pressurization was significantly increased compared to healthy subjects and the highest pressurization was observed in untreated achalasia patients. Both untreated and treated symptomatic achalasia patients (43 (33-55) mmHg; 25 (16-32) mmHg) showed a significantly higher esophageal body pressurization during RDC compared to treated asymptomatic patients (11 (8-15) mmHg; *P*<.001). EGJ basal pressure after the RDC was significantly higher in untreated achalasia patients compared to healthy subjects and treated achalasia patients. In none of the achalasia patients an after-contraction was observed. In healthy subjects in 73% of the cases the RDC was followed by an after-contraction.

Figure 2 shows the distribution of esophageal body pressurization at the final 5 seconds of the RDC between subgroups. The data in **table 2** show that esophageal body pressurization can discriminate between all subgroups. Based on the higher 90th percentile of esophageal body pressurization in healthy subjects we estimated a cut-off for normality of 13 mmHg. This was confirmed by a ROC curve for esophageal body pressurization which showed a diagnostic threshold range of 10.5-16.5 mmHg, with an optimal cut-off of 12.5 mmHg (sensitivity 96%; specificity 93%) with an area under the curve (AUC) of 0.98 (95% CI: 0.96-1.0). As demonstrated in **figure 2**, 9 out of 30 (30%) successfully treated patients had a higher esophageal body pressurization than the 90th percentile cut-off value. This is in strong contrast to 30 of 30 (100%) untreated patients and 26 of 30 (87%) treated symptomatic patients. For IRP-RDC, the cut-off for normality determined by the 90th percentile in healthy subjects was 8.6 mmHg. The ROC curve for IRP-RDC showed a higher diagnostic threshold, with a range of 8.4-12.3 mmHg and optimal cut-off of 11.5 mmHg (sensitivity

93%; specificity 93%) with an AUC of 0.96 (95% CI: 0.90-1.0). The data in **table 2** show that IRP-RDC can adequately discriminate between the subgroups.

Table 2. Rapid drinking challenge

	Healthy subjects	**Untreated**	**Treated with symptoms**	**Treated without symptoms**	***P*-value**
Time (s)	15 (12-19)	21 (17-31)*	18 (15-21)	20 (14-28)	<.01
Number of swallows	11 (9-13)	11 (9-14)	9 (8-11)	11 (9-14)	.05
Basal EJG pressure (mmHg)	3 (1-5)	24 (19-33)*^#	14 (10-23)*	14 (10-17)*	<.01
EGJ relaxation pressure (IRP-RDC) (mmHg)	4 (1-6)	24 (16-28)*^#	14 (10-20)*#	9 (5-12)*	<.01
Pressurization last 5 seconds (mmHg)	6 (3-7)	43 (33-55)*^#	25 (16-32)*#	11 (8-15)*	<.01
Basal EGJ pressure after RDC (mmHg)	14 (5-30)	40 (21-51)*^#	13 (7-24)	14 (11-17)	<.01
After contraction (n (%))	22 (73%)	0 (0%)	0 (0%)	0 (0%)	-

***** *P*<.001 vs healthy subjects; ^*P*<.001 vs treated with symptoms; # *P*<.001 vs treated without symptoms (*P*<.0011 after Bonferroni correction). Data are presented as median (IQR) or number (n (%)).

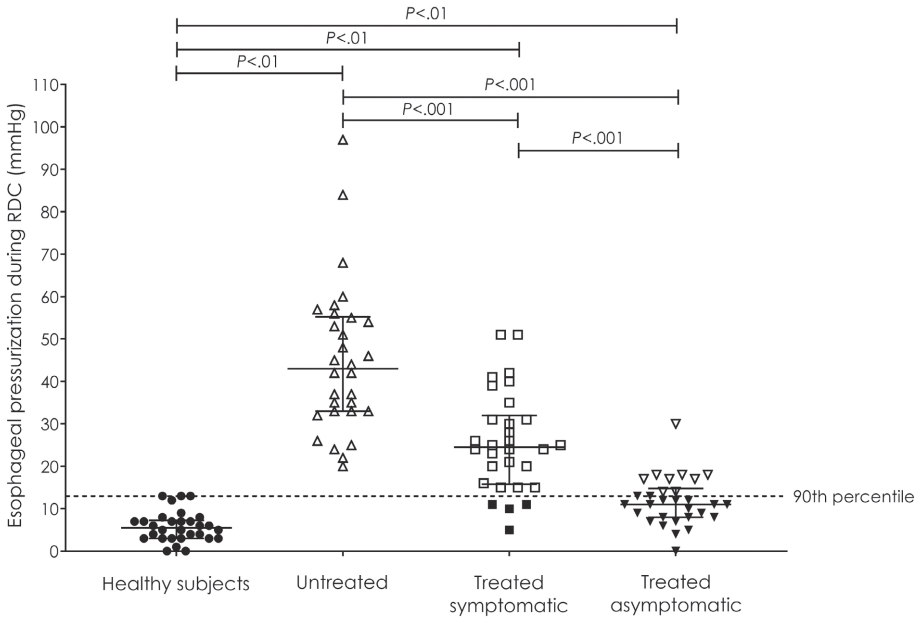

Figure 2. Esophageal pressurization during RDC of all groups. Healthy subjects had a significantly lower esophageal pressurization (6 (3-7) mmHg) compared to all achalasia groups (overall, *P*<.01). Both untreated and treated symptomatic achalasia patients (43 (33-55) mmHg; 25 (16-32) mmHg) showed a significantly higher esophageal pressurization during RDC compared to treated asymptomatic patients (11 (8-15) mmHg; *P*<.001). The cut-off for normality was based on the 90th percentile of healthy subjects, 13 mmHg. All untreated patients had a higher pressurization than the cut-off value, for symptomatic treated patients this was 87% (n=26) and for treated asymptomatic patients 30% (n=9).

Rapid drinking challenge in relation to esophageal emptying, EGJ relaxation pressure (IRP) and symptoms

A strong correlation was observed between esophageal stasis after 2 and 5 minutes at TBE and esophageal body pressurization during RDC (**figure 3**; stasis at 2 min r=0.70, *P*<.01; stasis at 5 min r=0.75, *P*<.01 Spearman's rank). Of all the achalasia patients, 29 patients (2 untreated, 3 treated with symptoms, 24 treated without symptoms) had none or minimal esophageal stasis (0-1 cm) at 5 minutes during TBE. Esophageal body pressurization was significantly lower in achalasia patients with none or minimal esophageal stasis compared to those with more than 1 cm esophageal stasis (11 (8-17) mmHg versus 32 (23-46) mmHg, *P*<.001). EGJ basal and relaxation pressure during complete RDC were moderately related to esophageal stasis (**figure 3**; EGJ basal pressure versus stasis at 2 min r=0.50, *P*<.01; stasis at 5 min r=0.56, *P*<.01; EGJ relaxation (IRP-RDC) pressure versus stasis at 2 min r=0.56, *P*<.01; stasis at 5 min r=0.61, *P*<.01 Spearman's rank).

Integrated relaxation pressure (IRP) measured during HRM was strongly associated with esophageal emptying measured by TBE (**figure 3**; stasis at 2 min r=0.63, *P*<.01; stasis at 5 min r=0.66, *P*<.01 Spearman's rank). Achalasia patients with none or minimal esophageal stasis at the end of TBE (29 patients; 2 untreated, 3 treated with symptoms, 24 treated without symptoms) had a significantly lower IRP compared to achalasia patients with more than 1 cm esophageal stasis (10 (7-12) mmHg versus 22 (16-33) mmHg, *P*<.001). The height of esophageal body pressurization during RDC was strongly related to EGJ basal pressure and IRP on HRM (basal EGJ pressure r=0.73; IRP r=0.74, both *P*<0.01 Spearman's rank). Achalasia patients with an IRP <15 mmHg (38 patients; 10 treated with symptoms, 28 treated without symptoms) had significantly lower esophageal body pressurizations compared to achalasia patients with an IRP >15 mmHg (12 (8-17) mmHg versus 35 (24-48) mmHg, *P*<.001).

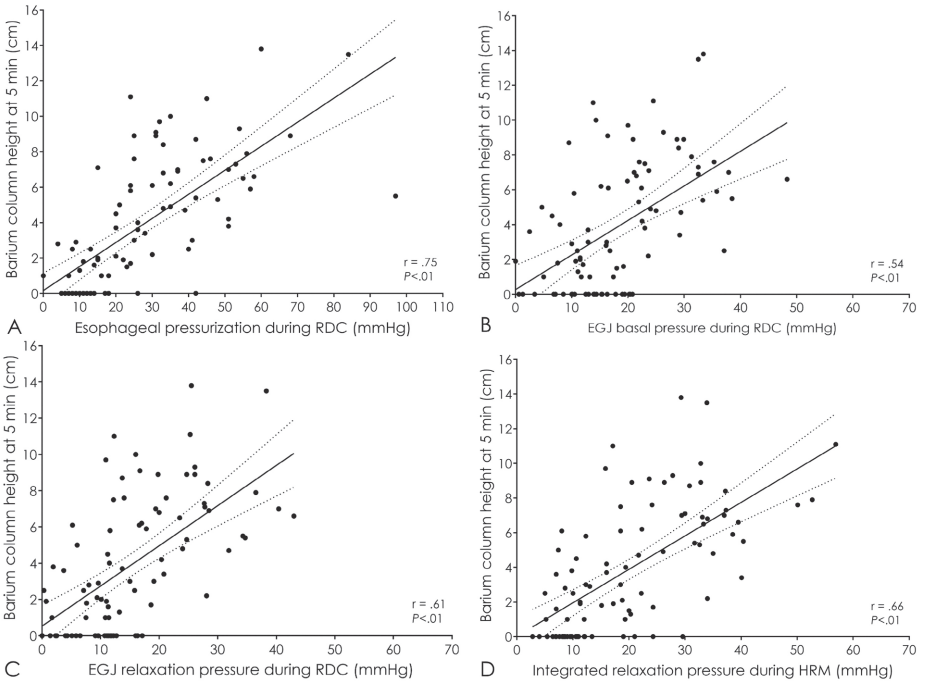

Figure 3. Correlation between barium column height at 5 minutes on TBE versus outcome of RDC (esophageal body pressurization (A), EGJ basal and relaxation pressure (IRP-RDC) (B; C)) and integrated relaxation pressure (IRP) during HRM (D). Esophageal body pressurization had the best correlation with barium column height (r=0.75, *P*<.01) compared to the other two outcome parameters of RDC, EGJ basal and relaxation pressure. A strong correlation was observed between esophageal pressurization and barium column height at 5 minutes on TBE (r=0.75, *P*<.01), comparable to the standard predictor of esophageal stasis, the IRP (r=0.66, *P*<.01).

To assess the effect of esophageal width on esophageal body pressurization during the RDC, the maximal diameter of the barium column was measured. A wider esophagus was not negatively correlated with esophageal body pressurization during RDC (r=0.47, *P*<.01). All outcome parameters, IRP during HRM, esophageal stasis on TBE, esophageal body pressurization and IRP during RDC, strongly correlated with the Eckardt symptom score (IRP r=0.75; esophageal stasis r=0.73; pressurization r=0.72, IRP-RDC r=0.63, all *P*<0.001 Spearman's rank).

All untreated achalasia patients had an IRP4 >15 mmHg and esophageal pressurization during RDC above the cut-off for normality of 13 mmHg. In only 7% (n=2) of these patients esophageal stasis at TBE was inconsistent, showing no stasis (**figure 4**). Discrepancy between esophageal stasis on TBE and esophageal body pressurization was noted in 3 treated symptomatic patients (10%), of which two showed normal pressurization but significant stasis on TBE and had an IRP >15 mmHg (**figure 4**). In 9 (30%) treated symptomatic patients, discordance was observed between esophageal stasis on TBE and IRP, 8 patients had stasis and esophageal body pressurization above normality but an IRP <15 mmHg. Within the group of asymptomatic treated achalasia patients the highest degree of discordance between outcome parameters was observed. Inconsistency between esophageal stasis and esophageal body pressurization was seen in 11 patients (37%) (**figure 4**). Discordance between IRP and TBE or RDC was seen in 8 (27%) and 9 (33%) asymptomatic treated patients, respectively (**figure 4**). The sensitivity and specificity of esophageal pressurization during RDC to adequately predict stasis on TBE was 90% and 66% respectively, versus 77% and 83% with IRP. In other words, if no pressurization occurred during the RDC, the probability of measuring significant stasis at the TBE is very small.

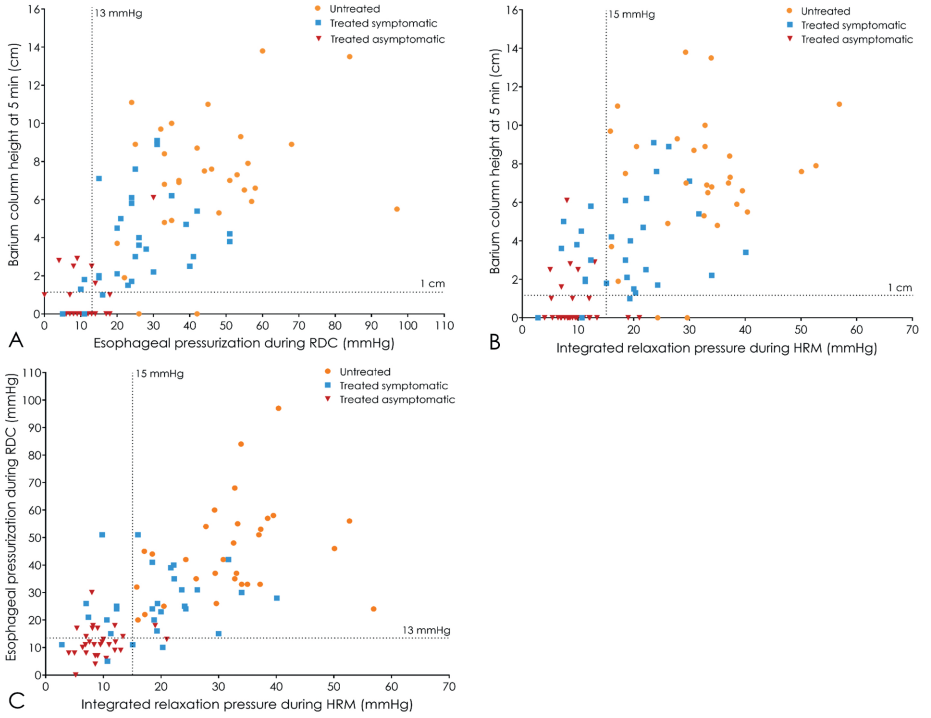

Figure 4. Relation between esophageal body pressurization during RDC, barium column height at 5 minutes on TBE and IRP during HRM. Discordance between pressurization and barium column height (A) was seen in 2 (7%) of the untreated patients, 3 (10%) of the treated symptomatic patients and 11 (37%) of treated asymptomatic patients. Discordance between barium column height and IRP (B) was seen 2 (7%) of the untreated patients, 9 (30%) of the treated symptomatic patients, and 8 (27%) of treated asymptomatic patients. Discordance between pressurization and IRP (C) was seen in none of the untreated patients, 10 (33%) of the treated symptomatic patients and 9 (30%) of treated asymptomatic patients.

DISCUSSION

The aim of this prospective study was to evaluate if a rapid drinking test (RDC) during HRM can assess esophageal stasis in achalasia comparable to stasis on TBE. Our data showed that esophageal body pressurization during RDC strongly correlates with esophageal stasis on TBE in achalasia patients, comparable to the standard predictor of stasis on TBE, the IRP. Additionally, RDC could adequately identify clinical response to treatment and help to make a diagnosis in case of doubt. The correlation between symptoms and the outcome parameters of the RDC was compatible with the manometric and radiographic predictors of successful treatment. Based on these findings we conclude that the RDC is as useful as TBE in measuring esophageal stasis and propose to add this simple test to each HRM study in achalasia patients. It may even make TBE unnecessary in cases where information on esophageal diameter is not required. To illustrate this, if no pressurization is observed during RDC, the probability of measuring stasis on TBE is very small and one could consider to refrain from using the TBE.

As the introduction of HRM, data suggest that provocative tests, like a rapid drinking challenge (RDC) or multiple rapid swallows (MRS), provide additional information to the single swallows of the standard HRM protocol and increases the sensitivity to detect esophageal motility disorders.[14–17,19,20] Provocative tests enhance central and peripheral deglutitive inhibition which normally results in complete inhibition of the esophageal body and complete relaxation of the EGJ, followed by a peristaltic contraction and EGJ after-contraction.[12–16] Two types of provocative tests have been used: a short rapid drinking test, referred as multiple rapid swallows (MRS), with 5-10 rapid swallows of 2 ml to assess inhibitory mechanism and peristaltic reserve[12,13,18,19], and a rapid drinking challenge (RDC) with 100-200 ml free drinking to assess EGJ obstruction.[2,14,15,20] It has been suggested that both MRS and RDC can help to distinguish patients with border-line motility disorders after the standard single swallows for example in patients with a differential diagnosis between absent contractility and type I achalasia.[14] Additionally, MRS detects incomplete inhibition and abnormal pressure response in some patients with a normal standard HRM but with esophageal symptoms implying ineffective esophageal motility. Marin et al and Ang et al were the first to perform studies with RDC during HRM in untreated achalasia patients.[14,15] Their results showed a sustained hyperpressive or obstructive pressure pattern in the esophageal body and a high pressure gradient across a non-relaxed EGJ in these patients during a RDC, similar to our data.[14,15] Whether the cause of the pressurization is increment of contractile activity due to lack of inhibitory mechanisms or increased bolus retention due to retention of large volumes remains speculative.[14,18] The preserved motor activity observed in achalasia patients by other studies could be related to the type of

provocative test that was carried out, the MRS instead of the RDC used in our study. The RDC is designed to assess EGJ obstruction which results in stasis by inadequate opening of the EGJ as shown in our study.[2,20,24] To discriminate achalasia subtypes by a provocative test, the MRS seems preferable.[18] The aim of our study was to assess esophageal stasis during HRM in achalasia patients and compare this to the TBE protocol. Therefore, we only performed a RDC to detect EGJ obstruction and pressurization and excluded the MRS from this study protocol. MRS could be added to a HRM study to better observe esophageal peristaltic reserve and integrity of deglutitive inhibition in patients with esophageal symptoms.

HRM is considered as the gold standard to diagnose achalasia, it can be used to analyze the function and contractile activity of the esophagus.[25] TBE is a supplementary test for achalasia and provides information on stasis and esophageal width. The finding of stasis on TBE could indicate that a patient with recurrent symptoms could benefit from retreatment, while absence of stasis would support a more expectative approach. For the follow-up and evaluation of treatment outcome in achalasia the choice for the optimal test is still a matter of debate. Both tests provide valuable and complementary information but have limitations.[2] HRM provides limited information on bolus retention and is difficult to perform in a dilated esophagus because occlusive pressure is needed to measure pressure changes. Disadvantages of TBE are the exposure to ionizing radiation and minimal data on esophageal contractile activity. Simultaneous assessment of esophageal motility and esophageal stasis in one test would optimize the diagnostic process of achalasia and could be realized by adding a RDC to the standard HRM protocol. Cho et al have analyzed the relation between esophageal stasis during RDC on HRM and retention observed on TBE in both untreated and treated achalasia patients.[2] Unlike in our study, concurrent impedance monitoring was used to objectify stasis during HRM. The study showed a good correlation between impedance bolus height during RDC and the barium column height at 5 minutes on TBE.[2] Additionally, impedance bolus height showed fair to moderate correlation with EGJ function on HRM and symptoms which was similar to TBE.[2] Comparing these data with the findings of this study, esophageal body pressurization during RDC seemed of an equivalent value to assess esophageal stasis as impedance bolus height. However, correlations between esophageal body pressurization on RDC and manometric parameters or symptoms were stronger compared to impedance bolus height. A major disadvantage of impedance monitoring used as a test for esophageal stasis in achalasia, is the risk of low baseline impedance levels and air entrapment in the proximal esophagus which limits its value.[2,26,27] Therefore, based on the current data, we conclude that esophageal body pressurization is the best metric to analyze esophageal stasis during RDC on HRM. Recently, a

study of Gabieta-Sonmez et al confirmed the strong correlation between RDC and the outcome of TBE in untreated achalasia.[28] Interesting, in contrast to our findings, the IRP during RDC seemed the best predictor of stasis on TBE.[28] The reason for this difference could be twofold. First of all the number and type of patients included were different. We included 60 achalasia patients (untreated/symptomatic treated/asymptomatic treated) and 30 healthy subjects compared to 30 patients with dysphagia of which 23 had treated or untreated achalasia. Secondly, the analysis of the RDC was different which could also explain the difference. We did show however, that the IRP-RDC, comparable to esophageal body pressurization, can adequately differentiate between achalasia and healthy subjects. The optimal diagnostic threshold for differentiation was 11.5 mmHg (range 8.4-12.3 mmHg), which was similar to cut-off of 12 mmHg demonstrated by Ang et al and Marin et al.[15,29] Despite the fact that a RDC can adequately identify esophageal stasis, it remains to be determined if it can substitute TBE. TBE is the only test that provide information on the width and sigmoid deformation of the esophagus in achalasia which are important features that influence the type of treatment. Another reason to proceed with TBE in follow-up would be if esophageal pressurization is influenced by the esophageal width. In our study no negative correlation was observed between the height of esophageal pressurization and esophageal width.

Concerning the follow-up and evaluating treatment efficacy in achalasia, previous studies conclude that esophageal emptying measured by stasis on TBE is superior to all HRM metrics in assessing treatment outcome.[2,4,5,11] Our findings showed that the RDC could adequately identify treatment response, similar to TBE. Discrepancy between symptoms and the outcome of RDC or TBE was predominantly observed in effectively treated patients. Previous studies have also shown that the correlation between symptoms and esophageal stasis on TBE can be variable after treatment.[4,6,30,31] Future studies that follow achalasia patients in time, with pre- and posttreatment studies, should determine whether HRM with RDC alone or both HRM with RDC and TBE is most effective to evaluate treatment effect and predict symptom recurrence.

This study related esophageal stasis during a manometric RDC using 200 ml water with stasis on TBE after drinking 200 ml low-density barium sulfate. Barium sulfate is more viscous than water and this could influence the degree of bolus clearance. Omari et al showed in healthy subjects that increasing bolus viscosity was associated with higher peristaltic peak pressure and intrabolus pressure during HRM which reduced bolus clearance.[32] Similar findings were observed when the bolus volume was increased.[32] The strong correlation between esophageal body pressurization during RDC and barium column height on TBE in this study also suggests that an increased volume

is important to analyze esophageal emptying. It would be interesting to use a more viscous liquid during RDC to observe if the correlation with TBE would increase. Beside the bolus viscosity, the position of performing the RDC during HRM and a TBE was different, a semirecumbent position versus a standing upright position. Less hydrostatic pressure of the fluid column, due to the semirecumbent position during the RDC, could have led to increased esophageal pressurization. However, in all achalasia patients and healthy subjects the RDC was performed in a similar position and we observed that 70% of the treated asymptomatic patients had similar bolus clearance compared to healthy subjects. Furthermore, our results of the RDC in semirecumbent position of untreated achalasia patients are similar to the findings of Ang et al and Marin et al, that both performed the RDC in upright sitting position.[14,15] The difference in bolus viscosity and test position could have influenced the results, however the outcome between and within the four different study groups seemed adequate and consistent.

This study had some limitations. To date, our study describes the largest number of achalasia patients with different clinical profiles undergoing a RDC during HRM. Unfortunately, patients were not followed in time which makes it difficult to conclude if RDC can completely substitute TBE to analyze esophageal emptying and predict symptom recurrence. On the other hand, we clearly showed that RDC can detect esophageal stasis and effectively differentiate treatment success. Furthermore, no new specific RDC metrics were developed but current HRM metrics were used to analyze RDC. Previous studies also used HRM metrics and this far there is no agreement on a common standard analysis for RDC. However, the outcome of the RDC was quite consistent and no apparent disparity between patients was observed.

In conclusion, presence of esophageal pressurization during a RDC is a reliable measure of stasis in achalasia and allows to assess response to treatment to a degree comparable to TBE. Therefore, we propose to add this simple and inexpensive test to each HRM study in achalasia patients. Long-term data would be of value to evaluate if HRM with RDC could completely substitute TBE.

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Diagnostic features of malignancy-associated pseudoachalasia

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4

ABSTRACT

Background

Pseudoachalasia is a condition in which clinical and manometric signs of achalasia are mimicked by another abnormality, most often a malignancy.

Aim

The aim of this study was to identify risk factors that suggest presence of malignancy-associated pseudoachalasia.

Methods

In this retrospective cohort study achalasia patients newly diagnosed by manometry were included. Patients with a normal initial endoscopy, clinical and manometric signs of achalasia who were afterwards found to have an underlying malignant cause were classified as pseudoachalasia. Clinical and diagnostic findings were compared between malignant pseudoachalasia and achalasia.

Results

We included 333 achalasia patients (180 male, median age 50 (38-62)). Malignant pseudoachalasia was diagnosed in 18 patients (5.4%). Patients with malignant-associated pseudoachalasia were older at time of diagnosis (67 (54-71) vs 49 (37-60) years), had a shorter duration of symptoms (6 (5-10) vs 25 (11-60) months) and lost more weight (12 (9-17) vs 5 (0-12) kg). In 61% of the pseudoachalasia patients the OGJ was difficult or impossible to pass during endoscopy, compared to 23% in achalasia. Age ≥55 years (OR 5.93), duration of symptoms ≤12 months (OR 14.5), weight loss ≥10 kg (OR 6.73) and difficulty passing the OGJ during endoscopy (OR 6.06) seemed associated with a higher risk of malignant pseudoachalasia.

Conclusion

Advanced age, short duration of symptoms, considerable weight loss and difficulty in passing the OGJ during endoscopy, are risk factors that suggest potential malignancy-associated pseudoachalasia. To exclude pseudoachalasia, additional investigations are warranted when two or more risk factors are present.

INTRODUCTION

Idiopathic achalasia is a primary motility disorder of the oesophagus caused by loss of neurons in the myenteric plexus which induces aperistalsis and impaired relaxation of the lower oesophageal sphincter (LOS). Patients typically present with dysphagia, regurgitation of food, chest pain and weight loss.[1] Manometry is the gold standard to diagnose achalasia. Pseudoachalasia is a condition in which clinical and manometric features of idiopathic achalasia are mimicked by another abnormality, most often a malignancy. In 1947, Ogilvie was the first to describe that malignant involvement of the oesophagus can resemble idiopathic achalasia.[2] Since this observation many case reports and series are published that describe this phenomenon with a diversity of underlying causes. In 70% of the patients with pseudoachalasia a primary or secondary malignancy is involved.[3,4] The most common causative tumours of pseudoachalasia are a carcinoma of the oesophagus or cardia.[3–9] Pseudoachalasia can also be seen as a paraneoplastic manifestation of malignancies.[10] It is important to recognize pseudoachalasia early to prevent inappropriate therapeutic intervention and delay in appropriate treatment. However, identification of pseudoachalasia is challenging because both clinical and diagnostic features are comparable to idiopathic achalasia. The diagnostic approach of patients suspected for achalasia starts with endoscopy and in case no abnormalities are seen, a manometry and barium oesophagogram are performed. In literature it is described that manometry cannot distinguish between achalasia and pseudoachalasia and that the barium oesophagogram is of limited value in discriminating between the two.[4,11] Endoscopy seems a reliable tool to diagnose tumours or strictures of the oesophagus or cardia. However, a tumour can only be diagnosed by endoscopy if it passes the submucosal layer, which is highly variable per patient. Thus, discriminating between achalasia and malignancy-associated pseudoachalasia seems challenging with the standard diagnostics. The aim to prevent missing malignant pseudoachalasia leads to many requests for additional radiological imaging and endoscopic ultrasound resulting in high costs and a burden to patients, while only 4-5% of the endoscopic-negative patients manometrically diagnosed with achalasia appears to have pseudoachalasia.[3,4] Obviously, early recognition of malignancy-associated pseudoachalasia is important to prevent delay in appropriate treatment. However, reliable discriminating features for pseudoachalasia are lacking. Therefore the aim of this study was to identify risk factors that suggest presence of malignancy-associated pseudoachalasia that warrant additional investigation.

MATERIALS AND METHODS

Subjects and inclusion criteria

For this retrospective cohort study we included adult patients (≥18 years) in whom a new manometric diagnosis of achalasia was made in our centre between January 2000 and December 2014. Manometric criteria for achalasia were defined as absent peristalsis and impaired relaxation of the lower oesophageal sphincter (LOS). During the study period the technique of the manometry catheters evolved, from conventional (water-perfused catheter, with perfused Dent sleeve) to high-resolution manometry (solid-state, HRM), but the standardized protocol for assessing oesophageal motility remained similar. The catheter was placed transnasally and positioned such that it recorded from hypopharynx to the stomach. During manometry, patients were in supine position and swallowed 10 water boluses of 5 mL with an interval of 20 s. For conventional manometry impaired LOS relaxation was defined as less than 50% relaxation relative to the basal LOS pressure or a nadir pressure ≥10 mmHg during swallow-induced relaxation.[12] Impaired LOS relaxation during HRM was determined by an integrated relaxation pressure (IRP) >15 mmHg.[13] This study was evaluated by the local Medical Ethical Committee and approved (August 2013, number W13_180#13.17.0225).

Pseudoachalasia

Patients were classified as having pseudoachalasia when the initial endoscopy showed no relevant abnormalities, clinical and manometric signs were typical for achalasia, no operations or other conditions in the past that are known to induce oesophageal obstruction such as fundoplication, oesophageal trauma surgery and gastric banding were present and only later during additional testing or treatment a malignant lesion was found to be the underlying cause.

Data collection and analysis

Medical records of eligible patients were reviewed. Clinical, endoscopic, manometric and radiological findings were evaluated and described. Type of symptoms was assessed and the Eckardt symptom score was used to express the severity of symptoms. This score reflects the sum of symptom scores for dysphagia, regurgitation and chest pain (0=absent, 1=occasionally, 2=daily, 3=each meal) with additionally the score of weight loss (0=no weight loss, 1=<5 kg, 2=5-10 kg, 3=>10 kg).[14] Duration of symptoms was determined by the onset of the first symptoms until the initial diagnosis of achalasia by manometry. For endoscopy we assessed whether there was stasis of liquids/foods in the oesophagus, a dilated oesophagus, mucosal abnormalities or difficulties passing the OGJ. Any biopsies that were taken were described. For manometry the following features were analysed; type of manometry, oesophageal contraction pattern, basal LOS pressure and if available LOS

relaxation pressure or IRP. All radiological investigations that were performed to diagnose achalasia or pseudoachalasia were analyzed. As part of the diagnostics of achalasia, patients underwent an oesophageal video fluoroscopy or a timed barium oesophagogram to assess oesophageal emptying. Delayed emptying of contrast, narrowing of the OGJ, distension of the oesophagus and barium column height in case of stasis were noted. Achalasia treatment was evaluated and the type of treatment was described in case it was performed in patients with pseudoachalasia before the underlying cause was revealed. The investigation that eventually revealed the underlying cause of pseudoachalasia was reported. Data of achalasia patients were compared to patients with malignancy-associated pseudoachalasia, to identify risk factors for pseudoachalasia.

Statistical analysis

Continuous data are presented as median (interquartile range, IQR) according to distribution. Categorical data are presented in percentages. Data of achalasia patients and patients with malignant pseudoachalasia, were compared using Mann-Whitney U-test in case of continuous data and Chi-square test or Fisher's exact for categorical data. Differences were considered statistically significant when $P<.05$. All reported P-values are 2-tailed. Receiver operator characteristics (ROC) curves were plotted for continuous variables that raised a significantly higher suspicion of pseudoachalasia, to determine optimal cut-off values. The optimal cut-off value was defined as the cut-off corresponding to the point of the ROC curve closest to the sensitivity=1 specificity=1 optimum. For each applicable variable the optimal cut-off and area under the curve (AUC) of the ROC curve were displayed. Univariable logistic regression analysis was performed, to observe if obtained cut-off values were useful indicators to discriminate between pseudoachalasia and achalasia, expressed as odds ratio (OR) with corresponding 95% confidence intervals (CI). Interacting variables were checked using multivariable analysis. For the multivariable analysis, variables were selected based on content validity described in previously literature and a significant P-value ($P<.05$). Statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, United States).

RESULTS

Study inclusion

From January 2000 until December 2014 554 individual patients with idiopathic achalasia were seen at the clinic. Of these patients, 221 were excluded because the primary diagnosis was made before the year 2000 (n=147), they were diagnosed at childhood (n=20), another motility disorder was diagnosed (n=52) or achalasia was part of the Triple A syndrome (n=2). Eight patients were identified with a benign cause of pseudoachalasia (gastric banding; Nissen

fundoplication; leiomyoma; 2x fibrosis by thorax trauma (stabbing); fibrosis post-radiotherapy for bilateral breast carcinoma; stenotic peptic lesion). These patients were excluded from the analysis because prior medical history made secondary achalasia very likely and the aim of the study was to select patients in which this was not the case. In the end, 333 patients (180 male, age 50 (38-62) years) were included for final analysis.

Pseudoachalasia

Of the 333 patients diagnosed with achalasia, 18 patients (5.4%) were diagnosed with malignant pseudoachalasia. **Table S1** (added as Supplement material) shows the clinical and diagnostic findings of the 18 patients with malignancy-associated pseudoachalasia. In all cases symptoms of achalasia were caused by tumor compression and invasion. None of the patients had a paraneoplastic syndrome. In 89% of our patients a primary malignancy caused pseudoachalasia and in the other two patients mediastinal/peritoneal metastasis of breast cancer gave rise to pseudoachalasia. Both patients were previously curatively (7 and 9 years disease free) treated for breast cancer by mastectomy combined with chemo- and radiotherapy. Gastric adenocarcinoma was observed in 33% (n=6) of the patients with pseudoachalasia, oesophageal adenocarcinoma in 28% (n=5), oesophageal squamous cell carcinoma in 17% (n=3) and 11% (n=2) had an adenocarcinoma of the pancreas tail. In none of the patients the initial endoscopy had revealed malignancy. However, in 61% the OGJ was difficult to pass and in 7 patients inflamed, erosive mucosa was seen in the distal oesophagus. In 2 of 7 patients it was interpreted as reflux oesophagitis. Biopsies revealed no abnormalities (64%) or mild to severe inflammation (36%). Stasis of food was seen in 22% of the patients. In all patients manometry was typical of achalasia. Basal LOS pressure was normal, 33 (22-39) mmHg, but relaxation was not (LOS relaxation pressure (n=3) 25 (13-25 mmHg) and IRP (n=8) 26 (23-37) mmHg). The contraction pattern was failed in 4 patients, simultaneous in 8 patients and panoesophageal pressurization was observed in 6 patients. Oesophagogram (n=16) was typical for achalasia in 75% of the patients, showing stasis and/or a widened oesophagus.

The interval between manometry and diagnosis of pseudoachalasia varied considerably (range 0 days - 5 months). In 28% (n=5) of the patients pseudoachalasia was eventually diagnosed by a second or third endoscopy with biopsies, in 28% (n=5) by CT scan of thorax/abdomen, in 16% (n=3) by endoscopic ultrasound (EUS) and in 28% (n=5) during achalasia treatment (4 times during pneumodilation and 1 time during Heller myotomy). Four of the 10 patients diagnosed by endoscopy or CT-scan, had already undergone achalasia treatment with botulinum toxin injections and/or pneumodilation. The total number of investigations that needed to be performed before pseudoachalasia was diagnosed ranged from

4 to 10, with a median of 6 (5-7). Curative resection was performed in 7 patients with an oesophageal or cardia carcinoma. All other patients underwent palliative treatment, radiotherapy and/or chemotherapy.

Malignancy-associated pseudoachalasia versus achalasia

Clinical and diagnostic findings

As shown in **tables 1** and **2**, there were several differences in presentation and diagnostic findings between patients with malignant pseudoachalasia and achalasia. Patients with pseudoachalasia were older at the time of diagnosis (67 (54-71) years vs 49 (37-60) years, *P*<.001). There were no differences observed in the symptoms dysphagia, regurgitation, chest pain and dyspepsia that were reported. However, heartburn was never reported by patients with malignancy-associated pseudoachalasia, compared to 28% of the achalasia patients (*P*<.01). Analyzing symptoms using the Eckardt symptom score, we observed a significantly higher score in patients with malignant pseudoachalasia (9 (8-10) versus 7 (6-9), *P*<.01). However, when the Eckardt symptom score was calculated without including weight loss no difference was seen between malignancy-associated pseudoachalasia and achalasia (6 (6-7) versus 6 (5-7), *P*=.06). Patients with pseudoachalasia had a shorter duration of symptoms compared to achalasia patients (6 (5-10) months versus 25 (12-60) months, *P*<.001) and lost significantly more weight (12 (9-17) kg versus 5 (0-12) kg, *P*<.01). In 61% of the patients with malignant pseudoachalasia the OGJ was difficult or impossible to pass during endoscopy, compared to 23% in achalasia (*P*<.001). Manometric studies in both groups were typical of achalasia. No differences were observed in basal LOS pressure, relaxation pressure, contraction pattern or achalasia subtype. An oesophagogram was performed in 16 patients with malignant pseudoachalasia. In 75% of the patients it was suggestive of achalasia which was significantly lower compared to the 94% in achalasia (*P*<.05). This difference could be explained by the lower proportion of patients with malignant pseudoachalasia showing stasis at the oesophagogram compared to achalasia (75% vs 94%, *P*<.05).

Table 1. Clinical findings of patients with malignant pseudoachalasia and achalasia

Clinical variables	Malignant pseudoachalasia	Achalasia	*P*-value
Number	18	315	
Male gender (%)	67	53	.27
Age at diagnosis (years (IQR))	65 (54-71)	49 (37-60)	<.001
Tobacco use (%)	47	51	.78
Alcohol use (%)	63	78	.25
Symptoms (%)			
Dysphagia solids	100	100	1.00
Dysphagia liquids	78	78	.98
Regurgitation	83	86	.75
Chest pain	61	73	.29
Dyspepsia/pain upper abdomen	28	22	.58
Heartburn	0	28	<.01
Eckardt symptom score (score (IQR))	9 (8-10)	7 (6-9)	<.01
Eckardt symptom score corrected for weight loss (score (IQR))	6 (6-7)	6 (5-7)	.061
Duration of symptoms (months (IQR)	6 (5-10)	25 (12-60)	<.001
Weight loss (kg (IQR))	12 (9-17)	5 (0-12)	<.01
Weight loss time (months (IQR))	6 (5-9)	6 (0-15)	.98

IQR, interquartile range

Cut-off values clinical variables and risk analysis

The clinical variables age, duration of symptoms and weight loss were significantly different between malignancy-associated pseudoachalasia and achalasia. Optimal cut-off values were determined for these continuous variables using ROC curves to optimize differentiation between malignant pseudoachalasia and achalasia (**figure 1**). For age at diagnosis the ROC curve showed that 55 years yielded the optimal combination of sensitivity and specificity. The area under the ROC curve (AUC) was 0.75 (95% CI: 0.65-0.86, *P*<.001). Assessing the ROC curve for duration of symptoms, the optimal cut-off value was determined at 12 months with an AUC of 0.85 (95% CI: 0.74-0.95, *P*<.001). The optimal cut-off value for weight loss was 10 kg with an AUC of 0.72 (95% CI: 0.63-0.82, *P*<.01). **Table 3** shows that over 70% of the patients with malignant pseudoachalasia are within the created cut-off values , compared to less than 40% of achalasia patients (*P*<.01).

Table 2. Diagnostic findings of patients with malignant pseudoachalasia and achalasia

Diagnostic variables	Malignant pseudoachalasia	Achalasia	*P*-value
Number	18	315	
Manometry (n (%)) Conventional (%) HRM (%)	18 (100) 56 44	315 (100) 54 46	
Basal LOS pressure (mmHg (IQR))	33 (22-39)	25 (19-35)	.18
LOS relaxation pressure (mmHg (IQR))	27 (13-27)	18 (11-26)	.46
IRP (mmHg (IQR))	31 (24-39)	24 (18-33)	.12
Contraction pattern (%) Failed Simultaneous Non-transmitted Spastic and simultaneous Panoesophageal pressurization	 17 50 0 0 33	 25 55 0.3 3 16.7	.51
Subtypes (%) Type I Type II Type III	 13 88 0	 26 60 14	1.00
Oesophagogram (n (%) Suggestive of achalasia (%) Stasis of contrast (%) Widened oesophagus (%) Barium column height at 5 minutes (cm (IQR))	 16 (89) 75 75 75 6 (1-10)	 284 (95) 94 94 87 7 (4-11)	 <.01 <.01 .19 .41
Endoscopy (n (%)) Stasis/retention (%) Widened oesophagus (%) Difficult/impossible to pass OGJ (%)	18 (100) 22 33 61	308 (98) 38 44 23	 .17 .39 <.001

IQR, interquartile range

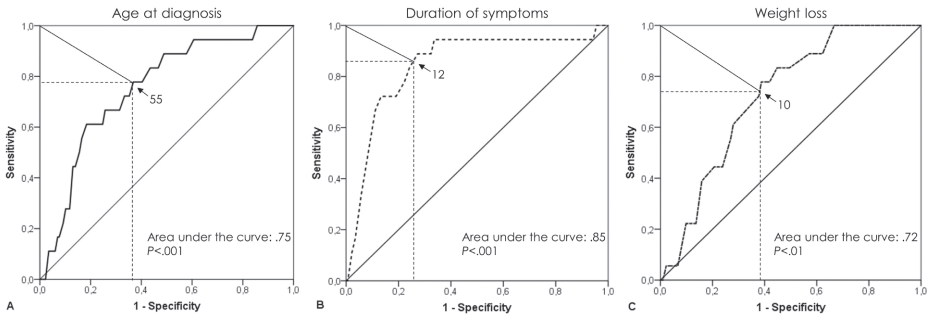

Figure 1. Receiver operating characteristics curves including area under the curve of three relevant clinical variables A) age at diagnosis, B) duration of symptoms and C) weight loss that help discriminate between malignancy-associated pseudoachalasia versus achalasia. For each clinical variable the optimal cut-off value was determined, indicated by the dotted lines and arrows. Age at diagnosis: 55 years; duration of symptoms: 12 months; weight loss: 10 kg.

Table 3. Univariable and multivariable logistic regression analyses of clinical and diagnostic risk factors of malignant pseudoachalasia

			Univariable analysis		Multivariable analysis	
Clinical variables	**Malignant pseudoachalasia**	**Achalasia**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age ≥55 years (%)	72	35	4.78 (1.66-13.8)	.004	5.93 (1.50-23.4)	.011
Duration symptoms ≤12 months (%)	89	27	21.3 (4.80-94.6)	<.001	14.5 (2.96-71.0)	.001
Weight loss ≥10 kg (%)	72	38	4.28 (1.49-12.3)	.007	6.73 (1.60-28.3)	.009
			Univariable analysis		**Multivariable analysis**	
Diagnostic variables	**Malignant pseudoachalasia**	**Achalasia**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Stasis of contrast (%)	75	94	0.18 (0.05-0.62)	.007	0.24 (0.05-1.21)	.083
Difficult/ impossible to pass LOS (%)	61	23	5.34 (1.99-14.3)	.001	6.06 (1.62-22.6)	.007

OR, odds ratio; CI, confidence interval

Univariable analysis of the clinical cut-off values and previous significant diagnostic variables showed that both clinical and diagnostic variables were risk factors for pseudoachalasia (**table 3**). Assessing the independent effect of each risk factor with multivariable analysis, age ≥55 years, duration of symptoms ≤12 months, weight loss ≥10 kg and difficulty passing the OGJ by endoscopy were associated with a higher risk of having pseudoachalasia (**table 3**). Stasis at oesophagogram did not seem to be an independent diagnostic risk factor. **Table 4** and **figure 2** show the distribution of patients focused at the number of positive clinical risk factors or combined clinical and diagnostic risk factors in malignancy-associated pseudoachalasia versus achalasia. 88% of the patients with malignant pseudoachalasia had two or more clinical risk factors compared to only 25% in the achalasia group. Two patients with malignant pseudoachalasia had only 1 clinical risk factor which was substantial weight loss and short duration of symptoms, respectively. When adding the diagnostic risk factor, difficulty passing the OGJ by endoscopy, 100% of the malignant pseudoachalasia patients had two or more risk factors compared to only 35% of the achalasia patients. A high specificity (77-99.7%) and reasonable sensitivity (28-50%), with a fair to good positive predictive value (6-80%) was observed when two or more risk factors were present. Based on these data, a cut-off of two or more factors for the combined clinical and diagnostic risk factors seemed indicative of an increased risk of malignancy-associated pseudoachalasia.

Table 4. Distribution of patients with malignant pseudoachalasia or achalasia depending on the number of risk factors for malignant pseudoachalasia

Only clinical risk factors	**Malignant pseudoachalasia**	**Achalasia**	**Sensitivity / Specificity**	**Positive predictive value**
Number	18	315		
0 risk factors	0 (0%)	93 (30%)	0% / 71%	0%
1 risk factor	2 (11%)	143 (45%)	11% / 55%	1%
2 risk factors	8 (44%)	64 (20%)	44% / 80%	11%
3 risk factors	8 (44%)	15 (5%)	44% / 95%	35%
Clinical and diagnostic risk factors	**Malignant pseudoachalasia**	**Achalasia**	**Sensitivity / Specificity**	**Positive predictive value**
Number	18	315		
0 risk factors	0 (0%)	77 (24%)	0% / 76%	0%
1 risk factor	0 (0%)	128 (41%)	0% / 59%	0%
2 risk factors	5 (28%)	73 (23%)	28% / 77%	6%
3 risk factors	9 (50%)	36 (11%)	50% / 89%	20%
4 risk factors	4 (22%)	1 (1%)	22% / 99.7%	80%

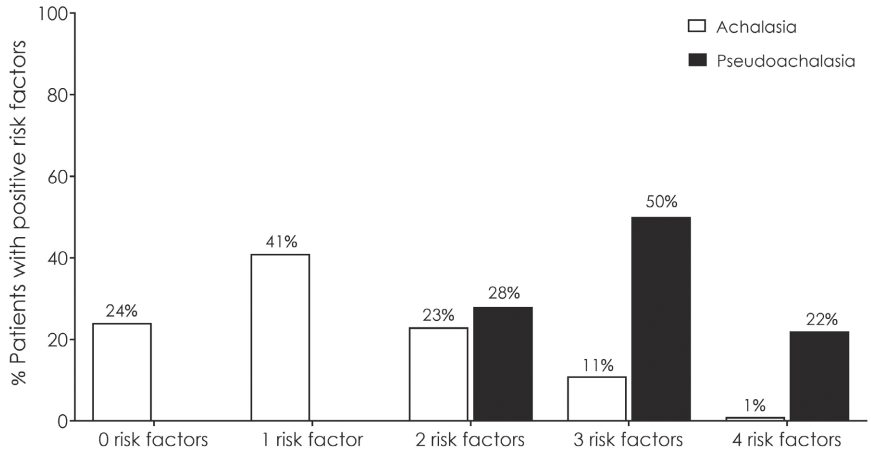

Figure 2. Risk of malignant pseudoachalasia based on the number of risk factors. The percentage of patients with malignant pseudoachalasia (n=18) or achalasia (n=315) depending on the number of risk factors displayed. The probability of malignant pseudoachalasia increased when 2 or more risk factors were present.

Frequency of additional imaging in achalasia

Additional imaging by CT-scan or EUS was performed in 107 (34%) achalasia patients. Of these patients, 88 underwent either a CT-scan (n=43) or EUS (n=45) and 16 underwent both investigations. One patient underwent a CT-

scan 3 times and in 2 patients 4 investigations were performed which were all negative for pseudoachalasia. In 49% of the achalasia patients imaging was performed in case of zero (9 patients) or one (43 patients) positive clinical risk factor. Taking both clinical and diagnostic risk factors into account, in 41 (38%) patients a CT-scan, EUS or both were executed while zero or one risk factor for pseudoachalasia was present. In 69 (22%) patients a chest X-ray and/or abdominal ultrasound were performed, all without abnormalities.

DISCUSSION

In this retrospective cohort study we wanted to identify risk factors that can help discriminate between malignant pseudoachalasia and achalasia. The results indicate that age ≥55 years, a duration of symptoms ≤12 months, weight loss ≥10 kg and difficulty in passing the OGJ during endoscopy, are risk factors that suggest potential malignancy-associated pseudoachalasia. We suggest that additional investigations are warranted when achalasia patients have two or more of these risk factors present. Conventional diagnostics for achalasia such as manometry and oesophagogram, are not useful for differentiation between pseudoachalasia and achalasia. From our study we could not conclude which type of investigation should be used to detect pseudoachalasia, as cases were identified with repeated endoscopy, endoscopic ultrasound and CT.

Compared to the current literature, this study described the largest cohort of malignant pseudoachalasia patients.[3,4,6,15–17] Between 2000 and 2014, 18 patients with malignancy-associated pseudoachalasia were diagnosed which was 5.4% of all achalasia patients. These proportions are comparable to previous studies that described rates of pseudoachalasia between 1.5% and 4.7%.[3,4,6,15] Comparing clinical features of malignant pseudoachalasia with achalasia, we observed that advanced age, short duration of symptoms and considerable weight loss were suggestive of malignancy-associated pseudoachalasia. No differences were observed in the type of symptoms. However, when symptoms were classified according to the Eckardt score, there was a significant higher score in the pseudoachalasia group compared to achalasia which was not previously described. However, weight loss, which is also taken into account in this score, seemed to be the culprit. When the Eckardt score was corrected for weight loss, no difference was observed. The clinical characteristics that seemed useful indicators of pseudoachalasia were similar to the features described in earlier studies.[3,5,6,9,15,17] However, previous studies omitted to identify useful and relevant cut-off values for the clinical risk factors. The established cut-off values; age ≥55 years, a duration of symptoms ≤12 months and weight loss ≥10 kg respectively, showed a high specificity (55-95%) which makes it useful tools in the clinical decision making whether or not to perform additional investigations to exclude pseudoachalasia.

In addition to clinical risk factors, we also searched for diagnostic risk factors. Conventional diagnostics for achalasia, manometry and oesophagogram, could not distinguish between malignant pseudoachalasia and achalasia. Regardless whether conventional or high-resolution manometry was used, in both pseudoachalasia and achalasia absence of peristalsis with a normal to high basal LOS pressure and dysrelaxation of the LOS was observed. No objectified stasis during an oesophagogram seemed suggestive of pseudoachalasia. However, when adjusted for interacting variables with multivariable analysis this difference was not observed and therefore not qualified as a risk factor. Interestingly, previous studies showed that an oesophagogram could be of value in distinguishing pseudoachalasia from achalasia.[6,11,18] A narrowed distal oesophageal/OGJ segment of ≥3.5 cm with asymmetry and filling defects or an oesophageal diameter of 4 cm or less at its widest point, was suggestive of pseudoachalasia.[6,11,18] In none of our patients these signs were present. Our study showed that difficult or no passage of the OGJ at initial endoscopy was suggestive of pseudoachalasia, similar to the findings of Tracey et al.[19] Comparable to other studies, no other endoscopic findings could distinguish between pseudoachalasia and achalasia. [3,4,9] Biopsies should always be taken if endoscopic passage of the OGJ is difficult, however there is a reasonable chance of false negativity as also shown in our study. This emphasizes the importance to analyse all risk factors instead of one and consider redo-endoscopy.

Differentiation between malignancy-associated pseudoachalasia and achalasia clearly increased with the presence of two or more risk factors, this accounted for 100% in pseudoachalasia compared to 36% in achalasia. The risk factors showed a reasonable sensitivity (0-50%) with a high specificity (59-99.7%) to exclude pseudoachalasia when all risk factors were present. The positive predictive value ranged from 0% at the presence of 1 risk factor to 80% for all risk factors. The relative low prevalence of pseudoachalasia in this cohort resulted in a moderate positive predictive value which indicates that these risk factors could lead to overdiagnosing possible pseudoachalasia in achalasia patients. However, it may be argued that this is better than missing a diagnosis of cancer. Based on the data, we conclude that an achalasia patient is at risk for pseudoachalasia when two or more risk factors are present and consequently warrants additional investigations.

Like in other series, several of our pseudoachalasia patients were diagnosed during achalasia treatment or even afterwards.[4,6,9] This emphasizes the difficulty to differentiate between malignant pseudoachalasia and achalasia. In none of the pseudoachalasia patients the initial endoscopy revealed a malignancy. All tumours probably involved the muscle layers and/or submucosa but did not yet disrupt the mucosa which hampered endoscopic visualization. From

our data it seemed that a second/third endoscopy or CT-scan was the most effective way of diagnosing pseudoachalasia. However, 40% of these patients had already undergone achalasia treatment and the additional diagnostics were performed because of recurrent symptoms. In total 12 patients with malignant pseudoachalasia underwent a CT-scan, but in only 5 patients it revealed the malignancy. EUS was assessed in 5 patients and in 3 of these patients pseudoachalasia was diagnosed. Therefore, from our study we could not recommend a specific type of investigation that explicitly should be used to diagnose pseudoachalasia. The American College of Gastroenterology advises to perform EUS in case pseudoachalasia is suspected.[20] EUS can rule out an infiltrating tumour but also provide supportive evidence of achalasia when a thickened circular muscle layer is observed.[20,21] Other advantages of EUS are that biopsies can be taken, there is no exposure of ionizing radiation and it can easily be performed in conjunction with an endoscopy or pneumodilation.[21,22] Licurse et al showed that the CT-scan still is a useful technique for differentiating pseudoachalasia and achalasia.[23] In case of pseudoachalasia, the CT-scan can show asymmetric oesophageal wall thickening, a mass around the OGJ and mediastinal lymphadenopathy.[23] A major advantage is that metastases can be observed and also tumours that cause achalasia as part of a paraneoplastic syndrome.[23] The 4 pseudoachalasia patients that underwent achalasia treatment all experienced quick recurrence of symptoms. Therefore, additional diagnostics should always be performed in achalasia patients that have symptoms shortly after treatment. Additional imaging by CT-scan or EUS was performed in 107 (34%) achalasia patients. Interesting, 38% of these patients were according to our data not at risk for pseudoachalasia because less than 2 risk factors were present. In the future additional imaging should be more restrained in this group.

Besides that the identified risk factors can prompt addition to diagnostic investigations in patients with multiple risk factors present, it can also help to reduce performing additional tests in other patients. The observation that all pseudoachalasia patients had at least 2 risk factors present suggests that additional testing is not required in patients with none or just one risk factor. This would lead to a significant reduction in the number of EUS and CT scans, reducing patients' discomfort, radiation exposure and costs to society.

This study has limitations. First, it is a retrospective study. For the collection of the data we focused on the available reports, investigations and patient records. As a consequence, in some cases interpretation of the data was needed which could have caused information bias. We tried to minimize this by reviewing these data twice through 2 independent researchers. Furthermore, our hospital is a referral clinic for achalasia and all patients are screened for trial participation and hence, patient records are very complete from first presentation. A second

potential limitation is the relatively small number of patients with malignant pseudoachalasia compared to achalasia. However, the number of cases was larger than described in previous studies. The limited cases of malignant pseudoachalasia influenced the type of statistical analysis that was performed. The aim of the study was not to develop a prediction model for pseudoachalasia but to give insight in the causality of risk factors that possible indicate pseudoachalasia. Therefore, in the multivariable analysis only variables with a P-value <.05, conformed by content validity based on previously literature, were included.

In conclusion, advanced age (55 years or older), short duration of symptoms (12 months or less), considerable weight loss (10 kg or more) and difficulty in passing the OGJ during endoscopy, are risk factors that suggest potential malignancy-associated pseudoachalasia. The results suggest that, to exclude pseudoachalasia, additional investigations are warranted when achalasia patients have two or more of risk factors. The conventional diagnostics for achalasia are not useful for differentiation. Additional testing is not required for achalasia patients that have none or just one risk factor.

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SUPPLEMENT MATERIAL

Supplement table S1. Clinical and diagnostic findings per patient with malignancy-associated pseudoachalasia

Sex	Age	Eckardt score	Duration (months)	Weight loss (kg)	Endoscopy*	Manometry	Oesophagogram	Etiology
M	45	10 (Dysphagia solids; regurgitation; retrosternal pain)	11	16	Stasis of food; dilated; aperistaltic; narrowed OGJ easy to pass (n=2) Biopsy initial endoscopy: NA	Conventional Simultaneous contractions; LOS basal pressure 35 mmHg; no LOS relaxation	TBE Stasis; luminal dilation; barium column height 10 cm at 5 min; distal tapering OGJ	Adenocarcinoma cardia diagnosed during PD
F	82	10 (Dysphagia solids and liquids; regurgitation; retrosternal pain)	6	20	No stasis, not dilated ; ulcer at Z-line ; OGJ easy to pass (n=2) Biopsy initial endoscopy: no abnormalities	HRM Panoesophageal pressurization; LOS basal pressure 33 mmHg; IRP 37 mmHg; type II	Standard Stasis; luminal dilation	Adenocarcinoma cardia diagnosed during second PD
F	69	10 (Dysphagia solids and liquids; regurgitation; retrosternal pain)	6	12	No stasis; not dilated; spastic oesophagus; OGJ difficult to pass; stenotic with normal mucosa (n=2) Biopsy initial endoscopy: no abnormalities	HRM Panoesophageal pressurization; LOS basal pressure 77 mmHg; IRP 53 mmHg; type II	TBE Stasis; luminal dilation; barium column height 15 cm at 5 min; distal tapering OGJ	Adenocarcinoma cardia diagnosed during second endoscopy
M	67	7 (Dysphagia solids; retrosternal pain)	5	11	No stasis; dilated; OGJ easy to pass; some swelling of cardia folds (n=1) Biopsy initial endoscopy: no abnormalities	Conventional Simultaneous contractions; LOS basal pressure 35 mmHg; no LOS relaxation	TBE No stasis; no luminal dilation; barium column height 0 cm at 5 min	Adenocarcinoma cardia diagnosed by CT-scan after treatment with PD and botox

Supplement table S1. Continued

Sex	Age	Eckardt score	Duration (months)	Weight loss (kg)	Endoscopy*	Manometry	Oesophagogram	Etiology
F	74	8 (Dysphagia solids and liquids; retrosternal pain; dyspepsia)	6	10	No stasis, not dilated; OGJ difficult to pass; stricture; stomach some hard, thick folds (n=1) Biopsy initial endoscopy: no abnormalities	Conventional Simultaneous contractions; LOS basal pressure 33 mmHg; no LOS relaxation	NA	Linitis plastic diagnosed by EUS
M	65	9 (Dysphagia solids and liquids; regurgitation)	6	16	No stasis; not dilated; OGJ easy to pass; slight inflammation mucosa of cardia and corpus stomach (n=1) Biopsy initial endoscopy: no abnormalities	HRM Panoesophageal pressurization; LOS basal pressure 25 mmHg; IRP 23 mmHg; type II	TBE Stasis; luminal dilation; barium column height 8 cm at 5 min; distal tapering OGJ	Linitis plastic diagnosed by CT-scan
M	56	7 (Dysphagia solids and liquids; regurgitation; retrosternal pain; dyspepsia)	6	5	No stasis, not dilated; OGJ difficult to pass; stricture with irregular mucosa (n=2) Biopsy initial endoscopy: NA	HRM Panoesophageal pressurization; LOS basal pressure 25 mmHg; IRP 26 mmHg; type II	TBE Stasis; luminal dilation; barium column height 2.5 cm at 5 min	Adenocarcinoma oesophagus diagnosed during second endoscopy
M	60	9 (Dysphagia solids and liquids; regurgitation; retrosternal pain)	3	15	No stasis, not dilated; OGJ easy to pass; 1 cm linear erosion (n=3) Biopsy initial endoscopy: mild to chronic inflammation and low grade dysplasia	HRM Panoesophageal pressurization; LOS basal pressure 43 mmHg; IRP 35 mmHg; type II	TBE Stasis; luminal dilation; barium column height 7.3 cm at 5 min	Adenocarcinoma oesophagus diagnosed during third endoscopy after 2x PD

Supplement table S1. Continued

Sex	Age	Eckardt score	Duration (months)	Weight loss (kg)	Endoscopy*	Manometry	Oesophagogram	Etiology
M	54	8 (Dysphagia solids and liquids; regurgitation)	5	3	No stasis, not dilated; OGJ impossible to pass by normal endoscope (n=2) Biopsy initial endoscopy: No abnormalities	Conventional Simultaneous contractions; LOS basal pressure 33 mmHg; no LOS relaxation	TBE Stasis; luminal dilation; barium column height 12.5 cm at 5 min; distal stenosis, narrowing OGJ	Adenocarcinoma oesophagus diagnosed by EUS
M	71	8 (Dysphagia solids; regurgitation; dyspepsia)	16	10	No stasis, not dilated; OGJ difficult to pass; stenotic segment distal oesophagus with ulcerative mucosa (n=3) Biopsy initial endoscopy: severe inflammation	Conventional Simultaneous contractions; LOS basal pressure 10 mmHg; no LOS relaxation	TBE Stasis; luminal dilation; barium column height 0 cm at 5 min; distal stenosis, narrowing OGJ	Adenocarcinoma oesophagus diagnosed by second EUS
M	81	7 (Dysphagia solids and liquids; regurgitation)	3	9	No stasis, dilated; OGJ difficult to pass; stenotic segment distal oesophagus (n=2) Biopsy initial endoscopy: no abnormalities	Conventional Simultaneous contractions; LOS basal pressure 32 mmHg; LOS relaxation pressure 13 mmHg	Standard Stasis; luminal dilation; hypotonic oesophagus without peristalsis	Adenocarcinoma oesophagus diagnosed during first PD
M	52	9 (Dysphagia solids and liquids; regurgitation)	4	20	Stasis of food; dilated; OGJ difficult to pass; ulcerative mucosa (n=3) Biopsy initial endoscopy: chronic inflammation and candida	Conventional Simultaneous contractions; LOS basal pressure 35 mmHg; no LOS relaxation	NA	Squamous carcinoma oesophagus diagnosed during third endoscopy

Supplement table S1. Continued

Sex	Age	Eckardt score	Duration (months)	Weight loss (kg)	Endoscopy*	Manometry	Oesophagogram	Etiology
F	69	10 (Dysphagia solids and liquids; retrosternal pain)	10	12	No stasis, not dilated; OGJ easy to pass (n=2) Biopsy initial endoscopy: no abnormalities	HRM Panoesophageal pressurization and simultaneous; LOS basal pressure 23 mmHg; IRP 39 mmHg; type II	TBE No stasis; no luminal dilation; barium column height 0 cm at 5 min	Squamous carcinoma oesophagus diagnosed during second endoscopy
M	32	12 (Dysphagia solids; regurgitation; retrosternal pain; dyspepsia)	180	20	Stasis, dilated; OGJ difficult to pass; some inflamed mucosa of distal oesophagus (n=2) Biopsy initial endoscopy: NA	Conventional Failed contractions; LOS basal pressure 15 mmHg; no LOS relaxation	TBE Stasis; luminal dilation; barium column height 6.3 cm at 5 min; distal stenosis OGJ	Squamous carcinoma oesophagus diagnosed during Heller myotomy
M	50	11 (Dysphagia solids and liquids; regurgitation; retrosternal pain)	5	16	No stasis, not dilated; OGJ easy to pass (n=2) Biopsy initial endoscopy: No abnormalities	HRM Panoesophageal pressurization and simultaneous; LOS basal pressure 20 mmHg; IRP 25 mmHg; type II	TBE Stasis; luminal dilation; barium column height 5.3 cm at 5 min	Adenocarcinoma pancreas tail diagnosed by CT-scan
M	69	9 (Dysphagia solids and liquids; regurgitation; dyspepsia)	6	30	Stasis; dilated; OGJ difficult to pass; some inflammation (n=3) Biopsy initial endoscopy: chronic inflammation	Conventional Simultaneous contractions; LOS basal pressure 43 mmHg; no LOS relaxation	TBE Stasis; luminal dilation; barium column height 5.9 cm at 5 min	Adenocarcinoma pancreas tail diagnosed by CT-scan after treatment with 2xPD

Supplement table S1. Continued

Sex	Age	Eckardt score	Duration (months)	Weight loss (kg)	Endoscopy*	Manometry	Oesophagogram	Etiology
F	66	8 (Dysphagia solids and liquids; regurgitation)	7	7	No stasis; dilated; OGJ difficult to pass (n=2) Biopsy initial endoscopy: slight inflammation	Conventional Failed contractions; LOS basal pressure 89 mmHg; LOS relaxation pressure 30 mmHg	Standard No stasis; luminal dilation	Metastasis breast carcinoma during PD
F	72	6 (Dysphagia solids and liquids; regurgitation; retrosternal pain)	12	3	No stasis; not dilated; OGJ easy to pass (n=1) Biopsy initial endoscopy: NA	HRM Failed contractions; LOS basal pressure 21 mmHg; IRP 18 mmHg; type I	Standard No stasis; no luminal dilation	Metastasis breast carcinoma diagnosed by CT-scan after PD due to quick recurrent symptoms

OGJ, oesophagogastric junction; EUS, endoscopic ultrasound; HRM, high-resolution manometry; IRP, integrated relaxation pressure;LOS, lower oesophageal sphincter; PD, pneumodilation; NA, not applicable; TBO, timed barium oesophagogram.
*In case ≥2 endoscopies are performed the most appealing finding is described.

Part II
Treatment

Effect of peroral endoscopic myotomy versus pneumatic dilation on symptom severity and treatment outcomes among treatment-naive patients with achalasia: a randomized clinical trial

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5

ABSTRACT

Importance

Case series suggest favorable results of peroral endoscopic myotomy (POEM) for achalasia treatment. Data comparing POEM with the standard treatment, pneumatic dilation, are lacking.

Objective

To compare the effects of POEM versus pneumatic dilation as initial treatment of treatment-naive patients with achalasia.

Design, Setting and Participants

This randomized multicenter clinical trial was conducted at 6 hospitals in the Netherlands, Germany, Italy, Hong-Kong and United States. Adult patients with newly diagnosed achalasia and an Eckardt score greater than 3 who had not undergone previous treatment were included. The study was conducted between September 2012 and July 2015, the duration of follow-up was 2 years after the initial treatment, and final date of follow-up was November 22, 2017.

Interventions

Randomization to receive POEM (n=67) or pneumatic dilation with a 30-mm and a 35-mm balloon (n=66), with stratification according to hospital.

Main outcomes and measures

The primary outcome was treatment success (defined as an Eckardt score ≤3 and the absence of severe complications or re-treatment) at 2-year follow-up. A total of 14 secondary endpoints were examined among patients without treatment failure, including integrated relaxation pressure of the lower esophageal sphincter via high-resolution manometry, barium column height on timed barium esophagogram and presence of reflux esophagitis.

Results

Of the 133 randomized patients, 130 (mean age 48.6 years; 73 [56%] male) underwent treatment (64 in the POEM group and 66 in the pneumatic dilation group) and 126 (95%) completed the study. The primary outcome of treatment success occurred in 58 of 63 patients (92%) in the POEM group vs 34 of 63 (54%) in the pneumatic dilation group; difference of 38% (95% CI:22-52), *P*<.001). Of the 14 prespecified secondary endpoints, no significant difference between groups was demonstrated in 10 endpoints. There was no significant between-group difference in median integrated relaxation pressure (9.9 mmHg in the POEM group vs 12.6 mmHg in the pneumatic dilation group; difference 2.7 mmHg [95% CI, -2.1-7.5]; *P*=.07) or median barium column height (2.4 cm in the POEM group vs 0 cm in the pneumatic dilation group; difference 2.3 cm [95% CI, 1.0-

3.6]; *P*=.05). Reflux esophagitis occurred more often in the POEM group than in the pneumatic dilation group (22 of 54 [41%]) vs 2 of 29 [7%]; difference 34% [95% CI,12%-49%), *P*=.002). Two serious adverse effects, including 1 perforation, occurred after pneumatic dilation, while no severe complications occurred after POEM.

Conclusions

Among treatment-naive patients with achalasia, treatment with POEM, compared with pneumatic dilation resulted in a significantly higher treatment success rate at 2 years. These findings support consideration of POEM as an initial treatment option for patients with achalasia.

INTRODUCTION

Achalasia is an esophageal motility disorder characterized by absent peristalsis in the esophageal body and impaired relaxation of the lower esophageal sphincter (LES), which hampers esophageal emptying, that typical results in symptoms of dysphagia, regurgitation of food, chest pain and weight loss.[1] Treatment for patients with achalasia involves medical, endoscopic, and surgical options. Endoscopic pneumatic dilation is the most commonly performed treatment worldwide for patients with achalasia. The procedure is minimally invasive and long-term therapeutic success, defined as a reduction of the Eckardt score ≤3 and the absence of the need for re-treatment, is 50-85%.[2–5] Approximately 1-3% of the endoscopic pneumatic dilations are complicated by a perforation.[2,6,7] Laparoscopic Heller myotomy combined with an antireflux procedure offers a more permanent solution for patients with achalasia, with success rates of 80-90%.[2,3,6] However, this technique is considerably more invasive and can be associated with severe complications like transmural perforation (4-10%), bleeding or infection, and, therefore, is generally considered as treatment for patients who not respond to pneumatic dilation.[6]

In 2009, peroral endoscopic myotomy (POEM) was introduced as an alternative treatment option for patients with achalasia.[8,9] The technique allows myotomy to be performed endoscopically.[8] Advantages of POEM include a lack of abdominal incisions, rapid recovery, possibility to create a longer proximal myotomy, and high efficacy.[8,10,11] Findings of case series have led to increased adoption of POEM.[8,9,12–15] However, data comparing POEM with the current treatment options in a randomized clinical trial are lacking. Because pneumatic dilation is considered the current standard of care for patients with achalasia, and some clinicians are questioning whether more invasive procedures than pneumatic dilation, such as POEM or laparoscopic Heller myotomy, should be contemplated as first-line treatment, a primary comparison between POEM and pneumatic dilation is relevant. Therefore, the aim of this study was to compare the effects of POEM vs pneumatic dilation as the initial treatment for treatment-naive patients with idiopathic achalasia.

METHODS

Study design

This was a multicenter randomized clinical trial. Patients seen in 6 hospitals with expertise in achalasia management in the Netherlands, Germany, Italy, Hong Kong and the United States between September 2012 and July 2015 were included. The institutional review board of each hospital approved the study protocol (**supplement 1**). Written informed consent was obtained from each included patient before enrollment and randomization. Patients were followed up 3 months, 1 and 2 years after initial treatment. The primary endpoint

was measured at the 2-year follow-up. A Data and Safety Monitoring Board (DSMB) reviewed the safety and efficacy of the treatment groups each time 20 consecutive patients were included. The statistical analysis plan is available in **supplement 2**.

Patients and eligibility criteria

Adult patients aged 18 to 80 years were eligible for enrollment if they were newly diagnosed with symptomatic achalasia, had an Eckardt symptom score greater than 3, and had an American Society of Anesthesiologists classification of I to II (range, I-IV; I indicates a healthy patient; II: indicates a mild systemic disease).[16] The Eckardt symptom score assesses the severity of achalasia symptoms by combining the sum of symptom frequency scores for dysphagia, regurgitation and chest pain (range for each symptom 0-3; 0 indicates absent; 1, occasionally; 2, daily; 3, at each meal) and a weight loss score (range for each symptom 0-3; 0 indicates no weight loss; 1, <5 kg of weight loss; 2, 5-10 kg of weight loss; 3, >10 kg of weight loss), resulting in a range of 0 (the lowest severity of symptoms) to 12 (the highest severity of symptoms).[17] Diagnosis of achalasia was based on high-resolution manometry (HRM) findings and defined as absent peristalsis with impaired relaxation of the LES reflected by an integrated relaxation pressure (IRP) of at least 15 mmHg.[18] Patients were excluded if they had previous endoscopic or surgical treatment for achalasia, except for botulinum toxin injections received more than three months before inclusion. Detailed eligibility criteria are provided in **supplement 1**.

Randomization and masking

Web-based randomization assigned patients to undergo a POEM or pneumatic dilation in a 1:1 ratio with a random block size of 8 and with stratification according to hospital. Study staff enrolled the patients. Randomization concealment for the type of treatment was maintained for both patients and study staff until official study enrollment. Blinding for treatment was not possible because of the different technical approach of each procedure.

Interventions

Pneumatic dilation

Pneumatic dilation was performed by experienced endoscopists who had each performed more than 20 pneumatic dilations. Under fluoroscopic guidance a Rigiflex balloon (Boston Scientific) was positioned at the esophagogastric junction and dilated at a pressure of 5 PSI for 1 minute, followed by dilation with 8 PSI for another minute. Initial pneumatic dilation was performed using a 30-mm balloon. Symptoms were evaluated 3 weeks after the procedure, and if the Eckardt score was greater than 3, a subsequent pneumatic dilation with a 35-mm balloon was scheduled (**efigure 1, supplement 3**). Patients with an

Eckardt score ≤3 underwent a HRM and if the IRP was ≥10 mmHg, a second pneumatic dilation with a 35-mm balloon was scheduled (**efigure 1, supplement 3**). All patients randomized to receive pneumatic dilation underwent 1 or 2 pneumatic dilations within 6 to 8 weeks after randomization. Follow-up started after the first performed pneumatic dilation, but assessment of the secondary endpoints was carried out after the last performed pneumatic dilation. Patients were instructed to adhere to a liquid diet for 3 days and ingest only clear liquids before the procedure. The patients were instructed not to ingest any food or liquids by mouth for 8 hours before the procedure. After each pneumatic dilation, a proton pump inhibitor (PPI, once daily for 2 weeks) was prescribed.

Peroral endoscopic myotomy

POEM is an advanced endoscopic procedure and was performed by expert endoscopists who had each performed more than 20 POEM procedures. POEM was performed while the patient received general anesthesia with endotracheal intubation and was in the supine position. The patient's mouth, throat and esophagus were rinsed with saline and chlorhexidine. The POEM procedure was then performed as described by Inoue et al.[8] Detailed information on the full procedure is described in **eAppendix 1** in **supplement 3**. Patients were admitted to the hospital the day before or the day of the procedure (depending on the travel distance of each patient) and discharged the day after. Patients undergoing POEM were instructed to adhere to the same diet as patients undergoing pneumatic dilation before the procedure. On the day of the procedure, antibiotics (metronidazole plus cefazoline) and a double-dose PPI were administered to the patient intravenously. The day after the procedure, patients were discharged after fluoroscopy was performed to rule out leakage or perforation. At discharge, patients were advised to adhere a liquid diet for 1 day followed by a soft diet for 2 weeks and were prescribed a PPI (once-daily for 2 weeks).

Outcomes

The primary outcome was treatment success at the 2-year follow-up, defined by an Eckardt score less than or equal to 3 and the absence of severe treatment-related complications or the need for endoscopic or surgical re-treatment. Time to treatment success was measured from the date of initial treatment, or the first treatment session for patients in the pneumatic dilation group, until the last follow-up visit or the end of the study. Secondary outcomes were assessed at baseline and 3 months, 1 year and 2 years after initial treatment, with the main time point at 2 years, and included the following: Eckardt score, basal LES pressure and IRP on HRM findings, esophageal stasis and diameter evaluated by timed barium esophagogram, complication rate, the rate of endoscopic or surgical re-treatment, presence of reflux esophagitis based on endoscopy

findings, esophageal acid exposure, reflux symptoms, PPI use and general health-related (physical and mental aspects) and achalasia related quality of life.

Reflux symptoms were analyzed with the Gastroesophageal Reflux Disease Questionnaire (GERDQ) and quality of life was assessd with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Achalasia Disease-Specific Quality-of-Life (achalasia-DSQoL) questionnaire. [19–21] The GERDQ ranged from 0 to 18, in which a score of at least 8 was highly suggestive for GERD.[19] The SF-36 measured general quality of life by scoring mental and physical aspects, which ranged from 0 to 100, with higher scores indicating a better quality of life.[20] The achalasia-DSQoL measured quality of life related to achalasia and scores ranged from 10 to 33, in which lower scores indicated a better quality of life.[21] After treatment, an IRP less than 15 mmHg, measured via HRM and a barium column less than 5 cm and/or greater than 50% improvement of stasis on timed barium esophagogram indicated a successful treatment.[22–25] Presence of any grade of reflux esophagitis after treatment was considered as clinically relevant. Complications were classified as serious adverse events (severe) or adverse events (mild) (detailed classification criteria are provided in **eAppendix 2** in **supplement 3**).

Clinical assessment and follow-up

At baseline, medical history was obtained and physical examination and routine laboratory tests were performed (**efigure 1** in **supplement 3**). Patients completed the GERD-Q, SF-36 and achalasia-DSQoL questionnaires. HRM was performed to diagnose achalasia and to differentiate into achalasia subtypes.[18] Upper endoscopy and a timed barium esophagogram were performed to quantify esophageal stasis by measuring barium column height at 5 minutes on radiographic images after ingesting 200 mL of low density barium sulphate suspension during a time window of 30 to 60 seconds.[26]

Symptoms and questionnaires were assessed and HRM and timed barium esophagogram were performed 3 months, 1 year and 2 years after treatment. (**efigure 1** in **supplement 3**). Esophageal 24-hour pH-impedance monitoring was performed after PPI cessation for at least 7 days at the 1 year follow-up to evaluate esophageal acid exposure (percentage pH <4). Upper endoscopy was performed at 1-year and 2-year follow-up visits. For the 2 year follow-up, patients who were taken PPIs did not have to discontinue PPI use. Severity of reflux esophagitis was scored according to the Los Angeles classification, with no reflux esophagitis to mild esophagitis classified as grade A to B and severe esophagitis as grade C to D.[27] Grade A was defined as at least 1 mucosal break with a length of less than or equal to 5 mm that did not extend between the tops of 2 mucosal folds, B as at least 1 mucosal break with a length greater than 5 mm that did not extend between the tops of 2 mucosal folds, C as at least 1

mucosal break that was continuous between the tops of 2 or more mucosal folds and involving less than 75% of the esophageal circumference, and D as at least 1 mucosal break that is continuous between tops of 2 or more mucosal folds and involving at least 75% of the esophageal circumference.[27] After treatment, PPI was started for patients who experienced reflux symptoms independent of time in follow-up or when reflux esophagitis was observed during upper endoscopy.

Re-treatment after unsuccessful treatments

Patients in whom initial pneumatic dilation was unsuccessful underwent re-treatment with pneumatic dilation with a 40-mm balloon, and, if symptoms persisted, they were offered POEM (**supplement 1**). Re-treatment for patients in whom initial POEM was unsuccessful consisted of pneumatic dilation, starting with a 30-mm balloon and followed by a 35-mm balloon and 40-mm balloon if necessary (**supplement 1**). Follow-up after re-treatment was continued according to protocol following initial treatment.

Statistical methods

Based on assumed success rates of 90% for POEM[12,14,15] and 70% for pneumatic dilation[2–5] after 2 years, a difference of at least 20% in success rates between the treatments was hypothesized for purposes of sample size calculations. With 62 patients per treatment group (124 patients in total), the study would have 80% power to detect the described difference in success rate, with a 2-sided alpha level of 0.05. To account for an estimated 5% loss to follow-up, the aim was to enroll 130 patients. The data and safety monitoring board was assigned to advise on early termination of the study because of unacceptable occurrence of serious adverse events (SAEs), defined as an incidence of SAEs greater than 10% per treatment group, or because of futility.

Primary analysis, of the primary and secondary outcomes was conducted at 2-year follow-up and included all patients, except patients who did not undergo treatment after randomization or who were lost to follow-up (modified intention-to-treat analysis). Patients were analyzed according to their randomization group. In case of unsuccessful treatment, patients were excluded from further analysis of the secondary outcomes. The per-protocol analysis included patients who received treatment according to the study protocol and was only performed for the primary outcome. Missing data for the primary outcome were addressed by performing a post hoc sensitivity analysis using multiple imputation with 5 iterations. Post hoc analyses were performed for adjustment of the primary outcome by center and interaction with achalasia subtype. Additionally, primary and secondary outcomes at 3-months and 1-year follow-up and efficacy of re-treatment with pneumatic dilation after treatment failure were assessed post hoc.

Continuous data are presented as mean (SD) or median (interquartile range [IQR]), according to distribution. Categorical data are presented in percentages. Continuous data were compared using unpaired Student's t-test or Mann-Whitney U-test and categorical data were analyzed by Chi-square or Fisher's exact test. Absolute differences of comparative results were calculated by subtracting percentages, means or medians of the groups and calculating the 95% CIs of the difference. Linear mixed models for repeated measures during follow-up, were used to analyze the effect of treatment type on continuous secondary outcome parameters with fixed effect for time and treatment. A random intercept was set for each patient to capture the correlation among measurements within the same patient. Pneumatic dilation was used as the reference and nonparametric data were first log transformed. Success rates in the two treatment groups were analyzed by comparing percentages using Chi-square and post hoc logistic regression. To adjust for the heterogeneity of centers on the primary outcome, a post hoc analysis was performed using mixed-effect logistic regression with center as a random intercept. To study the interaction of achalasia subtype on treatment in relation to primary outcome, a post hoc subgroup analysis was performed using logistic regression including interaction variables, with pneumatic dilation and subtype II achalasia as references. *P* values less than .05 were considered statistically significant. All reported *P* values are 2-tailed. Findings for the secondary endpoints are considered exploratory as adjustment for multiple comparison was performed post-hoc by the Holm-Bonferroni method. Statistical analysis was performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY, United States) and R software version 3.4.0.

RESULTS

Enrollment and patient characteristics

Between September 2012 and July 2015, 133 patients with achalasia were randomized, of whom 67 were randomly assigned to receive POEM and 66 to receive pneumatic dilation (**table 1**). Three patients randomized to POEM never underwent treatment (**figure 1**). The final date of follow-up was November 22, 2017.

A total of 130 patients were included in the analyses (64 in the POEM group and 66 in the pneumatic dilation group; age range 18-80 years; mean age, 48.6 years; 73 [56%] men (**figure 1**). Four patients were lost to follow-up during the study. In the pneumatic dilation group, 50 patients underwent 2 dilations and 16 patients were only treated by a 30-mm balloon. The single pneumatic dilation was in 10 patients according to the protocol, but 6 patients refused to undergo an additional HRM because of complete symptom relief. These patients were not excluded from follow-up. Median (IQR) follow-up time for the POEM group was 24 months (24-24 months) compared to 24.5 months (24-25 months) in the pneumatic dilation group. Baseline characteristics were similar between groups (**table 1**).

Table 1. Baseline characteristics of patients in POEM and pneumatic dilation treatment groups.

	POEM	**Pneumatic dilation**
Number of patients treated	64	66
Allocation per center (n (%))		
Amsterdam UMC, Netherlands	38 (59%)	36 (55%)
Evangelische Krankenhaus Düsseldorf, Germany	8 (12.5%)	10 (15%)
Agostino Gemelli University Hospital Rome, Italy	8 (12.5%)	9 (13.5%)
Prince of Wales Hospital Honkong, China	7 (11%)	9 (14%)
Helios Klinikum Krefeld Düsseldorf, Germany	2 (3%)	1 (1.5%)
Northwestern Memorial Hospital Chicago, USA	1 (1.5%)	1 (1.5%)
Gender (n (%))		
Male	33 (52%)	40 (61%)
Female	31 (48%)	26 (39%)
Age (year (median (IQR))	47 (37-56)	50 (32-62)
Weight (kg (mean (SD))	71.5 (16.1)	69.6 (13.9)
BMI (kg/m^2 (mean (SD))	23.2 (3.7)	23.4 (4.1)
Achalasia subtype (n (%))[a]		
Type I	10 (16%)	21 (32%)
Type II	42 (65%)	39 (59%)
Type III	12 (19%)	6 (9%)
Eckardt score (median (IQR)[b]	8 (6-9)	7 (5.8-9)
Basal lower esophageal sphincter pressure (mmHg; median (IQR))	31 (25-45)	32.8 (24.4-45.1)
Integrated relaxation pressure (mmHg; median (IQR))	26.4 (20.2-34.9)	28.5 (20.4-37.3)
Barium column height (cm; median (IQR))	7.2 (4.5-9.2)	6.7 (3.0-10.1)
Barium column diameter (cm; median (IQR))	3.5 (2.7-4.5)	3.3 (2.8-4.3)
Achalasia DSQoL (median (IQR)[c]	25 (22-27)	24 (22-26)
GERD-Q (median (IQR)[d]	8 (6-11)	8 (6-10)
SF-36 (median (IQR)[e]		
Physical Component Summary Score	46.3 (39.9-49.9)	45.6 (38.7-50.9)
Mental Component Summary Score	45.7 (35.6-54.6)	45.2 (36.8-53.5)

[a]Achalasia subtypes according to observations during high-resolution manometry: type I 100% failed peristalsis; type II 100% failed peristalsis,panesophageal pressurization ≥20% of swallows; type III no normal peristalsis, premature/spastic contractions ≥20% of swallows.
[b]Eckardt score: achalasia symptoms, range 0-12, highest score indicated most pronounced symptoms.
[c]Achalasia-DSQoL: quality of life related to achalasia, range 10-33, lower score indicated better quality of life.
[d]GERD-Q: gastroesophageal reflux disease, range 0-18, score ≥8 was highly suggestive for presence of GERD.
[e]SF-36: general quality of life consisted of Physical Component Summary Score, range 0-100, and Mental Component Summary Score, range 0-100, higher score indicated better quality of life.

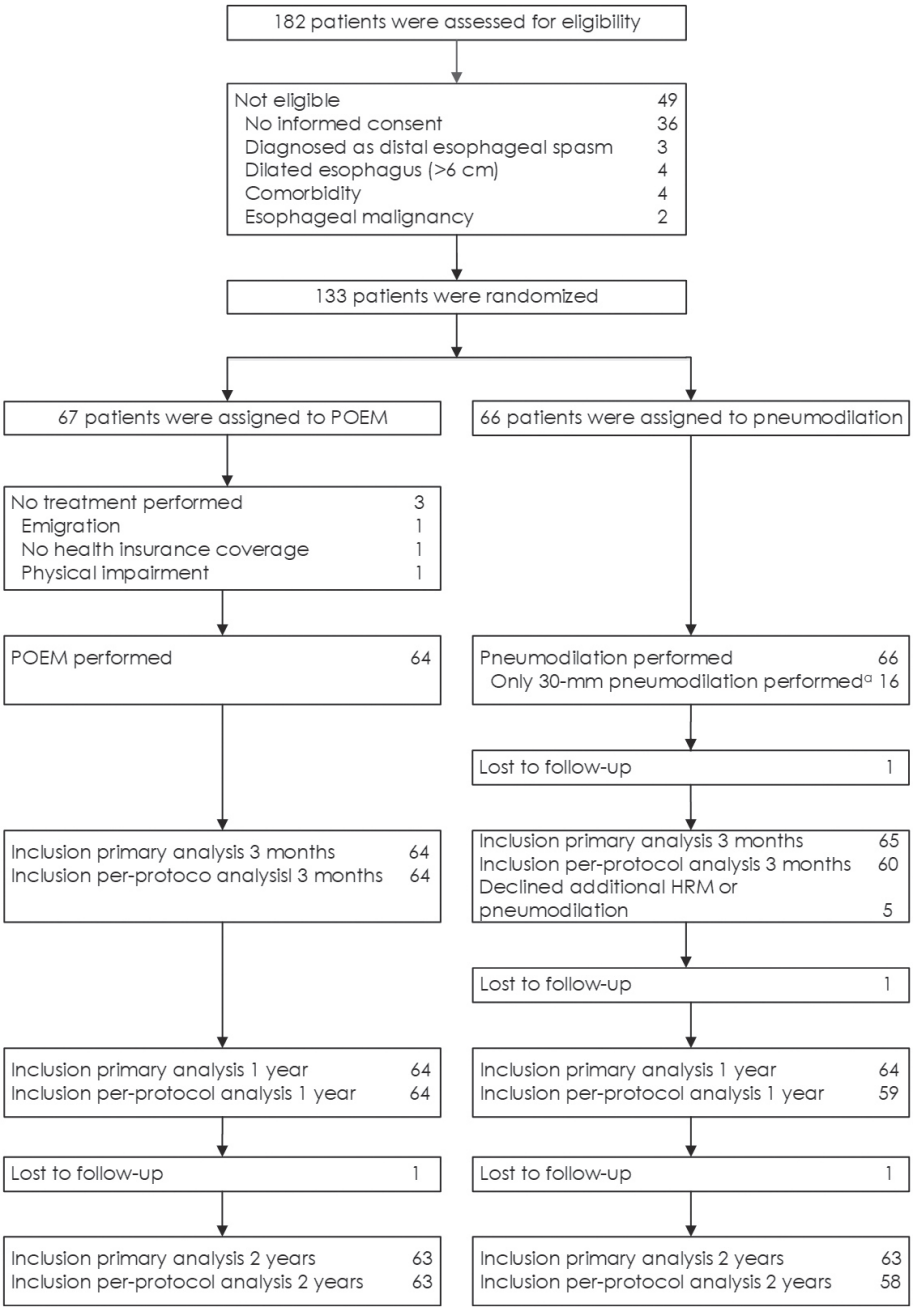

Figure 1. Enrolment, randomization and follow-up according to the primary and per-protocol analysis.
POEM: peroral endoscopic myotomy; HRM: high-resolution manometry.
[a]Only underwent a pneumatic dilation with a 30-mm balloon.

Primary outcome

Analysis of the primary outcome showed higher treatment success at 2-year follow-up in the POEM group (58 of 63 patients [92%]), than in the pneumatic dilation group (34 of 63 patients [92%]) (absolute difference, 38% [95% CI, 22%-52%]; P<.001; risk ratio 1.71 (95% CI, 1.34-2.17); **table 2**). In the pneumatic dilation group, 1 patient had an unsuccessful treatment related to an SAE, which involved a perforation that occurred during a pneumatic dilation with a 30-mm balloon (**table 2** and **figure 2**). The other patients who had unsuccessful initial treatment were all symptomatic after treatment (ie, Eckardt score >3; median [IQR] score after treatment, 4 [4-5.3] and required re-treatment (**figure 2**). Four of the 29 patients (14%) in whom pneumatic dilation was not successful underwent dilation with a 30-mm balloon only. Two of these patients were not treated according to the protocol because they refused additional HRM.

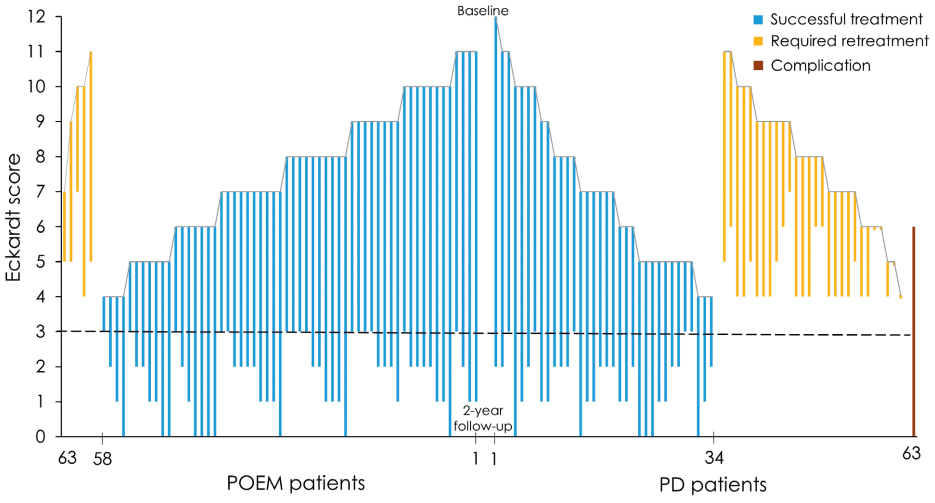

Figure 2. Eckardt score at baseline and 2-year follow-up for POEM and pneumatic dilation divided into successful treatment, required re-treatment or complication.
Each vertical line represents an individual patient. Patients who achieved an Eckardt score of ≤3, vertical line ends at or below the dashed horizontal line, had an adequate symptom control and were considered successfully treated. Patients with a post-treatment Eckardt score of 4 or higher, vertical line ends above the dashed horizontal line, were considered treatment failures.

Table 2. Primary outcome at 2 years, 3 months and 1 year of follow-up according to type of treatment.

Primary outcome	POEM		Pneumatic dilation		Unadjusted absolute difference % (95% CI)*	Unadjusted risk ratio (95% CI)	*P***
	n	% (SD)	n	% (SD)			
2-year follow-up (primary endpoint) Overall treatment success	58/63	92 (3.4)	34/63	54 (6.3)	38 (22, 52)	1.71 (1.34, 2.17)	<.001
Reasons for failure*							
Eckardt score >3	5/63	8 (3.4)	28/63	44 (6.2)	36 (20, 50)		<.001
Re-treatment	5/63	8 (3.4)	26/63	41 (10.5)	33 (17, 47)		<.001
Treatment related SAEs	0/63	0 (0)	1/63	1.6 (1.6)	1.6 (-5, 10)		1.0
3 months follow-up (secondary endpoint) Overall treatment success	63/64	98 (1.8)	52/65	80 (5)	18 (7, 30)	1.23 (1.09, 1.40)	.001
Reasons for failure*							
Eckardt score >3	1/64	2 (1.8)	12/65	18 (4.8)	16 (5, 29)		.002
Re-treatment	1/64	2 (1.8)	11/65	17 (4.7)	15 (4, 27)		.004
Treatment related SAEs	0/64	0 (0)	1/65	2 (1.7)	2 (-5, 9)		1.0
1-year follow-up (secondary endpoint) Overall treatment success	61/64	95 (2.7)	42/64	66 (5.9)	31 (17, 45)	1.45 (1.21, 1.75)	<.001
Reasons for failure*							
Eckardt score >3	3/64	5 (2.7)	21/64	33 (5.9)	28 (14, 42)		<.001
Re-treatment	3/64	5 (2.7)	19/64	30 (5.7)	25 (11, 38)		<.001
Treatment related SAEs	0/64	0 (0)	1/64	1.6 (1.6)	2 (-5, 9)		1.0

Data are presented as numbers (n), percentages (SD) or absolute difference (95% CI).
*Not mutually exclusive.
**Chi-square.

Secondary outcome

Reflux Esophagitis, PPI Use and Reflux Symptoms

At 2-year follow-up 54 of 58 patients (93%) in the POEM group and 29 of 34 (85%) in the pneumatic dilation group underwent endoscopy (*P*=.28). Reflux esophagitis was observed significantly more frequently in patients treated with POEM than with pneumatic dilation (22 of 54 patients [41%] in the POEM group, of whom 19 [35%] were assigned grade A-B and 3 [6%] were assigned grade C, vs 2 of 29 [7%] in the pneumatic dilation group, all of whom were assigned grade A; absolute difference, 34% [95% CI, 12%-49%]; *P*=.002). Reflux symptoms and daily use of PPI were significantly more frequent in patients treated with POEM (**table 3**). The median (IQR) percentage of time with esophageal pH less than 4 during pH-impedance measurement at the 1-year follow-up was not significantly different between the POEM group (7.0% [1.1-21.3%] vs the pneumatic dilation group (3.0% [1.0-10.2%]) (absolute difference, 4% [95% CI, 0%-8.2%], *P*=.95).

Eckardt Score, HRM, Timed Barium Esophagogram and Quality of Life

The primary analysis showed no significant difference in Eckardt score, IRP and basal LES pressure based on HRM findings, barium column height and diameter during timed barium esophagogram, or quality of life at the 2-year follow-up after post hoc adjustment for multiple comparisons (**table 3**). Additional linear mixed-model analysis showed that, adjusted for repeated measures over time, the esophageal diameter of patients who underwent POEM was 0.1 cm wider than patients who underwent pneumatic dilation (**table 3**). No significant difference in outcomes of the other secondary end points was observed between the treatment groups over time.

Re-treatment

POEM was unsuccessful in 5 of 63 patients (8%), who then underwent re-treatment with pneumatic dilation (**figure 2**). Re-treatment was successful in 4 of the 5 patients (80%) patients (**eTable 1** in **supplement 3**). Treatment with pneumatic dilation was unsuccessful in 29 of 63 patients (46%) (**figure 2**). Additional treatment with pneumatic dilation was performed in 23 of the 29 patients (79%; 3 declined, 2 received POEM and 1 received laparoscopic Heller myotomy; **eTable 1** in **supplement 3**). Recurrent symptoms were observed in 9 of the 23 patients (39%), who then underwent POEM. The total number of treatments performed was 75 in the POEM group and 162 in the pneumatic dilation group (*P*<.001). The post hoc analysis, which evaluated the association between an additional pneumatic dilation with a 40-mm balloon and treatment success of pneumatic dilation, showed an improved success rate of pneumatic dilation (48 of 63 patients [76%]), but it was still less than the success rate for POEM (58 of 63 patients [92%]) (absolute difference, 16% [95% CI: 2%-30%], *P*=.008; **eTable 1** in **supplement 3**).

Table 3. Secondary outcomes at 2 years of follow-up according to type of treatment.

Secondary outcome 2-year follow-up	POEM (n=58)	Pneumatic dilation (n=34)	Unadjusted absolute difference (95% CI)	*P* (post-hoc P)***	β-coefficient***	*P (post-hoc P)***
Eckardt score (median (IQR))[b]	2 (1-3)	2 (1-2)	0 (-1, 1)	.47 (.97)	-	-
Integrated relaxation pressure (mmHg; median (IQR))	9.9 (7-14)	12.6 (7.4-19)	2.7 (-2.1, 7.5)	.07 (.56)	-0.09 (-0.21, 0.04)	.19 (0.76)
Basal LES pressure (mmHg; median (IQR))	13.6 (9-19.5)	20.5 (8.4-32)	6.9 (-7.5, 21.3)	.58 (.58)	-0.13 (-0.26, -0.01)	.04 (.23)
Barium column height (cm; median (IQR))	2.3 (0-3.7)	0 (0-2.5)	2.3 (1, 3.6)	.05 (.45)	0.60 (-0.28, 1.49)	.18 (.9)
Barium column diameter (cm; median (IQR))	2.6 (2.1-3.5)	2 (1.5-2.9)	0.6 (0.3, 0.9)	.01 (.11)	0.10 (0.03, 0.16)	.004 (.03)
Achalasia DSQoL (median (IQR))[c]	14 (12-17)	14 (11-17)	0 (-3, 3)	.52 (.96)	0.02 (-0.03, 0.06)	.45 (.99)
GERD-Q (median (IQR))[d]	7 (6-8)	6 (6-8)	1 (0, 2)	.003 (.04)	0.06 (0.01, 0.11)	.02 (.16)
GERD-Q ≥8 (% (SD))	40 (6.4)	27 (7.6)	13 (-7, 32)	.2 (.98)	-	-
SF-36 (median (IQR))[e] Physical Component Summary Score Mental Component Summary Score	 54.1 (50.9-57.9) 54 (50.3-57.2)	 53.8 (46.1-57.6) 52.9 (48.3-56)	 0.3 (-4.3, 4.9) 1.1 (-1.6, 3.8)	 .49 (1.0) .49 (1.0)	 0.002 (-0.03, 0.03) 0.01 (-0.02, 0.04)	 .88 (.88) .57 (.97)
Endoscopic reflux esophagitis (n and % (SD))[f] Grade A (n (%)) Grade B (n (%)) Grade C (n (%)) Grade D (n (%))	22/54 41 (6.5) 17 (31) 2 (4) 3 (6) 0 (0)	2/29 7 (4.7) 2 (7) 0 (0) 0 (0) 0 (0)	34 (12, 49)	.002 (.03)	-	-
PPI use (n and % (SD)) Reflux esophagitis (n (%)) No reflux esophagitis (n (%))	24/58 41 (6.5) 10 (42) 14 (58)	7/34 21 (7) 0 (0) 7 (100)	20 (1, 38)	.004 (.04)	-	-

Data are presented as numbers (n), percentages (SD), median (IQR) or absolute difference (95% CI).
*Mann-Whitney or Chi-square. **P adjusted for multiple comparison. ***β-coefficient representing the difference in outcome of continuous secondary endpoints between treatment groups, adjusted for repeated measurements within patients over time and measured by linear mixed model with pneumatic dilation as the reference treatment.
[b/c/d/e] See Table 1 for scale definitions.
[f]Severity of reflux esophagitis according to the Los Angeles classification: grade A-B is mild esophagitis, grade C-D is severe esophagitis.

Complications and Adverse Events

In total 7, SAEs occurred during the study, of which 2 were related to pneumatic dilation and the other 5 occurred independent of a study intervention. One of the SAEs related to pneumatic dilation was a perforation after dilation with a 30-mm balloon, requiring endoscopic closure, antibiotics and 13 days of hospitalization. This patient was considered to have an unsuccessful treatment. Another patient was admitted for 1 night after undergoing pneumatic dilation because of severe chest pain without signs of perforation. The patient continued the study and was considered to have a successful treatment. Detailed information on SAEs independent of the study interventions is provided in eAppendix 3 in Supplement 3. Adverse events were more common after POEM (42 of 63 patients [67%]) vs pneumatic dilation (14 of 63 patients [22%]. Adverse events in the POEM group were related to reflux esophagitis (n = 29), reflux symptoms (n = 8), Candida esophagitis (n = 2), ulcer at the esophagogastric junction that healed after PPI treatment (n = 2) and periprocedural mucosal tear that was treated conservatively and healed at endoscopy performed one week later (n = 1). In the pneumatic dilation group reported adverse events were reflux esophagitis (n = 7), reflux symptoms (n = 7), Candida esophagitis (n = 1) and belching/dyspepsia (n = 1).

Sensitivity and Per-Protocol Analysis

Post hoc sensitivity analysis of the primary outcome using multiple imputation for missing data, revealed a higher success rate for POEM (58 of 64 patients [91%]) compared with pneumatic dilation (35 of 66 patients [53%]) at the 2-year follow-up (absolute difference, 38% [95% CI: 21%-51%]; *P*<.001; risk ratio, 1.71 [95% CI, 1.34, 2.18]). The per-protocol analysis of treatment success at the 2-year follow-up showed a higher success rate for POEM (58 of 63 [92%]) compared with pneumatic dilation (31 of 58 [53%]) (absolute difference, 39% [95% CI: 22%-53%]; *P*<.001; risk ratio, 1.72 [95% CI, 1.34, 2.21]; **eTable 2**, **supplement 3**). Post hoc per-protocol analysis of treatment success at 3 months and 1 year also revealed a higher success rate with POEM vs pneumatic dilation (**eTable 2** in **supplement 3**).

Post Hoc Outcomes

Post hoc analysis of outcomes at 3 months and 1 year showed a higher success rate of POEM compared with pneumatic dilation (**table 2**). Secondary end points were also evaluated 3 months and 1 year after initial treatment. No significant differences were observed in Eckardt score, IRP and basal LES pressure based on HRM findings, barium column height and diameter during timed barium esophagogram, or quality of life after post hoc adjustment for multiple comparisons (**eTable 3** in **supplement 3**). Endoscopy at the 1-year follow-up was completed in 59 of 61 patients (97%) in the POEM group and 36 of 42 patients (85%) in the pneumatic dilation group (*P*=.66). Endoscopy was

performed after PPI cessation for at least 7 days and reflux esophagitis was found in significantly more patients in the POEM group (29 of 59 patients [49%], of whom were assigned grade A-B and 8% were assigned grade C-D) vs the pneumatic dilation group (4 of 36 [11%]), all of whom were assigned grade A-B) (absolute difference 38% [95% CI: 17%-53%]; *P*<.001; **eTable 3** in **supplement 3**). Reflux symptoms and PPI use showed no statistically significant difference between treatment groups (**eTable 3** in **supplement 3**).
Adjusting the primary outcome for the different centers revealed an odds ratio of 12.3 ([95% CI: 4.2-37.3]; *P*<.001) for treatment success, in favor of POEM. This was comparable to the unadjusted odds ratio of 9.89 [95% CI, 3.5-28], *P*<.001). The interactions between treatment, achalasia subtype and the primary outcome were not statistically significant, with P values ranging from .23 to .35. In **eTable 4** in **supplement 3**, adjusted odds ratios are presented and show that the effect of POEM and pneumatic dilation on treatment outcome was not related to achalasia subtypes.

DISCUSSION

In this randomized clinical trial that compared POEM with pneumatic dilation as the initial treatment for treatment-naive patients with achalasia, POEM resulted in a significantly greater treatment success at 2 years. However, development of reflux esophagitis was more frequent after POEM than after pneumatic dilation, and POEM was associated with increased PPI use.

To our knowledge, this is the first randomized clinical trial that evaluated POEM as an initial treatment for achalasia. The efficacy of POEM in this study was similar to the results reported in uncontrolled prospective and retrospective studies, which showed therapeutic success of 80% to 97% after 12 months or more.[12–15] The definition of success in these studies was an Eckardt score less than or equal to 3, the need for re-treatment, or both. Some studies have suggested that the recurrence rate after POEM could further increase with time.[9,28] However, most of the prospective studies were not restricted to treatment-naive patients with achalasia, which makes direct comparison difficult. In previous studies involving laparoscopic Heller myotomy, efficacy at 5 years decreases to 80% to 85%.[3,5] Outcome data for POEM with such a long follow-up is not available, but it can be anticipated that POEM most likely will perform similarly to laparoscopic Heller's myotomy because 1-year and 2-year follow-up data reveal similar success rates.[2,6] Randomized clinical trials comparing POEM to laparoscopic Heller myotomy are necessary to answer that question. The observed success rate of 92% at 2 years in this trial should be considered as a medium-term outcome and follow-up data at 5 years will help to provide information about the duration of the treatment effect.

The data confirmed that POEM was a technique with a low risk of major complications because SAEs were not observed in the POEM group. For pneumatic dilation, the rate of perforations was 1.5% despite the use of the smallest (30-mm) balloon for the initial pneumatic dilation. This finding was within the reported range of complication rates of previous studies.[2,6,7] Although POEM is more invasive and requires more technical endoscopic skills, the risk of severe complications was not higher than with pneumatic dilation, especially when performed by experienced endoscopists.[6,7,29]

Treatment success of pneumatic dilation ranged between 54% to 80% during the study, which is on the lower end compared to other studies, ranging from 50% to 85%.[2–5,30] One reason for this discrepancy could be the pneumatic dilation protocol that was followed in the current study. Patients were considered to have unsuccessful treatment after 1 or 2 pneumatic dilation procedures with a 35-mm or smaller balloon. Other studies included an additional pneumatic dilation with a 40-mm balloon in cases of clinical recurrence or extra dilation series with 2 or 3 pneumatic dilations. procedures [2–5] Some evidence suggests that repeated dilation is accepted and reflects daily clinical practice.[3–5] However, patients will experience persistent or recurrent symptoms after previous pneumatic dilations as failed treatment. Pursuing another series of pneumatic dilations would be a second treatment. Furthermore, each time a pneumatic dilation is performed there is a perforation risk and multiple pneumatic dilation sessions form a potential bias in the comparison to 1 treatment intervention. Therefore, the effect of just 1 series of pneumatic dilations was compared to the effect of POEM. However, 23 of the 29 patients whose treatment was unsuccessful in this study were subsequently treated with a 35-mm balloon, a 40-mm balloon, or both. Of these 23 patients, 9 (39%) still had persistent symptoms and underwent POEM. The additional pneumatic dilation increased treatment success of pneumatic dilation to 76%, but this was still lower than the 92% success rate of POEM. Follow-up after re-treatment was less than 6 to 12 months in most patients, which cannot imply successful treatment. Previous data suggest that if symptoms do not improve after a pneumatic dilation series with a 30-mm and/or 35-mm balloon, it is unlikely that symptoms will improve after dilation with a 40-mm balloon.[6,31] The minimal expected effect after additional pneumatic dilation with a 40-mm balloon was another reason not to include subsequent dilation sessions in the protocol. The 2011 trial of Boeckxstaens et al[2] differed from the current trial in that the former had a more aggressive dilation protocol and excluded participants with serious dilation complications after pneumatic dilation from further analysis. If that trial had used the same definition of treatment success as the current study, the success rate of pneumatic dilation would be lower and comparable to the success rate of this study.

The major disadvantage of POEM is the high incidence of reflux esophagitis. In this study, 49% of the patients had reflux esophagitis at the 1-year follow-up, and 8% had a severe grade. Endoscopy after 1 year was performed while PPI use in patients was discontinued, revealing the high incidence of this complication. Endoscopy after 2 years was performed while PPI use in patients receiving acid suppression was continued, which resulted in lower rates of esophagitis. Not all patients with reflux esophagitis had reflux symptoms. The frequent occurrence of reflux disease after POEM was previously described in a multicenter case-control study of 282 patients in which endoscopic or pH-metric evidence of reflux disease after POEM was found in 58% of the patients, including endoscopic esophagitis in 23%.[10,15] Furthermore, a 2016 study by Jones et al[32] showed that the results of pH-metry after POEM did not correlate with the severity of reflux symptoms. Werner et al reported that 9 of 29 patients (31%) with a good clinical outcome and no reflux esophagitis at short-term endoscopy 3 to 6 months after undergoing POEM developed mild reflux esophagitis at later follow-up.[28] These studies illustrate the high risk of reflux esophagitis after POEM and underline the need of PPI use and endoscopic follow-up, because patients are often asymptomatic. However, the substantial prevalence of reflux esophagitis is not exclusively a problem associated with POEM. Randomized clinical trials showed that 20% of the patients treated with laparoscopic Heller myotomy developed reflux esophagitis, and both retrospective and prospective long-term follow-up (5-20 years) studies reported use of antireflux medication in 39% to 65% of patients and Barrett epithelium in 13% of these patients.[2,3,33–35] Thus, although an endoscopic or laparoscopic myotomy is highly effective for achalasia, it disrupts the antireflux barrier and causes significant reflux esophagitis.

The higher medium-term efficacy of POEM demonstrated by this study does not imply that pneumatic dilation should be abandoned. POEM is more time-consuming, significantly more invasive, and more likely to cause reflux esophagitis. Thus, it seems reasonable to offer both to treatment-naive patients with achalasia and counsel them to select treatment based on patient's characteristics, personal preference, comorbidity and disease subtype.

The strengths of this randomized clinical trial were the substantial number of patients included, the use of objective measures to analyze treatment success and esophageal function, the use of adequately trained endoscopists to perform the procedures, and the stratification of the randomization by center. Furthermore, this was the first study, to our knowledge, in which POEM was compared with an alternative achalasia treatment in a randomized trial.

LIMITATIONS

This study had several limitations. First, a strict intention-to-treat analysis was not performed. Patients who were randomized but never underwent treatment or who were lost to follow-up after treatment, were excluded for the primary analysis. The number of patients excluded was small and, combined with the large treatment effect, it seems unlikely that this would affect the main conclusions. A sensitivity analysis of the primary outcome, accounting for lost to follow-up, further confirmed this. Second, the start time for follow-up was treatment initiation rather than randomization. Because of the dilation series in the pneumatic dilation group, follow-up time slightly differed between the two treatment groups (24 months for the POEM group vs 24.5 months for pneumatic dilation group). The reason for evaluation after the last performed dilation in the pneumatic dilation group, was to compare a complete dilation series to a single POEM procedure. Because there was a minor difference in follow-up time, it seems unlikely that study conclusions were affected by this. Third, primary and secondary outcome were assessed at 2-year follow-up. Consequently, no conclusions can be drawn for treatment success of POEM for the longer-term treatment success of POEM, especially because achalasia is a lifelong chronic disease. Fourth, like most endoscopic or surgical studies that evaluate new interventional techniques, this trial had an unblinded design. A blinded trial would have required that patients in the pneumatic dilation group underwent general anaesthesia and hospital admission and patients assigned to POEM would have had to undergo a sham pneumatic dilation.

CONCLUSIONS

Among treatment-naive patients with achalasia, treatment with POEM, compared with pneumatic dilation, resulted in a significantly higher treatment success at 2 years. These findings support consideration of POEM as an initial treatment option for patients with achalasia.

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SUPPLEMENT MATERIAL
Supplement 1
Study protocol POEMA Trial

1. Introduction

Idiopathic achalasia is a rare motility disorder of the oesophagus with an annual incidence rate of 1 per 100,000 persons.[1] Achalasia is characterised by aperistalsis of the oesophageal body and dysrelaxation of the lower oesophageal sphincter caused by progressive destruction and degeneration of the neurons in the myenteric plexus. This leads to subsequent retention of food and saliva in the oesophagus, resulting in the typical symptoms of achalasia such as dysphagia, chest pain, regurgitation of undigested food and weight loss. At the long term, incomplete oesophageal emptying and reflux result in an increased risk for development of squamous cell carcinoma of the oesophagus.[1,2] The cause of the neuronal degeneration found in achalasia is unknown.[3]

Treatment of achalasia is focused on symptom relief, which is obtained by destroying the occluding function of the spastic lower oesophageal sphincter. Usually, the first step is endoscopic dilation of the lower oesophageal sphincter using a pneumatic balloon.[4,5] However, a disadvantage of this treatment is the high chance of symptom recurrence which requires subsequent treatment sessions. Also, approximately 3% of the endoscopic pneumodilations (PD) is complicated by a perforation, which is a potentially life-threatening situation.[6] When symptoms recur after endoscopic balloon dilation a surgical myotomy can be considered. During a surgical myotomy the circular muscle fibers of the lower oesophageal sphincter are cut laparoscopically and this results in a lower recurrence rate than pneumodilation.[7] However, this technique can also be associated with severe complications, is more invasive and is more expensive as it involves laparoscopic instrumentarium. Currently, endoscopic pneumodilation is the first choice of treatment in patients with achalasia and surgical myotomy is generally performed in case of symptom recurrence after initial pneumodilation.

Recently, per-oral endoscopic myotomy (POEM) has been introduced as an alternative to surgical myotomy.[8] The POEM technique is entirely endoscopic and is performed under total anesthesia at the endoscopy suite. Using an endoscopic knife, an entry to the submucosal space is made in the oesophagus and after creating a submucosal tunnel towards the lower oesophageal sphincter the circular muscle layers are cut. At the end of the procedure the mucosal opening is closed with clips. In our centre we have now treated more than 10 patients successfully with POEM and we were able to confirm the positive findings in symptom improvement and lower oesophageal sphincter pressure reduction reported by the German and Japanese pioneers of the technique.[8,9]

2. Hypothesis

We hypothesize that POEM has a higher long-term efficacy than PD in treatment of therapy-naive patients with idiopathic achalasia.

3. Aim

To compare the efficacy of POEM to the efficacy of PD as the initial treatment of symptomatic idiopathic achalasia.

4. Study design

This is a multi-centre randomised clinical trial in which a new treatment (POEM) will be compared to the gold standard (PD). The primary endpoint will be measured at two years after treatment and follow up will be extended up to five years.

5. Primary outcome

- Treatment success, defined as:
  - An Eckardt score of 3 or less
  - The absence of the need for endoscopic or surgical retreatment in the period between the first treatment session (first and optional second dilation within first 3 months) and the endpoint
  - The absence of severe complications associated with treatment.

6. Secondary outcomes

- Quality of life and achalasia-specific quality of life
- Stasis in the oesophagus, measured with a timed barium oesophagogram
- Presence of reflux symptoms, reflux oesophagitis and excessive oesophageal acid exposure
- Lower oesophageal sphincter pressure and integrative relaxation pressure (IRP4), as measured with high-resolution manometry
- Complications of the treatment, defined as any unwanted events that arise following treatment and/or that are secondary to the treatment. Complications are classified as “severe” when these result in admission > 24 hours or prolongation of an already planned admission of >24 hours, admission to a medium or intensive care unit, additional endoscopic procedures, or blood transfusion or death. Other complications are classified as “mild”.
- The need for endoscopic or surgical retreatment after the initial treatment session

7. Population

7.1 Subjects

Adult patients with symptomatic idiopathic achalasia that have not undergone endoscopic or surgical treatment for achalasia before.

7.2 Inclusion criteria

- Presence of achalasia, as shown on oesophageal manometry
- Eckardt score > 3
- Age between 18-80 years
- Signed written informed consent
- ASA class I or II

7.3 Exclusion criteria

- Previous endoscopic or surgical treatment for achalasia, except botulinium toxin injections
- Previous surgery of the stomach or oesophagus
- Known coagulopathy
- Presence of liver cirrhosis and/or oesophageal varices
- Presence of eosinophilic oesophagitis
- Presence of Barrett's oesophagus
- Pregnancy at time of treatment
- Presence of a stricture of the oesophagus
- Presence of malignant or premalignant oesophageal lesions
- Presence of an extensive, tortuous dilated oesophageal body (S-shape)
- Presence of a diverticula in the distal oesophagus

8. Methods

8.1 Study protocol

Study enrolment and randomisation

In the AMC, patients will be approached that visit the outpatient clinic of the Motility centre of the Gastroenterology department. Patients should be diagnosed with achalasia by manometry using the predefined manometric criteria and have not undergo surgical or endoscopic treatment for achalasia before. Eligible patients will be given a verbal explanation of the study. Each patient will receive a patient information brochure about the study and an informed consent form for participation. Patients will be given sufficient time to read the information and ask questions. Before any study procedures or randomisation are initiated the patient must sign the informed consent form.

There is no time frame for the randomisation. When participants are recruited for the study the time to consider participation in the study is unlimited. Before randomisation the patient must have signed the informed consent form. Randomisation will be done using a web-based program and is stratified for each centre, so that the number of patients treated with POEM or pneumatic dilation is similar for each centre. The randomisation for the two treatments will be 1:1.

Baseline

At baseline, patients will undergo oesophageal manometry, timed barium oesophagogram and upper endoscopy. A venous blood withdrawal is performed to screen for abnormalities in blood count, chemistry lab and clotting. If any of these tests have been performed within the last 6 months and of high quality (at the discretion of the investigator) it is not required to repeat this. Questionnaires regarding symptoms and quality of life (see 8.4) are filled in by the patients.

General follow up

Patients that are randomised to endoscopic balloon dilation will be asked to fill in an Eckardt score three weeks after the dilation. If this score is still more than 3, they will be scheduled to undergo a second pneumatic dilation, but now using a 35 mm balloon (**figure 1**). Manometry is performed if the Eckardt score is 3 or less. If the manometry shows an IRP of more than 10, patients will also undergo a second pneumatic dilation (with a 35 mm balloon).

Manometry and timed barium oesophagography are performed and questionnaires are filled in all patients 3 months after treatment and at 1, 2 and 5 years after treatment. Twenty-four hour pH-impedance monitoring is performed one year after treatment to evaluate oesophageal acid exposure. Upper endoscopy is performed at 1, 2 and 5 years after treatment.

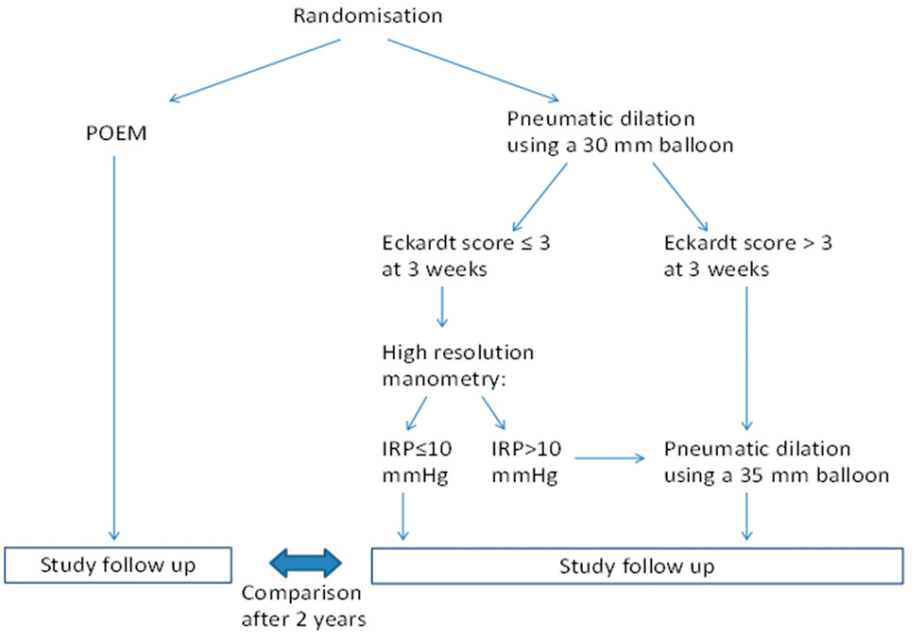

Figure 1. Treatment algorithm used in this study

Table 1. Schedule of baseline and follow-up examinations.

	Baseline	3 weeks*	3 months	1 year	2 years	5 years
Blood count, chemistry, clotting	X					
Questionnaires	X	Eckardt*	X	X	X	X
Timed barium oesophagogram	X		X	X	X	X
Manometry	X	If Eckardt >3*	X	X	X	X
Upper endoscopy	X			X	X	X
pH-impedance monitoring				X		

*only for patients randomised to balloon dilation.

8.2 Pneumodilation (PD)

In this study pneumodilation will only be performed by experienced endoscopists, that have performed over 20 pneumodilation procedures. Patients are asked to use clear fluids only starting 24 hours before the procedure and nil per mouth starting 8 hours before the procedure. Under fluoroscopic guidance a Rigiflex balloon (Boston Scientific) is positioned at the esophagogastric junction and dilated at a pressure of 5 PSI, followed by dilation with 8 PSI for one minute (**figure 2**).[8,10] The initial pneumatic dilation is performed using a 30-mm balloon. Three weeks later the symptoms of patients are evaluated using the Eckardt score. If the Eckardt score is still higher than 3, a subsequent dilation with a 35-mm balloon is scheduled. If the Eckardt score is less than 3 a subsequent high-resolution manometry is scheduled. If this shows an integrative relaxation pressure (IRP4) of more than 10 mmHg, a subsequent dilation with a 35-mm balloon is scheduled as well. In total, patients will thus undergo one or two pneumatic dilations in the first 6 weeks. A second dilation within this 6 week period is not considered a failure but considered part of the regular treatment. PPI are taken orally in a single daily dose for two weeks after each dilation.

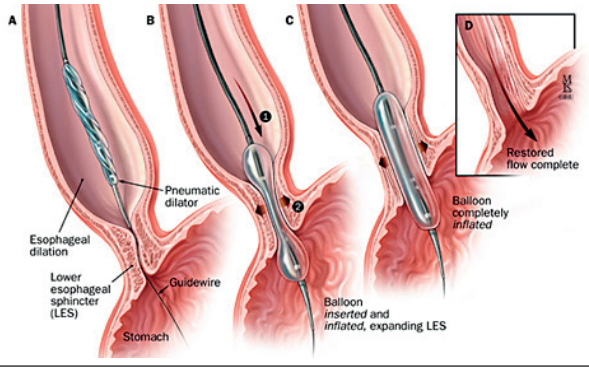

Figure 2. Schematic outline of a pneumatic balloon dilation

8.3 Per-oral endoscopic myotomy (POEM)

In this study POEM will only be performed by experienced endoscopists, that have performed over 10 POEM procedures. Patients are admitted two hours prior to the POEM procedure and are discharged the next day. Patients are asked to use a diet with clear fluids starting 24 hours before the procedure and nil per mouth starting 8 hours before the procedure. On the day of the procedure, antibiotics and double dose PPI (proton pump inhibitor) are administered intravenously. A PPI will be taken orally for two weeks in a single daily dose starting at the day of treatment. POEM is performed under general anesthesia and with endotracheal intubation. The mouth, throat and esophagus are rinsed with saline and chlorhexidine (40–60 ml). POEM procedures are then performed as described by Inoue et al. (**figure 3**).[8]

A forward-viewing upper endoscope (GIF H180J; Olympus, Hamburg, Germany) is used with a transparent distal cap (MH 588; Olympus). Carbon dioxide gas is used for insufflation during the procedures. An endoscopic dissection knife (KD-640L TriangleTipKnife; Olympus) is used to access the submucosa, to create the submucosal tunnel, and also to divide circular muscle fibers over a minimum length of 6 cm in the esophagus, and 2 cm onto the cardia according to the standards of surgical myotomy. An electrogenerator (Erbe Vio 300D; Erbe Elektromedizin, Tübingen, Germany) is used with Endocut Q mode (effect 2) to open the mucosa, and spray coagulation mode (effect 2, 50 watt) to dissect the submucosa and divide the muscle fibers. A coagulating forceps (FD-410LR Coagrasper; Olympus) is used for hemostasis as needed. Closure of the mucosal entry site is performed using standard endoscopic clips (HX-110UR EZ Clip Reusable Rotatable Clip Fixing Device and HX-610-135L Single Use Clips; Olympus).

On the next day postoperative fluoroscopy is performed to rule out a leak at the esophageal closure site before discharge. Patients are kept nil per mouth until after the fluoroscopy and are kept on a liquid diet for an additional 24 h. Patients are discharged with single dose PPI and a soft diet for 2 weeks.

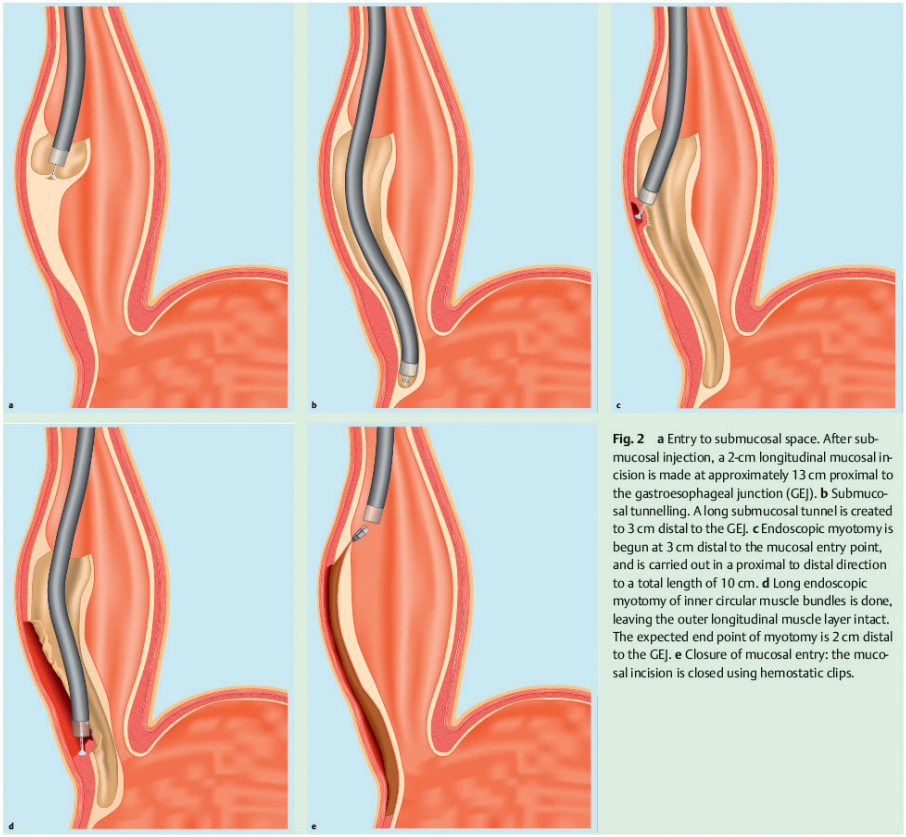

Fig. 2 **a** Entry to submucosal space. After submucosal injection, a 2-cm longitudinal mucosal incision is made at approximately 13 cm proximal to the gastroesophageal junction (GEJ). **b** Submucosal tunnelling. A long submucosal tunnel is created to 3 cm distal to the GEJ. **c** Endoscopic myotomy is begun at 3 cm distal to the mucosal entry point, and is carried out in a proximal to distal direction to a total length of 10 cm. **d** Long endoscopic myotomy of inner circular muscle bundles is done, leaving the outer longitudinal muscle layer intact. The expected end point of myotomy is 2 cm distal to the GEJ. **e** Closure of mucosal entry: the mucosal incision is closed using hemostatic clips.

Figure 3. Schematic outline of the POEM procedure [11]

8.3.1 Risk of complications in POEM from recent clinical studies

So far there is limited information about the complications related to the POEM procedure because it is a relative new procedure and long-term follow-up is not yet available. Serious adverse events are not described in the previous studies that performed POEM. The main preoperative complications that are described are subcutaneous emphysema, pneumoperitoneum and pneumothorax. Transmural openings into the mediastinum and into the peritoneal cavity caused emphysema, pneumoperitoneum and pneumothorax. During POEM the inner circular muscle layer is separated from the outer longitudinal muscle layer, leaving the longitudinal muscles intact.[9] The longitudinal muscle fibers are extremely thin, so minor damage can lead to transmural dissections into the mediastinum and peritoneal cavity.

Subcutaneous emphysema was treated conservatively and in all cases the emphysema resolved spontaneously in 2-3 days after surgery. The treatment of

the pneumoperitoneum occurred in all patients during the operation. A needle or canula of 18G was placed in the abdominal wall which gave directly relieve.[8,9] A pneumothorax was a rare complication and in all cases thoracic drainage was administered during the operation which gave immediately relieve. Other described rare complications preoperatively were a minor bleeding, controlled by endoscopic coagulation, and small perforations which were clipped.

Postoperative complications were rare. One article described pneumothorax as an important postoperatively complication.[12] The treatment was in most patients conservatively and in some patients a thoracic drainage was administered, dependent on the lung compression volume. An uncommon postoperative complication was a delayed hemorrhage, one day after the operation. This occurred in one patient and was probably caused by a bleeding in the submucosal tunnel. A three-cavity tube was placed by endoscopy into the stomach and lower part of the esophagus to compress the bleeding. After four days the tube was removed without further complications. Another rare complication was a superficial ulcer (Forrest III) at the cardia that was detected with a control endoscopy two days after POEM. This was only seen in one patient. The patient had to continue PPIs and the hospital stay was extended. The control endoscopy 7 days after the procedure showed healing of the ulcer.

The average follow-up after the procedure described in the different articles was 3-5 months. No serious complications were observed during this follow-up period. Furthermore none of the patients developed recurrent symptoms and symptoms of gastro-esophageal reflux or reflux esophagitis were minimal.

8.3.2 Risk of complications in POEM in the first treated patients of the AMC

In the AMC the POEM procedure is performed in more than 10 patients. There were no serious adverse events (SAEs) preoperative or postoperative. Preoperative two adverse events occurred in different patients. In one patient a minor bleeding occurred during the cutting of the circular muscle layer which was easily controlled by endoscopic coagulation. To be certain that the patient didn't develop a rebleed, the patient stayed longer at the recovery for close monitoring. Another adverse event that occurred during the procedure was a pneumoperitoneum due to small transmural dissections into the mediastinum. The pneumoperitoneum caused a temporary elevation of intraperitoneal pressure which was relieved with an 18G canula, placed in the abdominal wall during the procedure. The adverse events didn't extend the hospital admission and reintervention was not needed.

Postoperative complications didn't occur. At this moment the follow-up period of the treated patients is 1-6 months. None of the treated patients developed

recurrent symptoms so far and also gastro-esophageal reflux symptoms aren't registered.

8.4 Questionnaires

- Eckardt score, which is the sum of symptom scores for dysphagia, regurgitation, chest pain and weight loss. Each symptom is scored from 0 to 3. The minimum score is 0, the maximum 12. (see appendix A for explanation of the calculation of the score)
- Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36], The SF-36 mental and physical summary scores (which range from 0 to 100, with higher scores indicating better well-being) measure general aspects of health quality of life (12).
- The validated Achalasia Disease-Specific Quality-of-Life questionnaire (achalasia-DSQoL).[13]
- The Gastroesophageal Reflux Disease Questionnaire (GerdQ) is a self-assessment questionnaire that can be used for the diagnosis and follow-up of gastroesophageal reflux disease, and measures both symptoms and impact of symptoms on person's daily life

8.5 Timed barium oesophagogram

In the timed barium oesophagogram technique, upright frontal spot films of the oesophagus are obtained at 1, 2, and 5 min after ingestion of 100-200 ml of low-density (45% weight in volume) barium sulphate (volume of barium determined by patient tolerance).[14] This is a routine clinical test that is used to measure oesophageal emptying and reflects oesophageal function.

8.6 High resolution manometry of the oesophagus

High resolution manometry of the oesophagus (pressure measurement) is the gold standard to diagnose achalasia and is used in clinical practice to evaluate the effect of the treatment. High resolution manometry is performed using a catheter that is introduced into the oesophagus transnasally. Patients will swallow 10 small sips of 5 mL of water and presence of peristalsis, spasms and lower oesophageal sphincter pressure and relaxation during swallowing are evaluated. Classification of achalasia will be done using the revised Chicago classification.[15] In routine clinical practise oesophageal manometry is often performed in patients with achalasia.

8.7 Impedance-pH recording

It is known that patients that underwent pneumodilation or myotomy are prone to develop gastro-oesophageal reflux disease and often have a high oesophageal acid exposure time.[16] Twenty-four hour impedance-pH recording is performed to assess the degree of oesophageal acid exposure. During the

test, a small catheter is introduced transnasally into the oesophagus.[17] This catheter consists of impedance and pH sensors that measure reflux episodes and 24 hour data is stored on a datalogger which patients carry on their belt. Measurements are performed after cessation of acid-suppressive medication for at least 7 days. Measurements are analyzed for acid exposure time (time with pH<4), number of acid and number of weakly acid reflux episodes and duration of reflux episodes.In the analysis of the pH sginals, episodes with pH < 4 caused by stasis-associated acidification of oesophageal contents will be discarded. Impedance-pH monitoring is a routine clinical test for assessment of oesophageal acid exposure.

8.8 Upper endoscopy

The main reason to perform upper endoscopy at baseline is to exclude pseudoachalasia and other causes of dysphagia. After treatment, the main reason to perform upper endoscopy is to investigate whether oesophagitis is present. The degree of oesophagitis is scored according to the LA classification.[18] Upper endoscopy is performed after cessation of acid-suppressive medication for at least 10 days. Upper endoscopy is performed according to the local routine protocol, sedation with midazolam and/or fentanyl is possible if patient prefers this. It is routine clinical practise to perform regular upper endoscopies in patients with achalasia.

8.9 Withdrawal of individual subjects

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.9 Premature termination of the study

Efficacy data of the study will be monitored by the investigators, mainly by the PI, in cooperation with the DSMB. The study can be early terminated because of clear benefit, harm or futility. Because the first results of the POEM in the AMC and other foreign centres are promising, symptom improvement and lower oesophageal sphincter pressure reduction are comparable to the current two treatments, it is not likely this study will be terminated prematurely. However the aim of this study is to look at the efficacy of POEM versus PD and therefore we need to define stopping regulations for the study of the primary endpoint, treatment success.

The stopping regulation will only be based on the occurrence of severe complications, SAEs, associated with the treatment and re-intervention postoperative. After each inclusion of 20 participants the study team and the DSMB will discuss the data and review the stopping regulations.The incidence of SAEs in pneumodilation is normally around the 5%. Because POEM is a new procedure at the moment the incidence of SAEs is unknown. One of the

stopping regulations concern SAEs and states that the incidence of SAE's in both groups shouldn't exceed 10%. The other stopping regulation is if the incidence of re-intervention exceeds 20%, 1 year postoperative. This is applicable for both treatments. For pneumodilation the incidence for re-intervention is estimated on 10%, 1 year postoperative.

9. Safety

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 Adverse and serious adverse events

Pneumodilation is a safe and regularly performed procedure for patients with achalasia. In this study the procedure will be performed by experienced endoscopists, that have performed over 20 pneumodilations. Complications due to a pneumodilation are rare and the main complication is an oesophageal perforation. The treatment of a perforation is frequently conservatively, total restriction of food and drinks and intravenous antibiotic therapy. In some cases surgery is needed. The incidence of a perforation during pneumodilation is approximately 3%.[6]

POEM is a relative new procedure in the treatment of achalasia. In Germany and Japan the first POEM procedures were performed and in the AMC so far 10 patients are treated with POEM. Because the follow-up of the first patients is only 3-5 months, nothing is known about long-term complications or efficacy. Major complications that can occur during the procedure are a bleeding or oesophageal perforation. Treatment can directly be performed during the procedure by clipping the bleeding or perforation. In some cases a surgical procedure can be needed. Furthermore POEM can be complicated by minor complications, like pneumoperitoneum and postoperative subcutaneous emphysema. Pneumoperitoneum can be relieved by a puncture of the abdominal wall using an 18-gauge needle during the procedure. Postoperative subcutaneous emphysema is usually self-limiting and additional treatment is not needed. So far the only complications that occurred in the treated patients of the AMC were a minor bleeding that was stopped during the procedure and one patient developed a pneumoperitoneum which relieved by a puncture of the abdominal wall using an 18-gauge needle during the procedure.

All the additional measurements that are performed before and after treatment are safe procedures and routinely performed in the clinical setting. Possible complications are mainly due to placement of the catheters and endoscope. The catheters can give discomfort in the nose and pharynx. Furthermore in rare cases a mucosal bleeding of the nose, caused by the catheter, can occur which never need extra treatment. The endoscope can give discomfort in the pharynx.

All adverse events reported spontaneously by the subject or observed by the investigators will be recorded in a database. The Data Safety Monitoring Board will be informed about the adverse events.

All serious adverse events (SAEs) will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. The SAEs will be reported within 15 days after the sponsor is first notified of the SAEs. The SAEs that result in death or are life treating will be reported expedited through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. This will not occur later than 7 days after the coordinating investigators and principal investigator have knowledge of the SAE(s). This first report is preliminary and within 8 days after submission of the first report a final report will be submitted.

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to another medical specialist. Furthermore a Data Safety Monitoring Board will be informed about the adverse events that occur.

9.4 Data Safety Monitoring Board (see also the DSMB charter)

A Data Safety Monitoring Board (DSMB) is established. In total the DSMB will consist of four members, an epidemiologist, a surgeon, a paediatrician specialised in gastroenterology and a gastroenterologist. None of the members have a conflict of interest with the sponsor of the study. Personal details of the DSMB members can be found in the DSMB charter which also describes in detail the function, aims and responsibilities of the DSMB. In short the DSMB will act in an independent, expert and advisory capacity to monitor participant safety and evaluate the efficacy and the overall conduct of the study. The DSMB will be informed about adverse events and serious adverse events that occur during the study. The advice(s) of the DSMB, in case it influences the set-up of the study, will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.

10. Statistical analysis and randomisation

We aim to perform an intention to treat analysis. After testing for normality, pairwise comparisons will be performed between the two treatment arms for all primary and secondary outcomes. Categorical variables will be compared using the Chi-square test. The success rates of the two treatment arms will be compared using log-rank tests on Kaplan-Meier estimates.

Randomisation will be done using a web-based online available program and is stratified for each participating centre.

11. Sample size analysis

Recently reported complication free success rate of a two step PD strategy is 68% at two years.[6] Long term outcome data of POEM is lacking but at three months a success rate of 94% has been described.[9] Assuming success rates of 70% for PD and 90% for POEM after two years, we estimated that with 62 patients in each group, the study would have 80% power to detect a significant difference in success rate between PD and POEM with a two-sided alpha level of 0.05. To cope with an estimated 5% loss to follow-up, we aim to enrol 130 patients.

12. Privacy

The data of the subjects are coded in order of participation. The code and the data are stored in different locations. The code can only be seen by the investigators. Qualified authorities can get insight in code and data, but only when accompanied by the investigators. Data will be stored 20 years after closure of the trial.

13. Ethical consideration

The protocol of this study will be submitted to the Medical Ethical Committee of the Academic Medical Center and will not start before formal approval has been granted. Participants will be given oral and written explanation about the study, before they give written informed consent. Subjects are allowed to withdraw informed consent without providing arguments.The study will be registered at ClinicalTrials.gov and the results will be published in a peer-reviewed scientific journal.

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15 APPENDIX A

Calculation of the Eckardt score

Each patient has to answer four questions that concern different symptoms. Per symptom they have to mark the degree of severity of the specific symptom. Each symptom is scored from 0-3 and the Eckardt score is the sum of symptom scores. The minimum score is 0 and the maximum score is 12. A high Eckardt score indicates severe complaints due to achalasia.

Score	**0**	**1**	**2**	**3**
Questions/Symptoms				
Dysphagia (difficulty or pain during swallowing)	No (0)	Occasionally (1)	Daily (2)	At each meal (3)
Regurgitation (food is coming back in to the mouth)	No (0)	Occasionally (1)	Daily (2)	At each meal (3)
Chest pain	No (0)	Occasionally (1)	Daily (2)	At each meal (3)
Weight loss	0 kg (0)	0-5 Kg (1)	5-10 kg (2)	> 10 kg (3)

16. ADDENDUM

16.1 Treatment failure in the POEMA Trial

Description of treatment failure

Study subjects are considered treatment failures in case the **Eckardt score is > 3 within the first 2 years of follow-up, retreatment is indicated or a treatment related SAE occured** after the initial treatment. This means that the study subjects did not achieve the primary endpoint, 2 years after the initial treatment, due to recurrent symptoms.

The vast majority of failed study subjects will need retreatment and the indication for retreatment should be based on the symptoms of the subject (Eckardt > 3) in combination with:

- Considerable LES pressure or IRP (> 10mmHg) on HRM.
- Significant stasis on timed barium esophagogram.
- Clinical judgement and expert opinion of the treating physician.

16.2 Treatment of treatment failures (figure 1)

POEM procedure

Study subjects failed on POEM will be retreated with pneumodilation. The first step is to perform a pneumodilation with a 30 mm rigiflex balloon in a single session. The effect of the pneumodilation should be evaluated by the Eckardt score. In case the Eckardt is >3 a new pneumodilation should be scheduled with one step larger balloon size. There is no limit to the number of pneumodilations that can be performed after a failed POEM.

Pneumodilation with 30 and 35 mm balloon

Study subjects failed on the initial pneumodilations (30 and 35 mm rigiflex balloon) within the first year of follow-up will be retreated with a pneumodilation using a 40 mm rigiflex balloon. In case subjects fail more than 1 year after the initial pneumodilations they will be retreated with a pneumodilation using a 35 mm and 40 mm rigiflex balloon.

This is in contrast with the previous versions of the protocol concerning treatment failure that stated that these patients should be subsequently treated with a POEM procedure. The reason to retreat the patients first with a third pneumodilation of 40 mm is that the optimal pneumodilation protocol is used in this way. After the additional pneumodilation(s) symptoms should be evaluated by the Eckardt score. In case the Eckardt is >3 the patient can be scheduled for a POEM procedure.

16.3 Follow-up of treatment failures

In principal, study subjects that failed on the initial treatment (2x pneumodilation or POEM) achieved the primary endpoint at that moment. For these patients page 49, study termination, of the CRF should be filled in.

It is very important to continue to collect the data of the treatment failures because sub-analyses of these data can be performed at the end of the study. Therefore, follow up will be the same as the study protocol; follow-up should be scheduled with regard to the date of the initial treatment.

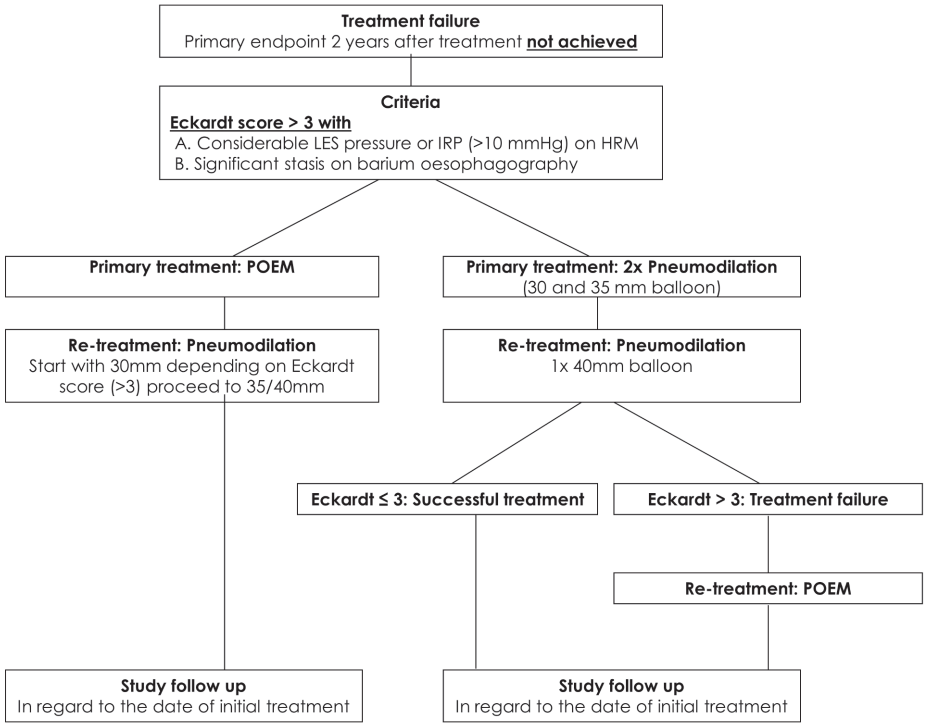


Figure 1. Treatment failure algorithm

Supplement 2

Statistical analysis plan

Pneumodilation Or Endoscopic Myotomy in achalasia (POEMA) Trial

1. Introduction

In this multicenter randomized controlled trial, the efficacy of a new treatment for achalasia, peroral endoscopic myotomy (POEM) is compared to the current standard treatment: pneumodilation. In the study protocol extended information is provided on the trial design, randomization procedure including stratification factors, sample size, stopping regulation and management of adverse and serious adverse events. The trial is designed to recruit 130 patients in total and the primary endpoint will be measured two years after treatment. Follow-up of the patients will be extended up to five years. This document will provide information on the statistical analysis of the data after two-year follow-up. Data will be collected at baseline and after treatment, at 3 months, 1 and 2 years follow-up.

2. Primary outcome

The primary outcome of this study is treatment success at 2 years, defined as an Eckardt score ≤3 in the absence of severe complications (SAE) or need for endoscopic or surgical retreatment. The success rates in the two treatment groups will be analyzed by comparing proportions by Chi-square.

3. Secondary outcome

Different parameters will be analyzed as secondary outcome measures:

- Eckardt score
- Lower esophageal sphincter pressure and integrative relaxation pressure (IRP), as measured with high-resolution manometry
- Esophageal stasis and diameter measured with a timed barium esophagogram
- Presence of reflux symptoms, reflux esophagitis and esophageal acid exposure
- Health related quality of life and achalasia-specific quality of life
- Complication rate
- Number of endoscopic or surgical retreatment

The parameters are measured at baseline, 3 months, 1 and 2 years follow-up. Continuous data will be presented as mean with standard deviation (SD) or median with interquartile range (IQR) or range, according to distribution. Categorical data will be presented in percentages with SD. Continuous data will be compared using unpaired Student's t-test or Mann-Whitney U-test and categorical data will be analyzed by Chi-square or Fisher's exact test. To account for repeated measures linear mixed model is used. The effect of treatment type

on continuous outcome parameters, like Eckardt score and IRP is analyzed with fixed effect for time and treatment.

4. Missing data

Any missing data are reported. Patients that are lost to follow-up before treatment failure or the primary endpoint at 2-year follow-up, will be excluded from the analysis because the primary outcome is unknown. Previous collected data of these patients on earlier follow-up moments will not be discarded and used for outcome analysis at these time points. We assume that the estimated lost to follow-up of patients without a primary outcome of 5% is realistic and will not influence data analysis with the current sample size. However, an additional sensitivity analysis, addressing missing data for the primary outcome by multiple imputation will be performed.

Missing data of the secondary outcome parameters will be excluded from the analysis. Fifty percent of the secondary outcome parameters is categorical data which makes multiple imputation difficult and the option last case carried forward was assessed as outdated. If a patient had withdrawn consent no further data will be collected. However, data collected thus far will be used for analyses.

5. Analysis methods

Two types of analyses will be performed: 1) intention-to-treat in which patients at time of treatment failure will be excluded from further analysis; 2) per protocol excluding patients that not followed the treatment protocol. The intention-to-treat analysis will be used as the main analysis. Patients will be analyzed according to their randomization group. Primary and secondary outcomes at 3 months and 1 year follow-up and the efficacy of retreatment with PD after treatment failure will be assessed as post-hoc anal

Supplement 3

eAppendix

eAppendix tables and figures

eAppendix references

Abbreviations:
GERD-Q – Gastroesophageal reflux disease questionnaire
HRM – High-resolution manometry
IQR – Interquartile range
IRP – Integrated relaxation pressure
LES – Lower esophageal sphincter
POEM – Peroral endoscopic myotomy
PPI – Proton pump inhibitors
SAE – Serious adverse event
SD – Standard deviation
TBE – Timed barium esophagogram

1. Interventions

1.1 Peroral endoscopic myotomy

Peroral endoscopic myotomy (POEM) was carried out under general anesthesia with endotracheal intubation. The procedure was then performed as described by Inoue et al.[1] A forward viewing upper endoscope (GIF H180J; Olympus, Hamburg, Germany) with a transparent distal cap (MH 588; Olympus or Fuijfilm) was used. Carbon dioxide gas was used for insufflation during procedures. An endoscopic knife (KD-640L TriangleTipKnife: Olympus) was used to access the submucosa, create the submucosal tunnel and divide the circular muscle layer in the distal esophagus and 2-3 cm onto the cardia, including cutting the lower esophageal sphincter (LES). An electrogenerator (Erbe Vio 300D; Erbe Elektromedizin, Tübingen, Germany) was used to open the mucosa and the spray coagulation mode was selected to dissect the submucosa and cut the muscle fibers. The mucosal entry site was closed by standard endoscopic clips (HX-110UR EZ Clip Reusable Rotatable Clip Fixing Device and HX-610-135L Single Use Clips; Olympus).

2. Adverse events

2.1 Definition of serious/severe and mild adverse events

Adverse events were defined as any unwanted event that occurred following the study treatment, secondary to the study treatment or unrelated to study treatment during follow-up. Adverse events were defined as severe (serious) based on the following criteria

- Unexpected hospital admission for >24 hours or prolongation of a planned hospital admission for >24 hours related or unrelated to the study treatment
- Admission to a medium or intensive care related to the study treatment
- Additional endoscopic procedures within 24 hours after the study treatment
- Need of blood transfusion after the study treatment
- Death, related or unrelated to the study treatment

Adverse events not fulfilling the above described criteria were classified as mild.

3. Results

3.1 Serious adverse events independent of study intervention

One patient in the pneumodilation group developed a herpes encephalitis with a bilateral thalamus infarct and post-treatment had severe lateralization and aphasia. Consequently, further follow-up according to study protocol was not possible. This patient had recurrent symptoms at 1-year follow-up even before the SAE occurred and was already considered a treatment failure. Three patients had a myocardial infarction during the study period, two in the pneumodilation group and one in the POEM group, these were deemed to be unrelated to achalasia or its treatment. All three patients could continue the study follow-up. One patient was diagnosed with a renal cell carcinoma that was treated by nephrectomy. This patient was treated by pneumodilation and could continue study follow-up.

Tables and figures

eTable 1. Overview of type of retreatment after treatment failure and the additional effect of the pneumodilation 40 mm on treatment success.

	POEM (n=63)	**Pneumatic dilation (n=63)**	***P****
Treatment failures 2-year follow-up (n and % (SD))	5/63 8 (3.4)	29/63 46 (6.3)	<.001
Type of retreatment (n (%))			-
Pneumodilation 30 mm	1 (20)	-	
Pneumodilation up to 35 mm	2 (40)	3 (10)	
Pneumodilation up to 40 mm	1 (20)	11 (38)	
Pneumodilation up to 40 mm + POEM	-	9 (31)	
Pneumodilation up to 40 mm + laparoscopic Heller myotomy	1 (20)	-	
POEM	-	2 (7)	
Laparoscopic Heller's myotomy	-	1 (4)	
None / unknown	-	3 (10)	
Total number of treatments including retreatment (n)	75	162	<.001
Overall treatment success including pneumodilation 40 mm (n and % (SD))	58/63 92 (3.4)	48/63 76 (6.4)	.008

Data are presented as numbers (n) or percentages (SD).
*Chi-square.

eTable 2. Primary outcome per-protocol analysis at 2 years, 3 months and 1-year of follow-up according to type of treatment.

Primary outcome per-protocol	POEM		Pneumatic dilation		Unadjusted absolute difference (95% CI)	Risk ratio (95% CI)	*P**
	n	% (SD)	n	% (SD)			
2-year follow-up (primary endpoint) Overall treatment success	58/63	92 (3.4)	31/58	53 (6.6)	39 (22, 53)	1.72 (1.34, 2.21)	<.001
3 months follow-up (secondary endpoint) Overall treatment success	63/64	98 (1.8)	47/60	78 (5.3)	20 (8, 33)	1.26 (1.10, 1.44)	<.001
1-year follow-up (secondary endpoint) Overall treatment success	61/64	95 (2.7)	38/59	64 (6.3)	31 (16, 45)	1.48 (1.34, 2.21)	<.001

Data are presented as numbers (n), percentages (SD) or absolute difference (95% CI).
*Chi-square.

eTable 3. Secondary outcomes at 3 months and 1-year of follow-up according to type of treatment.

Secondary outcome 3 months follow-up	**POEM (n=63)**	**Pneumatic dilation (=52)**	**Unadjusted absolute difference (95% CI)***	***P**(post-hoc p)****
Eckardt score (median (IQR))[a]	1 (0-2)	1.5 (1-2)	0.5 (0, 1.5)	.009 (.09)
Integrated relaxation pressure (mmHg; median (IQR))	8.7 (5.4-14.3)	11.8 (7.7-14.3)	3.1 (0.1, 6.1)	.13 (.99)
Basal LES pressure (mmHg; median (IQR))	11.7 (7.2-15.8)	12.1 (8.9-19.9)	0.4 (-4.6, 5.4)	.45 (.99)
Barium column height (cm; median (IQR))	0 (0-2)	0 (0-3.7)	0 (-1.1, 1.1)	.47 (1.0)
Barium column diameter (cm; median (IQR))	2.1 (1.9-2.7)	2.3 (1.9-2.8)	0.2 (-0.1, 0.5)	.7 (1.0)
Achalasia DSQoL (median (IQR))[b]	12 (11-15)	13 (11-16)	1 (-1, 3)	.08 (.72)
GERD-Q (median (IQR))[c]	6 (6-7)	6 (6-8)	0 (0, 0)	.84 (.84)
GERD-Q ≥8 (% (SD))[c]	21 (5.1)	27 (6.2)	6 (-11, 23)	.43 (.97)
SF-36 (median (IQR))[d]				
Physical Component Summary Score	55.4 (50-58.6)	54.9 (44.1-57.9)	0.5 (-3.4, 4.4)	.3 (.99)
Mental Component Summary Score	53.6 (46.9-57.8)	54.5 (47.6-56.5)	0.9 (-8.7, 10.5)	.84 (.84)
Secondary outcome 1 year follow-up	**POEM (n=61)**	**Pneumaticdilation (n=42)**	**Unadjusted absolute difference (95% CI)***	***P**(post-hoc p)****
Eckardt score (median (IQR))[a]	1 (0-2)	1 (0-2)	0 (-1, 1)	.98 (.98)
Integrated relaxation pressure (mmHg; median (IQR))	9 (6.6-15.4)	11 (8.6-15.6)	2 (-0.5, 4.5)	.83 (1.0)
Basal LES pressure (mmHg; median (IQR))	13.9 (8.1-18.5)	14.7 (10.6-26)	0.8 (-1.9, 3.5)	.11 (.88)
Barium column height (cm; median (IQR))	1.7 (0-3.3)	0 (0-2.4)	1.7 (-0.8, 4.2)	.1 (.90)
Barium column diameter (cm; median (IQR))	2.5 (2.1-3)	2.1 (1.6-2.6)	0.4 (-0.6, 1.4)	.004 (.05)
Achalasia DSQoL (median (IQR))[b]	14 (11-17)	13 (11-15)	1 (-1, 3)	.29 (.99)
GERD-Q (median (IQR))[c]	6 (6-8)	6 (6-7)	0 (-1, 1)	.03 (.36)
GERD-Q ≥8 (% (SD))[c]	30 (5.9)	16 (5.7)	14 (-6, 24)	.11 (0.99)

eTable 3. Continued

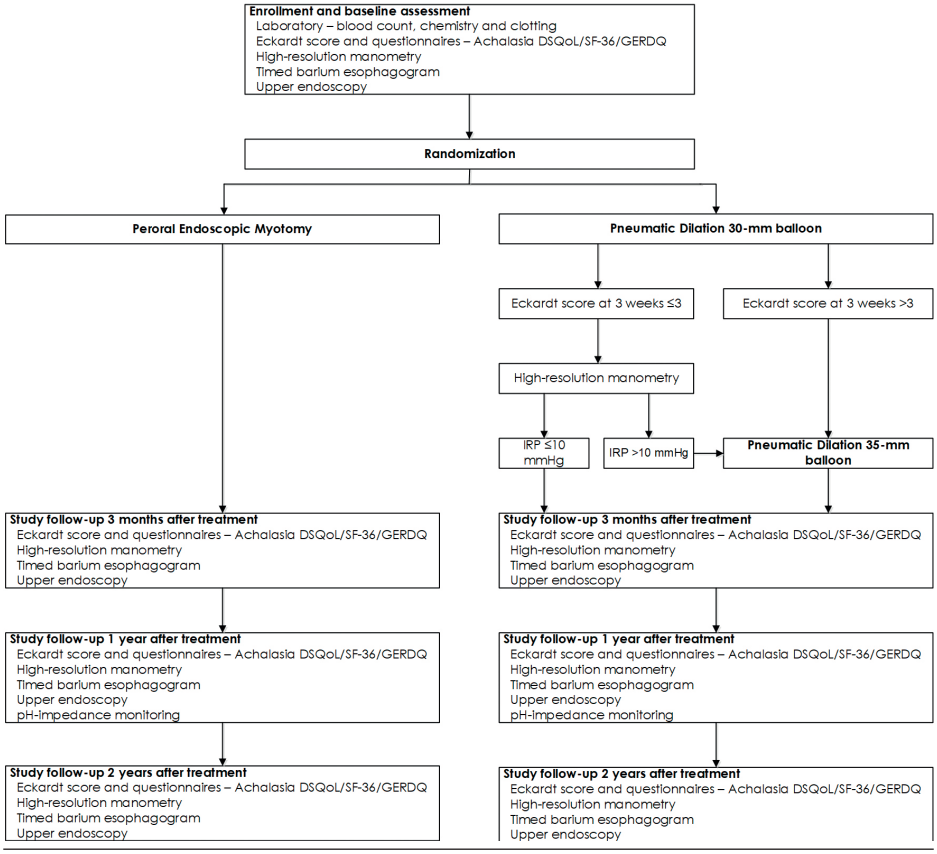
SF-36 (median (IQR))[d]	53.5 (49.1-57.8)	54.2 (51.3-56.8)	0.7 (-1.6, 3)	.38 (1.0)
Physical Component Summary Score	54.4 (50.5-57.7)	53.5 (47.3-56.1)	0.9 (-1.1, 2.9)	.27 (1.0)
Mental Component Summary Score				
Endoscopic reflux esophagitis (n and % (SD))	29/59 49 (6.5)	4/36 11 (5.2)	38 (17, 53)	<.001 (<.001)
Grade A (n (%))	15 (26)	1 (3)		
Grade B (n (%))	9 (15)	3 (8)		
Grade C (n (%))	3 (5)	0 (0)		
Grade D (n (%))	2 (3)	0 (0)		
PPI use (n and % (SD))	14/61 23 (5.4)	6/42 14 (5.4)	9 (-8, 24)	.28 (.98)
Reflux esophagitis (n (%))	8 (57)	1 (17)		
No reflux esophagitis (n (%))	6 (43)	5 (83)		

Data are presented as numbers (n), percentages (SD), median (IQR) or absolute difference (95% CI).
* Absolute difference of the median or proportion **Mann-Whitney or Chi-square. ***P adjusted for multiple comparison.
[a]Eckardt score: achalasia symptoms, range 0-12, highest score indicated most pronounced symptoms.
[b]Achalasia-DSQoL: quality of life related to achalasia, range 10-33, lower score indicated better quality of life.
[c]GERD-Q: gastroesophageal reflux disease, range 0-18, score ≥8 was highly suggestive for presence of GERD.
[d]SF-36: general quality of life consisted of Physical Component Summary Score, range 0-100, and Mental Component Summary Score, range 0-100, higher score indicated better quality of life.

eTable 4. Logistic regression analysis of the primary outcome (treatment success) in relation to treatment, subtype and treatment x subtype interaction.

Primary outcome 2-year follow-up	**Adjusted odds ratio (95% CI)**	***P***
Treatment[a]	22.2 (4.69-105.4)	<.001
Achalasia subtype		
Subtype I	2.41 (0.76-7.65)	.33
Subtype II[b]	1.0	.14
Subtype III	1.1 (0.20-6.22)	.91
Achalasia subtype x POEM		
Subtype I	0.19 (0.01-2.96)	.35
Subtype II[b]	1.0	.23
Subtype III	0.20 (0.01-3.04)	.25

[a]Pneumodilation served as the reference category
[b]Served as the reference category.



eFigure 1. Treatment and study follow-up algorithm for POEM and pneumodilation.

After the first pneumodilation with a 30-mm balloon the effect was evaluated by the Eckardt score at 3 weeks. A second pneumodilation with a 35-mm balloon was performed in case the Eckardt score was >3 or ≤3 with an IRP >10 mmHg.

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Challenges of peroral endoscopic myotomy in the treatment of distal esophageal spasm

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ABSTRACT

Objective

Distal esophageal spasm (DES) is a rare motility disorder characterized by premature and rapidly propagated contractions of the distal esophagus. Treatment options are limited and often poorly effective. Peroral endoscopic myotomy (POEM) seems an effective and attractive new treatment option for DES. In this case report we describe some of the difficulties that could arise.

Materials and methods

A 84-year old man with therapy-refractory DES and complaints of severe dysphagia and chest pain underwent a POEM procedure under general anesthesia. A longer myotomy was performed to cleave the circular muscle layer from start till end of the spastic contractions.

Results

The length of the myotomy was 16 cm. Hyperactive spastic contractions during the procedure complicated the creation of the submucosal tunnel, extended the duration (134 minutes vs 60-90 minutes for achalasia), increased postoperative pain and prolonged hospital admission. Intravenously nitroglycerin peroperative diminished spastic contractions. Postoperative a remnant of spastic contractions was present, proximal to the myotomy, causing persistent symptoms.

Conclusion

Performing POEM for DES is challenging due to reactive hyperactive spastic contractions during the procedure causing technical difficulties and an extended procedure. A long myotomy, several centimeters above the proximal border of the spastic region, is essential to prevent remnants of spasticity.

INTRODUCTION

Distal esophageal spasm (DES) is a rare motility disorder associated with dysphagia and chest pain.[1, 2] It is characterized by premature and rapidly propagated contractions of the smooth muscle in the distal esophagus. High-resolution manometry (HRM) is the gold standard to diagnose DES reflected by a reduced distal latency (premature contraction) and spastic contractions.[3] Treatment of DES remains challenging because the treatment options are limited, poorly effective or have a transient effect. Here we describe a case of an 84-year old man with DES refractory to conventional therapy who was treated with peroral endoscopic myotomy (POEM). POEM is a promising, effective and permanent treatment for DES, however in this case we highlight some of the difficulties that could arise.

Case and procedure

An 84-year old man was referred for dysphagia for solids and liquids, occasional regurgitation and episodic chest pain for many years. There was no weight loss. He had a history of pure sensory stroke without permanent damage, hypercholesterolemia, ACTH deficiency resulting in hyponatremia and hypoglycemia treated with hydrocortisone. Furthermore he was taking acetylsalicylic acid, simvastatin, dipyridamole, pantoprazole and vitamin D. Seven months before referral an upper endoscopy showed no abnormalities of the esophagus and biopsies were negative for eosinophilic esophagitis. Conventional manometry revealed simultaneous high-amplitude contractions and normal relaxation of the lower esophageal sphincter (LES).[4] DES was diagnosed. After failure of treatment with nifedipine, sublingual nitroglycerin, proton pump inhibitors and endoscopic botulinum toxin injections the patient was referred to our center. The Eckardt score (symptom score assessing dysphagia, regurgitation, chest pain and weight loss in achalasia) was five.[5] HRM revealed simultaneous, hypertensive and distally repetitive contractions with a normal LES relaxation (integrated relaxation pressure (IRP) of 8.3 mmHg) and distal latency of 3 seconds, compatible with DES (**figure 1a**). A barium esophagogram showed delayed passage of barium contrast along the entire esophagus with tertiary, spastic contractions, resembling a corkscrew (**figure 1b**). POEM was purposed and the patient gave informed consent for this procedure. The procedure and follow-up was performed according to the Declaration of Helsinki.

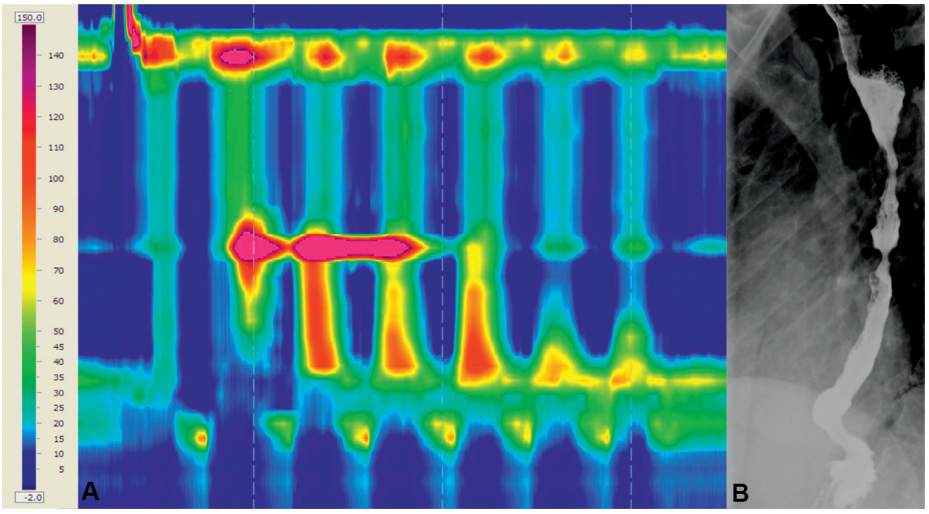

Figure 1. High-resolution manometry (A) and barium esophagogram (B) before treatment. The high-resolution manometry (HRM) shows simultaneous, hypertensive and distally repetitive contractions after a swallow with a normal LES relaxation (integrated relaxation pressure (IRP) of 8.3 mmHg) and distal latency of three seconds typical for DES. On the barium esophagogram tertiary, spastic contractions are seen, resembling a corkscrew and passage of barium contrast is delayed.

POEM, as described by Inoue et al, was performed under general anaesthesia.[6] It was decided to perform a longer myotomy of the circular muscle layer than usual and the mucosal entry was made more proximal, 19 cm above the esophagogastric junction. The myotomy was started 3 cm below the mucosal entry with a total length of 16 cm, 14 cm in the esophagus and 2 cm in the stomach. Hyperactive spastic contractions during the procedure complicated the creation of the submucosal tunnel and made the duration of the procedure longer (134 minutes vs 60-90 minutes for achalasia). Therefore, 0.9 mg nitroglycerin (in total) was given intravenously which diminished the spastic contractions. A pneumoperitoneum was effectively desufflated. Postoperatively the patient experienced retrosternal pain which was treated by paracetamol, metamizol and morphine. The water-soluble contrast radiograph of the esophagus the next morning showed a stenosis proximal of the incision with a prestenotic dilation which was attributed to edema and spasm (**figure 2**). This was associated with severe dysphagia. The dysphagia improved two days after the procedure and the patient was discharged. At three months follow-up the symptoms of the patient had improved further, resulting in an Eckardt score of two. However, the patient still experienced dysphagia and occasional episodes of non-passage. HRM demonstrated that proximal to the myotomy a small segment with hypertensive and spastic contractions was still present (**figure 3a**). The barium esophagogram showed a proximal prestenotic dilation

(**figure 3b**). No further treatment was performed because the symptoms were acceptable for the patient.

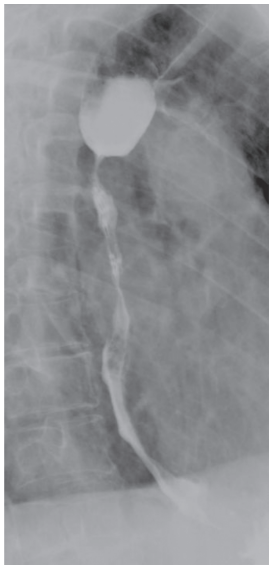

Figure 2. Radiograph with water-soluble contrast one day after POEM procedure. It demonstrates a stenosis proximal of the incision with a prestenotic dilation which is attributed to edema and spasm and caused severe dysphagia for the patient.

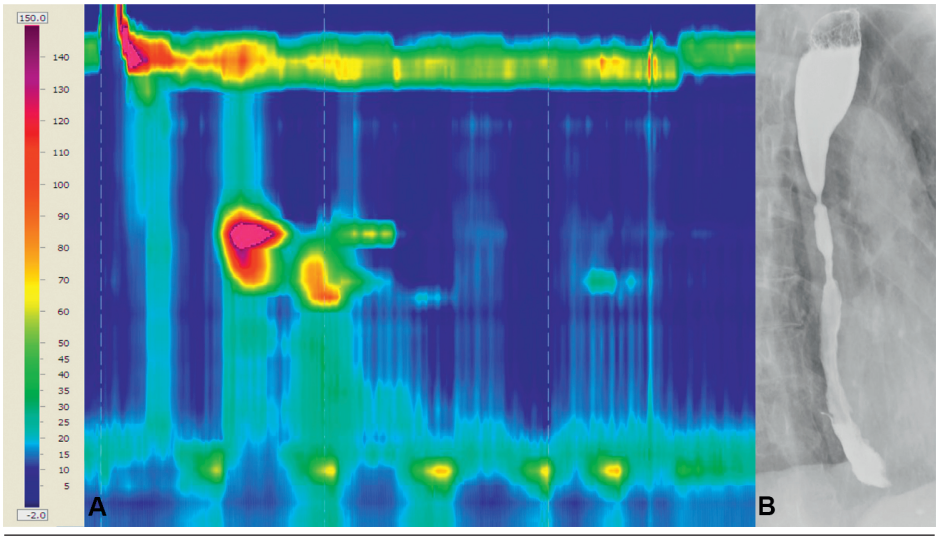

Figure 3. High-resolution manometry (A) and barium esophagogram (B) three months after POEM procedure. Proximal to the myotomy a small segment with hypertensive and spastic contractions is still present on the high-resolution manometry. The barium esophagogram confirms this by showing a proximal prestenotic dilation. These findings explain the cause of high dysphagia the patient still experienced after treatment.

DISCUSSION

The premature and rapidly propagated contractions in DES are caused by the impairment of esophageal inhibitory neural function. Treatment is challenging and in many patients medical treatment is insufficient. POEM has been introduced for achalasia treatment as a less invasive alternative to Heller myotomy.[6,7] For DES, POEM has the advantage over laparoscopic Heller myotomy that the myotomy can be more extended, also cleaving the circular muscles in the mid and proximal esophagus.[8-10] However, this case shows that POEM for DES can be challenging and we have learned two lessons. First, reactive spastic contractions during and after the procedure may complicate execution of the technique and lengthen the procedure, increase post-operative pain and prolong hospital admission. Nitroglycerin during the procedure can be helpful. Second, the myotomy should start more proximally than usual, at least several centimeters above the proximal border of the spastic region. Otherwise a remnant of spastic contractions proximal to the myotomy will remain, causing persistent symptoms. HRM can be helpful for guidance. A recent systematic review and meta-analysis on POEM for spastic esophageal disorders which included achalasia type III, distal esophageal spasm and hypercontractile (Jackhammer) esophagus, revealed that POEM is a safe and highly effective treatment for this type of disorders.[11] The tailored procedure with an extended myotomy is a major advantage over other therapeutic options for DES. Based on the literature and our experience we conclude that POEM is a promising treatment for patients with therapy-refractory DES, however the above described caveats should be taken into account.

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Part III
Long-term follow-up

Reflux symptoms and oesophageal acidification in treated achalasia patients are often not reflux related

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ABSTRACT

Objective

After treatment, achalasia patients often develop reflux symptoms. Aim of this case-control study was to investigate mechanisms underlying reflux symptoms in treated achalasia patients by analysing oesophageal function, acidification patterns and symptom perception.

Design

Forty treated achalasia patients (mean age 52.9 years; 27 (68%) men) were included, 20 patients with reflux symptoms (RS+; Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) ≥8) and 20 without reflux symptoms (RS-: GORDQ <8). Patients underwent measurements of oesophagogastric junction distensibility, high-resolution manometry, timed barium oesophagogram, 24-hour pH-impedance monitoring off acid-suppression and oesophageal perception for acid perfusion and distension. Presence of oesophagitis was assessed endoscopically.

Results

Total acid exposure time during 24-hour pH-impedance was not significantly different between patients with (RS+) and without (RS-) reflux symptoms. In RS+ patients, acid fermentation was higher than in RS- patients (RS+: mean 6.6% (95% CI: 2.96 to 10.2%) versus RS-: 1.8% (95% CI: -0.45 to 4.1%, *P*=.03) as well as acid reflux with delayed clearance (RS+: 6% (95% CI:0.94 to 11%) versus RS-:3.4% (95% CI: -0.34 to 7.18%), *P*=.051). Reflux symptoms were not related to acid in both groups, reflected by a low Symptom Index. RS+ patients were highly hypersensitive to acid, with a much shorter time to heartburn perception (RS+: 4 (2-6) versus RS-: 30 (14-30) min, *P*<0.001) and a much higher symptom intensity (RS+: 7 (4.8-9) versus RS-: 0.5 (0-4.5) Visual Analogue Scale, *P*<.001) during acid perfusion. They also had a lower threshold for mechanical stimulation.

Conclusion

Reflux symptoms in treated achalasia are rarely caused by gastro-oesophageal reflux and most instances of oesophageal acidification are not-reflux related. Instead, achalasia patients with post-treatment reflux symptoms demonstrate oesophageal hypersensitivity to chemical and mechanical stimuli, which may determine symptom generation.

INTRODUCTION

Achalasia and gastro-oesophageal reflux disease (GORD) represent opposite ends of the spectrum of oesophagogastric junction (OGJ) dysfunction. Achalasia is a rare oesophageal motility disorder characterized by absent peristalsis of the oesophageal body and impaired relaxation of the lower oesophageal sphincter (LOS), which hampers oesophageal emptying. GORD is one of most common gastrointestinal disorders worldwide and is the result of an unusually weak OGJ which induces retrograde flow of gastric content into the oesophagus resulting into troublesome symptoms and/or mucosal damage.[1] Treatment of achalasia focuses on symptom relief achieved by disruption of the LOS, compromising the OGJ barrier against reflux. Post-treatment, the prevalence of reflux symptoms and/or reflux oesophagitis in achalasia patients varies between 5 and 60%.[2–6] The variability in reflux prevalence is related to the definition and measurement of reflux and to the type of treatment, since there is a higher rate of reflux symptoms after laparoscopic or endoscopic myotomy without fundoplication compared to pneumodilation or myotomy with fundoplication.[2–9] Studies in these patients showed that reflux symptoms, pH monitoring and/or reflux oesophagitis in post-treatment achalasia patients correlate poorly.[10–15] True reflux as the cause of reflux symptoms was inconsistently observed. Nevertheless, it is common practice to consider reflux symptom of treated achalasia patients as GORD and start proton pump inhibitors (PPI), which has variable efficacy. The underlying mechanisms of these symptoms are thus poorly investigated, which hampers adequate and tailored treatment. Therefore, the aim of this study was to thoroughly investigate the mechanisms underlying reflux symptoms in treated achalasia by analysing oesophageal function, acid exposure, acidification patterns, symptom perception and reflux oesophagitis.

MATERIALS AND METHODS

Study subjects and inclusion criteria

In this prospective observational case-control study, treated adult (≥ 18 years) achalasia patients visiting the outpatient clinic of the Gastroenterology and Hepatology Department of the Amsterdam UMC were approached to participate in the study. Patients were allocated into two groups depending on whether or not reflux symptoms were present. Treated achalasia patients with a total score of ≥8 on the Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) were classified as having reflux symptoms (RS+) and a score ≤8 as without reflux symptoms (RS-).[16,17] The GORDQ is a widely used, validated, 6-item self-report questionnaire, evaluating reflux symptoms (heartburn, regurgitation and chest pain), sleep disturbance by reflux and antacid use, range per item 0-3 with a minimum total score of 0 and a maximum score of 18.[16,17] The GORDQ was completed whilst the patients were off acid suppression. All included achalasia patients were ≥6 months post-treatment and in clinical remission for achalasia,

defined as an Eckardt score ≤3. The Eckardt symptom score assesses the severity of achalasia symptoms by the sum of symptom frequency scores for dysphagia, regurgitation and chest pain (range 0-3: 0: absent; 1: occasionally; 2: daily; 3: every meal) combined with a weight loss score (range 0-3: 0: no weight loss; 1: <5 kg weight loss; 2: 5-10 kg weight loss; 3: >10 kg weight loss) resulting in a minimum score of 0 until a maximum score, indicating most pronounced symptoms, of 12.[18] In all patients, the diagnosis of achalasia was previously confirmed by oesophageal manometry before treatment, showing absent peristalsis and impaired LOS relaxation. Treatment consisted of endoscopic pneumodilation, laparoscopic Heller's myotomy with Dor fundoplication 180° and/or peroral endoscopic myotomy (POEM). Pneumodilations started with a 30-mm balloon, followed by a 35-mm balloon and in case of persistent symptoms a 40-mm balloon was used. Detailed eligibility criteria are provided in the study protocol (online supplementary 1 and 2).

The study was registered in the Dutch trial registry before the start of the study (NTR3838, trialregister.nl). Written informed consent was obtained from all patients before study participation. Normal values for acid sensitivity in healthy subjects were obtained in a previous study.[19]

Study protocol

Measurements were performed on two subsequent days after cessation of PPI, H2-receptor antagonists and/or prokinetic medication for 1 week (figure 1). Baseline data and questionnaires (Eckardt score, GORDQ, Reflux Disease Questionnaire (RDQ), Achalasia Disease-Specific Quality-of-Life questionnaire (Achalasia-DSQoL) and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)) were assessed before the measurements.[20,21] One day before the measurements, patients were restricted to a liquid diet, followed by an overnight fast to minimize possible oesophageal stasis. **Figure 1** displays the study protocol with the subsequent measurements that were performed during two study days including time intervals. On the first day, the distensibility of the OGJ was measured and oesophageal sensitivity for a mechanical stimulus was assessed (using EndoFLIP (Endo Functional Luminal Imaging Probe)), and stationary high-resolution manometry (HRM), acid perfusion test and a prolonged combined HRM and pH-impedance monitoring were performed. Thereafter the patients were dismissed, fitted with equipment for 24-hour ambulatory pH-impedance measurement. The next day, the 24-hour reflux monitoring was terminated and a timed barium oesophagogram was performed. Oesophagogastroduodenoscopy was not part of the protocol but in all patients performed off acid suppression as part of routine clinical practice before study participation. All measurements were analysed in a blinded fashion by the investigators.

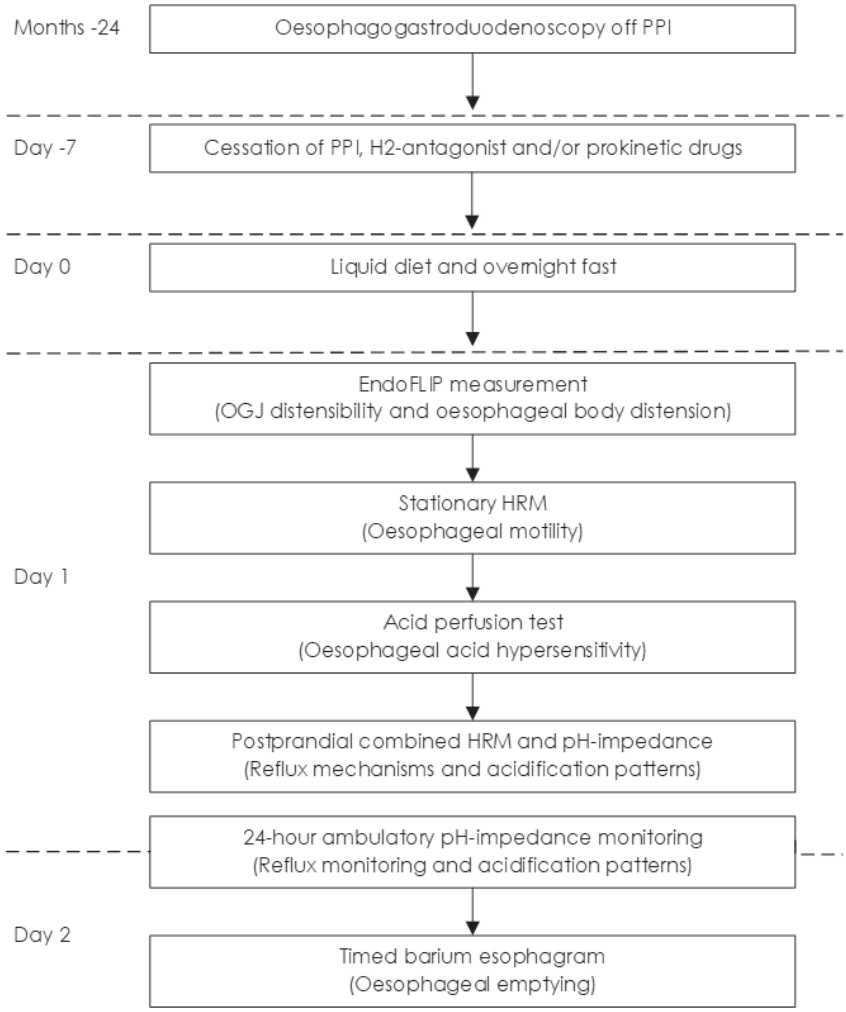

Figure 1. Study protocol.

Abbreviations: EndoFLIP, Endo Functional Luminal Imaging Probe; HRM, high-resolution manometry; OGJ, oesophagogastric junction; PPI, proton pump inhibitors.

OGJ distensibility measurement and assessment of perception of oesophageal distension

To measure OGJ distensibility the Endo Functional Luminal Imaging Probe (EndoFLIP, Medtronic, Sunnyvale, California, USA) was used. By the use of impedance planimetry, EndoFLIP measures cross-sectional areas in the alimentary tract.[22] Description of the EndoFLIP and the protocol to measure OGJ distensibility was previously described.[23] The OGJ distensibility was determined at the 50 mL volume by dividing the median minimal cross-

sectional area, reflecting the OGJ, by the median intrabag pressure during the complete recording period, expressed as mm^2/mmHg.

After measuring OGJ distensibility, the catheter was placed 10 cm above the OGJ to evaluate perception of oesophageal distension. The EndoFLIP bag was inflated from 20 to 70 mL, with a 10 mL increase of volume each minute. After each inflation, patients were asked to notify their first perception of the mechanical stimulus and to score the intensity of their perception on a Visual Analogue Scale (VAS), a horizontal 100-mm line marked with 'no pain' and 'most extreme pain'.

High-resolution manometry

HRM was performed using a 22-channel water-perfused catheter (Laborie, Williston, Vermont, USA) with an incorporated infusion channel until the end of the catheter. The proximal, first 15 channels were spaced at 2-cm intervals, followed by 6 channels at 1-cm intervals for measuring the LOS and the last channel at the end of the catheter to measure gastric pressure. The catheter was introduced transnasally and positioned to measure from hypopharynx to stomach. Following a standardized protocol, patients were placed in supine position (20°) and received 10 boluses of 5 mL water with an interval of 20 seconds. Prior and subsequently to the swallows, a period of 30 seconds not swallowing was assessed for baseline measures. Manometric signals were recorded with a frequency of 20 Hz. The HRM studies were analysed by dedicated software (Laborie, Williston, Vermont, USA), according to the Chicago classification V.3, adjusted for water-perfused values.[24,25] The following key oesophageal pressure topography metrics were assessed: OGJ basal pressure at end-expiration, the 4-s integrated relaxation pressure (IRP), distal contractile integral, distal latency, peristaltic integrity using the 20 mmHg isobaric contour and intrabolus pressure pattern with ≥30 mmHg isobaric contour.[24,26] OGJ/LOS pressure was referenced to gastric pressure and oesophageal contraction metrics to atmospheric pressure.[24,26]

Acid perfusion test

An acid perfusion test was performed according to a previously described protocol.[19] The water-perfused HRM catheter was used with the incorporated infusion channel 6 cm above the OGJ. Patients were in semi-recumbent position. After an adaptation period of 10 minutes, perfusion with a neutral solution (saline, NaCl 0.9% at pH 6.5) was performed for 10 minutes, followed by an acidic solution (0.1 N HCl at pH 1.1) for 30 minutes. The perfusion rate was 8 mL/min. Patients were blinded for the nature of the solutions and unaware of the switch to acid perfusion. The time to first perception of heartburn and time to discomfort were noted. Symptom severity was scored every 2 minutes on a VAS, a horizontal 100-mm line marked with 'no pain' and 'most extreme

pain' labelled at the beginning and end of the line. Perfusion was stopped when symptoms were intolerable. A perfusion sensitivity score was calculated as follows: [(total perfusion time – lag time to perception) x maximum VAS], conform previously described methods.[19,27] Patients with a first perception of heartburn within 20 minutes after acid perfusion were considered increased hypersensitive to acid.[19]

Postprandial stationary HRM and pH-impedance measurement

Combined HRM and pH-impedance monitoring was performed after the acid perfusion test. The pH-impedance catheter consisted of 6 impedance segments and 1 ISFET pH electrode (Unisensor AG, Attikon, Switzerland) and was placed next to the HRM catheter, with the pH electrode 5 cm above the upper border of the LOS. The impedance segments were located at 2-4, 4-6, 6-8, 8-10, 14-16 and 16-18 cm above the upper border of the LOS. A second pH catheter without impedance electrodes was placed 10 cm above the upper border of the LOS to detect the proximal extent of reflux or acidification beside the impedance measurement. Low distal baseline impedance tracings could prevent adequate detection of proximal acid exposure. Impedance (50 Hz), pH and pressure (20 Hz) signals were recorded and stored on a computer with dedicated software (Laborie, Williston, Vermont, USA). After an adaptation period of 30 minutes, intragastric infusion of a standardized high-caloric liquid meal, 250 mL nutrient drink (600 kcal, 18 g protein, Nutridrink Compact Protein, Nutricia, Zoetermeer, The Netherlands) diluted by 150 mL water, was started. For the perfusion the incorporated infusion channel of the HRM catheter was used with a perfusion rate of 13 ml/min during 30 min. This was followed by a postprandial measurement during 120 minutes. Impedance and pH tracings were analysed for acid patterns (see definitions below), acid exposure time (percentage of time pH <4), occurrence of reflux episodes according to previously described criteria and discriminating reflux from fermentation.[28,29] Combined HRM and pH-impedance monitoring was used to detect mechanisms of acid exposure (e.g. swallow induced, transient LOS relaxation) and clearance.

Twenty-four-hour ambulatory pH-impedance monitoring

After the combined HRM and pH-impedance monitoring, the HRM and single pH catheter were removed. The pH-impedance catheter stayed in place and was used for a 24-hour ambulatory measurement. The catheter was connected to a digital data logger (Laborie, Williston, Vermont, USA) to store pH and impedance signals at a frequency of 50 Hz. During the measurement, patients were instructed to consume meals and drinks at fixed times during the day and report symptoms in a diary. Analysing the ambulatory pH-impedance measurements, we distinguished five different acidification patterns: A) acid reflux with normal clearance: rapid pH drop to below 4, drop rate ≥1 pH unit

per second, lasting between 10 seconds and 5 minutes[28,29]; B) acid reflux with delayed clearance: rapid pH drop to below 4, drop rate ≥1 pH unit per second, lasting longer than 5 minutes; C) acid fermentation: slow pH drop to below 4, drop rate <1 pH unit per minute, lasting longer than 5 minutes; D) stasis of recently ingested acidic food or drink: pH drop to below 4 during meal/drink, persisting longer than 5 minutes after meal/drink; E) unclassified: pH drop to below 4 not meeting criteria for any of the acid patterns described above (**figure 2**). Low distal baseline impedance levels prevented the use of impedance for defining the observed acidification patterns. Impedance was used to identify prolonged acidification by further decrease of impedance levels (distal and proximal), clearance of acidification and air trapping. All acid episodes (pH < 4) were analysed according to the predefined acidification patterns. Total acid exposure time, percentage of time pH <4, during the complete measurement and in upright and supine position were assessed. An acid exposure time >6% was considered pathological.[29] The correlation between symptoms and acid patterns was analysed, with a positive correlation when symptoms were notified within 2 minutes from the start of the acid pattern. The Symptom Index (SI) was calculated by the number of symptoms associated with reflux as a percentage of the total number of symptoms. The optimal SI threshold was set at ≥50% of reported reflux symptoms.[27] The symptom association probability was not calculated because in patients with achalasia the number of total acid reflux episodes cannot be determined reliably. Baseline impedance levels were measured every two hours in the proximal channel at 17 cm above the LOS and in the most distal channel at 3 cm above the LOS, as previously described.[30] A 30-second time window was selected to calculate the baseline impedance by averaging the raw impedance values during this time period. The median values for proximal and distal impedance levels were calculated for the 24-hour measurement based on the 2 hours data.

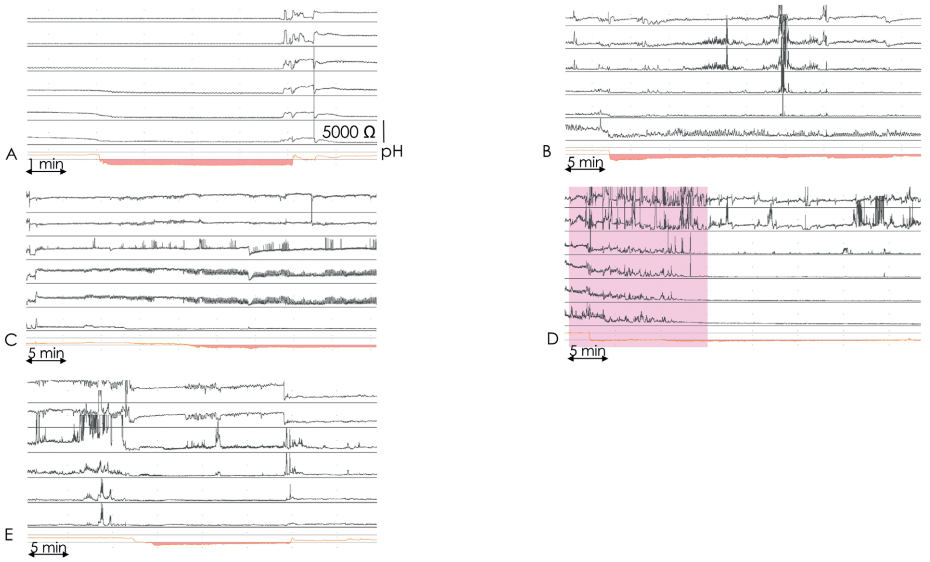

Figure 2. Oesophageal acidification patterns observed during pH-impedance monitoring.
A. Acid reflux with normal clearance: rapid pH drop to below 4, drop rate ≥1 pH unit per second, lasting between 10 seconds and 5 minutes.
B. Acid reflux with delayed clearance: rapid pH drop to below 4, drop rate ≥1 pH unit per second, lasting longer than 5 minutes.
C. Acid fermentation: slow pH drop to below 4, drop rate <1 pH unit per minute, lasting longer than 5 minutes.
D. Stasis of recently ingested acidic food or drink: pH drop to below 4 during meal/drink, pH below 4 persisting longer than 5 minutes after meal/drink. The pink-coloured area indicates meal/drink ingestion.
E. unclassified: pH drop to below 4 not meeting criteria for any of the acid patterns described above.

Timed barium oesophagogram and oesophagogastroduodenoscopy

A timed barium oesophagogram was performed on the second day, after the 24-hour pH-impedance monitoring. Patients were instructed to ingest a maximal tolerable amount of low density barium sulphate suspension up to 200 mL within 30-60 seconds in an upright, slight left posterior oblique position.[31] Radiographs were taken at 0, 1, 2 and 5 minutes after ingestion of the suspension.[31] To evaluate oesophageal emptying the barium column height at 5 minutes was measured from the OGJ to the top of the barium column in centimetres. Adequate oesophageal emptying was defined as ≤1 cm barium column height at 5 minutes. The maximal oesophageal diameter was measured by the oesophageal width at 5 minutes.

All patients had undergone an oesophagogastroduodenoscopy off PPI within 24 months before study participation. Severity of reflux oesophagitis was scored according to the Los Angeles classification.[32]

Statistical analysis

An assumed 45% difference in objectified reflux episodes, between reflux symptomatic and asymptomatic treated achalasia patients, was hypothesized for the purpose of sample size calculations. With 19 patients in each group, the study would have 80% power to detect significant differences in outcome parameters that could give insight in the underlying mechanism of reflux symptoms. To compensate for technical failures, the aim was to enrol 20 patients per group, with a 1:1 allocation per group based on treatment type and gender.

Continuous data are presented as mean (SD or 95% CI) or median (IQR), according to distribution. Categorical data are presented as percentages. Continuous data were compared by unpaired Student's t-test and one-way analysis of variance or Mann-Whitney U-test and Kruskal-Wallis, according to distribution. Categorical data were analysed by Chi-square and Fisher's exact test. Relationships between parameters were analysed by linear regression analysis, (Pearson's or Spearman's correlation, r) or logistic regression analysis (OR with 95% CI). The time to perception during the acid perfusion test, was compared by the log rank test on Kaplan-Meier curves. A subgroup analysis of the outcome parameters of 24-hour pH-impedance, oesophagogastroduodenoscopy and provocation tests was also performed per treatment, laparoscopic Heller's myotomy versus POEM. For both treatments, patients primarily treated by Heller's myotomy or POEM were taken together with patients who failed on pneumodilation and retreated by Heller's myotomy or POEM. Differences were considered statistically significant when $P<.05$. All reported p-values are two tailed. Statistical analysis was performed using IBM SPSS Statistics V.24 (IBM Corporation, Armonk, NY, United States).

Patient and public involvement

Patient involvement started at study inclusion. Patients assessed the burden of the study and gave feedback for adjustments on the study design for further studies. Patients were not involved in development of the research question, outcome measures or study design. Patients' personal results of the measurements were shared on request. After publication, the article will be disseminated to all study participants and shared on the Dutch achalasia patient Facebook page.

RESULTS

Patient characteristics

In total, 40 previously treated patients (mean age 52.9 years; 27 (68%) men) were included between March 2013 and December 2015, of whom 38 completed the study. Two patients failed to complete the study; one due to intolerance of the two catheters during prolonged stationary HRM/pH-impedance monitoring

and the other because OGJ passage by HRM catheter did not succeed despite multiple attempts. The patient characteristics are shown in **table 1**. Age, body mass index, treatment type and Eckardt score were similar between the groups with (RS+) and without (RS-) reflux symptoms. The duration of PPI use since first prescription was significantly longer in patients with reflux symptoms, with a median period of 41 (19-82) months.

Table 1. Baseline characteristics of treated achalasia patients with (RS+) and without reflux symptoms (RS-).

	Patients with reflux symptoms (RS+) (n=19)	**Patients without reflux symptoms (RS-) (n=19)**	***P***
Sex (n (%))			.73
Male	11 (63)	12 (68)	
Female	8 (37)	7 (32)	
Age (years; mean (SD))	53.8 (13)	52.7 (13.5)	.80
BMI (kg/m^2; mean (SD))	25.7 (4.5)	25.7 (3.1)	.94
Achalasia subtypes at diagnosis (n (%))			.39
Type I	8 (42)	5 (26)	
Type II	10 (53)	13 (69)	
Type III	1 (5)	1 (5)	
Disease duration (years; (mean (SD))	7.8 (6.9)	8.3 (6.3)	.81
Eckardt score (median (IQR))	2 (1-3)	2 (1-2)	.43
GORDQ (median (IQR))[§]	11 (11-13)	6 (6-7)	<.001
Achalasia treatment (n (%))			.5
Pneumodilation[#]	1 (5)	1 (5)	
Laparoscopic Heller's myotomy	5 (26)	4 (21)	
Peroral endoscopic myotomy	5 (26)	6 (32)	
Pneumodilation* and laparoscopic Heller's myotomy	6 (32)	5 (26)	
Pneumodilation* and peroral endoscopic myotomy	2 (11)	3 (16)	
PPI use (n (%))	19 (100)	4 (21)	<.001
Time PPI use post-treatment (months; (median (IQR))	41 (19-82)	0 (0-4)	<.001

Abbreviations: BMI, body mass index; IQR, interquartile range; PPI, proton pump inhibitor; SD, standard deviation.
[§]GORD-Q: gastro-oesophageal reflux disease questionnaire, range 0-18, score ≥8 was highly suggestive for presence of GORD.
[#]Pneumodilation up till 35-mm balloon.
*Pneumodilation up till 40-mm balloon.

Ambulatory 24-hour pH-impedance monitoring

An overview of the outcome parameters during the 24-hour ambulatory pH-impedance monitoring is shown in **table 2**. Surprisingly, no significant differences between the RS+ and RS- groups were observed in total, upright or supine acid exposure, nor in percentage of patients with pathological acid exposure. In 16% (3/19) of RS+ and in 26% (5/19) of RS- achalasia patients acid exposure was completely absent (*P*=.43).

Episodes of acid reflux with normal clearance were rare in both groups (RS+: median 1 (0-2) versus RS-: 0 (0-1), *P*=.11; **table 2**). RS+ achalasia patients had significantly more episodes of acid fermentation and unclassified acidification compared to RS- achalasia patients (**table 2**). In RS+ achalasia patients, acidification was more often due to acid fermentation compared to those without reflux symptoms (RS+: mean 6.6%, 95% CI 3.0% to 10.2% versus RS-: 1.8%, 95% CI -0.45% to 4.1%; *P*=.03) and acid reflux with delayed clearance was also more often seen in these patients (RS+: mean 6%, 95% CI 0.94% to 11.0% versus RS-: 3.4%, 95% CI -0.34% to 7.2%, *P*=.051; **table 2**). In RS- achalasia patients, the dominant acidification pattern was stasis of ingested acidic food or drink (RS+: 2.3%, 95% CI -0.04% to 4.6% versus RS-: mean 7.6%, 95% CI -0.12% to 15.3%; *P* =.18; **table 2**).

During 24-hour pH-impedance monitoring the total number of reported reflux symptoms for all patients in the RS+ group was 84, compared to 7 symptom episodes in the RS- group (RS+: median symptoms per patient 4 (3-5) versus RS-: 0 (0-2), *P*<.001). Not a single patient had a SI of ≥50%, indicating poor specificity of their symptoms for acidification events. In the RS+ group, symptoms with a positive association were related to acid reflux with delayed clearance. All symptoms in the RS- group had a negative symptom correlation. No difference in baseline impedance levels was observed between the RS+ and RS- groups (**table 2**).

Table 2. Outcome of 24-hour pH-impedance monitoring of treated achalasia patients with (RS+) and without reflux symptoms (RS-).

	Patients with reflux symptoms (RS+) (n=19)	**Patients without reflux symptoms (RS-) (n=19)**	***P***
24-hour pH-impedance monitoring			
Acid exposure time (AET: % of time pH <4; mean (95% CI))			
Total	13.8 (6.7 to 20.9)	10.9 (4.4 to 17.3)	.53
Upright	10.9 (4.4 to 17.4)	6.6 (2.6 to 10.6)	.24
Supine	17.7 (7.9 to 27.5)	16.4 (4.1 to 28.8)	.86
Pathological acid exposure (AET pH <4 in >6%; n (%))	14 (74)	10 (53)	.18
Acidification patterns (% of time; mean (95% CI))			
Acid reflux with normal clearance	0.2 (0.06 to 0.28)	0.09 (0.01 to 0.16)	.39
Acid reflux with delayed clearance	6 (0.94 to 11.0)	3.4 (-0.34 to 7.18)	.051
Acid fermentation	6.6 (2.96 to 10.2)	1.8 (-0.45 to 4.10)	.03
Stasis of ingested acidic food	2.2 (-0.04 to 4.55)	7.6 (-0.13 to 15.3)	.18
Unclassified	1.8 (-0.49 to 4.11)	0.01 (-0.02 to 0.04)	.11
Number of acidification events (median (IQR))			
Acid reflux with normal clearance	1 (0-2)	0 (0-1)	.11
Acid reflux with delayed clearance	1 (0-3)	0 (0-1)	.07
Acid fermentation	1 (0-3)	0 (0-0)	.002
Stasis of ingested acidic food	0 (0-1)	0 (0-2)	.54
Unclassified	0 (0-1)	0 (0-0)	.008
Number of patients per acidification pattern (n (%))			
Acid reflux with normal clearance	10 (53)	5 (26)	.10
Acid reflux with delayed clearance	12 (63)	6 (32)	.051
Acid fermentation	13 (68)	4 (21)	.004
Stasis of ingested acidic food	6 (32)	8 (42)	.50
Unclassified	8 (42)	2 (11)	.03
Number of symptoms (median (IQR))	4 (3-5)	0 (0-2)	<.001
Baseline impedance (Ω; median (IQR))			
Proximal	2327 (1853-2836)	2638 (1659-3108)	.93
Distal	487 (69-696)	476 (338-741)	0.84

Abbreviations: AET, acid exposure time; IQR, interquartile range; CI, confidence interval.

Postprandial stationary HRM and pH-impedance measurement

The postprandial HRM and pH-impedance measurement revealed no difference in acid exposure or acidification patterns between RS+ and RS- achalasia patients (**table 3**). Only 18% (n=7/38) of all patients had acid exposure at all during the 2-hour postprandial measurement. In these patients (RS+: n=5 versus RS-: n=2), acid exposure was due to acid reflux with normal or delayed clearance. Prolonged acidification was only seen in two patients, one patient in each group. None of the reflux episodes were detected by the proximal pH probe. Low baseline impedance tracings prevented exact localisation of the proximal extent of each reflux episode, based on the position of the proximal pH probe is was at least below 10 cm. The main mechanism associated with these reflux episodes was swallow-induced reflux in both groups. Transient LOS relaxations

were not observed at all. In both groups, none of the reported symptoms during the 2-hour postprandial measurement were related to reflux or acid exposure.

Table 3. Outcome of postprandial combined HRM and pH-impedance monitoring of treated achalasia patients with (RS+) and without reflux symptoms (RS-).

	Patients with reflux symptoms (RS+) (n=19)	**Patients without reflux symptoms (RS-) (n=19)**	***P***
Postprandial combined HRM and pH-impedance measurement			
Presence acid exposure (n (%))	5/19 (26)	2/19 (11)	.41
Acid exposure time (AET: % of time pH <4; mean (95% CI)	1.9 (-1.06 to 4.85)	2.6 (-2.67 to 7.87)	.81
Acidification patterns (% of time; mean (95% CI))			
Acid reflux with normal clearance	0.3 (-0.06 to 0.78)	0 (0 to 0)	.09
Acid reflux with delayed clearance	1.4 (-1.48 to 4.18)	2.5 (-2.78 to 7.80)	.69
Acid fermentation	0 (0 to 0)	0 (0 to 0)	1.0
Stasis of ingested acidic food	0 (0 to 0)	0 (0 to 0)	1.0
Unclassified	0.2 (-0.21 to 0.60)	0 (0 to 0)	.53
Number of acidification events (median (IQR))			
Acid reflux with normal clearance	0 (0-2)	0 (0-0)	.04
Acid reflux with delayed clearance	0 (0-1)	0 (0-1)	.97
Acid fermentation	0 (0-0)	0 (0-0)	1.0
Stasis of ingested acidic food	0 (0-0)	0 (0-0)	1.0
Unclassified	0 (0-1)	0 (0-1)	.32
Number of patients per acidification pattern (n (%))			
Acid reflux with normal clearance	4 (21)	0 (0)	.04
Acid reflux with delayed clearance	1 (5)	1 (5)	1.0
Acid fermentation	0 (0)	0 (0)	1.0
Stasis of ingested acidic food	0 (0)	0 (0)	1.0
Unclassified	1 (5)	0 (0)	.32
Number of symptoms (median (IQR))	0 (0-1)	0 (0-0)	.02

Abbreviations: AET, acid exposure time; HRM, high-resolution manometry; IQR, interquartile range; CI, confidence interval.

Oesophagogastroduodenoscopy

The presence of reflux oesophagitis during oesophagogastroduodenoscopy was not significantly different between RS+ and RS- achalasia patients (**table 4**). In both groups, the severity of reflux oesophagitis, when present, was classified as grade A or B.

Table 4. Results of oesophageal function tests, endoscopy and questionnaires in treated achalasia patients with (RS+) and without reflux symptoms (RS-).

	Patients with reflux symptoms (RS+) (n=19)	**Patients without reflux symptoms (RS-) (n=19)**	***P***
High-resolution manometry			
Basal LOS pressure (mmHg, median (IQR))	3 (2-6)	3 (3-6)	.88
Integrated relaxation pressure (mmHg, median (IQR))	6.2 (2.1-8.7)	5.9 (4.1-9)	.87
Classification of oesophageal contractility			1.00
Failed contractility (n (%))	13 (68)	13 (68)	
Weak contractility (n (%))	6 (32)	6 (32)	
OGJ distensibility (at 50 mL: mm^2/mmHg, median (IQR))	5.3 (4.5-6.9)	5.3 (4.5-6.9)	.18
Timed barium oesophagogram			
Barium column at 5 min (cm, median (IQR))	1 (0-2)	1.8 (0-2.5)	.34
Barium column at 2 min	1.6 (0-2)	2.4 (1-3.5)	.10
Oesophageal diameter (cm, median (IQR))	2.1 (1.8-3)	2.5 (2-3.4)	.12
Endoscopy			
Reflux oesophagitis (n (%))	10 (53)	4 (21)	.91
Grade A	5/10 (50)	2/4 (50)	
Grade B	5/10 (50)	2/4 (50)	
Questionnaires (median (IQR))			
RDQ total score[§]	1.9 (1.4-3.3)	0.3 (0-0.6)	<.001
Heartburn	3 (2-4.3)	0 (0-1)	<.001
Regurgitation	1 (0.8-2.8)	0 (0-0.3)	<.001
Dyspepsia	1.8 (0-4)	0 (0-0.5)	<.002
GORD	2.1 (1.5-2.8)	0.3 (0-0.8)	<.001
Achalasia-DSQoL[#]	19 (14-22)	13 (12-16)	<.005
SF-36*			
Physical component summary score	51 (46-55)	54 (51-58)	.06
Mental component summary score	57 (53-60)	54 (53-58)	.37

Abbreviations: DSQoL, Disease-Specific Quality of Life questionnaire; GORD, gastro-oesophageal reflux dimension; IQR, interquartile range; LOS, lower oesophageal sphincter; OGJ, oesophagogastric junction; RDQ, reflux disease questionnaire; SF-36, 36-item short-form health survey.
[§]RDQ: reflux disease questionnaire, 12-item questionnaire, providing a score for each typical reflux symptom on a Likert scale, range 0-5. Per domain the mean score was calculated per patient.
[#]Achalasia-DSQoL: quality of life related to achalasia, range 10 to 33, lower score indicated better quality of life.
*SF-36 score consisted of a physical and mental component summary score, each ranged from 0 to 100, with higher scores indicating better quality of life.

Provocation tests: acid perfusion and oesophageal distension

The outcome parameters of the acid perfusion test are shown in **figure 3**. RS+ achalasia patients were much more sensitive to acid perfusion, as evidenced by a shorter time to perception of heartburn compared to the RS- achalasia patients and normal values of healthy subjects (RS+: median 4 (2-6) min; RS-: 30 (14-30) min; HS: 30 (10-30) min, log rank *P*<.001). Sensitivity values of RS- achalasia patients were comparable to healthy subjects. The perceived symptom intensity for heartburn or discomfort was also significantly higher in the RS+ group compared to the RS- group and healthy subjects (RS+: median

VAS 7 (4.8-9) versus RS-: VAS 0.5 (0-4.5); RS+: VAS 7 (4.8-9) versus HS: VAS 1.6 (0.4-2.4), both *P*<.001). Consequently, the perfusion sensitivity score was significantly higher in the RS+ group compared to the RS- group and healthy subjects (RS+: median 139 (65-173) versus RS-: 0 (0-99); RS+: 139 (65-173) versus HS: 0 (0-92), both *P*<.001). The scores for symptom intensity and perfusion sensitivity of RS- achalasia patients were similar to the scores of healthy subjects. In 26% (5/19) of the RS+ achalasia patients and 11% (2/19) of the RS- achalasia patients, the acid perfusion test was prematurely stopped due to intolerable pain.

In one patient, oesophageal distension by EndoFLIP could not be performed due to vasovagal syncope during the measurement. In 22% (4/18) of the RS+ and in 5% (1/19) of the RS- achalasia patients, pain and discomfort prevented full completion of the distension protocol. Perception of distension in RS+ achalasia patients occurred at a lower balloon volume (RS+: median 50 (38-70) mL versus RS-: 70 (50-70) mL, *P*=.03) and with a higher intensity (RS+: median VAS 3 (1.1-7.4) versus RS-: VAS 0 (0-2.8), *P*=.03). The distension score was significantly higher in RS+ achalasia patients (RS+: median 47 (0-166) versus RS-: 0 (0-18), *P*=.03).

All RS+ achalasia patients had a decreased perception threshold to acid and 67% (12/18) had a decreased perception threshold for mechanical distension, indicating visceral hypersensitivity in these patients. In contrast, 53% (10/19) of RS- achalasia patients did not experience any heartburn or discomfort during acid perfusion and 68% (13/19) lacked any symptoms during distension.

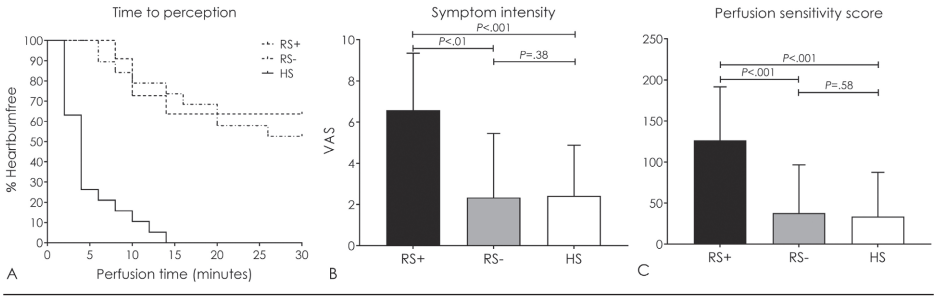

Figure 3. Results of acid perfusion test in treated achalasia patients with reflux symptoms (RS+), without reflux symptoms (RS-) and healthy subjects (HS).
A. Lag time to initial heartburn perception.
B. Maximum symptom intensity expressed by Visual Analogue Scale (VAS).
C: Perfusion sensitivity score ((total perfusion time – lag time to perception) x VAS).

HRM, timed barium oesophagogram and OGJ distensibility

All patients completed the HRM, timed barium oesophagogram and OGJ distensibility measurements, data are shown in **table 4**. No differences were

observed in OGJ distensibility and outcome parameters of HRM and timed barium oesophagogram between achalasia patients with and without reflux symptoms.

Questionnaires

Outcomes of the questionnaires are presented in **tables 1** and **4**. The GERDQ and RDQ scores were significantly higher in RS+ achalasia patients. The Eckardt score and general quality of life, scored by the SF-36, were similar between the groups. Achalasia-related quality of life was significantly decreased in RS+ patients, reflected by a higher overall score.

Factors related to acid hypersensitivity, acid exposure and acidification patterns

When lumping all patients regardless of presence of reflux symptoms, patients with hypersensitivity to acid perfusion (n=25/38, 66%) did not have higher acid exposure times or more often reflux oesophagitis compared to achalasia patients without hypersensitivity to acid perfusion (online **supplementary 1**, **table 1**). Outcomes of baseline impedance, oesophageal function and emptying were also not significantly different (only supplementary 2, table 1). However, patients with acid hypersensitivity were also more sensitive to mechanical distension, which is reflected by a perceived perception at a lower balloon volume (median balloon volume 50 (40-70) mL versus 70 (65-70) mL, *P*=.01) and a higher distension sensitivity score (median 47 (0-160) versus 0 (0-7), *P*=.02).

Statistically significant correlations were found between acid exposure and OGJ distensibility (r=0.403, p=0.012), basal LOS pressure (r=-0.348, *P*=.032) and barium column height during timed barium oesophagogram (r=-0.347, *P*=.033). All patients with pathological acid exposure, independent of reflux symptoms, had an increased OGJ distensibility, lower basal LOS pressure and an adequate oesophageal emptying (online **supplementary 1**, **table 2**).

Analysing the acidification patterns in absence of reflux symptoms revealed significant negative correlations between barium column height at 5 minutes during timed barium oesophagogram and either acid reflux with delayed clearance (OR 0.53 (95% CI 0.3 to 0.93), *P*=.03) or acid fermentation (OR 0.52 (95% CI 0.29 to 0.93), *P*=.03). Stasis of ingested acidic food or drink showed the opposite, a positive correlation with barium column height was observed, but this correlation was not significant (OR 1.4 (95% CI: 0.95 to 2.1), *P*=.09). Other outcome parameters (eg, OGJ distensibility, IRP and Eckardt score) were not significantly correlated with the different acidification patterns.

Subgroup analysis of outcome parameters per treatment group

Online **supplementary 1, table 3** shows the outcome of the 24-hour impedance measurement, oesophagogastroduodenoscopy and provocation tests according to treatment, laparoscopic Heller's myotomy versus POEM. Total and supine acid exposure were significantly increased in achalasia patient treated by POEM compared to laparoscopic Heller's myotomy. However, the number of patients with pathological acid exposure was comparable. No differences were observed in acidification patterns, reflux oesophagitis or chemical and mechanical oesophageal sensitivity. The observed acidification was in both treatment groups mainly determined by acid reflux with delayed clearance, acid fermentation and stasis of ingested acidic food.

DISCUSSION

This study was designed to allow a thorough investigation of reflux symptoms in treated achalasia patients and to increase the understanding of the underlying mechanisms by analysing oesophageal function, acid exposure, acidification patterns, symptom perception and reflux oesophagitis. The most important findings made in this study are that reflux symptoms in treated achalasia patients are rarely caused by gastro-oesophageal reflux and that oesophageal hypersensitivity to chemical (acid) and mechanical (distension) stimuli is likely to play a substantial role.

Treatment of achalasia focuses on disrupting the LOS, compromising the barrier against reflux of gastric content. The reported prevalence of presumed reflux-related complications after achalasia treatment is variable, ranging from 5 to 60%.[2–6] In part, this variability is likely to be related to treatment type, with lower occurrence rates after pneumodilation (5-25%) and higher rates after laparoscopic or endoscopic myotomy (20-60%).[2–9] However, the reported prevalence of gastro-oesophageal reflux after achalasia treatment also depends on the criteria used to define 'reflux'. Most studies used presence of reflux symptoms and/or presence of oesophagitis, whereas it has been shown that, in treated achalasia, there is considerable discordance between reflux symptoms, oesophageal acid exposure as measured with pH monitoring and presence of oesophagitis.[2,6,10–15] It has also been put forward that combined pH-impedance monitoring, as was used in our study, is essential to differentiate between true reflux, stasis and fermentation.[10,12] Overestimation of the role of gastro-oesophageal reflux in these patients led to prescribing PPI as the standard treatment, which has a variable efficacy as it treats acid reflux but not acidification of oesophageal contents by other causes. The advent of POEM, which has been shown to be associated with a high post procedural prevalence of oesophagitis, further underlines the need of better understanding of this problem.[3,4,8] The present study had the objective to provide a complete image

of reflux-related factors involved in the generation of post-treatment reflux symptoms and signs in achalasia patients by analysing oesophageal function, acid exposure, acidification patterns, symptom perception and mucosal status. To our knowledge, equally extensive studies on this subject have not been performed thus far.

Our study has confirmed that pathological acid exposure, defined as time with oesophageal pH <4 greater than 6%, is very common in treated achalasia patients (63% (n= 24/38) of patients) with a comparable frequency after laparoscopic Heller's myotomy with Dor fundoplication (55% (n=11/20)) as POEM (81% (n=13/16)). However, the results of our study also show that this is not predominantly caused by acid reflux with normal or delayed clearance but that it is largely due to other mechanisms, such as acid fermentation and stasis of ingested acidic food, resulting in oesophageal acidification. Furthermore, the prevalence of pathological acid exposure was not significantly different in treated achalasia patients with and without reflux symptoms (74% and 53%, respectively). Most importantly, however, in none of the 19 patients with reflux symptoms a positive temporal association between acidification events and symptom episodes could be demonstrated. Since the results of this study strongly support the notion that reflux symptoms in treated achalasia patients are not primarily related to (increased) gastro-oesophageal reflux, treatment with a PPI is likely to be ineffective in most of these patients.

Treated achalasia patients with reflux symptoms had a higher sensitivity to acid perfusion and to mechanical distension than patients without reflux symptoms. Patient characteristics, such as achalasia subtype, type of treatment and disease duration, seemed not to influence enhanced sensitivity. Thus far, evaluation of acid sensitivity in achalasia patients with reflux symptoms has only been performed in untreated patients and showed that the prevalence of oesophageal acid sensitivity was lower in these patients compared to a group of patients with GORD.[33] This could suggest that the content of acid and its volume influences oesophageal sensitivity, which is previously described.[34,35] However, acid hypersensitivity is also present in patients with non-erosive reflux disease, a group of patients with fewer reflux episodes and acid exposure compared to patients with GORD.[34,36] In these patients, acid hypersensitivity seems associated with impaired mucosal integrity, increased activation of oesophageal nociceptors and visceral sensitization, peripherally or centrally mediated.[19,37,38] All of the five acidification patterns described in this paper – acid reflux with normal clearance, acid reflux with delayed clearance, acid fermentation, prolonged oesophageal acidity after ingestion of acidic food and unclassified acidity – might act as triggers for the development of peripheral and central sensitization. Hypothetically, sensitization in achalasia

patients, treated or untreated, could also be evoked by stasis of non-acid food remnants. Furthermore, it has been demonstrated that a difference in psychological perception of anxiety and stress can also influence visceral sensitivity.[39,40] The relation between psychological stressors and chemical or mechanical oesophageal perception was not analysed in this study. Given the conceptual importance of hypersensitivity in treated achalasia patients with reflux-like symptoms, studies exploring the efficacy of visceral analgetics such as citalopram or amitriptyline seem warranted.

In contrast to the observed chemical and mechanical hypersensitivity, previous studies describe hyposensitivity to these stimuli in achalasia patients post-treatment.[39,41] The pathophysiology of the described hyposensitivity in achalasia is incompletely understood. It is hypothesized that in addition to motor neuron loss, sensory neurons are affected and/or desensitized, especially in longstanding disease.[39] Although, achalasia patients without reflux symptoms demonstrated decreased chemical and mechanical sensitivity compared to the symptomatic patients, no difference in the outcome of the acid perfusion test with healthy subjects was observed. In addition, no difference in disease duration, achalasia subtype or treatment was seen. Based on these data, it cannot indisputable be concluded that oesophageal hyposensitivity explains the absence of symptoms in the asymptomatic reflux group.

Among the four patterns leading to prolonged acidification in achalasia patients, acid fermentation of oesophageal food residues has gained most attention in previous studies.[10,12,42] In their in vitro study, Crookes et al observed that the pH of saliva incubated with chewed food at body temperature slowly drifted to a median pH of 4, in a period of approximately 6 hours.[10] The acid fermentation observed in our study showed a more rapid pH drift and often reached values below 4, with the lowest pH ranging from 3 to 1. We propose that the quicker pH drop observed in our study may be the result of, the contribution of bacterial overgrowth in the oesophagus leading to a quicker fermentation process and prolonged delayed clearance in supine position. In addition, it cannot completely be excluded that some pH drops, interpreted as acid fermentation, are the result of pH drift, or contact of the pH electrode with small particles of acidic food or stomach content. However, we feel that the use of an ISFET pH electrode makes pH drift as a cause of the phenomenon unlikely. Of the other three acidification patterns, acidic food-induced stasis could be implicative of failed treatment and diagnostics to evaluate oesophageal clearance should be considered.

Baseline impedance levels were substantially reduced in all achalasia patients, which made us decide not to use impedance for the classification of acidification

patterns. No correlations were observed between baseline impedance levels and acid exposure or acid hypersensitivity. Low baseline impedance levels are common in achalasia patients and caused by stasis of luminal content, dilated oesophageal lumen and ineffective motility leading to ineffective clearance and mucosal damage.[43,44] Although interpretation of impedance can be difficult in achalasia patient it helped to identify prolonged acidification, clearance of acidification and air trapping. The use of pH-impedance monitoring is therefore essential for understanding acidification in achalasia patients.

This study shows that the causes underlying reflux symptoms in treated achalasia are diverse. For an adequate diagnosis and tailored treatment of these symptoms, a step-wise approach is advised that starts with an oesophagogastroduodenoscopy. When reflux oesophagitis is observed, acid suppression should be started combined with lifestyle advice. In case of persistent symptoms or absent reflux oesophagitis a 24-hour pH-impedance monitoring should be performed to assess the relative contribution of the various mechanisms leading to oesophageal acidification. Acid reflux with normal and delayed clearance can be treated by increasing the PPI dose or adding an H2-recept antagonist. When acid fermentation predominates, avoidance of meals shortly before bedtime and drinking water after meals may be advised. In case symptoms persist, acid hypersensitivity should be considered in both groups and a perception-modulating antidepressant could be considered. Patients with pathological acid exposure due to acidic food-induced stasis or physiological or absent acid exposure should undergo a timed barium oesophagogram to evaluate oesophageal emptying or an OGJ distensibility measurement. If oesophageal clearance or OGJ distensibility is severely impaired, retreatment for achalasia may be considered. For patients with physiological or absent acid exposure and adequate oesophageal clearance, a therapeutic trial that aims to reduce oesophageal hypersensitivity can be considered.

In conclusion, reflux symptoms in treated achalasia patients are rarely caused by gastro-oesophageal reflux and most instances of oesophageal acidification in these patients are not reflux induced. Rather, increased oesophageal sensitivity to chemical and mechanical stimuli may determine the generation of reflux symptoms in these subjects. These observations have implications for the

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SUPPLEMENT MATERIAL

Supplement 1

Appendix

1. Study subject and inclusion criteria

1.1 Eligibility criteria

Tables

1. Factors related to acid hypersensitivity.
2. Factors related to pathological acid exposure.
3. Outcome 24-hour pH-impedance, oesophagogastroduodenoscopy and provocation tests per treatment group.

1. Study subject and inclusion criteria
1.1 Eligibility criteria

Inclusion criteria

Treated achalasia patients with gastro-oesophageal reflux symptoms

- Diagnosis of idiopathic achalasia confirmed by oesophageal manometry that shows the following criteria:
  - Aperistalsis or simultaneous contractions in the oesophageal body.
  - LOS dysrelaxation.
- Treatment of achalasia with one of the following procedures:
  - Endoscopic balloon dilatation
  - Surgical Heller myotomy
  - Per-oral endoscopic myotomy (POEM)
- Minimum total score on the Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) of ≥ 8.
- Gastro-oesophageal symptoms after treatment lasting more than 3 months.
- Age 18-80 years.
- Written informed consent.

Treated achalasia patients without gastro-oesophageal reflux symptoms

- Diagnosis of idiopathic achalasia confirmed by oesophageal manometry that shows the following criteria:
  - Aperistalsis or simultaneous contractions in the oesophageal body.
  - LOS dysrelaxation.
- Treatment of achalasia with one of the following procedures:
  - Endoscopic balloon dilatation
  - Surgical Heller myotomy
  - Per-oral endoscopic myotomy (POEM)
- Maximum total score on the Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) of < 8.
- No gastro-oesophageal symptoms after treatment.
- Age 18-80 years.
- Written informed consent.

Exclusion criteria

Treated achalasia patients with gastro-oesophageal reflux symptoms

- Pseudoachalasia.
- Upper gastrointestinal malignancy.
- Chagas disease.
- Peptic ulcer disease.
- Inability to stop PPI, H2-receptor antagonist or prokinetic drug for two weeks
- Presence of an extremely dilated oesophagus body >5 cm

Treated achalasia patients without gastro-oesophageal reflux symptoms

- Pseudoachalasia.
- Upper gastrointestinal malignancy.
- Chagas disease.
- Peptic ulcer disease.
- Inability to stop PPI, H2-receptor antagonist or prokinetic drug for two weeks
- Presence of an extremely dilated oesophagus body >5 cm

Tables

Table 1. Factors related to acid hypersensitivity.

	Patients with acid hypersensitivity (n=25)	**Patients without acid hypersensitivity (n=13)**	***P***
Achalasia subtype at diagnosis (n (%))			.64
Type I	9 (36)	4 (31)	
Type II	15 (60)	8 (62)	
Type III	1 (4)	1 (8)	
Achalasia treatment (n (%))			.90
Pneumodilation[#]	1 (4)	1 (8)	
Laparoscopic Heller's myotomy	7 (28)	2 (15)	
Peroral endoscopic myotomy	7 (28)	4 (31)	
Pneumodilation* and laparoscopic Heller's myotomy	7 (28)	4 (31)	
Pneumodilation* and peroral endoscopic myotomy	3 (12)	2 (15)	
Disease duration (years (mean (SD))	8.2 (7.0)	7.8 (5.7)	.85
24-hour pH-impedance monitoring			
Acid exposure time (AET: % of time pH <4; mean (95% CI))			
Total	13.9 (7.3 to 20.5)	9.2 (3.4 to 14.9)	.33
Upright	10.8 (5.3 to 16.2)	4.8 (2.2 to 7.4)	.05
Supine	18.0 (7.7 to 28.4)	15.2 (4.1 to 26.3)	.73
Pathological acid exposure (AET pH<4 in >6%; n (%))	17 (68)	7 (54)	.39
Baseline impedance (Ω; median (IQR))			
Proximal	2411 (1649-3150)	2220 (1780-2773)	.55
Distal	487 (368-660)	476 (339-750)	1.00
Endoscopy			
Reflux oesophagitis (n (%)	11 (44)	3 (23)	.29
High resolution manometry			
Basal LOS pressure (mmHg, median (IQR))	3 (2-6)	3 (3-7)	.70
Integrated relaxation pressure (mmHg, median (IQR))	6.6 (3.3-8.6)	5.9 (3.7-9.3)	.87
OGJ distensibility (at 50 mL, mmHg/m^2, median (IQR))	5.2 (4.5-7.0)	4.8 (2.7-5.8)	.11
Timed barium oesophagogram			
Barium column at 5 min (cm, median (IQR))	1.4 (0-2.5)	1.7 (0-2.6)	.81
Oesophageal diameter (cm, median (IQR))	2.5 (2-3.1)	2.3 (2-2.8)	.93
Perception oesophageal mechanical distension			
Volume first perception (mL, median (IQR))	50 (40-70)	70 (65-70)	.01
Symptom intensity (VAS, median (IQR))	2.9 (0.3-5.9)	0 (0-1.9)	.05
Distension sensitivity score (median (IQR))	47 (0-160)	0 (0-7)	.02

Abbreviations: AET, acid exposure time; CI, confidence interval; LOS, lower oesophageal sphincter; OGJ, oesophagogastric junction; IQR, interquartile range; VAS, visual analogue score.
[#]Pneumodilation up till 35-mm balloon.
*Pneumodilation up till 40-mm balloon.

Table 2. Factors related to pathological acid exposure.

	Patients with pathological acid exposure (n=24)	**Patients without pathological acid exposure (n=14)**	***P***
BMI (kg/m^2; mean (SD))	26.2 (4.3)	24.8 (2.7)	.27
High resolution manometry			
Basal LOS pressure (mmHg, median (IQR))	3 (2-4.8)	4.6 (3-9.3)	.034
Integrated relaxation pressure (mmHg, median (IQR))	6.2 (3.1-8.7)	6.4 (4-10.5)	.56
OGJ distensibility (at 50 mL, mmHg/m^2, median (IQR))	5.5 (4.6-7.0)	4.6 (3.4-5.5)	.032
Timed barium oesophagogram			
Barium column at 5 min (cm, median (IQR))	0 (0-1.8)	2.5 (1.2-3.1)	.002
Oesophageal diameter (cm, median (IQR))	2.2 (2-3)	2.7 (2-3.4)	.18
24-hour pH-impedance monitoring			
Baseline impedance (Ω, median (IQR))			
Proximal	2163 (1865-2739)	2763 (1585-3260)	.23
Distal	487 (347-730)	493 (348-702)	.88
Acid perfusion test			
Time to perception (min, median (IQR))	8 (4-27.5)	9 (5.5-30)	.46
Symptom intensity (VAS, median (IQR))	5.5 (0.6-8)	4.1 (0-7)	.48
Perfusion hypersensitivity score (median (IQR))	82 (1-135)	64 (0-170)	.82
Perception oesophageal mechanical distension			
Volume first perception (mL, median (IQR)	70 (50-70)	60 (40-70)	.60
Symptom intensity (VAS, median (IQR))	1.5 (0-4.3)	1 (0-5.2)	.82
Oesophageal distension sensitivity score (median (IQR))	0 (0-84)	9 (0-174)	.61

Abbreviations: BMI, body mass index; CI, confidence interval; LOS, lower oesophageal sphincter; IQR, interquartile range; OGJ, Oesophagogastric junction; VAS, visual analogue score.

Table 3. Outcome 24-hour pH-impedance, oesophagogastroduodenoscopy and provocation tests per treatment group.

	Laparoscopic Heller's myotomy (n=20)	**Peroral endoscopic myotomy (n=16)**	***P***
24-hour pH-impedance monitoring			
Acid exposure time (AET: % of time pH <4; mean (95% CI))			
Total	8.1 (3.6 to 12.5)	19.1 (10.2 to 28.1)	.02
Upright	6.5 (2.3 to 10.7)	12.5 (5.4 to 19.6)	.12
Supine	9.6 (3.4 to 15.9)	28.5 (13.3 to 43.7)	.02
Pathological acid exposure (AET pH<4 in >6%; n (%))	11 (55)	13 (81)	.16
Acidification patterns (% of time; mean (95% CI))			
Acid reflux with normal clearance	0.08 (0.01 to 0.14)	0.2 (0.06 to 0.33)	.10
Acid reflux with delayed clearance	2.8 (0.07 to 5.57)	7.6 (1.1 to 14.1)	.16
Acid fermentation	3.5 (0.8 to 6.12)	5.6 (1.4 to 9.8)	.34
Stasis of ingested acidic food	3.8 (-1.04 to 8.58)	6.7 (-0.9 to 14.6)	.46
Unclassified	0.3 (-0.1 to 0.73)	1.8 (-0.98 to 4.6)	.28
Number of acidification events (median (IQR))			
Acid reflux with normal clearance	0 (0-1)	0.5 (0-2.8)	.15
Acid reflux with delayed clearance	0 (0-1)	1.5 (0-3)	.07
Acid fermentation	0 (0-1.8)	0.5 (0-2.5)	.57
Stasis of ingested acidic food	0 (0-1)	0 (0-2)	.23
Unclassified	0 (0-1)	0 (0-0.8)	.79
Number of patients per acidification pattern (n (%))			
Acid reflux with normal clearance	6 (30)	8 (50)	.22
Acid reflux with delayed clearance	8 (40)	10 (63)	.18
Acid fermentation	8 (40)	9 (56)	.33
Stasis of ingested acidic food	6 (30)	7 (44)	.39
Unclassified	6 (30)	4 (25)	.74
Endoscopy			
Reflux oesophagitis (n (%))	7 (35)	7 (44)	.59
Acid perfusion test			
Time to perception (min, median (IQR))	6 (4-20)	14 (4-30)	.26
Symptom intensity (VAS, median (IQR))	5.4 (1.1-7.8)	3.8 (0-7.9)	.65
Perfusion sensitivity score (median (IQR))	112 (8-172)	35 (0-110)	.12
Perception oesophageal mechanical distension			
Volume first percepton (mL, median (IQR)	60 (40-70)	70 (50-70)	.36
Symptom intensity (VAS, median (IQR))	3 (0-5.2)	1.2 (0-2.6)	.26
Distension sensitivity score (median (IQR))	13 (0-170)	0 (0-71)	.26

Abbreviations: AET, acid exposure time, CI, confidence interval; IQR, interquartile range; VAS, visual analogue score.

Screening for dysplasia with Lugol chromoendoscopy in longstanding idiopathic achalasia

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ABSTRACT

Background

Achalasia patients with longstanding disease are considered to be at risk for developing esophageal cancer. Endoscopic screening is not standardized and detection of dysplastic lesions is difficult, for which Lugol chromoendoscopy could be helpful. Aim was to evaluate the efficacy of screening for esophageal dysplasia and carcinoma in patients with longstanding achalasia using Lugol chromoendoscopy.

Methods

In this cohort study achalasia patients underwent 3-annual screening by Lugol chromoendoscopy between January 2000 and March 2016. Patients with low-grade dysplasia (LGD) underwent yearly screening, patients with high-grade dysplasia (HGD) or carcinoma were treated.

Results

In total 230 achalasia patients (144 male, median age 52 years (43-63)) at first endoscopy) were included. Three patients (1.3%, 2 male, age 68 (50-87)) developed esophageal squamous cell carcinoma (ESCC), without LGD at the preceding screening. Incidence rate for ESCC was 63 (95% CI 13-183) per 100.000 persons-years. LGD was observed in four patients (1.7%, 2 male, age 64 (57-73)), without progression to HGD/ESCC during a follow-up of 9 (7-14) years. ESCC/LGD was diagnosed 30 (14-36) years after onset of symptoms and 22 (4-13) years after diagnosis. Lugol chromoendoscopy tripled the detection rate of suspected lesions (111 lesions white light versus 329 lesions Lugol), but only 8% was histopathological confirmed ESCC or LGD.

Conclusion

Achalasia patients with longstanding disease (>20 years) have an increased risk to develop esophageal dysplasia and carcinoma. Endoscopic screening using white light and Lugol chromoendoscopy does not accurately identify precursor lesions for ESCC and therefore cannot be systematically recommended.

INTRODUCTION

Achalasia is a rare esophageal motility disorder, characterized by absent peristalsis in the esophageal body and impaired relaxation of the lower esophageal sphincter (LES) hampering normal esophageal emptying. It is caused by loss of inhibitory postganglionic neurons in the myenteric plexus of the esophagus.[1,2] As the etiology of this neuronal loss remains unknown, treatment is confined to disruption of the LES.

Despite adequate treatment, achalasia is associated with an increased risk for esophageal cancer.[3–5] The underlying pathophysiological mechanism is assumed to be multifactorial. Poor esophageal emptying may lead to increased bacterial growth, chemical irritation and inflammation which may trigger dysplastic changes of the esophageal epithelial cells, ultimately resulting in esophageal squamous cell carcinoma (ESCC).[6] In addition, treatment aims a reduction in LES pressure which in combination with absent peristalsis may lead to increased acid exposure, esophagitis, Barrett's esophagus and eventually adenocarcinoma.[7–9] However, the exact risk for ESCC or adenocarcinoma is still a matter of debate. For ESCC, a 10-50 fold increased risk has been described.[3–5,10–13] The risk of developing adenocarcinoma seems substantially lower, varying between 0.5-10 fold.[8,9,14,15] This variation can be explained by differences in study design (retrospective vs prospective), length of follow-up (5-23 years) and number of included patients (67-1318).[5] Based on these discrepancies, limited data on cancer screening and its cost-effectiveness, current guidelines advise against regular endoscopic follow-up.[16,17] However, as the risk of esophageal cancer seems to increase with the duration of achalasia, screening could be beneficial in high-risk patients with >10-15 years of symptoms.[4,9,18] Moreover, achalasia patients with esophageal carcinoma frequently present in an advanced stage with poor prognosis, because these patients are used to dysphagia and do not easily report worsening of symptoms.[4,19] Together with the assumption that achalasia patients are at risk for esophageal cancer, one could argue that endoscopic screening may be justified in patients with longstanding achalasia to early detect dysplastic lesions.

Detection of dysplastic lesions with conventional endoscopy is difficult, especially in achalasia patients due to the presence of stasis of contents in the lumen, esophagitis and esophageal hyperkeratosis. Chromoendoscopy with Lugol has proven to increase the sensitivity for detecting ESCC and its precursors lesions to 91-100%.[20–23] Lugol reacts with glycogen present in normal esophageal mucosa yielding a brown-green color of the mucosa. Dysplastic lesions do not stain as they lack glycogen and thus can be visualized more efficiently.[20] Performing advanced endoscopic imaging techniques could therefore lead to improved cancer screening. Hence, aim of the study was to

evaluate the efficacy of screening for esophageal dysplasia and carcinoma in patients with longstanding achalasia using Lugol chromoendoscopy. Secondly, we wanted to determine the incidence rate of esophageal carcinoma in this patient population.

MATERIALS AND METHODS

Study patients

For this cohort study we included patients that underwent follow-up for achalasia between January 2000 and March 2016 in two university hospitals, i.e. the Academic Medical Center of Amsterdam and the University Hospital of Leuven. Both hospitals are tertiary referral centers for patients with esophageal motility disorders. As part of the standard of care for achalasia, dysplasia screening in treated achalasia patients started in 2000 in Amsterdam and in 2013 in Leuven. For all patients, the diagnosis of achalasia was based on esophageal manometry, defined as absent peristalsis with impaired relaxation of the lower esophageal sphincter (LES). For conventional manometry, a nadir pressure ≥10 mmHg during swallow-induced relaxation was defined as impaired LES relaxation.[24] Impaired relaxation during high-resolution manometry (HRM) was considered if the integrated relaxation pressure over 4 seconds (IRP4) was >15 mmHg.[25] Patients had been treated by botox injections, pneumodilation, Heller myotomy (transthoracic, transabdominal or laparoscopic), peroral endoscopic myotomy (POEM) or a combination of these treatments. The choice of initial treatment and treatment for recurrent symptoms depended on patient preference and recommendation of the treating physician. The study was evaluated and approved by the Medical Ethical Committee of both hospitals, Academic Medical Center (Amsterdam, the Netherlands; November 1999, number MEC 99/176 #99.17.817) and University Hospital Leuven (Leuven, Belgium; February 2013, number ML8992).

Study design

Screening

Consecutive patients with treated achalasia were invited to undergo dysplasia screening by endoscopy. Starting from 2000, patients were invited for 3-annual screening independent of the disease duration. From 2010 onwards, only patients with a disease duration of at least 10 years were invited. All patients that underwent a screening endoscopy were included in this study. Screening was performed by Lugol chromoendoscopy. Patients followed a liquid diet for 3 days and an overnight fast before endoscopy to prevent aspiration and inadequate screening due to stasis of food. Screening endoscopy was repeated every 3 years if no abnormalities were found. In case histopathology showed low-grade dysplasia or indefinite for dysplasia, chromoendoscopy was repeated every year. Patients with high-grade dysplasia or carcinoma were treated by

endoscopic resection, surgery or curative/palliative radiotherapy depending on the stage of disease.

Chromoendoscopy with Lugol

Upper endoscopy was performed using the GIF160Q or GIF180Q endoscope (Olympus Europe, Hamburg, Germany) or the EG-2990Zi endoscope (Pentax Medical, Tokyo, Japan). All patients were given topical pharyngeal anesthesia with lidocaine (xylocaine) and if needed sedation with intravenous midazolam. Endoscopy started with an extensive inspection of the esophagus with white light to assess suspicious lesions, reflux esophagitis and Barrett's esophagus. Reflux esophagitis was classified according to the Los Angeles classification.[26] Stasis of food, liquid or mucus was noted. Before Lugol staining, the esophageal mucosa was cleaned with acetylcysteine and/or distilled water. Subsequently, the esophagus was stained with Lugol's iodine solution (2% solution in NaCl 0.9%, 10 or 20 ml) using a spray catheter. Excessive Lugol solution was aspirated and the esophagus was carefully inspected for unstained or poorly stained lesions (**figure 1**). Biopsies were taken of all unstained or poorly stained areas, independent of the size of the lesion. During the first screening endoscopies in 2000 also random biopsies were taken. As none of these random biopsies showed abnormalities it was decided to only take biopsies of suspected lesions observed during white light, Lugol staining or both. Biopsies were fixed in formaldehyde for further histopathological assessment. Lugol staining was not performed in case of stasis of food or incomplete cleaning of the mucosa, severe reflux esophagitis, refusal or patient's intolerance.

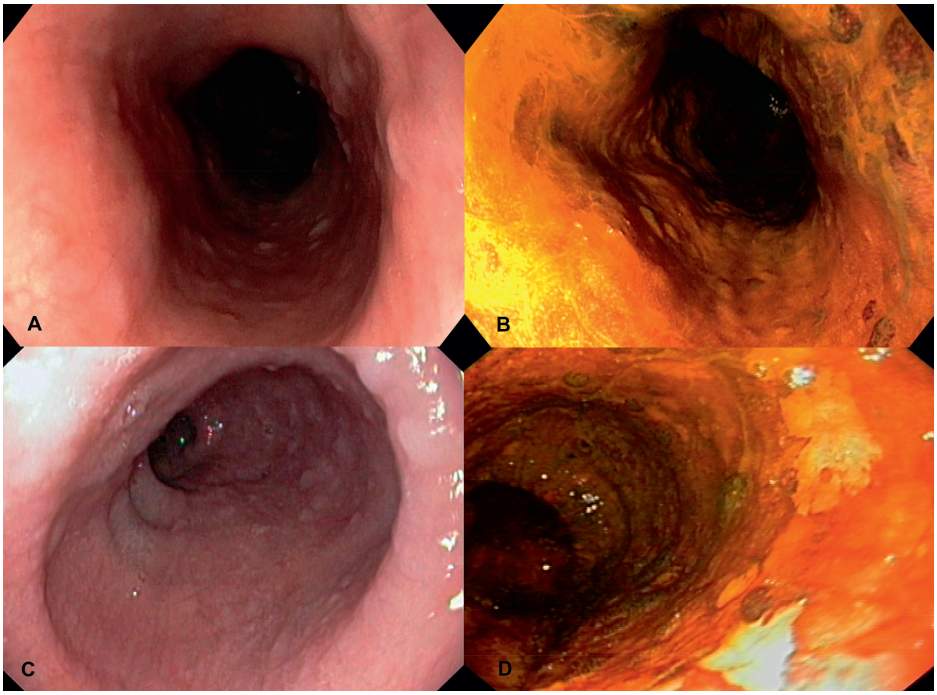

Figure 1. White light images (A/C) and corresponding Lugol chromoendoscopy images (B/D) of 2 achalasia patients. Figure 1A shows a widened esophagus with some hyperplastic squamous epithelium (glycogenic acanthosis). Lugol staining does not reveal unstained lesions in this patient (B). Images of the second patient with white light show also a wide esophagus with acanthosis (C). After Lugol staining two unstained lesions are visible (D), histopathology of the biopsies revealed low-grade dysplasia.

Histopathological assessment

Biopsies fixed in formaldehyde were embedded in paraffin, sectioned and stained with hematoxylin and eosin and evaluated by a pathologist with expertise in gastrointestinal diseases. Dysplasia was evaluated according to the criteria of the World Health Organization and defined as: negative for dysplasia, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD) or invasive neoplasia/carcinoma.[27] In case of dysplasia a second expert pathologist was consulted. Besides dysplasia, biopsies were assessed for inflammation, Barrett's epithelium, intestinal metaplasia, candida esophagitis and hyperkeratosis.

Data collection

Clinical characteristics were retrieved from medical records and questionnaires assessing alcohol consumption, tobacco use, medical history and medication use completed before the endoscopy. Timed barium esophagograms were performed according to a standardized protocol to assess esophageal

emptying.[28] In short, the patient ingested 200 ml low density barium sulphate suspension in an upright position and X-rays were taken at 0, 1, 2 and 5 minutes after ingestion.[28] The height of the barium column at 5 min was assessed to determine completeness of emptying.[29] The most recent performed timed barium esophagogram (TBE) was assessed when it was not performed directly after endoscopy.

Statistical analysis

Individual person-time at risk was calculated by subtracting the date of first symptoms of achalasia from the first observed event of LGD, HGD or esophageal carcinoma in the study period, or the end of follow-up caused by lost to follow-up or the end of the study period. Individual person-time at risk was also calculated for the years after diagnosis of achalasia. Incidence rates for esophageal carcinoma were calculated by dividing the observed number of esophageal carcinomas within the study period by the sum of individual person's years after onset of symptoms. Incidence rates were presented per 100.000 persons years with accompanying 95% confidence interval (CI), analyzed by OpenEpi (Open Source Epidemiologic Statistics for Public Health, Version 3.03a. www.OpenEpi.com). The Kaplan-Meier method was used to represent cumulative incidence rates of LGD and ESCC. Continuous data were presented as mean ± SEM or median (interquartile range (IQR) or range) according to distribution. Categorical data were presented in percentages. Continuous data were compared using the Mann-Whitney U-test and categorical data were analyzed by Chi-square or Fisher's exact. Differences were considered statistically significant when $P<.05$. All reported p-values were 2-tailed. Statistical analysis was performed using IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY, United States).

RESULTS

Patient characteristics and follow-up

In total, 230 achalasia patients (144 male (63%)) were included in the study, 198 patients in the Academic Medical Center Amsterdam and 32 patients in the University Hospital of Leuven. **Table 1** displays all patient characteristics, including type of treatment, alcohol and/or tobacco use and endoscopic screening.

At the end of the study, the onset of symptoms was <10 years in 18 patients, 10-20 years in 115 patients and ≥20 years in 97 patients. The person years at risk observed in this study was 4791 years after the start of symptoms and 3636 years after diagnosis. During the study, 48 (21%; 34 male) patients were lost to follow-up. Of these, 11 (9 male; age 67 (IQR 58-77)) died after a median follow-up of 21 (IQR 11-27) years. Four patients died from non-achalasia related causes, in seven patients the cause of death was unknown. The other 37 patients (25

male; age 59 (IQR 48-74)) were lost to follow-up after a median follow-up of 14 (8-21) years after symptoms and 11 (5-20) years since diagnosis.

Table 1. Patients characteristics and follow-up

	Achalasia patients (n=230)
Age at diagnosis (year (IQR))	41 (32-54)
Diagnostic delay (months (IQR))	31 (12-85)
Gender (male) (n (%))	144 (63%)
Treatment (n (%))	
Botox injections	2 (1%)
Pneumodilation	138 (60%)
Heller myotomy	24 (10%)
POEM	11 (5%)
Pneumodilation and Heller or POEM	53 (23%)
Pneumodilation, Heller and POEM	2 (1%)
PPI use after treatment (n (%))	108 (47%)
Alcohol use (n (%))	108 (56% of 193)
Tobacco use (n (%))	70 (37% of 188)
Age during first screening endoscopy (year (IQR))	54 (43-63)
Time from symptoms till first screening endoscopy (year (range))	15.4 (1-66)
Time from diagnosis till first screening endoscopy (year (range))	10.5 (0-47)
Follow-up from symptoms till study endpoint (year (IQR))	17 (12-28)
Follow-up from diagnosis till study endpoint (year (IQR))	12 (8-21)
Follow-up during study (month (IQR))	56 (14-104)
Lost to follow-up (n (%))	48 (21%)
Person years at risk since symtoms	4791
Person years at risk since diagnosis	3636

Data are presented as median (interquartile range; IQR or range) or number (n (%)).
POEM, peroral endoscopic myotomy.

Endoscopic screening

In total 539 endoscopies were performed, with a median number of 2 endoscopies (IQR 1-3). At time of first endoscopy 68% (n=157) of the patients had ≥10 years of symptoms, at the end of the study this was 92% (n=212). Regarding the follow-up after diagnosis, first endoscopic screening was performed in 46% (n=105) of the patients after ≥10 years after diagnosis. At the end of the study this was 67% (n=154).

Throughout the study 7% of the patients missed 1 or more endoscopies that were planned according to the screening interval of 1 or 3 years. In total only 22 scheduled endoscopies were not performed for various reasons. Of the 539

screening endoscopies 12% (n=63) were performed without the use of Lugol. Adverse events were observed in four of the 230 patients (1.7%), chest pain and nausea were reported after Lugol staining. Consecutive screening endoscopies (n=7) in these patients were performed without Lugol staining. Other reasons not to perform Lugol chromoendoscopy were distress of the patient during the endoscopy (n=2), severe reflux esophagitis (n=12), candida esophagitis (n=2), hyperkeratosis (n=5), severe stasis of food/liquid (n=12) or no reason was reported (n=23). In only 6% (n=14) of the included patients a screening endoscopy with Lugol was never performed throughout the study. Stasis of food or liquid was observed in 27% (n=63) of the patients during 1 or more endoscopies. In most cases food or liquid could be flushed and aspirated. Reflux esophagitis was noted in 34% (n=78) of the patients during 1 or more endoscopies. During 113 endoscopies reflux esophagitis was observed and classified as grade A in 54%; grade B in 30%; grade C in 13% and grade D in 3%.

Esophageal carcinoma

In 7 patients (3%) esophageal carcinoma or LGD was detected during screening. Of these patients, 3 developed ESCC (1.3%; 2 male). The observed incidence rate for ESCC in our population was 63 (95% CI 13-183) per 100.000 persons-years.

All three patients developed ESCC after >30 years (median 36 (range 35-66)) of symptoms and >20 years (median 33 (range 22-34)) after diagnosis (**figure 2 and 3**). The median age was 68 (range 50-87) years. Endoscopic screening started at 19, 24 and 33 years after diagnosis. In two patients, ESCC was diagnosed during screening, at the second and third screening endoscopy, and detected both with white light and Lugol chromoendoscopy. Of note, no suspected areas were detected on previous screening endoscopies, for both patients 3 years earlier. However, in both patients stasis of food/liquid and reflux esophagitis grade B were observed. One patient was diagnosed with a superficial ESCC (T1N0M0) in the distal esophagus and underwent a radical esophagectomy. The patient is still disease-free, 11 years after surgery. The other patient was diagnosed with a more invasive ESCC (T1-2N0M) and underwent brachy- and radiotherapy but died 8 months after diagnosis. In the third patient, ESCC was detected during a diagnostic upper endoscopy because of dysphagia, dyspnea and severe weight loss, two years after a negative screening endoscopy. During this screening endoscopy, Lugol staining was not performed because of stasis but neither white light endoscopy nor random biopsies revealed abnormalities. Of interest, the initial screening endoscopy, 24 years after achalasia diagnosis, did reveal LGD. Following annual screening endoscopies (n=5) were all negative for LGD or ESCC but persistently showed food stasis. Lugol staining could still be performed during these endoscopies. Endoscopic ultrasound showed

extensive mediastinal ingrowth and lymphadenopathy (T3N1M0) and palliative radiotherapy was started. The patient died 1.5 months after diagnosis.

All three patients were Caucasian. Two patients had a history of smoking with over 20 pack years. None of the patients had a history of alcohol abuse. At the time of diagnosis of ESCC two patients reported increased symptoms of achalasia. Two patients had been treated with pneumodilation and one had undergone a Heller myotomy.

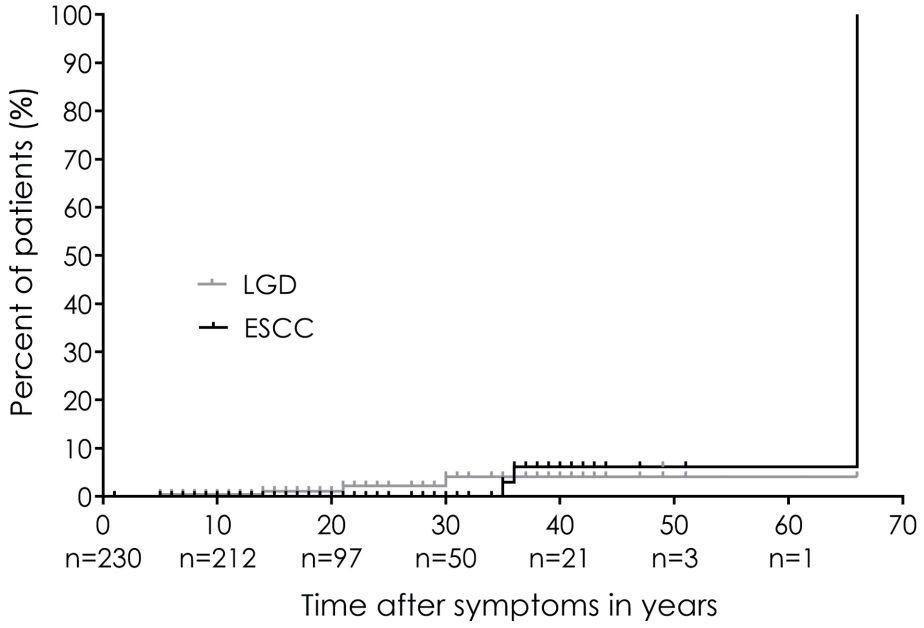

Figure 2. Cumulative incidence curve for low-grade dysplasia (LGD) and esophageal squamous cell carcinoma (ESCC) at onset of symptoms of achalasia. The incidence for LGD starts rising after 20 years of achalasia symptoms and for ESCC after 30 years. Patient numbers for the follow-up at 0, 10, 20, 30, 40, 50 and 60 years after symptoms are shown at the bottom of x-axis.

Dysplasia

LGD was diagnosed in four patients (1.7%; 2 male), 18 (range 5-30) years after symptom onset and 13 (range 1-29) years after diagnosis. One patient had LGD at <10 years after start of symptoms, the other patients after ≥10 years (**figure 2**). LGD was observed in two patients <10 years after diagnosis of achalasia, for the other patients this was >20 years (**figure 3**). The median age of the patients at time of first observed LGD was 64 (range 57-73) years. Screening started at 1, 15 and 29 years after diagnosis of achalasia. Two patients were diagnosed with LGD during the first screening endoscopy, 1 and 29 years after diagnosis. LGD was detected in the other two patients during the second (3 years after

first screening) and third (6 years after first screening) screening endoscopy, 4 and 21 years after diagnosis. Annual screening of these patients resulted in a total of 26 follow-up endoscopies. During 8 endoscopies LGD was reconfirmed, 7 times in the same patient with longest disease duration. None of the four patients developed HGD or esophageal carcinoma during a median follow-up of 9 (IQR 7-14) years.

The ethnical background of one patient was Asian, the other three patients were Caucasian. Two patients had a history of smoking with over 20 pack years. None of the patients had a history of alcohol abuse. At the time of diagnosis of LGD, none of the patients experienced severe symptoms. All patients were treated by pneumodilation.

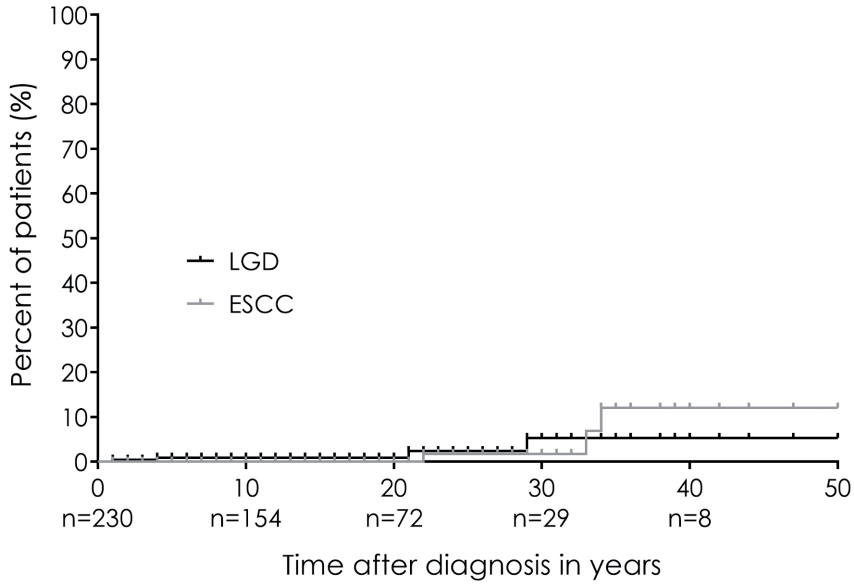

Figure 3. Cumulative incidence curve for low-grade dysplasia (LGD) and esophageal squamous cell carcinoma (ESCC) after diagnosis of achalasia. The incidence for both LGD and ESCC starts rising after 20 years of diagnosis. Patient numbers for the follow-up at 0, 10, 20, 30 and 40 years after diagnosis are shown at the bottom of x-axis.

Detection lesions by white light and Lugol staining

In total, 539 endoscopies were performed in 230 patients. During 79 of these 539 endoscopies (14.6%), 111 suspected lesions were detected (**table 2**). Lugol staining was performed in 476 of the 539 endoscopies (88.3%). During 173 of the 476 Lugol chromoendoscopies (36.3%), 329 suspected lesions were detected, an increase of 218 suspected lesions compared to white light (**table 2**). However, only 8% of these lesions were histopathologically confirmed as dysplasia or carcinoma.

In two patients, ESCC was diagnosed during screening endoscopy. The suspected areas (4 lesions in total) were detected both with white light and Lugol staining. In addition, 23 LGD lesions confirmed by histopathology, were detected during 14 screening endoscopies in 5 patients. These LGD lesions were all detected by Lugol staining (detection rate: 23 of 23 lesions,100%), while white light endoscopy failed to detect 8 of the 23 lesions (detection rate:15 of 23 lesions, 65%). Histopathological assessment of the other unstained lesions detected by Lugol staining showed inflammatory changes due to reflux or unknown cause (241 lesions, 73%), Barrett's epithelium (3 lesions, 1%), hyperkeratosis (16 lesions, 5%) or no abnormalities (43 lesions, 13%).

Table 2. Number of lesions per endoscopy detected with white light and Lugol staining.

Number of endoscopic lesions	**White light** *Endoscopies (n)*	**Lugol staining** *Endoscopies (n)*
0	460	303
1	59	78
2	14	59
3	3	19
4	1	11
5	1	4
6	1	2
Total suspected areas	111	329

In total 15 lesions detected by white light revealed to be ESCC or LGD versus 23 lesions with Lugol staining.

The diagnostic accuracy of Lugol chromoendoscopy was measured based on the first screening endoscopies performed at the beginning of the study in 2000, where also random biopsies were taken of unsuspected lesions. Of the first 230 endoscopies, biopsies were taken in 112 patients. In 44 of these patients no suspected lesions were observed after Lugol staining, while in total 202 random biopsies were taken. None of these biopsies showed dysplasia. In the other 68 patients, Lugol detected 129 unstained lesions of which biopsies of 3 lesions in 3 patients revealed low-grade dysplasia. The sensitivity of Lugol chromoendoscopy in the first years of screening was 100% (3/3), with a specificity of 62% (202/328) and a positive predictive value of 2.3% (3/129).

Factors associated with dysplasia

The cumulative incidence of LGD and ESCC, represented by the Kaplan-Meier curves in **figure 2** and **3**, shows that most cases of LGD and ESCC occur after >20 years of onset of symptoms or diagnosis. Esophageal dysplasia or carcinoma developed after a median disease duration of 30 (IQR 14-36) years and 22 (IQR

4-33) years after diagnosis. In the groups from 0-10 years (n=18) and 10-20 years (n=115) after onset of symptoms, 1 case of LGD was detected in each subgroup. Most lesions were detected in the ≥20 years group (n=97) with 3 cases of ESCC and 2 cases of LGD. The likelihood of developing esophageal dysplasia or carcinoma tended to increase after a longer presence of symptoms and disease duration. The overall incidence rate for ESCC was 63 (95% CI 13-183) per 100.000 person-years. Specifying the incidence rate for ≥20 years after onset of symptoms, showed an incidence for ESCC of 98 (95% CI 20-287) per 100.000 person-years. The prevalence of developing dysplasia or ESCC in this subgroup was 5.2%, 5 cases of LGD/ESCC in a group of 97 patients.

There was no significant difference in the risk of developing esophageal dysplasia or carcinoma between patients with and without endoscopic stasis (4 of 59 (6.8%) patients with stasis versus 3 of 164 (1.8%) patients without stasis, *P*=.09). However, food/liquid stasis was observed in all three patients that developed ESCC and once in one patient that developed LGD. TBE was performed in 75% (n=172) of the patients around the time of screening endoscopy. Patients with stasis of food/liquid during endoscopy had a significantly higher barium column height after 5 min at TBE compared to patients without endoscopic stasis (3 (IQR 2-6) cm patients with endoscopic stasis (n=47) versus 0 (IQR 0-3.6) cm patients without endoscopic stasis (n=125), *P*<.01). TBE was performed in 2 of the 3 patients with ESCC and showed stasis in both patients. The patient with LGD with endoscopic stasis also showed stasis during TBE.

DISCUSSION

In this prospective cohort study, we evaluated the efficacy of screening for esophageal dysplasia and carcinoma in patients with longstanding achalasia using Lugol chromoendoscopy. We found an incidence rate for ESCC of 63 per 100.000 person years, with an increased cancer risk after a longer disease duration. ESCC was only observed after >30 years of onset of symptoms and >20 years after diagnosis. LGD occurred mainly after >10 years of onset of symptoms and generally remained stable for a long time or even could not be reconfirmed during subsequent endoscopies. LGD thus did not progress into HGD or cancer. Furthermore, patients that developed ESCC were not consistently identified beforehand, as precursor lesions were only found once in one of the three patients during previous screening endoscopies. Lugol staining increased the detection rate of dysplastic lesions with 35% however, nonspecific staining frequently occurred (92%) and ESCC was also detected by white light. Lugol chromoendoscopy did not reveal relevant precursor lesions and the additional value for screening in achalasia is therefore questionable. The low yield of detecting precursor lesions during chromoendoscopies hampers adequate risk stratification for ESCC. Therefore, we conclude that endoscopic screening for

esophageal dysplasia and carcinoma in achalasia using white light and Lugol chromoendscopy should not be systematically recommended.

The increased risk of esophageal cancer in achalasia has previously been described with incidence rates varying between 58-335 per 100.000 persons. The incidence rate of 63 per 100.000 found in our study is at the lower end.[4,9–13,18,30] In our cohort all patients with esophageal cancer were diagnosed with ESCC, similar to other large cohort studies.[10,12,13,18,30] For the period 2000-2015 the annual incidence for ESCC in the general Dutch and Belgium population varied from 2.8-4.5 per 100.000 persons, unadjusted incidence rates.[31,32] Comparing this to the incidence rate of our cohort, there is a 14 to 23-fold increased risk for achalasia patients to develop ESCC. Previous studies described a similar increased risk of 10-50 fold.[3,5] In our study, ESCC developed after a median time of 35 years after onset of symptoms and 33 years after diagnosis. This is in line with previous studies in which the time between achalasia symptoms and the development of esophageal cancer varied from 10 to 32 years.[4,9,11,13,18,30] An increased risk of 22 to 35-fold for ESCC was observed when only patients with over >20 years after onset of symptoms were analyzed. Based on these data and previous studies, endoscopic screening could be considered in achalasia patients with longstanding disease, >20 years after diagnosis.

Current guidelines do not recommend regular cancer screening for achalasia patients.[16] In general, screening is only proposed when early detection can lead to adequate therapy and significant reduction in cancer related mortality and/or morbidity. Although screening is not advocated in guidelines, some expert centers for achalasia do perform screening endoscopies but without consensus regarding timing of initial endoscopy or frequency.[33] The main reason to perform screening, is that the prognosis is majorly determined by the stage of disease at time of detection.[4] In our cohort, two of the three patients that developed ESCC were detected by screening. Only one of the three patients was diagnosed with an early stage ESCC and treated curatively. Previous studies have demonstrated that the risk for ESCC is strongly dependent on the grade of dysplasia. In a high-risk, non-achalasia population in northern China, patients with LGD had a 5% chance to develop ESCC within 3.5 years and 24% within 13.5 years.[34] In our study screening endoscopies detected LGD in four patients, mainly after >10 years of onset of symptoms. None of these patients developed HGD or ESCC after a median follow-up of 9 years. The dysplastic lesions stayed stable or could even not be relocated during subsequent endoscopies. For the patients diagnosed with ESCC, previous screening endoscopies revealed only once LGD in one patient that was not found during following endoscopies. Our data show that screening did not prevent the development of ESCC in our cohort but did detect cancer in an early stage in one patient leading to curative treatment.

Furthermore, the study suggests that there is no relevant precursor lesion that identifies achalasia patients with a higher risk of developing esophageal carcinoma. Based on the knowledge that the absolute risk of esophageal cancer in achalasia is relatively low, combined with the fact that so far relevant precursor lesions are lacking, regular cancer screening in achalasia patients cannot be recommended.

Lugol dye detected all areas of ESCC and LGD. Without Lugol, 3 patients would not have been diagnosed with LGD. However, during annual screening endoscopies in these patients, Lugol voiding lesions could be found but none of the biopsies reconfirmed LGD. In total, Lugol staining detected 329 unstained lesions in the study population of which 92% appeared to be false positive, mainly caused by reflux- and nonspecific inflammatory changes. The use of molecular markers could help to better identify patients at risk for developing esophageal carcinoma. Previous studies on biomarkers for esophageal carcinoma in achalasia focused on immunohistochemistry and found an overexpression of p53 mutation in patients with ESCC and LGD.[7,35,36] A different method would be DNA fluorescence in situ hybridization (FISH), a cytogenetic technique that can be applied to endoscopic brushing specimens of esophageal mucosa as previously performed in Barrett's esophagus.[37] Further studies are needed to evaluate the role of biomarkers in the cancer risk stratification and screening strategy of achalasia.

Since our data suggests that systematic screening of all achalasia patients is not cost-effective, better risk stratification to identify patients at high risk to develop cancer seems desirable. Impaired esophageal emptying leading to stasis of food and gastric content causing bacterial growth, chemical irritation and inflammation of the esophageal mucosa which triggers hyperplastic and dysplastic changes, is thought to be the underlying mechanism of ESCC in achalasia.[6] All three patients with ESCC had chronic food/liquid stasis during endoscopic screening and at the time of diagnosis. One of the patients with LGD had endoscopic stasis during screening. However, no significant difference was observed in the risk of developing LGD or ESCC between patients with and without endoscopic stasis. Probably, this can be explained by the low number of patients with LGD or ESCC. Our data seem to suggest that impaired esophageal emptying contribute to and increased cancer risk. Furthermore, we showed that the majority of patients with ESCC or LGD were diagnosed after >20 years of onset of symptoms and diagnosis. Other risk factors for esophageal carcinoma, like alcohol and tobacco use could be added to the risk stratification. We observed that for both ESCC as LGD most patients had a history of tobacco us with >20 pack years. Concerning the screening interval between endoscopies our data suggest that a 3 year interval is not necessary for low-risk patients

without stasis. However, studies with longer screening intervals are needed to confirm this. In addition, we believe that before any regular cancer screening for achalasia is considered, future studies are needed to develop adequate risk stratification based on the previous mentioned patient characteristics.

One of the shortcomings in this prospective cohort study is the relatively high loss to follow-up of 22%. Although, the patient characteristics of this group did not differ in major aspects (age, gender and disease duration), we cannot exclude an overestimation of the risk of ESCC. In addition, the study was performed at two large tertiary referral centers, which constitutes a possible selection bias. However, the incidence rate we described is comparable to previous studies making this less likely.

In conclusion, achalasia patients with a longstanding disease duration (>20 years) have an increased risk to develop esophageal dysplasia and carcinoma. Endoscopic screening using white light and Lugol chromoendoscopy does not accurately identify precursor lesions for ESCC and therefore cannot be systematically recommended.

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Thesis summary
Discussion and future perspectives

9

THESIS SUMMARY

Achalasia is a relatively rare chronic esophageal motility disorder, causing esophageal dysfunction. It is characterized by aperistalsis of the esophageal body and impaired relaxation of the lower esophageal sphincter (LES) leading to incomplete esophageal emptying with subsequent symptoms of dysphagia, regurgitation, chest pain and weight loss. Although achalasia is an acknowledged and well-defined disease for more than half a century, in the last two decades advancements in diagnostic testing and treatment of achalasia significantly changed the vision and therapeutic strategy. Studies described in this thesis attempt to break down more barriers for this disease by assessing the new diagnostic tools and treatment options including enhancement of long-term follow-up, with the goal to further optimize the clinical management of achalasia.

Part I – Diagnostic management

The first part of this thesis consists of studies that effectuate and improve current diagnostic testing of achalasia. Esophageal high-resolution manometry (HRM) is the gold standard for diagnosing esophageal motility disorders like achalasia, due to the high diagnostic accuracy, reproducibility and inter-observer consistency. HRM uses key metrics, defined by the Chicago Classification, to assess esophageal motility disorders. The key HRM metrics are: 1) deglutitive relaxation across the lower esophageal sphincter (LES)/ esophagogastric junction (EGJ) by integrated relaxation pressure (IRP); 2) esophageal peristalsis/ contractility by distal contractile integral (DCI), that measures esophageal contractile vigor (amplitude, duration and length of contraction) and pattern (contiguity of contraction); 3) latency of deglutitive inhibition by distal latency (DL), observing the time from start of the swallow till arrival of the esophageal contraction in the distal esophagus; 4) esophageal pressurization by isobaric contour to analyze outflow obstruction. **Chapters 2** and **3** focus on the use of HRM in diagnostic management of achalasia, exploring its accuracy, the feasibility and usefulness of current outcome metrics and new provocative function tests.

In **chapter 2** a prospective cohort study is described of a specially defined group of 13 patients with a normal upper endoscopy, clinical and radiological features of achalasia but not fulfilling the diagnostic HRM criteria for the diagnosis: absent peristalsis and incomplete relaxation of the lower esophageal sphincter (LES) / esophagogastric junction (EGJ) reflected by an integrated relaxation pressure (IRP) >15 mmHg. All HRM studies of these patient showed absent peristalsis but the IRP values were within the upper limit of normal, all <15 mmHg, presuming normal relaxation pressure across the EGJ. However, clear stasis was seen on timed barium esophagogram (TBE) in line with their obstructive symptoms, suggestive of outflow obstruction at the EGJ. The aim was to objectify the presumed outflow obstruction at the EGJ by measuring

EGJ distensibility using impedance planimetry (EndoFLIP) to support the diagnosis of achalasia. Once confirmed, achalasia treatment was performed and its effect assessed by repeating measurements at 3 months follow-up. With impedance planimetry, a balloon with increasing distension volumes evaluates EGJ opening and thereby its distensibility. In all patients EGJ distensibility was significantly reduced compared to healthy subjects. Actually, similar low values as seen in treatment-naïve achalasia patients were observed. Treatment significantly improved symptoms and normalized EGJ distensibility in all patients. This study indicates that in patients with clinical features of achalasia but inconclusive diagnosis by HRM based on borderline IRP values, timed barium esophagogram or EndoFLIP can help to diagnose achalasia and if confirmed, should be treated as such.

Standard or timed barium esophagogram and provocative function tests during HRM can be supportive in diagnosing esophageal motility disorders in case key HRM metrics are inconclusive. The rapid drinking challenge (RDC), consisting of rapidly ingesting 200 ml of water, is a provocative test that is used to test for EGJ outflow obstruction during HRM. For achalasia, standard or timed barium esophagogram (TBE) is considered a complementary diagnostic test that observes esophageal stasis as a degree of esophageal emptying and provides information on the esophageal contour/diameter. However, it exposes patients to ionizing radiation and an additional test. In **chapter 3**, RDC during HRM studies of achalasia patients were assessed to see if esophageal stasis could be observed similar as with TBE and may refrain performing TBE when information on the esophageal diameter is unnecessary. The response to RDC was measured by basal and relaxation pressure across the EGJ and esophageal pressurization during the RDC. HRM with RDC and TBE were performed in achalasia patients that were treatment-naive, post-treatment with and without recurrent symptoms and healthy subjects. The findings were that all achalasia patients had a significantly higher esophageal pressurization, EGJ basal and relaxation pressure during RDC than healthy subjects. Esophageal pressurization during RDC was strongly correlated to the barium column height at TBE, reflecting esophageal stasis. Additionally, RDC could reliably identify clinical response to achalasia treatment equivalent to the predictors of standard HRM and TBE. This confirms the value of adding RDC to HRM studies of achalasia patients and may withhold the use of TBE in these patients.

Benign or malignant abnormalities involving the esophagus, EGJ or (proximal) stomach can mimic clinical and diagnostic features of achalasia, a condition described as pseudoachalasia. In most cases a primary (esophageal, EGJ or gastric cardia carcinoma) or secondary malignancy is the underlying cause. Early recognition of malignancy-associated pseudoachalasia is important

to prevent delay in appropriate treatment. However, discriminating this condition from achalasia with the standard diagnostics (medical history, esophagogastroduodenoscopy, HRM and TBE) is challenging. **Chapter 4** presents risk factors that suggest the presence of malignancy-associated pseudoachalasia, based on a large retrospective cohort of newly diagnosed idiopathic achalasia patients including overtime diagnosed pseudoachalasia patients. In a cohort of 333 achalasia patients, 5.4% (18 patients) were diagnosed with malignant pseudoachalasia of which 50% during or after primary achalasia treatment. At time of achalasia diagnosis advanced age of ≥ 55 years, short duration of symptoms of ≤ 12 months, weight loss of ≥ 10 kg and difficulty in passing the EGJ during initial esophagogastroduodenoscopy were identified as risk factors for potential malignancy-associated pseudoachalasia. Outcome metrics of HRM and TBE were not discriminating. Qualitative/multivariate assessment of the risk factors showed that additional investigations to exclude an underlying malignancy are warranted in achalasia patients with two or more of these risk factors present at time of primary diagnosis. Based on this study, no recommendation could be made on the specific type of additional investigation that certainly diagnoses malignancy-associated pseudoachalasia.

Part II – Treatment

Achalasia treatment currently involves pharmacological (oral nitrates or calcium channel blockers, botulinum toxin injections), endoscopic (pneumatic dilation) and surgical (laparoscopic Heller myotomy) options focused on reducing LES obstruction to improve esophageal emptying. Worldwide, endoscopic pneumatic dilation is the most performed first-line treatment for achalasia. Peroral endoscopic myotomy (POEM) was introduced in 2009 as an alternative, minimally invasive endoscopic treatment option for achalasia with high efficacy rates. However, direct comparison with current standard of care was lacking. **Chapter 5** describes the results of a large multicenter randomized clinical trial, comparing the effects of POEM versus pneumatic dilation as the initial treatment for treatment-naive patients with idiopathic achalasia. Six hospitals in the Netherlands, Germany, Italy, Hong Kong and the United Stated conducted the trial and included 133 achalasia patients of which 67 were randomized to POEM and 66 to pneumatic dilation with a 30-mm and 35-mm balloon. Primary outcome was treatment success at 2-year follow-up, defined as an Eckardt score ≤3 and the absence of severe complications or re-treatment. Secondary pre-specified endpoints, included outcome parameters of HRM (basal pressure and IRP of the LES) and TBE (esophageal stasis and diameter), complication and re-treatment rate, presence of reflux esophagitis, esophageal acid exposure, proton pump inhibitor (PPI) use, questionnaires on quality of life and reflux symptoms. Of the 133 randomized patients, 130 underwent treatment of which 64 underwent POEM and 66 pneumatic dilation. In total, 4 patients were lost

to follow-up. Treatment success at 2-year follow-up was significantly higher in patients treated with POEM (95%; 58 of 63 patients) compared with pneumatic dilation (54%; 34 out of 63 patients). Two serious adverse events occurred after pneumatic dilation, including 1 perforation, while none occurred after POEM. Of the 14 pre-specified secondary end points, no significant difference between groups was demonstrated in 10 end points. Reflux esophagitis was significantly more present after POEM (41%; 22 out of 54) compared with pneumatic dilation (7%; 2 out of 29), with a more severe grade of esophagitis and increased PPI use in the POEM group. The findings of this trial support consideration of POEM as an initial treatment option for patient with achalasia. The prevalence of reflux esophagitis after POEM is however substantial and for patients often asymptomatic. Consequently, the use of PPI and endoscopic follow-up after POEM should be addressed in the long-term.

In addition to achalasia, POEM seems an effective treatment for distal esophageal spasm (DES) refractory to medical therapy. DES is an esophageal motility disorder characterized by premature and rapidly propagated esophageal contractions with normal LES relaxation causing dysphagia and chest pain. Standard treatment options are pharmacological (calcium channel blockers; PPI; nitrates or botulinum toxin injections) with a poor and transient effect. With POEM an extended myotomy can be performed, cleaving the circular muscle of the distal and mid esophagus, potentially establishing a permanent effective treatment for DES. **Chapter 6** presents the challenges and difficulties that can arise performing POEM in DES patients. In the described case of a therapy-refractory DES patient, hyperactive spastic esophageal contractions during the POEM procedure gave technical challenges for creating the submucosal tunnel and extended the procedure time compared to achalasia patients (134 versus 60-90 minutes). Per-procedural nitroglycerin intravenously diminished the spastics contractions. Post-procedurally, increased retrosternal pain and dysphagia attributed to edema and spasm, led to a prolonged hospital admission. At 3 months follow-up symptoms were improved but the patient still experienced proximal dysphagia and occasional episodes of non-passage due to a remnant of hypertensive and spastic muscle proximal of the start of the myotomy causing a prestenotic dilation. Based on this experience we conclude that POEM is a promising treatment for patients with therapy-refractory DES. However, the described caveats of reactive per- and postprocedural spastic esophageal contractions complicating the technical execution and duration of POEM and the proximal start of the myotomy above the proximal border of the spastic region to prevent a muscle remnant, should be taken into account.

Part III – Long-term follow-up

Achalasia is a chronic disease with an indication for life-long follow-up to evaluate symptom control, disease-related complications and treatment-related side-effects. One of the major treatment-related concerns is reflux symptoms and/or reflux esophagitis since achalasia treatment aims to disrupt the LES which compromises the EGJ barrier against reflux. Although these symptoms are considered to be related to gastroesophageal reflux, patients have a variable response to acid suppression and studies show a poor correlation with pH-monitoring and/or reflux esophagitis. **Chapter 7** focusses on reflux symptoms in previously treated achalasia patients (after pneumatic dilation, Heller myotomy or POEM) and attempts to identify the underlying mechanisms of these symptoms. A prospective observational case-control study was performed that included 40 treated achalasia patients with and without reflux symptoms. Patients underwent measurements to evaluate esophageal function (esophageal motility by HRM; esophageal emptying by TBE; EGJ distensibility by EndoFLIP), acid exposure and acidification patterns (by 24-hour ambulatory pH-impedance monitoring and postprandial stationary HRM and pH-impedance monitoring), symptom perception (esophageal sensitivity to acid using an acid perfusion test and mechanical distension by EndoFLIP) and esophagitis (by esophagogastroduodenoscopy). Measurements were performed after cessation of PPI, H2-receptor antagonist and/or prokinetic medication for 1 week. Total acid exposure time during 24 hours and results of post-prandial pH-impedance monitoring were comparable between patients with and without reflux symptoms. Reflux symptoms during pH-impedance monitoring were not related to acid in both groups. Esophageal acidification after achalasia treatment, independent of symptoms, was however frequently observed during pH-impedance monitoring which was partially reflux induced but largely due to acid fermentation and acidic-food-induced stasis. The predominant acidification patterns in patients with reflux symptoms were acid fermentation and acid reflux with delayed clearance. Acid perfusion tests revealed that patients with reflux symptoms were highly sensitive to acid, with a shorter time to heartburn perception and a higher symptom intensity of heartburn. The sensitivity for mechanical distension was also significantly higher in this group. No differences were observed between the groups in esophageal motility, esophageal emptying, EGJ distensibility and frequency of endoscopic reflux esophagitis. Based on these findings, it can be concluded that reflux symptoms in treated achalasia patients are rarely caused by gastroesophageal reflux but instead esophageal hypersensitivity to chemical and mechanical stimuli may generate these symptoms. Presence of esophageal acidification after achalasia treatment is however common but this is rarely reflux related. Altering the diagnostic approach of reflux symptoms in treated achalasia patients is therefore needed and will lead to a more tailored-approached

treatment that no longer should be limited to acid suppression but also targets on reducing esophageal acidification and esophageal hypersensitivity.

Achalasia patients with longstanding disease are considered to be at risk to develop esophageal carcinoma compared to the general population. The assumed cause of this disease-related complication seems two-fold: (1) poor esophageal emptying may lead to increased bacterial growth, chemical irritation and inflammation triggering dysplastic mucosal changes leading to esophageal squamous cell carcinoma (ESCC) (2) absent EGJ barrier post-treatment combined with aperistalsis may lead to increased acid exposure, esophagitis and Barrett's esophagus with eventually adenocarcinoma. Timely identification of esophageal carcinoma is important since the prognosis is mainly determined by the stage of the disease at time of diagnosis. Endoscopic screening in longstanding achalasia is not standardized and detection of dysplastic lesions is difficult in these patients. In **chapter 8** the efficacy of screening with lugol chromoendoscopy for esophageal dysplasia and carcinoma in patients with longstanding achalasia is evaluated. In a cohort of 230 achalasia patients screening with white light and lugol chromoendoscopy was performed every three years during a period of 16 years. Initially this was done independent of disease duration, later after a disease duration of at least 10 years. Once dysplastic lesions were detected screening became annually and patients with high-grade dysplasia of esophageal carcinoma were treated. Three patients in this cohort (1.3%) developed ESCC, without precursor lesions, low-grade of high-grade dysplasia, at preceding screening endoscopy. The incidence rate for ESCC was 63 per 100.000 person-years, 14- to 23-fold compared to the general population. Low-grade dysplastic lesions were observed in four patients (1.7%), without progression to high-grade dysplasia or carcinoma during 9-year follow-up. Both ESCC and low-grade dysplasia developed in patients with a disease duration of >20 years. The use of lugol chromoendoscopy tripled the detection rate of suspected esophageal lesions compared to white light, but resulted in a low specificity of histological proven abnormalities. This study confirms that achalasia patients with longstanding disease (>20 years) have an increased risk to develop esophageal dysplasia and carcinoma. However, systematic endoscopic screening in achalasia using white light and lugol chromoendoscopy does not accurately identify precursor lesions for esophageal carcinoma which hampers adequate risk stratification and therefore cannot be recommended.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Advancements in the development of diagnostic and therapeutic options have significantly changed the management of achalasia in the past decade and enhanced the knowledge on this esophageal motility disorder. The implementation of high-resolution manometry (HRM) with pressure topography led to a major reclassification in diagnosing esophageal motility disorders. To analyze HRM studies a new classification system was introduced, the Chicago Classification.[1] The Chicago Classification developed standardized HRM metrics that increased the detection of clinically relevant esophageal motility disorders and identified three achalasia subtypes. Coincident with the introduction of HRM, an innovative endoscopic therapeutic intervention was developed for achalasia: the peroral endoscopic myotomy (POEM), a treatment with assumed disease- and patient-tailored advantages.[2] The clinical implication of these innovations for patients with achalasia remains to be further determined and also raises new clinical questions on this disease. Studies addressed in this thesis contribute to the improvement of the clinical management of achalasia and focused on I) optimizing the diagnostic management of achalasia by exploring the value of current and additional diagnostic tools, II) evaluating the efficacy of new and current achalasia treatments, and III) enhance strategies for the long-term follow-up of achalasia patients. This chapter elaborates on the impact and consequences of the study findings for the current management of achalasia and assesses the barriers that are settled or still need to be addressed.

Optimizing diagnostic management of achalasia

Symptom assessment

Of all esophageal motility disorders achalasia is the most well-defined. Despite this, a diagnostic delay often occurs as symptoms are not directly recognized, not disease-specific leading to an erroneous diagnosis of for example gastro-esophageal reflux disease and with an incidence of 1-2.2 cases per 100,000 individuals it is a relative rare disease with low awareness by clinicians outside gastroenterology.[3-5] The most common first sign of achalasia is dysphagia for solids and/or liquids.[6 7] In combination with other esophageal symptoms like regurgitation and chest pain there is a clear indication for an esophagastroduodenoscopy to rule out intrinsic mechanical esophageal or oropharyngeal disorders. When esophagogastroduodenoscopy excludes order disorders a diagnosis of achalasia should be considered and referral to the gastroenterologist is indicated for excluding esophageal motility disorders by HRM and barium esophagogram. A careful medical history is important as it can help to discriminate between achalasia and pseudoachalasia (**chapter 4**). Benign causes of pseudoachalasia can often be identified by the clinical history (eg fundoplication or gastric band). Detecting malignancy-associated pseudoachalasia is more difficult as it can mimic all symptoms and endoscopic,

radiographic and manometric findings of achalasia, while early diagnosing of a malignancy has major clinical implications. The study described in **chapter 4** explored potential patient-specific risk factors that discriminate malignant pseudoachalasia from achalasia. Older patients (≥ 55 years), short duration of symptoms (≤ 12 months), severe weight loss (≥ 10 kg) and difficulty passing the esophagogastric junction (EGJ) by endoscopy were associated with a higher risk of malignant pseudoachalasia. Based on these data a model was produced in which the presence of two or more risk factors increased the risk for malignancy and only in these patients additional testing is warranted. This recommendation is recently adopted by the European and American guideline on the management of achalasia. [8 9] Both in this study as the literature, the choice of the best additional diagnostic testing (repeated endoscopy, endoscopic ultrasound (EUS) or CT) to rule out malignancy-associated pseudoachalasia remains to be determined.[8 10 11] Repeating endoscopy with an option for concurrently EUS seems preferably as the majority of cases result from malignant obstruction at the EGJ and difficulty passing the EGJ by the endoscope is inherent to subjectivity.[12 13] In addition, besides ruling out an infiltrating tumor, EUS can further make achalasia more likely when a thickened circular muscle layer is observed.[11 14] To further optimize the model and find the best additional test to diagnose malignant pseudoachalasia multicenter prospective data acquisition should be set up.

Diagnostic testing

The gold standard to diagnose achalasia is by esophageal manometry, with the defining characteristics of incomplete LES relaxation and absent peristalsis upon deglutition. [1 15] Worldwide, HRM largely replaced conventional manometry because increased pressure sensors in the catheter in combination with colored pressure topography plots led to a higher diagnostic accuracy, improved reproducibility and inter-observer consistency of esophageal motility disorders.[16-18] With the use of HRM new objective diagnostic metrics were developed to define esophageal motility and conceptualized in the Chicago Classification.[1 17 19 20] Within this classification a standardized HRM protocol, diagnostic thresholds and a hierarchical classification scheme for esophageal motility disorders are developed over the years.[1] HRM increased the knowledge on esophageal peristalsis and EGJ function but with its high accuracy also led to overdiagnosing of minor motility disorders without clinical relevance. Expanding research and clinical applications of HRM in the last years led to insights that further allowed refinement of the Chicago Classification. Achalasia is categorized as an EGJ outflow disorder: an abnormal integrated relaxation pressure (median relaxation pressure across the EGJ, IRP ≥ 15 mmHg) and absent peristalsis.[1] As the disease develops slowly, with a gradual transition from normal peristalsis and EGJ relaxation to absent peristalsis and EGJ outflow obstruction,

a conclusive diagnosis by HRM can be missed and supportive diagnostic testing is needed.[1 21] **Chapter 2** studied a subgroup of patients with clinical and radiological features of achalasia but an inconclusive HRM diagnosis based on a low to normal IRP with absent peristalsis. Esophageal stasis on timed barium esophagogram suggested EGJ outflow obstruction but was not confirmed by an increased IRP. With additional impedance planimetry measurements by the Endo functional luminal imaging probe (EndoFLIP), the stiffness and opening of the EGJ (EGJ distensibility) was evaluated during volumetric distension of the EndoFLIP balloon.[22-24] In the group of patients we studied, EGJ distensibility was reduced, comparable to achalasia patients with an increased IRP on HRM.[25-28] The fact that this subgroup of patients all responded to achalasia treatment further confirmed the diagnosis of achalasia in these patients. Data showed that approximately 10% of patients with typical clinical and/or radiological features of achalasia have an inconclusive diagnosis by HRM with the standard protocol of ten single water swallows.[29] HRM provides a surrogate measure of EGJ opening because relaxation is measured passively.[25] In case of a low baseline LES pressure or dilated esophagus a sufficient intrabolus pressure may not be generated to increase IRP to pathological levels.[29 30]

In the diagnostic work-up for achalasia clinicians should be aware of inconclusive diagnosis of achalasia by HRM. This can be related to IRP values to the upper limit of normal and appreciable peristalsis with changing position in the setting of achalasia type I and II.[1] Conform the subgroup described in **chapter 2**, these patients should all undergo supportive testing by TBE or EndoFLIP when the main presenting symptom is dysphagia. Both TBE and EndoFLIP should both be seen as complementary test to HRM in diagnosing achalasia and EGJ outflow obstruction in case of inconclusive diagnosis. An inconclusive diagnosis for achalasia type III is related to evidence of peristalsis during HRM and should be classified as EGJOO with spastic features.[1] Treatment in these patients should be restrained and only indicated in case of clinical relevant symptoms in combination with supportive testing for obstruction at the EGJ by TBE or EndoFLIP.[1] Although HRM is not flawless, clinical guidelines on achalasia and the Chicago Classification still consider HRM as the gold standard for diagnosing achalasia and currently refrain a primary diagnosis of achalasia by only TBE or impedance planimetry with EndoFLIP because esophageal contractility cannot be adequately observed by these modalities.[1 8]

In the last years studies on EndoFLIP has demonstrated its clinical utility in achalasia as a diagnostic tool and to measure response to therapy.[24] One of the advantages over HRM is that it also can be used during upper endoscopy. EGJ distensibility is used as a metric to diagnose impaired LES relaxation and/or mechanical obstruction at the EGJ. In the evaluation of esophageal outflow

obstruction, stasis during TBE had a good correlation with EGJ distensibility, outperforming HRM metrics.[31 32] Recent studies showed that endoFLIP (FLIP 2.0 panometry) can provide information on esophageal contractile patterns by luminal distension of the balloon in the esophageal body.[31 33] However, with this technique distension-induced contractions are assessed rather than swallow-induced contractions, it requires sedation and differentiation between the three achalasia subtypes is so far not possible. For the evaluation of treatment efficacy of achalasia, EndoFlip may serve as a complementary test to HRM and TBE or as an alternative of these modalities.[23 25 26]

Timed barium esophagogram can assess esophageal stasis in achalasia as a reflection of EGJ outflow obstruction and provides information on the anatomy of the esophagus. Similar to EndoFLIP this modality is complementary to HRM in the diagnostic work-up of achalasia. For the evaluation of treatment outcome, assessing esophageal emptying by stasis on timed barium esophagogram is superior to all HRM metrics.[34-37] However data on predicting long-term treatment success are conflicting. [35 38-40]

Besides EndoFLIP and/or timed barium esophagogram supportive manometric measurements in the HRM standard protocol can also assist in case of inconclusive diagnosis of achalasia. In the latest Chicago Classification different provocative tests are suggested. In **chapter 3** one of these provocative tests was studied, the rapid drinking challenge (RDC). This provocative test was reliable in assessing outflow obstruction in achalasia patients at diagnosis comparable to TBE, reflected by incomplete deglutitive inhibition of the LES with an elevated IRP and (pan)esophageal pressurization during the RDC. The RDC was also helpful in cases of an inconclusive diagnosis of achalasia, revealing (pan)esophageal pressurization during the entire test. In addition, treatment response could be adequately identified by the RDC. The determined outcome parameters of the RDC were compatible with the current standard predictors of treatment outcome; symptomatic measures, stasis during TBE and the manometric IRP. Other provocative manometric tests that can serve as supportive data in case of an inclusive diagnose by HRM are multiple rapid swallows, solid test swallows, solid test meal, post-prandial meal and pharmacological provocation tests (amyl nitrite or cholecystokinin).[1] In the current Chicago Classification none of these tests are definitely recommended to support or exclude the diagnosis of achalasia in case of doubt, a second diagnostic modality (timed barium esophagogram or EndoFLIP) should always be performed.[1 41] Based on the data described in **chapter 3** the RDC could be a good candidate to develop as a supportive validated manometric test in case of an inconclusive diagnosis of achalasia. Future advancements in HRM including adding impedance may further improve diagnostic criteria for achalasia and strengthen the clinical

relevance of the provocative tests.[41] Furthermore, prospective studies and randomized controlled trials that perform follow-up of achalasia patients over time, with pre- and post-treatment evaluation by the different diagnostic modalities, could further determine the best strategy for the diagnostic work-up, evaluating treatment efficacy and predicting symptom recurrence.

Efficacy of new and current achalasia treatments

The treatment of achalasia is challenging as no curative therapy is available and the disease course is chronic with a risk on recurrent treatments. All treatments focus on symptom improvement by optimizing esophageal emptying by destructing the LES. Options for treatment are pharmacological, endoscopic or surgical. As a pharmacological treatment option only botulinum toxin injections have proven its efficacy when injected in the LES.[42 43] As the response fades within 6-12 months guidelines suggest that this treatment should be reserved for patients not capable undergoing a more invasive treatment.[8 9] Most well-known treatment modalities are pneumatic dilation and laparoscopic Heller myotomy. Pneumodilation is worldwide the most commonly performed therapy as it is minimal invasive with a long-term success rate of 50-85%.[44-47] Therefore it is often used as a first-line treatment. However multiple dilation sessions can be needed to remain symptom free. The laparoscopic Heller myotomy combined with an antireflux procedure offers a more permanent solution with success rates of 80-90% after 5 years.[44 45 48] This treatment is often reserved for those with treatment failure with pneumodilation, as it is more invasive with a higher risk on complications.[48] In the last decade POEM was introduced as a new treatment option. POEM was rapidly adopted as a treatment option for achalasia because of its high efficacy, endoscopically performed myotomy and low complication rate and quickly became a possible first-line treatment option for achalasia, in the absence of comparative trials. In **chapter 5** the first randomized controlled trial with POEM is described and compared its efficacy with pneumatic dilation in treatment naive achalasia patients. POEM had a significantly higher treatment success rate at 2-year follow-up compared to pneumatic dilation (92% versus 54%) with similar safety data. The high incidence of reflux oesofagitis and consequently PPI use was however a major disadvantage of POEM. Data on the five-year follow-up were recently published and showed a persistent significantly higher long-term treatment success for POEM of 81% compared to 40% in the pneumatic dilation group.[49] These data suggest that POEM could be proposed as one of the first-line treatment options.[49 50] The relative low success rate of pneumodilation in our study can be explained by the dilatation protocol that was used, defining the need for repeated dilations during follow-up as a failure. Repeated pneumodilations occurs during clinical practice but can also be considered as a new treatment with potential risks, therefore POEM was compared with

only a single pneumatic dilation session.[49 50] In addition, a part of the patients failed in the pneumatic dilation group subsequent underwent pneumatic dilation up till a 40-mm balloon which increased the treatment success to 76% at 2-year follow-up but was still significantly lower than the 92% success rate in the POEM group, questioning the value of repeated dilations. Previous studies on laparoscopic Heller myotomy show similar efficacy rates (80-85%) at 5-year follow-up compared to POEM.[44] The advantage of laparoscopic Heller myotomy is the additional antireflux procedure that is performed. However studies showed that in 20% of the patients developed reflux esophagitis after laparoscopic Heller myotomie. [45 51] Although the data suggest to abandon pneumodilation as a treatment for achalasia, it still should be offered as therapeutic option as it is minimal invasive with a low risk on reflux oesophagitis.

The ultimate goal for achalasia treatment is a patient-tailored approach. A recent systematic review explored potential patient-specific preditors.[52] In total of 34 predictors were identified but only age and manometric subtype were found to have a strong cumulative level of evidence.[52] Younger patients (<40-45 years) have a higher chance on failure after pneumodilation.[52 53] Manometric subtype III was associated with a poor treatment outcome, while subtype II has the highest success rates for all treatment types.[52 53] Based on these patient characteristics, patient's preference and clinical expertise a shared decision on the treatment should be made.

The incidence of reflux esophagitis after POEM is a concern and was still high at 5-year follow-up in the randomized trial, with a percentage of 33%.[49] The severity of reflux oesofagitis is however usually mild and adequately treatable with PPI, but endoscopic follow-up is indicated. It is the question if there are predisposing factors that are related to reflux esophagitis in POEM. The length and the thickness of the myotomy could play a role, but data are conflicting.[54] Other possible contributing factors are a high BMI, alcohol consumption and pre-existing reflux symptoms.[55] In these patients a different initial treatment such as laparoscopic Heller myotomy or pneumodilation can be considered. Furthermore transoral incisionless fundoplication or anti-reflux mucosectomy could be of use in severe reflux oesofagitis after POEM.[56 57] The potential and efficacy of these techniques for achalasia patients should be further explored. Another potential complication of the endoscopic and surgical myotomy is the formation of a blown-out myotomy in the distal esophagus, resulting in a pseudodiverticulum that can progressively enlarge and compromise esophageal emptying mandating surgery in the future.[58 59] Cases for both Heller myotomy and POEM are described and a longer full-thickness myotomy seems to increase the risk of a blown-out myotomy.[58] Future studies have to reveal

the optimal technique to perform the myotomy and identifying risk factors to prevent a blown-out myotomy.

Improving the long-term follow-up in achalasia

The ultimate goal of achalasia treatment is a low recurrence rate without treatment related side-effects. The current randomized controlled trials, meta-analysis on these trials and prospective studies on the different treatment modalities give increasing insight about the long term treatment effects for achalasia.[44 49 50 60 61] It is important to study pre-procedural predictors of treatment outcome to develop patient-tailored treatment. However, developing a standardized follow-up protocol post-treatment is also a priority. Lacking an universal definition on treatment failure and the variability between symptoms and objective outcome measures complicates the development of a standardized follow-up protocol to determine treatment efficacy.[8 62] The type of symptom seems to be leading in the choice of additional testing. Timed barium esophagogram and impedance planimetry by EndoFLIP seems useful to objectify persistent outflow obstruction in case of recurrent dysphagia.[8 35 36 63] For chest pain an additional HRM can be considered for examples to exclude spastic contractions.[8] As recurrent symptoms can have a variability of underlying causes, development of standardized objective test protocol should be developed.

Furthermore, selecting a treatment after symptom recurrence is challenging as prospective studies on retreatment are lacking, especially on LHM and POEM. A recent randomized study on failure after LHM showed a higher success rate for POEM than PD after 1 year, although with a higher incidence of reflux esophagitis.[64] For recurrence after POEM only case series are described that showed that both re-POEM as LHM have modest efficacy rates, 80-63% vs 45% observed during a short term follow-up.[65-67] For now guidelines advice all three treatment modalities (PD, LHM and POEM) are possible in case of failure. Improving our understanding on risk factors for treatment failure and knowledge on follow-up post-procedure will help to further optimize treatment and the options for retreatment.

An expected side effect of destruction of the LES by achalasia treatment is gastro-esophageal reflux. Post-treatment, the prevalence of reflux symptoms and/or reflux oesofagitis varies between 5% and 60%.[48 50 51 60 68] This variability is related to the definition of reflux, treatment modality for achalasia and type of measurement used to define reflux. [48 50 51 60 68-71] In **chapter 7** the underlying mechanism of these reflux symptoms was studied. The data showed that reflux symptoms in treated achalasia were rarely caused by true gastro-esophageal reflux. Pathological acid exposure during pH-impedance monitoring was commonly observed post-treatment, independent of the type of achalasia

treatment. However, this was not predominantly caused by acid reflux but largely due to acid fermentation or acidic food-induced stasis. Furthermore, none of the patients with reflux symptoms had a positive association between acidification events and their reflux symptoms. Patients with reflux symptoms did have esophageal hypersensitivity to chemical and mechanical stimuli that seem to play an important role in generating these symptoms. The observed discordance between reflux symptoms and objective signs of gastro-esophageal reflux in this study and previous literature suggest an altered diagnostic and treatment approach in these patients as the underlying causes are diverse.[72-77] Consequently treatment of reflux symptoms should no longer be focused on solely acid suppression but also targeting esophageal acidification and esophageal hypersensitivity. Future studies should be performed to understand the pathophysiology of the esophageal hypersensitivity in these patients as a target for therapy with for example visceral analgetics.

A long-term consequence of achalasia is the increased risk for esophageal cancer, especially in longstanding disease.[78-80] Compared to the general population it is estimated that this risk is 10-50 fold increased for squamous cell carcinoma and 0.5-10 for adenocarcinoma, independent of the type of treatment.[78 79 81-84] Chronic irritation of the esophageal mucosa due to poor esophageal emptying or acid exposure after disrupting of the LES seem to increase the risk of esophageal carcinoma.[78-80 85 86] Current guidelines advise against regular endoscopic screening due to the controversy in the exact cancer risk caused by differences in study design, length of follow-up and number of included patients.[80] However, endoscopic screening could be beneficial in patients with longstanding disease in combination with the current advanced endoscopic imaging techniques. In **chapter 8** we aimed to evaluate the efficacy of screening for esophageal dysplasia and carcinoma in achalasia patients with a disease duration of at least 10 years using chromoendoscopy with Lugol. In accordance to the literature achalasia patients with a longstanding disease duration, more than 20 years, had a 14- to 23-fold increased risk on esophageal carcinoma. [78 79 81-84] Endoscopic screening using white light and Lugol chromoendoscopy did not accurately identify precursor lesions for esophageal carcinoma. Therefore systematic endoscopic screening for esophageal cancer cannot be recommended. However, the threshold of upper endoscopy should be low in patients with longstanding disease in combination with recurrent symptoms and/or signs of impaired esophageal emptying.[8]

Breaking down barriers: now and the future

This thesis attributed to the clinical implications of the diagnostic and therapeutic advancements for achalasia in the last two decades. One of the major unanswered question is the pathophysiology of the neuronal loss at the

myenteric plexus in this disease. The general hypothesis is that achalasia is an auto-immune disorder targeting esophageal myenteric neurons by a cell- and antibody mediated response triggered by a viral infection, in genetically predisposed patients. Identifying the responsible antigen and genes would help to eventually prevent to develop achalasia or at least could stop the neuronal loss by targeted therapy.

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Addendum

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A

NEDERLANDSE SAMENVATTING

Achalasie is een relatief zeldzame chronische motiliteitsstoornis van de slokdarm die leidt tot een sterke afname van de slokdarmfunctie. De ziekte wordt gekenmerkt door afwezige peristaltiek van de slokdarm en niet relaxeren van de onderste slokdarmsfincter (LES) waardoor de slokdarm onvoldoende ledigt wat leidt tot klachten als dysfagie, regurgitatie, retrosternale pijn en gewichtsverlies. Achalasie is in de afgelopen 50 jaar een duidelijk omschreven en erkend ziektebeeld geworden. De afgelopen twee decennia hebben technologische ontwikkelingen op het gebied van diagnostiek en behandeling de visie en therapeutische strategie voor deze ziekte aanzienlijk veranderd. In dit proefschrift worden deze nieuwe mogelijkheden op het vlak van diagnostiek en therapie geëvalueerd, inclusief de impact van deze chronische ziekte op de lange termijn, met als doel het beleid voor achalasie in de huidige praktijk te verbeteren.

Deel I - Diagnostiek

Het eerste deel van het proefschrift bestaat uit studies die de huidige diagnostiek voor achalasie evalueren en verbeteren. Hoge-resolutie manometrie (HRM) is de gouden standaard voor het diagnosticeren van motiliteitsstoornissen van de slokdarm zoals achalasie. Dit komt door de hoge diagnostische nauwkeurigheid, reproduceerbaarheid en interobservationele betrouwbaarheid bij beoordeling van de HRM. Voor de analyse van de HRM wordt er gebruik gemaakt van gestandaardiseerde uitkomstparameters, gedefinieerd bij de Chicago Classificatie, om de slokdarmmotiliteit te beoordelen. Dit zijn: 1) slik-geïnduceerde relaxatie van de LES / gastro-oesofageale overgang door meten van de relaxatie druk (integraded relaxation pressure, IRP); 2) peristaltiek/contractiliteit van het slokdarmlichaam door distale intraluminale contractie druk (distal contractile integral, DCI) waarbij de kracht (intraluminale drukverhoging, duur en lengte contractie) en het patroon (continue of onderbroken contractie) van slokdarmcontracties wordt beoordeeld; 3) snelheid van de slokdarmcontractie door distale latentie (distal latency, DL), waarbij de tijdsduur vanaf de start van een slik tot aankomst van de slokdarmcontractie in de distale slokdarm wordt gemeten; 4) intraluminale drukopbouw in de slokdarm door isobarische drukcontour ter beoordeling van slokdarmlediging. **Hoofdstuk 2** en **3** beschrijven studies waarin de nauwkeurigheid en bruikbaarheid van deze gestandaardiseerde HRM uitkomstparameters voor de diagnose achalasie worden beoordeeld en de toegevoegde waarde van een nieuwe provocatietest tijdens HRM metingen bij achalasie patiënten worden geëvalueerd.

Hoofdstuk 2 beschrijft een prospectieve cohort studie van een groep van 13 patiënten met klinisch en radiologische kenmerken passend bij achalasie, normale gastroscopie, maar waarbij de diagnose niet kan worden gesteld

op basis van de diagnostische criteria bij HRM: afwezige peristaltiek en incomplete relaxatie van de LES / gastro-oesofageale overgang geduid als een IRP >15 mmHg. Alle HRM metingen van deze patiënten toonde afwezige peristaltiek maar een IRP waarde onder de afkapwaarde van 15 mmHg, suggestief voor normale relaxatie van de LES / gastro-oesofageale overgang. Aanvullende getimede bariumslikfoto toonde echter forse stase van contrast in de slokdarm, passend bij de dysfagie klachten van patiënten en suggestief voor outflow obstructie ter plaatse van de gastro-oesofageale overgang. Het doel van de studie was om deze outflow obstructie aan te tonen middels distensibiliteitsmetingen van de gastro-oesofageale overgang ter bevestiging van de diagnose achalasie. Indien de diagnose kon worden bevestigd, ondergingen patiënten behandeling voor achalasie en werd 3 maanden later het effect hiervan beoordeeld met nieuwe metingen. De distensibiliteit van de gastro-oesofageale overgang werd gemeten middels impedantie planimetrie (EndoFLIP) waarbij een ballon met oplopend ballonvolume de opening van de gastro-oesofageale overgang beoordeelt en daarmee de distensibiliteit; rekbaarheid. Bij alle patiënten was de distensibiliteit van de gastro-oesofageale overgang sterk verlaagd ten opzichte van gezonde vrijwilligers en vergelijkbaar met onbehandelde achalasie patiënten. Achalasie behandeling gaf een significante verbetering van de klachten en een normale distensibiliteit van de gastro-oesofageale overgang in alle patiënten. Op basis van deze resultaten kan worden geconcludeerd dat patiënten met klinische kenmerken van achalasie maar bij wie middels HRM de diagnose niet kan worden gesteld op basis van de IRP, aanvullende getimede bariumslikfoto of EndoFLIP de diagnose alsnog kan bevestigen en deze patiënten achalasie behandeling moeten ondergaan.

Standaard of getimede bariumslikfoto en provocatietesten tijdens HRM kunnen bijdragen aan het diagnosticeren van motiliteitsstoornissen van de slokdarm wanneer de standaard uitkomstparameters van de HRM inconclusief blijken. De snelle drinktest (rapid drinking challenge; RDC), achtereenvolgend 200 ml water drinken, is een provocatietest uitgevoerd tijdens een HRM meting ter beoordeling van outflow obstructie ter plaatse van de gastro-oesofageale overgang. Voor achalasie wordt de standaard of getimede bariumslikfoto gezien als een complementair diagnosticum naast HRM, ter beoordeling van oesofageale stase als uiting van slokdarmlediging en het vastleggen van de diameter en/of contour van de slokdarm. Patiënten worden hiermee echter wel blootgesteld aan radiologische straling en een extra onderzoek. In **hoofdstuk 3** wordt beoordeeld of met de snelle drinktest tijdens HRM metingen bij achalasie patiënten adequaat oesofageale stase kan worden geobjectiveerd, zoals ook met een getimede bariumslikfoto. Hierdoor zou afgezien kunnen worden van een getimede bariumslikfoto als aanvullend diagnosticum wanneer informatie over de diameter en/of contour van de slokdarm niet

noodzakelijk is. Als uitkomstparameters van de snelle drinktest werd de basale en relaxatie druk gemeten ter plaatse van de gastro-oesofageale overgang en oesofageale intraluminale drukopbouw (pressurisatie) tijdens de test. HRM metingen met snelle drinktest (RDC) en getimede bariumslikfoto's werden verricht bij onbehandelde achalasie patiënten, behandelde achalasie patiënten met en zonder klachten en gezonde vrijwilligers. In vergelijking met gezonde vrijwilligers hadden alle achalasie patiënten een significant hogere oesofageale intraluminale drukverhoging, basale en relaxatie druk tijdens de snelle drinktest (RDC). De oesofageale intraluminale drukverhoging tijdens de snelle drinktest (RDC) had een zeer goede correlatie met de hoogte van de bariumkolom in de slokdarm tijdens de getimede bariumslikfoto en lijkt een goede, vergelijkbare parameter voor oesofageale stase te zijn. Verder konden de uitkomstparameters van de snelle drinktest (RDC) betrouwbaar de effectiviteit van achalasie behandeling inschatten, vergelijkbaar met predictie parameters van HRM en getimede bariumslikfoto. Deze studie bevestigt de toegevoegde waarde van de snelle drinktest bij alle HRM metingen voor achalasie patiënten en zou de aanvraag voor getimede bariumslikfoto als additioneel diagnosticum kunnen reduceren.

Benigne of maligne afwijkingen van de slokdarm, gastro-oesofageale overgang of (proximale) maag kunnen symptomen en diagnostische kenmerken van achalasie simuleren, dit fenomeen wordt beschreven als pseudoachalasie. Vaak is de oorzaak een primaire (carcinoom uitgaande van slokdarm, gastro-oesofageale overgang of cardia van de maag) of secundaire maligniteit. Vroege diagnose van pseudoachalasie op basis van een maligniteit is wenselijk om vertraging van behandeling te voorkomen, echter is het onderscheid met achalasie op basis van de standaard diagnostiek (anamnese, oesofagogastroduodenoscopie, HRM en getimede bariumslikfoto) lastig te maken. **Hoofdstuk 4** beschrijft risicofactoren voor maligniteit-geassocieerde pseudoachalasie, gebaseerd op een groot retrospectief cohort van patiënten met primaire idiopathische achalasie inclusief patiënten waarbij uiteindelijk pseuodachalasie is gediagnosticeerd. Van een cohort van 333 achalasie patiënten werd in 5.4% van de patiënten (18 patiënten) de diagnose maligniteit-geassocieerde pseudoachalasie gesteld, waarbij in 50% dit tijdens of na initiële achalasie behandeling werd gediagnosticeerd. Ten tijde van de achalasie diagnose bleken gevorderde leeftijd van ≥ 55 jaar, korte duur van symptomen ≤ 12 maanden, gewichtslies van ≥ 10 kg en duidelijk weerstand van de endoscoop bij passeren van de gastro-oesofageale overgang bij oesofagogastroduodenoscopie aantoonbare risicofactoren voor maligniteit-geassocieerde pseudoachalasie. Met HRM en getimede bariumslikfoto kon geen onderscheid gemaakt worden tussen de twee ziektebeelden. Aanvullende analyse van de risicofactoren toonde aan dat bij achalasie patiënten met twee

of meer risicofactoren ten tijde van de primaire diagnose, aanvullend onderzoek ter uitsluiting van een onderliggende maligniteit geïndiceerd is. Op basis van deze studie kon geen advies worden gegeven over de keuze van aanvullende diagnostiek om de diagnose maligniteit-geassocieerde pseudoachalasie met zekerheid vast te stellen.

Deel II – Behandeling

De huidige behandelopties voor achalasie zijn medicamenteus (botox injecties, oraal nitraten of calciumantagonisten), endoscopisch (pneumodilatatie) of chirurgisch (laparoscopische Heller myotomie) en alle gericht op verlagen van de druk van de LES om slokdarmlediging te bevorderen. Wereldwijd is endoscopische pneumodilatatie de meeste uitgevoerde eerstelijnsbehandeling voor achalasie. Perorale endoscopische myotomie (POEM) werd in 2009 ontwikkeld als een alternatieve, minimaal invasieve endoscopische behandeling voor achalasie met een hoge effectiviteit. Echter een vergelijking met de standaardbehandelingen ontbrak. **Hoofdstuk 5** beschrijft de resultaten van een grote multicenter gerandomiseerde klinische trial waarbij de behandeleffecten van POEM worden vergeleken met pneumodilatatie als initiële behandeling voor patiënten met onbehandelde idiopathische achalasie. De trial werd uitgevoerd in zes ziekenhuizen in Nederland, Duitsland, Italië, Hong Kong en de Verenigde Staten waarbij 133 achalasie patiënten werden geïncludeerd waarvan 67 patiënten werden gerandomiseerd voor POEM en 66 patiënten voor pneumodilatatie met een 30-mm en 35-mm ballon. Primaire uitkomstmaat was behandelsucces na 2 jaar follow-up, gedefinieerd als een Eckardt score ≤3 en de afwezigheid van ernstige complicaties of herbehandeling. Secundaire uitkomstmaten waren parameters van HRM metingen (basale rustdruk en IRP van de LES) en getimede bariumslikfoto (oesofageale stase en diameter), frequentie van complicaties en herbehandeling, aanwezigheid van refluxoesofagitis, oesofageale zuurexpositie, gebruik van protonpompremmers (PPI), vragenlijsten over kwaliteit van leven en reflux symptomen. Van de 133 gerandomiseerde patiënten, ondergingen 130 patiënten een behandeling waarvan 64 een POEM procedure en 66 pneumodilatatie. Gedurende de studie raakten 4 patiënten lost to follow-up. De mate van behandelsucces na 2 jaar follow-up was significant hoger na POEM (95%; 58 van de 63 patiënten) in vergelijking met pneumodilatatie (54%; 34 van 63 patiënten). Twee ernstige ongewenste behandelinggerelateerde uitkomsten werden geobjectiveerd na pneumodilatatie, waarvan 1 een perforatie betrof, terwijl dit na POEM in geen van de patiënten werd gezien. Er werden geen verschillen gevonden tussen de twee behandelgroepen bij 10 van de 14 secundaire uitkomstmaten. Refluxoesofagitis werd significant vaker gezien na POEM (41%; 22 van de 54 patiënten) in vergelijking met pneumodilatatie (7%; 2 van de 29 patiënten), waarbij in de POEM groep de ernst van de oesofagitis en mate van PPI

gebruik ook hoger was. De uitkomsten van deze trial ondersteunen het inzetten van POEM als een initiële behandeling voor achalasie. De prevalentie van refluxoesofagitis na POEM is echter substantieel en voor patiënten vaak asymptomatisch. Het gebruik van PPI en endoscopische follow-up na POEM moet daarom voor de lange termijn worden overwogen.

Behoudens voor achalasie, lijkt POEM ook een effectieve behandelmogelijkheid voor therapieresistente distale slokdarmspasmen. Distale slokdarmspasmen is een motiliteitsstoornis van de slokdarm gekenmerkt door premature en snel opvolgende slokdarmcontracties met normale relaxatie van de LES / gastro-oesofageale overgang. De aandoening kan leiden tot klachten als dysfagie en retrosternale pijn. De standaardbehandeling is medicamenteus (calciumantagonisten; PPI; nitraten of botox injecties) met een matig en tijdelijk effect. Met POEM kan een uitgebreide myotomie worden verricht middels het klieven van de circulaire spierlaag van distaal tot mid oesofageaal, leidend tot een permanente effectieve behandeling voor distale slokdarmspasmen. **Hoofdstuk 6** toont de uitdagingen en complicaties die kunnen optreden bij het uitvoeren van een POEM in patiënten met slokdarmspasmen. In de beschreven casus van een therapieresistente patiënt met slokdarmspasmen, zorgden reactieve spastische slokdarmcontracties gedurende de POEM procedure voor een technische uitdaging bij het uitvoeren van de submucosale tunnel en verlengden deze de duur van de procedure ten opzichte van achalasie patiënten (134 versus 60-90 minuten). Het gebruik van nitroglycerine intraveneus per-procedureel verminderde de slokdarmspasmen. De behandeling resulteerde in verlengde ziekenhuisopname door aanhoudende retrosternale pijn en dysfagie ten gevolge van lokaal oedeem en post-procedurele reactieve spasmen. Drie maanden na behandeling waren de symptomen evident verbeterd. Echter was er nog sprake van proximale dysfagie en episodes van non-passage veroorzaakt door een resterende hypercontractiele en spastische spierlaag proximaal van het begin van de myotomie, resulterend in prestenotische dilatatie. Op basis van deze ervaring kan geconcludeerd worden dat POEM met uitgebreide myotomie een veelbelovende behandeling bij patiënten met therapieresistente slokdarmspasmen lijkt. Echter moet men bedacht zijn op de beschreven beperkingen van reactieve per- en post-procedurele spastische slokdarmcontracties die de technische uitvoering en duur van de POEM procedure kunnen compliceren en ervoor zorgen dat de myotomie begint boven de proximale grens van de spastische contracties, ter preventie van een resterende spastische spierlaag.

Deel III – Lange termijn follow-up

Achalasie is een chronische ziekte met de indicatie voor levenslange follow-up ter evaluatie van symptomen en ziekte- en behandelinggerelateerde

complicaties. Een van de meest voorkomende behandelinggerelateerde complicaties is refluxklachten en/of refluxoesofagitis. De behandeling van achalasie is namelijk gericht op het opheffen van de obstructie ter plaatse van de LES waardoor de barrièrefunctie van de gastro-oesofageale overgang tegen reflux vanuit de maag wordt geschaad. Hoewel deze symptomen altijd in verband gebracht worden met gastro-oesofageale reflux blijkt het effect van zuurremming bij deze patiënten variabel en tonen studies een slechte correlatie met pH-meting en/of refluxoesofagitis.

Hoofdstuk 7 focust op refluxklachten bij behandelde achalasie patiënten na pneumodilatatie, Heller myotomie of POEM en poogt de onderliggende mechanismen van deze klachten vast te stellen. Hiervoor is een prospectieve observationele case-controle studie uitgevoerd waarbij 40 behandelde achalasie patiënten met en zonder refluxklachten werden geïncludeerd. Patiënten ondergingen onderzoeken ter beoordeling van de slokdarmfunctie (slokdarmmotiliteit met HRM; slokdarmlediging met getimede bariumslikfoto; distensibiliteit van de gastro-oesofageale overgang met EndoFLIP), slokdarm zuurexpositie en zuurpatronen (middels 24-uur pH-impedantie metingen en postprandiale stationaire gecombineerde HRM en pH-impedantie meting), symptoomperceptie (slokdarmgevoeligheid voor zuur met slokdarmzuurperfusietest en voor mechanische distensie met EndoFLIP) en refluxoesofagitis (met oesofagogastroduodenoscopie). De onderzoeken werden uitgevoerd 1 week na staken van zuurremmende medicatie (PPI of H2-receptor antagonist) of prokinetica. Er was geen verschil in de totale zuurexpositietijd tijdens 24-uurs en post-prandiale pH-impedantie meting bij patiënten met en zonder refluxklachten. Refluxklachten waren in beide groepen niet gecorreleerd aan zuur. Echter episodes van langdurige stase van zuur in de slokdarm was in beide groepen frequent aanwezig. Dit werd deels veroorzaakt door reflux vanuit de maag maar voornamelijk door fermentatie van voedsel en stase van voeding met hoge zuurgraad. Patiënten met reflux klachten waren tijdens de slokdarmzuurperfusietest erg gevoelig voor zuur, met een kortere tijd tot de eerste perceptie van zuurbranden en een hevigere intensiteit van zuurbranden. De gevoeligheid voor mechanische distensie was ook significant hoger in deze groep. Er werd geen verschil tussen beide groepen gevonden in slokdarmmotiliteit, slokdarmlediging, distensibiliteit van de gastro-oesofageale overgang en de frequentie van endoscopische refluxoesofagitis. Op basis van deze bevindingen kan geconcludeerd worden dat refluxklachten bij behandelde achalasie patiënten zelden veroorzaakt wordt door gastro-oesofageale reflux maar dat hypersensitiviteit van de slokdarm voor chemische en mechanische stimuli een belangrijke rol lijkt te spelen bij het ontstaan van deze klachten. Stase van zuur in de slokdarm na achalasie behandeling komt echter wel frequent voor maar is zelden gerelateerd aan

gastro-oesofageale reflux. Aanpassing van de diagnostische benadering van refluxklachten bij behandelde achalasie patiënten is dus geïndiceerd en zal leiden tot een meer patiëntgerichte behandeling die niet langer beperkt blijft tot zuurremming maar zich ook gericht op het reduceren van stase van zuur en hypersensitiviteit van de slokdarm.

Patiënten met lang bestaande achalasie hebben een verhoogd risico op de ontwikkeling van de slokdarmcarcinoom ten opzichte van de algehele bevolking. De onderliggende oorzaak hiervan is vermoedelijk tweeledig: (1) verminderde slokdarmlediging kan leiden tot bacteriële overgroei, chemische irritatie en inflammatie met als gevolg premaligne dysplastisch mucosale afwijkingen en uiteindelijk plaveiselcelcarcinoom van de slokdarm; (2) de afwezige barrièrefunctie van de gastro-oesofageale overgang na achalasie behandeling gecombineerd met afwezig slokdarmperistaltiek kan leiden tot toegenomen zuurexpositie vanuit de maag, oesofagitis, Barrett oesofagus en uiteindelijk adenocarcinoom van de slokdarm. Tijdige detectie van slokdarmcarcinoom is belangrijk omdat de prognose voornamelijk bepaald wordt door het ziektestadium ten tijde van diagnose. Gestandaardiseerde endoscopische screening bij patiënten met lang bestaande achalasie wordt echter niet standaard uitgevoerd en detectie van premaligne afwijkingen in de slokdarm bij deze patiënten is moeilijk. In **hoofdstuk 8** wordt de effectiviteit van endoscopische screening voor premaligne afwijkingen en slokdarmcarcinoom bij patiënten met lang bestaande achalasie middels lugol chromoendoscopie beoordeeld. In een cohort van 230 patiënten met achalasie werd een 3-jaarlijkse endoscopische screening met standaard witlicht-endoscopie en lugol chromoendoscopie verricht over een periode van 16 jaar. Initieel gebeurde dit onafhankelijk van de ziekteduur, in verloop van de studie bij een ziekteduur van minimaal 10 jaar. Indien premaligne afwijkingen werden aangetoond werd de screening geïntensiveerd naar jaarlijks en patiënten met bewezen premaligne afwijkingen met hooggradige dysplasie of slokdarmcarcinoom werden hiervoor behandeld. In het cohort werden drie patiënten (1.3%) gediagnosticeerd met plaveiselcelcarcinoom van de slokdarm zonder dat er premaligne slokdarmafwijkingen, laaggradig dan wel hooggradige dysplasie, waren gevonden bij voorgaande endoscopische screening. De incidentie voor plaveiselcelcarcinoom op basis van dit cohort was 63 per 100.000 persoonsjaren, een 14 tot 23 keer zo hoog risico ten opzichte van de algehele bevolking. Premaligne slokdarmafwijkingen met laaggradige dysplasie werden in vier patiënten (1.7%) gedetecteerd zonder progressie naar hooggradige dysplasie of slokdarmcarcinoom gedurende een follow-up periode van 9 jaar. De detectie van zowel plaveiselcelcarcinoom als premaligne slokdarmafwijkingen was in alle gevallen bij achalasie patiënten met een ziekteduur van >20 jaar. Lugol chromoendoscopie verdriedubbelde

de detectie van verdachte slokdarmafwijkingen ten opzichte van standaard witlicht-endoscopie, echter met een lage specificiteit voor histopathologisch bewezen afwijkingen. De studie bevestigt dat patiënten met lang bestaande achalasie (ziekteduur >20 jaar) een verhoogd risico hebben op het ontwikkelen van premaligne slokdarmafwijkingen en slokdarmcarcinoom. Systematische endoscopische screening bij achalasie met standaard witlicht-endoscopie dan wel lugol chromoendoscopie, leidt echter niet tot adequate detectie van premaligne slokdarmafwijkingen voor slokdarmcarcinoom waardoor geen risicostratificatie kan worden verricht en deze screening dus niet wordt aanbevolen.

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PHD PORTFOLIO

Name PhD student: Fraukje A. Ponds
PhD-period: Sept 2011 - Dec 2015
Supervisor: prof dr. Albert J. Bredenoord
Co-supervisor: prof. dr. A.J.P.M. Smout, prof. Dr. P. Fockens

PhD training	Year	Workload (ECTs)
General courses (graduate school)		
Clinical Epidemiology	2011	0.9
Pubmed	2011	0.3
Basic course legislation & organization of clinical research (BROK)	2012	1.0
Practical Biostatistics	2012	1.1
Evidence based searching	2012	0.3
Postgraduate course Advanced Immunology	2012	2.9
Oral presentation in English	2012	0.8
Scientific writing in English	2013	1.5
Project management	2013	0.6
Seminars, workshops and master classes		
Bi-weekly seminars in gastroenterology	2011 - 2015	1.5
Bi-weekly clinical motility meeting	2011 - 2015	1.5
Gut club	2011 - 2015	1.5
UEG Basic science course: use of human tissue in Gastroenterology	2013	1.0
Oral presentations		
United European Gastroenterology Week (1x)	2013	0.5
Voorjaars- en najaarscongres NVGE (4x)	2013, 2014	2.0
Digestive Disease Week (1x)	2014	0.5
International round the table POEM conference	2013	0.5
Gut club meeting	2012	0.5
Day at the motility lab	2012	0.5
Science day AMC	2013	0.5

PhD training (continued)	Year	Workload (ECTs)
Poster presentations		
Digestive Disease Week (3x)	2013, 2014, 2016	1.5
United European Gastroenterology Week (1x)	2014	0.5
Federation of Neurogastroenteroloy and Motility meeting (1x)	2018	0.5
(Inter)national conferences		
Digestive Disease Week (3x)	2013, 2014, 2016	1.5
United European Gastroenterology Week (2x)	2013, 2014	1.0
Federation of Neurogastroenterology and Motility Meeting	2018	0.5
Voorjaars- en najaarscongres NVGE (5x)	2013, 2014, 2015	2.5
Amsterdam Live Endoscopy	2012, 2013, 2014	1.5
Teaching	**Year**	**Workload (ECTs)**
Lecturing		
Elective gastroenterology course 2nd year medical students	2014-2015	1.0
Tutoring		
Bachelor thesis medical student: Ingmar van Raath	2013-2014	1.0
Bachelor thesis medical student: Sherin Mohamed	2014-2015	1.0
Parameters of esteem	**Year**	
NVGE travel grant	2014	
UEGW travel grant	2013	
Other		
Organizing committee WIT (Wetenschaps) festival	2015	2.0

ABOUT THE AUTHOR

Fraukje Ponds was born on the 4th of November 1984. She grew up in Hengelo, a city in Twente, in the East of the Netherlands together with her parents and older brother. She enjoyed her childhood living there and graduated from high school, Lyceum De Grundel, in 2003. After high school, she studied International Relations and International Organization for one year, before she attended Medical School at the University of Groningen in 2004.

Her interest in Gastroenterology and Hepatology started during her studies by becoming a team member of the liver transplantation group and clinical rotations during her master, which she performed in Groningen, Zwolle and abroad. She went to Australia for a scientific internship which enhanced her enthusiasm for research. Furthermore, she performed clinical internships in Uganda and Kenia. The final elective clinical internship was at the departments of Gastroenterology and Hepatology and Gastrointestinal Surgery at the Sint Antonius Hospital in Nieuwegein.

After obtaining her medical degree in 2011, she started as a PhD student in the Academic Medical Center in Amsterdam at the department of Gastroenterology and Hepatology under supervision of prof. dr. Arjan Bredenoord, prof. dr. André Smout and prof. dr. Paul Fockens. Her research focused on the diagnosis, treatment and follow-up of achalasia, resulting in this thesis. During her PhD she performed a research fellowship at the Northwestern Memorial Hospital in Chicago under supervision of prof. dr. John Pandolfino.

After traveling through the United States and Central America, she started in April 2016 with her specialization in Gastroenterology and Hepatology at the Academic Medical Center, currently Amsterdam University Medical Centers (Amsterdam UMC), in Amsterdam. She worked at the Onze Lieve Vrouwe Gasthuis (OLVG), Slotervaart Hospital and the Amsterdam UMC all in Amsterdam, and currently at the Spaarne Gasthuis in Haarlem.

During her specialization she obtained a degree in Clinical Business Administration at the TIAS School for Business and Society in Utrecht. She lives together with Maarten and her daughter Jans in Haarlem. In January 2024 she will finish her specialization and will start a Gastrointestinal Oncology fellowship at the Antoni van Leeuwenhoek Hospital in Amsterdam.

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Te beginnen met de patiënten, want zonder hen geen ziekte en geen reden tot onderzoek. Patiënt zijn overkomt je, dit is nooit een keuze. Om deel te nemen aan wetenschappelijk onderzoek daarentegen, kies je heel bewust. Voor dit proefschrift hebben meer dan 500 patiënten bijgedragen aan de verschillende onderzoeken die zijn uitgevoerd. Het is bijzonder het vertrouwen te krijgen van patiënten, die hun bijdrage leveren om de zorg een stapje te verbeteren. Met veel plezier kijk ik terug op deze patiëntencontacten. Zij hebben mij geleerd hoe belastend een chronische ziekte kan zijn en dat ziektes makkelijk uitspreekbare namen moeten krijgen in plaats van achalasie.

Dan mijn promotieteam. Ik ben zeer dankbaar voor de kans die jullie mij hebben geboden, het geduld - wat ik behoorlijk op de proef heb gesteld - en het vertrouwen in het eindresultaat dat er nu ligt.

Beste Arjan, ik heb veel bewondering voor je visie op onderzoek en zorg, het talent nooit achterom te kijken en ben jaloers op je pragmatiek en timemanagement. Doordat voor mij niet alles zwart/wit is en tijd een rekbaar begrip, waren er momenten dat we niet op dezelfde golflengte zaten. Toch leidden onze verschillen tot zeer mooie uitkomsten. Het feit dat jij zo jong professor bent geworden, toont je gedrevenheid en kunde. Dat je de juiste balans hebt gevonden tussen onderzoek, kliniek en een druk gezinsleven is bewonderingswaardig. Voor mij is 1 kind al aanpoten. Dank voor je toegankelijkheid, betrokkenheid en blijvende vertrouwen in de afronding van dit proefschrift.

Beste André, ben ik dan nu echt je laatste promovenda? Het zal een gemis zijn voor velen. Jouw kritisch blik en uitzonderlijk taalgevoel hebben menig onderzoeksvoorstel, artikel, presentatie en dus dit proefschrift naar een hoger niveau getild. Jij bent in staat altijd de pijnpunten bloot te leggen en oplossingen aan te dragen als het onderzoek vastloopt. Verder lukt het weinig mensen om in alle berichten die ze sturen een grap te verwerken. Het resulteerde altijd in een (glim)lach, zelfs als je vroeg naar mijn voortgang.

Beste Paul, je bent onmisbaar geweest voor het realiseren van de POEMA trial. Op de endoscopiekamer ga je geen enkele uitdaging uit de weg met je enorme

handigheid en rust. Jij bent in staat om een groot probleem te reduceren tot iets kleins. Ik heb dit mogen ervaren tijdens mijn onderzoek, maar ook in je rol als afdelingshoofd. Het is een groot voorrecht om tijdens mijn opleiding zoveel van je te mogen leren, zowel binnen als buiten de endoscopiekamer.

Geachte leden van de promotiecommissie, prof. dr. Bergman, prof. dr. Schijven, prof. dr. Benninga, prof. dr. Sifrim, dr. Felt-Bersma, dr. Poley, bedankt voor het kritisch beoordelen van dit proefschrift en de bereidheid zitting te nemen in mijn promotiecommissie. Dear professor Sifrim, I am honored that an international expert is willing to be part of my Doctorate Committee.

Het motiliteitsteam, spin in het web. Zonder jullie zijn wij onderzoekers nergens. De vele uren die jullie hebben bijgedragen aan mijn onderzoeken zijn ontelbaar en van grote waarde.
Lieve Aaltje, een even grote kletskous als ik. Wat een geluk dat jij mij ondersteunde bij de POEMA trial, als ik een cijfer was vergeten had jij deze reeds genoteerd. De uitstapjes naar Rome en Düsseldorf waren onvergetelijk. Hoe konden wij nou weten dat Italianen daadwerkelijk altijd antipasti, primi en secundi piatti eten...Ik ben blij dat we nog steeds zo goed contact hebben.
Jac, je kennis en kunde gecombineerd met droge humor en betrokkenheid zijn goud waard. De Refluxstudie was ons gezamenlijke project, zonder jou was ik nu nog aan het analyseren. Dank voor je rust, reddingen bij lastige metingen of moeilijk te plaatsen katheters en je luisterend oor op vele gebieden.
Ramona, een superplanner met het hart op de tong en een meesterbakker. Dankzij jou liep de poli perfect, waren patiënten altijd op tijd geïnformeerd en kon ik zo nodig op vrijdagmiddag stoom afblazen of gewoon kletsen. Je cakes en taarten zijn legendarisch.
Sem, dank voor het uitvoeren van de vele motiliteitsonderzoeken, ondervangen van de telefoontjes van patiënten en je hulp als het toch weer allemaal uitliep.

Kort wil ik ook een aantal mensen van het Tytgat instituut bedanken. Op zoek naar een speld in de hooiberg, namen jullie me aan de hand mee in de wereld van het lab. De ideeënstroom bleef ondanks de tegenslagen komen: in het lab is het nooit klaar. Uiteindelijk delfde het labwerk het onderspit en hebben alleen de klinische studies dit boekwerk gehaald. Rene, Wouter, Olaf, Sara, Caroline en Francisca veel dank voor jullie begeleiding!

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For the POEMA trial I would like to thank all the medical specialists and nurses for the great teamwork and cooperation to make this trial such a success. It was an example of how we should perform research for rare diseases. It was always great to catch up during conferences and many thanks for the warm welcome in your hospitals during trial visits. For me, it was a blast. A special acknowledgment to Prof. Dr. J.E. Pandolfino. Dear John, thank you for the opportunity of the research fellowship in Chicago. I learned a lot from the research meetings, your out-of-the-box thinking, the out-patient clinic and about hospital care in the United States. Dear Dusty, you showed me around, always available for questions and discussing papers, a big thanks to you.
Barbara, hoewel je geen co-auteur bent op de stukken in dit boek, ben en blijf je wel erg belangrijk voor het uitvoeren van de POEMs. Leerzaam om toen en nu bij je op de endoscopiekamer te mogen staan, je endoscopie-skills zijn jaloersmakend. Dank ook voor het sparren tijdens goede koffie. Ik hoop in de toekomst ooit ESDs van je te leren met Nederlandstalige hits op de achtergrond.

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Oude motiliteits-onderzoekers: Wout, Boudewijn, Pim, Bram, Marijn, Froukje en Thomas er gaat niets boven een maandagochtend waarbij onder het genot van koffie er gefilosofeerd wordt over de aan- of afwezigheid van slokdarmcontracties en de fameuze gekleurde lijntjes. Het was een feest om op congressen de motiliteitssessies met jullie af te gaan en veel dank voor de sparsessies over statistiek, METC-protocollen en presentaties. Verder heb ik met de meesten van jullie mogen werken in de kliniek waar we elkaar als vanzelfsprekend opnieuw op sleeptouw namen. Dan de jonge garde, Willemijn, Renske, Laura, Jeroen, Marlous, Thijs en Elise dank dat jullie mij adopteerden als ik weer even langs kwam hoppen.

Tytgat-vrienden. Werken in een kamer zonder ramen creëert onvermijdelijk een band. Want: who needs sunshine? Kirsten, Tessa, Noortje, Bram en Sascha de kamer van het eerste uur, daarna aangevuld met Hannah, Joep, Marijn, Maxime en Anne. Slap ouwehoeren bij het zoveelste bakkie Nespresso, de dagelijks NU achterklap update, de cola-momenten op het voetenplein, zwoegen boven databases/protocollen/abstract/figuren (you name it), de vreugde van een eigen koelkast en elkaars telefonist zijn. Wij, brachten de zon zelf wel in de kamer. Nu in de kliniek kunnen we ook bij elkaar terecht.

Nog kort mijn favo buurvrouwen op rechts: Noortje, Hannah en Marijn. Aan enkele woorden of een blik hadden we altijd meer dan genoeg. Het is een feest dat dit tot op heden nog steeds het geval is en ik de beslommeringen rondom werk en dagelijkse bezigheden altijd met jullie kan delen.

Alle andere oud arts-onderzoekers, waarbij ik met het merendeel ook werk of gewerkt heb als collega AIOS. Jarenlang met elkaar samenwerken schept een enorme band, in fases zie je elkaar vaker dan je vrienden. Dank voor alle borrels, gezelligheid op congressen, hardloop- en wielrenrondjes, skisessies en het bijspringen waar nodig.
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Verder wil ik alle AIOS/ANIOS-collega's, MDL-artsen, Internisten, verpleegkundigen, endoscopie-verpleegkundigen en ondersteunend personeel van afdeling Interne Geneeskunde en MDL van het OLVG, afdeling MDL uit MC Slotervaart, Amsterdam UMC en het Spaarne Gasthuis bedanken voor de samenwerking de afgelopen jaren. Ik heb veel van jullie geleerd. Jullie hebben mij de mogelijkheid gegeven om me verder te ontwikkelen als dokter en als persoon, dat deed en doe ik in elk ziekenhuis met veel plezier. Ik kijk er naar uit om in de toekomst met jullie te blijven samenwerken. Extra woord van dank aan mijn verschillende opleiders: Carl Siegert, Marcel Weijmar, Annekatrien Depla, Pieter Stokkers, Bert Baak, Kristien Tytgat, Maarten Jacobs en Stijn van Weyenberg. Jullie zijn er altijd voor ons als AIOS. En verder nog Pau, wat was het fijn samen in het OLVG. Eerst allebei als AIOS en later jij als 'mijn baas'. Voor ons veranderde er helemaal niets. Ik mis onze roze band sessies in het park en wandelingen door de Rivierbuurt.

Vrienden en vriendinnen, het is af!
Mijn Twentse maiden van thuis/thuis. Wat begon met een potje pool, nu 25 jaar geleden, is uitgegroeid tot een onvoorwaardelijke hechte vriendschap. Jullie zijn me zeer dierbaar. Zonder onze etentjes, feestjes, logeerpartijen, koffies en talloze belletjes was dit boek er nooit gekomen.
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kenmerkt onze vriendschap:.....Huisje, Boompje, Beestje!! Ik zie ons al zitten als grijze, rimpelige omaatjes later.
Geneeskunde matties Mirjam (Smirrie) en Janneke (grote Jans). Smirrie wie had dat nou ooit kunnen bedenken, allebei IO/IB en daarna samen Geneeskunde. We spreken elkaar minder frequent maar je blijft mien moat. Jansie, van Zwollywood naar samen op avontuur in Oeganda en Kenia. We zouden er een boek over kunnen schrijven, beginnend met de legendarisch uitspraak: "Westlife, music that never goes out of time". Als we elkaar zien is het als vanouds. ZOTTE meiden, roze en groen blijf je je hele leven! Dank voor de vriendschap.
Roy, een avontuurlijke salsaman met surfketting, zo werd je door Heleen geïntroduceerd. Je bleek ook een nerd met Excel. Figuur 2 in hoofdstuk 5 was er niet geweest zonder jou, 'the Roy Figure'.
De vrienden van Maarten, die ik ook een beetje mijn vrienden mag noemen. Dank voor jullie afleiding in de vorm van etentjes, borrels of wielrentochten en het op sleeptouw nemen van Maarten in de weekenden wanneer ik weer moest typen. In het bijzonder, Jet en Wil wat zijn wij met z'n drieën een goede match!

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A