Reflux disease and achalasia: Failure of the gatekeeper
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Citation for published version (APA):

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Chapter 1

General introduction

In part adapted from:

Pathophysiology and management of gastroesophageal reflux disease
Wout Rohof, David Hirsch, Guy Boeckxstaens

New insights in pathophysiology and management of achalasia
Wout Rohof, Guy Boeckxstaens

Treatment of the patient with achalasia
Wout Rohof, Guy Boeckxstaens
The esophagogastric junction

The junction between the esophagus and stomach is a highly specialized region, composed of the lower esophageal sphincter (LES) and crural diaphragm. Together these structures have to reassure that a bolus of food can enter the stomach, whereas reflux of gastric contents across the esophagogastric junction (EGJ) into the esophagus should be prevented. Yet, the high-pressure zone should allow retrograde passage of gastric contents into the esophagus in the occasion of vomiting or venting of accumulated air during belching.

The LES is a specialized thickened region of the circular muscle layer of the distal esophagus, extending over an axial distance of 3-4 cm. By generating a myogenic tonic resting pressure higher than the intragastric pressure, the LES provides sufficient protection against the pressure gradient between the stomach and esophagus. The latter results from the fact that abdominal pressure is higher than thoracic pressure. However, during episodes of acute abdominal pressure increments, such as inspiration, straining, coughing, sneezing or laughing, this pressure gradient increases well above LES pressure. Hence, an additional compensatory mechanism is required. This task is fulfilled by the second component of the EGJ or the crural diaphragm. The crural diaphragm forms a canal through which the esophagus enters the abdomen and is anchored to the LES by the phreno-esophageal ligament. Since the two components are anatomically superimposed, contraction of the striated muscle of the crural diaphragm during inspiration or straining exerts a pressure on the LES, leading to a dynamic and powerful increase in EGJ pressure. Hence, the LES and crural diaphragm are considered the internal and external sphincter of the EGJ, and together these structures act in concert to prevent gastroesophageal reflux.

Conversely, the EGJ has to be able to relax briefly upon swallowing to allow passage of ingested food towards the stomach. This task is fulfilled by the deglutitive inhibition which is mediated by the vagal inhibitory pathway. In short, efferent stimuli travel from the dorsal motor nucleus of the vagal nerve to the myenteric plexus in the sphincter. In the plexus efferent neurones can either increase or decrease LES tone by stimulation of inhibitory or excitatory motor neurones respectively. The postganglionic inhibitory myenteric neurones innervating the LES are nitricergic in nature, and act by releasing nitric oxide. Swallow-induced relaxation of the LES results from activation of the inhibitory motor innervation of the sphincter, thereby allowing passage of a food bolus or saliva.

Thus, the complicated task of the EGJ is to prevent gastroesophageal reflux while passage through the sphincter has to be permitted and stasis of food, fluids and saliva avoided. Dysfunction of this “gatekeeper” may result in the two typical examples of esophageal motility disorders, i.e. gastroesophageal reflux disease (GERD) and achalasia. The pathophysiology and management of these disorders represent the topic of the two parts presented in this thesis.
PART I: Gastroesophageal reflux disease

When reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications, it is referred to as GERD. GERD is one of the most common digestive diseases in the Western world, with typical symptoms such as heartburn, regurgitation or retrosternal pain reported by 15-20% of the general population. The majority of patients has mild to moderate complaints. Nevertheless, increased exposure of the esophageal epithelium to noxious gastric contents may lead to complications such as erosive esophagitis, Barrett’s esophagus, peptic strictures and even esophageal carcinoma.

Given the high prevalence of GERD, understanding of the pathophysiology is of great importance. The pathophysiology is multifactorial, including dysfunction of the EGJ, gastric and esophageal motility, differences in the composition of the refluxate and the presence of visceral hypersensitivity. Clearly, GERD most commonly is the result of incompetence of the gatekeeper between the stomach and the esophagus. The two most important factors contributing to this incompetence are the physiological occurrence of transient lower esophageal sphincter relaxations (TLESRs) and the anatomical distortion of the LES and crural diaphragm, i.e. a hiatal hernia.

Transient lower esophageal sphincter relaxations

Transient lower esophageal sphincter relaxations (TLESRs) are the predominant mechanisms underlying gastroesophageal reflux, both in normal subjects and in GERD patients. A TLESR is a vago-vagally mediated motor pattern triggered by activation of vagal afferents in the cardia of the stomach by various stimuli, of which gastric distension is the most important. In response to gastric distention, vagal afferents are activated triggering neurons in the dorsal motor nucleus of the vagus nerve to initiate the specific motor pattern underlying TLESRs. The latter are characterized by a rapid relaxation of the LES, esophageal shortening and inhibition of the crural diaphragm, believed to be the physiological mechanism by which the stomach vents gas. The frequency of TLESRs in GERD patients is not different from that of normal subjects. However, the occurrence of acid reflux during a TLESR is twice as high in GERD patients compared to healthy controls. Until recently, it was unclear why reflux should be more acidic in GERD patients, mainly in patients with a hiatal hernia.

Hiatal hernia

In the presence of a hiatal hernia, the capacity of the EGJ to prevent reflux is hampered, mainly as a result of the migration of the stomach through the diaphragmatic hiatus into the mediastinum separating the high pressure zones of the LES and the crural diaphragm. In addition, the hiatal sac can function as a reservoir from fluid can re-reflux into the esophagus after swallowing or during periods of low sphincter pressure.
A hiatal hernia is associated with more severe erosive esophagitis and Barrett’s esophagus. This increase in esophageal injury is due to a prolonged acid exposure time, which in its turn results from a larger number of reflux episodes in patients with hiatal hernia than in those without, and a prolonged acid clearance time. In contrast to earlier believes, a hiatal hernia is a dynamic entity - as through axial movement of the LES through the diaphragmatic hiatus, the length of the hiatal hernia can differ in time. When the LES and diaphragm are spatially separated, the rate of reflux episodes is almost doubled compared to the period when there is no hiatal hernia. The increase in reflux episodes is mainly explained by increased reflux due to other mechanisms than TLESRs. Indeed, half of the reflux episodes in GERD patients with a hiatal hernia occur during swallowing or straining. Moreover, during spatial separation, the rate of acid reflux episodes during a TLESR is doubled compared to the rate without spatial separation, most likely due to alteration of the position of the gastric acid pocket.

**Acid pocket**

Most reflux episodes occur after a meal, when the stomach is filled with ingested food. In contrast to the believe that meal ingestion buffers gastric acid, acid reflux episodes occur even in the early postprandial period. Fletcher et al. elegantly showed that gastric acid floats on top of the meal acting as a reservoir from which acid can enter the esophagus during episodes of opening of the EGJ. Using a gradual pull-through pH-metry, they discovered a highly acidic zone of approximately 2 cm near the EGJ in the postprandial state. This gastric acid pocket accounted for the lower pH of the refluxate compared to the gastric postprandial pH.

Recently, the existence of the acid pocket was confirmed using scintigraphy in both healthy subjects and GERD patients. GERD patients have larger acid pockets whereas the proximal extent of the acid pocket is closer to the LES in patients than in healthy subjects. Most importantly, Beaumont et al. demonstrated that the major risk factor for acid reflux is the presence of a hiatal hernia and the position of the acid pocket relative to the diaphragm. Clearly, if the acid pocket extends into the hiatal opening or is located above the diaphragm, the pocket is the source of refluxate, resulting in a five-fold increased risk of having acid reflux. Moreover, in patients with a large hiatal hernia it was demonstrated that the hiatal sac can function as a reservoir from which fluid can re-reflux into the esophagus during swallowing and straining. This explains the increased risk to have acidic gastroesophageal reflux during a TLESR, when the LES relaxes after swallowing or when LES pressure is low in patients with a hiatal hernia.

**Perception of reflux episodes**

There is a striking discrepancy between the actual and perceived number of reflux episodes. Although it is well established that reflux episodes underlie the typical symptoms of GERD, i.e. heartburn and regurgitation, it is important to emphasize that not all reflux episodes are
perceived. Using 24h pH and multi intraluminal impedance monitoring, Bredenoord et al. showed in a group of GERD patients off proton pump inhibitors (PPIs) that symptoms only occurred during 203 of 1807 reflux episodes (11%). Possible factors that increase the likelihood of perception are episodes with a larger pH drop, a high proximal extent of the refluxate, a lower nadir pH and a longer clearance time. The actual symptom perception occurs in the central nervous system and is determined by various factors, including visceral sensitivity, central sensitivity and psychological factors.

Treatment
The current choice of treatment of GERD is undoubtedly acid suppression, for which PPIs are most frequently used. PPIs have been abundantly shown to reduce the number of acid reflux episodes and esophageal acid exposure. Thereby, PPIs reduce symptoms of heartburn, achieve a high rate of mucosal healing and normalize quality of life of patients with GERD. Of note, the use of PPIs is safe; although chronic use can result in side effects such as osteoporosis and increased risk for intestinal infections. Moreover, in approximately 30% of patients PPI-treatment fails to completely resolve symptoms. Especially treatment in non erosive reflux disease patients can be difficult with failure rates up to 40%, emphasizing that there is certainly a need for improvement of the management of GERD. Because of the high prevalence of GERD, refractory GERD symptoms are a large clinical problem and press a high burden on current health care facilities. Furthermore, therapeutic options for this patient group are limited with only laparoscopic fundoplication as an alternative treatment.

Reflux related symptoms resistant to PPI treatment are mainly associated to weakly acidic reflux episodes. The mechanisms that contribute to refractory symptoms are however incompletely understood. Suggested mechanisms include heightened perception of esophageal sensation, increased reflux rate or volume and persistent impaired mucosal integrity. To what extent these mechanisms interact and contribute to PPI resistant symptoms has not been prospectively evaluated in PPI responders versus non-responders. In chapter 2 esophageal sensitivity, mucosal integrity, and postprandial reflux parameters were compared in patients with refractory symptoms to patients without GERD symptoms during PPI treatment.

Obviously, there is still a need for improvement of GERD therapy. In this thesis we have focussed on two treatment strategies: First, the inhibition of TLESRs is a potential target in GERD therapy, especially in patients with symptoms resulting from non-acid reflux. Inhibitors of TLESRs, i.e. reflux inhibitors, would in contrast to PPIs not only reduce acid reflux, but all reflux episodes, irrespective of the chemical composition. Second, as the acid pocket is the most important source of postprandial reflux episodes in GERD, it represents an alternative therapeutic target.
Therapy aimed at TLESRs
As reflux mainly occurs during TLESRs, this motor pattern is an interesting target for new drug development. For most of these studies the number of TLESRs is used as the primary outcome variable, which emphasizes the importance of accurate detection of TLESRs. Previously TLESRs were scored using strict criteria designed for water perfused manometry with a sleeve sensor. Recently, high resolution manometry has been introduced, which uses closely spaced pressure sensors, spanning from the pharynx to the gastric lumen, incorporating both esophageal sphincters. The higher spatial resolution of high resolution manometry in combination with the use of an isocountour plot provides a better understanding of the complex functional anatomy of the esophageal sphincters and peristalsis. In chapter 3 we studied to what extent this new technique is superior to conventional manometry to depict TLESRs.

Several neurotransmitters along the pathway of transmission of TLESRs have been identified. Subsequently, it has been shown that several (ant-)agonists of these receptors indeed reduce the number of TLESRs, and thereby reduce the number of reflux episodes. Of these, the γ-aminobutyric acid type B (GABA\textsubscript{B}) receptor and the metabotropic glutamate receptor type 5 (mGluR5) are the most promising. The GABA\textsubscript{B} receptor agonist baclofen has proven to inhibit 60% of TLESRs and reflux episodes in healthy volunteers. Four weeks of baclofen in GERD patients showed a significant reduction in acid exposure and symptoms. However, baclofen generates significant central side effects as sedation, dizziness and nausea in a large part of patients, as the GABA\textsubscript{B} receptor is also abundant in the central nervous system. Central side effects were also observed during treatment with other reflux inhibitors, such as GABA\textsubscript{A}-agonists and cannabinoid-agonists. Instead, more peripherally acting compounds might still reduce TLESRs but without central side effects. However, the exact location of the receptors involved in TLESR neural pathway has not been evaluated in humans. To optimise bench to bedside translation, we aimed to analyse the presence of the mGluR5, GABA\textsubscript{B}, GABA\textsubscript{A} and cannabinoid receptors along the pathway of transmission of TLESRs. To this end we performed immunohistochemical stainings for these receptors in human nodose ganglion, the nucleus of the solitary tract, the dorsal motor nucleus of the vagal nerve, and the myenteric plexus of the LES in chapter 4.

The metabotropic glutamate receptor is structurally related to the GABA\textsubscript{B} receptor. Agonists of the mGluR5 subtype have shown to be potent inhibitors of TLESRs in ferrets and dogs. A study with riluzole, an aspecific inhibitor of excitatory amino acids (glutamate, aspartate), showed a significant reduction of TLESRs evoked by gastric balloon distension. Interestingly, mGluR5 antagonism has been shown to reduce visceral pain, enhancing the potential benefit for patients with visceral hypersensitivity. In chapter 5 we investigated the effect of AZD2066, a novel selective, non-competitive antagonist of mGluR5 on the frequency of TLESRs and determined its safety and tolerability profile.
Therapy aimed at the acid pocket

As previously discussed, the position of the pocket relative to diaphragm is largely determined by the presence of a hiatal hernia. Especially in patients with a large hiatal hernia, the acid pocket is frequently located above the diaphragm, facilitating the occurrence of acid reflux events. Hence, the acid pocket represents a unique therapeutic target. For example, drugs affecting the position or acidity of the acid pocket may alter acid exposure and represent an alternative approach to treat GERD. Although the therapeutic importance of PPIs is generally accepted, it remains unclear to what extent these drugs affect the size, pH and position of the acid pocket, contributing to their mechanism of action. Therefore we studied the effect of PPI on the characteristics of the acid pocket in chapter 6, and related this to the effect of PPIs on reflux episodes.

The position of the acid pocket relative to the crural diaphragm is an important determinant of the acidity of the refluxate. Interestingly, 74-85% of reflux episodes are acidic when the acid pocket is located above or at the level of the diaphragm. In contrast, only 7-20% of reflux episodes are acidic if the acid pocket is located below the diaphragm. Prokinetic agents like macrolides increase gastric emptying and in addition increase proximal stomach tone and LES pressure. These properties make these compounds interesting candidates to alter the acid pocket position. In a recent study in lung transplant patients, Azithromycin, a macrolide similar in structure and function to erythromycin, reduced the rate of - mainly acid- reflux episodes, suggesting a potential effect on the acid pocket. In chapter 7 we determined the effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period in GERD patients.

An alternative approach to macrolides is the use of alginates. Alginates are natural polysaccharide polymers isolated from brown seaweed. On contact with gastric acid, they precipitate into a low density viscous gel or raft of near neutral pH in a matter of seconds. With the pH change, the sodium bicarbonate contained in the alginate-antacid formulation releases carbon dioxide, which is then trapped in the alginate gel causing it to float to the top of the gastric contents like a ‘raft’. Hence, alginate-based formulations with sodium bicarbonate may induce direct and immediate neutralisation of the acid pocket. The raft of the original alginate based formulation (Gaviscon) remains in the stomach for up to 4 hours. Potentially, this raft floats on top of the acid pocket, thereby altering the position of the acid pocket. In chapter 8 we aimed to visualize the location of Gaviscon relative to the acid pocket and to assess the effect of alginates-antacid formulations on reflux parameters and the position of the acid pocket. We compared the outcome parameters of the alginate-based formulation to antagel, a commonly used antacid.
PART II: Achalasia

Achalasia is a primary esophageal motor disorder characterized by the absence of peristalsis and a defective relaxation of the LES, resulting in impaired bolus transport and stasis of food in the esophagus. The incidence of achalasia is approximately 1 per 100,000 persons per year, with a peak around the 5th decade of life. Typical symptoms of achalasia include dysphagia, regurgitation and weight loss.

Pathophysiology

The pathophysiology of achalasia is still incompletely understood, but histological examination reveals a significant decrease in the number of myenteric neurons in the distal esophagus and at the level of the LES. Why these neurons gradually disappear in patients with achalasia remains however unclear. In the past decade, evidence has accumulated suggesting that achalasia may be an immune-mediated inflammatory disorder. More detailed examination of resection specimens shows infiltration of myenteric ganglia with CD3/CD8 positive lymphocytes expressing activation markers. In addition, IgM antibodies and evidence of complement activation was shown within myenteric ganglia. Finally, antibodies against myenteric neurons have been repeatedly shown in serum of achalasia patients, especially in patients with a specific HLA genotype, namely those carrying the DQA1*0103 and DQB1*0603 alleles. These findings all point towards an immune-mediated origin of the myenteric ganglionitis observed in achalasia. The exact stimulus initiating this immune response or the antigen targeted remains however to be identified. One of the potential triggers for the development of immune-mediated diseases is an infection. Especially in auto-immune diseases, characterized by immune-mediated inflammation to self antigens, viral or bacterial infections may trigger the cascade of events in genetic susceptible patients. Similar, Facco et al. provided evidence that human herpes simplex virus type 1 (HSV-1) could be the infectious trigger leading to immune-mediated destruction of esophageal neurons in achalasia. They demonstrated activation of T cells of achalasia patients by HSV-1 antigens leading to T cell proliferation and cytokine production. The knowledge that HSV-1 is a neurotropic virus with a predilection for the squamous epithelium could also explain why the loss of neurons in achalasia is region-specific and largely limited to the LES and esophagus (in some patients extending to the proximal stomach). Based on these data, the hypothesis is now forwarded that achalasia may be an auto-immune disorder due to an aberrant immune response in genetically susceptible individual triggered by a viral infection.

Diagnosis

A patient with achalasia typically presents with dysphagia for solids and liquids, regurgitation of undigested food, weight loss and retrosternal pain. The first diagnostic step is to rule out anatomical lesions using endoscopy or radiology. In early stages, both endoscopy and radiology
may be completely normal. In advanced cases, endoscopy may reveal a dilated esophagus with retained food and some increased resistance at the EGJ. Radiological examination may show a typical ‘bird-beak’ image at the junction, with a dilated esophageal body, sometimes with an air-fluid level. It is now generally accepted that esophageal manometry, preferably high resolution manometry is the gold standard to diagnose achalasia. Manometry typically shows an aperistaltic esophageal body, sometimes with elevated intra-esophageal pressure due to stasis of food and saliva, in combination with incomplete relaxation of the LES upon deglutition. Based on the residual esophageal wave pattern on high resolution manometry, 3 manometric can be identified: in type I only minimal contractility is observed in the esophageal body; in type II, intermittent periods of compartmentalized esophageal pressurization is recorded; and in type III, spastic contractions are measured in the distal esophagus.

**Treatment**

To date, mainly due to a lack in pathophysiological insight, treatment is confined to mechanical disruption of the LES, rather than restoring esophageal motility. Treatment modalities available for this purpose include mainly pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM).

Pneumodilation disrupts the LES by forceful inflation of an air-filled balloon. For this technique, a non-compliant Rigiflex balloon (Boston Scientific, Nanterre, France) is inserted over an endoscopically placed guide wire, and positioned at the level of the LES. Under fluoroscopic guidance, the balloon is inflated until the waist caused by the impression of the EGJ is completely obliterated. Usually, a graded distension protocol with increasing balloon sizes (30, 35 and 40 mm) is used, leading to success rates of 70-80%. Treatment success further increases to more than 90% when redilation is allowed in case of recurrent symptoms.

During LHM, the esophagogastric junction is laparoscopically approached and both muscle layers of the LES are cleaved with an extension of the incision of 2-3 cm over the proximal stomach. A Heller myotomy is usually combined with an anti-reflux procedure, lowering the incidence of gastroesophageal reflux disease after treatment from 32 to 8.8%. In a recent meta-analysis including 3086 patients by Campos et al., success rates were as high as 89% (77-100%) after a mean follow up of 35 months. However, similar to pneumatic dilation, treatment success rates of LHM decline with time to 60%, as demonstrated in several studies with a follow up of 6-10 years.

For many years, repeated endoscopic PD has been the treatment of choice. With the introduction of laparoscopic surgery, however, the enthusiasm for the surgical approach has markedly increased. It has to be emphasized though that comparison of success rates reported in literature for PD and LHM is difficult as different outcome measures are used. Moreover, data are rather conflicting:
a retrospective longitudinal study of 1181 patients with a follow up of 10 years showed that patients treated with PD had to undergo retreatment more often than those who had LHM (64% vs 38%).\textsuperscript{79} In contrast, a cross-sectional follow up study by Vela et al, showed similar success rates for PD and LHM.\textsuperscript{76} Finally and most importantly, randomized studies with sufficient statistical power comparing these two major treatment options were lacking. Therefore we conducted a randomised controlled trial in 5 European countries in which PD and LHM were compared as initial treatment for idiopathic achalasia (chapter 9).

By defining risk factors for failure/success, it might be possible to design an individualized therapy for the patient with achalasia. For instance, in patients treated with PD, redilation is more often needed in younger and male patients (<40 years),\textsuperscript{80} suggesting that LHM should be preferentially offered to younger, male patients with a low surgical risk.\textsuperscript{74} In addition, data have been reported that clinical outcome is determined by the manometric subtype. Recently, Pandolfino et al. identified three subtypes of achalasia based on the residual esophageal pressure wave pattern.\textsuperscript{70} In 83 patients mainly treated with PD, success rates were significantly higher for type II achalasia (96%) compared to type I (56%) and type III (29%) achalasia. In a subsequent study reporting on 246 patients treated with LHM, the differences in treatment success between the subtypes were confirmed, with success rates of 85%, 95% and 70% for type I, II and III respectively.\textsuperscript{81} Potentially, achalasia subtype classification could be used to determine the choice of treatment. However, currently available studies had a different definition of treatment success and patients were not followed up prospectively.\textsuperscript{70,81,82} The study population of the randomized European trial is however ideally suited for this purpose. In chapter 10 we determined whether the subtype of achalasia could determine the type of treatment.

\textbf{Follow up}

Follow up of patients with achalasia is not only important to obtain optimal symptom control, but also to prevent possible complications such as esophageal decompensation.\textsuperscript{73,74} Furthermore, patients with achalasia have an increased risk to develop dysplasia and eventually even esophageal squamous cell carcinoma.\textsuperscript{83,84} Current guidelines do not advice on follow up of patients with achalasia.\textsuperscript{85,86} However, several studies have proposed to perform regular follow up visits to decide on retreatment, preferably based on a functional test such as a timed barium esophagogram.\textsuperscript{71,87} Earlier studies have demonstrated that treatment success of PD and LHM gradually decreases in patients with longstanding disease (≥10 yr) to 40-60%.\textsuperscript{72,79,88,89} Importantly, however, additional treatment both after initial PD or LHM has satisfactory results with success rates of 60-80% and improvement of esophageal emptying.\textsuperscript{72,74,76,79} The decision to retreat patients may be a clinical challenge, especially as patients get used to certain level of symptoms or adapt their diet. Furthermore, symptoms and functional data such as stasis on a barium swallow or
LES pressure not always match. Timely detection of patients in need for additional treatment may be important to avoid long-term complications such as esophageal decompensation.\textsuperscript{74,92} However, current guidelines do not advice on how follow up of patients with achalasia should be performed.\textsuperscript{46,48} Currently, several objective risk factors for the need for retreatment during follow up are known. For instance, patients with a LES pressure >10 mmHg after treatment as determined during esophageal manometry have an increased risk for retreatment. Therefore, several centres determine LES pressure after therapy to assess the need for additional treatment.

A second potential parameter is to determine esophageal stasis on esophagograms after ingestion of barium after treatment. Vaezi et al have demonstrated that 90% patients with esophageal stasis need additional treatment within a year, even in case of few or no symptoms shortly after initial treatment.\textsuperscript{92} In chapter 11 we determined which of these tests best predicts the need for retreatment in patients with longstanding achalasia, and therefore should be advocated as objective tool to decide on retreatment during follow up.

The absence of correlation between LES pressure and stasis on a timed barium swallow is incompletely understood. A significant proportion of patients with persistent symptoms has a low or even absent LES pressure.\textsuperscript{93-95} Interestingly, these patients often have incomplete esophageal emptying on a timed barium esophagogram and a significant proportion of these patients benefits from additional treatment. As shown by Pandolfo et al. flow across the EGJ is mainly determined by its distensibility in response to increased intraluminal pressure.\textsuperscript{96} We hypothesized that in achalasia, although LES pressure will definitely contribute, other factors such as fibrosis due to previous treatment or natural history of the disease may impair distensibility and subsequently EGJ opening. Reduced distensibility even in the absence of LES pressure may therefore explain why esophageal emptying on timed barium esophagogram may be impaired. In chapter 12, we determined EGJ distensibility in patients with achalasia using the Endo functional luminal imaging probe (EndoFLIP) during volume controlled distensions.\textsuperscript{97,98} We compared its ability to predict clinical success with that of LES pressure and esophageal emptying.

Another potential long-term complication of achalasia is the development of esophageal squamous cell carcinoma. Several studies have shown that the relative risk of developing esophageal carcinoma with achalasia is increased, ranging from 0- to 50-fold.\textsuperscript{83,84,99} Recently, a long-term prospective trial demonstrated a hazard ratio of 28 for esophageal carcinoma in patients with achalasia compared to matched controls.\textsuperscript{83} In line with this, we observed a mortality rate of 19% due to esophageal carcinoma in a cohort of patients with longstanding achalasia in a retrospective study.\textsuperscript{88} Mainly as symptoms of esophageal carcinoma are misinterpreted as exacerbation of symptoms related to achalasia, the diagnosis is mostly made in a late and advanced stage of disease, illustrating the need for early detection of dysplastic lesions. Conventional endoscopy of
the esophagus is however not sensitive to detect dysplasia. Hence, most lesions are detected in an advanced stage. Potentially, the aid of Lugol’s staining could be used to detect early dysplastic lesions. For instance, Lugol’s staining is shown to have sensitivity as high as 96% for detection of dysplastic lesions in squamous epithelium. In Chapter 13 we determined if Lugol’s staining could be used as a tool for repetitive screening in patients with achalasia.

In summary, the main focus of this thesis was to improve our understanding in the pathophysiology and treatment of dysfunction of the esophagogastric junction. Many challenging questions have arisen for both GERD and achalasia. In part I we focussed on a more pathophysiologically orientated treatment in GERD, with TLESRs as a target for new therapy. Subsequently we studied the effect of several medical treatments such as acid suppression, prokinetics and alginates on the formation and position of the postprandial acid pocket. In part II, the results of a randomized study comparing the two standard treatments for achalasia are presented, and we determined whether subgroups of patients could benefit from one of the two treatments. Lastly we investigated the follow up protocol, by determining the best follow up test and the need for a screening program to timely detect esophageal carcinoma. In the general discussion (Chapter 14) the main findings of the studies presented in this thesis, the implications for current treatment and research in the future are discussed.
REFERENCE LIST

18. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol 2001;96(9):2569-74.


