Reflux disease and achalasia: Failure of the gatekeeper
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SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

The complicated task of the esophagogastric junction 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 represented the topic of the two parts presented in this thesis.

PART I: GASTROESOPHAGEAL REFUX DISEASE

Gastroesophageal reflux is a physiological phenomenon but becomes pathological if troublesome symptoms and/or complications occur. Gastroesophageal reflux disease is one of the most common gastro-intestinal disorders and can present with typical symptoms such as regurgitation and heartburn, or extra-esophageal symptoms such as cough and laryngitis. The different phenotypes range from non-erosive reflux disease, through reflux esophagitis and Barrett’s esophagus. Increased esophageal acid exposure is the most important hallmark of the disease. The mainstay of GERD treatment therefore is acid suppression, most commonly achieved with the use of proton pump inhibitors (PPIs). The efficacy of PPIs is very high for the treatment of erosive esophagitis, especially for the healing of the esophageal injury. However, there is mounting evidence that reflux symptoms persist in a high proportion (30%) of patients despite PPI therapy, and this is associated with decreased psychological and physical well-being. These are the patients that are seen in daily clinical practice by the gastroenterologist, and confront us with diagnostic and therapeutic challenges.

To study the factors that influence persistent GERD symptoms we studied patients with persistent symptoms on PPI treatment in chapter 2 and compared them to GERD patients without symptoms during PPI use. We observed no significant differences in mucosal permeability, the position of the acid pocket, the rate of acid reflux and the pH of the acid pocket in responders and partial responders. In contrast, esophageal sensitivity to distension, the number of reflux episodes and proximal extent were significantly increased in partial responders. Based on these results, we concluded that an increased number of proximal reflux events in a hypersensitive esophagus are associated with persistent symptoms and thereby lead to partial PPI failure in GERD.

From a therapeutic point of view, this implies that further acid suppression will not lead to a reduction in persistent symptoms. Instead, insight into the multifactorial pathophysiology of GERD is needed to develop new anti-reflux therapies. Most commonly gastroesophageal reflux disease
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. Pharmacological inhibition of TLESRs is a promising therapeutic approach because it has the potential to reduce most types of reflux. This is particularly relevant for patients who have troublesome reflux symptoms despite acid suppression from PPI use, because weakly acidic and weakly alkaline reflux play a significant role in symptom generation in this group.\textsuperscript{5,7}

Inhibition of TLESRs via interaction with the receptors involved in the underlying neural pathway has been identified as a novel therapeutic target, and new pharmacological agents inhibiting TLESRs are evaluated in clinical trials.\textsuperscript{8,9} 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. Recently, high resolution esophageal pressure topography has been introduced and is now considered the new standard to study esophageal and lower esophageal sphincter (LES) function.\textsuperscript{10} In chapter 3 we performed a head-to-head comparison between high resolution esophageal pressure topography and conventional sleeve manometry for the detection of TLESRs. We demonstrated that high resolution esophageal pressure topography detected significantly more TLESRs associated with a reflux event compared to sleeve manometry. This resulted in an increase in sensitivity for detection of TLESRs with reflux from 86% to 96% for sleeve manometry and high resolution esophageal pressure topography respectively. Therefore we concluded that high resolution esophageal pressure topography is superior to sleeve manometry for the detection of TLESRs associated with reflux, and that this technique should preferentially be used in clinical trials evaluating the number of TLESRs.

Reflux inhibitors target receptors along the neural pathway involved in the triggering of TLESRS such as mGluR5, GABA and cannabionid receptors. Numerous studies in animals and humans have demonstrated that (ant)agonism of these receptors can lead to a reduction in TLESRs and reflux episodes. The distribution of receptors along the neural pathway involved in the triggering of TLESRs, had however only been studied in animals. To optimise bench to bedside translation in the development of new reflux inhibitors, we analyzed the distribution of mGluR5, GABA\textsubscript{A}, GABA\textsubscript{B}, CB1 and CB2 receptors in human nodose ganglion, the brain stem and the myenteric plexus of the esophagus. Similar to previous animal studies, all receptors were abundantly expressed in the brain stem, and all but GABA\textsubscript{A}\textsubscript{A1} were present in the nodose ganglion and myenteric plexus of the LES. These findings are in line with the central side effects reported during treatment with
reflux inhibitors such as GABA<sub>B</sub> receptor agonists and mGluR5 antagonists, and underscore that peripheral acting compounds may still be effective as reflux inhibitors.

In chapter 5 we performed a randomized, double-blind, crossover phase 1 study in healthy volunteers, to study the effect of a novel mGluR5 receptor antagonist (AZD2066) on TLESRs and reflux episodes. A single oral 13 mg dose of AZD2066 was found to reduce the numbers of TLESRs and reflux episodes by 27% and 55% respectively compared with placebo. In addition, AZD2066 had an acceptable safety and tolerability profile. Based on these results we concluded that mGluR5 antagonism represents an interesting new avenue for reflux inhibitor treatment of GERD. It should be noted however that in a similar designed study the GABA<sub>B</sub>-receptor agonist lesogaberan was previously shown to reduce the number of reflux episodes in healthy volunteers to a greater extent than AZD2066 did in the current study. Lesogaberan has since been discontinued owing to a lack of evidence for a clinically significant effect as an add-on to PPI therapy in patients with reflux symptoms despite PPI treatment. Currently, there is no reflux inhibitor available on the market with an acceptable efficacy and side effect profile. Nevertheless, the concept of direct inhibition of the most important mechanism underlying reflux episodes (i.e. TLESRs) remains very promising. In the upcoming years, additional research has to sort out whether a safe and effective reflux inhibitor can be developed that significantly reduces symptoms refractory to PPIs.

Most (acid) 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 esophagogastric junction. This unbuffered pool of gastric acid is referred to as the gastric acid pocket. The position of the acid pocket relative to the crural diaphragm is an important determinant of the acidity of the refluxate. In GERD, proximal extension of the acid pocket above the diaphragm increases the risk for acid reflux. The acid pocket is therefore an important source of postprandial acid in GERD and, as such, represents a unique therapeutic target. In the next chapters of this thesis we tested the hypothesis that the acid pocket is a therapeutic target in patients with GERD for several medical treatments using concurrent scintigraphy, high resolution manometry and pH-impedance monitoring in a postprandial research protocol.

In chapter 6 we studied to what extent changes in position, size and acidity of the acid pocket contributed to the therapeutic effect of PPIs. We demonstrated that also during PPI treatment gastric secretions accumulate on top of the ingested food and form a pocket. Proton pump inhibitors do not alter the number of reflux events, but increase the pH of the acid pocket which in its turn leads to the increased pH of reflux events. Therefore we concluded that the acid pocket is still the source of refluxate during treatment with PPI, and as such represents a potential target for additional therapy.
In chapter 7 we studied the effect of Azithromycin, a macrolide antibiotic with gastrokinetic properties, on acid pocket position and acid exposure in GERD patients off PPI. Azithromycin reduced the number of acid reflux episodes and esophageal acid exposure in GERD patients, especially in patients with a small hiatal hernia. This effect was mainly caused by a more distal position of the acid pocket, probably resulting from a reduction of the hiatal hernia size. These data for the first time indicated that modulation of the position of the acid pocket had an impact on the acidity of the refluxate.

Alginate-antacid formulations are frequently used to treat GERD and are proposed to be efficient through formation of a floating raft after reaction with the acid pocket. To evaluate this hypothesis, we visualized the alginate raft relative to the position of the acid pocket in chapter 8, and compared its effect on gastroesophageal reflux to a commonly used antacid. The alginate formulation and the acid pocket were visualized using scintigraphy with radioactive indium and technetium-pertechnetate respectively. Reflux episodes were detected using concurrent high-resolution manometry and pH-impedance monitoring. We demonstrated that the alginate-antacid labeling persisted in the proximal stomach for the entire study period co-localizing with the acid pocket and displacing it distally. In addition, the alginate-antacid reduced acid reflux events by more than 75% compared to an antacid alone. These findings demonstrate that alginate formulations directly target the acid pocket with a non-systemic, alginate-antacid formulation for the treatment of postprandial acid reflux in GERD.

Future perspectives
Gastroesophageal reflux disease remains a complex disease with multiple factors involved. In this thesis we mainly focussed on the pathophysiology and additional treatment options of GERD patients with refractory symptoms during PPI use. Most patients with true GERD have at least a partial response to PPIs. Moreover, PPIs have a good safety profile, are widely available and are very effective in the treatment of reflux esophagitis. Therefore, acid suppression by means of PPIs will remain the mainstay of GERD therapy, and additional studies should mainly focus on the treatment of refractory symptoms during PPI use. The studies in this thesis illustrate how insight in pathophysiology can lead to new treatment options in these patients. We demonstrated that visceral hypersensitivity and frequent reflux episodes with a high proximal extent contribute to residual symptoms in patients with recurrent symptoms on PPI therapy. Moreover, the acid pocket is still the source of refluxate during treatment with PPI, and as such represents a potential target for additional therapy. Potential additional treatment options therefore include pain modulators, reflux inhibitors and treatment aimed at the acid pocket. Recent exploring studies already demonstrated the potential benefit of these approaches: For instance, Viazis et al compared citalopram 20 mg as a pain modulator to placebo in 75 patients with refractory GERD.
symptoms on twice daily PPI. Interestingly, success rate of treatment was significantly higher in the patients receiving citalopram (62%, n=39) compared to patients receiving placebo (33%, n=36).\textsuperscript{17} Second, in a large clinical trial, we have previously demonstrated that treatment with the reflux inhibitor lesogaberan resulted in a significantly larger proportion of responders to treatment compared with placebo.\textsuperscript{8} It has to be emphasized however that the proportion of responders was small (16% vs. 8% of patients), and therefore the development of lesogaberan has since been discontinued. Finally, a recent study in patients with non-erosive reflux disease demonstrated that supplementing PPI therapy with alginates more than doubled the number of patients who experienced complete reflux symptom relief (26% vs. 57% respectively).\textsuperscript{18} Treatment with alginates is of particular interest as it interacts directly with the acid pocket, is not systemically absorbed and therefore has very limited side effects. In the near future, more studies are awaited in which the benefits of these drugs as add-on treatment to PPIs are evaluated. Moreover, studies have to address which patients benefit most from which add-on treatment. Eventually, guidelines have to be established how patients with refractory PPI symptoms should be diagnosed and treated to ultimately improve quality of life of our patients.

PART II: ACHALASIA

In the second part of this thesis we studied the treatment and follow up of 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.\textsuperscript{19} The characteristic feature of achalasia is the loss of enteric neurons in the myenteric plexus, leading to severely disturbed esophageal motility and typical symptoms such as dysphagia, regurgitation and weight loss.\textsuperscript{20} Mainly due to a lack in pathophysiological insight, treatment of achalasia aims at relieving functional obstruction at the level of the esophagogastric junction. For many years, repeated endoscopic pneumodilation (PD) had been the treatment of choice leading to therapeutic success in 70-80%.\textsuperscript{21,22} There was a growing enthusiasm in favor of laparoscopic surgery, based on recent publications showing excellent results from single-center series.\textsuperscript{23-25} In chapter 9 we described a large randomized controlled trial comparing laparoscopic Heller myotomy (LHM) with Dor fundoplication and PD. We demonstrated that the success rate, defined as the reduction in Eckardt symptom score below 4, was comparable for both treatments. Using this criterion, the success rate for surgery was 93% and 90% after 1 and 2 years of follow-up respectively compared to 90% and 86% for PD. Redilation, allowed once during the first 2 years of follow up, was performed in 23 of 95 patients after PD (25%). No difference in the level of esophageal stasis or in the quality of life measured by SF-36 was observed. To what extent failure rates may increase in time as more than 3 dilation series are required to maintain patients in
clinical remission remains to be seen. Nevertheless, with the data currently available after a mean follow up of 43 months, both pneumatic dilation and LHM can be offered as effective treatment to patients with achalasia.

By defining risk factors for failure/success it might perhaps be possible to design an individualized therapy for the patient with achalasia. Pandolfino et al recently described three manometric subtypes based on the residual esophageal manometric pattern: In type I, no pressure waves can be recorded in the distal esophagus, type II is characterized by panesophageal pressurisation, whereas in type III at least 20% of swallows reveals rapidly propagating or spastic contractions.24 Importantly, recent studies have suggested that treatment efficacy of LHM and PD strongly varies depending on the manometric subtype.26,27 In chapter 10, we performed an ad hoc analysis to the randomized controlled trial described in chapter 9 to define whether the subtype classification of achalasia could predict outcome. Moreover, we aimed to determine whether the subtype should dictate the choice of treatment, i.e. LHM or PD. In short, in the randomized European trial, both type I and II patients had similar, high success rates after either LHM or PD. Patients with type III, however, had a lower response rate, in particular those who underwent PD. Based on these results, one could argue that LHM might be the preferred treatment option in patients with type III achalasia, though the number of patients studied so far is rather small.

Since we cannot cure the motor abnormalities of achalasia, recurrences after any form of treatment will occur with longer follow-up periods. Treatment success gradually decreases in patients with longstanding disease (≥10 yr) to 40-60%.22,28-30 Importantly, however, additional treatment, both after initial PD or LHM, has satisfactory results with success rates of 60-80% and improvement of esophageal emptying.22,23,31,32 Follow up of patients with achalasia is not only important to ensure optimal symptom control, but also to prevent possible complications such as esophageal decompensation. Timely detection of patients in need for additional treatment is indicated to avoid these long-term complications. The decision to retreat patients may be a difficult one, and objective quantification of esophageal and LES function seems indicated by means of measurement of LES pressure or detection of esophageal stasis on a timed barium esophagogram. In chapter 11 we studied a cohort of patients with achalasia with a mean follow up of 26 years after diagnosis. This study shows that stasis on a timed barium esophagogram but not basal LES pressure is an important predictor of recurrent symptoms and the need for retreatment in patients with longstanding achalasia. Therefore, patients should preferentially be followed up using a timed barium esophagogram. When significant stasis on a timed barium esophagogram is observed, even in the presence of a LES pressure < 10 mmHg, additional therapy may be warranted.
A significant proportion of patients with persistent symptoms has a low or even absent LES pressure. Interestingly, these patients often have incomplete esophageal emptying on a timed barium esophagogram. Reduced distensibility even in the absence of LES pressure may therefore explain why esophageal emptying on timed barium esophagogram may be impaired. We tested this hypothesis in chapter 12 by measuring EGJ distensibility, esophageal stasis and LES pressure. We demonstrated that EGJ distensibility, but not LES pressure, strongly correlated with clinical response to treatment: impaired EGJ distensibility is observed in 92% of patients with recurrent symptoms, whilst only 42% of these patients had an elevated LES pressure. Moreover, patients with impaired EGJ distensibility had recurrent symptoms and impaired esophageal emptying, even if LES pressure was low. Based on these findings, we concluded that EGJ distensibility is a better parameter to evaluate the efficacy of treatment in patients with achalasia compared to LES pressure.

Chronic irritation of the esophageal mucosa, due to poor emptying or excessive reflux of gastric contents, is a risk factor to develop esophageal carcinoma. Patients with achalasia have an increased risk for esophageal carcinoma, i.e. adenocarcinoma as well as squamous cell carcinoma. In chapter 13 we confirmed that patients with achalasia have an increased risk for esophageal carcinoma. In addition, we demonstrated that Lugol staining, significantly increased the detection rate of dysplasia compared to white light endoscopy. To increase probability for detection during screening and thereby cost-effectiveness, risk factors for dysplasia need to be recognized. Esophageal squamous cell carcinoma only occurred after a median time of 26 years after the diagnosis of achalasia in our cohort. This time after diagnosis is in line with five earlier studies, in which the time between symptoms of achalasia and the diagnosis of ESCC varied from 24 to 32 years. These data suggest that screening for dysplasia should be performed in patients with a long history of dysphagia (>15-20 years), especially those with long-term esophageal stasis.

**Future perspectives**

In summary, due to the lack of understanding of the pathogenesis of achalasia, initial treatment still focuses on mechanical disruption of the LES, rather than on restoring esophageal motility. We demonstrated that a graded pneumodilation protocol with the possibility for redilation in case of recurrent symptoms is as successful as LHM, and leads to comparable drop in LES pressure, reduction in esophageal stasis and improved quality of life. The long-term results of the randomized achalasia trial, with at least five years of follow up, are expected in the upcoming year. These results will be of imminent importance to determine whether pneumodilation also has comparable success to LHM with longer follow up.

Recently, a new endoscopic technique termed peroral endoscopic myotomy (POEM) was described to treat achalasia. In this technique, the endoscopist creates a submucosal tunnel to reach the LES.
and to dissect the circular muscle. Initial studies reported very high success rates of 94-100%, even following multiple previous dilations. Although POEM has generated excellent initial results and great enthusiasm among endoscopists, it should be emphasized though, that follow up of these studies is still short and thus longer follow up is absolutely needed before this new technique can be accepted. Moreover, randomized studies comparing POEM to pneumodilation or LHM should be performed and such studies are presently in progress. Ideally, the choice of treatment should be based on risk factors such as achalasia subtype and age in order to generate an individualized therapeutic strategy. The current randomized trials comparing POEM to pneumatic dilation and LHM are ideally suited to further determine risk factors for treatment failure. Using these risk factors, the best available option for a specific patient can be sought.

An interesting alternative approach would be to transplant neuronal stem cells. In mice, neuronal stem cells injected in the pylorus survived and even expressed nitric oxide synthase. Such approach could lead to a completely restored sphincter function and peristalsis. Recently, it was even shown that neural stem cells can be isolated from mucosal biopsies, creating possibilities to treat achalasia. Clearly, a lot of research remains to be done further exploring this approach. Until more insight in pathophysiology leads to a better targeted therapy, possibly thus even restoring esophageal motility, treatment will be aimed at mechanical disruption of the LES.

With adequate follow up and timely retreatment significant morbidity and possibly late complications such as esophageal decompensation and esophageal carcinoma can be avoided. Based on the studies in this thesis we concluded that regular follow up visits may be indicated, not only to inform about symptoms, but also to perform a timed barium esophagogram in order to assess esophageal emptying. Clearly, prospective trials are required to confirm the benefit of (serial) functional testing and early additional treatment for the prevention of long-term complications. One can hypothesize that risk factors can also be determined for esophageal decompensation and for esophageal dysplasia or carcinoma. For instance, patients with type I achalasia already have a wide and elongated esophagus at diagnosis, and as indicated by our data are prone to develop further esophageal widening during follow-up. Especially for these patients repetitive functional testing and early additional treatment might be indicated to avoid this complication. On the other hand, we showed that patients with type II achalasia respond best to treatment with better symptom control, reduced need for retreatment and diminished stasis. These data would suggest that type II patients may be less likely to develop complications. Clearly, prospective studies are required to prove this hypothesis, which in view of the low incidence of achalasia will be almost impossible to achieve.

Early detection of curable, dysplastic lesions in patients with achalasia is essential to reduce mortality related to esophageal carcinoma. Therefore, alternative screening tools should be applied.
To avoid numerous screening endoscopies, ideally, patients should be stratified according to their risk to develop dysplasia and cancer. Patients who develop esophageal cancer had a long history of dysphagia in combination with long-term esophageal stasis.\textsuperscript{11,15-17} For now we would therefore recommend to only screen patients with long-term achalasia on a 3-year basis. Another potential approach could be the use histopathological markers such as p53 or Ki67 immunoreactivity. In patients with achalasia, overexpression of p53 is observed in 82% of patients with squamous cell carcinoma and 67% of patients with dysplasia, even 6 years (range 1-11) prior to the diagnosis of carcinoma or dysplasia.\textsuperscript{61} Further studies involving biomarkers might therefore be extremely useful to stratify patients according to their risk to obtain for squamous cell carcinoma.

Clearly, after diagnosis, achalasia is a lifelong disease for which adequate treatment and follow up is indispensable. With the right approach most patients can have good quality of life, and serious morbidity and complications can be avoided.


