The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease
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Summary and conclusions
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Gastro-esophageal reflux disease (GERD) is undoubtedly one of the most common gastrointestinal disorders. Increased esophageal acid exposure is one of the most important hallmarks of GERD. GERD is characterised by symptoms of heartburn, acid regurgitation and retrosternal pain.\(^1\) Symptoms are present in 30-40% of the Western population and about 5% suffer from daily symptoms.\(^2\) The junction between the esophagus and the stomach is a specialized region, composed of the lower esophageal sphincter (LES) and crural diaphragm.\(^3\) Together these structures function to prevent gastric reflux into the esophagus while at the same time the passage of ingested food into the stomach must be guaranteed. Incompetence of the esophagogastric junction (EGJ) is recognised as most important mechanism allowing reflux to occur. 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 gastroesophageal junction (EGJ), ie. a hiatal hernia (HH).

Anatomical separation of the lower esophageal sphincter and the crural diaphragm lead to an altered pressure profile and significantly impaired anti-reflux barrier function of the esophago-gastric junction (EGJ).\(^4\) Previous studies showed that the hiatal sac can function as a reservoir from which fluid can re-reflux into the esophagus after swallowing or during periods of low sphincter pressure.\(^5\) Indeed, it has been shown that patients with a hiatal hernia have increased esophageal acid exposure and increased prevalence of reflux esophagitis caused by impaired refluxate clearance and a weakened gastroesophageal junction.\(^4-8\) However, the exact role and underlying mechanism of a hiatal hernia in the pathogenesis of excess reflux remains controversial. Some authors report an increased number of TLESRs in patients with a hiatal hernia, whereas others find no differences.\(^9, 10\) Moreover, it is unclear why reflux should be more acidic in patients with a hiatal hernia.

Transient lower esophageal sphincter relaxations (TLESRs) are accepted as major underlying mechanism for reflux, both in healthy subjects and in GERD patients.\(^11-14\) A TLESR is a well defined motor pattern consisting of a prolonged relaxation of the LES, accompanied by the inhibition of the crural diaphragm and occurring in the absence of a swallow.\(^15\) As TLESRs account for the majority of reflux episodes, one would assume that GERD patients have more TLESRs compared to healthy subjects. However, studies have reported conflicting results with both increased and equal rates in GERD patients compared to controls.\(^16-19\) Moreover, the overall rate of (acid and no-acid) reflux is comparable in healthy subjects and GERD patients.\(^20, 21\) So far, it remains unclear why patients have an increased percentage of TLESRs accompanied by acid reflux. Possibly, differences in compliance, ie. distensibility, of the esophagogastric junction (EGJ) and differences in the presence or localization of the postprandial acid pocket are involved.\(^22-25\)

In the current thesis, we have further investigated the pathophysiology of GERD, focussing on TLESRs, the mechanical properties of the EGJ, and the role of the acid pocket as the major determinant of the acidity of the refluxate. In addition, we have evaluated the effect
of new drugs intervening with the occurrence of TLESRs as potential new treatment of GERD.

In chapter 2, we focussed on esophageal compliance as a factor contributing to increased reflux in patients with GERD. It was previously hypothesized that increased compliance facilitates reflux as a lower abdominal pressure is required to open the EGJ and the diameter of the EGJ is larger at a given pressure. Recently, a new technique has been developed and validated to measure the compliance upon radial expansion of the oesophagus. On the basis of impedance planimetry, an already established technique for performing bag distensions in the gastrointestinal tract, a functional lumen imaging probe (FLIP) has been constructed that measures the cross sectional areas at several sites in a saline-filled bag. We used FLIP to demonstrate that EGJ compliance is increased in GERD patients compared to healthy subjects. We also showed that a Nissen fundoplication restores EGJ compliance to normal. In line with this, esophageal acid exposure was increased in GERD patients compared to healthy subjects, and normalized after a Nissen fundoplication. To what extent normalization of compliance is a target for pharmacological treatment, remains to be studied.

Conversely, whereas increased compliance can lead to impaired resistance to flow, decreased compliance will lead to a stiff esophagus and by consequence may contribute to dysphagia. Resection of the mucosa is currently a new approach to treat patients with a Barrett’s esophagus. Barrett’s esophagus is a pre-malignant condition, which increases the risk of developing esophageal adenocarcinoma. Especially in patients where a dysplastic lesion has developed, this lesion but also the entire segment of Barrett’s mucosa will be removed by endoscopic procedures. Endoscopic ablation treatment has emerged as a safe and effective alternative to invasive surgery for selected patients with early Barrett’s neoplasia. Drawbacks of these techniques, however, include esophageal scar and stricture formation, resulting in decreased compliance. Recently, a relatively new ablation technique, stepwise circumferential and focal radiofrequency ablation using the HALO-system, has been developed. In contrast to previous ablation techniques, the energy is delivered to the superficial mucosal layer, a feature which is crucial to reduce scar formation thereby preventing subsequent stenosis and/or dysphagia. In chapter 3, we used the FLIP technique and conventional manometry to evaluate the effect of HALO ablation of the esophageal mucosa on compliance and esophageal function. Patients with Barrett’s esophagus often have large hiatal hernias. In line with this, we found an increased compliance of the EGJ in Barrett patients compared to healthy subjects. Besides this increased compliance, esophageal function was not further hampered by endoscopic ablation of the Barrett segment, illustrating that this technique is not only safe but also preserves the mechano-elastic properties of the esophagus.

In the next section of this thesis, the role of the acid pocket in the occurrence of acidic reflux was studied. Recently, it was demonstrated that the buffering capacity of a meal is not equally distributed in the stomach. At the level of the EGJ, a pocket of unbuffered gastric acid can be detected, resulting from gastric acid floating on top of the meal.
This acid pocket may represent a reservoir from which acid will escape into the esophagus during periods of low LES pressure. As the number of TLESRs and the risk to have reflux is equal in healthy subjects and in GERD patients, the position of the acid pocket might play an important role in the determination of the acidity of the refluxate. In this thesis, we hypothesized that the position of the acid pocket relative to the diaphragm, rather than its size, could be an important determinant of acid exposure in the distal esophagus. Especially in patients with a large HH, the acid pocket may be trapped in the hiatal sac above the diaphragm, facilitating the occurrence of gastroesophageal reflux. In chapter 4, we introduced a new scintigraphic method for continuous visualization of the acid pocket to evaluate the importance of its position relative to the diaphragm in the pathogenesis of GERD. Besides a significantly enlarged acid pocket compared to healthy subjects, the acid pocket is captured in the hiatal sac in patients with a large HH, leading to increased reflux and acidic coating of the distal esophagus. These findings indicate that entrapment of the acid pocket above the diaphragm contributes to the increased risk of acid reflux in patients with a large hiatal hernia. Based on these observations, we hypothesized that the position of the acid pocket immediately before and during a TLESR is a major determinant of the chemical composition of the refluxate and that this position is determined by the presence of a hiatal hernia. In chapter 5, we showed that acid reflux during a TLESR occurs more often in patients with a HH, especially in those with a large HH, even in the early postprandial period. Furthermore, we demonstrated that the risk to have acid reflux is mainly determined by the position of the acid pocket relative to the diaphragm, and that the position of the acid pocket is in turn significantly influenced by the presence of a hiatal hernia. Together, these findings provide new insight in our understanding of the role of a hiatal hernia in the pathophysiology of GERD, and for the first time provide an explanation for the increased occurrence of acidic reflux during TLESRs in GERD patients.

In the last section of this thesis, new drugs aimed at reducing the number of TLESRs were evaluated. The current choice of treatment of GERD is undoubtedly acid suppression. However, PPI treatment increases the pH of the refluxate but leaves the number of reflux events unaffected. With the introduction of impedance monitoring, it is becoming clear that weakly acidic and even alkaline reflux may also play a role in the generation of reflux symptoms. Therefore, there is still a need for improvement of GERD therapy, i.e. the development of drugs that reduce reflux of gastric contents, irrespective of their chemical composition. As TLESRs are the most important mechanism underlying reflux, pharmacological inhibition of TLESRs is a potential target in the treatment of GERD, especially in patients with PPI resistant symptoms resulting from non-acid reflux. The GABA\textsubscript{A} receptor agonist baclofen, a potent inhibitor of TLESRs, has been extensively investigated in patients with GERD. Both in healthy subjects and patients with GERD, baclofen reduces esophageal acid exposure and diminishes reflux-associated symptoms. In contrast to acid suppressive agents, inhibitors of TLESRs reduce both the number of acid and non-acid reflux episodes and hence are referred to as reflux inhibitors. It should be stressed though that this is only true if TLESRs are a major mechanism of reflux. Importantly, previous
studies have demonstrated that in the presence of a hiatal hernia, other mechanisms, such as abdominal straining and swallow induced reflux become more important.\textsuperscript{10, 12} Hence, the efficacy of reflux inhibitors could be significantly hampered, compromising the potential clinical use of this class of drugs in this subgroup of patients. In chapter 6, we compared the efficacy of baclofen in GERD patients with and without a hiatal hernia during PPI treatment. Our major finding was that even in the presence of a large hiatal hernia, baclofen still significantly reduced the total number of reflux episodes, mainly due to reduction of non-acid reflux episodes. These findings strengthen the therapeutic potential for reflux inhibitors as additional therapy in GERD patients with incomplete response to acid suppression.

Although effective, treatment with baclofen induces central side effects such as sleepiness and dizziness, making it less attractive for wide clinical use. Therefore, other reflux inhibitors with a better safety profile are currently being developed. Like GABA\textsubscript{A} receptor agonists, we demonstrated that GABA\textsubscript{A} receptor agonists (chapter 7) and the cannabinoid receptor agonist Δ\textsuperscript{9}-THC (chapter 8), also reduce the number of TLESRs in dogs and human. Although we showed that Δ\textsuperscript{9}-THC reduces the occurrence of TLESRs by more than 50%, there are several reasons why the use of Δ\textsuperscript{9}-THC is not an attractive approach to treat GERD. First of all, administration of THC resulted in significant central and cardiovascular side effects. Secondly, the LES pressure and spontaneous swallowing were both significantly reduced by THC, facilitating reflux and impairing the clearance of refluxate respectively. Recently, the effect of a new GABA\textsubscript{B} agonist, AZD9343, was evaluated in a phase I study and its activity was compared to that of baclofen (chapter 9). AZD9343 significantly inhibits the increase in TLESRs evoked by meal ingestion, increases basal LES pressure, reduces the number of acid reflux episodes and total acid exposure time, and reduces spontaneous swallowing. These findings further confirm that the concept of GABA\textsubscript{B} receptor stimulation is a very promising approach for treating GERD patients. New agents devoid of side effects and with a higher efficacy are, however, awaited.

Gastro-esophageal reflux disease remains a complex disease, with multiple factors involved. Our findings in this thesis might guide us in the management of GERD. We clearly demonstrate that the acid pocket is an important determinant of the chemical composition of the refluxate. From a therapeutic point of view, this would imply that reduction of the size of the acid pocket by acid suppression could contribute to the beneficial effect of proton pump inhibitors in GERD.\textsuperscript{42} Furthermore, pharmacological agents which alter the position of the acid pocket by either inhibition of the postprandial fundic tone or enhancement of gastric emptying might be effective in reducing acid reflux. Of course, this needs to be further studied. In the second part of this thesis, we illustrated that reflux inhibitors represent an interesting and new approach to treat GERD patients. As it will be impossible for these agents to beat the efficacy of proton pump inhibitors, this new class of drugs will rather be used as “add-on” medication for GERD patients responding partially to PPIs. In this respect, most of these patients with persistent symptoms will have a large hiatal hernia. An important issue related to this is whether reflux inhibitors will be effective in this subgroup of patients, especially as other mechanisms than TLESRs will be involved. Although we showed
that baclofen is indeed effective in these patients, the underlying mechanism responsible for the effect was not assessed and deserves to be further studied. Finally, whether reflux inhibitors like GABA_B agonists will reach clinical application will largely depend on the possibility of pharmaceutical companies to develop agents with an acceptable efficacy and without any side effects. An important step in this direction is being made as illustrated by the recent development of new GABA_B agonists, as tested in this thesis. Moreover, a phase II trial has recently been completed showing positive results in GERD patients with PPI resistant symptoms. These findings are extremely important as they bring the concept of reflux-inhibitors as new GERD therapeutics another step closer to clinical practice. Although future studies will have to confirm this concept, this result once more illustrates how insight in pathophysiology can lead to more efficient treatment of a disease and eventually leads to improvement of the quality of life of our patients.

Reference List

Chapter 10


