The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease
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Chapter 1

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Reflux of gastric contents into the esophagus is a physiologic phenomenon in most subjects, but becomes pathological when it causes troublesome symptoms or complications.1 Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders, with typical symptoms as heartburn, regurgitation or retrosternal pain reported by 15-20% of the general population at least once a week.2-3 The majority of patients has mild to moderately severe complaints. Nevertheless, increased exposure of the esophageal epithelium to gastric acid and/or bile may lead to complications such as esophagitis, peptic strictures, Barrett's esophagus, dysplasia and ultimately esophageal carcinoma.4,5

The junction between the esophagus and the stomach is a specialized region, composed of the lower esophageal sphincter (LES) and crural diaphragm.6 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. Gastric contents are continuously driven towards the esophagus by a pressure gradient between the stomach (positive) and the thorax (negative). In healthy subjects, the LES generates a tonic pressure of 15-30 mmHg above the intragastric pressure7, strongly varying during the day8 and accounting for approximately 90% of the basal LES pressure. As reflux mainly occurs when LES pressure is below 5 mmHg, basal LES pressure should be sufficient to protect against the pressure gradient between the stomach and the esophagus. However, during straining and inspiration, the gradient increases and an additional compensatory mechanism is required. This function is fulfilled by the crural diaphragm, which contracts during each inspiration.9-11 Together these structures generate a constant high pressure zone to prevent reflux of gastric contents into the esophagus. On the other hand, to allow passage of food and avoid stasis, the LES has to relax upon swallowing via input from inhibitory neurons. Somewhat related to the latter, the high pressure zone should also allow retrograde passage of gastric contents into the esophagus during vomiting and venting of accumulated air during belching.

Clearly, GERD is the result of failure of this anti reflux barrier. 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.

In the presence of a hiatal hernia, the capacity of the gastroesophageal junction to prevent reflux of gastric contents into the esophagus is hampered, mainly by the anatomical separation of the LES and the crural diaphragm.12 In addition, 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. 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.13-17 In contrast to earlier believes, the presence of a hiatal hernia is a rather dynamic process. Even in healthy subjects, intermittent separation of the two pressure zones (LES and crural diaphragm) has been shown to occur18, a phenomenon accompanied by increased GER. 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.\textsuperscript{19, 20} Moreover, it is unclear why reflux should be more acidic in patients with a hiatal hernia.

To date, TLESRs are believed to underlie belching and are considered the main mechanism underlying GER in both healthy subject and GERD patients.\textsuperscript{21-24} 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.\textsuperscript{25} TLESRs are triggered by gastric distension resulting from an increased activation of gastric mechanoreceptors in the subcardiac region of the stomach. This leads to activation of a reflex pathway involving gastric vagal afferents, brainstem integrative circuits, and efferent inhibitory pathways to the LES and crural diaphragm.\textsuperscript{24} Vagal cooling and cervical vagotomy abolish the triggering of TLESRs, indicating that TLESRs are mediated by a vago-vagal pathway.\textsuperscript{26, 27} 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.\textsuperscript{28-31} Moreover, the overall rate of (acid and no-acid) reflux is comparable in healthy subjects and GERD patients.\textsuperscript{32, 33} Evidence for an increased percentage of TLESRs accompanied by an acid reflux episode in GERD patients compared to healthy subjects is more convincing.\textsuperscript{8, 21, 22, 29} 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.\textsuperscript{12, 34-36}

Increased compliance of the EGJ may facilitate reflux in two ways.\textsuperscript{35} First, the intra-abdominal pressure required to open the EGJ may be lower. Secondly, a relaxed EGJ may open wider than normal at a certain pressure, resulting in a reduced resistance for reflux to occur. Recently, a new technique has been developed and validated to measure the compliance upon radial expansion of the oesophagus.\textsuperscript{37-39} On the basis of impedance planimetry, an already established technique for performing bag distensions in the gastrointestinal tract,\textsuperscript{40-42} a functional lumen imaging probe (FLIP) has been constructed that measures the cross sectional areas at several sites in a saline-filled bag. In chapter 2 we used the FLIP to study possible differences in compliance of the EGJ in GERD patients and healthy subjects. As anti-reflux surgery aims to restore the distensibility of the EGJ\textsuperscript{43, 44}, we additionally studied patients who had undergone a Nissen fundoplication. Furthermore, the FLIP was used to evaluate whether esophageal function and compliance were hampered by endoscopic ablation of Barrett’s esophagus (chapter 3).

Recently, Fletcher et al. 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.\textsuperscript{34} This phenomenon has been forwarded as explanation for the discrepant observation that the pH of the postprandial esophageal refluxate can be lower than the pH in the gastric corpus. The acid pocket may represent a reservoir from which acid will escape into the esophagus during periods of low
LES pressure. This will be most pronounced in patients with a hiatal hernia, whereby the acid pocket might be trapped within the hiatal sac. So far, studies on the acid pocket have been performed using single pH pull through measurements shortly after a meal. Such measurements provide insufficient detailed information on the dynamics in time of the acid pocket to study its importance in gastroesophageal acid exposure. To this end, continuous registration of the acid pocket is required. We previously reported preliminary evidence that the acid pocket can be visualized using single photon computed tomography (SPECT) of the stomach. This technique is based on the principle that i.v. injected technetium-99m (99mTc)-pertechnetate is taken up by the gastric mucosa and, like chloride ions, is secreted by parietal cells together with gastric acid. As a result, it accumulates into the stomach providing a non-invasive approach to continuously visualize the acid pocket. In chapter 4 we used this technique to continuously visualize the acid pocket and assess its location relative to the SCJ and crural diaphragm in healthy subjects and GERD patients with and without a hiatal hernia during a 2 hour postprandial period. 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 chapter 5 we hypothesized that the localization of the acid pocket relative to the crural diaphragm and the presence of a hiatal hernia are of great importance in the occurrence of acid reflux. We assessed the position of the acid pocket just prior to the start of a TLESR in order to identify risk factors for acid reflux to occur.

The current choice of treatment of GERD is undoubtedly acid suppression. Healing of the mucosa is achieved within eight weeks of treatment with proton pump inhibitors (PPIs) in the majority (>90%) of patients with esophagitis. However, PPI treatment increases the pH of the refluxate but leaves the number of reflux events unaffected. Moreover, up to 40% of GERD patients fail to respond symptomatically, either partially or completely, to a standard dose of PPI. 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. To date the most potent pharmacological agents to reduce the rate of TLESRs are γ-aminobutyric acid type B (GABAB) receptor agonists. The GABAB receptor agonist baclofen, used in the treatment of spasticity, has shown to reduce the rate of TLESRs and the number of acid reflux episodes in normal subjects and in GERD patients. This effect most likely depends on inhibition of mechanosensitive gastric vagal afferents and their central synaptic connections with brain stem neurons, leading to a raised threshold for action potential firing and reduction of transmitter release, respectively. As baclofen crosses the blood brain barrier it causes central side effects like sleepiness and dizziness. This side effect profile makes it less attractive for clinical use. Therefore, other reflux inhibitors with a better safety profile are
currently being developed. It should be stressed though that reflux inhibitors will only be beneficial if TLESRs are the major mechanism of reflux in the subgroup of patients with PPI resistant symptoms. Importantly, in the presence of a hiatal hernia, other mechanisms, such as abdominal straining and swallow induced reflux become more important.\textsuperscript{20, 22} 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. Therefore, we performed a study whereby we assessed the efficacy of the reflux inhibitor baclofen on the reduction of gastroesophageal reflux between GERD patients with no hiatal hernia and those with a large hiatal hernia during PPI treatment (chapter 6).

Besides GABA\textsubscript{B} receptors, GABA\textsubscript{A} receptors are also widely expressed in the central and peripheral nervous systems, and mediate fast postsynaptic inhibition. GABA\textsubscript{A} agonism has been found to excite\textsuperscript{63}, inhibit\textsuperscript{64} or have no effect\textsuperscript{65} on vagal afferents, the key initiators of TLESRs. On the other hand, GABA\textsubscript{A} receptors mediate inhibition in the dorsal vagal complex, the central relay station translating afferent signalling into efferent firing producing TLESRs. In chapter 7, we assessed the potential of GABA\textsubscript{A} receptors for peripheral agonistic effects by determining GABA\textsubscript{A} receptor subunit expression in the dog nodose ganglion, the origin of vagal afferents. Furthermore, to characterize peripheral and central involvement of GABA\textsubscript{A} receptors in the regulation of TLESRs, the effects of two centrally acting GABA\textsubscript{A} agonists, muscimol and THIP, and the non-selective, peripherally acting agonist isoguvacine, as well as the positive GABA\textsubscript{A} modulator diazepam were studied in a dog model. Cannabinoid (CB) receptors, like GABA\textsubscript{B} receptors, belong to the superfamily of G protein-coupled receptors.\textsuperscript{66, 67} There are two types of cannabinoid receptors, the CB1 and CB2 receptor. CB1 receptors are mainly localised in the central nervous system whereas CB2 receptors are particularly associated with the immune system. A study in dogs showed that the CB receptor agonist WIN 55,212-2 reduced the occurrence of TLESRs in response to gastric distension by 80%.\textsuperscript{68} A study in ferrets confirmed the involvement of CB1 receptors in the central regulation of LES relaxation and showed the presence of CB1 receptors in the brain centres involved in the triggering of TLESRs.\textsuperscript{69} These data indicate that CB1 agonists may be clinically useful to reduce TLESRs in humans and may have the potential to be used as reflux inhibitors. In chapter 8, we first evaluated whether delta\textsuperscript{9}-tetrahydrocannabinol (Δ\textsuperscript{9}-THC, dronabinol, Marinol\textsuperscript{®}) had an inhibitory effect in dogs on the triggering of TLESRs. The pharmacodynamic/-kinetic relationship in dogs was then used to design a study in healthy volunteers evaluating its effect on the occurrence of meal-induced TLESRs. The compound AZD9343 is a full agonist of the human GABA\textsubscript{B} receptor, and dose dependently inhibits the number of TLESRs in dogs, with a maximum of approximately 60%.\textsuperscript{70} In addition, the effect of AZD9343 on TLESRs remained unaltered during 14 days of treatment in dogs, suggesting the absence of tolerance development, an important feature when a drug may be given on a chronic basis. First tolerance studies in man with AZD9343 showed reversible and short-lasting paresthesiae at the highest dose levels, without any further significant clinical findings (unpublished results). In chapter 9 we performed a phase
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In summary, in the current thesis, we have further investigated the pathophysiology of GERD, focussing on TLESRs, the elastomechanical 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, studies that have contributed to the introduction of new GABA\textsubscript{B} agonists as potential new treatment of GERD. A Phase II trial has recently been completed with positive results bringing the concept of reflux-inhibitors as new GERD therapeutics another step closer to clinical practice.

Reference List


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