The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease
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Chapter 5

The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and GERD patients

Submitted

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Chapter 5

Abstract

Introduction: Gastroesophageal (GER) reflux occurs twice as much during transient lower esophageal sphincter relaxations (TLESR) in GERD patients compared to healthy volunteers (HV). However, the mechanisms underlying this difference remain unclear. The aim of this study was to assess whether the localisation of the postprandial acid pocket and its interaction with a hiatal hernia (HH) play a role in the occurrence of acidic reflux during TLESRs.

Methods: 10 HV (22-53, 7 M) without HH and 22 GERD patients (19-66, 12M, 12 patients with HH < 3cm (s-HH), 10 patients with a HH ≥ 3cm (l-HH)) were studied. During gastroscopy, both the squamocolumnar junction and diaphragmatic impression were marked with a radio-labelled clip. To visualize the acid pocket, 99mTc-pertechnetate was injected iv and scintigraphic images were acquired up to 2 hrs postprandial in 15-secs frames. In addition, combined manometry and impedance was performed using a 8 channel water perfused sleeve catheter and 5 impedance sensors with the most distal sensor located 3cm above the upper border of the LES. Furthermore, pH-metry was performed using a 4 channel pH catheter with the most proximal sensor 2cm above the upper border of the LES, one sensor located in the LES and two sensors located in the proximal stomach.

Results: The rate of TLESRs and the % associated with reflux (acid and non-acid) was comparable between the three groups. Acidic reflux occurred significantly more often during a TLESR in GERD patients compared to HV (HV: 3%, s-HH: 43%, l-HH: 64%). Immediately before a TLESR, the acid pocket was more frequently located within the hiatus or above the diaphragm in GERD patients compared to HV (HV: 22%, s-HH: 55%, l-HH: 76%). Acidic reflux during a TLESR was significantly more frequent when the acid pocket extended into the hiatal opening or was located above the diaphragm in all three groups compared to a subdiaphragmatic localization (HV: 74% vs 7%; s-HH: 72% vs 21%; l-HH: 85% vs 20% of TLESRs, p<0.001). The risk to have reflux during a TLESR did not differ between GERD patients and HV when corrected for the position of the acid pocket relative to the diaphragm. In a multivariate analysis, the presence of a hiatal hernia (OR 5.26) and the supradiaphragmatic position of the acid pocket (OR 5.33) were identified as major independent risk factors for acidic reflux to occur.

Conclusion: Our findings suggest that the increased number of TLESRs associated with acidic reflux in GERD patients compared to HV results from different dynamics (position) of the acid pocket due to the presence of a HH.
Introduction

Increased esophageal acid exposure is one of the most important hallmarks of gastroesophageal reflux disease (GERD). GERD is characterised by symptoms of heartburn, acid regurgitation and retrosternal pain. Symptoms are present in 30-40% of the Western population and about 5% suffer from daily symptoms. 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. It is widely accepted that transient lower esophageal sphincter relaxations (TLESRs) are the main mechanism underlying the occurrence of gastroesophageal reflux in both GERD patients and healthy subjects. Although some authors suggest that the number of TLESRs is increased in GERD patients contributing to increased acidic reflux, these data are rather controversial and not confirmed by others. In contrast, several studies agree that the risk to have acidic reflux during a TLESR is twice as large in GERD patients compared to healthy subjects. The underlying mechanism for this observation however remains unclear. The presence of a hiatal hernia is one of the most important risk factors for GERD. 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). Moreover, Pandolfino et al. clearly demonstrated that a hiatal hernia was also associated with an increased distensibility of the (EGJ). Due to this change in mechanical properties of the EGJ, the risk to have liquid reflux increases, which was suggested to contribute to the increased acid exposure observed in HH patients. Recent studies however show no difference in liquid reflux between GERD patients and healthy controls, making it unlikely that changes in distensibility can explain the increased occurrence of acidic reflux during a TLESR in GERD patients. The fact that liquid reflux is more frequently acidic in GERD patients rather suggests that differences in acid or meal distribution in the proximal stomach or entrapment of acid in the hiatal sac must be involved. So far, however, no evidence is available supporting this hypothesis. With the description of a postprandial acid pocket just distal of the squamocolumnar junction (SCJ) in healthy subjects by Fletcher et al., the acid environment in the proximal stomach has gained enormous interest. By escaping the buffering effect of the meal, this unbuffered pool of acid provides a source for gastric acid refluxing into the esophagus. Several pH pull through studies confirmed the presence of the acid pocket, but this technique only provides information during a very brief period of time and thus is not suitable to study whether the position of the acid pocket determines the risk to have acidic reflux. Recently, we developed a new technique allowing continuous scintigraphic visualisation of the acid pocket in relation to the SCJ. When $^{99m}$Tc-pertechnetate is injected i.v., it is secreted by parietal cells and subsequently accumulates into the gastric lumen. Using SPECT scanning, 3D images clearly showed that the accumulation of scintigraphic activity in the proximal stomach is not located within the stomach wall, but is a reservoir of secreted fluid. Therefore, we are confident that our technique reliably and continuously visualizes the position of the acid pocket...
pocket. Using this technique, we showed that the acid pocket is enlarged and extends more proximal in GERD patients compared to healthy subjects, especially in GERD patients with hiatal hernia. Moreover, in a substantial amount of patients with a large hiatal hernia, the acid pocket was located within the hiatal sac above the diaphragm. Based on these observations, we hypothesized that 1. the position of the acid pocket immediately before and during a TLESR is a major determinant of the chemical composition of the refluxate and 2. that this position is determined by the presence of a hiatal hernia. To evaluate these hypotheses, we continuously monitored the position of the acid pocket and simultaneously measured LES function and gastroesophageal reflux in healthy subjects and GERD patients with a small or large hiatal hernia.

**Materials and Methods**

**Subjects**

Studies were performed in 12 healthy volunteers (mean age 32 (22-53), 7 men) and 22 GERD patients (mean age 52 (19-66), 12 men), of which 12 patients had no or a small hiatal hernia < 3 cm (s-HH) and 10 patients had a large hiatal hernia ≥ 3 cm (l-HH). All healthy subjects were free of any gastrointestinal symptoms and did not take any medication known to influence gastrointestinal motility. Only healthy subjects with a normal upper endoscopy and no hiatal hernia were included. GERD patients were selected based on the presence of esophagitis obtained during a previous upper endoscopy or by the presence of chronic heartburn symptoms responsive to proton pump inhibitor therapy. None of the subjects had a history of gastrointestinal surgery or took any medication known to influence gastrointestinal motility at the time of the study. The use of proton pump inhibitors was discontinued for a minimum of 5 days prior to the study. Intake of alcohol and nicotine was not allowed 12 and 4 hours prior to the study, respectively. Each subject gave written informed consent to participate in the study, which was approved by the Medical Ethical Committee of the Academic Medical Center.

**Study design**

All studies were performed after an overnight fast. During upper endoscopy, performed after xylocaïne throat spray, both the squamocolumnar junction and diaphragmatic impression were marked with a 99mTc-pertechnetate-labelled endoscopic clip (Boston Scientific International, Jeffersonville, USA). After endoscopy, subjects were imaged fluoroscopically in the upright and supine position to assess the exact size of the hiatal hernia. The position of the diaphragmatic impression and the proximal extent of the gastric folds were ascertained from liquid barium swallows. The size of the hiatal hernia was measured using image analysis software and a ruler to correct for magnification. The l-HH patients had ≥ 3cm axial herniation of the gastric folds. Approximately 90 minutes after upper endoscopy, combined esophageal manometry-multichannel intraluminal impedance (EM-MII), pH-metry and
scintigraphy were performed. To record TLESRs and reflux episodes, the EM-MII catheter (prototype developed by Taher Omari, Adelaide, Australia) was introduced through an anaesthetised nostril and positioned so that the sleeve straddled the LES. To measure acidic reflux, a specially designed 4 channel pH catheter (Zinetics 24ME multi-use pH catheter, Medtronic A/S Skovlunde, Denmark) was introduced through an anaesthetised nostril and positioned with the most proximal pH electrode located 2 cm above the proximal margin of the LES, the 2nd pH electrode 4 cm distal to the proximal pH electrode, i.e. within the LES, the 3rd and 4th pH electrodes were located 6 and 9 cm distal to the proximal pH electrode, respectively. Thereafter, 450 MBq 99mTc-pertechnetate was injected intravenously for visualization of the acid pocket. Thirty minutes after injection, the subjects received a meal (510 kcal), consisting of two pancakes (2x100g) with jam (2x15g) and orange juice (200ml). After the meal, EM-MII, pH and scintigraphic recordings were performed for two hours. Studies were performed in the sitting position, with the subjects leaning backwards against the gamma camera, and their upper body was restrained by a vacuum blanket to minimise movement.

Recording methods

Manometry
The EM-MII catheter consisted of a 8 lumen water perfused manometric assembly, with a sleeve sensor incorporated at its distal end to monitor LES pressure. A side hole at the distal margin of the sleeve monitored gastric pressure; esophageal body pressure was recorded 3, 6, 9, 12 and 15 cm above the sleeve. A side hole in the pharynx monitored swallows. Each lumen was perfused with degassed distilled water at 0.1 ml min⁻¹, using a pneumohydraulic capillary perfusion pump (Dentsleeve Pty, Wayville, South Australia). Pressures were sensed by external transducers connected to a polygraph (Solar System, Medical Measurement Systems, Enschede, The Netherlands).

Impedance
The EM-MII catheter contained 5 pairs of cylindrical electrodes, each 4mm in axial length and spaced at 3cm intervals. Each pair formed an impedance measurement segment, with the segments located 3, 6, 9, 12 and 15cm above the sleeve. The electrodes were connected to an impedance transducer and data was sampled at a frequency of 50 Hz.

pH recording
A four-channel antimony pH catheter with external reference was used. Before and after the study the pH electrodes were calibrated at room temperature using pH 1.0 and 7.0 buffer solutions (Medtronic A/S, Skovlunde, Denmark). Calibration at room temperature was corrected by the computer software for pH measurements at body temperature. Signals were digitalised, computer-processed, stored and analysed using commercially available software (MMS, Enschede, The Netherlands).
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**Scintigraphy**

Prior to each endoscopy, two stainless steel clips were radio-labelled by evaporating small drops of $^{99m}$Tc pertechnetate on the curved inside of one jaw with subsequent covering of this jaw with a thin layer of liquid plaster. Finally, approximately 3 MBq $^{99m}$Tc pertechnetate was attached to each clip, remaining fixed under previously tested liquid and acidic conditions. Dynamic scintigraphic images were acquired on a gamma camera system (Orbiter, Siemens Medical Solutions), equipped with a low energy all purpose collimator. Thirty minutes after intravenous injection of 450 MBq $^{99m}$Tc pertechnetate, a baseline scan was made to identify the marked SCJ and hiatal hernia. Subsequently, after the meal, multiple acquisitions were made up to two hours (480 views, 15 seconds/view, 120 minutes total acquisition time). Each acquisition was processed on a Hermes processing station (Hermes, Nuclear Diagnostics, Stockholm, Sweden) for further analysis.

**Data analysis**

Basal LES pressure was measured at end-expiration relative to intragastric pressure, and was determined as visual means of one-minute periods every 15 minutes. TLESRs were evaluated according to previously published criteria\(^{21}\): 1) absence of swallowing for 4 s before to 2 s after the onset of LES relaxation, 2) relaxation rate of $\geq 1$ mmHg s\(^{-1}\), 3) time from onset to complete relaxation of $\leq 10$ s, and 4) nadir pressure of $\leq 2$ mmHg. LES relaxations associated with a swallow and fulfilling the above mentioned criteria 2, 3 and 4 that lasted more than 10 seconds were included as TLESR. TLESRs were counted for each subject during the 2 postprandial hours. In addition, the percentage of TLESRs accompanied by an acidic reflux episode was determined, as well as the proportion of acidic reflux episodes associated with a TLESR. Total acid exposure time was calculated either at the level of the LES and at 2cm above the LES.

Reflux was defined as either pure liquid, pure gas or a mixture of liquid and gas detected by impedance. Liquid reflux was defined as a retrograde 40% fall in impedance from baseline starting at the most distal impedance site. Gas reflux was defined as a rapid increase in impedance ($3k\Omega/s$), occurring simultaneously in at least two impedance sites, in the absence of swallowing. Mixed reflux was defined as gas reflux occurring during or immediately before liquid reflux.\(^{12, 13}\) Each reflux episode as recorded by impedance was classified as: 1) acidic reflux, with a pH fall from above to below 4; 2) non-acidic reflux; 3) reflux during pull through.

The radio-labelled clips were scintigraphically visualized as clear dots. The distance between the pocket and the SCJ during a TLESR was measured with the centre of the endoscopic clip marking the position of the SCJ. The position of the acid pocket relative to the diaphragm was determined by visual positioning of the acid pocket below, above or just overlapping the diaphragmatic clip.
Statistics

Data is presented as mean ± SEM in case of a normal distribution or as median and interquartile range for variables with a skewed distribution. For statistical analysis, unpaired Student’s t-test or Mann Whitney test were used. To identify independent risk factors for the occurrence of acidic reflux during a TLESR, a multivariate analysis was performed. Since we had multiple outcomes from the same individual, correlation of the intra-individual outcomes had to be taken into account. The effect of the covariables on acidity was fitted via a logistic regression model with a random intercept (package lme4 in the statistical software program R (The R Foundation for Statistical Computing, Vienna, Austria). Acidic reflux was used as continuous variable and odds ratios (OR) were calculated. A P-value < 0.05 was considered as statistically significant.

Results

Reflux during TLESRs: HV vs HH patients

A total of 374 TLESRs was identified during the 2 hr postprandial period; 152 in HV, 124 in s-HH patients and 98 in l-HH patients. The number of TLESRs per subject was comparable in HV and GERD patients (Table 1). Of all TLESRs, the majority was accompanied by a reflux episode as recorded with impedance (HV: 88.0 ± 4.7%; s-HH: 89.8 ± 3.1%; l-HH: 92.1 ± 3.2%). The composition of the refluxate is listed in table 1.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>HV (n = 12)</th>
<th>s-HH (n = 12)</th>
<th>l-HH (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLESRs (median (IQR))</td>
<td>12.5 (7.8-16.8)</td>
<td>11.0 (9.0-12.0)</td>
<td>11.0 (8.0-13.0)</td>
</tr>
<tr>
<td>TLESRs with reflux (%)</td>
<td>88.0 ± 4.7</td>
<td>89.8 ± 3.1</td>
<td>92.1 ± 3.2</td>
</tr>
<tr>
<td>- liquid (%)</td>
<td>36.9 ± 10.0</td>
<td>13.5 ± 2.5</td>
<td>21.9 ± 7.7</td>
</tr>
<tr>
<td>- mixed (%)</td>
<td>39.8 ± 8.0</td>
<td>69.3 ± 6.4 *</td>
<td>63.5 ± 10.1</td>
</tr>
<tr>
<td>- gas (%)</td>
<td>23.3 ± 8.1</td>
<td>17.2 ± 6.0</td>
<td>14.6 ± 4.9</td>
</tr>
</tbody>
</table>

Data is presented as mean ± SEM or as median (IQR). * P<0.05 compared to healthy subjects.

Acidic reflux during a TLESR occurred more frequently in patients with a HH. The % of TLESRs accompanied by acidic reflux was significantly higher in l-HH compared to s-HH and HV (Figure 1A). This difference was most pronounced at 2 cm above the LES. Total acid exposure was also increased in patients with a HH. Especially in patients with a l-HH, % time pH<4 was much higher both at the level of the LES and 2 cm above the LES (Figure 1B).

Compared to HV, the refluxate in GERD patients extends significantly higher into the esophagus, especially in patients with a large HH (proximal extent, measured from the upper margin of the sleeve: HV 7.3 ± 0.4 cm; s-HH 8.8 ± 0.3 cm (P = 0.002); l-HH 11.5 ± 0.4 cm (P < 0.001)). When the acid pocket was located above the diaphragm, the proximal
extent of the refluxate was 11.3 ± 0.5 cm. This was significantly increased compared to episodes with the acid pocket located distally to the diaphragm (8.5 ± 0.4 cm, P < 0.001) or extending into the SCJ (9.1 ± 0.4 cm, P = 0.003).

Timing of reflux

Acidic reflux occurred throughout the entire study in all groups (Figure 2). In HV, the highest rate of acidic TLESRs occurred between 40 and 60 min after the meal (55min (IQR: 35-86 min)). In s-HH patients, acidic TLESRs were most frequent during the first postprandial hour (43min (IQR: 19-75min)), whereas in l-HH patients, acidic TLESRs occurred equally throughout the entire study (53min (IQR: 20-86 min)).

Acid pocket position prior to a TLESR and the occurrence of acidic reflux

We hypothesized that the position of the acid pocket would largely determine the risk to have acidic reflux during a TLESR. Therefore, we determined the position of the acid pocket relative to the most important anatomic landmarks, the SCJ and the diaphragm, immediately before the occurrence of a TLESR (Figure 3). As shown in Figure 4, the acid

Figure 1. A) The percentage of TLESRs associated with acidic reflux is significantly increased in GERD patients compared to HV. B) Acid exposure is significantly increased in patients with a large hernia. Data is presented as median and IQR. * P < 0.05 compared to HV.

Figure 2. Timing of individual TLESRs accompanied by acidic reflux. Acidic reflux occurred throughout the entire study in all groups, especially in l-HH patients. In HV and s-HH patients, most acidic TLESRs occurred during the first postprandial hour.
The acid pocket and TLESRs

The acid pocket and TLESRs pocket was mostly located below the diaphragm in HV. In contrast, in the presence of a HH, the acid pocket was more frequently located above the level of the diaphragm (Figure 4A). Importantly, when the acid pocket was located below the diaphragm immediately before a TLESR, non-acidic reflux occurs (left panels), whereas acidic reflux occurs when the acid pocket is extending into the hiatus (upper right panel) or located above the diaphragm (lower right panel).

Figure 3. Representative scintigraphic images of the acid pocket prior to a TLESR in relation to the SCJ and diaphragm in HV (upper panels) and l-HH patients (lower panels). When the acid pocket is clearly located below the diaphragm immediately before a TLESR, non-acidic reflux occurs (left panels), whereas acidic reflux occurs when the acid pocket is extending into the hiatus (upper right panel) or located above the diaphragm (lower right panel).

pocket was mostly located below the diaphragm in HV. In contrast, in the presence of a HH, the acid pocket was more frequently located above the level of the diaphragm (Figure 4A). Importantly, when the acid pocket was located below the diaphragm, only 7-20 % of TLESRs was accompanied with acidic reflux in all three groups studied (Figure 4B). When the acid pocket was above the diaphragm before the onset of the TLESR, this percentage increased significantly to more than 74-85% in all groups, including healthy subjects (Figure 4B). In parallel, the number of non-acidic reflux episodes was clearly increased when the
Acid pocket was located below the diaphragm (Figure 4C), an observation which was most frequent in HV (Figure 4A).

A similar analysis was performed evaluating the relationship between the position of the acid pocket relative to the SCJ and the occurrence of acidic reflux during a TLESRs, however no relationship could be detected (data not shown).

**Figure 4.** Position of the acid pocket immediately before the start of a TLESR

(A) Note that in HV, the acid pocket is located below the diaphragm during most TLESRs. This in contrast to l-HH patients.

(B) When the acid pocket is extending into the hiatus or is located above the diaphragm, most TLESRs are associated with acidic reflux. (C) Non-acidic reflux mainly occurred when the acid pocket was located below the diaphragm, both in HV and in GERD patients.

Acid pocket position and the occurrence of acidic reflux during mechanisms different from TLESRs

Also for reflux episodes not related to a TLESR, we evaluated the importance of the position of the acid pocket to have acidic reflux. A total of 49 reflux episodes were recorded in 19 subjects (2 in HV, 8 in s-HH, 9 in l-HH patients). Almost half of the episodes were related to abdominal straining (49%). Other mechanisms were cough (12%), swallow induced (12%), deep inspiration (10%) and low LES pressure (16%). Most episodes were non acidic (67%). When the acid pocket was located below the diaphragm, 93.9% of the reflux episodes were accompanied by non-acidic reflux. In contrast, when the acid pocket was located
above the diaphragm or extending into the hiatus, 85.7% and 88.9% of the reflux episodes are accompanied by acidic reflux, respectively.

**Esophageal shortening during TLESRs and the occurrence of reflux**

In the majority of TLESRs, we observed a proximal movement of the clip positioned at the SCJ in all groups (Figure 5), corresponding with esophageal shortening (% TLESRs with shortening: HV: 56 ± 10 %; s-HH: 62 ± 10%; l-HH: 77 ± 7 %). The mean length of shortening was 2.4 ± 0.2 cm, 3.0 ± 0.1 cm and 2.6 ± 0.3 in HV, s-HH and l-HH patients, respectively. No differences were observed between acidic or non-acidic reflux. Our scintigraphic technique was however not suited (too few pictures per time unit) to perform any further detailed analysis on shortening.

![Figure 5](image)

**Figure 5.** Illustration of esophageal shortening as it was observed during TLESRs. A clear upwards movement of the SCJ clip occurred, returning to its former position directly after.

**Factors associated with acidic reflux**

Multivariate regression analysis identified the presence, but not the size of a hiatal hernia, and the position of the acid pocket above the diaphragm or extending into the SCJ as independent risk factors for the occurrence of acidic reflux during a TLESR (Table 2). On the other hand, the distance between the acid pocket and the SCJ was protective against acidic reflux.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hial hernia</td>
<td>5.26</td>
<td>1.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>position of acid pocket</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- supradiaphragmatic</td>
<td>5.33</td>
<td>1.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>- in hiatus hernia</td>
<td>2.69</td>
<td>0.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>distance between pocket and SCJ during TLESR (cm)</td>
<td>0.39</td>
<td>0.30</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Discussion

In the present study, we showed that 1. acidic 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, 2. that the risk to have acidic reflux is mainly determined by the position of the acid pocket relative to the diaphragm, and 3. that the position of the acid pocket is significantly influenced by the presence of a hiatal hernia. These findings provide further 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.

For years, it is known that patients with a large HH are more prone to have acidic reflux than patients with no or a small hernia.22-27 Low LES pressure, impaired clearance and accumulation of gastric contents in the hiatal sac, thereby facilitating reflux during swallow induced LES relaxation, are proposed as possible mechanisms for this increased acid exposure. It has previously been suggested by Pandolfino et al. that a positive pressure gradient between the stomach and esophagus, developed by repositioning of the SCJ to a supradiaphragmatic position, is a prerequisite for reflux to occur.28 This pressure gradient can be achieved by abdominal straining, inspiration or positioning of the EGJ above the diaphragm into the thoracic cavity. In the setting of a hiatal hernia, this separation is pre-existent. In addition, Bredenoord et al. recently reported episodes of intermittent separation of the LES and diaphragm, both in GERD patients and in healthy subjects.29, 30 Moreover, in that study, reflux occurred more frequently during evident spatial separation of the diaphragm and LES.30 It is most likely that, in the setting of normal anatomy, repositioning of the EGJ above the diaphragm occurs as a result of esophageal shortening.28, 31, 32 In the present study, we confirmed the occurrence of esophageal shortening, a phenomenon associated with TLESRs.28, 31, 32 Due to the limited number of images per time unit, however, our scintigraphic technique does not allow to determine the precise relationship between shortening, timing of LES relaxation and the occurrence of reflux.

Although the presence of a hiatal hernia and the phenomenon of esophageal shortening are important factors in the occurrence of gastroesophageal reflux, it remains unexplained why acidic reflux occurs more frequent in GERD patients compared to healthy controls, especially in the postprandial period when acid is thought to be buffered by the meal. Comparable to Sifrim et al.12, 13, the risk to have (acid and non-acid) reflux in our study is comparable in healthy controls and GERD patients. In contrast, and in line with previous studies8, 33-35, acidic reflux is more frequently acidic in GERD patients compared to HV, most pronounced in patients with a large HH. This observation rather suggests that differences in acid or meal distribution in the proximal stomach or entrapment of acid in the hiatal sac must be involved. Our study is the first study to provide evidence supporting this hypothesis. We showed that the position of the acid pocket above the diaphragm is a major risk factor for acidic reflux to occur during a TLESR. Indeed, when the acid pocket is located above the diaphragm or is extending into the hiatal opening, 70-85 % of all TLESRs is accompanied by acidic reflux. In contrast, when the acid pocket is located below the diaphragm prior to a TLESR, only
7-20% is accompanied by an acidic reflux episode. Most importantly, this observation not only holds for GERD patients, but even for healthy volunteers, illustrating its importance in determining the composition of the refluxate. As a consequence, factors influencing the position of the acid pocket relative to the diaphragm will have a major impact on the risk to have acidic reflux during episodes of an insufficient anti-reflux barrier. Most likely, the most important factor determining the position of the acid pocket is the presence of a HH. Indeed, in patients with a HH, the acid pocket was located more frequently above the diaphragm compared to HV (76 % versus 22 %). Multivariate regression analysis revealed the presence of a hiatal hernia and a supradiaphragmatic acid pocket position as major independent risk factors for acid reflux to occur, with odds ratios above 5. This supradiaphragmatic position occurred more frequently with increasing size of the hernia. In line with this supradiaphragmatic position, the % of TLESRs accompanied by acidic reflux is highest in patients with a large HH. Whereas in HV only 3 % of all TLESRs was associated with acid reflux, this was increased to 43 % and 64 % in patients with respectively a small and large HH. The combination of a positive pressure gradient due to the hernia and acid trapped within the hiatal sac almost guarantees the occurrence of acidic reflux during TLESRs or when LES pressure is low. Even in HV, most acidic reflux episodes occurred when the acid pocket was extending into the hiatus during a TLESR. This phenomenon could be explained by the intermittent spatial separation of the LES and diaphragm. Bredenoord et al. showed that maximum separation was approximately 2.5 cm, both in HV and in small hernia patients. When during this separation the acid pocket is migrating upwards with the LES, a situation comparable with a small hernia is formed, promoting acidic reflux. Thus, any extension of the acid pocket above the diaphragm seems to be sufficient to promote acidic reflux, as long as it occurs in the presence of a positive pressure gradient caused by separation of the LES and diaphragm, both in HV and in GERD patients. In contrast, when the acid pocket was located below the diaphragm, reflux was mainly non-acidic. Our hypothesis is further strengthened by the observation that not only during TLESRs, but also during reflux episodes caused by other mechanisms, the position of the acid pocket is of major importance. Although most reflux episodes related to mechanisms different from TLESRs were non-acidic, a supradiaphragmatic position of the acid pocket resulted in acidic reflux in 85-89 % of these episodes. Half of the reflux episodes not related to a TLESR occurred during straining. During straining, although a positive pressure gradient is clearly present, still the majority of all reflux events was non acidic because of a subdiaphragmatic position of the acid pocket. Recently, the role of the acid pocket in the occurrence of acidic reflux was questioned as a disparity was suggested between the time course of the acid pocket and that of the occurrence of acidic reflux. This conclusion was based on the assumption that the acid pocket exists for only 60-90 min after meal intake, whereas acidic reflux episodes would appear mainly during the second postprandial hour. We clearly showed that acidic reflux occurs throughout the entire study period in both HV and GERD patients. Moreover, in patients with a HH, the highest rate of acidic reflux episodes occurs during the first
postprandial hour. These findings argue against the suggestion that acidic reflux hardly occurs directly postprandial due to buffering of the meal\(^\text{13}\), but favour the assumption that the position of the acid pocket determines whether refluxate is acidic or not. This was indirectly supported by our observation that the occurrence of acidic reflux during TLESRs in time parallels the presence of the acid pocket. TLESRs accompanied by acidic reflux were most prevalent between 45 and 60 min after the meal in HV and s-HH GERD patients, the time window in which the size of the acid pocket is maximal and in close proximity to the SCJ.\(^\text{20}\) In patients with a large hiatal hernia, acidic reflux during TLESRs was recorded throughout the entire study, coinciding with entrapment of the acid pocket in the hiatal sac as visualized on the scintigraphic images.

What is the clinical impact of our findings? First of all, our data provide additional evidence highlighting the importance of a hiatal hernia in the pathogenesis of GERD. In addition, we 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. Vo et al. indeed demonstrated that PPI treatment decreases the amount and size of postprandial acid pockets.\(^\text{17}\) Furthermore, pharmacological agents, like baclofen or prokinetics might be effective, at least in part, by altering the position of the acid pocket due to inhibition of the postprandial fundic relaxation\(^\text{38, 39}\) or by enhancement of gastric emptying\(^\text{40}\), respectively. Finally, especially in patients with a large HH, the acid pocket will be entrapped in the hiatal sac and will easily enter the esophagus during episodes of low LES pressure. To what extent reflux inhibitors or drugs increasing LES pressure will be efficient to prevent reflux under these conditions, is rather questionable and deserves further study. In these patients, it would therefore be more appropriate to surgically correct the large HH and to reposition the stomach and the acid pocket within the abdominal cavity.

In summary, this study demonstrates that the observation that GERD patients more often have acidic reflux during a TLESR compared to HV results from differences in the dynamics of the postprandial acid pocket. Supradiaphragmatic localization of the pocket was more frequent in GERD patients, especially those with a large HH, and was associated with a 5 fold risk to have acidic reflux. These findings in combination with previous results on the dynamics of the acid pocket contribute to a better understanding of the pathogenesis of GERD and further stress the importance of a HH in promoting acidic reflux.

Reference List


7. Mittal RK, McCa...


