Reflux disease and achalasia: Failure of the gatekeeper
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Chapter 6
Proton pump inhibitors reduce the size and acidity of the acid pocket
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Submitted
ABSTRACT

Background and aims:
The gastric acid pocket is increasingly recognized as reservoir from which acid reflux events originate. Its position is a major determinant of acid reflux during transient relaxations of the lower esophageal sphincter. To what extent changes in position, size and acidity of the acid pocket contribute to the therapeutic effect of proton pump inhibitors (PPIs) is unknown. The aim of this study was therefore to determine the effect of PPI treatment on the acid pocket in gastroesophageal reflux disease (GERD) patients.

Methods:
Thirty-six GERD patients (off PPI: n=18; on PPI: n=18, 19M 15F age 55 yrs) underwent concurrent high resolution manometry (HRM) and pH-impedance following a standardized meal. The acid pocket was visualized using scintigraphy after intravenous administration of $^{99m}$Tc-pertechnetate. The size of the acid pocket was measured and its position was determined relative to the diaphragm using radionuclide markers on the HRM catheter. At the end of the study, the acid pocket was aspirated to determine the pH.

Results:
The number of reflux episodes was comparable on and off PPI, but the rate of acid reflux episodes was significantly reduced on PPI. On PPI, the acid pocket was smaller and more frequently located below the diaphragm compared to off PPI. The pH of the acid pocket was significantly lower off PPI (n=6) compared to on PPI (n=16) (0.9 [range 0.7 to 1.2] vs. 4.0 [range 1.6 - 5.9] p<0.001). The pH of the acid pocket correlated significantly with the nadir pH of the refluxate (r=0.72, p<0.01)

Conclusion:
Also during PPI treatment, the acid pocket most likely represents the reservoir from which reflux occurs, and that the effect of PPIs on the size, acidity and position of the acid pocket contributes to the clinical success of PPIs in GERD.
Despite the buffering effect of the ingested food, most acid reflux episodes and associated symptoms occur in the postprandial period. This phenomenon appears to be a paradox, but is explained by the postprandial formation of a floating pool of acid on top of the ingested food. From this so-called acid pocket, highly acidic liquid can reflux into the esophagus during transient lower esophageal sphincter relaxations or other episodes promoting gastroesophageal reflux, both in patients with gastroesophageal reflux disease (GERD) and healthy subjects. Hence, the acid pocket can be considered as the reservoir from which acidic fluid refluxes into the esophagus.

We previously demonstrated that the position of the acid pocket largely depends on the presence of a hiatus hernia and is a major determinant of the risk to have acid reflux. Notably, when the acid pocket is located below the diaphragm or in the gastric fundus, only 11% of episodes is acidic, while the majority of episodes is acidic when the pocket is located in the hiatus or even above the diaphragm (62% and 91% respectively), underlining the importance of the acid pocket in the pathophysiology of GERD.

Proton pump inhibitors (PPIs) have been abundantly shown to reduce the number of acid reflux episodes and esophageal acid exposure. Previously it was thought that the reduction in acid production in the stomach by PPIs would lead to less reflux episodes. However, studies with pH-impedance demonstrated a similar number of reflux episodes (non-acid + acid) on and off PPIs. On PPIs, acid reflux is only observed in 20% of reflux episodes, and most reflux episodes are weakly acidic or alkaline. Currently, the effect of PPIs on the acid pocket is unknown. As PPIs reduce acid secretion, the acidity and volume (and indirectly position) of the acid pocket may be altered, potentially contributing to the reduction in acidic reflux events. More insight into the effect of PPIs on the acid pocket could improve insight in persistent symptoms on PPIs, and thereby potentially lead to better treatment options. Therefore, the aim of this study was to determine the effect of PPIs on the size, position and acidity of the acid pocket. If the acid pocket is still present during PPI therapy, this might represent a target for further therapy.

**PATIENTS AND METHODS**

**Patients**

The study was performed in 36 patients with proven GERD, defined by the presence of esophagitis observed during upper endoscopy and/or impedance-pH-metry with an acid exposure of >4.5%, in combination with typical GERD symptoms. None of the patients had undergone previous gastrointestinal surgery or was taking medication known to influence esophageal motor function.
The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands. Written informed consent was obtained from all subjects before enrolment in the study.

**Study set-up and protocol**

Eighteen patients on PPI were compared to 18 patients off PPI. In the latter group of patients, PPIs were stopped at least 7 days before the study day. All subjects were studied after an overnight fast. Reflux episodes were detected using concurrent HRM and pH-impedance monitoring, and scintigraphy was performed to determine the size of the acid pocket and the position of the pocket relative to the crural diaphragm. Thirty minutes prior to the start of these measurements, 350 MBq of $^{99m}$Tc-pertechnetate was injected intravenously. Pertechnetate behaves as a chloride ion, and is secreted by the parietal cells of the stomach. Using scintigraphy, the formation of the acid pocket can be observed after the meal as pooling of $^{99m}$Tc-pertechnetate in the proximal stomach as validated previously.

![Figure 1](image_url)

**Figure 1** | Figure 1 represents a spatiotemporal plot of the esophagus, alongside the catheter set-up and a representative scintigraphic image. Two radionuclide markers are attached to the HRM catheter (marked by yellow dots), which can be observed on the scintigraphic image (II), marked by white arrows. The spatiotemporal plot of the HRM and pH-impedance recording (I) shows a mixed reflux episode during a TLESR in a patient with a large hiatal hernia. The LES is marked with A, and the upper and lower borders of the crural diaphragm are marked with B and C respectively. The distances from A, B and C to the upper and lower marker are measured. In addition, the distance from the markers to acid pocket is measured in the scintigraphic image. Using these distances, the position of the acid pocket is classified as below the diaphragm, at the level of the diaphragm or above the diaphragm. In this example, the acid pocket is located below the diaphragm. The pH of the refluxate is weakly acidic (pH 5.8).
To determine the exact location of the high resolution manometry (HRM) catheter during scintigraphy, 2 sealed markers impregnated with topical \textsuperscript{99m}Tc-pertechnetate were attached to the catheter before introduction, one to the distal end of the catheter and one between sensor 11 and 12. These markers were used to integrate manometry and scintigraphy as described in detail below. The HRM catheter and the pH-impedance catheter were inserted through an anaesthetized nostril. The HRM catheter was positioned with the most distal sensors located in the stomach, and the pH-sensor of the pH-impedance catheter was positioned 5 centimetres above the upper border of the LES. (Figure 1)

Patients were positioned in the upright position in front of the scintigraphy camera. After a baseline fasting recording of 5 minutes, patients consumed a standardized meal consisting of 200 ml orange juice and two pancakes with jam (510 kcal). After the meal, concurrent scintigraphic, HRM and pH-impedance recordings were acquired for 105 minutes. At the end of the protocol, the acid pocket was aspirated through the 0.9 mm working channel of the HRM catheter. The marker at the distal tip of HRM catheter was used to position the opening of the working channel at the level of the acid pocket and to accurately aspirate the fluid of the pocket. The pH of the fluid was measured before storage.

Recording methods
High resolution manometry was performed using a 21 lumen water perfused HRM catheter (MMS, Enschede, the Netherlands) with a diameter of 4.0 mm. Eleven distal side holes were positioned at 1 cm intervals, and the 10 proximal side holes were spaced at 3 cm intervals as depicted in Figure 1. The side holes were perfused with distilled water at 0.15 mL/min, using a pneumohydraulic capillary perfusion pump (MMS, Enschede, the Netherlands) and hydraulic flow restrictors. The working channel had a diameter of 0.9 mm with the opening located at the distal tip of the catheter. Pressure sensors were zeroed before insertion and data was collected and analyzed with a MMS Solar system (MMS, Enschede, the Netherlands).

We used a combined pH-impedance catheter (Unisensor, Atikon, Switzerland), containing 6 pairs of impedance electrodes and 1 ISFET pH sensor that allowed impedance recordings at 3, 5, 7, 9, 15 and 17 cm above the upper border of the LES and pH recording at 5 cm above the LES. The pH electrode was calibrated before each study using buffers solutions of pH 4.0 and 7.0 (Medtronic A/S, Skovlunde, Denmark).

Dynamic scintigraphic images were acquired on a gamma camera system (Diacam; Siemens Medical Solutions, Illinois, USA), equipped with a low-energy all purpose collimator. Dynamic recordings were made for 2 hours (720 views, 10 s/view, 120 min total acquisition time). Every acquisition was processed on a Hermes processing station (Hermes Medical Solutions, Stockholm, Sweden) for further analysis.
Data analysis

Scintigraphic images were analysed using calibrated Hermes software. The size and nuclear counts of the acid pocket were determined by drawing an area of interest (ROI) over the acid pocket in the proximal stomach in images taken at 10 minutes intervals. The acid pocket could be visualized starting from 15 minutes postprandially. Background activity measured in an area of equal size adjacent to the stomach was deducted from activity counts.

Each liquid or mixed reflux event detected by impedance was classified as acidic reflux when pH < 4, as weakly acidic when pH ≥ 4 and pH < 7 and as non-acidic when pH ≥ 7. Impedance segments were used to determine proximal extent of refluxate. A liquid reflux was defined as a fall in impedance of ≥ 40% of baseline impedance starting at the most distal segment and propagating retrograde to at least the next measuring segment. Mixed reflux was defined as gas reflux occurring during or immediately before liquid reflux.

For each reflux episode, HRM recordings were used to determine the exact distance from the crural diaphragm to the markers on the catheter for the position of the acid pocket and to the LES for hiatal hernia size. The lower and upper border of the crural diaphragm and the middle of the LOS zone were determined. (Figure 1) Hiatal hernia size was defined as the distance from the lower end of the diaphragm to the middle of the LOS.(9)

For each reflux event, the position of the acid pocket was determined relative to the diaphragm. For this purpose, HRM recordings were used to determine the exact position of the crural diaphragm and LES, relative to the markers on the catheter. (Figure 1) Subsequently, calibrated Hermes software was used to measure the distance of the proximal end of the gastric acid pocket to the markers on the catheters on one image prior to the reflux event to calculate the distance between the acid pocket and the crural diaphragm. Measurements of the distances between the acid pocket and the diaphragm were made through a straight line in a planar posterior view of the stomach. On scinitigraphy, the pocket was identified as a clear pool of radiolabelled activity in the proximal stomach. With these distances, the exact location of the acid pocket relative to the crural diaphragm could be calculated. The position of the acid pocket was classified in three categories: below the diaphragm, at the level of the diaphragm or above the level of the diaphragm.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM Corporation, Somers, NY, United States). Data are presented as mean ± SEM when parametric or median [IQR] when non-parametric. Parametric data were compared using a Student’s t-test, and non-parametric data using a Mann-Whitney U test. Comparison of proportions was performed using Fisher’s exact testing. Pearson’s
correlation was used for correlations. All p-values were two-tailed and a p-value < 0.05 was considered as statistically significant.

RESULTS

Patients

All 36 patients completed the study protocol. Eight patients on PPI used omeprazole, 5 used pantoprazole and 5 used esomeprazole. Dosage varied from 20 mg (1 patient), 40 mg (7 patients) to 40 mg bid (8 patients). In the group of patients that discontinued PPI use for 1 week, 7 patients normally used bid PPI. Patient characteristics of the two patient groups are shown in Table 1. No difference was observed in age and sex in the two patient groups. In addition, hiatal hernia size as measured using HRM recordings was similar.

<table>
<thead>
<tr>
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<th>Off PPI (n=18)</th>
<th>On PPI (n=18)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 ± 1.4</td>
<td>55 ± 4.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hiatal hernia size (cm)</td>
<td>2.7 ± 0.2</td>
<td>2.4 ± 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>PPI bid</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Persistent symptoms (SAP &gt;95%)</td>
<td>8</td>
<td>9</td>
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</table>

Table 1 | Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Off PPI (n=18)</th>
<th>On PPI (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial reflux events (nr)</td>
<td>14 ± 2.1</td>
<td>15 ± 2.6</td>
<td>0.81</td>
</tr>
<tr>
<td>Acid reflux events (nr)</td>
<td>4.5 [2.0-14]</td>
<td>2.0 [0-3.0]</td>
<td>&lt;0.05</td>
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<td>Acid reflux events (%)</td>
<td>51 ± 7.9</td>
<td>21 ± 5.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weakly acid reflux (nr)</td>
<td>5.0 [3.0-6.5]</td>
<td>9.0 [7.0-18]</td>
<td>&lt;0.01</td>
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<td>Weakly acid reflux (%)</td>
<td>49 ± 7.9</td>
<td>79 ± 5.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Esophageal acid exposure (%)</td>
<td>11 ± 3.5</td>
<td>2.2 ± 1.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Proximal extent (cm)</td>
<td>10 ± 0.6</td>
<td>9.9 ± 0.5</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Table 2 | Reflux episodes

The total postprandial number of reflux episodes was similar in patients on PPI compared to those off PPI (15 ± 2.6 vs. 14 ± 2.1, p=0.81, Table 2). As expected, the number of acid reflux episodes was reduced on PPI (4.5 [2.0-14] vs. 2.0 [0-3.0], p=0.04), while the number of weakly acid reflux episodes was increased on PPI (5.0 [3.0-6.5] vs. 9.0 [7.0-18], p<0.01). In line, PPI treatment
decreased esophageal acid exposure (11 ± 3.5% vs. 2.2 ± 1.0%, p=0.02), and significantly increased nadir pH of refluxate (1.2 [1.0-3.5] vs. 3.2 [2.8-4.1], p=0.02). No difference in proximal extent of refluxate was observed between on and off PPI (10 ± 0.6 cm vs. 9.9 ± 0.5 cm, p=0.80).

**The effect of PPIs on the acid pocket**

All patients off PPI showed an acid pocket, compared to 16 out of 18 patients on PPI. (p=0.49) In 2 patients on PPI, no pooling of $^{99m}$Tc-pertechnetate in the proximal stomach was observed. Proton pump inhibitors significantly reduced the size of the acid pocket (off PPI: 15 ± 0.9 cm² vs. on PPI: 10 ± 1.3 cm², p<0.01, Figure 2.). In addition, the mean number of counts in the acid pocket was significantly lower on PPI, suggesting that the secretion of $^{99m}$Tc-pertechnetate into the pocket was reduced by PPIs (2762 ± 265 vs. 1566 ± 210 counts/10s, 43%, p<0.001, Figure 2). The acid pocket size significantly correlated with the number of counts, demonstrating that the reduction in $^{99m}$Tc-pertechnetate secretion by PPI treatment leads to a smaller acid pocket (r=0.76, p<0.001).

At the end of the study, a clear acid pocket was visualised scintigraphically in the proximal stomach in all patients off PPI and in 16 of 18 patients on PPI. To confirm that this scintigraphic activity indeed resulted from radiolabelled acid pooled on top of the meal, the radioactive material was aspirated through the working channel (mean 60 mL of transparent mucoid fluid). Scintigraphic activity in the proximal stomach disappeared after aspiration in both patient groups. The pH of the aspirated acid pocket fluid was significantly higher during PPI treatment (0.9 [0.8-1.1] vs. 3.9 [2.8-5.1], p<0.001, Figure 3a).

**Acid pocket as a source of refluxate**

To support the assumption that the acid pocket is the reservoir from which reflux occurs, we determined the relationship between the pH of the acid pocket and the pH of the reflux episodes. Interestingly, the pH of the aspirate was strongly and significantly correlated with the pH of the reflux events (r=0.72, p<0.01) (Figure 3.) Especially when the pocket is located above the diaphragm, the relation between the pH of the pocket and refluxate is excellent (r=0.88, p<0.001). In line, we found a strong inverse correlation between the acid pocket pH and the rate of acid reflux episodes (r=−0.79, p<0.01) and esophageal acid exposure time (r=−0.72, p<0.01), demonstrating that an increase in acid pocket pH leads to a reduction in the rate of acid reflux and esophageal acid exposure.
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Figure 2 | In Figure 2A and B the size and nuclear activity of the acid pocket are depicted off and on PPI. As demonstrated in Figure 2A, the size of the acid pocket is significantly smaller on PPI compared to off PPI during the entire postprandial period (area under the curve p<.01). In addition, the number of counts in the area of interest is significantly lower on PPI compared to off PPI (p<.01). This demonstrates that less gastric secretion is present in the acid pocket during treatment with PPI. Tested using a Student’s t-test on area under the curve values.

Figure 3 | As demonstrated in Figure 3A, the nadir pH of reflux episodes was significantly increased by PPIs. Proton pump inhibitors also significantly increased the pH of the acid pocket (3B). As demonstrated in figure 3C, the pH of the acid pocket had a good correlation with the nadir pH of refluxate (r=0.72).

As a more proximal position of the acid pocket is an important risk factor for acid reflux, we analyzed the effect of PPI treatment on the position of the acid pocket prior to reflux episodes. Compared to off PPIs, the pocket was more often located below the diaphragm in patients on PPIs (40±6.5% vs. 60±6.9% of reflux episodes, p=0.04) (Figure 4). When the acid pocket was located below the diaphragm, the risk for acidic reflux was only 15 ± 5.5% off PPI and 7.0 ± 3.0% on PPI (p=0.20). When the acid pocket was located at the level of the diaphragm, so in the hiatus, 76 ± 6.7% of reflux events off PPI was acidic, whereas 46 ± 12% of reflux episodes was acidic on PPI (p=0.11). Finally, when the acid pocket was located above the diaphragm, the refluxate was acidic in 95 ± 3.9% of reflux episodes off PPI, compared to 49 ± 7.5% of reflux episodes on PPI (p<0.01). (Figure 4) The reduced rate of acidic reflux episodes when the pocket is located above the diaphragm is probably explained by the increased pH of the acid pocket on PPIs. This is supported
by the excellent correlation (r=0.88) of the pH of the pocket and refluxate when the pocket is located above the diaphragm. In contrast, no correlation of the pH of the acid pocket and refluxate is found when the pocket is located below the diaphragm (r=0.41, p=0.08).

We hypothesized that the smaller size of the pocket on PPIs may contribute to a more distal position. Indeed, the rate of acid pocket located below the diaphragms correlated with the count number and size of the acid pocket (r=0.47, P<0.01). Subsequently we analysed whether changes in hiatal hernia size contributed to the more distal position on PPI. However, hiatal hernia size was similar on and off PPI therapy (2.7 ± 0.2 cm vs. 2.4 ± 0.4 cm, p=0.34). In addition, we found no difference in spatial separation rate of the hiatus hernia (70 ±7.0% vs. 56±10%, p=0.20).

**Acid reflux episodes on PPI**

Acid reflux episodes still occurred during PPI treatment. From earlier studies, it is known that acid reflux more often leads to heartburn compared to non-acid reflux episodes. Therefore we compared the acidity, size and position of the acid pocket in acid reflux episodes to non-acid reflux episodes (pH>4). For this analysis, only patients on PPI were analysed. Notably, we found that esophageal acid exposure time is 4.0 ± 2.0 % when the acid pocket was acidic, compared to 0.2 ± 0.4% when the pocket was not acidic. Due to the low number of patients (8 vs. 8), this difference was not significant (p=0.17). Also during PPI use, acidic reflux episodes occurred primarily when the pocket was located above (17 of 35 reflux episodes [49%]) or at the level of the diaphragm (35 of 74 [46%]) compared to when the pocket was below the diaphragm (10 of 134 [7%], Figure 4).

**Figure 4** | The position of the acid pocket is an important determinant in the acidity of the refluxate. On PPI the acid pocket is significantly more often located below the diaphragm compared to off PPI (*<0.05, Student’s t-test). As demonstrated in the right image, a more proximal position of the acid pocket leads to a higher acid reflux rate, also on PPI. However, the risk for acid reflux is significantly lower on PPI compared to off PPI when the pocket is located above the diaphragm. This is probably attributable to the higher pH (>4 in 50%) of the acid pocket on PPI.
These data suggest that the risk for acid reflux is mainly determined by the pH of the pocket. When the pocket is acidic, acid reflux mainly occurs when the pocket is located at the level or above the diaphragm, i.e. when the acid pocket is the source of refluxate.

**DISCUSSION**

In the present study, 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. When the pocket is not acidic, the risk for acidic reflux events is negligible, irrespective of its position. When the pocket is acidic, the position of the pocket is a major determinant of acid reflux during transient relaxations of the lower esophageal sphincter, also during acid suppression. Taken together, these data demonstrate that also during PPI use, the acid pocket can act as a reservoir from which liquid refluxes into the esophagus, and that mainly the change in the pH of the acid pocket leads to the reduction in acid reflux events.

After meal intake, the acid pocket escapes the buffering effect of the ingested food and floats in the proximal stomach. There, this pocket functions as a reservoir from which acid refuxes into the oesophagus. If the pocket is located above the diaphragm or in the hiatus, acid reflux is highly likely to occur (70-90%), in contrast to when the pocket is located below the diaphragm (10%). Moreover, it was demonstrated that modulation of the acid pocket to a more distal position leads to less acidic reflux events, confirming that the acid pocket is a potential therapeutic target in the treatment of GERD. Not only H+ ions are taken up and secreted into the stomach by parietal cells, but also $^{99m}$Tc-pertechnetate when injected intravenously. As a result, the acid pocket can be visualized using $^{99m}$Tc-pertechnetate on scintigraphy. We previously validated that postprandial pooling of $^{99m}$Tc-pertechnetate in the gastric cardia indeed represents the gastric acid pocket. Moreover, aspiration from this pocket revealed highly acidic fluid and nuclear activity scintigraphically disappeared after aspiration. Hence, this technique is ideally suited to visualize the acid pocket, and determine the effect of treatment on the pocket. In the current study, we determined how PPIs affect properties of the acid pocket and determined whether this contributes to the therapeutic effect of these drugs.

Interestingly, we demonstrated for the first time that also during acid suppression, a postprandial 'acid' pocket is formed in the large majority of GERD patients (89%). This might be explained by incomplete blocking of acid secretion by PPIs. As demonstrated in early in vitro studies with omeprazole, PPIs do not fully suppress acid production in parietal cells. Moreover, in vivo, acid
inhibition is never complete because of continued synthesis of new proton pumps.\textsuperscript{24} Ongoing acid secretion into the pocket is supported by a pH of the pocket below 4 in 50\% of our patients on PPI. On the other hand, the acid pocket not only consists of acid secreted by the parietal cell. It is known that \textsuperscript{99m}Tc-pertechnetate is also secreted by mucoid cells. For instance, in patients with severe atrophic gastritis with achlorhydria, thus in absence of parietal cells, \textsuperscript{99m}Tc-pertechnetate is still secreted into the gastric lumen.\textsuperscript{15} Comparably, in GERD patients with suppression of acid secretion, the observed formation of a large postprandial pocket with a pH of 4-6 is therefore probably also in part attributable to secretion by mucoid cells. Either way, based on the findings from this study we can conclude that also during acid suppression, a pocket of gastric secretions floats on top of the ingested food.

Although the acid pocket was still present, PPIs significantly influenced its properties. The most important effect of PPIs on the pocket is the reduction of its acidity. Aspiration of the pocket on PPIs revealed fluid with a pH of 4.0 (range 1.6-5.9), compared to highly acidic fluid with a pH of 0.9 (range 0.7-1.2) off PPI. Importantly, the pH of the acid pocket correlated well with the nadir pH of refluxate \((r=0.72)\) and inversely with the rate of acid reflux \((r=-0.78)\). Moreover, when the pH of the aspirated pocket was over 4, the esophageal acid exposure was very low (0.2\%). Especially when the pocket is located above the diaphragm, the correlation between the pH of the pocket and refluxate is excellent \((r=0.88, p<0.001)\). Taken together, this confirms that PPIs significantly increase the pH of the acid pocket, which largely determines the pH of the refluxate.

Previously, we demonstrated that if the pocket is located in the hiatus or in the hiatal sac, the pocket functions as a reservoir from which acid refluxes into the oesophagus.\textsuperscript{2,3} In the current study we showed that also on PPI, significantly more acid reflux episodes occur when the acid pocket is located at the level or above the diaphragm compared to below the diaphragm (46\% and 49\% compared to 7\% respectively). This demonstrates that also on PPI a more proximal position of the acid pocket is associated with acid reflux events. Interestingly, on PPIs, the pocket was more often located below the diaphragm compared to off PPIs (60\% vs. 40\%). The difference in acid pocket position cannot be explained by altered gastric motility, as PPIs have no impact on upper gastrointestinal motility.\textsuperscript{18} Furthermore, in the current study we did not find an effect from PPIs on hiatal hernia size. In contrast, the effect of PPIs on the position may be explained by the effect on acid pocket size. As previously demonstrated, off PPIs, the acid pocket in GERD patients is larger compared to controls.\textsuperscript{2} Hence, the pocket extends very close to, or even across, the squamocolumnar junction in GERD patients off.\textsuperscript{2,3} As measured by scintigraphy, PPIs reduced the nuclear counts and thus the secretion of \textsuperscript{99m}Tc-pertechnetate into the acid pocket by 43\%, leading to a reduction in size of 33\%. As a smaller acid pocket is associated with a more distal position, we argue that acid suppression results in a smaller and more distally located acid pocket, which in its turn leads to less acid reflux events.
In approximately 30% of patients PPI-therapy fails to resolve symptoms, either partially or completely. As demonstrated by Zerbib et al, remaining heartburn during PPI use is more often caused by acid reflux than by weakly acid reflux. In addition, Karamanolis et al demonstrated that 16% and 32% of the symptomatic subjects on double dose and standard dose PPIs, respectively, have abnormal pH tests. If one accepts that the acid pocket is still the source of the refluxate for acid reflux during PPI use, therapeutic strategies directly intervening with the pH of the acid pocket may possibly prove effective in preventing persistent heartburn on PPI. However, in a recent systematic review handling 6 studies with in total 174 GERD patients with persistent reflux symptoms during PPI use, it was demonstrated that more than 80% of reflux-related symptoms were attributable to weakly acid reflux. Only a minority of symptoms is caused by acid reflux (17%). Therefore, obviously, a strategy to prevent all sorts of reflux episodes (acid and non-acid) such as fundoplication or possibly reflux inhibitors would prove a better solution for reflux-related symptoms, irrespective whether reflux originates from the acid pocket.

A possible shortcoming of this study is that this study did not have a cross-over design. However, due to the radiation burden, a cross-over design was not approved by the ethics committee. To compensate, a larger number of GERD patients was included compared to previous studies of similar design. Furthermore, baseline characteristics such as hiatal hernia size, PPI dosage and number of patients with persistent symptoms were matched. Therefore we are confident that our study was adequately powered and patient groups were comparable.

In conclusion, the effect of PPIs of the acid pocket largely contributes to their effectiveness in the treatment of GERD. During acid suppression the pocket still acts as a reservoir for liquid reflux. As the pH of the acid pocket is increased, the pH of the refluxate is as well. In patients with ongoing acid reflux on PPI, the acid pocket represents a potential target for additional therapy.
REFERENCES


