The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease
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Does the presence of a hiatal hernia affect the efficacy of the reflux inhibitor baclofen during add-on therapy?

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Abstract

Introduction: Reflux inhibitors, like the GABA_B receptor agonist baclofen, block transient lower esophageal sphincter relaxations (TLESRs) and are proposed as add-on therapy in patients with PPI resistant gastroesophageal reflux. However, as other mechanisms of reflux become more important in the presence of a hiatal hernia (HH), the efficacy of reflux inhibitors to reduce acid and non-acid exposure may be hampered. Therefore, we compared the effect of baclofen in patients with no HH and those with a large HH during PPI treatment.

Methods: 27 GERD patients on PPI were included: 16 had no hiatal hernia (−HH) and 11 had a large hiatal hernia ≥ 3 cm (+HH). During PPI treatment, the effect of baclofen (3x20mg) on acid and non-acid reflux was evaluated in a randomized, double-blind, placebo controlled cross-over study. Reflux was measured during 24 hours using combined esophageal impedance and pH metry.

Results: The majority of reflux events consisted of both gaseous and liquid reflux with a significant increase in non acid, mixed reflux episodes in +HH patients compared to −HH patients. Acid exposure time was in the normal range in both patient groups during both placebo and baclofen. Baclofen significantly reduced the total amount of reflux episodes with 36% in −HH patients and 43% in +HH patients, but did not change the amount of acid reflux episodes or total acid exposure time.

Conclusion: The present study demonstrates that baclofen is also effective in GERD patients with a large hiatal hernia, further underscoring the potential of reflux inhibitors as treatment of GERD.

Trial registration number: NTR1401
Introduction

Gastroesophageal reflux disease (GERD) is a common disease characterised by symptoms like heartburn, acid regurgitation and retrosternal pain, resulting from prolonged acid exposure of the esophageal mucosa. At present, the treatment of choice for GERD is undoubtedly acid suppression with healing rates of esophagitis approximating 70-90 %. However, acid suppression renders acid reflux episodes non-acid, but does not reduce the number of reflux episodes, possibly explaining why symptom control by proton pump inhibitors (PPI) is incomplete in approximately 30% of patients. Ongoing non-acid reflux can indeed cause symptoms and, especially when bile acids are present, may lead to mucosal damage.

Transient lower esophageal sphincter relaxations (TLESRs) are the predominant mechanism underlying reflux of both acid and non-acid gastric content. Another important factor leading to incompetence of the anti-reflux barrier is the presence of a hiatal hernia. This anatomic abnormality may promote reflux via several mechanisms. Acid trapped within the hiatal sac will easily reflux after swallowing or when LES pressure is low. In addition, the spatial dissociation of the two components of the sphincter, the LES and crural diaphragm, leads to reduced basal pressures and an increased susceptibility to reflux. As a result, esophageal acid exposure and the severity of esophagitis are increased in patients with a large hiatal hernia. Finally, some investigators suggest an increased frequency of TLESRs in the presence of a hiatal hernia contributing to increased acid exposure. Others however failed to confirm these findings.

To date the most potent pharmacological approach to reduce the rate of TLESRs is activation of γ-aminobutyric acid type B (GABA_B) receptors. The selective GABA_B receptor agonist baclofen, used in the treatment of spasticity, indeed reduces the rate of TLESRs and the number of acid reflux episodes in normal subjects and in GERD patients. In addition, PPI persistent symptoms were improved when baclofen was added to the PPI regimen. It should be emphasized though that most studies with baclofen have been performed in GERD patients with mild reflux disease, mostly without a hiatal hernia. Only one study reported on the effect of baclofen in GERD patients which included patients with a hiatal hernia. However, no details on the size of the hiatal hernia and its impact on efficacy were mentioned. Based on the aforementioned impact of a hiatal hernia on reflux mechanisms, i.e. other mechanisms than TLESRs contribute to exposure of the distal esophagus to gastric contents, the efficacy of reflux inhibitors as add-on therapy may be greatly impaired in this subgroup of patients. Therefore, the aim of the present study was to compare the effect of baclofen on gastroesophageal reflux between GERD patients with no hiatal hernia and those with a large hiatal hernia during PPI treatment. The study was performed during PPI treatment, as the most likely indication for reflex inhibitors like baclofen, will be as add-on treatment, that is during PPI therapy.
Material and Methods

Subjects
Patients aged over 18 years, both males and females, all taking a PPI (qd or bid) for typical gastroesophageal reflux symptoms for at least three months prior to the study were enrolled. PPI therapy was continued during the entire study. None of the patients had a history of gastrointestinal surgery or took any medication known to influence gastrointestinal motility during the study. As baclofen lowers the threshold for seizures, patients with a family history of epilepsy were excluded. Each patient gave written informed consent to participate in the study, which was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam, The Netherlands.

Study design
The effect of baclofen was evaluated in a randomized, double-blind, placebo controlled study. In a two-period cross-over design subjects received 12 days of treatment with placebo or baclofen while PPI treatment was continued. A combined esophageal impedance and pH metry was performed at the end of the treatment period. Baclofen and placebo were added three times daily with meals. The initial dose consisted of 3 x 5 mg baclofen. Every fourth day, the dose was increased by 5 mg three times daily until a dose of 20 mg three times daily was reached after 10 days. Baclofen was given in increasing doses to avoid possible side effects. On day 11, ambulatory pH and impedance monitoring was performed while therapy was continued. Each study period was separated by a washout period of at least seven days. Prior to the study, esophageal manometry was performed to determine the LES location followed by fluoroscopy to assess the exact size of the hiatal hernia. Combined pH-impedance studies were performed after an overnight fast. The combined pH-impedance catheter was introduced through an anaesthetised nostril and positioned with the pH electrode 5 cm above the proximal margin of the LES. The catheter was firmly attached with adhesive tape to the patient’s nose and cheek and connected to a portable data logger (Ohmega, MMS, Enschede, The Netherlands). Patients went home and were instructed to fill out a diary indicating the time of meal consumption, supine position and symptoms. The choice of breakfast and lunch was unrestricted, however for dinner a standardized meal of approximately 750 kCal was provided. Patients were instructed to eat exactly the same on both study days. Patients returned the following day for removal of the catheter and data were transferred to a personal computer for analysis.

Recording methods
A combined MII-pH catheter (VersaFlex, Alpine Biomed, Skovlunde, Denmark), containing 6 pair of impedance electrodes and 1 antimony pH sensor with internal reference was used. The impedance electrodes measured 4 mm in axial length and were spaced at 2 cm intervals. The design of the catheter allowed impedance recordings at 3, 5, 7, 9, 15 and 17 cm above the upper border of the LES and pH data at 5 cm above the LES. Impedance and
pH data were sampled at a frequency of 50 and 1 Hz, respectively and stored on a portable data recorder (Ohmega, MMS, Enschede, The Netherlands). Before each study, the pH electrode was calibrated at room temperature using pH 4.0 and 7.0 buffer solutions (Merck, Darmstadt, Germany and Medtronic A/S, Skovlunde, Denmark, respectively). Calibration at room temperature was corrected by the computer software for pH measurements at body temperature.

**Data analysis**

At the end of the 24 hour recording period, data were transferred and analysed manually using dedicated software (MMS, Enschede, The Netherlands). Meal periods were excluded from the analysis. The upright, postprandial and supine period were analysed separately. The postprandial period consisted of two hours after each meal. 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 fall in impedance of \( \geq 40\% \) of baseline impedance starting at the most distal segment and propagating retrograde to at least the next measuring segment. Pure gas reflux was defined as a rapid (\( >3000\ \Omega/s \)) rise in impedance, 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.\(^{15, 37}\) Each reflux episode as recorded by impedance was classified as: 1) acid reflux, with a pH fall from above to below 4; 2) weakly acidic if nadir pH was between 4 and 6.5 and; 3) weakly alkaline reflux if nadir pH was above 6.5.\(^{38, 39}\) For the purpose of this study we decided to group weakly acidic and weakly alkaline reflux episodes as non acid reflux. The proximal extent of each reflux episode was evaluated and the percentage of reflux episodes that reached the most proximal impedance segment was calculated for each subject. Bolus clearance time was calculated as the time elapsed between bolus entry and bolus exit at 3 cm above the LES. Acid clearance time and total acid exposure were calculated automatically. A reflux episode was considered temporally associated with a symptom if the patient recorded a symptom within 2 min after a reflux episode.

**Statistical analysis**

Statistical analysis was performed using SPSS 12.02 software for Windows. The Wilcoxon signed rank test was used for paired data (placebo vs baclofen) and the Mann-Whitney U test for unpaired data analysis (hernia vs non hernia patients). The correlation between the size of the hiatal hernia and reflux parameters was determined using the Spearman rank correlation coefficient, performed using Prism software version 4.00 (GraphPad, CA). A P-value < 0.05 was considered statistically significant. Data are presented as median and interquartile range because of the skewed distributions.
Chapter 9

Results

Subjects
Twenty-seven patients were included in the study (15 men, median age 54, range 22-66) of which 16 had no hiatal hernia (−HH, 8 men, median age 54, range 22-62) and 11 had a large hiatal hernia ≥ 3 cm (+HH, 7 men, median age 58, range 44-66). Hiatal hernia size measured 3.6 ± 0.3 cm in +HH patients. Four patients discontinued the study prematurely; one patient because of side effects (dizziness), one patient could not tolerate the MII-pH catheter and two patients because of personal reasons. Consequently, the data of 23 patients, 12 −HH and 11 +HH patients, were used for analysis.

Side effects
No side effects occurred during placebo. During baclofen, side effects were reported by 9 patients (35 %). All reported side effects were of mild to moderate intensity and were tolerated well. Somnolence was most commonly (n = 6) reported as side effect. Other reported side effects were dizziness (n = 3) and nausea (n = 2). Most side effects occurred during the highest dose of baclofen.

Reflux episodes

No hiatal hernia
During placebo, a total of 694 reflux episodes was recorded in −HH patients (56 (43-66)/patient). Of these, 672 occurred in the upright position, of which 467 during the postprandial period and only 22 reflux episodes were recorded in the supine position. The majority of reflux episodes consisted of mixed reflux (49.4 (42.9-53.4) %), whereas 24.0 (10.9-34.0) % was pure liquid and 23.3 (9.3-44.6) % consisted of pure gas reflux. Of all reflux episodes, 219 (9 (5-30)/patient) were acidic (31.6 %). After treatment with baclofen, the total amount of reflux episodes was significantly decreased to a total of 475 (40 (27-50)/patient), P < 0.01 (Figure 1A), corresponding with a reduction of 35.6 (13.3-46.6) %. Reflux in the upright position was significantly reduced from 672 to 462 episodes, corresponding with a reduction of 28.6 (5.9-40.7) % (P < 0.02). Postprandial reflux was also significantly reduced from 467 to 320 episodes, corresponding with a reduction of 30.5 (-4.5-52.6) % (P < 0.02). Reflux in the supine position was not significantly changed by baclofen from 22 to a total of 13 episodes (Figure 2).

Baclofen significantly reduced the total amount of pure gas reflux episodes in −HH patients (P = 0.04), but not the amount of mixed (P = 0.05) and liquid (P = 0.20) episodes (Figure 3A). The composition of the refluxate was not significantly changed by baclofen (Figure 3B). Although the amount of acid reflux episodes was decreased to a total of 174 (6 (2-21)/patient) (36.6 %), this was not significantly changed compared to placebo (Figure 1).

Bolus clearance in −HH patients was not changed by baclofen (placebo: 16.4 (11.9-23.0) s; baclofen: 15.2 (12.0-19.0) s, ns).
The efficacy of baclofen in the presence of a hiatal hernia

**Large hiatal hernia**

In +HH patients, a total of 1157 reflux episodes were recorded (95 (87-141)/patient) during placebo, significantly increased compared to –HH patients ($P = 0.001$). Of these, 1102 episodes occurred in the upright position, of which 819 during the postprandial period and only 55 reflux episodes were recorded in the supine position. There was a significant correlation ($r = 0.57; P < 0.005$) between the size of the hiatal hernia and the amount of reflux episodes measured during placebo. The difference between –HH and +HH patients was mainly due to a significant increase in non acid reflux episodes in +HH patients (*Figures 1A+3A*).

Comparable to –HH patients, the majority of reflux episodes consisted of mixed reflux (59.3 (33.7-69.6) %), with 21.3 (13.7-31-4) % liquid reflux and 16.7 (14.1-37.6) % pure gas reflux (*Figure 3B*). Of all reflux episodes, 253 (18 (4-30)/patient) were acidic (21.9 %). No correlation ($r = 0.01; P = 0.95$) was found between the size of the hiatal hernia and the amount of acid reflux episodes.

During baclofen treatment, the total amount of reflux episodes was significantly reduced to 644 (69 (32-74)/patient), $P = 0.003$), corresponding with a reduction of 43.3 (27.5-58.5) %. However, the total number of reflux episodes was still significantly increased compared to –HH patients ($P < 0.05$). Reflux in the upright position was significantly reduced from 1102 to...
602 episodes, corresponding with a reduction of 40.9 (30.0-59.0) %, \( P = 0.003 \). Moreover, postprandial reflux was significantly reduced from 819 to 398 episodes, corresponding with a reduction of 46.6 (32.4-64.5) % (\( P = 0.003 \)). Reflux in the supine position was not significantly reduced by baclofen from 55 to a total of 42 episodes (Figure 2).

**Figure 2.** Total reflux episodes during the upright, postprandial and supine period in patients without and with HH. Baclofen significantly reduced reflux during the upright period, mainly due to a reduction of postprandial reflux episodes. * \( P < 0.05 \) compared to placebo.

**Figure 3.** A) Individual number of mixed, liquid and gas reflux episodes in –HH and +HH patients during placebo and baclofen. B) The composition of the refluxate in –HH and +HH patients represented as % of mixed, liquid and gas. Data is presented as mean.
* \( P < 0.05 \) compared to placebo; § \( P < 0.05 \) compared to –HH patients during the same treatment session.
Baclofen significantly reduced the amount of mixed \((P = 0.003)\) and pure liquid \((P < 0.02)\) reflux episodes, resulting in a composition of the refluxate of 54.5 (33.8-56.8) % mixed reflux, 21.9 (13.5-26.7) % liquid and 22.5 (15.9-53.8) % pure gas reflux (Figure 3). With a total of 185 (12 (2-22)/patient) acid reflux episodes (28.7 %), the amount of acid reflux episodes was not significantly affected by baclofen (Figure 1). Bolus clearance time was not changed by baclofen (placebo: 27.2 (20.3-29.3) s; baclofen: 22.7 (15.7-42.3) s, ns). However, bolus clearance time was significantly higher in +HH patients compared to −HH patients during both placebo \((P < 0.02)\) and baclofen \((P < 0.05)\).

### Acid exposure time

#### No hiatal hernia

During placebo, total esophageal acid exposure time in −HH patients was 5.8 (1.0-45.6) min, corresponding with a percentage of time with pH < 4 of 0.7 (0.1-3.4) %. The percentage of time with pH < 4 did not differ in the upright and postprandial period (upright: 0.8 (0.1-5.7) %; postprandial: 1.0 (0.2-3.2) %). In the supine position, acid exposure was negligible (0.0 (0.0-0.7) %).

After baclofen treatment, total acid exposure time was 3.6 (1.6-98.0) min and the percentage of time pH < 4 was 0.3 (0.2-7.3) %, both not significantly different compared to placebo (Figure 4). After baclofen, no significant changes in percentage of time with pH < 4 were observed for the upright (1.0 (0.3-12.2) %), postprandial (1.1 (0.2-17.3) %) and supine period (0.0 (0.0-4.2) %). Baclofen had no effect on acid clearance time (placebo: 48.0 (22.7-75.0) s; baclofen: 60.0 (21.5-108.0) s, ns).

![Figure 4. Percentage of time with esophageal pH < 4 in −HH and +HH patients. Acid exposure was not changed by baclofen in both groups. Although acid exposure was increased in +HH patients, this was not significant compared to −HH patients. Data are presented as median and interquartile range.](image)

#### Large hiatal hernia

In patients with a large hiatal hernia, total esophageal acid exposure time during placebo was 27.4 (2.4-128.7) min, with the percentage of time esophageal pH < 4 of 2.1 (0.2-10.3) %. Although increased compared to −HH patients, this difference did not reach statistical significance. The percentage of time with pH < 4 was slightly higher during the postprandial period compared to the upright position (upright: 1.8 (0.3-8.6) %; postprandial: 3.1 (0.4-17.9) %). In the supine position, acid exposure was negligible (0.0 (0.0-10.5) %).
During baclofen, total acid exposure time was 42.0 (4.8-49.1) min, with a percentage of time esophageal pH < 4 of 2.5 (0.4-4.1) %, both not significantly different compared to placebo (Figure 4). After baclofen, no significant changes in percentage of time with pH < 4 were observed for the upright (1.7 (0.5-5.6) %), postprandial (2.7 (0.4-6.4) %) and supine period (0.0 (0.0-5.0) %). No correlation \( (r = 0.2; \ P = 0.45) \) was found between the percentage of time with pH below 4 and hiatal hernia size. Baclofen had no significant effect on acid clearance time (placebo: 66.0 (42.0-114-0) s; baclofen: 56.6 (46.5-121.5) s, ns). Acid clearance time did not differ between –HH and +HH patients.

**Proximal extent**

**No hiatal hernia**

The total amount of reflux episodes extending to the most proximal impedance electrodes in –HH patients was significantly decreased after baclofen (placebo: 182 (9 (6-16)/patient); baclofen: 119 (6 (2-12)/patient), \( \ P < 0.05 \), corresponding with a reduction of 32.2 (4.7-83.8) %. The proportion of reflux episodes in which the liquid component of the refluxate reached the most proximal impedance segment was 19.0 (12.2-24.6) % during placebo and did not differ after baclofen treatment (14.1 (5.8-29.9) %, ns) (Figure 5).

![Figure 5](image)

**Large hiatal hernia**

Patients with a large HH did not exhibit significantly more proximal reflux compared to –HH patients on both study days. Although the amount of most proximal reflux episodes in +HH patients was significantly decreased after baclofen (placebo: 246 (21 (5-40)/patient); baclofen: 116 (15 (2-19)/patient), \( \ P = 0.005 \), corresponding with a reduction of 57.1 (21.7-75.0) %), the proportion of all reflux episodes which reached the most proximal extent was not significantly altered by baclofen (placebo: 21.8 (6.5-31-4) %; baclofen: 22.8 (4.0-24.3) %, ns) (Figure 5). No correlation was found between the size of the hiatal hernia and the proximal extent of the refluxate \( (r = 0.1; \ P = 0.75) \).
Symptoms

Only few symptoms were reported during both placebo and baclofen: 5 patients (3 –HH) recorded a total of 37 symptoms during placebo and 8 patients (6 –HH) recorded a total of 34 symptoms during baclofen. Reported symptoms were retrosternal pain (n = 7), belching (n = 1), regurgitation (n = 3), epigastric pain (n = 2), coughing (n = 1) and nausea (n = 2). Coughing was only reported during placebo, whereas epigastric pain was only reported during baclofen. Symptom index was 42.6 ± 19.2 % and 35.2 ± 16.5 % during placebo and baclofen, respectively (ns). Between individual patients, symptom index did not differ between placebo and baclofen.

Discussion

The GABA₉ receptor agonist baclofen, a potent inhibitor of TLESRs, has been extensively investigated in GERD patients. Based on the capacity of baclofen to inhibit both acid and non-acid reflux, reflux inhibitors could be of great value, especially in patients with PPI resistant symptoms resulting from non-acid reflux.⁹, ¹¹ It should be stressed though that this is only true if TLESRs are a major mechanism of reflux in this subgroup of patients. 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.¹³, ¹⁸ 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 the present study, we therefore compared the efficacy of baclofen in GERD patients with and without a hiatal hernia during PPI treatment. We preferred to study our patients during PPI treatment, mainly because the most likely indication for reflux inhibitors will be as add-on 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 during the postprandial period.

In contrast to previous studies³⁷, ³⁹-⁴¹, we included pure gas events (belches) in the reflux analysis, especially as belching and GER share the same mechanism.⁴² Moreover, almost 50% of GERD patients complain of excessive belching, which is often associated with concurrent symptoms of heartburn.⁴⁴ As a result, the median number of reflux episodes during placebo in our study is higher compared to previous impedance studies in GERD patients on and off PPIs.³⁷, ³⁹-⁴¹. In concordance with the literature, however, we found a significant higher reflux rate and bolus clearance time in +HH patients compared to –HH patients.¹⁸, ²⁴ Most likely, these differences are caused by facilitated occurrence of re-reflux from the hiatal sac and impaired peristalsis as often observed in +HH patients.¹⁹, ²¹, ⁴⁵, ⁴⁶ However, as previously shown³⁷, ⁴⁷, the proximal extent of the refluxate and acid exposure were comparable in +HH and –HH patients, suggesting a comparable volume of liquid refluxate or an increased compliance of the proximal esophagus, preventing a more proximal distribution of the increased reflux volume in patients with a hiatal hernia.
This is the first study comparing the efficacy of baclofen in patients with or without a HH. We showed a reduction of 43 % of reflux episodes in +HH patients, slightly higher than 36 % in –HH patients. This effect mainly results from a reduction of reflux during the postprandial period, suggesting that inhibition of TLESRs is the underlying mechanism of action, also in patients with a HH. In line with this, baclofen also reduced the number of reflux episodes extending into the proximal esophagus. The latter is of particular interest as Zerbib et al. recently reported that the proximal extent of the refluxate is the only factor associated with reflux perception in patients on PPI.48 Previously, Bredenoord et al. already showed that heartburn and regurgitation are more likely to be evoked when the proximal extent of the refluxate is high, the pH drop is large and acid clearance is delayed.49 Furthermore, Cicala et al. found that even in patients with non-erosive gastroesophageal reflux disease, the proximal extent of reflux is a major determinant of symptom perception.50 Cange et al. also reported a significant reduction in reflux episodes by baclofen in patients with a hiatal hernia. However, no details on the size of the hiatal hernia and its effect on efficacy were mentioned.33 So far, the only study assessing the effect of baclofen on reflux using combined pH-impedance consisted of a two hour period recording after a single dose of baclofen.31 In that study, baclofen reduced both acid and non acid reflux in healthy subjects and GERD patients off PPIs. As this study was performed in the right lateral position, results can not be extrapolated to the normal daily setting.

In contrast to the total number of reflux episodes, we found no significant reduction in the amount of acid reflux episodes or total acid exposure time. However, our patients were on PPI treatment with a good clinical response, resulting in an esophageal pH below 4 within the normal range during placebo (0.5 % and 2.1 % in –HH and +HH, respectively). Further reduction by baclofen hereby becomes difficult to demonstrate. Our findings are in line with those reported earlier by Koek et al.30 In that study, GERD patients with normal acid exposure under PPI but pathological duodenal reflux exposure underwent pH and Bilitec monitoring after a comparable baclofen dosing regimen. Baclofen did not change acid exposure, but significantly decreased duodenal reflux and improved PPI resistant reflux symptoms. On the other hand, Ciccaglione et al. and Cange et al. showed a reduction in acid exposure time by baclofen after 24 and 12 hours of pH monitoring, respectively, however, both studies were performed without the concurrent use of PPIs.33, 35

Patient selection in the present study was not based on persistence of symptoms during PPI treatment, but merely on typical reflux symptoms responding to acid suppression. Consequently, most patients experienced good to moderate effect by acid suppression therapy and hardly reported symptoms during the study. Although symptom assessment is undoubtedly the most important outcome parameter to evaluate clinical efficacy, the primary purpose of our study was to evaluate the effect of a hiatal hernia on the efficacy of a reflux inhibitor on reflux episodes and not on symptoms. The fact that baclofen was effective in reducing non acid reflux, even in patients with a large hiatal hernia, further supports the concept that reflux inhibitors may be beneficial in the treatment of PPI resistant symptoms. As shown in previous studies, this effect most likely results from a reduction in TLESRs, which have been reported to be increased in hernia patients.27 In addition, it has
been repeatedly shown that baclofen increases LES pressure\textsuperscript{28, 29, 32, 36}, a feature that may have additionally contributed to the reduction in reflux due to the improvement of the anti-reflux barrier. Finally, the finding that baclofen reduces the number of reflux episodes extending into the proximal esophagus, shown to be associated with reflux perception\textsuperscript{48}, further corroborates to the concept that baclofen or reflux inhibitors in general may be a new therapeutic approach to reduce PPI resistant GERD symptoms. Further studies in patients with GERD symptoms refractory to acid suppression are, however, warranted.

In summary, baclofen significantly reduced the amount of reflux episodes in GERD patients on PPI, even in the presence of a large hiatal hernia. This study strengthens the therapeutic potential for reflux inhibitors as additional therapy in GERD patients with incomplete response to acid suppression.

### Reference List


