

Gastric Fullness, Physical Activity, and Proximal Extent of Gastroesophageal Reflux

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OBJECTIVES: Proximal extent of gastroesophageal reflux (PER) is relevant for symptoms in GERD patients. It has been suggested that PER is determined by the volume of the refluxate that, in turn, might depend on the degree of gastric fullness. Abdominal straining, during ambulation, increases the likelihood of gastroesophageal reflux. We assessed the influence of gastric fullness and ambulation on proximal extent of reflux.

METHODS: PER was assessed in 37 patients with GERD undergoing ambulatory pH impedance monitoring. In 14 controls and 19 GERD patients, esophageal pH impedance and gastric emptying were also studied simultaneously in stationary conditions. We compared PER during fasting, early postprandial (before half emptying), and late postprandial periods in ambulatory and stationary conditions.

RESULTS: More reflux episodes reached the proximal esophagus in the postprandial period compared to fasting ($60\% \pm 4$ vs $29\% \pm 3$, $p < 0.05$). In stationary conditions, early postprandial reflux reached higher proximal extent than late postprandial reflux ($15 \pm 3\%$ vs $8 \pm 4\%$, $p < 0.05$). The proportion of reflux events reaching the proximal esophagus was significantly higher in ambulatory than in stationary conditions ($29 \pm 5\%$ vs $15 \pm 3\%$, $p < 0.05$).

CONCLUSION: Compared to fasting, reflux episodes occurring after the meals are more likely to reach higher proximal extent, particularly so during the early postprandial period. The highest proportion of postprandial proximal reflux occurred in ambulatory condition. These findings suggest that reducing meal volumes and early postprandial physical activity might contribute to decrease proximal extent of reflux and postprandial GERD symptoms.

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INTRODUCTION

Traditional evaluation of gastroesophageal reflux focuses on exposure of distal esophageal mucosa to acid, because most esophagitis lesions are located in this area. However, the majority of patients with gastroesophageal reflux disease (GERD) do not have esophagitis (1, 2) and the mechanisms underlying symptoms in these patients are not completely clear.

The proximal migration of reflux may be a factor involved in symptom elicitation. Multiple pH studies have shown that patients with GERD have more reflux events reaching proximal esophageal levels (3). This was true for patients with erosive and nonerosive GERD as well as for patients with GERD-related ORL and respiratory symptoms (4–7). Furthermore, perception of acid reflux can be influenced by its proximal extent. Reflux episodes reaching the proximal esophagus were more likely to be perceived by patients with typical GERD symptoms than those restricted to the distal

esophagus (8, 9). It has been suggested that the proximal extent of reflux is mainly determined by the volume of the refluxate that, in turn, might depend on the degree of gastric fullness (8). The volume of gastric contents depends on the ingested meal, air swallowed, gastric emptying rate, and gastric secretion. Early after the meals, the volume of gastric contents is maximal and decreases during the gastric emptying process to a minimal value during fasting (10, 11). Abdominal straining, during ambulation, increases the likelihood of gastroesophageal reflux (12–14). The relationship between the degree of gastric fullness and proximal extent of reflux has never been assessed.

Esophageal impedance-pH recording allows assessment of proximal extent of both acid and weakly acidic reflux. Like acid reflux, weakly acidic reflux can reach higher proximal extent in GERD patients compared to controls (15).

The aim of this study was to assess the relationship between gastric fullness and ambulation and proximal extent of acid and weakly acidic gastroesophageal reflux.

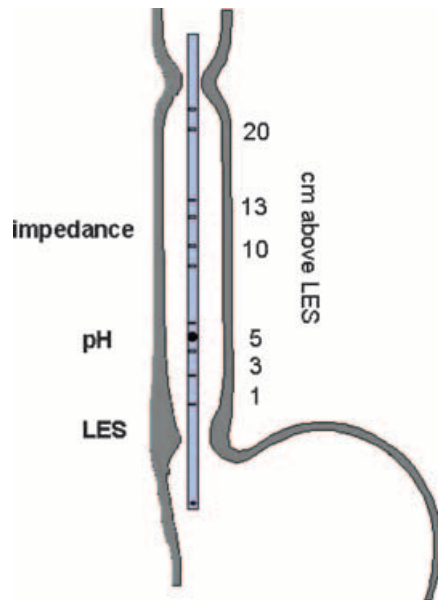


Figure 1. Schematic representation of the ambulatory pH impedance assembly.

METHODS

Subjects

Proximal extent of gastroesophageal reflux was evaluated from ambulatory 24-h pH impedance recordings in 37 patients with GERD (16 men; median age: 54 yr; range: 31–72 yr). All patients had endoscopic evaluation: nonerosive GERD ($n = 14$), esophagitis (Savary-Miller grade I = 9 patients, grade II = 8, grade III = 2); four patients had uncomplicated Barrett's esophagus. Fifteen patients had hiatus hernia proven by endoscopy. Concomitant esophageal pH impedance recording and scintigraphic gastric emptying were performed on 14 asymptomatic subjects (9 men; median age: 44.5 yr; range: 23–63 yr) and 19 GERD patients (11 men; median age: 52 yr; range: 28–73 yr). All patients had endoscopic evaluation: nonerosive GERD ($n = 6$), esophagitis (Savary-Miller grade I = 6 patients, grade II = 4 patients); 3 patients had uncomplicated Barrett's esophagus. Ten patients had hiatus hernia proven by endoscopy. None of the patients had undergone previous gastrointestinal surgery or was taking medication known to influence esophageal motor function. Acid suppression medication was stopped at least 1 wk before the studies. The protocol was approved by the University Hospital Ethics Committee and written informed consent was obtained from all subjects.

METHODS

Intraluminal Electrical Impedance and pH

Intraluminal electrical impedance was recorded with a 2.3-mm diameter polyvinyl assembly containing a series of cylindrical electrodes, each 4 mm in axial length, spaced at 2-cm intervals. Each pair of electrodes formed a measuring segment, 2 cm in length, corresponding to one recording

channel. Esophageal pH was measured with an antimony pH electrode. The pH impedance catheter input to a portable data logger (Prototype developed by Prof. Jiri Silny, femu – Research Center for Bioelectromagnetic Interaction, Aachen Germany) which sampled and stored the digitized data at 50 Hz per channel.

Before the start and at the end of the recording, the pH electrodes were calibrated using pH 1.0 and pH 7.0 buffer solutions.

Subjects were studied after an overnight fast of at least 10 h. The study day included three main meals (lunch, dinner on day 1, and breakfast on day 2). Prior to the ambulatory study, all subjects underwent a stationary esophageal manometry to determine the location of the lower esophageal sphincter (LES). After the stationary manometry, the combined pH impedance assembly was passed through the nose under topical anesthesia and positioned with the pH electrode at 5 cm above the LES. In this position, impedance was measured at 1, 3, 5, 10, 13, and 20 cm proximal to the LES (Fig. 1).

The patients were asked to remain upright during the day, and lie down only at their usual bedtime. Event markers on the monitor recorded meal times and posture changes.

Gastric Emptying

Gastric emptying of solid-liquids was simultaneously measured after breakfast on day 2. A standard breakfast meal was used, consisting of two pancakes prepared from a mixture containing cream (60 g), flour (30 g), sugar (15 g), and 1 egg labeled with 20 MBq Tc99m sulfur colloid and 200 ml full milk labeled with 2 MBq In-111-DTPA. Total caloric content was 700 kcal (protein 10%, fat 60%, and carbohydrate 30%).

The meal was consumed in a sitting position in 5-min period. Immediately after test meal ingestion simultaneous 1-min ^{99m}Tc (140 KeV, 20%) and ^{111}In (173 KeV, 15%; 247 KeV, 20%) images were taken every 10 min for 3 h, with the subjects sitting between the two detectors of a dual-head gamma camera.

DATA ANALYSIS

Gastroesophageal Reflux

Gastroesophageal reflux was detected by impedance and defined as a retrograde 50% fall in impedance from baseline in at least two distal recording sites. Changes in esophageal pH during reflux detected by impedance allowed classification of acid reflux when the pH fell from above to below 4, weakly acidic reflux when pH fell at least 1 unit but remained above 4, and weakly alkaline reflux when intraesophageal pH did not fall below 7 (15).

During reflux, drops of impedance in the mid- and upper esophagus indicated the proximal extent of the liquid refluxate (Fig. 2A, B). The percentage of reflux episodes that reached the impedance segments in the mid esophagus (13 cm above LES) and proximal (20 cm above LES) was calculated in each subject.

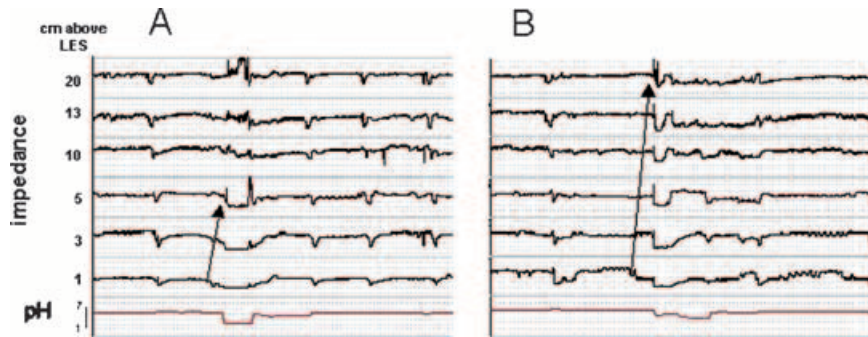


Figure 2. Examples of pH impedance recordings from a patients with GERD. Panel A shows a reflux event as a drop in impedance to less than 50% of baseline values, starting at 1 cm above the LES and moving orally up to 5 cm above the LES. The pH dropped from above to below 4 and was categorized as a distal acid reflux event. Panel B shows a reflux event as a drop in impedance to less than 50% of baseline values, starting at 1 cm above the LES and moving orally up to 20 cm above the LES. The pH dropped from 6.5 to below 4.2 and was categorized as a proximal weakly acidic reflux event.

Gastric Emptying

Half emptying time for solids was calculated and used to infer the degree of proximal gastric fullness in the early postprandial (before T1/2) and the late postprandial (after T1/2) periods (16). To assess proximal gastric emptying, a region of interest of the proximal stomach (ROI) was drawn using the mid length of the gastric longitudinal axis.

Protocol

The relationship between gastric fullness and proximal extent of reflux was studied as follows: (i) In patients with GERD, who underwent 24-h ambulatory pH impedance, we compared the proportion of reflux episodes that reached the middle and proximal esophagus in the postprandial period (first hour after the main meal) and fasting period (first hour before the main meal). (ii) In a different group of healthy volunteers and patients with GERD, who also had concomitant gastric emptying studies during the breakfast meal on day 2, we compared the proportion of reflux events reaching the middle and the proximal esophagus during the early and late postprandial periods. In these subjects, proximal extent of reflux was assessed both during ambulatory and stationary

sitting positions after a free meal and a standard scintigraphic meal, respectively.

Statistical Analysis

Data were expressed as mean (SEM) or medians (interquartile range) when required. In the analysis of pooled data, the proportion of reflux events, which reached the proximal esophagus during fasting and postprandial periods was compared using Fisher's exact test. In the per-individual analysis we have first calculated the proportion in each subject and then used a pair Wilcoxon test to compare between states. A *p* value lower than 0.05 was considered to be significant.

RESULTS

Proximal Extent of Reflux in Fasting and Postprandial Periods

In 37 patients we analyzed the proximal extent of 351 reflux events in the fasting period [9 (4–19)/patient] and 420 reflux events in the postprandial period [11 (5–23)/patient]. More reflux episodes reached the proximal esophagus during the postprandial period than during fasting. Nearly 75% of reflux events reached the mid esophagus (13 cm above LES) and 50% reached the proximal esophagus (20 cm above LES) in the postprandial period compared to 60% and 30% of reflux episodes reaching the mid- and proximal esophagus during fasting (Fisher's exact test; *p* < 0.001). The per-individual analysis confirmed the difference between proportion of mid- and proximal reflux observed with the pooled data assessment (74% ± 3 and 53% ± 4 in postprandial vs 60% ± 4 and 29% ± 3 in fasting). There was no difference in the proximal extent of reflux during the postprandial period between patients with and without hiatal hernia (79 ± 4 vs 74 ± 6 at 13 cm above LES and 56 ± 4 vs 54 ± 5 at 20 cm above LES).

Acidity of the Refluxate and Proximal Extent

During the fasting period, 65% of reflux episodes were acid, 29% weakly acidic, and 5% weakly alkaline. During the postprandial period 51% were acid, 41% weakly acidic, and 7%

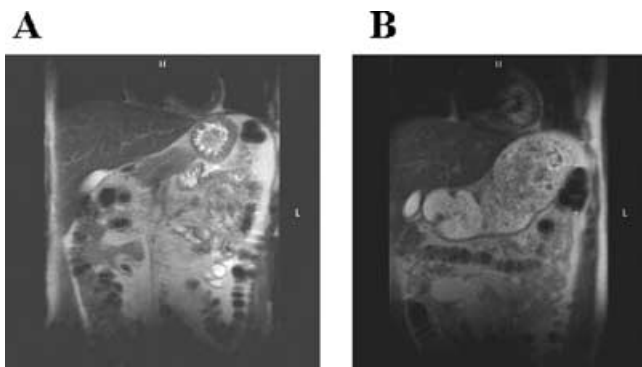


Figure 3. Examples of MRI imaging of gastric contents in a normal subject in supine position during fasting (A) and after a liquid-solid meal (B).

Table 1. Proximal Extent of Acid and Weakly Acidic Reflux in Fasting and Postprandial Periods

	Acid Reflux		Weakly Acidic Reflux	
	Fasting	Postprandial	Fasting	Postprandial
Number of reflux events at 5 cm above LES	229	218	122	202
Percentage of reflux detected at 13 cm above LES	70 ± 4	83 ± 4*	49 ± 6	68 ± 5*
Percentage of reflux detected at 20 cm above LES	32 ± 4	52 ± 4*	14 ± 4	46 ± 5*

* $p < 0.05$ versus fasting.

weakly alkaline. Both acid and weakly acidic reflux showed higher proximal extent during the postprandial period compared to fasting (Table 1).

Proximal Extent of Reflux in Early versus Late Postprandial Periods

Half emptying time for solids was used to identify the early (before half emptying) and late postprandial periods (after half emptying) in each subject. We analyzed 259 reflux events from all subjects (pooled data) during the early postprandial period [8 (1–30)/subject] and 160 reflux events during the late postprandial period [5 (1–18)/subject]. In sitting position, after a standard meal, the number of reflux episodes reaching the proximal esophagus almost doubled that observed during the late postprandial period. The per-individual analysis confirmed that early postprandial reflux is more likely to reach the proximal esophagus, and this was more marked in patients with GERD than in healthy subjects (Table 2).

Proximal Extent of Reflux in Ambulatory and Stationary Conditions

More reflux events reached the proximal esophagus during the first postprandial hour after free solid-liquid meals, in ambulatory conditions, than during the first hour after a standard scintigraphic meal in the same subjects in stationary sitting condition (Table 3).

Table 2. Proximal Extent of Reflux in Early Postprandial and Late Postprandial Periods

	Pooled Data Postprandial		Volunteers Postprandial		Patients Postprandial	
	Early	Late	Early	Late	Early	Late
Number of reflux events at 5 cm above LES	259	160	104	55	155	105
Percentage of reflux detected at 13 cm above LES	41 ± 5*	31 ± 6	32 ± 8	29 ± 9	48 ± 7*	33 ± 8
Percentage of reflux detected at 20 cm above LES	15 ± 3*	8 ± 4	14 ± 5	7 ± 3	17 ± 6*	9 ± 4

* $p < 0.05$ versus late postprandial.

Table 3. Proximal Extent of Reflux in Ambulatory Condition and Stationary Sitting Position

	Ambulatory	Stationary
Number of reflux events at 5 cm above LES	278	259
Percentage of reflux detected at 13 cm above LES	65 ± 4*	41 ± 5
Percentage of reflux detected at 20 cm above LES	29 ± 5*	15 ± 3

* $p < 0.01$ versus standard meal.

DISCUSSION

Proximal extent of reflux might be influenced by several factors including volume of the refluxate, abdomino-thoracic pressure gradient, compliance of the esophago-gastric junction, and esophageal body motor response. In this study we found that, compared to fasting, reflux episodes occurring after the meals are more likely to reach higher proximal extent, particularly so during the early postprandial period.

In our study we did not measure the volume of gastric contents, and we could not analyze the precise correlation between proximal extent of each individual reflux event with the corresponding gastric volume. However, imaging techniques have shown that gastric volume is nearly three times larger after the meals than during fasting (Fig. 3) and the volume of the proximal stomach is gradually decreasing with the gastric emptying process (17, 18). We assumed, therefore, that gastric contents is largest soon after the meal, decreases in the late postprandial period, and becomes the smallest during fasting. We compared, therefore, the proximal extent of reflux occurring at three different levels of gastric fullness.

So far, technical difficulties have precluded accurate estimation of reflux volume in physiological conditions. Most studies using aspiration or scintigraphic techniques were made in nonphysiological conditions (19, 20). The relationship between proximal extent of reflux and volume of the refluxate was illustrated by Orr *et al.* by perfusing 1 and 3 ml of acid in the distal esophagus in healthy subjects. The higher volume was associated with higher proximal migration (21).

Proximal extent of acid reflux seems to be relevant for both typical and atypical GERD symptoms. Weusten *et al.* first suggested that perception of reflux symptoms might depend on the proximal extent of the refluxate (8) and also showed that more reflux events have a longer distal duration and reach a higher proximal level in patients with GERD than in normal controls (3). More recently, Cicala *et al.* confirmed the higher proximal extent of reflux in patients with GERD and nonerosive GERD with otherwise normal distal acid exposure (9). Abnormal proximal acid exposure was also found in 44% of 34 patients with noncardiac chest pain (22) and proximal esophageal and hypopharyngeal acid exposure were increased among patients with laryngeal signs of GERD (4–7). Recent studies using pharyngeal impedance-pH recordings showed that gas reflux with weak acidity is frequent in patients with laryngeal lesions (23). Asthma patients with asymptomatic reflux had high amounts of proximal esophageal acid (24) whereas in patients with upper airway and additional GERD symptoms, proximal reflux episodes were frequent and correlated well with nocturnal cough (25).

In clinical practice, many patients report worsening of GERD symptoms after the meals, that is, postprandial regurgitation during daytime, awakening heartburn during night time (26, 27), or respiratory symptoms after a significant nighttime meal (28–30).

Are postprandial symptoms related to acid only, to an increased volume and proximal extent of reflux, or to both?

Heartburn and regurgitation may be elicited by chemical or mechanical stimulation. Intraesophageal acid perfusion induces heartburn in a pH dependent manner (31). In supine patients with GERD, omeprazole transformed most postprandial acid reflux events into weakly acidic reflux. In this setting, the postprandial symptom pattern switched from predominant heartburn to predominant regurgitation (32). On the other hand, esophageal distension with balloons can also induce heartburn (33–35).

The proximal extent of reflux might be relevant for symptoms by increasing the area of chemical stimulation and/or mechanical distension by recruiting more sensory receptors. Our study in upright subjects showed that reflux events during the early postprandial period are more likely to reach high proximal extent. This finding was significant and more marked in patients with GERD than in normal controls, suggesting impairment of defensive mechanisms such as resistance to retrograde flow at the esophago-gastric junction and/or the esophageal body motor response in GERD patients (36, 37).

The presence of hiatal hernia was not associated with a higher frequency of postprandial proximal reflux. Although these patients have a more compliant esophago-gastric junction that may allow larger reflux volume (37), distribution of the refluxate in these patients might differ from those without hernia due to a different esophageal body length or regional compliance.

In both ambulatory and stationary conditions, the postprandial reflux reached higher proximal extent than fasting

reflux. This high proportion of postprandial proximal reflux was more marked after nonstandard solid-liquid meals in ambulatory condition than after standard meals in sitting position. In the ambulatory condition, straining during physical activity could have influenced proximal extent of reflux. Straining significantly increases the likelihood of reflux during transient LES relaxation (12–14). Alternatively, the volume of the free meals could have been larger than that of the standard stationary meals. However, our standard meal consisted in 250 ml of milk, 105 g of solids, and delivered 700 kcal making it comparable with meals ingested by patients undergoing ambulatory pH recordings (38).

Recent studies have shown that patients with GERD and hiatal hernia may have increased reflux during exercise due to a combination of low-basal LES pressure, high compliance of the esophago-gastric junction, and straining (37, 39, 40). Our study suggests that ambulation after meals might increase proximal extent of reflux. Taken together, these data argue against the common clinical practice indicating light physical activity after meals in patients with GERD.

In summary, proximal extent of reflux is important for symptoms in patients with GERD and might be influenced by several factors including volume of the refluxate, abdominothoracic pressure gradient, compliance of the esophago-gastric junction, and esophageal body motor response. Compared to fasting, reflux episodes occurring after the meals are more likely to reach higher proximal extent, particularly so during the early postprandial period. The highest proportion of postprandial proximal reflux occurred in ambulatory condition. These findings suggest that reducing meal volumes and early postprandial physical activity might contribute to decrease proximal extent of reflux and postprandial GERD symptoms.

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