Responses to gastric distension in functional dyspepsia


Abstract

Background—Studies have shown that an altered visceral perception threshold plays a role in the pathogenesis of upper gastrointestinal tract symptoms in dyspeptic patients. However, it is not clear whether the compliance and adaptive relaxation of the proximal stomach contribute to the symptoms.

Aims—To investigate whether abnormal relaxation or adaptation of the proximal stomach during the interdigestive state and the postprandial phase could explain the symptoms of functional dyspepsia.

Subjects—Twelve volunteers and 12 patients with dysmotility-like functional dyspepsia were included in the study.

Methods—An electronic barostat was used to investigate adaptation to distension of the proximal stomach and accommodation in response to a liquid meal. Dyspeptic symptoms during distension and accommodation were assessed.

Results—When the subjects were in the fasting state, the pressure-volume curve showed slightly higher compliance in the dyspeptic patients (p<0.05). Patients not only had a higher score for nausea, bloating, and pain but also the increase in nausea and pain scores with intragastric pressure was higher than in volunteers (p<0.05). The increase in intragastric bag volume in response to a meal was significantly lower in patients (p<0.05). Both bloating and pain significantly increased in the patients (p<0.05), but not in the healthy volunteers.

Conclusions—Patients with functional dyspepsia show slightly higher compliance to mechanical distension. Their visceral perception of mechanical stress is enhanced. In contrast with the balloon distension, relaxation after a meal was less. Therefore the postprandial symptoms cannot be explained fully by greater global tension in the stomach wall, as assessed by the barostat technique. Visceral hypersensitivity plays a major role in the pathogenesis of the symptoms.

(Gut 1998;42:823–829)

Keywords: dyspepsia; gastric distension; gastric accommodation; gastric sensitivity

Functional dyspepsia, also known as non-ulcer or essential dyspepsia, is diagnosed in nearly one quarter of all patients with dyspeptic symptoms seen in gastroenterological practice. Patients with functional dyspepsia present with a diversity of symptoms, associated with the upper gastrointestinal tract, which include inability to finish a normal meal, feeling of fullness, distension, nausea, vomiting, epigastric pain, and bloating. Most of these symptoms occur postprandially.

Scintigraphic studies have shown a delay in gastric emptying in 29–50% of dyspeptic patients. In about 60% of patients, antral hypomotility and disorganised patterns of intestinal motility, and a reduced number of activity fronts with an antral component in the fasting state. These motility disorders are not a satisfactory explanation for the symptoms in all patients, since in a substantial subgroup of dyspeptic patients no motor abnormality can be found and moreover symptoms do not correlate well with manometric findings. Therefore other pathophysiological mechanisms may be involved in functional dyspepsia. For instance, it has been shown that the threshold for pain or discomfort in response to gastric distension, in the fasted state, is lower in patients with functional dyspepsia than in healthy volunteers. Troncon and coworkers inflated a plastic bag in the proximal stomach and measured pressures before and after a meal, without the use of a barostat. They found that, in contrast with controls, patients with functional dyspepsia showed no reduction in mean pressure in an intragastric balloon during and after the meal. However, it is not yet certain whether the symptoms are caused by hypersensitivity of the proximal stomach or by an alteration of the proximal stomach motor function. The aim of this study was to investigate adaptation of the proximal stomach to distension and accommodation in response to a liquid meal in functional dyspepsia. Furthermore, relations between dyspeptic symptoms and accommodation and distension in these patients were assessed.
The volume of air pumped into a polyethylene bag, maintained at a constant preselected mean pressure level by an electronic feedback mechanism.\(^1\)

The volume display of the barostat is derived from the measurement of the length of the rubber bellows in the barostat pump. The display was adjusted after withdrawal of known volumes, at a constant pressure of 2 mm Hg, from the barostat with a large syringe. A second calibration step was needed, because the rubber bellows deforms in proportion to the pressure in the barostat. Keeping the external volume constant, the pressure was increased and the decrease in the displayed volume was measured. This step was repeated at different external volumes but constant total volume of gas. In rigid cylinder barostats, one would expect a volume decrease according to Boyle’s law: \(\frac{dV}{dP} = \frac{-V}{P}\), where \(V\) is the total gas volume and \(P\) the pressure. We found a value of \(\frac{dV}{dP} = -5.76\) ml/mm Hg, which is about four times too high. Instead of using Boyle’s law with an unrealistic gas volume, we corrected all measurements by using the constant \(-5.76\) ml/mm Hg. All displayed volume changes can be thought of as a change due to pressure deviations from 2 mm Hg and the real changes in external volume, and were corrected accordingly.

By measuring pressure in the gastric bag as well as in the barostat pump, we found that maintenance of a constant pressure is best achieved with a catheter with a large inner diameter.\(^1\) Therefore we used a wide single-lumen catheter to connect the bag to the barostat pump.

This setup avoids the spontaneous oscillations often encountered with double-lumen catheters and feedback control from the gastric bag. Double-lumen catheters have a narrower flow channel and a greater pressure gradient between the bag and the barostat pump. A phase difference between the gastric bag and the barostat pump results in the oscillations. When the pressure in the barostat pump is not known, the volume cannot be corrected. In the dynamic state, only averaged pressures in barostat and gastric bag are equal, and pressure gradients over a narrow catheter can be appreciable; we found up to 20 mm Hg at high flow rates in a narrow catheter. Injection or aspiration of air was triggered when the pressure in the system differed from the preselected pressure by more than 0.2 mm Hg. A dynamic equilibrium establishes itself with equal mean pressures in the barostat and bag, and volumes can be calculated correctly from the volume and pressure in the barostat. The maximal rate of air flow was 2.4 litres per minute. The intragastric polyethylene bag (maximum volume 700 ml) was mounted on the tip of a single-lumen 14-F polyvinyl tube and connected to the barostat. Pressure and volume were recorded on a paper polygraph and stored in a computer. The barostat was used to assess the compliance of the proximal stomach in the fasting state and the response of the proximal stomach to a liquid meal.

EXPERIMENTAL DESIGN
The studies were performed after an overnight fast; patients had taken no medication for at least 48 hours. Participants were placed in a
sitting position (30° recumbent) and asked to relax comfortably. The lubricated bag, folded in a zigzag fashion, was introduced through the mouth into the proximal stomach. After the bag had been slowly inflated manually with 100 ml air to unfold it, it was completely deflated and, after a 10 minute interval, connected to the barostat.

Compliance measurement
First the minimal distending pressure (MDP) was determined as the lowest pressure level that provided a mean intrabag volume of 30 ml; at this pressure, respiratory induced volume changes could be distinguished. Starting at MDP, the pressure was increased stepwise every three minutes with 2 mm Hg increments. At each level, both the intragastric volume and the perception of symptoms elicited by gastric distension were recorded. The pressure was increased until the volume exceeded 650 ml, or when the subject indicated that no further distension could be tolerated. Then the pressure was decreased stepwise with 2 mm Hg steps, and intragastric volume only was measured.

Accommodation to a meal
After measurement of the compliance of the proximal stomach, intraballoon pressure was kept at atmospheric pressure (0 mm Hg) for a period of 10 minutes. Thereafter, a period of 45 minutes followed during which MDP + 1 mm Hg was maintained before the participants ingested the liquid meal. The subjects were asked to drink the meal at a rate of 200 ml/min. At a constant intragastric pressure of 1 mm Hg above the MDP, volume changes were recorded over 1.5 hours.

Assessment of gastrointestinal symptoms
During the compliance measurement, perception of gastric distension was scored just before the next increase in pressure, by using a visual analogue scale from 0 to 10 (0, absence of sensation; 10, unbearable sensation). The participants were informed about the possible sensations: nausea, bloating, and pain. Postprandially the sensations of nausea, bloating, and pain were scored every 10 minutes.

Meal
The meal, which had a volume of 200 ml, was composed of 34 g Nutrilose (a lactose free milk powder; Nutricia, Zoetermeer, The Netherlands), 14 g Fantomalt (dextrin-maltose; Nutricia), and water. Energy content was 200 kcal (1.0 kcal/ml); it was gluten- and lactose-free, with 9.8 g protein, 4.5 g fat, and 30.7 g carbohydrate.

DATA ANALYSIS
To construct the compliance curve, the average volume during the last minute of every three minute period was taken as intrabag volume at that pressure level. The compliance was taken as the regression coefficient of the steep part of the ascending branch of the volume-pressure curve. The difference between the rising and descending volume-pressure curve (“hysteresis”) was measured by subtracting the volume of the ascending curve from the descending curve at 0, 2, 4, 6, and 8 mm Hg above the MDP. The preprandial intragastric volume was measured, at a preselected level of MDP + 1 mm Hg, by averaging the volume over a 10 minute interval.
minute period. The response to a liquid meal was measured by averaging the intragastric bag volumes every four minutes and subtracting the averaged preprandial volume. The volume increase of the individual postprandial curves was expressed as the sum of these differences: the area above the curve (AAC).

The maximal relaxation volume ($\Delta V_{\text{max}}$) and the time ($t_{\text{max}}$) at which $\Delta V_{\text{max}}$ occurred were also determined.

The sensations, nausea, bloating, and pain, in relation to pressure levels and to the intragastric volumes (by grouping the volumes into 100 ml classes) were recorded.

**STATISTICAL ANALYSIS**

Statistical analysis of the differences between the functional dyspepsia patients and the controls was performed by analysis of variance. The Mann-Whitney U test was used to test the differences between patients and healthy volunteers for the hysteresis variable and the postprandial volume increase (AAC). $p<0.05$ was considered significant. Values are given as mean (SEM).

**Results**

**COMPLIANCE MEASUREMENT**

All healthy volunteers and dyspepsia patients completed the study. MDPs were similar in the dyspeptic patients and the controls (6.45 (0.5) and 6.5 (0.4) mm Hg respectively). As shown in fig 1, the pressure-volume curve in response to the stepwise pressure increase showed a larger volume at each pressure in the dyspeptic patients, resulting in a significant difference between the pressure-volume curves ($p<0.05$). The inflation curve showed a significantly steeper slope in the dyspeptic patients than in the controls (regression coefficient 53 (2.0) v 46 (3) ml/mm Hg; $p<0.05$), indicating a higher compliance of the proximal stomach in the dyspeptic patients.

The volumes during stepwise deflation of the intragastric bag remained higher than the volumes during inflation in both the patients ($p<0.001$) and the healthy volunteers ($p<0.001$). At MDP, the deflation curve also ended on a higher volume than the starting volume of the inflation (for the patients 35 (3) and 161 (41) ml for the start and end respectively, and for the controls 26 (4) and 171 (35) ml respectively). The mean volume differences between the ascending and descending parts of the curves in the dyspeptic patients (133 ml) and healthy volunteers (150 ml) were not significantly different ($p \approx 0.46$).

**ACCOMMODATION TO MEAL**

As shown in fig 2, the response to the meal began with an immediate rise in the volume in the intragastric bag (gastric relaxation). Figure
Gastric distension in functional dyspepsia

3 shows the mean increase in intragastric bag volume in the dyspeptic patients and healthy volunteers. The immediate rise in each group appeared to be the same; however, the controls continued to relax for a slightly longer period, thus reaching the maximum relaxation at a later time ($t_{max} = 17(2)$ vs $12(3)$ min; $p<0.01$). However, the mean relaxation volumes were not significantly greater at any specific time ($p \approx 0.18$), because of the large standard error of the mean. Because the relaxation in the volunteers remained slightly greater during the whole postprandial period, the time integrated mean. They found a higher, although not significant, compliance in patients. Troncon et al\textsuperscript{11} also did not use a barostat. They applied stepwise 30 ml volume distensions at one minute intervals and measured the resulting balloon pressure. Even though these studies evaluated compliance from pressure measurements at constant volume, whereas the barostat measures volumes at constant pressure, the results are not contradictory.

In addition to the effect of gradual distension of the proximal stomach, we studied the gradual return to baseline pressure. This was carried out by decreasing the pressure in steps of 2 mm Hg. In both patients and controls, the deflation curve showed higher volumes at every pressure level. The observed hysteresis phenomenon could be due to passive properties of the gastric wall,\textsuperscript{25} but also to active smooth muscle relaxation and contraction. The hysteresis was the same in patients and healthy volunteers. This implies that the proximal stomach, when looked upon as a distensible bag, has not only elastic but also viscous (relaxation) properties. Time of adaptation to a new pressure step is probably an important determinant of the final volume reached. The response to a pressure step consists of a relatively fast (less than a minute) adaptation, followed by a very slow increase. The hysteresis we found suggests that three minutes is not enough adaptation time to reach final equilibrium. The “true” compliance curve for long adaptation may be somewhere between the ascending and descending branches. That would also explain the baseline volume at MDP + 1 mm Hg, after 45 minutes adaptation time before we gave the meal. The preprandial volumes found were between values read from the ascending and descending branch of the compliance curves.

The slightly higher compliance in the dyspeptic patients seen in this study may be the result of lower activity of vagal excitatory cholinergic fibres or higher activity of vagal inhibitory non-adrenergic non-cholinergic fibres. It is also possible, however, that inhibitory reflexes mediated by sympathetic pathways are altered.

Gastric tone is due to sustained muscular contraction of the gastric wall. The contraction of the proximal stomach determines the balance between gastric accommodation and gastric emptying.\textsuperscript{18,22} This study shows a different mechanism for relaxation upon mechanical distension, which was slightly greater in patients, and postprandial relaxation, which was lower in patients. Lower postprandial relaxation of the fundus may result in a different fundal-antral distribution in the stomach and a change in emptying rate. In a barostat study on six patients who had consumed a liquid meal, Ropert et al\textsuperscript{4} also found altered postprandial relaxation. In four of these patients, the
emptied rate after a solid meal, measured on another day, was normal. The response to the liquid meal during the barostat study was particularly disturbed in these patients. The contribution of gastric emptying to postprandial symptoms in dyspeptic patients remains obscure, and can only be clarified by performing simultaneous barostat and emptying studies. Technical and radiation safety problems prevented us from doing so.

Mearin et al included patients with relatively mild symptoms, with a total symptom score of more than 6 out of a maximum of 15. In their study, the patients were asymptomatic after an overnight fast and asymptomatic after intubation on the minimal distending level. We selected a group of severely dyspeptic patients with predominantly dysmotility-like symptoms.18 Our patient selection only included those with at least two gastrointestinal symptoms.18 The symptoms showed no correlation with relaxation volume. In contrast with the higher compliance in the fasted state, the mean postprandial relaxation volumes in patients were lower than in volunteers, making it doubtful that postprandial volume or global stress in the gastric wall is the main cause of their increased postprandial symptoms. However, we cannot exclude the possibility that regions of higher stress exist locally in the gastric wall, which could cause the higher visceral sensitivity. In conclusion, this study shows that the proximal stomach of patients with functional dyspepsia show slightly increased compliance to mechanical distension in the fasting period, but decreased postprandial relaxation. The extent of postprandial relaxation did not correlate with the symptoms. The results of this study confirm that, in patients with functional dyspepsia, visceral hypersensitivity of the stomach plays a major role in their symptoms.

This study was presented in the Plenary Poster Session at the American Gastroenterology Association held in San Diego, 1995 and appeared in abstract form in Gastroenterology 1995;108:A488.

References
Gastric distension in functional dyspepsia

ERRATUM

The incorrect abstract was printed as TF294 in the 1998 BSG abstract book (Gut 1998;42:(suppl I):A74). The correct abstract is reproduced below.

DIFFERENT EFFECTS OF cagA vacuum [s1a/m1] H. PYLORI ON RAT GASTRIC MUCOSAL MICROCIRCULATION IN VIVO

Kelie N, Reed MWR, Morton D*, Altheron JC*, Jacob S*, Bardhan KD*;
Brown NJ: Departments of Surgical and Anaesthetic Sciences &
Biomedical Science, University of Sheffield; *District General Hospital,
Rotherham; *University Hospital, Nottingham

Background: We have previously demonstrated that pooled extracts of H. pylori from duodenal ulcer/gastriatis patients induce platelet aggregation but not leukocyte activation within rat gastric mucosal microcirculation (GMMC) in vivo [Gut 97;41:748-52]. However, the more pathogenic strains may exert greater effects on the microcirculation.

Aims: To determine the acute effects of two pure extracts of cagA vacuum[si1a/m1] strains, from two patients, on rat GMMC in vivo. Specifically, macromolecular leakage of labelled albumin, platelet and leukocyte activation and vessel diameters were assessed.

Methods: An incision made in the exteriorised stomach of anaesthetised rats (hypnorm/diazepam 1:1 ratio; 0.1mg/100g) allowed visualisation of the mucosal surface. 0.5mls of an aqueous extract from strain 60190 (n=12) or J104 (n=10) was administered topically. Acididine red (0.1ml/100g; i.a) was used to quantify leukocyte and platelet activity. Fluorescein-labelled albumin (0.2ml/100g; i.a) was used to quantify macromolecular leakage (MML) and alterations in capillary and post-capillary venule (PCV) diameters. Observations were made every 15 mins for 2 hrs using fluorescent in vivo microscopy.

Results: Strain 60190 induced significant sustained increases in MML, by 5 mins (41%; p<0.01). Less leakage was observed with J104 which was transient, reaching significance at 60 mins only (18%; p<0.05). 60190 induced rapid leukocyte adhesion within 5 mins (8.60 ± 2.67; p<0.05) with significant rolling leukocytes at 45 mins (2.90 ± 1.28; p<0.05). J104 induced significant leukocyte adhesion after 45 mins (11.65 ± 3.60; p<0.05). Platelet emboli were only observed with 60190 treated animals at 60 mins (2.3 ± 0.98; p<0.05). PCV vasoconstriction was observed only at 5 mins with 60190 (24.2μm ± 1.62μm to 18.84μm ± 1.81μm; p<0.05). Values represent mean above baseline ± S.E.M.

Conclusions: Extracts of H. pylori strains possessing both cagA and the vacA [s1a/m1] genotype are associated with marked disturbances within the GMMC. The data suggests that some cagA vacuum [s1a/m1] strains are more toxic and/or other genes may be involved.

Funded by Bardhan Research & Education Trust; Registered charity: 328452.