Gastric mechanosensory and lower esophageal sphincter function in rumination syndrome

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Thumshirn, Miriam, Michael Camilleri, Russell B. Hanson, Donald E. Williams, Alfred J. Schei, and Patricia P. Kammer. Gastric mechanosensory and lower esophageal sphincter function in rumination syndrome. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G314–G321, 1998.—Our hypothesis was that rumination syndrome is associated with gastric sensory and motor dysfunction. We studied gastric and somatic sensitivity, reflex relaxation of the lower esophageal sphincter (LES), and gastric compliance and accommodation postprandially and after glucagon. A barostatically controlled gastric bag and esophageal manometry were used to compare gastric sensorimotor functions and LES relaxation to gastric distension in 12 patients with rumination syndrome and 12 controls. During bag distensions, patients had greater nausea, bloating, and aggregate score, but not pain, compared with controls (P < 0.05). At 4 and 8 mmHg gastric distension, LES tone reduction was greater in patients than in controls (P < 0.05). Gastric compliance, accommodation to a standard meal, and response to glucagon were not different in patients and controls; however, 6 of 12 patients had no gastric accommodation; the latter patients had significantly greater pain perception during distension (P < 0.05) but normal somatic sensitivity compared with healthy controls. Rumination syndrome is characterized by higher gastric sensitivity and LES relaxation during gastric distension. A subgroup of patients also had absent postprandial accommodation.

lower esophageal sphincter relaxation; gastric tone; motility; sensation; barostat; Dent sleeve; accommodation; glucagon; cold stress

RUMINATION SYNDROME is a clinical syndrome characterized by virtually daily, effortless regurgitation of recently ingested food into the oropharynx without forceful retching. It is not associated with abdominal pain or nausea, and the regurgitant does not taste sour or bitter. Food may be partially or completely rechewed and reswallowed or expelled.

This syndrome has been described in almost equal prevalence among mentally retarded infants [6–10% (9, 39)] and institutionalized mentally retarded adults [8–10% (30, 31, 33)]. The syndrome is increasingly recognized as a cause of postprandial regurgitation in adolescents and adults of normal mental capacity (1, 8, 20, 21). The prevalence in the latter group is unknown because of the secretive nature of this condition in many patients and because of lack of awareness of this entity among physicians. In a tertiary referral population, patients had suffered from this condition for 2.75 yr (mean) and on average had consulted five physicians before correct diagnosis (20). Patients may seek medical attention because of weight loss, halitosis, indigestion, vomiting, or concern regarding an underlying medical disorder. Despite the increasing recognition of rumination as a cause of postprandial regurgitation in adults with normal mental capacity, there is still uncertainty concerning the classification of this syndrome (see DISCUSSION). Currently, treatment of rumination syndrome is unsatisfactory in part because the pathophysiological mechanism is unclear.

It appears that abdominal compression together with relaxation of the lower esophageal sphincter (LES) in the early postprandial period is responsible for the regurgitations. Manometric studies demonstrate evidence of a simultaneous increase in intraluminal pressure in the stomach and in several levels of the small intestine that is consistent with an increase in intra-abdominal pressure (1). It is unclear whether this is induced by diaphragmatic descent or by abdominal wall contraction or both. Others have documented the importance of LES relaxation as a prerequisite to regurgitation of gastric contents (6, 34). However, the cause of LES relaxation is unclear.

In another study of 38 patients, our group observed unequivocal evidence of increased intra-abdominal pressure in only about one-half of the patients evaluated by manometry of the stomach and small intestine (20). We noted that patients sometimes reported the sensation of a belch just before the experience of food arriving in the back of the throat (20). The belch reflex involves a vagally mediated, prolonged relaxation of the LES, which is thought to be induced by gastric distension with air (40).

Our hypothesis was that rumination is associated with sensorimotor dysfunction of the proximal stomach, specifically an increased gastric sensitivity to mechanical stimulation and a decreased gastric compliance and accommodation. To determine whether any changes in accommodation were specific to the meal response, we assessed the effect of intravenous glucagon, which is known to produce relaxation of the stomach (26), on proximal gastric tone. Our aim was to extend previous observations by examining proximal gastric compliance, tone, and perception during gastric distensions. A second aim was to assess the relationship between LES relaxation and proximal gastric stimulation by mechanical distension. The patients were carefully characterized for their clinical syndrome, including assessment of other gastrointestinal symptoms, pH reflux studies, gastric emptying, Minnesota Multiphasic Personality Inventory (MMPI), and somatic sensitivity using cold stress.
MATERIALS AND METHODS

Study Subjects, Clinical Diagnosis, and Routine Tests

Twelve patients, aged 18–48 yr [28.8 ± 3 (SE) yr; 10 women and 2 men], were selected on the basis of the following clinical criteria (20): repetitive regurgitation of recently ingested, recognizable food with rechewing, reswallowing, or spitting out; absence of sour or bitter taste of the regurgitant; and episodes of regurgitation starting during a meal or within 10 min postprandially and lasting at most 1–2 h. All symptom episodes were required to have symptoms for at least 3 mo and regurgitation episodes occurring for >3 days/wk. Exclusion criteria were evidence of organic upper gastrointestinal disease by esophagogastroduodenoscopy, evidence of an underlying disease that might have been associated with neuromuscular dysfunction of the upper gut such as diabetes mellitus or scleroderma, and previous abdominal surgery except for appendectomy, cholecystectomy, or gynecological surgery. As part of their clinical evaluation, patients underwent a prolonged esophageal pH monitoring study (duration 17–24 h) to exclude significant reflux (i.e., reflux >4% of time) in the supine position and to assess the mean pH in the postprandial period during which the vast majority of regurgitation episodes occurred. A radioscintigraphic study of gastric emptying of solids was also performed to exclude gastroparesis. In two patients a 5-h gastrointestinal manometry study was performed before entry into the study. This test revealed the characteristic manometric pattern of rumination, i.e., pressure spike waves synchronous with episodes of postprandial regurgitation (1), but was otherwise normal in the two patients. All medications known to alter gut motor and sensory function were discontinued at least 48 h before the physiological studies.

Healthy Controls

Twelve healthy volunteers, aged 24–45 yr [30.8 ± 2 (SE) yr; 7 women and 5 men], were recruited by public advertisement. None had significant gastrointestinal symptoms, significant psychological disorders, previous abdominal surgery except for uncomplicated appendectomy, or were taking any medication. The protocol was approved by the Institutional Review Board of the Mayo Clinic, and written informed consent was given by all patients and healthy controls.

Gastrointestinal and Psychological Symptom Profiles

A comprehensive, modified bowel disease questionnaire assembled from previously validated instruments (36) was used to assess symptomatology in all participants (patients and healthy controls). The MMPI (16, 28) was used to screen for psychological disorders in all participants. A detailed psychiatric history was obtained from all patients, and all patients were also assessed by a staff psychologist (D. E. Williams).

Assessment of Gastric Sensory and Motor Functions

A barostatic device (Distender Series II, G&J Electronics, Willowdale, Ontario, Canada) was used for measurement of gastric sensory and motor functions. A double-lumen assembly was inserted through the mouth so that a 1-liter capacity spherical polyethylene bag (Hefty Baggies, Mobil Chemical, Pittsford, NY) was positioned within the proximal stomach. Proper placement was confirmed fluoroscopically. The baseline operating pressure for each individual was set 1 mmHg above the pressure at which the polyethylene bag volume was greater than 30 ml, as in other studies in the literature (15, 26, 32). Air velocity for inflation was at 25 ml/s.

Perception during gastric mechanical distensions. Gastric perception was assessed in the fasting state by phasic distensions of the polyethylene bag performed in a randomized order at three different inflation pressures (6, 12, and 18 mmHg above the baseline operating pressure). Before the barostat bag distensions, a seven-point adjectival perception scale was reviewed with the subjects. The perceptions of three symptoms were recorded: 1) nausea, 2) bloating, and 3) abdominal discomfort (or pain for grades 5 and 6 of discomfort) and were graded as follows: 0, none; 1, vague; 2, mild; 3, moderate; 4, severe; 5, very severe; and 6, worst ever. Each of the three distensions was maintained for 1 min, and the subjects were asked to record their perceptions 30 s after the onset of each distension. The phasic distensions were separated by a 2-min interval with the bag at baseline operating pressure. There was minimal interaction between the subject and the investigator to avoid introducing any bias. This method of sensory assessment has been used extensively in this laboratory and has been shown to be responsive and reproducible in previous studies in the stomach (32) and colon (4, 31, 34).

Proximal gastric compliance. The gastric bag was distended in ramp fashion with 4-mmHg steps at 30-s intervals up to 24 mmHg above the baseline operating pressure or until the subject perceived abdominal discomfort. The bag was then deflated in ramp fashion (4-mmHg steps at 30-s intervals) until the intrabag pressure returned to the previous baseline operating pressure.

Proximal gastric tone. The method of measuring proximal gastric tone (3) was similar to that successfully used in previous studies in our laboratory (26, 32). Briefly, the polyethylene bag is infinitely compliant at the volumes of inflations in this study. It is kept under constant pressure within the proximal stomach by means of an electronic barostat. Changes in volume within the bag reflect changes in gastric contractility. Two types of contractile responses can be detected: 1) a slow baseline volume variation that reflects relaxation (increased volume) or increased tone or contraction (decreased baseline volume) and 2) phasic volume fluctuations (>5 ml over baseline, 5- to 40-s duration) from the baseline volume, which reflect contractions superimposed on the background state of contractility or tone. Tone was measured during fasting and postprandially and after intravenous injection of 1 mg glucagon. As stated previously, the latter is a stimulus that serves to check whether the stomach is able to relax (26).

Esophageal Manometry

An eight-lumen manometry assembly with ports 3 cm apart was used to record esophageal motility. The assembly incorporated a Dent sleeve, which was placed at the LES at the start of the procedure. The tube was perfused with distilled deionized water via a pneumohydraulic pump (perfusion rate 0.5 ml/min), and each port communicated with a strain gauge transducer to record intraluminal pressure (2).

Assessment of LES Relaxation During Gastric Distension

To compare the reflex responses of the LES to gastric distension, Dent sleeve recordings of LES tone at end-expiration were assessed for 5 min before the compliance measurements and during gastric compliance measurements with proximal gastric distension at 4 and 8 mmHg above baseline operating pressure to mimic pressures likely to be operating in the stomach postprandially. The ratio of postdistension to predistension LES tone was calculated for each distension pressure.
Assessment of Somatic Sensitivity by Cold Stress Test

The cold stress test was performed as previously described (13, 22, 37). Subjects were asked to immerse the nondominant hand up to the wrist in ice-cold water (0°C) for 60 s, withdraw the hand for 15 s, and then reimmerse the hand. The sequence of immersion and rewarming was continued to the point of maximum tolerance or for a maximum of 5 min. The potency of the stimulus could therefore be maintained throughout the procedure, and the tendency to pain adaptation was minimized. Test responses were assessed using the maximum duration of pain tolerance in seconds and pain intensity scores using a 100-mm visual analog scale (13).

Experimental Protocol

Figure 1 shows the experimental design of the study. All subjects were admitted to the Gastroenterology Diagnostic Center at St. Mary's Hospital after an overnight fast. Females of child-bearing potential had a negative plasma human chorionic gonadotropin pregnancy test. After per oral placement of the double-lumen assembly and the esophageal manometry tube, an esophageal pH probe was introduced through a nostril and positioned about 5 cm proximal to the esophagogastric junction with the aid of fluoroscopy. The polyethylene bag in the proximal stomach was slowly inflated with 300 ml of air via a syringe to unfold the bag and immediately deflated.

The subjects were seated upright at approximately an 80° angle in a bed, and the double-lumen assembly was connected to an electronic barostat. All recordings were made on a polygraph recorder and stored on a computerized recording system for later analysis.

Abdominal muscle contractions and respiratory movements were continually recorded from a pneumograph belt positioned around the mid-abdomen. Subjects were requested to avoid unnecessary movements, and the investigator was present throughout the study to record movements or other artifacts.

Recordings were carried out under fasting conditions and after the subjects drank 500 ml (500 Kcal) of chocolate-flavored Ensure (Abbott Laboratories, Columbus, OH) served at room temperature.

The experiment started with a 30-min period of equilibration, during which time baseline recordings were obtained. Proximal gastric compliance was next measured by ramp distensions of the intragastric bag. After a 15-min rest period, gastric perception was measured by phasic distensions of the intragastric bag. When the volume within the bag had returned to baseline after the last distension, the bag volume (i.e., proximal gastric tone) and esophageal manometry were monitored for at least 20 min before the meal. Subjects ingested the liquid meal with a straw over a 3- to 5-min period. Proximal gastric tone and the motor functions of the LES and esophagus were monitored continually for 1 h after the meal. Patients pressed an event marker whenever they experienced food regurgitation in the postprandial period. At the end of the 60-min postprandial period, the cold stress test was performed. Thirty minutes later, glucagon (Eli Lilly, Indianapolis, IN) was injected in a forearm vein as a 1-mg bolus, and gastric tone was recorded for at least 15 min. Glucagon is a polypeptide known to have a relaxant effect on the gastrointestinal tract (11, 26).

Data Analysis

The MMPI scores were summarized by an established computer program (28) and were reviewed together with the clinical assessment by the staff psychologist co-investigator (D. E. Williams) to reach a final diagnosis according to criteria given in the Diagnostic and Statistical Manual of Mental Disorders (10).

The individual scores for nausea, bloating, and discomfort on the seven-point adjectival scale (marked 0 to 6) during each of the three distensions were summed to provide an aggregate perception score for each subject (i.e., minimal score 0 and maximal score 18 for each distension or each symptom).

Gastric compliance was defined as the linear slope of a pressure-volume curve with values obtained during ramp inflations, where pressure (mmHg) is represented on the x-axis and bag volume (ml) on the y-axis.

LES tone was measured at end-expiration at 4 and 8 mmHg of gastric distension and compared with the LES tone at end-expiration averaged for 5 min before gastric disten-
sions. The ratios of postdistension to predistension measurements of LES tone were compared in the two groups.

A customized computer method (VAXLAB, Digital Equipment, Maynard, MS) was utilized to detect respiratory and motion artifacts on barostat recordings and to separate baseline gastric tone and phasic volume peaks.

Gastric tone was estimated from the baseline volume of the polyethylene bag, as in our previous studies (15, 32). For assessing accommodation postmeal, the averaged baseline barostat volume during the first 15 min postprandially was compared with the preprandial 15 min, and the percentage change in intrabag baseline volume was compared between the patients and controls. The percentage change in baseline bag volume relative to the fasting period was used to normalize for interindividual differences at baseline. Similarly, to assess accommodation postmeal, the averaged baseline barostat volume during the first 15 min postprandially was compared with the preprandial 15 min, and the percentage change in baseline bag volume relative to the fasting period was used to normalize for interindividual differences at baseline. Similarly, to assess accommodation postmeal, the averaged baseline barostat volume during the first 15 min postprandially was compared with the preprandial 15 min, and the percentage change in baseline bag volume relative to the fasting period was used to normalize for interindividual differences at baseline.

To calculate the circumferential wall tension (T) of the stomach at baseline operating pressure, we assumed that the air volume within the gastric bag conformed to a spherical shape. The radius (r) of the bag was estimated from the volume of the sphere, and wall tension was calculated from the estimated bag radius and the intragastric pressure (P) using Laplace’s law (sphere, $T = Pr/2$ (17, 25)). Results were expressed as Newtons/cm.

Statistical Analysis

Student’s unpaired t-test (two-tailed) was used to compare compliance, the ratio of postdistension to predistension LES tone, and perception scores. The Mann-Whitney rank sum test for nonparametric data was used to compare proximal postprandial gastric tone and postglucagon relaxation. Data in this manuscript are means ± SE if not otherwise indicated.

RESULTS

Clinical Characteristics of Patients

and Healthy Controls

There was no difference in age and body mass index between the patients and healthy controls (control data not shown). Patients had a mean duration of rumination syndrome of 2.6 yr (median 1.2 yr; range 6 mo-15 yr). The clinical characteristics of the 12 patients with rumination syndrome are shown in Table 1. The bowel disease questionnaire did not identify any other significant gastrointestinal symptoms except for constipation in 5 of 12 patients. Specifically, heartburn was not reported in 10 of 12 patients. The prolonged esophageal pH monitoring studies showed no reflux in the supine position; the average pH of refluxate during regurgitations in the postprandial period was 5.8 ± 0.2 (means ± SE).

Psychological Evaluation

According to MMPI analysis six patients had significant psychological disturbances: four depression and two chronic anxiety. Four of the six patients with normal postprandial gastric accommodation had psychological disorders on MMPI, whereas only two of the patients with impaired postprandial accommodation (see below) had abnormal MMPI. However, the clinical psychologist reported that two others in the latter group had psychological disturbances that were not detected by MMPI: posttraumatic stress disorder and depression. Thus there was an equal number of patients with psychological disturbances in the two groups.

Table 1. Clinical data of patients with rumination syndrome

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Length of History, yr</th>
<th>BMI, kg/m²</th>
<th>Weight Loss, kg</th>
<th>GE 2 h (normal 24–47%)</th>
<th>GE 4 h (normal 56–100%)</th>
<th>Prolonged Esophageal pH Monitoring</th>
<th>Psychiatric Assessment/MMPI</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>48</td>
<td>3</td>
<td>25.1</td>
<td>13</td>
<td>39</td>
<td>84</td>
<td>NA</td>
<td>Depression</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>19</td>
<td>1</td>
<td>18.3</td>
<td>13.6</td>
<td>RM</td>
<td>RM</td>
<td>NA</td>
<td>Posttraumatic stress disorder</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>19</td>
<td>0.75</td>
<td>27.5</td>
<td>16</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
<td>4.9 ± 0.2 Depression</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>35</td>
<td>0.75</td>
<td>22.9</td>
<td>29.5</td>
<td>88</td>
<td>96</td>
<td>No</td>
<td>6.1 ± 0.1 Normal</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>33</td>
<td>0.5</td>
<td>27.8</td>
<td>27</td>
<td>50</td>
<td>85</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>18</td>
<td>1</td>
<td>23.6</td>
<td>No</td>
<td>41</td>
<td>RM</td>
<td>No</td>
<td>5.9 ± 0.2 Normal</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>21</td>
<td>1.8</td>
<td>31.6</td>
<td>4.5</td>
<td>23</td>
<td>69</td>
<td>No</td>
<td>5.5 ± 0.1 Normal</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>36</td>
<td>1.8</td>
<td>21.6</td>
<td>30</td>
<td>25</td>
<td>70</td>
<td>No</td>
<td>4.8 ± 0.1 Chronic anxiety</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>18</td>
<td>1.25</td>
<td>22.3</td>
<td>No</td>
<td>41</td>
<td>56</td>
<td>No</td>
<td>5.8 ± 0.2 Chronic anxiety</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>35</td>
<td>15</td>
<td>16.4</td>
<td>4.5</td>
<td>50</td>
<td>84</td>
<td>No</td>
<td>7.1 ± 0.1 Depression</td>
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<tr>
<td>11</td>
<td>M</td>
<td>41</td>
<td>1</td>
<td>24.3</td>
<td>No</td>
<td>49</td>
<td>90</td>
<td>No</td>
<td>6.1 ± 0.2 Depression</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>22</td>
<td>4</td>
<td>13.7</td>
<td>10.5</td>
<td>RM</td>
<td>RM</td>
<td>Normal</td>
<td>Depression</td>
</tr>
</tbody>
</table>

Values for esophageal pH monitoring are means ± SE. BMI, body mass index; GE, gastric emptying; MMPI, Minnesota Multiphasic Personality Inventory; RM, regurgitated meal; Normal, performed at other institutions, normal report, patient reluctant to have repeat study; NA, not applicable (tube not tolerated or regurgitated postmeal).
Table 2. Perception scores during gastric distensions

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th></th>
<th>Ruminant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+6 mmHg</td>
<td>+12 mmHg</td>
<td>+18 mmHg</td>
<td>+6 mmHg</td>
</tr>
<tr>
<td>Aggregate score</td>
<td>4 ± 0.8</td>
<td>5.7 ± 1</td>
<td>7 ± 1</td>
<td>7 ± 1.2*</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5 ± 0.3</td>
<td>2.2 ± 0.4</td>
<td>2.8 ± 0.4</td>
<td>2.5 ± 0.4†</td>
</tr>
<tr>
<td>Bloating</td>
<td>1.8 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.6 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>2.1 ± 0.4*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9 ± 0.4*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4 ± 0.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 12/group. +6, +12, and +18 mmHg pressure above baseline operating pressure; aggregate score, sum of individual scores (0 to 6 scale) for nausea, bloating, and discomfort during each of 3 distensions. *P < 0.05 vs. healthy controls. †Subgroup with impaired gastric accommodation postmeal had increased discomfort perception (see text); P < 0.05 vs. healthy controls.

healthy controls (45 ± 2.1 ml/mmHg). At the baseline operating pressure in each individual, circumferential wall tension calculated using Laplace's law was similar in the two groups (patients 0.15 ± 0.02 vs. controls 0.15 ± 0.01 Newtons/cm). Fasting gastric tone expressed as the baseline bag volume was similar for the two groups (patients 218.1 ± 31.4 ml, controls 183.4 ± 22.5 ml).

Postprandial Gastric Tone

Regurgitation occurred in 6 of the 12 patients during the meal or the first 10 min postprandially. Four of the patients reswallowed the regurgitated food and two patients spit it out (maximal volume loss 150 ml). Episodes of regurgitation were excluded from calculations of postprandial tone. A 15-min postprandial period was used for analysis of gastric tone. After episodes of regurgitation, the location of the barostat bag in the proximal stomach was verified by fluoroscopy in the first two patients. Subsequently, fluoroscopy was not performed since intrabag volumes at the same baseline operating pressure were unchanged after the regurgitations and phasic volume fluctuations could be easily identified, suggesting that the bag was still in apposition with the gastric wall.

The overall postprandial accommodation, shown in Fig. 2, was not significantly different in the patient and control groups. However, there was a large interindividual variation in the gastric tone response to meal ingestion, especially in the patient group. Two types of gastric tone responses to meal ingestion within the patient group could be identified: a group of six patients had normal accommodation (median change in bag volume compared with fasting 59.3%, range 28.1 to 131.8%), defined as tone changes above the lowest observed in healthy controls (7.1%). A second group of six patients had absent or reduced accommodation (median change in bag volume −15.6%, range −90 to 2.7%), defined as tone changes below the 7.1% level, which was the lowest accommodation in the controls.

Food regurgitation during the study was not consistently associated with impaired gastric accommodation: three patients who regurgitated in the early postprandial period had a normal gastric accommodation response, whereas the remaining three patients showed no accommodation response.

Representative examples of the accommodation responses in the postprandial period are shown in Fig. 3.

Postglucagon Gastric Tone

Pharmacologically induced relaxation of the stomach with intravenous glucagon was not significantly different in patients and controls (change in bag volume in patients: median 88.9%, range 33%-264%; in controls: median 124.5%, range 22%-396%).

Esophageal Manometry and LES Relaxations

Baseline LES tone measured by the Dent sleeve was always >15 mmHg in all patients (27 ± 0.9 mmHg) and controls (30 ± 2.9 mmHg). The esophageal tracings also showed normal esophageal coordination during deglutition (data not shown). In response to gastric distension at 4 and 8 mmHg, both healthy and patient groups showed a reduction in LES tone (Fig. 4) as measured by the Dent sleeve. However, the postdistension-to-predistension ratio was significantly lower in patients with rumination syndrome (0.64 ± 0.04 at 4 mmHg and 0.61 ± 0.03 at 8 mmHg) compared with healthy subjects (0.78 ± 0.05 at 4 mmHg and 0.74 ± 0.05 at 8 mmHg), both P < 0.05.

Because there were postprandial regurgitation episodes in only six patients during these studies, and these were associated with either malpositioning of the
Dent sleeve or artifact during the regurgitation from repetitive rises in intra-abdominal pressure shown by simultaneous artifact in gastric and most esophageal manometric and sleeve sensors, we could not ascertain the function of the LES in relation to regurgitations or postprandial changes in gastric tone. Episodes of regurgitation were not associated with any drop in intra-esophageal pH below 4, presumably because of neutralization of gastric acid by the meal.

Somatic Sensitivity

None of the subjects tolerated the whole 5 min of somatic exposure to cold pain (Table 3). Four minutes were tolerated by 10 patients and 11 healthy volunteers; 2 patients and 1 volunteer completed only 2 min of the test. Although the duration of maximum pain tolerance was not different, rating at the point of maximal pain was significantly higher in patients than in controls (89 ± 4 vs. 70 ± 5 mm on the visual analog scale; P < 0.01).

DISCUSSION

This is the first study evaluating in detail the motor and sensory functions of the proximal stomach in patients with rumination syndrome. With regard to motor function, we demonstrated two types of accommodation after meal ingestion among patients with rumination syndrome: one subgroup with normal postprandial accommodation and a second group with diminished or absent accommodation. Clearly, diminished accommodation is of potential pathophysiological importance in a subset, not all, of these patients. This impaired accommodation was not due to the regurgitation episodes per se. It is conceivable that regurgitation itself may evoke motion artifacts or that abdominal muscle

Table 3. Cold stress test and pain perception

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset of pain, s</td>
<td>24.2 ± 6.1</td>
<td>34.6 ± 7.7</td>
</tr>
<tr>
<td>Threshold pain rating, vas, mm</td>
<td>51.3 ± 9.5</td>
<td>47.3 ± 6.1</td>
</tr>
<tr>
<td>Time to maximum pain tolerance, s</td>
<td>201.6 ± 21.8</td>
<td>227.9 ± 12</td>
</tr>
<tr>
<td>Maximum pain rating, vas, mm</td>
<td>89 ± 4*</td>
<td>70 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 12/group. vas, Visual analog scale. *P < 0.01 vs. controls.
contractions could artificially decrease intra-bag volume. However, we excluded episodes of regurgitation or movements that were associated with abdominal wall activity from the analysis of tone. Patients who regurgitated in the postprandial period were equally distributed among the two subgroups; thus we can exclude artifact from regurgitation as the reason for the differences in the two subgroups.

The cause for the absent accommodation is unclear from these studies. Our recent observation that regurgitations in this syndrome can be inhibited with cognitive behavioral therapy that includes muscle relaxation and diaphragmatic breathing (29) suggests that reflex accommodation might be modulated by descending influences from the brain or simply by inhibiting abdominal wall contraction.

Intravenous glucagon induced gastric relaxation in all participants. This suggests that an intrinsic muscle disorder is unlikely to have contributed to the absence of the gastric accommodation postprandially. In contrast to the differences in accommodation, proximal gastric compliance and wall tension were similar for patients and healthy controls, suggesting that baseline tone and gastric muscle elasticity across the wide range of pressures tested was similar in the two groups.

We also observed differences in sensation during gastric distension in patients with rumination and controls. Reduced postprandial accommodation theoretically may contribute to increased sensitivity as shown experimentally by altering tone pharmacologically (26). The increased sensitivity of the stomach to mechanical distension in patients with rumination syndrome suggests a primary visceral afferent hypersensitivity since gastric compliance was normal. We hypothesize that increased gastric sensitivity also contributes to the reduction in the LES tone observed. Thus gastric distension was associated with greater relaxation of the LES in patients with rumination syndrome than in controls. It is important to stress that in the patients with rumination syndrome, baseline LES tone was normal and prolonged esophageal pH monitoring studies showed no reflux in the supine position in these patients.

The increased gastric sensitivity and greater LES relaxation during gastric distension in these patients are similar to the spontaneous reduction in LES tone triggered by gastric distension in the belch reflex (40). This lowering of LES tone is likely to be physiologically important because it results in a reduction in the physical barrier to regurgitation. It provides an example of the importance of viscerovisceral reflexes and their perturbation in the context of nonstructural diseases in the proximal gastrointestinal tract.

What remains to be demonstrated is the mechanism of the retropulsive force that may be necessary for regurgitation to occur. The intragastric pressure can be increased by respiratory excursion of the diaphragm as well as by the hydrostatic force of the postprandial intragastric contents. Careful observation of patients during regurgitation episodes suggests that these are not always associated with evidence of forceful contraction of the abdominal muscles (20), which were previously considered the primary expulsive force for gastric contents (1). Our present data suggest that other motor dysfunctions might contribute to regurgitation episodes. Thus the failure of the stomach accommodation after a meal with increased fundic tone in one-half the patients might facilitate neural accommodation, LES relaxation.

Previous manometric studies (1) showed that in other patients, increased intragastric pressure postprandially also reflects increased abdominal pressure. This might allow regurgitation to occur even without forceful retching because the increased intragastric pressure would exceed the baseline tone of the sphincter. It is, however, unclear whether this intra-gastric pressure would regurgitate food to the oral cavity. Interestingly, some patients report the sensation of food reaching the level of the body of the esophagus, and not always reaching the throat or oral cavity.

We have also addressed other possible confounders of our observations in these patients: the role of generalized hypersensitivity and psychological disorders. The threshold time to experience somatic cold pain was similar in patients with rumination syndrome and controls, arguing against a generalized sensory hypersensitivity. There were significant psychological disturbances identified in the majority of our patients. These disturbances, mainly depression and anxiety reactions to stressfull life events, are consistent with previous reports in the literature (1, 21) reaffirming a psychological or psychiatric component in this disorder. However, in our experience, the psychological disturbances are relatively mild, and they may not contribute to the gastric motor dysfunction in these patients because the prevalence of psychopathology was similar in the subgroups with normal or impaired accommodation. It is possible that chronic stress contributes to the failure of the accommodation response [akin to the effects of acute, cold stress in humans (24)], or that stress modulates visceral perception (14) or sensitizes the reflex pathway (a "wind up" phenomenon (23)).

Is rumination syndrome a psychiatric disorder or a manifestation of a psychophysiological disturbance? In the Diagnostic and Statistical Manual of Mental Disorders (10) rumination is listed exclusively under "eating disorders of infancy." An association between rumination and bulimia nervosa has been described (12, 20), and rumination is recognized as a collateral behavior disorder among these patients. Rumination may be regarded as a "forme fruste" of other eating disorders such as bulimia, bulimarexia, or anorexia nervosa. In the latter groups, eating behavior, mood, body perception, and disturbances in neurohormonal function have been linked to changes in metabolism of several monoamines (such as norepinephrine, dopamine, serotonin) and endogenous opioids (5, 7, 18, 19). Whether similar neurohormonal changes are present in rumination syndrome is unknown and needs further investigation. However, there is increasing evidence that endogenous monoamines alter gastric mechanosensory function, through α2-adrenergic receptors (38) and 5HT1D recep-
Further physiological and pharmacological studies may shed important light on the mechanism of rumination and its pharmacological correction. This is particularly important for the subgroup of patients (at least 20% in our experience [29]) who do not respond to habit reversal with diaphragmatic breathing as part of a behavioral therapy.

In summary, our studies have enhanced our understanding of the motor and sensory dysfunctions of the proximal stomach and LES in rumination syndrome. Future studies need to address the effect of diaphragmatic breathing on LES relaxation during gastric distension.

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