Reflex control of intestinal gas dynamics and tolerance in humans

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Hence, we hypothesized that gas transit and tolerance is regulated by reflex mechanisms released by focal gut distension. To clearly establish whether these regulatory mechanisms depend on the site of stimulation, we selected two test sites widely apart (duodenum and rectum). Our specific aim was to compare the effects of distension at either of these two sites on gas transit and tolerance in healthy subjects. Intestinal gas dynamics were assessed using a new technique developed in our laboratory that measures gas evacuation and perception during continuous infusion of gas in the jejunum (29). The experiments were performed during duodenal infusion of nutrients at a rate that mimics the postprandial caloric load and induces retention of intestinal gas loads (32, 33).

MATERIALS AND METHODS

Participants

Twenty-four healthy individuals (10 women and 14 men; age range 19–31 yr) participated in the study after giving written informed consent. Subjects completed a preentry questionnaire to determine the absence of gastrointestinal symptoms, including constipation (36), difficult gas evacuation, feeling of excessive abdominal gas, or excessive gas evacuation. The studies were performed according to the Declaration of Helsinki, and the protocol for the study had been previously approved by the Institutional Review Board of the Hospital General Vall d’Hebron.

Intraluminal Tubes

**Jejunal tube assembly.** We used a multilumen polyvinyl tube assembly (4.9 mm OD) that incorporated a gas infusion channel (1.2 mm ID) with multiple side holes at the tip of the tube, a lipid infusion channel (1.2 mm ID) opening 20 cm proximally, and a distending bag (6 cm long, 18 cm perimeter, 150 ml capacity) made of ultrathin polyethylene mounted air-tight over the tube assembly with the distal end 5 cm from the tip (Fig. 1).

**Rectal tube assembly.** Another polyvinyl tube assembly (7 mm OD) incorporated a gas collection channel (3.5 mm ID) opening with multiple side holes over the distal 3 cm of the tube, and an oversized distending bag (25 cm perimeter, 400 ml capacity) mounted air-tight over the tube at 5-cm distance from the tip (Fig. 1). This tube arrangement allowed gas to be collected from the rectum also during rectal distension, because the surrounding bag never collapsed the gas collection channel.

**Measurement of Gas Transit**

**Jejunal gas infusion.** Gas was infused continuously in the proximal jejunum at 12 ml/min using a modified volumetric pump (Asid Bonz PP 50–300; Lubratronics, Unterschleissheim, Germany). We infused
Duodenal or rectal distension at fixed wall tension levels was performed by means of a computerized tensostat (10). The tensostat is a computerized air pump (Tensostat/Barostat; Sicie, Barcelona, Spain) connected via a double-lumen tube (2 mm ID for air transmission, i.e., inflation/deflation, and 0.8 mm ID for pressure transmission) to a high-compliance intraluminal bag. Oversized bags were used, and we assumed that, during the distension, air in the duodenum would conform to a cylindrical shape (6 cm long) and intrarectal air to a spherical shape. Based on transmural pressure (P) and volume (V), the system calculates the tension on the gut wall (T) by applying Laplace’s law (\( T = P \times R \) for the cylinder, and \( T = P \times R/2 \) for the sphere, where \( R \) is radius) and drives the pump to maintain the desired tension level. Transmural pressure in the duodenum and the rectum was calculated by subtracting from the intraluminal pressure the intra-abdominal pressure at each site. The latter was determined as the minimal distending pressure that detected respiratory variations (4, 10). The distension level was adjusted individually by applying stepwise increments every minute up to a level of clear perception without discomfort. A detailed description of the tensostat and validation studies has been published previously (10).

**Perception Measurement**

Subjective perception was measured at 10-min intervals during the studies, using a method that has been validated previously in detail and extensively used in visceral sensitivity studies (1, 2, 14, 29, 37). Abdominal perception was measured by means of four graphic rating scales graded from zero (no perception) to six (pain), specifically for scoring the following abdominal sensations: 1) pressure/bloating, 2) cramp/colicky sensation, 3) stinging sensation, and 4) other types of sensation (to be specified). Participants were asked to score any perceived sensation (1 or more perceived simultaneously) on the scales. If two or more sensations were simultaneously rated, the highest score, instead of the mean or the cumulative score, was computed for comparisons. In previous studies, we have observed that rectal distension in healthy subjects induces perception of sensations, such as rectal filling, repletion, desire to evacuate, and tenesmus, which are referred not to the abdomen, but deep into the pelvis-perineal region and invariably recognized by the subjects as originating from the right iliac fossae. Participants were instructed to mark the location, i.e., abdominal region(s) or extra-abdominal, where the sensations were perceived.

**Procedure**

During the 2 days preceding the study, participants were instructed to follow a diet excluding gas-producing foodstuffs. Participants were required to have one bowel movement within the 12 h before the study. Otherwise, the study was postponed. On the day of the study, participants were intubated after an 8-h fast. With the bag finely folded, the intestinal tube assembly was introduced orally and was positioned under fluoroscopic control with the gas infusion port located 5 cm caudally to the angle of Treitz, the distending bag in the distal duodenum, and the lipid infusion port in the proximal duodenum. The rectal tube was then introduced. The studies were conducted in a quiet, isolated room with the subjects placed supine in bed at an angle of 30°.
Before the study was started, the distending bag was unfolded by injecting air (50 ml in the duodenal bag and 100 ml in the rectal bag) under controlled pressure (<20 mmHg). The bag was then completely deflated and connected to the system, and the distending tension level was adjusted individually, as previously described (see Gut Distension).

After the start of the duodenal lipid infusion (15 min), gut distension either at the duodenum or the rectum (see below) and jejunal gas infusion were both started and maintained for the subsequent 3-h study period. To prevent oral pooling of secretions, the duodenal distension was discontinued for 1 min at 15-min intervals.

Experimental Design

Each subject participated in only one experiment. In three different groups of subjects (n = 8 each), studies were performed randomly either with duodenal distension, with rectal distension, or with sham distension, as control (Fig. 1).

Data Analysis

In each subject, the volume of gas retained within the gut at different time points was calculated as the difference between the volume of gas infused and the volume of gas recovered. The intensity of abdominal perception was measured by the score rated in the scales, as in Perception Measurement. In each subject, we also counted the number of times each abdominal sensation was scored to calculate the frequency (as percent distribution) of each specific sensation. In the anatomical questionnaire, the percentage of stimuli referred to over more than one abdominal region was calculated. Rectal perception was analyzed separately. Changes in abdominal girth throughout the study were referred to measurements taken at the beginning of the study before gas infusion was started.

Statistical Analysis

In each subject, perception and girth change data were averaged over 30-min intervals. In each group of subjects, mean values ± SE of the parameters measured were calculated. Because some subjects did not complete the procedure, the effects of the various stimuli tested were compared using in each subject the values corresponding to the last 30 min of the study. The Kolmogorov-Smirnov test was used to check the normality of data distribution. Comparisons of parametric data were performed by the Student’s t-test, paired for intragroup and unpaired for intergroup comparisons; comparisons of nonparametric data, including perception, were performed by the Wilcoxon signed-rank test for paired data and the Mann-Whitney U-test for unpaired data. The frequency of symptoms was compared by the Chi-square test.

RESULTS

Effect of Intestinal Nutrients (Control Experiments)

During the first 60 min of duodenal lipid infusion, gas evacuation from the rectum was slow, which resulted in some degree of retention. Later on, gas evacuation increased until steady-state dynamics were achieved and gas outflow matched inflow, which resulted in a fairly constant volume of gas being retained within the gut (375 ± 12 ml mean retention between 60 and 180 min of the study; Fig. 2). In this period, the number of gas evacuations was 14 ± 1/h with a mean volume of 50 ± 2 ml/evacuation. Overall, the subjects developed significant abdominal distension (7 ± 2-mm girth increment; P < 0.05). Recovery of SF6 was 97 ± 11% at 180 min.

All subjects but one who developed frank gas retention tolerated completion of the procedure with minimal symptoms (0.9 ± 0.4 score by the end of the study; Fig. 3), described as pressure/fullness (85 ± 12%), colicky sensation (28 ± 18%), and stinging sensation (32 ± 18%). These sensations were predominantly referred to the abdominal midline (65 ± 20% epigastrium, 71 ± 16% periumbilical, and 25 ± 19% hypogastrum) and in 63 ± 21% of the cases over more than one abdominal region.

Duodenal Distension

Mild duodenal distension accelerated gas transit and evacuation and modified the pattern of gas retention. Immediately after application, duodenal distension prompted gas evacuation (40 ± 16 ml during the first 10 min vs. 9 ± 7 ml in control studies; P < 0.01). During the 1st h, gas retention was only marginally smaller than in the control experiments (Fig. 2), but the latter effect of duodenal distension became more pronounced. At termination of the studies, the balance of gas retention was negative, i.e., subjects evacuated 120 ± 164 ml more gas than infused (P < 0.05 vs. control). During duodenal distension, the subjects did not develop objective abdominal distension (2 ± 1-mm mean girth increment; P < 0.05 vs. control). Recovery of SF6 was 96 ± 1% at 180 min.

Duodenal distension was adjusted individually at a level of mild abdominal perception (2.3 ± 0.2 score; 37 ± 8 g). However, perception steadily increased during the study (Fig. 3) up to a level of 4.4 ± 0.7 score in the last 30 min (P < 0.01 vs. initial perception and vs. control). Furthermore, one-half of the subjects did not tolerate completion of the procedure and required termination of the study at 112 ± 15 min. The volume of gas retention at termination of the study was not significantly different in the subjects that tolerated the procedure and in those that did not (−70 ± 164 and 102 ± 170 ml, respectively). The main symptoms were pressure/fullness (65 ± 15%), colicky sensation (63 ± 14%), and stinging sensation (28 ± 13%) and were referred to the epigastrium (45 ± 14%), periumbilical region (71 ± 11%), and hypogastrum (28 ± 13%), predominantly (in 79 ± 11% of the cases) over more than one area.
Fig. 3. Effect of gut distension on intestinal gas tolerance. In contrast to sham and rectal distension, duodenal distension induced progressively worsening abdominal symptoms, and 4/8 subjects required discontinuation of the study at 112 ± 15 min (P < 0.05 vs. sham and rectal distension). Data are average values over 30-min intervals.

Rectal Distension

Mild rectal distension markedly expedited gas transit and evacuation, an effect that was patent from the beginning of the study. During the first 10 min, 54 ± 15 ml were evacuated (P < 0.05 vs. control), and this expeditious evacuation was maintained throughout the study, which virtually prevented gas retention within the gut (Fig. 2). In fact, from 120 min onward, the balance of retention became negative, indicating that even gas present in the gut before the initiation of the study was being expelled. The number of evacuations was 15 ± 1/h with a mean volume of 55 ± 5 ml, and the subjects did not develop abdominal distension [2 ± 2-mm girth change; not significant (NS)]. Only one subject retained gas, exhibited substantial abdominal distension (13-mm girth increment), and required discontinuation of the study at 60 min. SF6 recovery at 180 min was 96 ± 3%.

Rectal distension was adjusted individually to induce mild rectal sensation (2.8 ± 0.1 score; P < 0.05 vs. control and duodenal distension; 38 ± 5 g). During the first 60 min of the study, rectal perception decreased to a level that was then sustained throughout the study and was comparable to the rectal perception reported both by the duodenal distension and control groups (1.8 ± 0.4, 1.5 ± 0.6, and 1.5 ± 0.4 score during the last 30 min of the study; NS). Abdominal perception was not significantly different from in the control experiments; it was initially very low, increased slightly during the first hour, and then remained stable until the end of the study (Fig. 3). During the last 30 min of the study, perception score was 2.6 ± 0.7, significantly lower than in the duodenal distension experiments (P < 0.05). The type of abdominal symptoms (63 ± 21% pressure/fullness, 63 ± 21% colicky sensation, and 16 ± 13% stinging sensation) and the referral pattern (55 ± 19% epigastrum, 73 ± 17% periumbilical region, and 28 ± 17% hypogastrium, with 54 ± 21% of the sensations perceived over more than one area) were not significantly different than in the control group.

Local Responses to Distension

Obviously, intra-abdominal pressure at the duodenal and rectal sites was markedly different (10 ± 1 and 20 ± 1 mmHg, respectively). Duodenal and rectal distensions were adjusted individually to produce mild perception, and the resulting tension levels were remarkably similar at both sites (37 ± 8 and 38 ± 5 g, respectively). However, at a fixed tension level, duodenal volume exhibited a progressive reduction along the study, reflecting a tonic contraction (from 55 ± 6 ml at the beginning to 33 ± 6 ml at the end of the study; P < 0.05; Fig. 4). By contrast, rectal volume exhibited an initial expansion, which then remained steady until the end of the study, but these rectal changes were not statistically significant (Fig. 4).

DISCUSSION

We have shown that intestinal gas dynamics are influenced by reflex mechanisms released by mechanical stimuli in the gut and that the specific effects on gas transit and perception depend on the site of stimulation.

For this study, we adapted a model of intestinal gas retention in healthy subjects (32, 33) based on the infusion of a physiological dose of lipids directly in the duodenum, which mimics the postprandial state (22). During duodenal lipid infusion, ~400 ml of the gas infused were retained in the gut. Taking into account that the fasting gut normally contains ~200 ml endogenous gas (29, 31, 35), the total volume of intraluminal gas (endogenous + infused) actually tripled. Gas evacuation was collected via an intrarectal cannula, thus preventing potentially confounding effects of the anus on gas retention.

Using this model, we have shown that either duodenal or rectal distension accelerated gas transit and eliminated the gas pooling by the end of the 180-min study period. However, the early effects of focal gut distension were remarkably different for each site. Thus, whereas duodenal distension had no significant effect on the initial gas retention, rectal distension accelerated gas evacuation and prevented retention from the very beginning of the experiment. By the end of the studies, however, both duodenal and rectal distension resulted in the evacuation of ~150 ml more gas than infused, a volume that probably represented most of the endogenous gas present in the gut at the beginning of the study (29, 31, 35). Hence, the
distension stimuli induced complete clearance of intestinal gas and reduced the dead space in the gut conduit to a minimum. The time point for inflection in the gas retention curve toward negative was similar in both duodenal and rectal distension groups, but during duodenal distension complete clearance took longer because of the initial retention. Hence, focal gut distension appears to trigger a gas propulsive activity that even overcomes the normal inhibitory effect of lipids.

Given the problems in standardizing gut distension in different individuals and at different regions of the gut, distensions were adjusted individually based on their intensity of conscious perception, at a level inducing mild sensation well below the discomfort threshold. Hence, the determinant of distension was the perceptual response. Once the distension level was established, the tension was kept constant over time by means of a computerized tensostat. The tensostat has been validated previously in the stomach (10) and the rectum (9), by means of a computerized tensostat. The tensostat has been established, the tension was kept constant over time below the discomfort threshold. Hence, the determinant of distension was the perceptual response. Once the distension level was established, the tension was kept constant over time by means of a computerized tensostat. The tensostat has been validated previously in the stomach (10) and the rectum (9), showing that perception depends on wall tension rather than on intraluminal pressure or volume. However, we wish to acknowledge that this concept has not been validated in the small bowel. Because the level of distension was adjusted based on perception, plausibly the same purpose would have been achieved using either fixed-volume or fixed-pressure distensions by means of a barostat. Perception at the selected distension levels was similar in the duodenum and the rectum (2.3 ± 0.2 and 2.8 ± 0.1 score, respectively; NS), and, interestingly, the tension levels applied at the two sites were remarkably similar (37 ± 8 and 38 ± 5 g, respectively; NS), whereas the intraluminal pressures (23 ± 3 and 34 ± 1 mmHg, respectively; P < 0.05) and the volumes (35 ± 6 and 168 ± 13 ml, respectively; P < 0.05) were different. During duodenal distension, abdominal perception progressively increased over time, even to uncomfortable levels in one-half of the subjects. We have shown previously that mild jejunal distension at fixed volume applied by means of a distending balloon and without concomitant gas infusion induced steady perception over time (28). In the present studies, during duodenal distension plus concomitant gas infusion, abdominal perception increased, and, although the methodology differed, i.e., the tensostat instead of the fixed-volume distension was used, it could be speculated that duodenal distension sensitized the gut to the gas overload via spatial summation phenomena known to heighten perception (28, 30). Rectal distension, in contrast, was not associated with significant abdominal perception. Hence, the effect of gut distension on perception of a gas load markedly depends on the area of stimulation. The spatial summation phenomena observed with duodenal, but not rectal, distension suggest that the gas load distended the small bowel rather than the colon, but the organization of the afferent input from different gut regions, small bowel, colon and rectum, remains largely unknown (15, 27). The type of abdominal symptoms and referral patterns were similar in the three study groups (duodenal, rectal, and control), providing further evidence that gut distension simply increased perception of the gas loads.

The tensostat also allowed study of the focal motor effects at the site of distension. The duodenum proximal to the gas infusion site exhibited a progressive reduction in volume, reflecting a contraction. In contrast, the rectum had a relaxed response. Conceivably, these changes in muscular tone were related to the intestinal motor response to the gas loads, since we have previously shown that prolonged distension of the jejunum does not induce any change in local muscular activity (contraction or relaxation; see Ref. 28). It is also unknown whether lipids act by relaxing the intestine and increasing capacitance or by increasing resistance resulting from segmental contractions (5, 8, 12, 17, 25). Bowel distensions have been shown to release inhibitory gastro-intestinal reflexes (23, 26), but stimulatory responses can also be elicited under some circumstances (5, 7, 19, 20). In this regard, the reduced dead space observed in our studies may be related to decreased capacitance secondary to tonic contraction of the intestine.

Evacuation of infused gas normally requires a lag time of ~1 h, during which the gas infused is retained in the gut (31, 32). However, this initial retention was not observed in a previous set of studies using an unperceived balloon to prevent gaseous backflow (29). Comparison of these early data with the results of the present studies would suggest that gas propulsive reflexes may also be released by unperceived gut stimuli and, hence, that they may operate under physiological conditions. It is conceivable that these reflexes are part of the physiological peristaltic reflex in response to an intraluminal bolus (5, 34). However, because in the present study only gut distensions above the perception threshold were tested, it cannot be excluded that perception of the distending stimulus had an added effect on enhanced gas clearance.

We have recently shown that patients with the irritable bowel syndrome and functional bloating have impaired dynamics and tolerance of intestinal gas loads (6, 31, 33), and it is plausible to speculate that such impaired gas handling may result from failure of the physiological reflex mechanism that normally propulsed and evacuates gas. This working hypothesis fits well within the framework of a sensory-reflex dysfunction in the pathophysiology of the irritable bowel syndrome and related functional disorders, as evidenced by other studies (11, 18).

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