

## INTESTINAL MOTILITY

# Impaired reflex control of intestinal gas transit in patients with abdominal bloating

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**Background:** Patients with abdominal bloating and distension exhibit impaired transit of intestinal gas which may lead to excessive gas retention and symptoms. Furthermore, we have previously shown that intestinal gas transit is normally accelerated by rectal distension. We hypothesise that in patients with functional bloating this modulatory mechanism fails and impairs gas transit.

**Methods:** In 12 healthy subjects and eight patients with abdominal bloating we compared, by paired studies, the effect of rectal versus sham distension on intestinal gas transit. Gas was infused into the jejunum (12 ml/min) for three hours with simultaneous perfusion of lipids into the duodenum (Intralipid 1 kcal/min) while measuring evacuation of gas per rectum.

**Results:** In healthy subjects, duodenal lipid infusion produced gas retention (409 (68) ml) which was prevented by rectal distension (90 (90) ml;  $p < 0.05$  v sham distension). In contrast, rectal distension in patients with abdominal bloating failed to reduce lipid induced gas retention (771 (217) ml retention during rectal distension v 730 (183) ml during sham distension; NS;  $p < 0.05$  v healthy controls for both).

**Conclusion:** Failure of distension related reflexes impairs intestinal gas propulsion and clearance in patients with abdominal bloating.

Intestinal gas transit and evacuation are normally modulated by reflex mechanisms so that healthy subjects tolerate a wide range of intraluminal gas loads without symptoms.<sup>1,2</sup> However, a large proportion of patients complaining of abdominal bloating, either with irritable bowel syndrome (IBS) or functional bloating, develop gas retention, abdominal distension, and symptoms in response to gas loads that are well tolerated by healthy subjects.<sup>2,3</sup> We have recently demonstrated that rectal distension accelerates gas transit in healthy subjects.<sup>4</sup> In the present study, we tested the hypothesis that this reflex mechanism fails in patients with bloating, impairing their ability to propel and evacuate intestinal gas. Hence we compared the effects of rectal distension on gas transit in patients with functional gut disorders complaining of abdominal bloating and in a cohort of healthy subjects. Intestinal gas transit was assessed by means of a gas challenge test, measuring rectal evacuation of gas infused into the jejunum.<sup>1</sup> The experiments were performed during duodenal perfusion of nutrients at a rate that slows down gas transit and induces retention of the gas infused in healthy subjects.<sup>5</sup>

## MATERIAL AND METHODS

### Participants

Eight patients complaining of abdominal bloating (six women, two men; aged 23–56 years) and 12 healthy individuals (six women, six men; aged 19–40 years) participated in the study. The predominant symptom in patients was abdominal bloating, with no detectable abnormalities in routine testing and no concomitant diseases. Five patients fulfilled the Rome II IBS criteria (three were constipation predominant and two diarrhoea predominant) and the other three patients fulfilled Rome II functional bloating criteria and had a normal bowel habit.<sup>6</sup> All patients were symptomatic at the time of the study. Healthy subjects completed a pre-entry questionnaire to determine the absence of gastrointestinal symptoms, including constipation,<sup>6</sup> difficult gas evacuation, feeling of excessive abdominal gas, or excessive gas evacuation. The study protocol was approved by the

Institutional Review Board of the University Hospital Vall d'Hebron, and all subjects gave written informed consent to participate in the study.

### Intraluminal tubes Orointestinal tube

A multilumen polyvinyl tube assembly incorporated a gas infusion channel (1.2 mm ID) opening at the tip of the tube and a lipid perfusion channel (1.2 mm ID) opening 20 cm proximally. The gas infusion port was fluoroscopically positioned 5 cm distal to the angle of Treitz and the lipid perfusion port in the proximal duodenum.

### Rectal tube assembly

A high compliance oversized bag (25 cm perimeter, 400 ml capacity) made of ultrathin polyethylene was airtight mounted over a polyvinyl tube assembly (7 mm OD) 5 cm from the tip. The assembly incorporated a gas collection channel (3.5 mm ID) opening by multiple side holes over the distal 3 cm of the tube, as well as inflation (2 mm ID) and pressure recording channels (0.8 mm ID) opening within the bag. Distension of the rectal bag never collapsed the internal gas collection channel.

### Measurement of gas transit Jejunal gas infusion

Gas was infused continuously into the proximal jejunum at 12 ml/min using a modified volumetric pump (Asid Bonz PP 50-300; Lubratronics, Unterschleissheim, Germany). We infused a gas mixture containing 88% nitrogen, 6.5% carbon dioxide, and 5.5% oxygen, bubbled into water for saturation, mimicking the partial pressures of venous blood gases to minimise diffusion across the intestinal-blood barrier.<sup>7,8</sup> To verify the completeness of recovery and absence of leaks, a non-absorbable stable gaseous marker, 5% sulphur

**Abbreviations:** SF<sub>6</sub>, sulphur hexafluoride; IBS, irritable bowel syndrome

hexafluoride (SF<sub>6</sub>), was added to the gas mixture during the first 10 minutes of the infusion.<sup>1-3 9</sup>

### Measurement of anal gas evacuation

Intestinal gas evacuation was collected via the rectal tube connected to a barostat,<sup>10 11</sup> and the volume of gas evacuated was continuously recorded on a paper polygraph (model 6006; Letica, Barcelona, Spain), as previously described.<sup>1</sup> A sample of gas evacuated (flatus) during each 30 minute period was stored in metal bags (gas collection 750 ml; Quin Tron, Milwaukee, Wisconsin, USA) for later analysis of SF<sub>6</sub> concentration by infrared absorbance after determination of standard curves.<sup>12</sup>

### Measurement of abdominal girth changes

Subjects were placed in bed (see procedure below) and then a non-stretch 48 mm wide belt with a metric tape measure was adjusted around the abdomen over the umbilicus by means of two elastic bands. Girth measurements were taken while the subjects were breathing in a relaxed manner as the average of inspiratory and expiratory determinations over three consecutive respiratory excursions, as described and validated previously.<sup>1</sup>

### Duodenal lipid infusion

The experiments were performed during continuous duodenal perfusion of a lipid emulsion (Intralipid 20%; Pharmacia and Upjohn, San Cugat del Vallés, Spain) at a rate of 0.5 ml/min (1 kcal/min) using a volumetric pump (Asid Bonz PP 50-300; Lubratronics, Unterschleissheim, Germany).

### Rectal distension

Distension at fixed wall tension levels was performed by means of a computerised air pump (Tensostat/Barostat, Sicie, Barcelona, Spain) connected to the rectal bag.<sup>13 14</sup> Assuming that during the distension air within the oversized bag conforms to a spherical shape, the tensostat calculates the tension on the rectal wall based on transmural pressure and volume, by applying Laplace's law ( $T = P \times R/2$ ), and drives the pump to maintain the desired tension level. Transmural pressure was calculated by subtracting from intraluminal pressure the intra-abdominal pressure determined at the beginning of the study as the minimal distending pressure that detected respiratory variations.<sup>11 13</sup> In each individual the distending tension level was then adjusted by applying 4 g stepwise increments every minute up to a level of clear perception without discomfort. A detailed description of the tensostat and validation studies have been published previously.<sup>13</sup>

### Perception measurement

Conscious perception was measured during the studies using a method that has been extensively used and previously validated in detail.<sup>1 15-18</sup> Abdominal perception was recorded using a graded questionnaire to score the intensity and type of sensations perceived, and an anatomical questionnaire to measure the location and extension of the perceived sensations. The graded questionnaire included four graphic rating scales specifically for scoring four possible abdominal sensations: (a) pressure/bloating; (b) cramp/colicky sensation, (c) stinging sensation, and (d) other type of sensation (to be specified). Each sensation was independently scored on the respective rating scale from 0 (no perception) to 6 (painful sensation). Participants were asked to score any abdominal sensation (one or more perceived simultaneously) on the scales but only the highest score, instead of the mean or cumulative score, was computed for comparisons. The questionnaire included an additional scale to score rectal perception, and a tick box (yes/no) to signal belching. The

questionnaire presented to patients had another tick box to signal the repetition of customary symptoms. The anatomical questionnaire incorporated a diagram of the abdomen divided into nine regions corresponding to the epigastrium, periumbilical area, hypogastrium, both hypochondria, flanks, and iliac fossae. Participants were instructed to mark the location (that is, abdominal region (s) or extra-abdominal) where the sensations were perceived.

### Procedure

During the two days preceding the study, participants were instructed to follow a diet excluding legumes, vegetables, garlic, onion, nuts, cereals, wholemeal bread, and fizzy drinks. The night before the study they had a light dinner that could consist of meat, fish, eggs, rice, pasta, and/or white bread but were instructed to avoid dairy products, salad, fruit, and alcoholic beverages. Patients were administered a glycerine suppository the night before the study. All participants were required to have one bowel movement within the 12 hours prior to the study or otherwise the study was postponed. On the day of the study participants were intubated after an eight hour fast. The studies were conducted in a quiet isolated room with the subjects placed supine in bed at an angle of 30°.

Before starting the study the rectal bag was unfolded by injecting 100 ml of air under controlled pressure (<20 mm Hg). The bag was then completely deflated and connected to the tensostat. Fifteen minutes after starting the duodenal lipid infusion rectal distension was applied. During duodenal lipid infusion and rectal distension gas was continuously infused into the jejunum and rectal gas evacuation was recorded for the subsequent three hour study period. Conscious perception and girth changes were measured at 10 minute intervals.

### Experimental design

#### Main studies

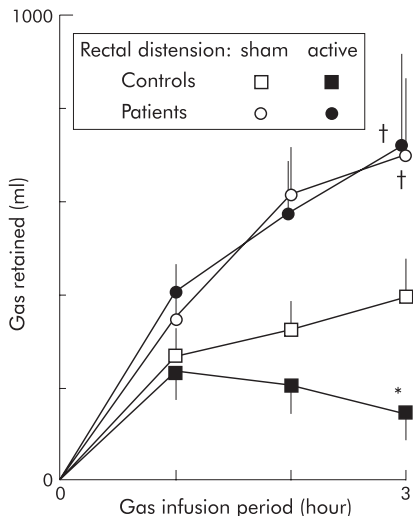
In patients (n = 8) and healthy controls (n = 8), the effects of rectal distension and sham distension (as control) were studied in random order on separate days with an interval of one week.

#### Ancillary study

The level of rectal distension tested in the main studies was individually adjusted, and was lower in patients than in controls (19 (3) g v 34 (4) g, respectively;  $p < 0.05$ ) due to their increased rectal perception. Hence to validate that the different effects of rectal distension in patients and healthy subjects was not related to the level of distension, in an additional group of healthy subjects (n = 4) the effect of 19 g rectal distension (the mean tension level applied to patients) and sham distension, as control, were studied in random order on separate days with a one week interval, following the same procedure as in the main studies.

#### Data analysis

In each subject the volume of gas retained within the gut was calculated as the difference between the volume of gas infused and the volume of gas recovered. Perception was measured by the score rated in the scales. In each subject we counted the number of times each abdominal sensation was scored in the repeat measurements during the study to calculate the frequency (as per cent distribution) of each specific sensation. In the anatomical questionnaire we calculated the percentage of sensations referred over each abdominal region, as well as the percentage referred over more than one region. Rectal perception was analysed separately. Changes in abdominal girth during the study

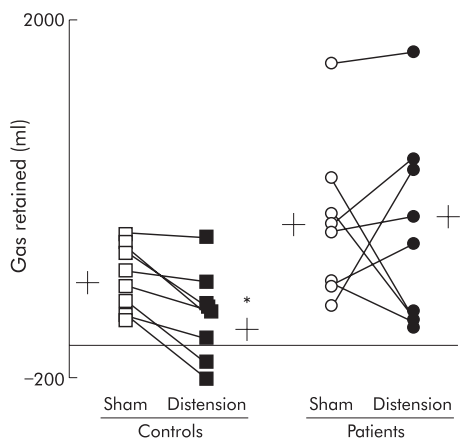


**Figure 1** Effect of gut distension on intestinal gas retention in healthy controls and patients with abdominal bloating. Rectal distension accelerated gas evacuation and prevented lipid induced retention in healthy subjects ( $p < 0.05$  v sham distension) but had no effect in patients. \* $p < 0.05$  versus sham; † $p < 0.05$  versus healthy controls.

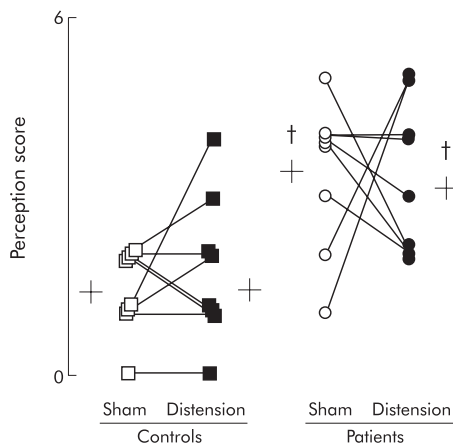
were referenced to girth measurement at the start of the study (that is, before gas infusion was started).

**Statistical analysis**

In each group of subjects, mean values (SEM) of the parameters measured were calculated. The Komolgorov-Smirnov test was used to check the normality of data distribution. Comparisons of parametric normally distributed data were performed by the Student's *t* test, paired tests for intragroup comparisons, and unpaired tests for intergroup comparisons; otherwise the Wilcoxon signed rank test was used for paired data and the Mann-Whitney U test for unpaired data. Correlations between paired data were examined by linear regression analysis. The frequency of sensations was compared using the  $\chi^2$  test. In each group of subjects we calculated the mean values (SEM) for the frequency of each sensation using individual data of per cent distribution.



**Figure 2** Individual data for gas retention by the end of the study.



**Figure 3** Effect of gut distension on abdominal perception. In healthy subjects, abdominal perception remained low during both sham and rectal distension. In contrast, patients with abdominal bloating developed significantly greater perception than healthy subjects under both study conditions (\* $p < 0.05$  v controls for both).

**RESULTS**

**Intestinal gas retention**

In healthy subjects, duodenal lipid perfusion induced retention of the gas infused but simultaneous rectal distension expedited gas transit and virtually abolished lipid induced gas retention (figs 1, 2). Patients with abdominal bloating exhibited significantly greater gas retention that was not modified by rectal distension (figs 1, 2). Rectal distension was individually adjusted at the beginning of the experiments to induce a mild rectal sensation but this perception level was achieved in patients at significantly lower rectal tensions than in healthy subjects (19 (3) v 34 (4) ml, respectively;  $p < 0.05$ ). However, in an additional group of healthy subjects, 19 g rectal wall tension, a level equivalent to that tested in patients, effectively expedited gas transit and reduced the volume of gas retained in the gut (198 (73) ml gas retention by the end to the experiments v 318 (74) ml during sham distension in the same subjects;  $p < 0.05$ ). By the end of the study, recovery of the SF<sub>6</sub> bolus administered at the beginning of the infusion was 97 (1)% in healthy subjects and 97 (2)% in patients, respectively (pooled data for experiments with and without rectal distension).

**Perception of rectal distension**

At the beginning of the studies, rectal distension induced a mild rectal sensation both in healthy subjects (score of 3.0 (0.1);  $p < 0.05$  v 0.4 (0.3) score during sham distension) and in patients (2.5 (0.2) score;  $p < 0.05$  v 0.8 (0.3) score during sham distension; NS v controls). Interestingly, 19 g rectal wall tension in healthy subjects induced significant effects on gas transit with insignificant rectal perception (score of 1.5 (0.6); NS v 0.3 (0.3) score during sham distension). In healthy subjects, rectal perception remained steady throughout the study period: by the end of the study the perception score was 2.7 (0.4) during rectal distension in the main studies, 1.0 (0.3) during sham distension, and 1.5 (0.6) during 19 g rectal distension in the ancillary studies (NS v beginning of the study for all). In contrast, rectal perception in patients progressively increased during the study up to a score of 4.1 (0.4) by the end of the experiments ( $p < 0.05$  v study start and v controls).

**Abdominal symptoms**

Intestinal gas retention was associated with abdominal distension ( $r = 0.62$ ;  $p < 0.0001$ ). Hence in healthy subjects

girth significantly increased during sham but not during rectal distension (5 (1) mm *v* 2 (1) mm increment by the end of the study;  $p < 0.05$ ) whereas in patients no difference was found between the two experimental conditions (6 (1) mm during sham and 4 (1) mm during rectal distension; NS).

In healthy subjects the gas challenge test was well tolerated. Interestingly, abdominal perception was similar during both sham and rectal distension, despite the fact that the former was associated with gas retention. In patients, perception was significantly higher and virtually identical during sham and rectal distension (fig 3). In the repeat measurement during infusion with sham rectal distension, healthy subjects reported pressure/bloating (57 (11)% of the time) and cramp/colicky sensations (42 (11)% of the times). These sensations were predominantly referred to the abdominal midline (35 (15)% epigastrium, 67 (14)% periumbilical, and 57 (15)% hypogastrum) and in 57 (17)% of cases over more than one abdominal region. Similar type of perception, although milder, was reported during rectal distension (data not shown). Patients also reported similar types of symptoms and referral patterns during both sham and rectal distension. Predominant symptoms in patients were pressure/bloating (53 (8)% of the time) and cramp/colicky sensation (27 (5)% of the time) which were referred to the abdominal midline (22 (7)% epigastrium, 58 (6)% periumbilical, and 65 (9)% hypogastrum; pooled data for sham and rectal distension). Patients tended to perceive these sensations more diffusely over their abdomen (in 78 (7)% of cases over more than the abdominal region; NS *v* controls). Interestingly, patients recognised the perceived sensations as their usual clinical symptoms on 95 (3)% of occasions.

### Rectal responses to distension

Intra-abdominal pressure estimates were 20 (1) mm Hg in controls and 18 (1) mm Hg in patients (NS *v* controls). At a fixed tension level, rectal volume tended to increase but the increment was not statistically significant (volume increased from 141 (17) ml at the beginning of the study to 230 (22) ml at the end in healthy subjects, and from 129 (17) ml to 160 (20) ml in patients; NS *v* study start and *v* controls for both). Intrarectal volume was smaller in patients due to the lower tension levels tolerated but overall compliance was similar in both groups.

## DISCUSSION

Our data indicate that patients with abdominal bloating have abnormal reflex control of intestinal gas transit which results in impaired tolerance of intestinal gas loads.

We have previously shown that in healthy subjects, intraluminal lipids dose dependently inhibit propulsion of intestinal gas loads, and that focal gut distension induces prokinetic activity that counterbalances the normal inhibitory effect of lipids.<sup>4</sup> Hence intestinal gas transit appears to be normally regulated by a fine balance of stimulatory and inhibitory reflexes. However, in contrast with healthy subjects, patients with abdominal bloating, both IBS and functional bloating have impaired handling of intestinal gas loads, resulting in gas retention, abdominal distension, and symptoms.<sup>2,3</sup> We have recently shown that these patients exhibit exaggerated responses to intestinal lipids: a low lipid dose, not producing detectable effects in healthy subjects, induced marked inhibition of gas transit in patients.<sup>19</sup> The present studies showed that not only is the inhibitory response to lipids upregulated but the prokinetic effect of focal gut distension also seems to be impaired. Indeed, rectal distension failed to induce propulsive reflexes, and by the end of the experiments patients retained about 1 litre more gas in the gut than healthy subjects. Hence patients complaining of

abdominal bloating have a gut motor dysfunction with impaired reflex control of gas propulsion.

Rectal distension was produced by means of a tensostat because it could "normalise" wall mechanoreceptor stimulation in subjects with different rectal compliance. Stimulus standardisation under these conditions could not have been achieved by applying either volume or pressure (barostat) driven distensions as perception seems to be related to wall tension rather than to intraluminal pressure or expansion.<sup>13,14</sup> We adjusted wall tension individually at the level of mild perception, well below the discomfort threshold. It is important to note that rectal distension did not influence perception of abdominal sensations during gas infusion in healthy subjects or in patients with abdominal bloating. Rectal distension neither modified the type of abdominal symptoms nor the referral pattern during infusion of gas.

As previously described,<sup>20</sup> patients exhibited rectal hypersensitivity, as evidenced by the significantly lower rectal wall tension required to induce perception. However, the lack of gas propulsion reflex seemed unrelated to the lower rectal tension tolerated by patients as in the ancillary study we showed that applying the same low tension level to healthy subjects as to patients effectively accelerated their gas transit. Nor could the presence of symptoms in patients explain their absent reflex on gas propulsion because we have previously shown that uncomfortable duodenal distension in healthy subjects stimulates gas propulsion.<sup>4</sup>

Evacuation of infused gas normally requires a lag time of approximately one hour, during which the gas infused is retained in the gut.<sup>2,21</sup> However, this initial retention was not observed in a previous set of studies using an unperceived balloon to prevent gaseous backflow.<sup>1</sup> These early data, together with the results of the present studies and particularly the ancillary experiment, would suggest that gas propulsive reflexes may also be released by unperceived gut stimuli and hence that they may operate under physiological conditions.

The tensostat also allowed study of the changes in tone at the site of distension. The rectum distal to the gas infusion site exhibited a progressive increment in intrabag volume, reflecting relaxation. Conflicting results have been reported with regard to the effect of rectal distension on phasic colonic motility,<sup>22,23</sup> which may be explained by the different experimental conditions tested, particularly the level of rectal distension. Nevertheless, the effects of rectal distension on phasic and tonic gut motor activity may well be different. We have previously shown that both types of motor activity evolve independently,<sup>24</sup> and gas movement might be determined by changes in capacitance produced by regional tonic contraction rather than by focal phasic contractions.

In conclusion, it is plausible to speculate that impaired gas handling in patients with bloating may result from failure of physiological reflexes that normally modulate gas accommodation, propulsion, and evacuation. The precise pathophysiological relevance of our data remains uncertain because in patients with either IBS or functional bloating, intestinal gas volume is similar to that in healthy subjects, at least under fasting basal condition.<sup>2,3,25</sup> Nevertheless, the added value of our observations rests in the objective demonstration of altered reflex control of gut motility in patients with abdominal bloating. These data are particularly relevant within the framework of a sensory reflex dysfunction in the pathophysiology of IBS and related functional disorders.<sup>26,27</sup>

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The Code aims to set a new basic standard for the ethical conduct of editors and sets out guidelines for quality and correcting the record, standing by decisions made, ethics committee approval, consent for publication confidentiality of submitted material, guidance to authors, pursuing misconduct, relationship to publishers, owners, and advertisers, and conflict of interest. The code also creates a mechanism to refer a complaint to COPE if an editor has breached the code.

The seminar will include:

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- COPE's new website—full text and keyword searching for COPE's advice on specific issues, for example research misconduct, conflict of interest, and deception
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