RECTO-COLONIC REFLEX IS IMPAIRED IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Patrick P.J. van der Veek, Marjan Steenvoorden, Jeroen Steens, Peter J. van der Schaar, Jessica Brussee, and Ad A. M. Masclee

Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Background: Motor and sensory dysfunction of the gut are present in a subset of patients with irritable bowel syndrome (IBS). Recent studies have demonstrated the presence of a recto-colonic inhibitory reflex in healthy humans. It is not known whether this reflex exists in IBS.

Methods: We studied rectal compliance, perception and the recto-colonic reflex by measuring volume responses of the descending colon to rectal distentions by barostat in 26 IBS patients and 13 healthy controls under both fasting and postprandial conditions.

Results: In the fasting state, rectal distention inhibited colonic tone and phasic motility to a similar extent in health and IBS. After a meal, rectal distention inhibited colonic tone and phasic motility to a lesser degree (P<0.05) in IBS than health. Under postprandial but not fasting conditions, rectal distentions of increasing intensity were associated with higher pain scores in IBS than in health.

Conclusion: Rectal distention inhibits tonic and phasic motility of the descending colon in healthy controls and in IBS patients. Postprandially this recto-colonic inhibitory reflex is impaired and attenuated in IBS patients compared to controls. These findings point to an altered reflex function in IBS and have implications for pathophysiology and therapy.
INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder that affects 5 to 20% of the general population and is characterized by recurrent abdominal pain and disturbed bowel habits. The pathophysiology of IBS is poorly understood, but disturbances at various levels of the brain-gut-axis have been identified, including post-inflammatory changes, inappropriate mucosal immune activation, hyperexcitability of spinal dorsal horn neurons and altered central processing of sensory afferent information. These alterations may result in visceral hypersensitivity, which is considered a hallmark of IBS. In addition, motor dysfunction may occur in IBS. However, disturbed gut motor and sensory functions are present only in a subset of IBS patients, emphasizing the need for alternative explanations for the pathophysiology of IBS.

Reflex inhibition of proximal gastrointestinal motor activity in response to stimulation of a distal segment of the small bowel has been demonstrated in healthy individuals. Recent observations in humans suggest the presence of recto-colonic and colorectal reflexes in the large bowel. These reflexes differ from the peristaltic reflex as they affect intestinal motility at much more distant segments. To date, the recto-colonic reflex has not been characterized in IBS.

Symptoms in IBS are typically provoked by a meal or, when already present, deteriorate postprandially. Simren et al. demonstrated that duodenal lipid perfusion reduces perception thresholds for first sensation, gas, discomfort and pain in IBS patients, but only for gas in healthy controls. These data suggest an exaggerated sensory response to a meal in IBS. Our aim was to evaluate the recto-colonic reflex in IBS patients under both fasting and postprandial conditions and to compare the results with those obtained in healthy controls.

METHODS

Subjects

Twenty-six IBS patients between 18 and 65 years of age were recruited at the outpatient department of Gastroenterology and Hepatology of the Leiden University Medical Centre (LUMC). The diagnosis of IBS was based on Rome II criteria. Medication for IBS was permitted but had to be stopped 4 days prior to the experiment. Thirteen healthy control subjects were recruited through advertisement. All participants provided informed consent and the LUMC ethics committee had approved the study protocol. Patient characteristics are shown in Table 1.
Table 1. Baseline characteristics of IBS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>IBS patients (n=26)</th>
<th>Controls (n=13)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>40.5 ± 15.8</td>
<td>37.2 ± 11.3</td>
</tr>
<tr>
<td>Females n (%)</td>
<td>16 (62)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Bowel habit n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhea</td>
<td>11 (42)</td>
<td>0</td>
</tr>
<tr>
<td>constipation</td>
<td>5 (19)</td>
<td>0</td>
</tr>
<tr>
<td>alternating</td>
<td>10 (39)</td>
<td>0</td>
</tr>
<tr>
<td>normal</td>
<td>0</td>
<td>13 (100)</td>
</tr>
</tbody>
</table>

Numbers within parentheses show percentages. IBS, irritable bowel syndrome; n, number of patients or controls.

Barostat

Two electronic barostats (Synectics Visceral Stimulator, Synectics Medical, Stockholm, Sweden) were used to study the recto-colonic reflex. One barostat was used to perform phasic rectal distentions, while the other measured changes in colonic tone. Pressure and volume were continuously monitored and recorded on a personal computer (Polygram for Windows SVS module, Synectics Medical, Stockholm, Sweden). The barostat assembly is shown in Figure 1.

Figure 1. Dual barostat assembly with one bag in the rectum (R) and one bag in the descending colon (C). Both bags are connected to separate barostats.
Experimental design

All experiments were performed on one day to reduce subject discomfort. Therefore, we were unable to randomize the intervention (meal versus fasting), but all measurements were performed in the same order, i.e. first under fasting and thereafter under fed conditions.

The bowel was cleansed with 2 liters of polyethylene glycol (KleanPrep®) the day before the experiment. After an overnight fast, subjects reported at our department at 7.30 AM and received a tap water enema. A flexible guide wire was placed in the transverse colon by endoscopy. Then a barostat catheter with bag was positioned over the guide wire into the descending colon under fluoroscopic control. A second barostat catheter was placed in the rectum, approximately 5 cm from the anal verge. Experiments were performed with subjects in a 10° recumbent supine position (Trendelenburg), lying in a bed.

The experimental protocol is shown in Figure 2. After a 30-min resting period, colonic operating pressure (OP, defined as the pressure that provides a continuous intrabag volume of 80 ml) was determined during slow ramp distention (1 mmHg/min increments until 80 ml bag volume was reached). Next, colonic bag pressure was set at OP and kept constant throughout the experiment. After 30 min, a rectal distention protocol was started, consisting of 5 phasic bag distentions of 10, 15, 20, 25 and 30 mmHg of 5 min duration each. Each distention was followed by a 5 min rest period at 5 mmHg. The rectal distention protocol ended after 50 min and was followed by a 30-min rest period while maintaining colonic bag pressure. After 15

Figure 2. Experimental design. Two identical phasic rectal distention paradigms were performed during fasting and after meal ingestion, while colonic bag pressure was set at operating pressure. Meal ingestion consisted of 200 ml of Nutridrink™ (t=115 min, black circle), followed by 40 ml of Nutridrink™ at the beginning of each rectal distention (grey circles). Urge and pain perception was scored at 30 sec after rectal distention onset (triangles).
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...subjects ingested a 200 ml liquid test meal (Nutrison™, Nutricia, Zoetermeer, The Netherlands; 600 kCal; 13% proteins, 48% carbohydrates, 39% fat). The rectal distention protocol was repeated 15 min after the onset of meal ingestion. An additional 40 ml of Nutrison™ was administered at the beginning of each rectal distention to maintain a nutritional steady state during the experiment. At the end of the experiment, the position of both bags was checked using fluoroscopy, and the bags were removed.

The perception of urge to defecate and abdominal pain was quantified on a 100-mm Visual Analogue Scale (VAS) at 30 sec after the onset of rectal distention, with end points ranging from ‘none’ to ‘unbearable’.

Data analysis
Rectal compliance was calculated by measuring the slope of the volume-pressure relationship from the onset of distention until the maximum pressure was reached. Mean colonic volumes during rectal distention were computed per minute. Subsequently, the relative change was calculated as the maximal volume per distention divided by the average volume in the 5-min pre-distention period (baseline volume). Phasic motility was defined as a 10% volume reduction below baseline, lasting for 10 - 60 seconds, and expressed as number of phasic volume events (PVEs)/5 min.

Statistical analysis
Linear mixed model analysis (SPSS for Windows 11.0.1, SPSS Inc., Chicago IL, USA) was performed to detect differences in colonic bag volume changes, perception scores and number of PVEs, over time, between patients and controls. Group, condition (rectal distention level) and group by condition interaction were analyzed as separate contributors to the model. Changes relative to the 10-mmHg distention and pre- and postprandial values within groups were analyzed using paired t statistics or Wilcoxon Signed Ranks Tests where appropriate. Between-group differences were compared by unpaired t statistics or Mann-Whitney tests. Correlations were calculated using Pearson’s linear regression analysis. Data are expressed as mean ± SD. P-values less than 0.05 were considered significant.

RESULTS
Baseline barostat characteristics
Rectal compliance was reduced in IBS patients compared to controls, but the difference was only significant in the fed state (patients versus controls, fasting state: 101 ± 35 ml/5 mmHg versus 131 ± 86 ml/5 mmHg, P=0.13; Fig 3A; fed state 110
Impaired recto-colonic reflex in IBS

± 37 ml/5 mmHg versus 140 ± 52 ml/5 mmHg, \( P=0.05 \); Fig 3B). However, analysis of covariance showed that postprandial compliance was not significantly different between health and IBS after adjusting for fasting compliance. No significant differences between patients and controls were found in baseline operating pressure,

\[ \text{colonic volume (ml)} \]

\[ \text{rectal pressure (mmHg)} \]

Figure 3A. Rectal compliance expressed as mean volumes (ml ± SEM) during successive distentions in healthy control subjects (squares) and IBS patients (triangles) under fasting conditions.

\[ \text{IBS} \]

\[ \text{controls} \]

Figure 3B. Rectal compliance expressed as mean volumes (ml ± SEM) during successive distentions in healthy control subjects (squares) and IBS patients (triangles) under postprandial conditions.
colonic bag volumes, and number of PVEs in the fasting state and colonic volumes and number of PVEs in the postprandial state (Table 2).

**Table 2.** Baseline barostat characteristics of IBS patients and controls

<table>
<thead>
<tr>
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<th>IBS patients (n=26)</th>
<th>Controls (n=13)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Fasting</strong></td>
<td></td>
<td></td>
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<tr>
<td>Operating pressure (mmHg)</td>
<td>14.5 ± 4.5</td>
<td>12.6 ± 4.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Baseline colonic volume (ml)</td>
<td>137 ± 42</td>
<td>122 ± 33</td>
<td>0.26</td>
</tr>
<tr>
<td>PVEs (n/5 min in predistention episode)</td>
<td>2.9 ± 2.8</td>
<td>3.7 ± 2.8</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Postprandial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline colonic volume (ml)</td>
<td>145 ± 42</td>
<td>125 ± 55</td>
<td>0.21</td>
</tr>
<tr>
<td>PVEs (n/5 min in predistention episode)</td>
<td>4.6 ± 2.3</td>
<td>4.3 ± 3.0</td>
<td>0.70</td>
</tr>
</tbody>
</table>

PVE, phasic volume event; IBS, irritable bowel syndrome.

**Colonic volume during rectal distentions**

Relative colonic bag volumes during rectal distentions in the fasting state are shown in Figure 4A. Mixed model analysis showed that colonic volumes differed across rectal distentions (condition, \( P<0.001 \)). However, the magnitude of colonic relaxation was not different between IBS patients and healthy controls (interaction, \( P=0.70 \)). Figure 5 represents an example of the colonic tracing during fasting in a healthy control subject.
During the postprandial period, the interaction between condition and group was significant ($P=0.01$), suggesting that the effect of rectal distention on colonic volume differed between patients and controls. Figure 4B suggests that colonic relaxation was less pronounced in IBS than in health.

**Figure 4B.** Colonic bag volumes (% ± SEM) relative to baseline during rectal distentions in healthy control subjects (grey bars) and IBS patients (black bars) under postprandial conditions.

**Figure 5.** Example of a colonic volume tracing (upper curve) during increasing phasic rectal distentions (lower curve) in a healthy volunteer. From 15 mmHg onward, colonic volume increases while the number of PVEs is reduced. The colonic bag volume returns to baseline after the rectal distention protocol has ended.
Phasic motility

During fasting, rectal distentions inhibited colonic motility, reflected by reduced number of PVEs to a similar degree in both groups (condition, \( P<0.001 \); group by condition interaction, \( P=0.41 \)) (Fig 6A).

In the absence of rectal distention, more PVEs were observed after compared to before a meal. The increase was significant in IBS patients from \( 3.4 \pm 2.6 \) to \( 4.6 \pm \)
2.3 PVE’s/5 min ($P=0.02$), but not in controls (from $3.9 \pm 3.4$ to $4.3 \pm 3.0$ PVE’s/5 min, $P=0.52$). During rectal distention after a meal, analysis of colonic PVEs revealed an interaction ($P<0.05$) between condition and group. Figure 6B suggests that more PVE’s occurred in patients compared to controls.

**Perception**

**Urge**

During fasting, urge scores increased similarly in patients and controls at increasing bag pressures (condition, $P<0.001$; group by condition interaction, $P=0.87$) (Fig 7A). Similarly, urge increased significantly in both groups after the meal (condition, $P<0.001$), without significant between-group differences ($P=0.95$ for the interaction).

![Figure 7A](image)

**Figure 7A.** Perception of urge to defecate during fasting in patients (open squares) and controls (open triangles) and after meal ingestion in patients (closed squares) and controls (closed triangles).

**Pain**

Under fasting conditions, pain scores in patients appeared higher compared to controls, but the interaction was not significant ($P=0.08$) (Fig 7B). Postprandially, the group by condition interaction for pain was significant ($P=0.01$). Figure 7B shows that pain after a meal was increased in IBS patients compared to controls.
DISCUSSION

This is the first study to compare fasting and postprandial recto-colonic reflexes in health and IBS. Colonic motility was characterized by assessing tone and phasic volume events with a barostat. Our results show that 1) in controls, colonic tone and phasic volume events decline during rectal distention under fasting and postprandial conditions, 2) during fasting, colonic relaxation during rectal distention is comparable between IBS patients and healthy controls, and 3) after a standardized meal, colonic relaxation during rectal distention is impaired in IBS patients compared to controls. Under fasting conditions, rectal distention inhibited colonic tone and phasic volume events in an intensity-dependent manner in both health and IBS.

Reflex inhibition of colonic motility during rectal distention has previously been demonstrated in humans. Law et al. showed that colonic bag volumes increased during ramp and phasic rectal distentions in healthy volunteers\textsuperscript{11}. In addition, our results also suggest for the first time that the magnitude of colonic relaxation was correlated to the intensity of rectal distention during fasting conditions. By contrast, Ng et al. reported that while 7 out of 14 subjects exhibited colonic dilatation during rectal distention, there was no significant overall group response\textsuperscript{12}. Among our healthy subjects, colonic volumes increased by 10% or more in 9 of 13 subjects during rectal distention by 25 mmHg and in 10 of 13 subjects during 30 mmHg distention. Our results therefore support the observations by Law et al.\textsuperscript{11} that a recto-colonic inhibitory reflex exists in humans. Differences in study design may explain the discrepancy between our study and a previous study\textsuperscript{12}. For instance, Ng studied the colonic
volume response to only one rectal distention, while in our study and that of Law et al. several rectal distentions were employed and a dose response relationship could be established. Recently, Ng et al. studied the colorectal reflex by dual barostat assembly and found the reflex to be significantly attenuated in IBS patients compared to controls.

Under postprandial conditions, reflex inhibition of colonic motility, as measured by colonic volumes, was impaired in IBS patients compared to healthy controls. It is unlikely that the differences were attributable to differences in baseline colonic bag volumes, which were not significantly different. However, similar to previous studies, IBS patients had an exaggerated postprandial colonic contractile response. Perhaps, exaggerated postprandial colonic motor activity impairs the ability of the colon to relax and thereby attenuates rectocolonic reflexes in IBS patients after a meal.

Consistent with previous studies, pain scores during rectal distentions were higher in IBS patients than in controls. Furthermore, patients experienced more pain in the fed state compared to controls, while preprandial pain scores were not different between groups. Simren et al. showed that duodenal lipid infusion reduced perception thresholds for first sensation, gas, discomfort and pain in IBS patients, but only for gas in healthy controls, suggesting an exaggerated sensory response to a meal or nutrients in IBS patients. Recently, Caldarella and colleagues demonstrated that intraduodenal infusion of lipids reduced thresholds for discomfort during rectal distention in IBS patients, but not in healthy controls. However, thresholds for perception were significantly lower in IBS compared to controls, with no additional effect of lipid infusion. Our findings confirm these findings, and clinical observations suggest that IBS symptoms deteriorate after a meal. However, the repeated distentions in our study may have also contributed to increased postprandial pain perception.

The role of postprandial recto-colonic inhibitory reflexes in the pathophysiology of IBS is not clear. Recent reports point to impaired reflexes at other locations in the gastrointestinal tract in patients with functional bowel disorders. For instance, impaired reflex fundic relaxation following intestinal administration of nutrients has been shown in patients with functional dyspepsia. Our finding that colonic relaxation during rectal distention is impaired after a meal, taken together with the more pronounced effect of a meal on rectal sensation in IBS compared to controls, is consistent with the hypothesis of a generalized disturbance of postprandial colonic sensori-motor functions in IBS. This impairment should primarily be looked upon as a marker of disturbed gastrointestinal motor and sensory function, perhaps attributable to autonomic dysfunctions. In addition, disordered reflexes may also contribute to IBS symptoms, particularly postprandial exacerbation.
Finally, all measurements were performed in the same order, i.e. increasing rectal pressure distentions during fasting conditions followed by the same sequence after a meal. This was done to minimize discomfort to participating subjects. This is, however, a potential limitation of the study.

In conclusion, we have demonstrated the existence of a recto-colonic inhibitory reflex in healthy individuals and in IBS patients. The magnitude of this response is in the same range in both groups under fasting conditions, but is impaired in IBS patients after a meal. Since the role of disturbed colonic motor and sensory function in IBS has not been fully elucidated, future studies should focus on the involvement of retrograde reflexes in the pathophysiology of functional bowel disorders and characterize recto-colonic reflex dysfunction in IBS subgroups.
REFERENCES