

# Gastrointestinal pH profile in subjects with irritable bowel syndrome

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## Abstract

**Aim** To investigate the small bowel pH profile and small intestine transit time (SITT) in healthy controls and patients with irritable bowel syndrome (IBS).

**Methods** Nine IBS patients (3 males, mean age 35 yr) and 10 healthy subjects (6 males, mean age 33 yr) were studied. Intestinal pH profile and SITT were assessed by a wireless motility pH and pressure capsule (Smart Pill). Mean pH values were measured in the small intestine (SI) and compared both within and between groups. Data presented as mean or median, ANOVA,  $P < 0.05$  for significance.

**Results** We found the pH for the first (Q1), second (Q2), third (Q3), and fourth quartile (Q4) of the SI in healthy versus IBS patients was  $5.608 \pm 0.491$  vs.  $5.667 \pm 0.297$ ,  $6.200 \pm 0.328$  vs.  $6.168 \pm 0.288$ ,  $6.679 \pm 0.316$  vs.  $6.741 \pm 0.322$ , and  $6.884 \pm 0.200$  vs.  $6.899 \pm 0.303$ , respectively. We found no significant group difference in pH per quartile ( $P=0.7979$ ). The proximal SI was significantly more acidic, compared to distal segments, in both healthy subjects and IBS patients ( $P < 0.0001$ ). We found no significant difference in the measured SITT between IBS and control groups with a mean SITT of  $218.56 \pm 59.60$  min and  $199.20 \pm 82.31$  min, respectively ( $P=0.55$ ).

**Conclusion** This study shows the presence of a gradient of pH along the SI, in both IBS and healthy subjects, the distal being less acidic. These findings may be of importance in small bowel homeostasis.

**Keywords** irritable bowel syndrome, small intestine transit time, pH, lactulose breath test

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## Introduction

Irritable bowel syndrome (IBS) is a disorder of high prevalence, significant morbidity, and cost burden [1,2]. There is currently no clear pathological or biochemical diagnostic markers for IBS and the diagnosis is based entirely on the clinical presentation. Intestinal transit is altered in IBS subjects; it tends to be accelerated in diarrhea-predominant (IBS-D), and delayed in constipation-predominant (IBS-C), or alternating IBS [3,4].

Previous transit studies in subjects with IBS were evaluated mostly with the use of lactulose hydrogen breath tests (LBT) and scintigraphy [5-10]. Scintigraphy is accepted as the standard method for assessing gastrointestinal (GI) transit due to its reproducibility [11], but is not widely available. The

Smart pill GI monitoring system consists of wireless motility capsule (WMC) that records intraluminal pH, pressure, and temperature as it traverses the GI tract, and wirelessly transmits the data to a portable receiver. The system can assess regional transit times (gastric, and colonic), and characterize pressure patterns and pH along the gut [12,13]. Emptying of the WMC correlates with solid-phase emptying and transit time measured by scintigraphy [6,14-16].

Recent data indicate that antibiotic therapy provides significant relief of IBS global symptoms [5,17]. A difference in bacterial milieu in the gut may result in changes in the pH profile, a product of bacterial fermentation. This in turn may affect biochemical processes such as digestive enzymes that are pH-dependent. A change in pH may interfere with metabolic processes required for digestion and contribute to symptoms of IBS. Differences in small intestine (SI) transit between IBS and control patients have been described, with accelerated small intestine (SI) transit time (SITT) in diarrhea-predominant and delayed SITT in IBS-C [2,4]. We hypothesized that there is a difference in pH profile between IBS and control subjects. This study was designed to assess SI pH profile in these two populations. We also hypothesized that the fermentation of lactulose by patients with excessive enteric bacteria will

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Conflict of Interest: None

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result in a change in the luminal pH that will be detected by the capsule as it travels through the SI. In a subset analysis, we assessed the pH profile in patients with an abnormal vs. normal LBT.

## Materials and Methods

### Study population

The IBS group included 9 patients (3 males, mean age 35 years), with IBS-D or alternating IBS, selected based on Rome III criteria. The control group included 10 healthy subjects, (6 males, mean age 33 years). Patients with any abdominal surgery were excluded. Medications affecting GI motility including calcium channel blockers, nitrates, and antispasmodics were stopped 7 days prior to the study.

### Study design and procedures

After an overnight fast subjects ingested an activated and calibrated Smartpill capsule (Smartpill corporation, Buffalo, New York). Thirty minutes after the capsule exited the stomach (determined by an abrupt rise of pH >4) all subjects ingested a standard dose of lactulose (20 mL, 10 g), a non-absorbable carbohydrate followed by 1-2 ounces of water. Once the smart pill capsule entered the colon, determined by the intraluminal pH, the study was concluded and the subjects were allowed to have a meal. If the capsule failed to enter the ileocecal junction within 7 h of ingestion the subjects were given the option to conclude the study or leave the research center with the data receiver to enable continued data acquisition from the capsule. Subjects who chose to leave the research center were required to return the data receiver the next day. At the end of the study, the data from the receiver was transferred to a PC via the docking station.

### Transit and pH monitoring

The SmartPill GI monitoring system is a wireless motility capsule (WMC) measuring 13x26 mm that provides an accurate measurement/recording of pH (range, 0.05-9.0 pH units), temperature (range, 25-49°C), and pressure (range, 0-350 mmHg) [13]. The capsule continuously records pH, pressure and temperature every 5 sec, 0.5 sec, and 20 sec respectively and transmits this data to a portable receiver which records all the values [13]. After completion of the study the data is then downloaded to a computer for data analysis.

Before the subjects ingested the lactulose, a baseline breath hydrogen sample was collected. Breath samples were then collected in 15 min intervals for 3 h. All breath samples were analyzed for hydrogen and methane, using a Model SC, Quintron gas chromatograph (Quintron Instrument).

### Data analysis

A sharp rise in pH identified passage of the capsule from the stomach to the SI while an abrupt drop in the intraluminal pH corresponds to passage of the capsule into the cecum [13]. Gastric emptying time (GET) was defined as the time interval between ingestion of the capsule and the time at which there was an abrupt rise in the pH of at least 3 pH units from the gastric baseline [13]. SITT was defined as the time interval between capsule entry into the duodenum and its entry into the cecum, defined as a distinct decrease in pH of greater than 1 unit for at least 5 min [13].

Mean pH was calculated along the four quarters of the SI. Since the data do not allow for localization of the capsule within the SI, we divided the SI into four equal quartiles of capsule residence (Q1 - Q4) in an attempt to match data to specific regions of the gut.

Normal LBT was defined as no rise of breath hydrogen (H<sub>2</sub>) or methane (CH<sub>4</sub>) concentration above 20 ppm before 90 min following ingestion [18].

### Statistical analysis

Data are represented as mean +/- SD, ANOVA, p<0.05 for significance. We compared quantitative data between the IBS subjects and healthy controls using the Wilcoxon rank sum test.

## Results

### Subject demographics

The mean age for the control and IBS group was 33 years and 35 years, respectively. In the healthy group, 7 patients had an abnormal LBT and 2 patients had a positive methane breath test. In the IBS group, there were a total of 7 patients with an abnormal LBT and no patients with a positive methane breath test. The demographic characteristics of all subjects were similar with the exception of ratio of men to women and methane-positive breath test (Table 1).

**Table 1** Comparison of demographics characteristics between control and irritable bowel syndrome study group

Characteristic	Control	IBS
Number, n	10	9
Age (yr), mean	33	35
Gender (female/male)	4/6	6/3
Abnormal breath test	7	7
Methane-positive breath test	2	0

IBS, irritable bowel syndrome; yr, year

**Table 2** An evaluation of mean pH of each quartile of the SI. There was no significant difference between groups in any of the variables

	1 <sup>st</sup> quartile	2 <sup>nd</sup> quartile	3 <sup>rd</sup> quartile	4 <sup>th</sup> quartile
pH (controls)	5.608 ± 0.49	6.200 ± 0.330	6.679 ± 0.320	6.884 ± 0.20
pH (IBS)	5.667 ± 0.300	6.168 ± 0.290	6.741 ± 0.32	6.899 ± 0.30

SI, small intestine; IBS, irritable bowel syndrome

### Intestinal pH profiles

There were significant changes in pH along the intestine in both groups. No significant difference was seen in the mean pH for both IBS and healthy subjects in all four quartiles of the SI ( $P=0.7979$ ). For the healthy group the mean pH ± SD for first (Q1), second (Q2), third (Q3), and fourth quartile (Q4) of the SI was  $5.608 \pm 0.491$ ,  $6.200 \pm 0.328$ ,  $6.679 \pm 0.316$ , and  $6.884 \pm 0.200$ , respectively. For the IBS group the mean pH ± SD for Q1, Q2, Q3, and Q4 was  $5.667 \pm 0.297$ ,  $6.168 \pm 0.288$ ,  $6.741 \pm 0.322$ ,  $6.899 \pm 0.303$ , respectively. There was a significant difference in mean pH values between the various pairs of quartiles within both control and IBS groups ( $p < 0.001$ ) except between Q3 and Q4 (Table 2).

### Transit time and gastric emptying comparison

There was no significant difference in the measured SITT between IBS and control groups ( $P=0.55$ ) (Table 3). The mean SITT for the control and IBS groups were  $199.20 \pm 82.31$  min and  $218.56 \pm 59.60$  min, respectively. The mean GET measured also failed to show a significance difference between IBS and control groups ( $P=0.37$ ). The mean GET (min) for the control and IBS groups were  $76.81 \pm 73.19$  min and  $51.23 \pm 59.11$  min, respectively.

### Abnormal LBT

There was an equal number of subjects with an abnormal LBT in both groups ( $n=7$ ). There was no significant difference in mean pH values along the SI between the 2 groups.

### Adverse events

No patients had capsule retention or any side effects with the exception of nausea and mild stomach discomfort.

### Discussion

Our results show a distinct pH gradient along the length of the SI with the proximal segments being more acidic. This gradient was present in both healthy subjects and patients with IBS, with no difference between the groups.

Previous studies using radiotelemetry capsules in healthy patients showed a gradual rise in luminal pH from the duodenum to the terminal ileum followed by a sharp descent in the cecum pH and a gradual rise along the remainder of the colon to the rectum. These studies showed that SI luminal pH ranged between 5.5-7.0 in the proximal SI, 6.5-7.5 in the distal SI followed by a sudden decline in cecal pH to 5.5-7.5; pH then slowly trended up along the remainder of the colon to 6.1-7.5 [19-26]. More recent studies, using the Smart Pill technology, showed similar pH pattern of the SI in healthy males and females [27,28]. However, to our knowledge, this is the first study to investigate pH changes along the SI in patients with IBS.

As gastric acid is emptied into the foregut, bicarbonate secretions work to buffer the acidic luminal pH of the proximal duodenum which accounts for the progressive rise in the luminal pH up to the terminal ileum. This is followed by emptying of SI contents into the cecum, characterized by a drop in pH by at least 1 unit. The acidity of the cecum can be attributed to colonic bacterial fermentation of carbohydrates into its byproducts of short chain fatty acids (SCFAs) mainly acetate, propionate, and butyrate [29]. Alterations in diet intake

**Table 3** SITT and GET between control and IBS groups and between subjects with and without abnormal lactulose breath test. Data as Mean ± SD. There was no significant difference between groups in any of the variables

	Control		IBS		Abnormal LBT		Normal LBT	
	GET	SITT	GET	SITT	GET	SITT	GET	SITT
Mean	76.81±73.2	199.20± 82.3	51.23±59.1	218.56±59.6	56.27±65.2	194.36 ±60.3	88.27 ±71	247.60 ±91
Median	44.63	188.50	29.50	251.00	28.17	188.50	68.00	263.00
Minimum	18.00	92.00	12.00	115.00	12.00	94.00	24.75	92.00
Maximum	216.2	327.00	192.7	265.00	216.17	265.00	192.67	327.00

GET, gastric emptying time; SITT, small intestinal transit time; LBT, lactulose breath test; IBS, irritable bowel syndrome

can affect intracolonic pH via SCFA production; Fiber, resistant starch, oligosaccharides, and non-absorbable carbohydrates such as lactulose are substrates for bacterial fermentation leading to an increase in SCFA production and increase in colonic acidity [29].

The reasons for the pH gradient in the SI are not clear, and seem to be contrary to what would be expected from bacterial concentration along the SI. Previous studies have shown that the concentration of bacteria along the gut increases distally. The concentration of gut bacteria rises exponentially from the often sterile duodenum and jejunum with a concentration from  $0^0$ - $10^4$  organisms per mL to  $0^0$ - $10^5$  organisms per mL in the proximal ileum,  $10^5$ - $10^8$  in the terminal ileum and  $10^{10}$ - $10^{12}$  in the cecum [30-32]. One would expect that greater bacterial counts and fermentation of luminal contents distally would result in a gradual decrease in pH, rather than increase in pH along the SI. The gradient itself however might be of importance as pH is an important factor in bacterial metabolic pathways, as well as targeted drug delivery to the SI by preparations that are pH dependent.

There is evidence that gut microbiota plays a role in the symptomatology of IBS. Treatment with antibiotics results in a significant improvement in symptoms during therapy, and more importantly, the beneficial effect is sustained following cessation of therapy [5,17]. Patients with IBS also have a higher prevalence of both abnormal lactulose and glucose breath tests [33]. The comparison between patients with abnormal vs. normal LBT showed no significant difference in pH profile along the SI between the two groups. There was a consistent trend toward a lower pH, in all intestinal quartiles, in those with abnormal LBT, perhaps suggesting the presence of larger bacterial counts in patients with positive test, resulting in more fermentation. The lack of significant difference may be due to a small sample size resulting in a type II error.

Results of SI transit in IBS patients are inconsistent and our results show no significant difference in SITT and GET between the IBS and control group [3,10]. The lack of difference may relate to the different techniques used to assess transit (labeled meal and LBT vs. the transit on an inert object such as the Smart Pill).

There are some limitations of our study that deserve comment. One obvious limitation is the small sample size. The use of lactulose given, which has been reported to cause acidification of luminal pH, may also have affected our pH recordings [21,34]. While lactulose has been shown to accelerate SITT, it was given after the capsule entered the SI, and hence it is possible that the capsule remained ahead of the lactulose during transit. Moreover, since both control and IBS subjects followed the same protocol, one would expect a potential effect of lactulose to be comparable among both groups.

In summary, this is the first study to evaluate the SI intraluminal pH in IBS subjects. Our study found a gradual rise in pH distally along the SI in both IBS and healthy subjects, with no significant difference between the groups. Moreover, we observed no significant difference in the SI pH profile in subjects with abnormal vs. normal breath test, although a

trend towards a lower pH in subjects with an abnormal breath test was noted. Further research may be needed to assess the effect of excess bacteria in the SI on intestinal luminal pH in patients with IBS.

### Summary Box

#### What is already known:

- Previous studies have described the pH changes along the gut in healthy subjects
- These studies showed a gradual rise in the pH from the duodenum to the terminal ileum followed by a sharp descent in the cecum pH and a gradual rise along the remainder of the colon to the rectum

#### What the new findings are:

- The study results showed a gradually less acidic pH of the small bowel distally in all subjects but failed to find a significant difference in the pH profile between IBS subjects and healthy controls

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