

Chapter 2

ABNORMALITIES OF LEFT COLONIC MOTILITY IN AMBULANT NON-CONSTIPATED PATIENTS WITH IRRITABLE BOWEL SYNDROME

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ABSTRACT

Objective: To evaluate left-colonic motility patterns recorded under physiological conditions during 24 hours in fully ambulant non-constipated IBS patients compared to healthy controls.

Methods: 42-hour manometry of the left colon was performed in 11 non-constipated IBS patients and 10 age/sex-matched healthy volunteers. On day 1 a 6-channel, 10-cm interval, solid-state catheter was positioned. Frequency, amplitude and motility index (MI) of segmenting pressure waves in the descending and sigmoid colon were calculated during the 24-hour study period on day 2. HAPCs were identified visually and their characteristics were calculated.

Results: In IBS patients a higher frequency of segmenting pressure waves was observed in the sigmoid colon compared to the descending colon ($p=0.006$). In contrast, no regional differences were observed in controls. Awakening ($p=0.048$) as well as having a meal ($p=0.024$) was associated with a smaller increase of contraction frequency in the descending colon of IBS patients compared to controls.

HAPCs occurred more frequently in IBS patients than in controls ($p=0.035$). HAPCs in IBS patients reached a more distal colonic level and occurred more frequently in clusters. Defecation in IBS patients, but not in controls was always preceded by a cluster of HAPCs.

Conclusion: Left colonic segmenting pressure waves and HAPC characteristics are altered in non-constipated IBS patients.

INTRODUCTION

Although the pathogenesis of irritable bowel syndrome (IBS) is still poorly understood altered small intestinal and colonic motor function and visceral hypersensitivity have been shown to be important etiological factors.¹ It has been shown that various stimuli, such as a meal, cause an exaggerated or prolonged distal colonic motility response in IBS patients.²⁻³ Several publications suggested that the incidence of colonic segmenting contractions is increased in constipation-predominant IBS and decreased in diarrhoea-predominant IBS.⁴⁻⁶ In patients with diarrhoea-predominant IBS a trend towards an increased number of propagated contractions was observed, while in idiopathic constipated patients a decreased number of High-Amplitude Propagated Contractions (HAPCs) was found.⁷⁻⁸

The findings mentioned above seem to correlate with the observations made in transit studies. Using scintigraphic techniques, accelerated transit through the ascending and transverse colon was observed in non-constipated IBS-patients and increased whole gut transit time in constipated IBS patients.⁹⁻¹⁰

However, human colonic motility is markedly different during sleep and in the awake state, and meals are known to be an inconsistent stimulus. Moreover, HAPCs are infrequent events that require prolonged manometric recordings to be identified.¹¹ Patients suffering from the irritable bowel syndrome have symptoms that may vary over time, in severity and character. A laboratory setting might influence symptoms and motility in IBS patients and volunteers.¹²⁻¹⁴

All previously published studies on colonic motility in IBS patients were performed in a laboratory setting, during a relatively short period of time, and / or shortly after a total colonic lavage or focussed on a small segment of the left colon.^{2-7 15 16} Only one prolonged ambulant manometry study was performed in IBS patients with constipation-predominant type and alternating bowel habits.¹⁷

Therefore we have evaluated left colonic motility patterns in fully ambulant IBS patients who were non-constipated, compared to healthy volunteers under near physiological conditions during a 24-hour manometry study.

The aim of the study was to detect differences between non-constipated IBS patients and controls in left colonic motility, in colonic response to physiologic stimuli, and in the incidence and characteristics of HAPCs.

METHODS

Subjects

IBS patients were recruited from the outpatient clinic of the department of Gastroenterology of the University Medical Center Utrecht. After exclusion of organic disease, subjects who fulfilled "Rome I" criteria for IBS and were not constipated were enrolled. Non-constipated was defined as having a mean stool consistency of ≥ 2.5 on a five-point scale (1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery). Age- and sex-matched healthy volunteers were recruited by advertisement and from our own files. Written informed consent was obtained from each subject and the Ethics Committee of the University Medical Center Utrecht approved the study protocol.

Study protocol

During 5 days preceding placement of the manometry catheter all subjects recorded defecation frequency and stool consistency in a diary. Colonic motility was studied using a 6-channel, 10-cm interval, solid-state catheter (Sentron, Roden, The Netherlands). On day 1 at 1.00 PM the left colonic region was cleaned by means of administration of an enema (Driehoek zeep in 2L water, Hartman Intradal B.V., Veenendaal, The Netherlands). Thereafter the manometric catheter was placed endoscopically. The procedure was performed without sedation and with minimal insufflation of air. The tip of the manometric catheter was grasped by a snare inserted into the colonoscope and the endoscope was introduced until the tip of the catheter had reached the splenic flexure. After removal of the endoscope, the catheter was pulled back under fluoroscopic control until the distal sensor was located in the rectosigmoid, 10 cm above the anal verge, and the most proximal sensor was in the distal transverse or proximal descending colon. The catheter was then secured to

the peri-anal skin with tape. The catheter was connected to a portable data logger with 4Mb of random access memory (MMS, Enschede, The Netherlands) using a sampling rate of 4 Hz for each of the six channels.

After placement of the catheter and start of the recording the subjects went home. Subjects were requested to maintain their normal daily routines as much as possible with the exception of performing strenuous exercise. During the manometric study subjects used a standard diet (see below). Smoking, drinking alcohol or coffee was prohibited for 24 hours prior and during the manometric study. All subjects were asked to register the time of awakening, the start and end of a meal, the feeling of urge or defecation and the time of retiring to bed by pushing an event marker on the data logger and by making a note in a diary.

Colonic pressures were recorded continuously for 42 hrs from 3.00 PM on day 1 until 9.00 AM on day 3. On day 3, the subjects returned to the gastrointestinal research lab. The position of the catheter was checked fluoroscopically. Thereafter the catheter was removed and data were transferred from the data logger to a personal computer.

Standardised Meals

During the manometric study the subjects used a standard diet. On day 2 a breakfast was taken containing 2218 kJ; protein 25 g, carbohydrate 53 g and fat 24 g. Lunch on day 2 consisted of chicken and rice and contained 2270 kJ; protein 30 g, carbohydrate 60 g, fat 20 g and 200 ml water. The evening meal contained 2370 kJ; protein 26 g, carbohydrate 60 g, fat 25 g.

On day 3 a breakfast as on day 2 was taken. Because of the home or work environment in which the ambulatory manometry was carried out no effort was made to fully synchronise the times of meal consumption in all subjects.

Analysis of manometric data

The motility data recorded on day 2 were analysed, i.e. from midnight on the day the catheter was positioned (day 1) until 24 hours later.

Colonic motility recordings were considered a failure when more than one of the 6 manometric sensors had failed or when less than 24 hours of continuous colonic motility had been recorded. Manometric data were analysed both visually and automatically using a dedicated computer program. Visual analysis was used to detect HAPCs and measure their characteristics (see below). The software calculated frequency, amplitude and motility index ($MI = \ln((n \times \Sigma \text{ amplitudes (in kPa)}) + 1)$) of all pressure waves detected at the 6 pressure sensors after baseline correction and elimination of artefacts.¹⁸

Analysis of segmenting pressure waves

In the final analysis of the segmenting pressure waves two pressure signals were selected, one from the sigmoid colon and one from the descending colon. This was done on the basis of fluoroscopic images obtained before and after the recording period.

For an *overall analysis* of 24-hour segmenting colonic motility the signals recorded on day 2 were divided into 24 successive one-hour blocks for which mean pressure wave frequency, amplitude and MI were calculated (descending and sigmoid colon).

For an analysis of *night-time colonic motility* a 6-hour night-time stretch was taken that ended 1 hour before awakening. Mean frequency, amplitude and MI were calculated for this 6-hour period. This was done on the basis of the subjects' individual times of awakening.

To study *day-time interdigestive* colonic motility the 2-hour pre-lunch period was analysed (120-0 minutes before the start of lunch).

The effect of *awakening* on colonic motility was studied by comparing signals recorded during the first 30 minutes after awakening with those recorded in a 30-minute period at night (150-120 minutes before awakening). None of the subjects started breakfast within the first 30 minutes after awakening.

The effect of *lunch* on colonic motility was studied by analysing three consecutive 30-minute periods; a preprandial period, an early postprandial and a late postprandial period. This was done on the basis of the subjects' individual times of lunch consumption.

High-Amplitude Propagated Contractions

HAPC characteristics that were recorded during day-time on day 2 (defined as the period that started when the subject arose in the morning and ended when the subject went to bed in the evening) were used for subsequent analysis. HAPCs were defined as pressure waves that propagate distally across at least 3 sensors, with a propagation rate of more than 0.3 cm/sec and an amplitude of at least 13.3 kPa (100 mmHg) in 2 sensors and at least 10 kPa (75 mmHg) in one other sensor. After identification of the HAPCs, their amplitude, duration, propagation velocity, propagation distance, site of origin and site of extinction were calculated in each subject.

Clustered HAPCs were defined as HAPCs preceded or followed by another HAPC within a time window of 3 minutes.

In addition, it was determined whether HAPCs were related to waking up, to a meal or to defecation. An HAPC was considered related to awakening when it occurred within 30 minutes after awakening. A meal-related HAPC was defined as one occurring within 60 minutes after the start of a meal. An HAPC was considered related to defecation when it preceded a bowel movement within 15 minutes.

Statistical analysis

Results are expressed in the text as mean \pm SEM.

The mean stool frequency and mean stool consistency, derived from the diary data, were analysed for group differences by unpaired Student t-tests.

To analyse differences in 24-hour motility variables between groups and between the two colonic levels within groups a General Linear Model for Repeated Measures (SPSS 7.0) was used. Motility variables in the subperiods (night-time, day-time interdigestive, effect of awakening and lunch) were compared using an unpaired Student t-test. Differences in motility variables derived from the two colonic levels studied were tested by paired t-tests.

RESULTS

Study group

Thirty subjects (15 patients, 15 age/sex-matched volunteers) were included in the study. In two volunteers and one patient the manometric catheter could not be positioned satisfactorily. In 3 volunteers manometric data were considered insufficient because of failure of more than one transducer. Two patients had a catheter expulsion on day 2. In one patient the second recording period was stopped prematurely due to peri-anal pain. Finally, 11 patients with IBS (5 M, 6 F; age: 37.6 ± 2.5 yr) and 10 healthy age- and sex-matched volunteers (4 M, 6 F; age: 38.0 ± 3.1 yr) were studied successfully. After a mean duration of monitoring of 40.8 ± 1.0 hr, fluoroscopic screening in the morning of day 3 revealed no major dislocation of the catheter. In all subjects at least one sensor was in the descending colon and the distal sensor was still in position (10 cm above the anal verge) on day 3.

Stool frequency and stool consistency

A trend towards a higher mean daily stool frequency was observed in the IBS patients (2.3 ± 0.5 versus 1.3 ± 0.1 , $p=0.072$; range: 0.8-5.6 in IBS versus 1.0-1.6 in controls). The mean stool consistency score was significantly higher in IBS patients than in healthy volunteers (3.3 ± 0.1 versus 2.9 ± 0.07 , $p=0.023$; range: 2.6-4.1 in IBS versus 2.3-3.0 in controls).

Colonic Motility

24-Hour motility

Overall 24-hour frequency, amplitude and motility index (MI) in IBS patients were not significantly different from those in controls, although amplitude ($p=0.092$) and motility index ($p=0.095$) in the sigmoid colon tended to be higher in IBS patients.

In IBS patients a significantly higher contraction frequency ($p=0.006$) and MI ($p=0.018$) was observed in the sigmoid colon compared to the descending colon. In contrast, no regional differences were observed in the healthy volunteers (Figure 1).

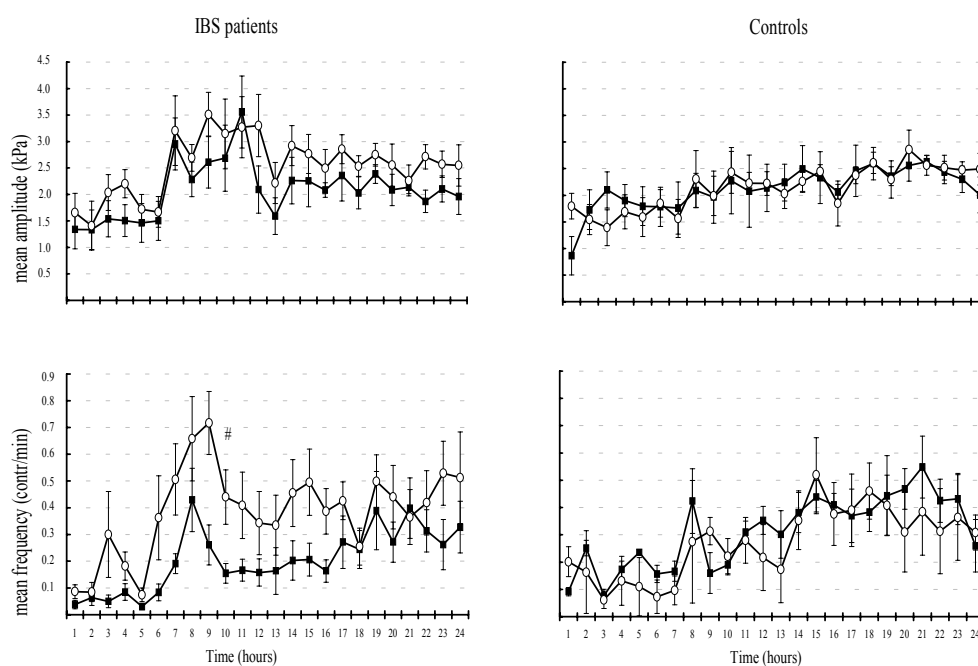


Figure 1. Frequency and amplitude of pressure waves in IBS patients and controls in the descending colon (closed rectangles) and sigmoid (open circles). In IBS patients frequency of contraction is higher in the sigmoid colon than in the descending colon (# $p=0.006$).

Motility at night

Analysis of colonic motility recorded during the night revealed no differences between IBS patients and controls.

In IBS patients a significantly higher frequency of contraction ($p = 0.029$) was recorded in the sigmoid colon compared to the descending colon, while no regional differences were observed in the controls (Table1).

Table 1: Segmenting colonic motility in total 24-hour period, at night and in the interdigestive period (mean \pm s.e.m.).

		Patients		Controls	
		Descend. Colon	Sigmoid Colon	Descend. Colon	Sigmoid Colon
24 hours	Frequency (/ min)	0.21 \pm 0.04	0.39 \pm 0.05 ^a	0.31 \pm 0.09	0.27 \pm 0.06
	Amplitude (kPa)	2.63 \pm 0.12	2.98 \pm 0.14	2.46 \pm 0.07	2.57 \pm 0.16
	Motility Index	11.87 \pm 0.50	13.56 \pm 0.28 ^b	12.54 \pm 0.49	12.36 \pm 0.52
Night	Frequency (/ min)	0.11 \pm 0.03	0.24 \pm 0.07 ^c	0.16 \pm 0.08	0.13 \pm 0.06
	Amplitude (kPa)	2.00 \pm 0.22	2.28 \pm 0.10	1.92 \pm 0.22	1.90 \pm 0.25
	Motility Index	6.93 \pm 0.93	8.21 \pm 0.99	7.57 \pm 0.79	6.76 \pm 0.95
Interdigestive	Frequency (/ min)	0.23 \pm 0.08	0.34 \pm 0.11	0.37 \pm 0.09	0.24 \pm 0.07
	Amplitude (kPa)	2.79 \pm 0.52	3.20 \pm 0.41	2.63 \pm 0.18	2.39 \pm 0.20
	Motility Index	6.17 \pm 0.94	7.37 \pm 0.71	7.66 \pm 0.74	6.70 \pm 0.69

a + b = sigmoid versus descending colon in IBS patients: ^a; p = 0.006, ^b; p = 0.018.

^c = sigmoid versus descending colon in IBS patients: ^c; p = 0.029.

Effect of awakening

Both in IBS patients and in controls awakening significantly increased the frequency of contraction as well as the MI. However, the increase in contraction frequency upon awakening in the descending colon was significantly lower in IBS patients than in controls (p = 0.048).

No significant differences in change of amplitude or MI were found between different groups or colonic regions (Figure 2).

Effect of lunch

In IBS patients lunch did not affect frequency and amplitude of contraction in descending or sigmoid colon. In healthy volunteers lunch significantly increased frequency of contraction (p=0.049) and MI (p=0.023) in the sigmoid colon but not in the descending colon.

IBS patients had a lower postprandial frequency of contraction and MI in the descending colon than controls, during both the early ($p=0.024$, $p=0.038$) and late postprandial periods ($p=0.014$, $p=0.009$).

In the total periprandial period (90 min) the frequency of contraction in the descending colon of IBS patients was significantly decreased compared to controls ($p = 0.030$). The MI in patients was significantly lower in the descending compared to the sigmoid colon ($p = 0.013$) (Figure 3).

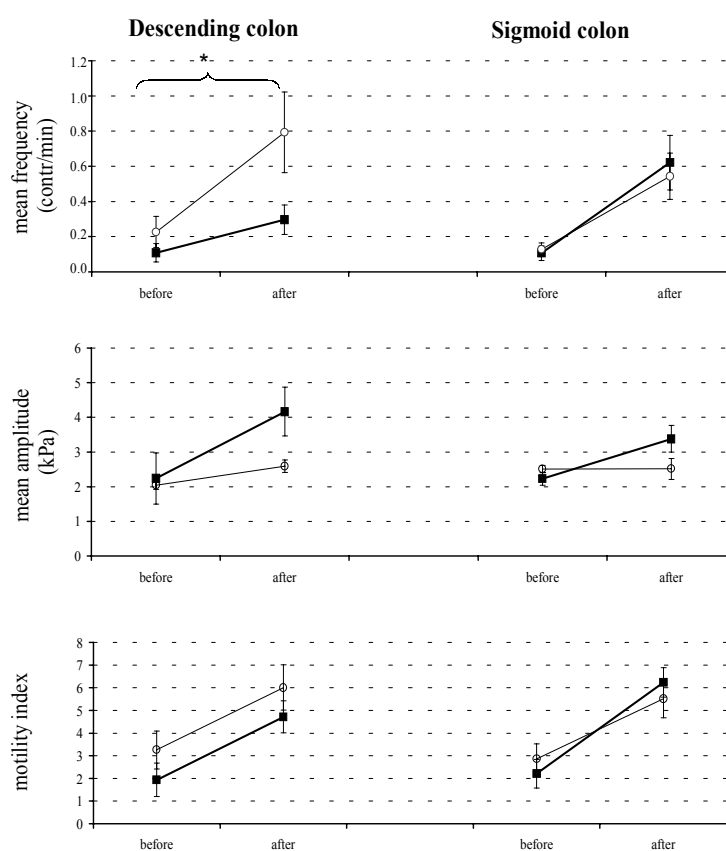


Figure 2. Effect of awakening on left colonic motility in IBS patients (closed rectangles) and controls (open circles) in descending and sigmoid colon. A decreased post awakening increase of frequency of contraction in the descending colon in IBS patients (* $p=0.048$).

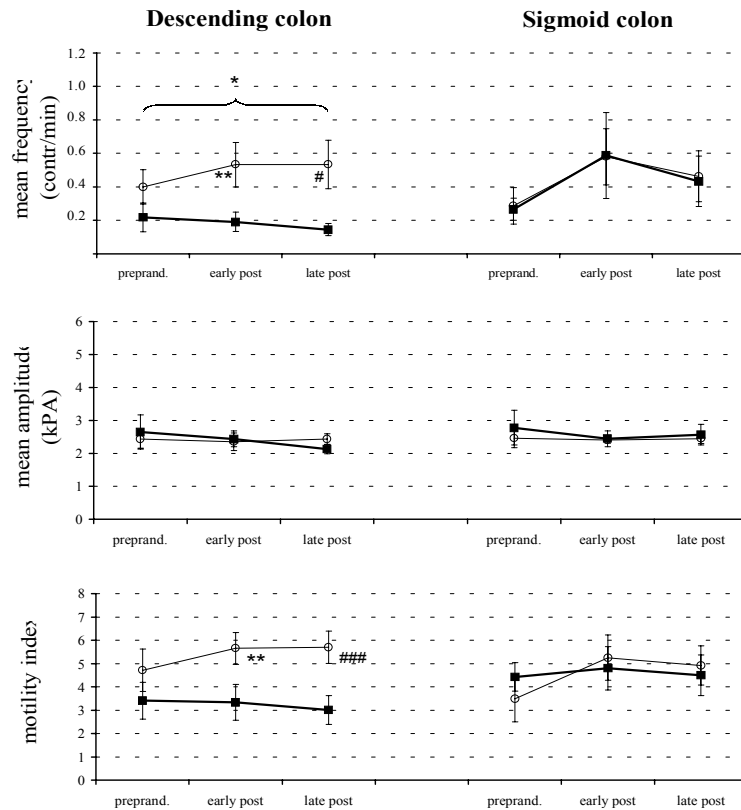


Figure 3. Effect of lunch on left colonic motility in IBS patients (closed rectangles) and controls (open circles) in descending and sigmoid colon.

Frequency of contraction. A decreased postprandial response of frequency of contraction in the descending colon (* p=0.030; ** p=0.024; # p=0.014).

Motility Index. Decreased postprandial motility indices in IBS patients in the descending colon (** p=0.038; ### p=0.009).

High-Amplitude Propagated Contractions

General characteristics

In the 21 subjects a total of 159 HAPCs were observed. 98 % of the HAPCs occurred while the subjects were awake. Only 3 HAPCs occurred during night-time; one volunteer had 2 HAPCs and one patient had 1 HAPC. The awake period on day 2 was 16.1 ± 1.1 h for IBS patients and 14.4 ± 2.4 h for controls. During this awake period the number of HAPCs was greater in the IBS patients than in the control group (10.0 ± 1.9

versus 4.6 ± 1.4 , $p=0.035$). This difference appeared to be caused by a greater number of HAPCs observed in the first half of the day in the IBS patients (patients versus volunteers: first half day: 8.3 ± 1.7 versus 2.7 ± 0.8 , $p=0.012$; second half day: 1.7 ± 0.6 versus 1.9 ± 0.6).

No differences between patients and controls were found in velocity, amplitude, duration or propagation distance of HAPCs (table 2).

Table 2: HAPC characteristics (mean \pm s.e.m.)

	Total Period	
	Patients	Controls
Number	10.0 ± 1.9	4.6 ± 1.4^a
Velocity (cm/s)	1.3 ± 0.0	1.3 ± 0.1
Amplitude (kPa)	24.8 ± 1.6	20.6 ± 1.6
Duration (sec)	16.3 ± 0.9	15.9 ± 1.0
Prop. Dist. (cm)	28.9 ± 1.8	27.2 ± 2.1

^a = IBS patients vs controls ; ^a : $p = 0.035$

21 % Of HAPCs in patients and 8 % of HAPCs in volunteers were related to getting up (ns). 33 % Of HAPCs in IBS patients and 16 % of HAPCs in healthy volunteers were related to defecation (ns). The percentage of meal-related HAPCs was 27 % in IBS patients and 24 % in controls.

HAPCs extinguished more distally in IBS patients. In IBS patients 94 % of HAPCs propagated to or beyond the sensor at 30 cm from the anus while in healthy volunteers only 60 % of HAPCs reached this level ($p=0.046$). In IBS patients 79 % of HAPCs propagated to the distal 20 cm of the left colon while only 44 % of HAPCs in controls reached this distal region ($p=0.036$) (Figure 4 and 5)

Clustered HAPCs

The total number of clusters was significantly greater in IBS patients than in healthy volunteers (2.8 ± 0.7 versus 1.0 ± 0.4 , $p = 0.031$). The number of HAPCs / cluster was similar in patients and controls (2.6 ± 0.2 versus 2.5 ± 0.5). All 12 bowel movements in

6 IBS patients and all 4 bowel movements in 4 healthy volunteers were preceded by one or more HAPCs. In the IBS patients all stools were preceded by a cluster of HAPCs. Of the control group three stools were preceded by single HAPCs and only one stool was preceded by a cluster of 7 HAPCs.

The other characteristics of clustered and non-clustered HAPCs were similar in IBS patients and controls except for a significantly higher peak amplitude of clustered HAPCs in IBS patients (25.3 ± 1.9 kPa versus 20.0 ± 1.0 kPa, $p = 0.031$).

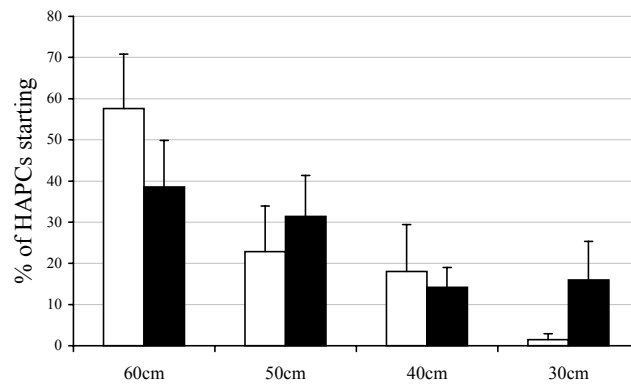


Fig. 4

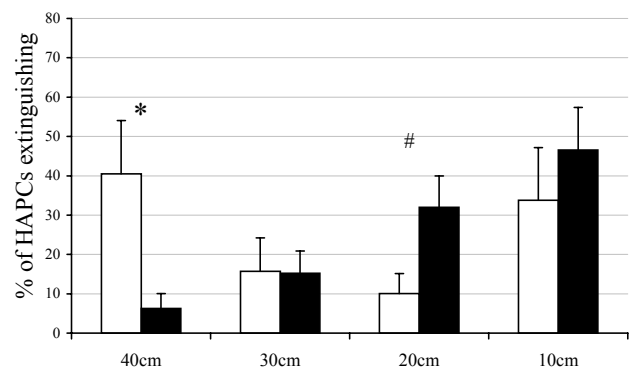


Fig. 5

Figure 4 and 5. Percentages of HAPCs starting and extinguishing on different colonic levels levels (cm proximal from anal verge) in IBS patients (solid bars) and controls (open bars). Higher percentage of HAPCs extinguishes in controls at 40cm compared to IBS patients (* $p=0.021$). Higher percentage of HAPCs extinguishes in IBS at 20 cm compared to controls (# $p=0.043$).

DISCUSSION

In the present study we used a prolonged ambulant manometric technique that allowed us to record motility and infrequent colonic events such as High-Amplitude Propagated Contractions after an adequate accommodation period of more than 10 hours, allowing refilling of the colon. We have used a low concentrated soap enema to clean the left side of the colon more than 10 hours before the 24 hour study period started. From human studies it is not known whether “normalisation” of colonic motility after bowel preparation and catheter placement in IBS patients is any different from healthy volunteers. The manometry catheter used had enough flexibility to follow the sigmoid curves and had enough stiffness not to be wrapped distally. The minor catheter tip dislocation downwards in some subjects was the result of remodelling of the colon on the catheter rather than expulsion of the catheter.

The IBS patients studied were not constipated, based on stool consistency score; a simple way to exclude constipated patients used in every day clinical practice.⁹ Our study contained a mixture of IBS patients with predominantly diarrhoea and patients with near normal soft stools. Of the IBS patients, four had frequent loose stools and were actual diarrhoea-predominant IBS-patients. Subgroup analysis was not done because of small numbers. Volunteers were age-and sex-matched. All subjects performed their usual daily activities in their usual environment, without having to adhere to a strict time schedule or laboratory setting.

In both study groups there were five smokers. They were not allowed to smoke cigarettes during the study which might have caused a certain amount of stress. However, these numbers were well balanced and we think that the request not to smoke during the study period did not influence the study results.

In our study we showed that the descending colon in non-constipated IBS patients has a lower overall frequency of contraction and motility index than the sigmoid colon, whereas healthy controls did not show regional differences in left colonic motility. In response to known colonic stimulants like getting up or having a meal, the non-constipated IBS patients had a significantly decreased response of frequency of

contraction and motility index in the descending colon as compared to healthy volunteers. Furthermore, IBS patients had a significantly decreased response of motility in the descending colon compared to their own sigmoid region. No significant differences were found in the mean pressure amplitudes in the two colonic regions or study groups postprandially or after awakening.

Earlier manometric studies of the postprandial response of the colon in IBS were limited to the sigmoid region and were carried out in unselected IBS patients. They showed an increased motility index in basal condition and after a stimulus.^{2 4 5 7} In a group of non-constipated IBS patients a decreased response of the descending colon to a meal was demonstrated by Vasallo et al..⁷ However, the preprandial motility index was higher in patients than in volunteers, the sigmoid colon was not studied and the study was performed in laboratory conditions. Bazzocchi et al. studied patients suffering from functional diarrhoea (not IBS patients) with increased motility indices in the descending colon compared to the transverse and sigmoid colon and observed a decreased postprandial colonic motility response in all three regions.¹⁶ A study recently published by Cole et al. in four small subgroups of IBS demonstrated higher study segment activity index and amplitudes in “spastic colon syndrome” than in “diarrhoea-predominant spastic colon” in the postprandial period (15-50cm from anus).⁶

We believe that our findings on left colonic segmenting pressure waves are in accordance with the earlier findings in IBS patients. However, our study demonstrates that important regional and diurnal differences exist in left segmenting pressure waves in non-constipated IBS patients. These regional differences underline the importance of checking the location of the used pressure ports during manometry studies.

HAPCs are thought to be the major motility pattern in the colon producing substantial transport distally over long distances.^{16 17 19-24} They appear to be necessary for normal bowel habits.^{20 23} A recently published study by Cook et al. in healthy volunteers showed that most movements of colonic content are related to pressure waves and that the effectiveness of transport by a propagating pressure wave sequence is influenced by its site of origin, amplitude and velocity.²⁴

We used a definition of HAPC that disqualified many pressure waves with intermediate amplitude. This may account for the differences in the number of HAPCs in our control group, compared to some other studies of colonic motility.^{7 22} Bazzocchi et al. showed that HAPCs occurred more frequently and propagated into the sigmoid region more often in patients suffering from functional diarrhea. In these patients HAPCs were the major propulsive force, propelling significantly more scintigraphic tracer than in healthy subjects. However, these patients were not suffering from IBS.¹⁶ Bassotti et al. found no significant differences in the number and characteristics of HAPCs in IBS patients with constipation-predominant or alternating bowel habits and controls.¹⁷

Our results show that in non-constipated IBS patients the number of HAPCs and their velocity is increased during the first half of the day. Clustered HAPCs were frequently observed in the non-constipated IBS patients and were related to all of the 12 bowel movements occurring in 6 IBS patients during the study-period. In contrast, in the control group only one out of 4 stools produced by 4 subjects was preceded by a cluster. Furthermore, the HAPCs in IBS patients more often reached the lower sigmoid level than HAPCs in controls which regularly extinguished in the descending colon.

We believe that these changes in HAPC number and characteristics may account for the higher stool frequency and soft stools as was observed in our non-constipated IBS patients. The higher number and velocity of HAPCs during the first half of the day may cause IBS patients to complain from stools in rapid succession during morning hours.

In summary, this study has shown that in non-constipated IBS patients, phasic motility of the left colon is different from that of healthy controls, with increased contractile activity of the sigmoid and decreased responsiveness of the descending colon. Furthermore, our results show that in non-constipated IBS patients HAPCs occur more frequently, occur more frequently in clusters, and propagate more distally. These abnormal left colonic motility patterns may contribute to the IBS symptoms observed in this patient group.

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