COLONIC SENSORY AND MOTOR FUNCTION IN IRRITABLE BOWEL SYNDROME AND DIVERTICULAR DISEASE

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SENSORISCHE EN MOTORISCHE FUNCTIE
VAN HET COLON
BIJ HET PRIKKELBAAR DARM SYNDROOM
EN DIVERTICULOSIS

(met een samenvatting in het Nederlands)

Proefschrift

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Voor mijn ouders

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Chapter 1

GENERAL INTRODUCTION

NORMAL MOTOR AND SENSORY FUNCTIONS OF THE COLON

The colon is the final organ in the gastrointestinal tract and it has the important role to determine frequency, consistency, and volume of stools and to maintain continence. In order to have adequate function, the motor and sensory activities of the colon have a number of tasks to perform:

1) mixing of the contents in order to facilitate transmural exchange and transport of water and electrolytes;
2) transport of colonic contents in a net aborad direction;
3) storage of the feces up to the time of voluntary evacuation;
4) perception of volume and nature of the contents of the rectum
5) rapid emptying of at least part of the colon at a socially convenient time.

Intestinal musculature behaves like an auto-excitable electrical syncytium consisting of interstitial cells of Cajal (ICCs) functioning as pacemakers, integrated within the bulk of musculature which generates forces for propulsion.[1] Throughout the gut, the muscle consists of circular and longitudinal layers. In the colon, the inner circular muscle is arranged in a tight spiral while the outer longitudinal muscle is concentrated into three bands, the taeniae. The colon can enlarge its lumen by relaxing its circular muscle thus ballooning out the haustra; it can form a narrower, triangular lumen by contracting circular muscle between the taeniae in ‘semilunar folds’ that act as functionally mobile mucosal indentations. Variations in cross-sectional diameter of the lumen propel the fecal bolus requiring very little muscular effort.[2]

Lining the bowel wall, the enteric nervous system (ENS) coordinates colonic motility and modulates visceroperception like a minibrain, able to function independently of extrinsic nervous connections. Three functional categories of neurons can be identified in the ENS. Sensory neurons with receptor regions are specialized for detecting thermal, chemical or mechanical stimuli and transform these into signals transmitted to other points in the nervous system. Mechanoreceptors are located in the mucosa, musculature,

serosal surface and mesentery and give information to the ENS on stretch-related tension and muscle length in the colonic wall, on the movement of luminal contents as they brush the mucosal surface and under pathological circumstances when mesenteric receptors are stimulated for gross movements of the organ.
It is still uncertain whether neuronal cell bodies of mechanoreceptors belong to dorsal root ganglia, enteric ganglia, or to both. Secondly, interneurons connected into networks, process sensory information and control the behavior of motor neurons. These neurons form integrative or reflex circuits that organize reflex responses to sensory inputs. Thirdly, motor neurons form the final common pathways for transmission of control signals to the effector systems: the muscle cell, secretory gland and blood vessel.
The autonomic nerve system (ANS) provides the pathways for input from the central nerve system to the ENS and for reflex actions, whereas the central nerve system (CNS) has a modulating function on colonic motor activity and sensory function and plays a role during voluntary defecation.[1]

More than 30 neurotransmitters released from nerves, endocrine-paracrine cells, and glands play a role in regulation of muscle contraction and inhibition.
5-Hydroxytryptamine (5-HT) plays an important role in the regulation of gastrointestinal motility and perception.[3] The largest pool of 5-HT in humans is concentrated in the gut, predominantly within the mucosal enterochromaffin cells and to a lesser extent, within those neurones that use 5-HT as a neurotransmitter.[4]

Phasic colonic motility, defined as colonic muscle contractions of short duration, is usually investigated by colonic manometry. Two types of catheters can be used: water-perfused and solid-state. A water-perfused catheter has the disadvantage that it requires a water pump system, thus making it unpractical for ambulant recordings. However, most studies on colonic motility were performed with this kind of catheter. Earlier studies were confined to the rectosigmoid region but after improvements of colonoscopic techniques, perfused catheters were placed into the mid and proximal

colon.[5-7] Miniaturized perfused catheters have recently been passed trans-nasally to reach the unprepared distal colon in healthy subjects within 24-30 hours. They are well tolerated for long periods and may improve spatial resolution of motor patterns using a high number of closely spaced recording sites.[8 9]

Solid-state catheters can be used with electronic data storage equipment allowing prolonged, ambulant registration. Current limitations of solid-state ambulatory colonic manometry are its high cost, catheter and pressure transducer fragility and inability to record from a large number of closely spaced recording sites.[10]

Disadvantages of trans-anal methods of catheter placement are the need for bowel preparation, colonoscopy and the risk of catheter displacement. One might expect that bowel preparation and colonoscopy, combined with sedation and refilling of the colon may have its effects on bowel motility recordings, when started shortly thereafter. However, a recent study showed motor activity not to be different between the uncleansed and cleansed colon, except for the infrequent high-amplitude propagated pressure waves, which occurred more frequently in the cleansed colon.[8] Catheter displacement is a problem that can be solved by clipping the catheter tip to the colonic wall or by using a rather rigid catheter that is adequately fixed to the perianal region.[11]

The predominant pressure pattern observed throughout the human colon is sporadic, phasic activity. This type of colonic motility does not seem to be highly organized. Propagation, if any, is over short distances only, in either direction. Probably this phasic activity causes to-and-fro motion of colonic content over short distances or retardation of colonic flow.[5 12] Prolonged colonic motility studies revealed that colonic motor activity is low before meals and minimal during sleep and increases significantly after meals and upon awakening in the morning.[7]

The best recognized colonic motor pattern is the high amplitude propagated contraction (HAPC) also known as high amplitude propagated pressure wave (HAPPW). Depending on definition, HAPCs occur infrequently (6-12 times in 24 hours) and seldom at night. HAPCs are related to the feeling of urge and defecation and have a maximum frequency after awakening and after a meal.[7-10 12 13] Recently, a study combining scintigraphy and pancolonic manometry demonstrated that most movements

of colonic content are related to propagated pressure waves. However, 86% of propagating sequences originating in the caeco-ascending colon were propulsive, whereas only 30% of propagating sequences originating at or distal to the hepatic flexure were propulsive. The effectiveness of transport increases with raised amplitudes and slowed velocity.[14]

The composition of the meal influences colonic postprandial motility. Carbohydrate meals induce colonic motor responses, but the effects are short-lived in comparison with those of fat meals.[15] Colonic phasic motility is not affected by gender. [16]

Colonic tone is exerted by sustained muscular contraction. A change in tone leads to relatively slow changes in colonic diameter and volume. The barostat was designed to evaluate tone of a hollow organ.[17] Since 1991 it has been used to study human colonic tone.[18] The barostat consists of an air pump controlled by a computer, maintaining a constant pressure in a bag located in a hollow organ. To achieve this, the barostat aspirates or inflates air out of or into the bag, and the changes in bag volume may reflect changes in the tone of the gut. Some calculations must be performed by the system to compensate for artifacts in pressure and volume measurements. Standardization of the bag and of procedures for determination of the operating pressure as well as a constant body position are important technical issues in performing a study on colonic tone.[19]

In the fasting state, the volume of an intracolonic bag is more or less constant. Five to 20 minutes after the start of a meal the volume of the bag consistently decreases, reflecting increased tone. This increase in tone lasts up to 3 hours, and is greater in the transverse than in the sigmoid colon. During sleep colorectal tone decreases and promptly increases to baseline after awakening.[18] The tonic response to a meal is much more marked in the distal than in the proximal colon.[20] Colonic tone is not affected by gender and rectal tone is not influenced by age.[16 21]

Colonic wall compliance reflects the capacity of the colonic wall to adapt to imposed distension. To evaluate compliance, one needs to measure the volume of a distending bag at each pressure step. Compliance is defined as the ratio dV/dP, which is the slope

of the volume-pressure curve and is expressed in ml/mmHg when isobaric distensions are performed. The shape of the volume-pressure curve is usually almost linear in the range of the intermediate pressure steps but may show inflection points at lower or higher pressure steps.

Compliance is influenced by many factors, including organ capacity, bowel wall tone, contractile activity, elastic properties and surrounding anatomy. Volume-pressure relationships measured with the barostat technique reflect bowel wall compliance better than older systems using syringes and latex balloons in which the elastic properties of the distending device may also influence outcome.[22 23] Compliance should be compared between studies only when it is measured in a similar way.[24]

There is very little data available on colonic compliance in healthy subjects as measured with the barostat technique.[16 21 24-26]

Colonic sensitivity is the subjective experience of conscious perception of colonic stimuli. Under physiological circumstances the perception of urge to defecate or to deflate gas are the only consciously perceived signals from the distal gastrointestinal tract.

Nowadays, the barostat is used to determine sensory thresholds and sensitivity scores for different types of sensation. Isobaric distensions are more reproducible between laboratories and between subjects than isovolemic distensions because the pressure scale compensates for the factors influencing bag volume: bag shape, gut wall compliance, contractile activity and subject's anatomy.

Various distension protocols have been used, the two main types being continuous, cumulative distension (ramp distension) and intermittent, rapid, short-lived distension (phasic distension). With rapid phasic distensions, pain thresholds are found at significantly lower levels than with cumulative ramp distensions.[24] A simple ascending staircase distension protocol, using intermittent phasic distensions of increasing magnitude, is frequently used for measuring sensitivity threshold because the procedure is easy and fast. Due to the predictability of the distension it is somewhat vulnerable to psychological influence. However, this method has been proven to yield reproducible

results.[27] [28] Perception can be scored using a visual analog scale (VAS) assessment at every distension step. Graded linear scales give a more sensitive and accurate representation of pain intensity than descriptive scales.[29]

COLONIC FUNCTION IN IRRITABLE BOWEL SYNDROME (IBS)

IBS is a functional bowel disorder in which abdominal discomfort or pain is associated with defecation or a change in bowel habits, which has features of disordered defecation.

IBS is very prevalent in developed countries with incidence rates of >15% in adolescents and adults, and with a higher incidence in women. IBS has a chronic relapsing course and overlaps with other functional gastrointestinal disorders. It is responsible for large direct medical expenses and indirect costs, including absenteeism from work.[30] [31]

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.[32]

Colonic motility in IBS

In IBS patients various stimuli, such as a meal, cause an exaggerated or prolonged distal colonic phasic motility response in IBS patients.[33] [34] It has been suggested that the incidence of colonic segmenting contractions is increased in constipation-predominant IBS and decreased in diarrhea-predominant IBS.[35-37] In patients with diarrhea-predominant IBS a trend towards an increased number of propagated contractions was observed, while in idiopathic constipated patients a decreased number of HAPCs was found.[38] [39]

Colonic tone, measured with the barostat technique, has only been studied in diarrhea-predominant IBS patients, showing a reduced postprandial increase in tone in the descending colon.[38]

A laboratory setting may influence symptoms and motility in IBS patients and volunteers.[40-42] All previously published studies on colonic motility in IBS patients were performed in a laboratory setting, shortly after a total colonic lavage or focused on the distal colon.[33-38] Only one prolonged ambulant manometry study was performed in IBS patients with constipation-predominant type and alternating bowel habits.[43]
Information regarding phasic motility patterns under physiologic recording conditions in non-constipated IBS patients is lacking. Therefore, in this thesis we will evaluate left colonic motility patterns in fully ambulant non-constipated IBS patients and healthy volunteers under physiological conditions during a 24-hour manometry study.

Colonic perception in IBS

Abnormal visceral perception has been shown to be more prevalent in IBS, with increased sensitivity to balloon distension in small bowel, colon and recto-sigmoid region.[24 44-46] Patients with IBS have normal or even increased thresholds for painful stimulation of somatic pain receptors.[47 48]
Lowered threshold of perception raises the possibility of an increased awareness of normal or abnormal motility as a factor in the development of abdominal symptoms in IBS. Until very recently only anecdotal literature suggests an association between (abnormal) small bowel or colonic motility and symptoms.[39 49 50] Recently an association between HAPCs and abdominal cramps was found in IBS patients exhibiting pain and diarrhea. However these HAPCs were stimulated by CCK and a high-caloric meal under laboratory circumstances.[51]
The association between HAPCs and spontaneously occurring pain in IBS patients has not been studied under physiologic conditions. Therefore the existence of such an association will be explored in this thesis using prolonged ambulant manometry.

Alosetron; a new drug in IBS

New insights into the pathogenesis of IBS have lead to the development of several new agents directed against visceral hypersensitivity and / or disordered motility.

Alosetron is one of these. It is a potent and highly selective 5-HT_3 antagonist that improves abdominal pain and discomfort, urgency, stool frequency, and stool consistency in female patients with diarrhea-predominant IBS.[52-55] Alosetron increases the compliance of the descending colon and has been shown to delay transit through the colon.[56 57]

The effect of a 5-HT_3 antagonist like alosetron on phasic motility of the left colon has not yet been evaluated. In this thesis we will study alosetron's effect on colonic motility in non-constipated IBS, using ambulatory 24-hour manometry.

COLONIC FUNCTION IN DIVERTICULAR DISEASE

Diverticular disease is the most common disorder of the human colon in economically developed countries, with incidence rates increasing with age, up to 30 % above the age of 60 years.[58-61]

Diverticular disease can be categorized into three groups: asymptomatic diverticular disease (ADD) in which multiple diverticula are present but symptoms are absent, symptomatic uncomplicated diverticular disease (SUDD) in which (left) abdominal pain is present, and symptomatic complicated diverticular disease (SCDD) where hemorrhage, peridiverticulitis, abscess, perforation, fistulae and bowel obstruction has occurred.[62]

Several pathophysiologic factors leading to the disease have been proposed, among which altered motility of the large bowel and changed bowel wall characteristics.

Colonic motility in diverticular disease.

Increased phasic motility in the diverticula-bearing part of the colon is thought to promote the development of pulsion diverticula at weak points of the bowel wall. However, in many patients with uncomplicated diverticular disease, a normal motility pattern is found.[63-68] A recent study in patients with SUDD, using prolonged manometry, has shown an overall increased basal motility, a decreased colonic motor

response to eating and an increased number of (retro-)propagated high-amplitude propagated pressure waves in the affected segments.[69] A change in bowel wall structure with narrowing of the bowel lumen is thought to be another component to the development of diverticular disease.[70 71]

Although increased colonic tone has been proposed as an important factor in the development of a narrowed sigmoid lumen, no information on the role of colonic tone in diverticular disease and its relationship to phasic motility can be found in the literature. In this thesis these factors will be explored using barostat technology.

Colonic wall characteristics and visceral perception in diverticular disease.

There is no evidence of an intrinsic change in the muscle cell to account for the thickening of the muscle layers in uncomplicated diverticular disease. Rather, the amount of elastin has increased in the taeniae coli compared with normal, age-matched controls, whereas the elastin content of the circular muscle is unchanged. The shortening of taeniae leads to "upbunching" of muscle, mesentery and mucosa, narrowing of the lumen and a seemingly thicker muscle layer.[71] Thickening of bowel wall suggests a decreased compliance. However, only one study has been performed in which wall compliance and perception were examined in an unselected group of patients with symptomatic and complicated diverticular disease. That study showed a reduced resistance to distension of the sigmoid. The desire to defecate was stimulated more readily by distension of the colon than the rectum and patients with diverticular disease developed a desire to defecate more readily than normal subjects.[63] However, the techniques used, including water-filled latex balloons, are now considered to be obsolete.

In this thesis we have used the barostat as a investigational tool to assess visceral perception and colorectal wall characteristics in symptomatic and asymptomatic uncomplicated diverticular disease.

THE FOLLOWING QUESTIONS WILL BE ADDRESSED IN THIS THESIS:

1. Is phasic motility of the left colon in ambulant non-constipated IBS patients different from that in healthy controls?

2. What is the effect of the $5HT_3$ -antagonist alosetron on left colonic motility and defecation characteristics in patients with non-constipated IBS and healthy volunteers as investigated by prolonged ambulatory manometry?

3. Is there a temporal relationship between pain episodes and high amplitude propagated pressure waves (HAPPWs) in non-constipated IBS patients and healthy volunteers?

4. Is the tonic and phasic rectal and colonic motility response to a meal altered in patients with asymptomatic diverticular disease and patients with symptomatic uncomplicated diverticular disease?

5. Do patients with asymptomatic and symptomatic uncomplicated diverticular disease have abnormal colonic and rectal wall compliance and does altered colorectal visceral perception play a role?

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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.

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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 x Σ amplitudes (in kPa)) +1)) of all pressure waves detected at the 6 pressure sensors after baseline correction and elimination of artefactsk.[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 ± 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).

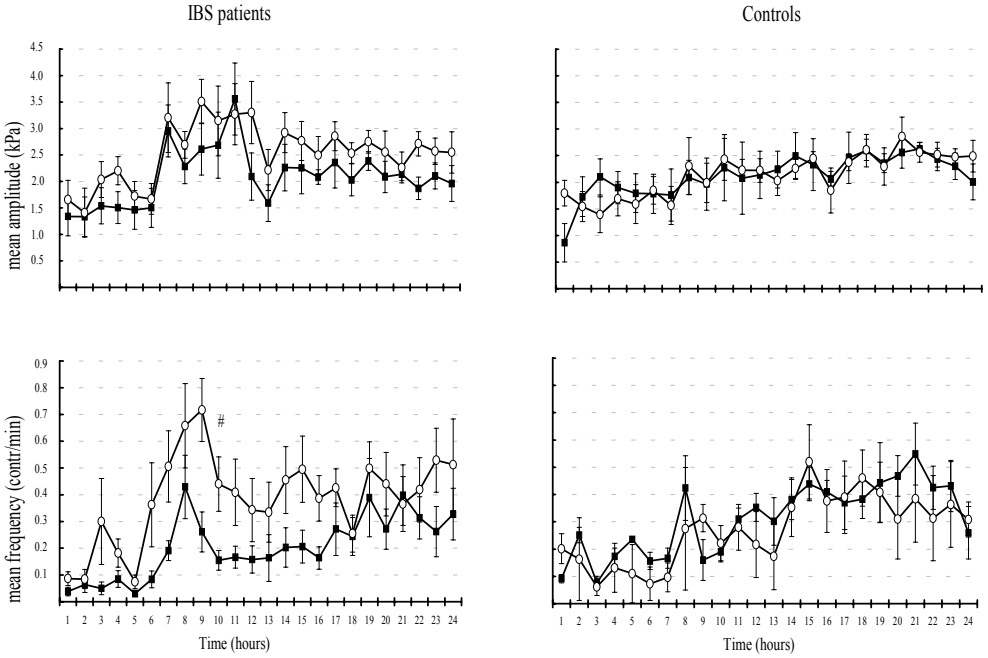

Figure 1. Frequency and amplitude of pressure waves in IBS patients and controls in the descending colon (closed rectangles) and sigmoid (open circles). In IBS patients frequency of contraction is higher in the sigmoid colon than in the descending colon (# p= 0.006).

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 ± s.e.m.).

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

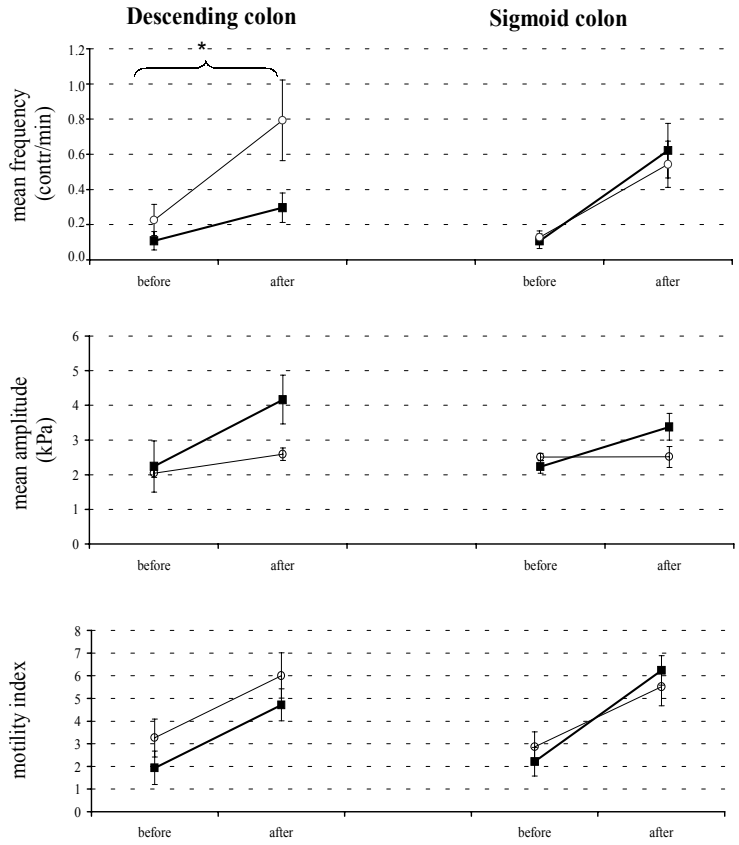

Figure 2. Effect of awakening on left colonic motility in IBS patients (closed rectangles) and controls (open circles) in descending and sigmoid colon. A decreased post awakening increase of frequency of contraction in the descending colon in IBS patients (* p=0.048).

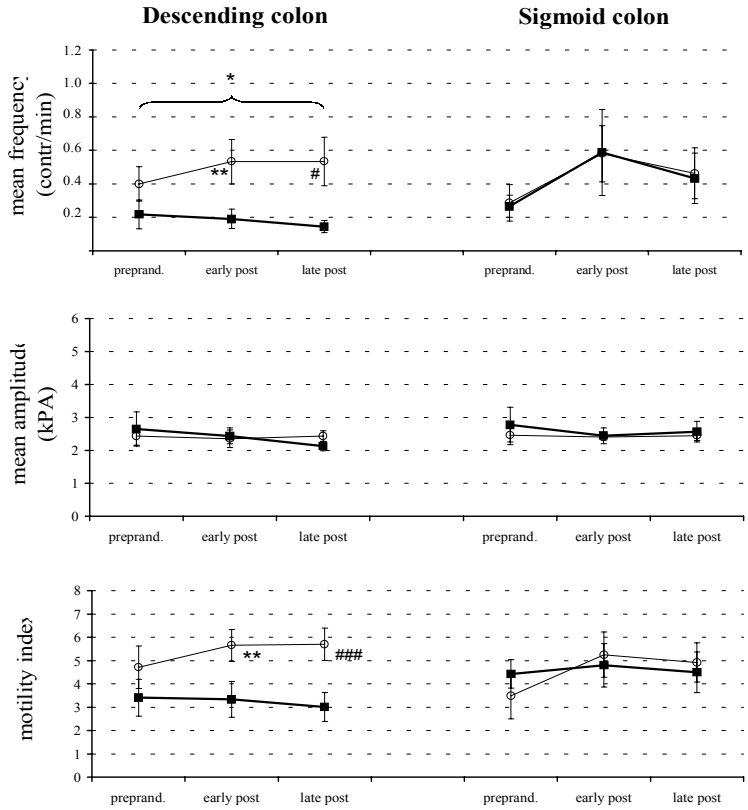

Figure 3. Effect of lunch on left colonic motility in IBS patients (closed rectangles) and controls (open circles) in descending and sigmoid colon.

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

veresus 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 ± 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).

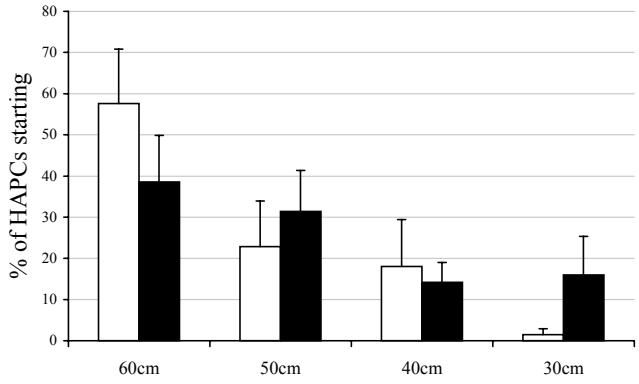

Fig. 4

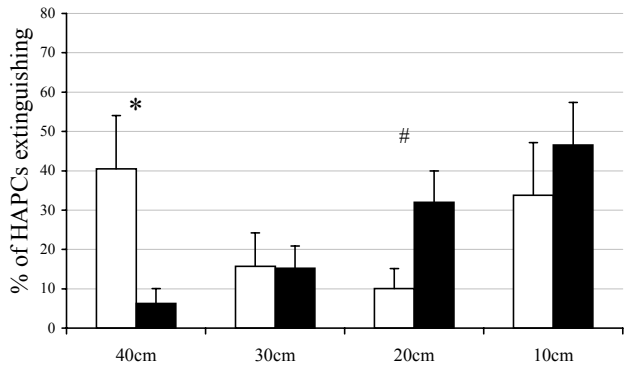

Fig. 5

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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Chapter 3

EFFECT OF ALOSETRON ON LEFT COLONIC MOTILITY IN NON-CONSTIPATED IBS PATIENTS AND HEALTHY VOLUNTEERS

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ABSTRACT

Background: Alosetron is a 5-HT_3 receptor antagonist reducing symptoms in female patients with diarrhea-predominant IBS, and is known to increase colonic transit time.

Aim: To study the effect of alosetron on left colonic phasic motility in ambulant non-constipated IBS patients and healthy volunteers.

Methods: In a double-blind, randomized, cross-over design, 10 IBS patients and 12 sex- and age-matched volunteers were treated for two 7-days periods with alosetron 4 mg bd or placebo bd. On day 6 of each treatment period a 6-channel solid-state manometric catheter was positioned in the left colon and 24 hour motility was studied on day 7. Periprandial phasic motility around dinner was evaluated in the descending and sigmoid colon. High-Amplitude Propagated Contraction (HAPC) frequency and characteristics were calculated.

Results: Alosetron appeared to increase overall periprandial frequency in the sigmoid colon ($p=0.043$) and mean amplitude of colonic contractions in the descending colon ($p=0.007$). HAPC frequency was higher on alosetron during the second half of the day for IBS patients ($p=0.002$) with increased mean HAPC propagation length ($p=0.001$). Stool frequency ($p=0.024$), and stool consistency score ($p=0.002$) were decreased by alosetron.

Conclusions: The 5-HT_3 receptor antagonist alosetron marginally increased left colonic periprandial phasic motility. Alosetron increased the number and propagation length of HAPCs which were paradoxically accompanied by a decrease in stool frequency and a firming of stool consistency.

INTRODUCTION

Although the pathogenesis of irritable bowel syndrome (IBS) is still poorly understood, altered intestinal motor function and visceral hypersensitivity have been shown to be important etiological factors.[1] Abnormal gastrointestinal motor function was frequently reported in IBS, not only in the colon, but also in the small intestine.[2-4]

The literature about colonic motor abnormalities in IBS is partly conflicting but older publications suggest that the incidence of segmenting contractions is increased in constipation-predominant and decreased in diarrhea-predominant IBS.[5 6] In addition to abnormalities in segmenting contractions, abnormalities in High-Amplitude Propagated Contractions (HAPCs) were found in IBS patients.[7] In those patients with diarrhea an increased incidence of HAPCs was observed, whereas constipated patients had less HAPCs than normals.[8 9]

In addition, colonic tone, as measured with the barostat technique, appears to be abnormal in IBS. In particular, the postprandial increase in tone was less prominent and shorter in duration in IBS patients than in healthy subjects.[8 10]

Recent evidence supports the hypothesis that, in a subset of IBS patients, symptoms are related to visceral hypersensitivity. Rectal balloon distension has been used as a model to examine visceral sensitivity and showed that patients with IBS are more sensitive to rectal distension than healthy volunteers.[11-15] However, the relationship between altered visceral sensitivity and abnormal motility has yet to be established.[16]

5-hydroxytryptamine (5-HT) plays an important role in the regulation of gastrointestinal motility and perception.[17] In diarrhea-predominant IBS patients, the postprandial increase in 5-HT plasma concentration was found to be significantly exaggerated.[18]

Alosetron is a potent and selective antagonist at the 5-HT_3 receptor.[19] Placebo-controlled clinical trials have shown that alosetron is of benefit in female patients with diarrhea-predominant IBS. In the clinical trials alosetron was well tolerated and improved abdominal pain and discomfort, urgency, stool frequency, and stool consistency.[20-22] Alosetron increases the compliance of the descending colon to distension and could thereby contribute to changes in perception of colonic distension

and improvement in symptoms of IBS.[23] Alosetron has been shown to have no overall effect on orocaecal transit time, but it increases whole gut transit time as a result of increasing left colonic transit time.[24]

The effect of alosetron on phasic left colonic contractions and HAPCs has not previously been studied.

The aim of this study was to examine the effects of orally administered alosetron (4mg twice daily) on left colonic motility in patients with non-constipated IBS and healthy volunteers. Since colonic motility in general is highly variable throughout a 24-hour period and HAPCs are infrequent colonic events, ambulatory colonic manometry over a 24-hour period was used.

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 IBS patients, diagnosed by Rome I criteria, who were non-constipated were enrolled. Based on medical history non-constipated was defined as having a 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. They had to be free from cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological and psychiatric disease, as determined by history, physical examination and laboratory tests (hematology, biochemistry, urine analysis).

Written informed consent was obtained from each subject and the Research Ethics Committee of the University Medical Center Utrecht approved the study protocol.

Study protocol

In a randomized, double-blind, placebo-controlled, two-way cross-over study (S3BB1007) the effects of alosetron 4 mg bid on colonic motility and defecation were evaluated. Each subject was treated with alosetron or placebo for 7 days (day 1-7) and then switched to the alternate treatment after a 2-4 week washout period. Each dose was taken before breakfast and evening meals. The manometric study of the left colon was performed from day 6 until the morning of day 8.

Ambulatory manometry of the colon was performed with a 6-channel solid-state catheter (Sentron, Roden, The Netherlands). In the afternoon of day 6 the left colon was cleaned by means of administration of an enema (20g soap in 2L water, Driehoek zeep, Hartman Intradal B.V., Veenendaal, The Netherlands). After cleaning of the left colon the manometric catheter incorporating 6 pressure transducers at 10-cm intervals, was placed endoscopically. The procedure was performed without sedation and with minimal insufflation of air.

The tip of the manometric catheter was attached to the colonoscope and introduced until the tip of the catheter reached the mid-transverse colon. Under fluoroscopic control the catheter was pulled back 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) and recordings continued until the removal of the catheter on day 8. A sampling rate of 4 Hz was used for each of the six channels.

After placement of the catheter the subjects returned home. Subjects were requested to maintain their normal daily routines as much as possible with the exception of performing strenuous exercise. During the motility study subjects were asked to maintain a standard diet (see below). Smoking, drinking alcohol or coffee was prohibited for 24 hours prior to and during the manometric study.

On day 8, the subjects returned to the unit and the position of the catheter was checked using fluoroscopy. The catheter was then removed and the data transferred from the data logger to a personal computer.
After the washout period the subjects switched to their second treatment period of 7 days. On the morning of day 6 and day 8 of the second treatment period, subjects returned again to the gastrointestinal research unit and the procedures described above were repeated.

Defecation characteristics

For 7 days proceeding each treatment period, and during treatment with alosetron and placebo, all subjects recorded their defecation characteristics, such as stool consistency and frequency, in a diary. The consistency of every stool was scored by the subjects on a 5-point scale: 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery.
During the colonic motility studies the subjects kept another diary in which meals, physical activities, urge to defecate, defecation characteristics, abdominal pain and discomfort were recorded. The start and finish of these events were also registered by pressing an event marker on the data logger.

Standardised meals

During the manometric study the subjects used a standard diet. On day 7 a breakfast was taken containing 2218 kJ; protein 25 g, carbohydrate 53 g and fat 24 g. Lunch on day 7 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.

Analysis of colonic motility

Only the motility data recorded on day 7 were analyzed, i.e. from midnight on the day the catheter was positioned until 24 hours later. The colonic motility recordings were considered a failure when more than one of the 6 manometric sensors had failed or when less than 18 hours of continuous colonic motility had been recorded. Manometric

data were analyzed both visually and automatically using a dedicated software programme.[25] This software programme calculated the frequency, amplitude and motility index (MI = ln ((n x Σ amplitudes) +1)) of all pressure waves detected at the 6 pressure sensors after base-line correction and elimination of artifacts.

In the analysis of the segmenting pressure waves, one signal recorded from the sigmoid -and one from the descending colon were selected. This was done on the basis of fluoroscopy images obtained before and after the ambulatory recording period. Analysis of phasic pressure waves was confined to signals recorded during four 15-min periods before -and eight 15-min periods after dinner from the sensors located in the descending colon and sigmoid. In each of these 15-min periods, mean frequency, amplitude and motility index were calculated.

The periprandial period was divided into three periods of one hour each: the four 15-min periods before dinner are called preprandial period, the first four 15-min periods after dinner are the early postprandial period and the last four 15-min periods are called late postprandial period. The mean frequency, amplitude and the motility index in these periprandial hours were calculated from the total number of contractions and the sum of amplitudes in four 15-min periods.

HAPCs, defined as pressure waves that propagate distally across at least 3 sensors, with a speed of more than 0.3 cm/sec and amplitude of at least 100 mmHg in 2 sensors and at least 75 mmHg in one other sensor, were analysed visually. HAPC characteristics that were recorded during day-time on day 7 (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. After identification of the HAPCs, their number, frequency, amplitude, propagation velocity, propagation distance and duration were calculated during this day-time period.

Analysis of stool characteristics

Mean stool frequency was determined during the first pre-treatment period of seven days. During treatment, a mean stool frequency was calculated from day 1 up to day 5 of each treatment period. Day 6 was the day of colonic cleaning and catheter placement

while day 7 was the analyzed period for colonic motility. The mean consistency/stool was calculated for the first pre-treatment period of seven days. During treatment a mean stool consistency was calculated from day 1 up to day 5 of each treatment period.

Statistical analysis

The mean contractile frequency, mean amplitude and motility index in the three periprandial hours were calculated and subsequently analyzed for all subjects together using the MIXED effects modeling procedure in SAS(R) software (version 6.12). The effect of alosetron on colonic motility was also investigated separately in IBS patients and in healthy subjects using analysis of variance. All analyses were done for both locations of the colon; the descending colon and the sigmoid colon.

Data from all six sensors were integrated in order to derive the HAPC data. The HAPC characteristics, duration (sec), amplitude (kPa), propagation length (cm), propagation velocity (cm/sec), and the incidence of HAPCs, were also analyzed as described above.

The mean stool frequency and consistency data collected prior to the treatment period were analyzed for group differences using independent student t-tests. Treatment effects on stool frequency and consistency were tested by paired t-tests.

RESULTS

Study group

Thirty-six subjects (18 patients, 18 healthy controls) were randomized to a treatment sequence. Data from 8 patients and 6 healthy volunteers could not be analyzed for various reasons (inadequate use of medication, incomplete follow-up, failure to position manometric catheter, catheter expulsion, and technical insufficiencies).

In total 10 patients with IBS (5 M, 5 F; age: 39.3 ± 8.0 yr.; height: 174.0 ± 9.8 cm; weight: 78.5 ± 16.9 kg) and 12 healthy age- and sex-matched controls (6 M, 6 F; age: 37.9 ± 8.9 yr.; height: 175.2 ± 8.8 cm; weight: 70.0 ± 12.5 kg) were studied successfully and only data obtained from these subjects were included in the statistical analysis.

Manometric data

Periprandial motility

During the periprandial period as a whole, alosetron slightly increased contractile frequency (p=0.043) in the sigmoid colon, whereas no effect of alosetron was observed in the descending colon. Also during the periprandial period as a whole, alosetron increased the mean amplitude of colonic contractions in the descending colon (p=0.007), whereas no effect was seen in the sigmoid colon (Table 1, Figure 1).

Table 1: Effect of alosetron on periprandial colonic motility

DINNER	Descending Colon		Sigmoid Colon	
	Placebo	Alosetron	Placebo	Alosetron
Frequency (contractions/min)				
Pre	0.29 ± 0.31	0.54 ± 0.53	0.46 ± 0.33	0.74 ± 0.58
Early	0.48 ± 0.34	0.75 ± 0.62	0.54 ± 0.36	1.04 ± 0.91
Late	0.32 ± 0.37	0.51 ± 0.52	0.42 ± 0.34	0.76 ± 0.79
Total	0.36 ± 0.29	0.60 ± 0.50	0.47 ± 0.28	[a] 0.85 ± 0.69
Amplitude (kPa)				
Pre	2.33 ± 0.76	2.90 ± 1.22	2.75 ± 0.78	2.86 ± 0.79
Early	2.54 ± 0.60	3.50 ± 2.04	2.86 ± 0.97	3.35 ± 1.30
Late	2.20 ± 0.58	2.59 ± 0.89	2.52 ± 0.63	2.71 ± 0.79
Total	2.46 ± 0.49	[b] 3.17 ± 1.34	2.77 ± 0.73	3.06 ± 0.74
Motility index (1-h periods)				
Pre	5.23 ± 2.82	6.99 ± 2.19	6.81 ± 2.33	[c] 7.94 ± 1.91
Early	7.19 ± 1.43	8.08 ± 1.73	7.38 ± 1.88	8.53 ± 2.18
Late	5.43 ± 2.60	6.53 ± 2.95	6.49 ± 2.32	6.96 ± 3.46
Total	8.67 ± 1.64	9.79 ± 1.77	9.44 ± 1.63	10.44 ± 1.91

Data = mean ± standard deviation

a) P = 0.043

b) P = 0.007

c) P = 0.044

High-Amplitude Peristaltic Contractions

Alosetron significantly increased the frequency of day-time HAPCs in the total study population (p =0.021). Analysis of the HAPC frequency data showed that IBS patients had a significant increase in the number of HAPCs during treatment with alosetron only in the second half of the day (p = 0.002) whereas alosetron had no significant affect on the number of HAPCs in healthy volunteers (Figure 2).

Alosetron significantly increased the mean propagation length of daytime HAPCs (p =0.001) (Table 2). There was no evidence of a difference between IBS patients and healthy volunteers (p=0.415). However, alosetron did not significantly affect HAPC duration, amplitude or propagation velocity.

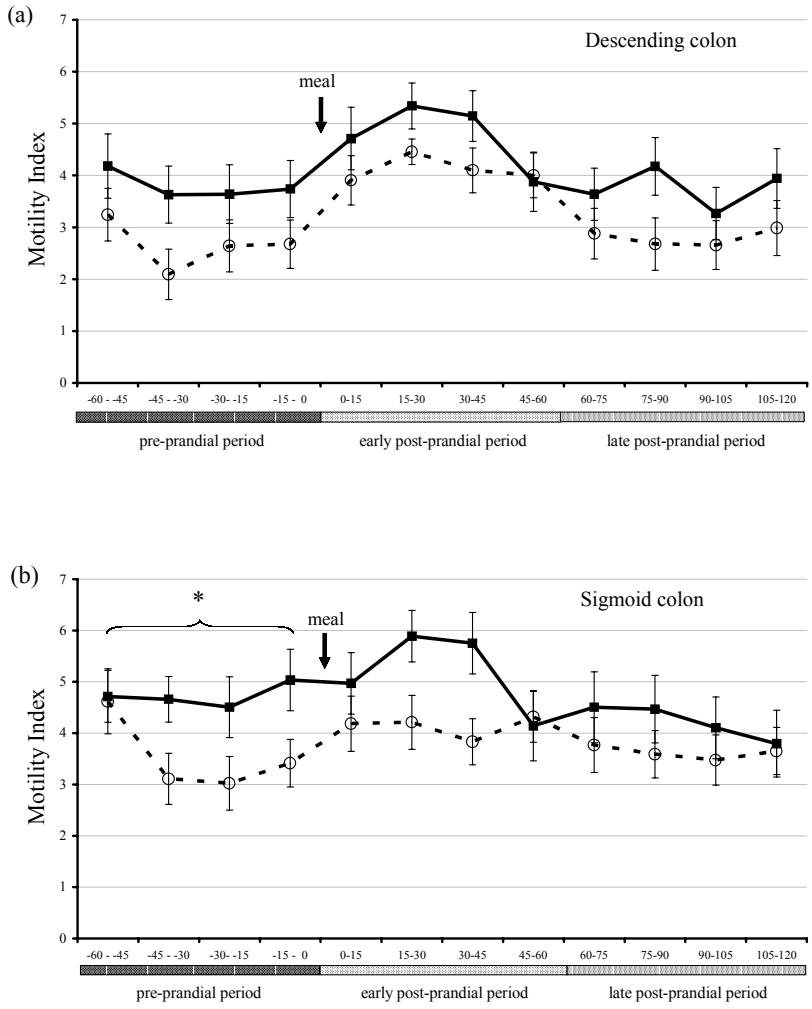

Figure 1 (a) Mean periprandial motility indices ± S.E.M. (15 minutes intervals) in all subjects (patients and volunteers) during treatment with alosetron (closed rectangles) or placebo (open circles) in the descending colon. (b) Mean periprandial motility indices ± S.E.M. (15 minutes intervals) in all subjects (patients and volunteers) during treatment with alosetron (closed rectangles) or placebo (open circles) in the sigmoid colon. Minor increase of motility indices during the preprandial period on alosetron (* p=0.044).

Stool frequency and stool consistency

During the pre treatment period a significantly higher mean stool frequency (2.3 ± 1.1 / day versus 1.1 ± 0.3 / day; p=0.003) was observed in the IBS patients compared to healthy volunteers. No difference in mean consistency score was observed between patients and volunteers during the pre-treatment period (3.2 ± 0.6 versus 3.0 ± 0.2).

Alosetron significantly decreased the stool frequency in the total study population from 1.8 ± 1.3 / day during placebo treatment to 1.4 ± 0.8 / day during alosetron treatment (p=0.024). Alosetron did not have a significant effect on stool frequency in IBS patients and healthy volunteers when each group was analyzed separately.

Alosetron significantly decreased the stool consistency score (i.e. stools became harder) in the total study population (from 3.0 ± 0.4 in the placebo group to 2.5 ±0.9 in the alosetron group; p=0.002). When analyzed separately, alosetron significantly decreased stool consistency score in the control group (from 2.9 ± 0.2 to 2.2 ± 0.8; p=0.010) but not in the IBS patient group (from 3.2 ± 0.5 to 2.8 ± 1.0; p=0.112).

Table 2: Effect of alosetron on HAPCs during daytime period

	Volunteers		IBS patients		
HAPC	Placebo	Alosetron.	Placebo	Alosetron	Between treatments
Frequency (no..HAPCs/h)	0.6± 0.7	0.7± 0.7	0.6± 0.4	0.8± 0.3	P=0.021
Velocity (cm/s)	1.3± 0.4	1.2± 0.5	1.3± 0.2	1.5± 0.6	n.s.
Amplitude (kPa)	22.4± 6.5	24.2± 5.5	24.9± 5.9	22.5± 4.6	n.s.
Duration (s)	16.3± 3.2	21.2± 8.1	17.1± 2.7	18.0± 2.9	n.s.
Propagation distance (cm)	28.4± 7.0	33.4± 4.7	29.6± 6.4	36.1± 6.2	P=0.001

Data = mean ± standard deviation

Adverse Events

Fourteen of the 16 subjects who experienced adverse events whilst receiving alosetron reported events which were classified as gastrointestinal in nature, of which 12 subjects (10 healthy volunteers, 2 IBS patients) experienced constipation, and 9 (8 volunteers, 1

patient) experienced abdominal discomfort and pain. Headaches were reported by 2 subjects whilst receiving alosetron, and by 1 subject on placebo. All adverse events resolved rapidly.

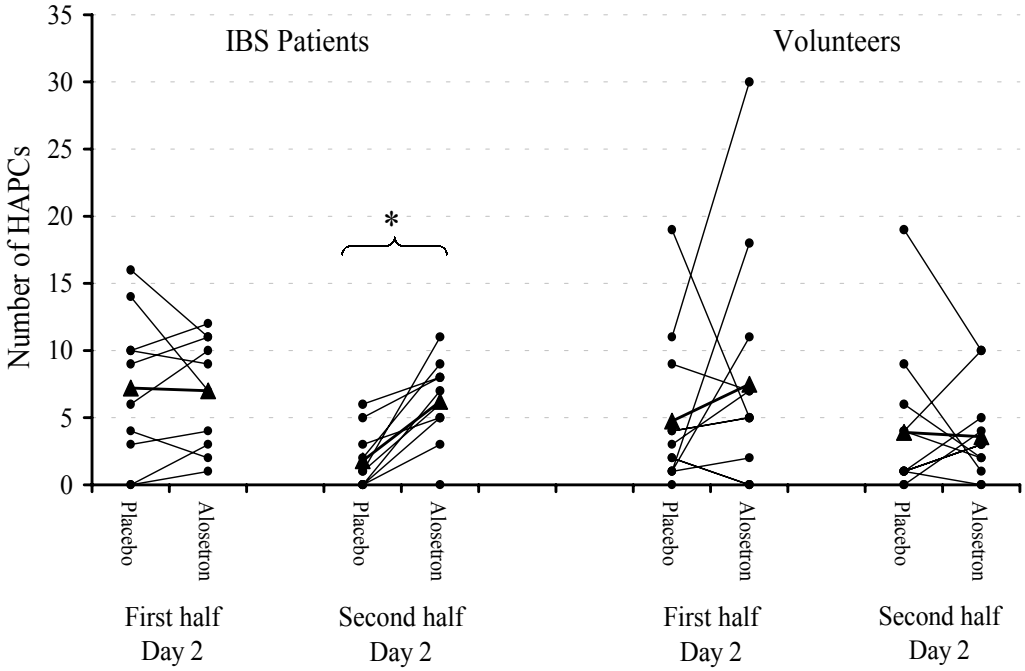

Figure 2. Number of HAPCs in individual IBS patients and volunteers during treatment with placebo and alosetron in the first and second half of the daytime period. The mean number of HAPCs is represented by filled black triangles. Increased HAPC frequency in second half of the daytime period in the patient group on alosetron (* p=0.002).

DISCUSSION

This is the first study evaluating the effect of alosetron on left colonic phasic motility in non-constipated patients with irritable bowel syndrome and healthy volunteers using prolonged ambulant manometry.

Although multiple comparisons were performed in this study and comparisons were not adjusted for multiplicity, we feel that the following conclusions are justified within the context of the exploratory analyses:1) alosetron affects left colonic motility in the peri-

prandial period in IBS patients as well as in healthy volunteers, 2) alosetron increases the HAPC frequency in IBS patients and propagation length in all subjects, 3) treatment with alosetron is accompanied by a decrease in stool frequency and consistency score, and 4) non-constipated IBS patients on alosetron appear to have less constipation and report less abdominal pain and discomfort compared to healthy volunteers.

Most studies on colonic motility in IBS patients have been performed in a laboratory setting, during a short period of time, and after a total colonic lavage.[5-11] In the present study we used a prolonged ambulant manometric technique with the advantage of recording multiple HAPCs in each subject after refilling of the colon.

This study demonstrates that 24-hour colonic manometry is feasible and well-tolerated. However, the failure rate of about 40% remains one of the major problems of this technique. Half of this failure rate was caused by technical problems such as failure of catheter placement, transducer failure, catheter expulsion and peri-anal pain.

Periprandial motility is thought to be changed in IBS patients and other studies suggest a postprandial increase in 5-HT plasma concentration in diarrhea-predominant IBS patients.[6-8 17 18] Periprandial motility was studied during the evening meal on day 7 because this meal was more than 26 h after partial colonic cleaning and was combined with alosetron or placebo.

HAPCs were analyzed during the daytime period on day 7, because it is known that hardly any HAPCs occur during sleep. During the 24-h period of day 7 only 2 % of the HAPCs were counted during the night-time in the placebo treatment period and 2.3 % of HAPCs were counted during the night-time in the alosetron treatment period. We were especially interested in the effect of alosetron on the diurnal occurrence of HAPCs: in healthy volunteers, HAPCs occur more often in the first part of the day.[26] For this reasons we analyzed the total daytime period as well as the first and second half of this daytime period separately.

We did not take the menstrual cycle into account for practical reasons. In our opinion there is not sufficient evidence to support the view that the influence of hormones on left colonic motility significantly increases the intrinsic variability as is measured in men. [27]

We found no significant differences between non-constipated IBS patients and healthy volunteers in terms of the periprandial motility index or 24-h HAPC frequency, regardless of whether the treatment received was placebo or alosetron. This might be due to patient selection, because non-constipated IBS patients can be considered as a mixture of diarrhea- predominant, alternating diarrhea and constipation, as well as pain-predominant IBS patients.

Our healthy subjects had a somewhat higher number of HAPCs during the control arm of the study. However, we had a wide spread of HAPC number in the healthy volunteer group with 2 subjects having a very high number of HAPCs (28 and 30) on day 7. We decided not to exclude these two outliers. Without these two subjects the effect of alosetron on HAPC frequency would have been more convincing.

Recently, colonic transit through the ascending and transverse colon has been shown to be related to stool weight.[28] Whole gut transit time, which is correlated to the stool form, and the stool frequency were significantly different in IBS patients reporting constipation compared with those reporting diarrhoea.[29] Houghton et al. showed that alosetron increases left colonic transit time.[24] Our results concerning stool characteristics (decreased stool frequency and consistency during alosetron treatment) are in line with the observed slowing of colonic transit.

The literature suggests that shortened colonic transit time, increased stool frequency and decreased stool consistency can be explained by a higher incidence of anally directed mass movements produced by a greater number of HAPCs and less segmenting non-propagated colonic contractions.[7 9 10 30 31]

Serotonin plays a role in physiological and pathological states in the human colon.[18 32-34] Bearcroft et al. showed an increase in serotonin release in response to a meal in female patients with diarrhea-predominant IBS.[18] In a study with the 5-HT_3 receptor antagonist ondansetron, it was found that selective blockade may blunt the postprandial tonic and phasic motor response in healthy volunteers.[30] In contrast, in this study, it appears that alosetron slightly increased the frequency and amplitude of left-colonic contractions.

HAPCs are the major motor events in the colon producing mass movements. HAPCs are related to defecation and the feeling of urge. The highest frequency is noted after meals and after awakening in the morning. Less HAPCs are recorded in the late afternoon and during the night.[26] Fewer HAPCs were counted in constipated patients, while a higher number was seen in patients with functional diarrhea.[9 10]

At present, no studies exist describing the effect of 5-HT_3 receptor antagonists on HAPC frequency.[17 32 33] The results of our study show that 5-HT_3 receptor blockade seems to increase HAPC frequency and propagation length, and that there may be more HAPCs in non-constipated IBS patients on alosetron during the second half of the day.

The paradox of a higher HAPC frequency and greater propagation distance accompanied by a decreased stool frequency and stool consistency, suggesting a delay in colonic transport, is difficult to explain. One might speculate that the incidence of non-propagating, segmenting contractions is increased by alosetron, leading to a longer colonic transit time and a higher stool consistency. This might further be promoted by retardation of proximal colonic emptying by alosetron, which was shown in patients with carcinoid diarrhoea.[34] Furthermore, alosetron increases the compliance of the descending colon to distension, which might have a negative effect on fecal transport.[23] Finally, the observed change in consistency may also be caused by an alosetron-induced decrease in water secretion in the small bowel.[34] More HAPCs might just be needed to transport the high viscosity fecal mass across the highly resistant left colonic region.

The most frequently reported adverse effect during alosetron treatment was constipation. Ten out of 12 subjects who experienced constipation on alosetron were healthy volunteers. This suggests that the positive results of alosetron in non-constipated IBS patients might partly be related to a shift to a normal defecation frequency and consistency.

The reduction in the number of days with urgency that was reported in a large placebo-controlled study is likely to be related to a decreased faecal mass, a decreased rectal compliance, restoring the reservoir function of the colon and rectum, and a reduced rectal sensory score.[21 23 35 36]

Alosetron has been shown to reduce abdominal pain in patients with irritable bowel syndrome, particularly in those with loose or watery stools.[20 21] The effect of alosetron on visceral perception might be accomplished by an increase in compliance or by directly influencing colonic afferents.[23 35 36]

In conclusion, the 5-HT_3 receptor antagonist alosetron appears to marginally increase left colonic periprandial phasic motility. Alosetron also increases the number and propagation distance of HAPCs, which is paradoxically accompanied by a decrease in stool frequency and a firming of stool consistency.

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Chapter 4

ASSOCIATION BETWEEN PAIN EPISODES AND HIGH-AMPLITUDE PROPAGATED PRESSURE WAVES IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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ABSTRACT

Objective: In the pathogenesis of Irritable Bowel Syndrome (IBS) both increased visceral sensitivity and altered colonic motility appear to play a role. The aim of this study was to quantify the temporal relationship between pain episodes and the occurrence of High-Amplitude Propagated Pressure Waves (HAPPWs).

Methods: 11 non-constipated IBS patients and 10 sex- and age-matched healthy volunteers were studied. On day 1 a solid-state manometric catheter was positioned in the left colon and connected to a data logger. Thereafter, the subjects went home. They pressed a button on the data logger at the beginning and end of each pain episode. The 24-h manometric signal recorded on day 2 was divided into consecutive 5-min periods. These periods were evaluated for the occurrence of pain and HAPPWs. The Fisher Exact test was applied to calculate the probability (P-value) that HAPPWs and pain episodes were unrelated. The Symptom Association Probability (SAP) was calculated as (1.0-P) x100%. A SAP of more than 95% was considered to indicate that the observed association did not occur by chance.

Results: In 4 out of 7 patients with pain on day 2, the SAP was greater than 95%. HAPPWs related to pain originated at a more proximal level ($p = 0.026$) and occurred earlier ($p = 0.007$) than HAPPWs not related to pain. The duration of a pain period was correlated to the number of pain-related HAPPWs in that period ($r = 0.906$, $p = 0.013$). Only 2 of the 10 healthy subjects experienced pain and these pain episodes were not associated with HAPPWs.

Conclusion: Using objective analysis techniques an association between pain episodes and HAPPWs was found in non-constipated IBS patients with pain. HAPPWs associated to pain are only slightly different from HAPPWs not associated to pain.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder with exacerbations, characterized by abdominal pain and/or discomfort and alterations in bowel habits. The etiology of IBS is unknown. However, life stresses and acute gastrointestinal infections seem to be related to the development of the irritable bowel syndrome in susceptible subjects.[1-3]

Several mechanisms may lead to the reported IBS symptoms. Altered motility and perception at the level of the small bowel and large intestine play a role. Both factors seem to be modulated by input from the central nervous system.[4]

Using manometric techniques several studies showed small intestinal motor abnormalities in IBS, especially clustered contractions.[5-7] It has been shown that various stimuli, such as a meal, cause an exaggerated or prolonged distal colonic motility response in IBS patients.[8 9] Colonic segmenting contractions were found to be increased in constipation-predominant IBS and decreased in diarrhea-predominant IBS .[10-12]

Abnormal visceral perception is suggested in a significant number of IBS patients by an increased sensitivity to balloon distension documented in small bowel, colon and recto-sigmoid region.[12-15]

Lowered threshold of perception during intestinal distension raises the possibility that an increased awareness of normal or abnormal motility is a factor in the pathogenesis of abdominal symptoms in at least a subset of IBS patients. Until very recently only anecdotal literature suggests an association between (abnormal) small bowel or colonic motility and symptoms.[16-18]

High-amplitude propagated pressure waves (HAPPWs) are infrequent colonic motility patterns, occurring approximately six times per day in healthy subjects. HAPPWs are thought to be the major force in the colon producing transport of colonic content in anal direction over long distances and appear to be necessary for normal bowel habits. HAPPWs are infrequently seen at night and occur more frequently after awakening or after a meal.[19-21] In patients with diarrhea-predominant IBS a trend towards an increased number of propagated contractions was observed, while in idiopathic constipated patients a decreased number of HAPPWs was found.[22 23] Only recently an association

between the occurrence of HAPPWs and abdominal cramps was found in IBS patients exhibiting pain and diarrhea. However these HAPPWs were stimulated by CCK and a high caloric meal under laboratory circumstances.[24]

The purpose of the present study was to test the hypothesis that under physiologic circumstances IBS patients perceive HAPPWs as painful. Abdominal pain and HAPPWs were recorded during a prolonged fully ambulatory manometric study of the left colon in non-constipated IBS patients and controls. The association between symptoms and HAPPWs was assessed by using a modification of the symptom association probability (SAP).[25] Additional objectives were to analyze HAPPW characteristics in IBS patients and healthy volunteers.

METHODS

Subjects

IBS patients were recruited from the outpatient clinic of the department of Gastroenterology of the University Medical Centre Utrecht. After exclusion of organic disease, subjects who were diagnosed by "Rome I" criteria for IBS and were not constipated were enrolled. Non-constipated patients were selected because HAPPWs occur less frequently in constipated patients.

Mean stool consistency score and mean stool frequency were calculated from the individual consistency and frequency scores recorded during a five-day period preceding the start of the recording period.

IBS patients were considered to be “non-constipated” when they had a mean stool consistency of > 2.5 on a 5-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 Centre Utrecht approved the study protocol.

Study protocol

Colonic motility was studied using a 6-channel, 10-cm interval, solid-state catheter (Sentron, Roden, The Netherlands). All subjects were asked not to use any pain medication during the 5 days prior nor during the manometric recording period. On day 1 between at 1.00 PM the left colon was cleaned by means of administration of a 2-L water enema containing 20g of soap (Driehoek zeep, Hartman Intradal B.V., Veenendaal, The Netherlands). Thereafter the manometric catheter was placed endoscopically. The tip of the manometric catheter was grasped by a snare and the endoscope was introduced until the tip of the catheter had reached the mid-transverse colon. This procedure was performed without sedation and with minimal insufflation of air.

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 were asked to maintain a standard diet. Smoking, drinking alcohol or coffee was prohibited for 24 hours prior to and during the manometric study. All subjects were instructed to fill in a diary to record the time of awakening and the time of retiring to bed, the start and end of a meal and pain episodes. In addition they were asked to press a button on the digital data logger at the beginning and end of each pain episode. The diary data regarding the onset and end of symptoms were used as a check of appropriate use of the event button. If a symptom was recorded in the diary but not with the event button, the time recorded in the diary was used for analysis; otherwise the times indicated by the event button were used.

Colonic pressures were recorded continuously for approximately 41 h, from 3.00 PM on day 1 until 9.00 AM on day 3, when the subjects returned to the laboratory. 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.

Analysis of manometric data

The motility data recorded on day 2 were analyzed, 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 on day 2 had been recorded.

Visual analysis was used to detect HAPPWs and to measure their characteristics. HAPPWs were defined as pressure waves that propagated distally across at least 3 sensors, with a propagation rate of more than 0.3 cm/sec and an amplitude of at least 100 mmHg in 2 sensors and at least 75 mmHg in one other sensor. After identification of the HAPPWs, their number, mean amplitude, peak amplitude, duration, propagation velocity, propagation distance, time of occurrence after getting up and site of origin and extinction were determined. A Clustered HAPPW was defined as a HAPPW preceded or followed by another HAPPW within a time window of 3 minutes.

Calculation of the Symptom Association Probability

The association between symptoms and colonic motor events was assessed using a modification of the symptom association probability (SAP) technique, which was originally developed for assessment of esophageal symptoms.[25]

The calculation of the SAP consisted of the following procedures. First, the 24-h manometry recording was divided into consecutive 5-min periods. Thereafter, all 5-min periods (288 in number) were evaluated for the occurrence of pain. Likewise all 5-min periods were analyzed for the presence of HAPPWs and classified as HAPPW-positive or HAPPW-negative.

Subsequently, a contingency table was constructed, containing 4 fields: one containing the number of 5-min periods with pain and HAPPWs (S^+H^+), one with the number of asymptomatic HAPPW-positive 5-min periods (S^-H^+), one with symptomatic 5-min periods without HAPPWs (S^+H^-), and one with the number of asymptomatic 5-min periods without HAPPWs (S^-H^-) (Table 1).

The Fisher Exact test was then applied to calculate the probability (P value) that the observed association between HAPPWs and pain occurred by chance. The Symptom Association Probability was calculated as (1.0 – P) x 100 % (25).

Table 1: Contingency table of patient nr 9

	Pain +	**Pain –**	
HAPPW +	1	4	**5**
HAPPW –	0	283	**283**
	1	**287**	**288**

Statistical analysis

An independent student t-test was used to compare characteristics of HAPPWs between IBS patients and volunteers and to compare characteristics of HAPPWs related and unrelated to pain.

Pearson's coefficient of correlation was used to examine the correlation between the number and duration of pain symptom episodes and the number of pain-related HAPPWs in IBS patients. All statistical tests were performed using the statistical software package SPSS (version 10.0, 1999, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study group

Twenty-seven subjects (13 patients, 14 age/sex matched healthy volunteers) were included in the study.

In 3 healthy subjects manometric data were considered of insufficient quality because of failure of more than one transducer. Two patients had major catheter displacement on day 2. One healthy volunteer requested to have the catheter removed prematurely.

Finally, 11 patients with IBS (5 M, 6 F; age: 37.6 ± 2.5 years) and 10 healthy age- and sex-matched healthy subjects (4 M, 6 F; age: 38.0 ± 3.1 years) were studied successfully. After a mean duration of monitoring of 41 hr, fluoroscopic screening in the morning of day 3 revealed no major dislocation of the proximal sensor. A trend towards a higher mean stool frequency was observed in the IBS patients (2.3 ± 0.5 versus 1.3 ± 0.1; p=0.072) . The mean stool consistency score was significantly higher in IBS patients than in healthy subjects (3.3 ± 0.1 versus 2.9 ± 0.07; p=0.023).

High-Amplitude Propagated Pressure Waves (HAPPWs)

In the IBS patients the number of HAPPWs was significantly higher than in healthy volunteers (p = 0.039). In 11 IBS patients 111 HAPPWs and in 10 controls 48 HAPPWs occurred. The number of clusters of HAPPWs was higher in IBS patients than in controls (p = 0.036). The peak amplitude of HAPPWs tended to be higher in IBS patients (p = 0.064) (Table 2).

Table 2: Differences between HAPPWs in IBS patients and healthy controls

HAPPW Characteristics	Patients	Controls
Number	111	48
Number (nr/subject)	10.1 ± 6.4*	4.8 ± 4.3
Mean amplitude (kPa)	24.2 ± 5.4	20.5 ± 4.8
Highest amplitude (kPa)	33.9 ± 7.7	27.6 ± 6.3
Distance of propagation (cm)	29.0 ± 5.1	27.5 ± 6.6
Duration of pressure wave (s)	16.2 ± 3.1	15.9 ± 2.6
Velocity of propagation (cm/s)	1.4 ± 0.3	1.2 ± 0.4
Time of occurrence after getting up	5.4 ± 2.9	5.8 ± 2.0
Starting level (sensor nr)	4.9 ± 0.9	5.4 ± 0.7
Extinction level (sensor nr)	2.0 ± 0.7	2.3 ± 0.8
% Clustered	60	40
Number of clusters	2.8 ± 2.2#	1.1 ± 1.1
HAPPWs / cluster	2.6 ± 0.6	2.5 ± 1.0

Data = mean ± standard deviation. * p = 0.039. # p = 0.036.

Symptom Association Probability (SAP)

During the 24-h study 7 of the 11 IBS patients experienced 1-3 pain periods. In total, these IBS patients had 11 symptom periods with a total duration of 169 minutes (0.5 – 45 min). All pain periods were self-limited. Only 2 of the 10 controls experienced a pain period (one each), with a duration of 0.5 and 32 minutes respectively.

Four of the 7 IBS patients, who experienced 6 abdominal pain episodes during the 24-h recording period, had SAP scores > 95% (96-99%). The 2 healthy volunteers experiencing abdominal pain had SAP values < 95% (0-2%) (Figure 1).

Table 3: Differences between HAPPWs associated with pain as compared to HAPPWs not associated to pain in IBS patients with SAP > 95%

HAPPW Characteristics	HAPPWs + Pain	HAPPWs -Pain
Number	14	25
Mean amplitude (kPa)	23.7 ± 8.1	25.6 ± 7.2
Highest amplitude (kPa)	34.4 ± 10.4	38.9 ± 8.9
Distance of propagation (cm)	26.7 ± 9.4	28.0 ± 8.7
Duration of pressure wave (s)	16.8 ± 4.4	16.9 ± 3.5
Velocity of propagation (cm/s)	1.3 ± 1.0	1.5 ± 0.7
Time of occurrence after getting up (h)	2.9 ± 1.0*	6.2 ± 5.5
Starting level (sensor nr)	5.5 ± 0.7#	5.0 ± 0.6
Extinction level (sensor nr)	2.6 ± 0.8	2.2 ± 0.7

Data = mean ± standard deviation. * p = 0.007. # p = 0.026.

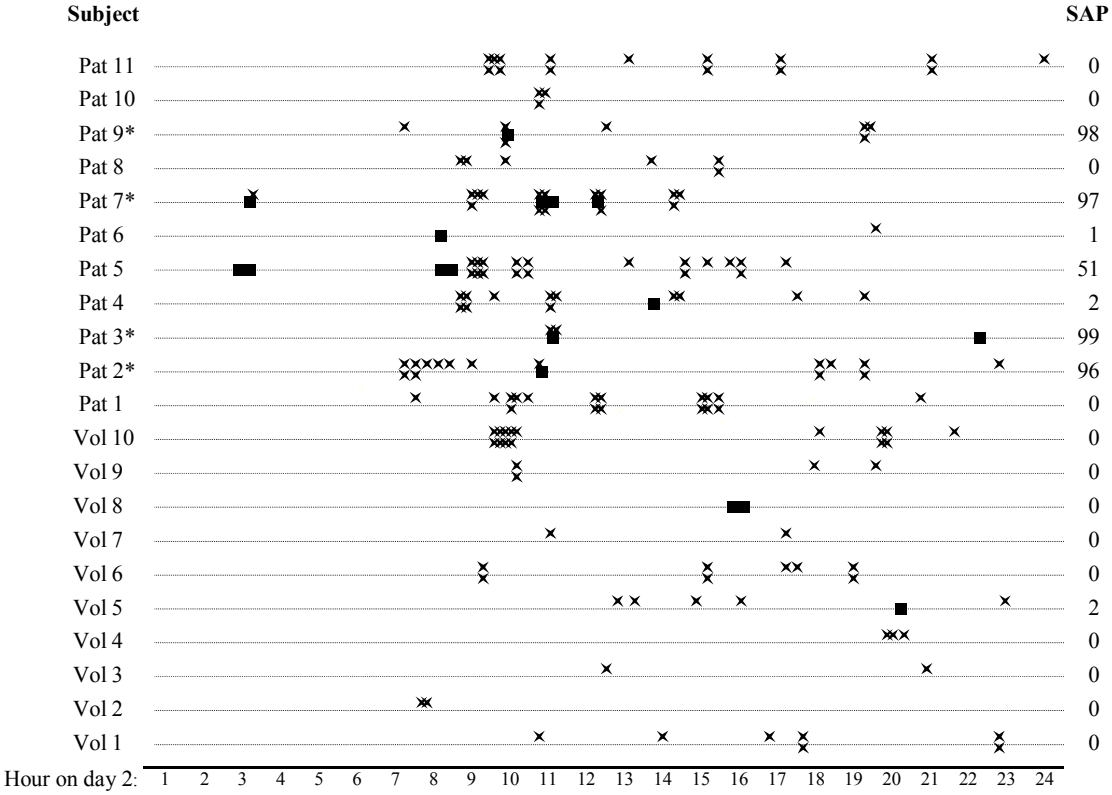

Figure 1: HAPPWs and pain periods (black bars) reported by the IBS patients (closed stars) and healthy volunteers. (* indicates patient with Symptom Association Probability > 95 %)

HAPPWs in patients with SAP > 95%

In the IBS patients with a SAP > 95% 13 HAPPWs were related to pain, while 25 HAPPWs were unrelated to pain. The pain-related HAPPWs occurred significantly earlier after getting up and started at a significantly more proximal level in the left colon than the pain-unrelated HAPPWs ($p = 0.007$, $p = 0.026$). Other HAPPW characteristics did not show any significant differences between pain-related and pain-unrelated HAPPWs (Table 3).

A significant correlation was found between the duration of a pain period and the number of HAPPWs related to that pain period ($r = 0.906$; $p = 0.013$) (Figure 2).

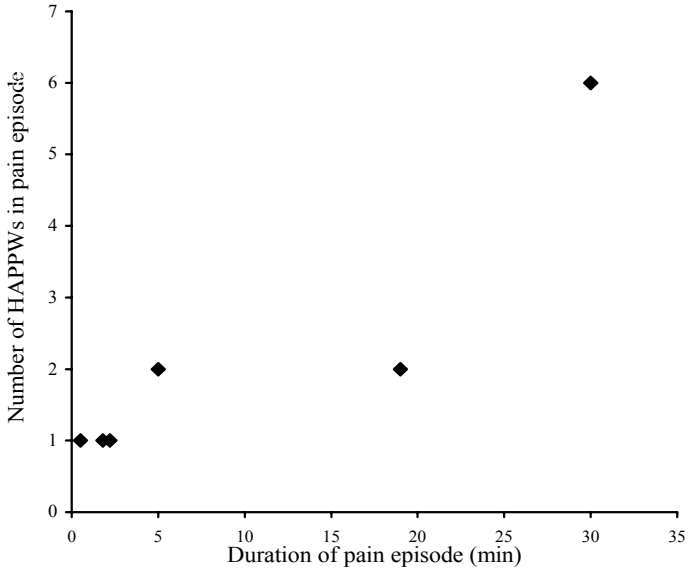

Figure 2: Correlation between the number of HAPPWs and the duration of the 6 pain episodes that occurred in the 4 IBS patients with a SAP > 95% ($r = 0.906$; $p = 0.013$).

DISCUSSION

This is the first study that has shown with objective analysis techniques, that an association exists between HAPPWs and pain in a subset of IBS patients studied under physiologic circumstances.

We have used a prolonged ambulant manometric technique that allowed us to record colonic motility after an accommodation period of more than 10 hr. The frequency and characteristics of HAPPWs in our controls are in accordance with those results performed during prolonged colonic manometry studies in the unprepared colon.[26] Therefore we believe that HAPPWs observed in our study were physiologic events.

Seven of our eleven IBS patients experienced pain during the 24-hour period analyzed; four of them had a SAP score > than 95% which implies that the probability that the association between HAPPWs and pain occurred by chance was less than 5%.

A significant correlation was found between the duration of a pain period and the number of HAPPWs related to it. Although the numbers of HAPPWs and clusters of HAPPWs were significantly higher in IBS patients, no differences were found in other HAPPW characteristics between both study populations. In IBS patients with a SAP score > 95% the pain-related HAPPWs occurred earlier after getting up and started at a more proximal level in the left colon than the HAPPWs not related to pain.

'Rome I Criteria' define IBS as a functional bowel disorder in which abdominal pain is relieved by defecation and/or is associated with a change in bowel habit, with disordered defecation and distension, suggesting that colonic motility might play an important role in the generations of IBS symptoms. Urge and defecation are thought to be preceded by mass movement of colonic content caused by HAPPWs.[19-23]

We used a modification of the "Symptom Association Probability", currently used in the diagnosis of gastro-esophageal reflux disease during ambulatory 24-h pH monitoring to quantify the temporal association between HAPPWs and pain in IBS patients and controls. In reflux disease the SAP is believed to be the best parameter to quantify the temporal association between reflux and symptoms.[25]

The rationale for choosing a 5-min episode was the following. The minimum HAPPW propagation velocity measured was 0.4 cm/s. An HAPPW with this speed would travel from the cecum to the rectum in about 6 min. From the start of the HAPPW in the cecum a sensation of pain might be perceived by the patient. However, an HAPPW generated in the cecum can not be detected by the manometric catheter in the left colon until it has travelled for 4 min through the proximal colon. In this situation pain may be experienced 4 min before the HAPPW is detected by the manometric device. On the other hand, some delay may occur in the reporting of pain episodes.

Although a statistically significant result does not prove a causal relationship, the SAP provides objective information on the probability that observed associations in time between HAPPWs and pain symptoms occur by chance. In case of a SAP > 95 %, the probability that the observed associations occurred by chance is less than 5 %.

In the literature convincing evidence for the existence of a direct relationship between colonic motor activity patterns and IBS symptoms under physiologic conditions cannot

be found. However, several reports suggest the existence of an association between abdominal pain and HAPPWs under laboratory circumstances. In a study by Bassotti et al. one patient with idiopathic chronic constipation who had a displacement of the manometry catheter due to kinking, reported pain during four consecutive HAPPWs.[18] Louvel et al. studied the effect of intrarectal and intracolonic glycerol injection on colonic phasic and tonic motility. Both injection sites induced HAPPWs, long-lasting hypo tonicity of the left colon and pain sensations. However, this complex experiment was set-up to study the effect of various drugs on glycerol-induced tonic and phasic colonic motility; a healthy control group was lacking.[27] A recently published study by Chey et al. in diarrhea- and pain-predominant IBS patients and healthy controls showed a very high HAPPW frequency in patients. In these IBS patients HAPPWs had raised peak amplitudes and 90% of HAPPWs was accompanied by pain. In this experiment the HAPPWs might have been induced and aggravated by administration of CCK followed by a high-caloric meal.[24 28] It is not known if glycerol and CCK induce hypersensitivity in IBS patients. Furthermore these studies were performed in a laboratory environment with subjects confined to a supine position, a few hours after total bowel lavage and positioning of a catheter under sedation.

In our study 4 IBS patients did not have any pain symptoms during the 24-hour motility study. This is not very surprising while it is well known that IBS symptoms vary greatly in time within the same individual.

It is conceivable that the 3 IBS patients and the 2 healthy controls with pain seemingly not associated to HAPPWs had pain induced by HAPPWs that had started in the right colon and extinguished before reaching our manometric device in the left colon. Other mechanisms of pain generation like abnormal small bowel motility, changed colonic tone or hypersensitivity of the colonic and rectal wall to distension, as well as modulation of colonic perception from the central nervous centre might co-exist in IBS.[14 15 29-33]

Another point of interest is that in most subjects who had pain episodes and a SAP > 95 %, many HAPPWs were recorded that were not associated to pain. HAPPWs related to pain in these patients showed no main differences from those not associated to pain.

They originated at a more proximal level in the left colon and occurred earlier in the day. It is likely that centrally mediated descending pain modulatory systems play a role in perception of HAPPWs in these fully ambulant IBS patients.[33]

Since the characteristics of HAPPWs associated to pain are hardly different from HAPPWs not associated to pain it is likely that allodynia (pain produced by a stimulus that does not normally produce pain), rather than hyperalgesia (reduced pain threshold and/or greater response to a painful stimulus) plays a role in pain generation in IBS patients with a SAP > 95%.

HAPPW-related pain periods probably do not play a major role in IBS patients with slow transit constipation where HAPPWs are thought to be decreased in number (18) and in patients in which pain follows defecation. We also believe that more continuous sensations of bloating and discomfort are likely to be caused by other mechanisms than short-lived phasic motor events.[34 35]

In conclusion, this is the first study demonstrating the existence of an association between HAPPWs and pain in IBS patients reporting pain symptoms under physiological conditions. HAPPWs associated to pain symptoms are only slightly different from HAPPWs not associated to pain. HAPPWs as a cause of pain in IBS may explain why pain is frequently relieved with defecation, commonly is related to a change in stool frequency or consistency and does rarely awake the patient from sleep.

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Chapter 5

TONE AND PHASIC MOTILITY OF THE LEFT COLON IN DIVERTICULAR DISEASE

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Submitted

ABSTRACT

Background & Aims: Asymptomatic diverticular disease (ADD) and symptomatic uncomplicated diverticular disease (SUDD) are common entities but their pathogenesis is still unclear. We aimed to assess whether rectal and sigmoid colonic tone and phasic motility play a role in diverticular disease and whether ADD and SUDD show distinct tonic and phasic motility patterns.

Methods: 9 ADD patients, 9 SUDD patients and 8 healthy controls were studied. Using a dual barostat device, tone in the rectum and sigmoid colon was recorded simultaneously before and after a 600-kCal liquid meal. Concurrently, four manometric pressure ports recorded phasic motility in the sigmoid colon.

Results: Rectal tone was not different between groups. In the sigmoid colon a trend towards lower volume at MDP+2mmHg was found in the SUDD group as compared to the ADD group ($p = 0.068$). Phasic motility, expressed as area under the curve, was higher in the ADD group than in the controls ($p = 0.020$) and marginally higher than in the SUDD group ($p = 0.056$). Both SUDD patients ($p = 0.018$) and controls ($p = 0.047$) showed an increase in motility after the meal while the ADD group did not show this phasic response.

In the SUDD group there was a significant negative correlation between sigmoid barostat volume and number of phasic pressure waves ($r_s = -0.768$, $p = 0.016$) as well as between barostat volume and AUC ($r_s = -0.723$, $p = 0.028$).

Conclusion: Patients with uncomplicated diverticular disease with and without lower gastrointestinal symptoms show differences in tonic and phasic motility in the sigmoid colon, indicating that not only symptoms but also motility is a discriminating factor in SUDD and ADD.

INTRODUCTION

Colonic diverticular disease has become increasingly prevalent among the population of economically developed countries.[1-4] Uncomplicated diverticular disease may or may not give rise to symptoms and the terms symptomatic uncomplicated diverticular disease (SUDD) and asymptomatic diverticular disease (ADD) have been used to describe these subgroups.[5 6]

Apart from a low-residue diet, increased motility in the diverticula-bearing colon is thought to be one of the mechanisms involved in the development of these pulsion diverticula. However, manometric studies in diverticular disease have yielded conflicting results.[7-16] A recent study in patients with SUDD using 24-hour manometry showed preprandial hypermotility, an abnormal colonic motor response to eating and an increased incidence of high-amplitude propagated pressure waves in the affected segments.[17]

A change in bowel wall structure and narrowing of bowel lumen is thought to be another component to the development of diverticular disease.[18 19] Colonic tone may be an important factor in the development of this narrowed sigmoid lumen. Raised basal and postprandial colonic tone may increase the percentage of pressure waves causing total occlusion of the lumen, leading to progressive stress upon the colonic wall.[13] However, no information on the role of colonic tone in diverticular disease and its relationship to phasic motility exists in literature.

In this study we evaluated colonic and rectal periprandial tone and phasic motility in patients with asymptomatic (ADD), and symptomatic (SUDD) uncomplicated diverticular disease and in healthy controls using a combined barostat-manometry technique.

METHODS

Patients

Nine patients (four men and five women), mean age 54 years (range 43-65), with a clinical diagnosis of symptomatic uncomplicated diverticular disease (SUDD) were recruited from the outpatient clinic of the department of Gastroenterology of the University Medical Center Utrecht. Diagnosis was based on left lower quadrant abdominal pain, the presence of more than four diverticula in the sigmoid colon, as diagnosed by barium enema or colonoscopy, and the absence of inflammatory or bleeding complications of diverticula in the medical history.

Nine patients (six men and three women), mean age 58 years (range 45-69), with a diagnosis of asymptomatic uncomplicated diverticular disease (ADD) were selected from the colonic polyp surveillance program, on the basis of having more than four diverticula in the sigmoid colon in the absence of abdominal complaints or complications of these diverticula in their medical history.

Eight healthy volunteers (five men and three women), mean age 51 years (range 43-60), were recruited by advertisement and from our own files.

None of the subjects had signs of systemic or other gastro-intestinal disease or a medical history of abdominal surgery. All subjects had normal bowel habits defined as a stool frequency of > 3 per week but < 3 per day and a stool consistency of 2.5-3.5 on a 5-point scale. None of the subjects used medication, including laxatives, on a regular base. Written informed consent was obtained from each subject and the Ethics Committee of the University Medical Center Utrecht approved the study protocol.

Barostat Device

A computer-driven volume-displacement device (Distender Series II Dual Drive Barostat, G&J Electronics Inc., Willowdale, Ontario, Canada) was used to inflate two polyethylene bags: one in the sigmoid colon and one in the rectum. The barostat device contained two independently functioning cylinders acting as non-compliant bellows, each having a capacity of 1200 ml. These reservoirs were connected via non-compliant

tubes to the polyethylene bags. The barostat device continuously measured the volume of air within these bags, which were maintained at a constant and pre-selected pressure level by an electro-mechanical feedback mechanism. In response to any change in pressure measured in the bag, the barostat injected or withdrew air at a speed of 1.9 L/min. At each pressure the barostat automatically calculated corrected volumes according to Boyle's law; changes in barostat volume are thought to reflect a change in tone of the gut.

Colonic probes

In the sigmoid a multi-lumen non-compliant polyethylene tube assembly incorporating a 10-cm long cylindrical 40-µm thick polyethylene bag, located 15 to 25 cm from the tip, and four manometric water-perfused sideholes was used (Dantec Medical, Skovlunde, Denmark). The four sideholes (inner diameter 0.8 mm) were located 15, 10 and 5 cm orad to the proximal end of the bag and 5 cm caudad to the distal end of the barostat balloon. The manometric sideholes were perfused with distilled water at a flow rate of 0.1 ml/min.

In the rectum a two-lumen polyethylene tube incorporating a 10-cm long polyethylene bag at its tip was used (Dantec Medical, Skovlunde, Denmark). The channel for air injection and evacuation had an inner diameter of 6 mm in both catheters, allowing an air flow of 35 ml/sec. Each catheter had a second channel which ended in the bag and was connected to the pressure transducer in the barostat.

The maximal capacity of each of the cylindrical bags (during table-top inflation) was 800 ml and their maximal diameter was 10 cm. Before each experiment, the bags, catheters and barostat were checked for air leaks by submerging the bags under water, maintaining a constant pressure of 20 mmHg for 10 minutes.

Pressures and volumes in the barostat balloon were stored (after analog-to-digital conversion at 4 Hz) using computer software (Protocol Plus data scanner, G&J Electronics Inc., Willowdale, Ontario, Canada). Pressure signals recorded from the perfused sideholes were computer-stored with a sampling rate of 4 Hz (MMS, Enschede, the Netherlands).

Colonic Intubation

At 8.00 a.m. participants were admitted to the clinical research center after overnight fasting. The colon was cleaned by a 1.5-L enema of polyethylene glycol and electrolytes (Klean-Prep, Norgine, Amsterdam, The Netherlands). At 9.00 a.m. the sigmoid catheter incorporating the polyethylene bag was placed endoscopically. This procedure was performed without sedation and with minimal insufflation of air. The tip of the manometric catheter was attached to the colonoscope and introduced until the tip of the catheter reached the descending colon and the polyethylene bag was located in the sigmoid colon with the distal pressure port 20 cm proximal to the anus. Then the second probe with the polyethylene bag on the tip was introduced into the rectum without endoscopic assistance. Positions of the barostat bags were verified by fluoroscopy.

Study Protocol

After introduction of the probes, all subjects were requested to remain in a 30^{o} supine position during the entire recording session, and they were asked not to make unnecessary movements.

One hour after placement of the sigmoid and rectal probe, the 'minimum distending pressures' (MDP) were defined for both rectal and sigmoid bag by recording the lowest pressure at which respiratory excursions were recorded as changes in barostat volumes. The 'operating pressure' was set at 2 mmHg above MDP. After another hour of accommodation, with both bags at operating pressure, a 10-min preprandial recording period was followed by ingestion of a 500 ml, 600-Kcal (35% fat, 49% glucose, 16% protein) liquid meal (Nutridrink, Nutricia, Zoetermeer, The Netherlands) that was consumed in five minutes, followed by a 20-min postprandial recording period.

Thereafter the experiment was finished and the probes were removed by gentle traction.

Parameters investigated

Manometric activity. Phasic pressure activity in the sigmoid manometric tracings, recorded 15, 10 and 5 cm proximal and 5 cm distal to the barostat bag was analyzed for one 10-min period before and two 10-min periods after the liquid meal. These three

periods will be referred to as preprandial period, postprandial period 1 and postprandial period 2, respectively. Manometric data were analyzed automatically using a dedicated computer program. The computer program calculated the mean amplitude (hPa) and mean duration (sec) of pressure waves, the number of pressure waves and the area under the curves (AUC, hPa.s) for each of the four channels in the three 10-min periods. During this periprandial period high-amplitude propagated pressure waves (HAPPWs) defined as pressure waves that propagate distally across at least three sensors, with a speed of more than 0.3 cm/s and an amplitude of at least 133 hPa in two sensors and at least 100 hPa in one other sensor, were analyzed visually.

Barostat tracings. The mean volume at 'operating pressure' was automatically calculated in both the rectal and sigmoid barostat bag for the three 10-min periods before and after the meal, using a computer program (Protocol Plus data scanner, G&J Electronics Inc., Willowdale, Ontario, Canada).

Correlation between manometric activity and barostat volume. In order to detect a relationship between the periprandial manometric parameters (frequency, amplitude, duration, AUC) and the periprandial sigmoid barostat volume correlation coefficients were calculated.

Statistical Analysis

Data are expressed as mean (± SEM).

To analyze differences in barostat volumes during the total periprandial period between groups a General Linear Model for Repeated Measures was used. Paired t-tests for single patient comparison and independent t-tests for group comparisons were used to evaluate differences between tone or AUC in the separate periprandial periods.

In analyzing the phasic pressure waves we restricted statistical comparisons to the AUC. Pearson's coefficient of correlation was used to examine the correlation between the sigmoid volume and phasic motility parameters. All analyses were conducted using the SPSS 7.0 statistical package.

RESULTS

Phasic motility in the sigmoid colon

ADD patients had significantly more sigmoid phasic motility, as expressed as AUC for the total periprandial period, than did the control group ($p = 0.020$). A trend towards a higher AUC was seen in the ADD group as compared to the SUDD group ($p = 0.056$). In the SUDD group the AUC was not significantly different from that in the control group.

The SUDD group ($p = 0.018$) and control group ($p = 0.047$) both showed a significant increase in phasic motility after the meal while the ADD group did not show a gastro-colonic response (Figure 1, Table 1).

During the 30-min study period, HAPPWs did not occur in any of the 26 subjects.

Table 1: Manometric findings in the sigmoid colon

		Preprandial	Postprandial 1	Postprandial 2	Total period
Number of contractions	Controls	11.4 ± 4.5	16.8 ± 4.7	15.0 ± 4.5	41.3 ± 11.2
	ADD	19.6 ± 4.2	23.8 ± 4.7	30.7 ± 4.0	74.0 ± 8.9
	SUDD	19.6 ± 6.4	26.1 ± 7.4	22.8 ± 5.4	68.4 ± 17.4
Mean amplitude (hPa)	Controls	22.8 ± 2.2	25.3 ± 1.8	24.9 ± 2.3	25.0 ± 1.5
	ADD	35.6 ± 4.5	34.0 ± 2.7	31.5 ± 2.5	33.5 ± 2.4
	SUDD	25.3 ± 1.8	29.0 ± 1.8	28.1 ± 2.2	29.0 ± 1.8
Mean duration (sec)	Controls	3.6 ± 0.8	4.3 ± 0.7	3.8 ± 0.8	4.0 ± 0.6
	ADD	5.1 ± 0.7	4.8 ± 0.6	4.6 ± 0.4	4.8 ± 0.5
	SUDD	3.0 ± 0.4	4.8 ± 1.0	3.5 ± 0.3	4.5 ± 1.0
AUC (hPa.sec)	Controls	1203 ± 538	1803 ± 511†	1779 ± 798	4563 ± 1323
	ADD	3351 ± 856#	3641 ± 832	4263 ± 997	11256 ± 2112*
	SUDD	1240 ± 455	2416 ± 750‡	2077 ± 699	5734 ± 1656

Data expressed as mean ± standard error of mean.
Statistical comparisons done for AUC only.

* ADD compared to controls: $p = 0.020$; ADD compared to SUDD: $p = 0.056$
\# ADD compared to controls: $p = 0.057$; ADD compared to SUDD: $p = 0.045$
† Controls: postprandial period 1 compared to preprandial period: $p = 0.047$
‡ SUDD: postprandial period 1 compared to preprandial period: $p = 0.018$

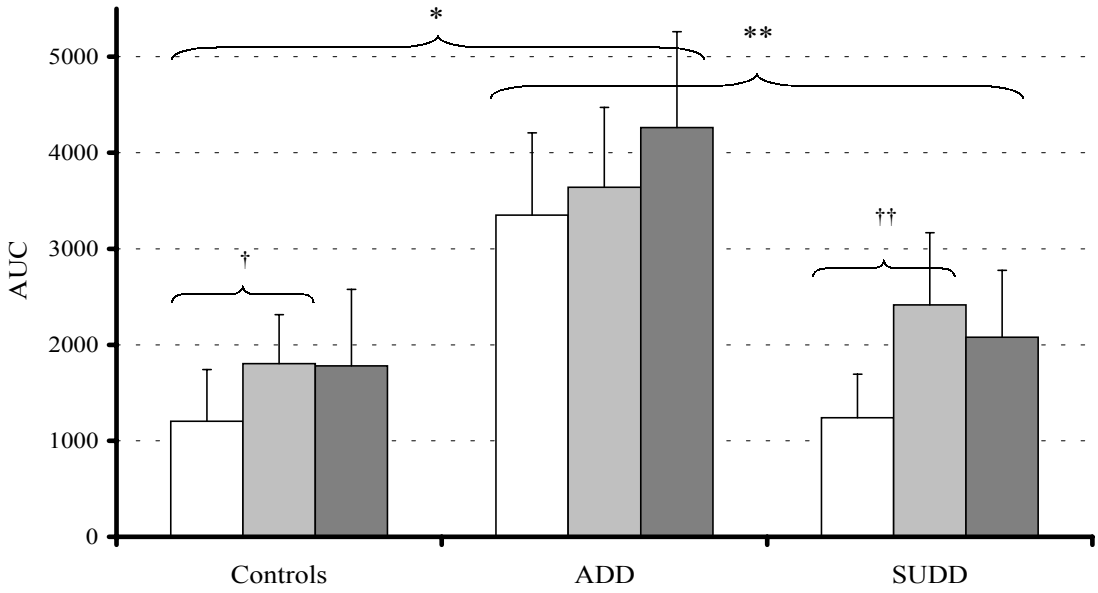

Figure 1. Area under the curve (AUC, hPa.s) for phasic motility in the sigmoid colon during the periprandial period. Preprandial (open bars), postprandial period 1 (light grey bars) and postprandial period 2 (dark grey bars).

Motility was increased in the ADD group as compared to the control group (* p = 0.020) whereas the difference between the ADD and the SUDD group just failed to reach statistical significance (** p = 0.056). Control and SUDD group showed a significant increase in motility after the meal († p = 0.047; †† p = 0.018).

Tone in rectum and sigmoid colon

The operating pressures (MDP + 2 mmHg) in the sigmoid colon and rectum were not significantly different between healthy controls (14.9 ± 1.3 and 18.3 ± 1.2 mmHg, respectively), ADD patients (16.8 ± 1.1 and 19.3 ± 0.9 mmHg, respectively) or SUDD patients (17.2 ± 1.2 and 20.4 ± 0.7 mmHg, respectively).

In the rectum no significant differences in tone were found between groups, neither in rectal volumes in the total periprandial period nor in the magnitude of reduction of rectal volume after the meal. In all three groups postprandial rectal volume was significantly lower than preprandial rectal volume (controls p = 0.009; ADD p = 0.026; SUDD p = 0.002), representing a physiologic postprandial increase in tone (Figure 2, Table 2).

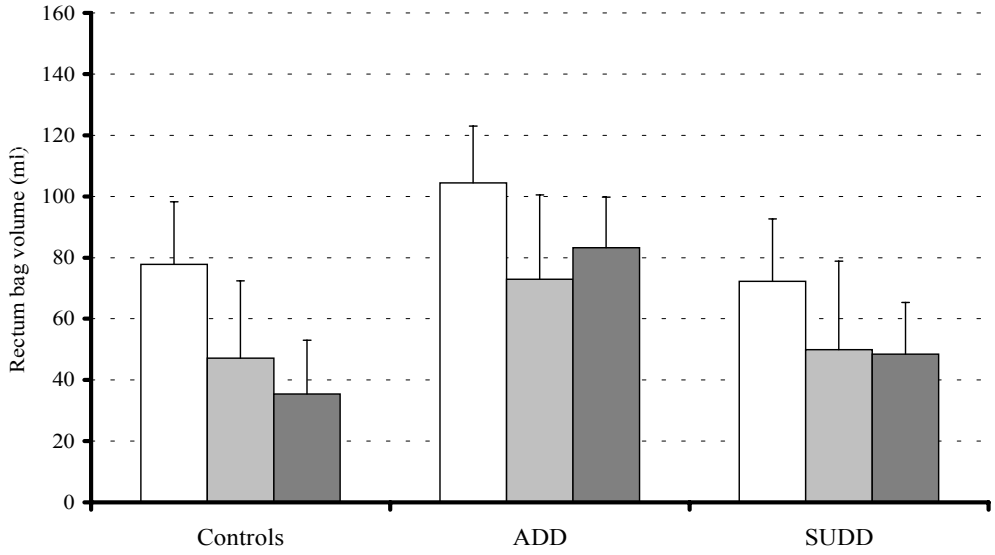

Figure 2. Barostat volumes in the rectum before the meal (open bars), and in postprandial period 1 (light grey bars) and postprandial period 2 (dark grey bars).
There were no significant differences between groups. In all three groups rectal volume decreased significantly after the meal (controls p = 0.009; ADD p = 0.026; SUDD p = 0.002).

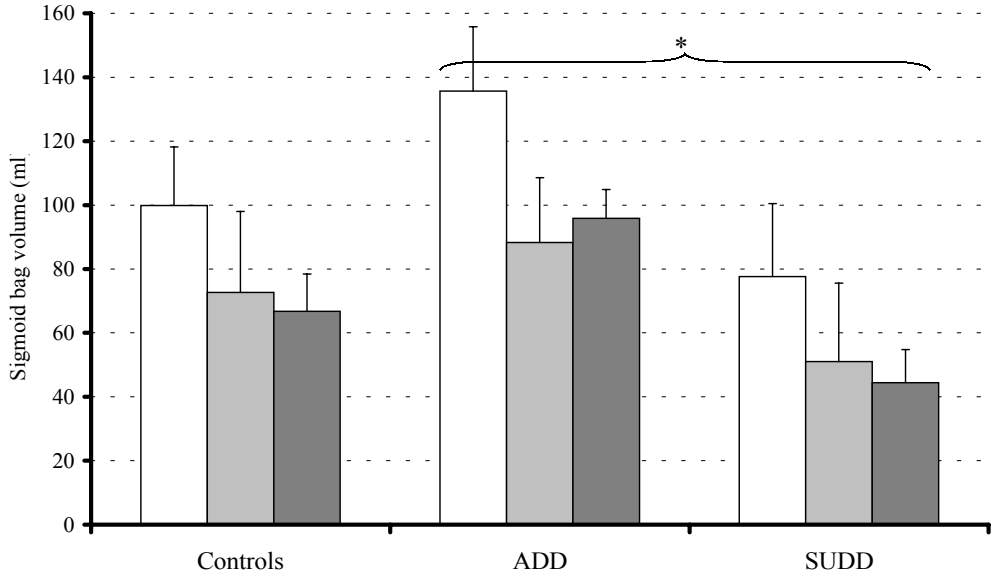

Figure 3. Barostat volumes in the sigmoid colon before the meal (open bars), and in postprandial period 1 (light grey bars) and postprandial period 2 (dark grey bars). Periprandial barostat volumes in the ADD group tended to be higher than in the SUDD group (* p = 0.068). In all three groups sigmoid volume decreased significantly after the meal (controls p = 0.001; ADD p = 0.002; SUDD p = 0.004).

In the sigmoid colon barostat volumes in the total periprandial period did not differ significantly in any of the patient groups as compared to the control group. However, a trend towards decreased sigmoid barostat volumes, was found in the SUDD group as compared to the ADD group ($p = 0.068$).

All groups had a prompt and highly significant decrease in sigmoid barostat volumes after ingestion of the meal (controls $p = 0.001$; ADD $p = 0.002$; SUDD $p = 0.004$). The volume reached in postprandial period 1 was maintained in the postprandial period 2. The magnitude of the volume reduction was not significantly different between groups, representing a postprandial tonic response in all three groups (Figure 3, Table 2).

Table 2: Volume in sigmoid colon and rectum; differences between groups

		Preprandial	Postprandial 1	Postprandial 2
Volume sigmoid colon (ml)	Controls	99.9 ± 18.2	72.7 ± 20.1	66.7 ± 22.8
	ADD	135.7 ± 25.3*	88.3 ± 20.2	95.9 ± 24.5#
	SUDD	77.7 ± 11.7	51.0 ± 9.0	44.4 ± 10.4
Volume rectum (ml)	Controls	77.8 ± 20.5	47.2 ± 18.6	35.4 ± 20.5
	ADD	104.4 ± 25.2	72.9 ± 27.5	83.3 ± 28.9
	SUDD	72.2 ± 17.9	49.9 ± 16.5	48.4 ± 16.9

Data expressed as mean ± sem
* Preprandial period: ADD compared to SUDD: P = 0.061
# Total periprandial period: ADD compared to SUDD: P = 0.068

Correlations between sigmoid volume and phasic motility

In the SUDD group a significant negative correlation between the sigmoid barostat volume and the number of phasic pressure waves ($r_s = -0.768$, $p = 0.016$) was found during the total 30-min period, as well as a significant inverse correlation between the barostat volume and AUC ($r_s = -0.723$, $p = 0.028$). No correlations were found between sigmoid barostat volume and periprandial phasic motility parameters in the control or ADD group.

DISCUSSION

In this study we compared patients with asymptomatic diverticular disease (ADD) and patients with symptomatic uncomplicated diverticular disease (SUDD), with healthy controls. A dual barostat device enabled us to measure simultaneously rectal and sigmoid volume as well as phasic motility in the sigmoid. When intraluminal pressure is kept constant, changes in colonic tone caused by contraction or relaxation of the colonic smooth muscle cells lead to sustained changes in luminal cross-sectional area and circumference. Since colonic surface area cannot easily be measured directly in vivo, it is assumed that the colon and rectum roughly behave like cylindrical structures, implying that variations in volume as measured by the barostat reflect fluctuations in colonic diameter, and are thought to reflect variations of tone of the bowel wall.[20]

In our study rectal volume at MDP+2 mmHg and the postprandial increase in rectal tone were not significantly different between groups. Therefore we believe that it is doubtful that tone in the rectum plays a major role in the pathophysiology of diverticular disease.

Sigmoid colonic volume tended to be lower in the SUDD group than in the ADD group. Although the ADD group had a comparable postprandial decrease in sigmoid volume, the postprandial sigmoid volume in ADD was still higher than the preprandial volume in the SUDD group. These findings suggest that the sigmoid of SUDD has a higher tone than that of ADD patients. If we assume that the sigmoid is cylindrical in both groups, the sigmoid of our patients with SUDD tended to be narrower than the sigmoid of the ADD patients, both before and after a meal.

Manometric detection of phasic contractions of the gut wall requires lumen occlusion. One would therefore expect that manometry would have detected more and stronger phasic contractions of the sigmoid in the SUDD patients than in the ADD patients, since the latter have a wider sigmoid. However, the opposite was found. We found that phasic motility, expressed as AUC, was significantly higher in the ADD group than in the control group and tended to be higher than in the SUDD group. The SUDD group and controls, but not the ADD group, demonstrated a postprandial increase in phasic motility. In the SUDD group exclusively, a significant negative correlation between the

sigmoid barostat volume and phasic motility was found which means that a decrease in sigmoid volume, i.e. an increase of tone, indeed is expected to stimulate phasic motility in this patient group.

In 5 of the 6 earlier studies on sigmoid motor activity in diverticular disease an increased phasic motility was found. [10-12] [21-23] However, all of these studies were performed in patients with various subtypes of diverticular disease grouped together. More recently, some studies investigated subgroups of diverticular disease. A study by Weinreich and Andersen found an exaggerated response to prostigmine in SUDD patients as compared to ADD patients and controls.[14] Trotman and Misiewicz found increased motility before and after a meal in patients who were asymptomatic at the time of the experiment.[15] In a study by Cortesini et al. 60 % of SUDD patients had increased motility indices as compared to ADD patients and controls. The maximum amplitude of pressure waves was significantly higher in SUDD than in ADD and controls during the 6-hour registration period, with peaks frequently exceeding 120 mmHg. No differences were found between ADD and controls.[5] Katschinski et al performed a combined myoelectric and manometric recording study of the sigmoid in SUDD, mixed IBS patients and controls. He found no significant differences in motility characteristics between groups using objective computer analyses.[16] A recent prolonged manometric study by Bassotti et al. in SUDD patients found a higher motility index only in the period before and not after a meal in the left colon. An increased number of HAPPWs contributed to the increased motility indices of SUDD patients.[17]

We could not confirm the increased periprandial phasic motility in the SUDD group, as found in some earlier studies, and rather found increased motility in ADD. This discrepancy might well be explained by the fact that, due to a relatively short observation period no HAPPWs, which usually have a great impact on motility indices or AUC, were observed in our study.

In conclusion, we have shown that sigmoid motor activities in patients with symptomatic uncomplicated diverticular disease differ from those in patients with asymptomatic diverticulosis. In SUDD the volume of the sigmoid colon tends to be lower than in ADD and phasic motility of the sigmoid tends to be decreased as compared to ADD. These observations indicate that not only symptoms but also motility in the sigmoid colon is a discriminating factor in these two groups of patients with uncomplicated diverticular disease.

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Chapter 6

COLORECTAL VISCERAL PERCEPTION IN DIVERTICULAR DISEASE

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Submitted

Abbreviations:

ADD: Asymptomatic Diverticular Disease
SUDD: Symptomatic Uncomplicated Diverticular Disease
IBS: Irritable Bowel Syndrome
MDP : Minimum Distension Pressure
GLM: General Linear Model for Repeated Measures

ABSTRACT

Background & Aims: The pathogenesis of asymptomatic diverticular disease (ADD) and symptomatic uncomplicated diverticular disease (SUDD) has not been elucidated. The aim of our study was to assess whether altered visceral perception or abnormal compliance of the colorectal wall play a role in these clinical entities.
Methods: Using a dual barostat device, sensations were scored and compliance curves were obtained using stepwise intermittent isobaric distensions during the preprandial period in the rectum and during the pre- and postprandial period in the sigmoid in 10 ADD patients, 11 SUDD patients and 9 healthy controls.
Results: In the rectum perception was increased in the SUDD group as compared to controls ($p = 0.010$) and ADD group ($p = 0.030$). Rectal compliance curves were not different between groups. In the sigmoid colon, perception in the pre- and postprandial period was increased in SUDD as compared to controls ($p = 0.018$) but not when compared to ADD.
In the rectum and the sigmoid colon, perception in the ADD group was not different from controls. Both in the rectum and in the sigmoid volume-pressure curves had comparable slopes (compliance) in all groups. However, pressure-volume curves were shifted downwards in SUDD as compared to ADD in the preprandial period ($p = 0.026$).
Conclusion: Symptomatic but not asymptomatic uncomplicated diverticular disease is associated with heightened perception of distension, not only in the diverticula-bearing sigmoid, but also in the unaffected rectum. This hyperperception is not due to altered wall compliance.

Keywords:
Diverticular disease; visceral perception; colonic wall compliance; barostat; sigmoid colon; rectum.

INTRODUCTION

Diverticular disease is a highly prevalent disorders in western countries, the incidence rising with increasing age, till 30 % above the age of 60 years. Probably 20-25% of cases go undetected, while 10-25% of patients under observation develop clinical signs of complications.[1-4] Three categories of diverticular disease can be distinguished: 1/ Asymptomatic diverticular disease (ADD), in which multiple diverticula are found at colonoscopy or barium enema, without related symptoms. 2/ Symptomatic uncomplicated diverticular disease (SUDD), in which diverticula and abdominal pain are present, with or without irregular bowel function. SUDD is also known as painful diverticular disease. 3/ Symptomatic complicated diverticular disease: diverticular disease in which hemorrhage, peridiverticulitis, abscess, perforation, fistula or bowel obstruction has developed.[5]

The pathogenesis of diverticular disease is still uncertain but is thought to be multifactorial. Patients with diverticular disease use significantly smaller quantities of dietary fibre than age-matched controls and geographic regions with low fibre intake have higher incidence rates of diverticular disease.[6-8]

Another factor thought to be involved in the pathogenesis of diverticular disease is increased phasic motility in the diverticula-bearing part of the colon, but the studies on this subject have yielded conflicting results.[9-14] A change in bowel wall structure is thought to be another component to the development of diverticular disease.[15 16] Symptoms in SUDD can be indistinguishable from those reported by patients with the irritable bowel syndrome (IBS). However, there are no data that indicate that IBS is a precursor of diverticular disease.[3 15 17] In IBS, increased visceral perception, with a decreased volume and pressure threshold for urge and or pain, was found in the rectum as well as at other intestinal levels and this abnormality is thought to be a hallmark of IBS.[18-21]

Only one study was performed that examined wall characteristics and perception in an unselected group of patients with diverticular disease. The techniques used in this 1969 study (including use of water-filled latex balloons) are now considered to be obsolete.[9] Nowadays, the barostat technique is considered to be the optimal tool to measure compliance and visceral perception, either by isobaric or isovolumetric distensions.[21-23]

The aim of our study was to assess sigmoid and rectal visceral perception as well as sigmoid and rectal wall characteristics in patients with asymptomatic and symptomatic uncomplicated diverticular disease and healthy controls.

METHODS

Study subjects

Eleven patients (five men and six women), mean age 56 years (range 43-68), with a clinical diagnosis of symptomatic uncomplicated diverticular disease (SUDD) were recruited from the outpatient clinic of the department of Gastroenterology at the University Medical Center Utrecht. This diagnosis was based on left lower quadrant abdominal pain, the presence of more than four diverticula in the sigmoid colon, as diagnosed by barium enema or colonoscopy, and the absence of inflammatory or bleeding complications of diverticula in the medical history. The selected patients had a relatively short history of abdominal symptoms (2 months – 6 years). Most of the patients fulfilled the Rome I symptomatic criteria for IBS, but two patients had had left lower abdominal pain for 2 and 3 months respectively and therefore did not meet the time limit of Rome I criteria (>6 months). Four of the SUDD patients were constipated as defined by the Thompson criteria for constipation.[24]

Ten patients (six men and four women), mean age 56 years (range 43-69), with a diagnosis of asymptomatic uncomplicated diverticular disease (ADD) were selected from the colonic polyp surveillance program. They were selected on the on the basis of having more than four diverticula in the sigmoid colon in the absence of abdominal complaints or complications of these diverticula in presence and past. None of them fulfilled the Rome I criteria for IBS and two were constipated as defined by the Thompson criteria.

Nine healthy controls (six men and three women), mean age 51 years (range 42-61), were recruited by advertisement and from our own files.

None of the subjects had signs of systemic or gastro-intestinal disease or a medical history of major abdominal surgery. All subjects, including patients, had normal bowel habits defined as a frequency of > 3 stools per week but < 3 a day and a soft to solid stool consistency.

None of the subjects used medication on a regular base. All participants were asked to stop all incidentally used laxatives and bulk agents one week before the start of the protocol.

Written informed consent was obtained from each subject and the Ethics Committee of the University Medical Center Utrecht approved the study protocol.

Barostat Device

A computer-driven volume-displacement device (Distender Series II Dual Drive Barostat, G&J Electronics Inc., Willowdale, Ontario, Canada) was used to inflate two polyethylene bags: one in the sigmoid colon and one in the rectum. The barostat device contained two independently

functioning cylinders acting as non-compliant bellows, each having a capacity of 1200 mL. Non-compliant tubes connected these reservoirs to the polyethylene bags. The barostat maintained a constant and pre-selected pressure level in the bag by an electro-mechanical feedback mechanism and continuously measured intrabag volume. In response to any change in pressure in the bag, the barostat injected or withdrew air to maintain the pre-selected pressure. Thus, the recorded changes in volume over time reflected changes in colonic tone.
The barostat apparatus included a built-in computer system that could be programmed to automatically perform distensions with fixed time-lag and bag pressure increments for both cylinders independently. At each pressure the barostat automatically calculated corrected volumes according to Boyle's law.
In this experiment we used the barostat to perform intermittent distensions, deflating the bag between each pressure-driven distension step, at an air flow rate of 1.9 L/min.

Colonic assemblies

A double-lumen non-compliant polyethylene tube (Dantec Medical, Skovlunde, Denmark) incorporating a polyethylene bag at 15 cm from the tip was used to perform distensions in the sigmoid colon. A similar polyethylene tube incorporating a polyethylene bag at its tip was used to perform distensions in the rectum. The channel for air injection and evacuation had an inner diameter of 6 mm in both catheters allowing an air flow of 35 ml/sec. The second channel had its side hole in the barostatic bag and this was used to measure the pressure in this bag. To each of the catheters a thin-walled (40 μm thick) polyethylene cylindrical bag, was attached. The maximum capacity of these bags was 800 ml, their maximum diameter was 10 cm (during table-top inflation) and their length 10 cm. Before each experiment, the bags, catheters and barostat were checked for air leaks by submerging the bags under water, while maintaining a constant pressure of 20 mmHg.

Study Protocol

At 8.00 a.m. participants were admitted to the clinical research center after overnight fasting. The colon was cleaned by a 1.5-L enema of polyethylene glycol and electrolytes (Klean-Prep, Norgine, Utrecht, the Netherlands). At 9.00 a.m. the sigmoid catheter incorporating the barostatic bag was placed endoscopically. The tip of the catheter was attached to the colonoscope and introduced until the tip of the catheter reached the descending colon and the bag was located in the sigmoid colon. The procedure was performed without sedation and with minimal insufflation of air. Then the second probe with the polyethylene bag at the tip was introduced

into the rectum without endoscopic assistance. Positions of the barostat bags were verified by fluoroscopy.

After introduction of the probes, all subjects were in a 30^{o} supine position during the entire recording session, and they were asked not to make unnecessary movements.

One hour after placement of the probes, the 'minimum distending pressure' (MDP) was defined for both rectal and sigmoid bag by recording the lowest pressure at which respiratory excursions were regularly recorded as changes in barostat volumes.

After another hour of baseline recording, with both bags at MDP + 2 mmHg, a series of 8 stepwise intermittent isobaric distensions (maintained for 2 min) were performed with 4-mmHg increments, deflating the rectal barostat balloon to MDP between two distensions during 2 min. The maximal pressure reached was 32 mmHg above MDP (distension step 8) or the pressure at which the subject perceived the maximal tolerable pain. After this rectal series and a 40-min baseline period at operating pressures, the same series as described above was performed in the sigmoid colon, with maximal pressure reached 28 mmHg above MDP (distension step 7) or the pressure at which the subject perceived the maximal tolerable pain, followed by a 10-min stabilizing period and a 20-min preprandial baseline recording.

Then a 600-kCal (16% protein, 49% glucose, 35% fat) liquid meal (Nutridrink, Nutricia, Zoetermeer, the Netherlands) was consumed in 5 min, followed by a 20-min postprandial period. Subsequently the same sigmoid distension procedures were carried out as described for the preprandial period.

Both during rectal and sigmoid distension the intensity of sensation to each distension step was scored. Prompted by a red light one min after the start of each distension, the subjects were asked to rate their sensation by pushing one button of an array of 7. Button 1 indicated "no sensation" and button 7 "maximal tolerable pain".

During distension of the rectum or sigmoid bag the pressure in the other bag (sigmoid and rectal respectively) was maintained at operating pressures. The subjects were instructed that they had the option to deflate the bags instantaneously at any time of significant discomfort by pressing a button on their electronic control panel. Subjects had no visual or auditory clues to anticipate the type or course of distensions.

After fluoroscopic control of the catheter position, the experiment was finished and the probes were removed. The duration of the experiment from probe placement until their removal was about 5 hours.

Parameters investigated

Perception score. The mean sensation score was assessed for every distension step.

Compliance. The volumes measured at 1 min after the onset of each of the distensions were used to construct the pressure-volume curves. The dV/dP relationship was analyzed by calculating the slope of the pressure-volume curve by means of linear regression analysis resulting in a compliance coefficient.

Statistical Analysis

Data are expressed as mean (SEM). To analyse differences in compliance curves and perception intensity curves between groups and between the pre- and postprandial state within groups, a General Linear Model (GLM) for Repeated Measures was used. Paired t-tests for within-patient comparison and t-tests for group comparisons were used to evaluate differences between compliance coefficients. All analyses were conducted using the SPPS 7.0 statistical package.

RESULTS

All subjects completed the experiment. None of the subjects used the emergency button on the control panel to deflate the balloon because of unbearable discomfort. None of the barostat bags was dislocated during the experiment, as checked by fluoroscopy.

Perception score

In the rectum perception scores in the distension series were significantly higher in the SUDD group than in controls ($p = 0.010$) and ADD group ($p=0.030$). No difference in perception scores were found between ADD and controls. (Fig. 1)

In the sigmoid colon, preprandial perception scores in the distension series were significantly higher in the SUDD group than in controls ($p = 0.018$) but not as compared to the ADD group.

Postprandially, in the sigmoid colon, comparable results were found with perception scores being significantly higher in the SUDD group than in controls ($p = 0.018$) but not significantly different from ADD. There were no significant differences in perception scores between ADD and controls, neither pre- nor postprandially. (Fig. 1)

Compliance

The operating pressures for the barostat bags in the sigmoid colon and rectum were not significantly different between controls (15 ± 1.3 mmHg and 18 ± 1.2 mmHg respectively), ADD (17 ± 1.1 mmHg and 19 ± 0.9 mmHg respectively) and SUDD patients (17 ± 1.2 mmHg and 20 ± 0.7 mmHg respectively).

Neither in the rectum, nor in the sigmoid there were differences between the three groups in the slope of the volume-pressure curves (dV/dP) (Fig. 2; Table 1). However, in the sigmoid colon, the preprandial volumes in SUDD patients were significantly lower than in the ADD patients ($p = 0.026$), due to a lower volume at MDP in the SUDD group. In the postprandial period a trend towards the same phenomenon was found ($p = 0.079$).

Ingestion of the meal had no significant effect on compliance (Fig. 2; Table 1)

DISCUSSION

In this study we have investigated two groups of patients with uncomplicated diverticulosis of the colon: one with asymptomatic diverticular disease (ADD) and one with symptomatic uncomplicated diverticular disease (SUDD), also called painful uncomplicated diverticular disease. We wished to examine whether visceral perception of the distension stimulus is different in these clinically distinct entities, and, if so, whether the differences could be explained by differences in compliance of the rectosigmoid. In the sigmoid colon, perception in the pre- and postprandial period was increased in SUDD patients as compared to controls. Rather unexpectedly we also observed increased perception scores in the rectum of SUDD as compared to ADD and controls. As will be discussed below, this increase in pain perception in the SUDD group was not due to a change in rectal wall characteristics.

Thus, in SUDD, increased perception appears to be present not only in the diverticula-bearing sigmoid colon but also in the unaffected rectum. This observation gives rise to the suggestion that patients with SUDD are in fact Irritable Bowel Syndrome (IBS) patients who also happen to have diverticulosis. Increased visceroperception in the rectum as well as in other parts of the alimentary canal is a well known feature of IBS. [18 20] It can be argued that some clinical observations suggest that IBS and SUDD are two distinct conditions without progression of one to the other. IBS patients often have a long history of abdominal complaints, starting at young adult age, whereas in many patients with symptomatic uncomplicated diverticular disease the onset of abdominal pain is shortly before the discovery of their diverticula.[3 15 17] However, these

observations do not take away the possibility that IBS patients with late symptom onset whose pre-existent diverticulosis is incidentally discovered during diagnostic work-up, are erroneously labeled as SUDD patients.

In our patients with uncomplicated diverticular disease bowel wall compliance was normal, not only in the rectum but also in the sigmoid, i.e., the resistance to distension was similar in ADD, SUDD and health. This also is an unexpected finding since a change in bowel wall structure is thought to be one of the components for the development of diverticular disease. In diverticular disease the amount of elastin in taeniae coli is increased, causing a shortening of taeniae and "upbunching" of muscle, mesentery and mucosa. The lumen narrows, the muscle layer seems increased and the gut is shortened.[15 16] One would expect that these changes could lead to a decreased compliance of the gut wall. However, in our study the SUDD group had significantly lower volumes on every pressure step as compared to the ADD group, without a change in wall compliance. A change in basal tone may explain this, and results in an increased lengthening of circular smooth muscle cells on every pressure distension in SUDD as compared to ADD at similar dV/dP when started at a lower sigmoid volume.

No alteration in compliance was observed in this study, whereas in diverticular disease, only one other distension study using water filled latex balloons was performed before, in which a decreased resistance to stretch of the sigmoid wall was found.[9] Pressure in a latex balloon, filled with progressive volumes of water was found to increase to a maximum, after which further increments of volume did not cause any further increase in pressure. The maximum was called the critical pressure. In patients with diverticular disease critical pressure was found to be half of the critical pressure of controls.[9] Postmortem distension studies yielded the same results.[25] It is now also accepted that latex balloons are far from ideal for studying colonic wall characteristics. First, a latex balloon has a compliance of its own that has to be corrected for. Secondly, at certain critical pressures, a latex balloon looses its elastic properties and becomes plastic, resulting in a balloon that can accommodate large volumes with little increase in pressure. In a rigid tube this may occur at a lower "critical pressure" than in a non-rigid tube.[23 26] Therefore, the results of our study cannot be compared with those obtained with a latex balloon.

In summary, the present study shows that patients with symptomatic uncomplicated diverticular disease (SUDD) show heightened visceral perception of distension stimuli applied to rectum and sigmoid colon which is not found in asymptomatic diverticulosis (ADD). The hyperperception is not due to an altered compliance of the gut wall. A study on perception and wall characteristics in SUDD patients as compared to age-matched patients with a long history of IBS without diverticula may resolve remaining questions.

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Table 1 Compliance (ml/mmHg) in rectum and sigmoid

	CONTROLS	ADD	SUDD
Rectum	7.5 ± 0.1	7.1 ± 0.7	9.2 ± 0.9
Sigmoid preprandial	4.1 ± 0.5	3.7 ± 0.5	4,1 ± 1.2
Sigmoid postprandial	4.7 ± 0.7	4.6 ± 0.9	3.9 ± 0.9

Data expressed as mean ± SEM.

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Fig. 1 Perception (score 1 = no sensation, score 7 = maximal tolerable pain) on stepwise isobaric distensions of the rectum and sigmoid colon during the preprandial period and in the sigmoid colon during the postprandial period in healthy controls (squares), ADD group (circles) and SUDD group (triangles).
* In the rectum the SUDD group had increased perception scores as compared to the control group (GLM: $p = 0.010$) and ADD group (GLM: $p = 0.030$).
# In the sigmoid colon in the pre- and postprandial periods, the SUDD group had increased perception scores as compared to the control group (GLM: $p = 0.018$).

Fig. 2 Volume-pressure curves in the rectum and sigmoid colon during the preprandial period and in sigmoid colon in the postprandial period on isobaric distensions in healthy controls (squares), ADD group (circles) and SUDD group (triangles).
Preprandially, the SUDD curve was shifted downwards as compared to the ADD curve (* GLM: $p = 0.026$).

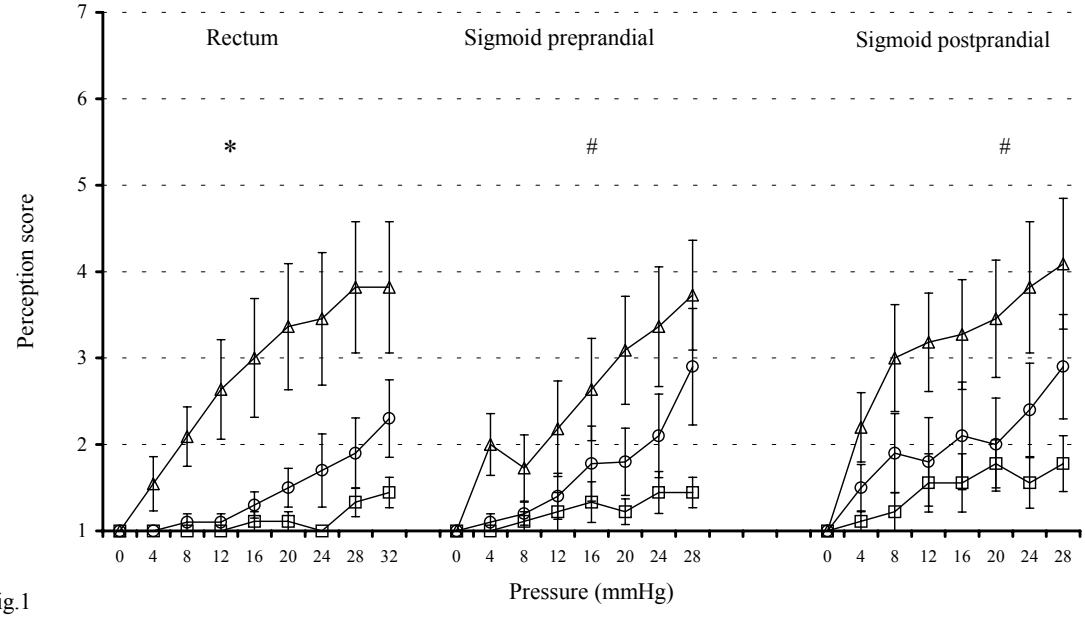
Rectum
Sigmoid preprandial
Sigmoid postprandial
*
#
#
Perception score
Pressure (mmHg)

Fig.1

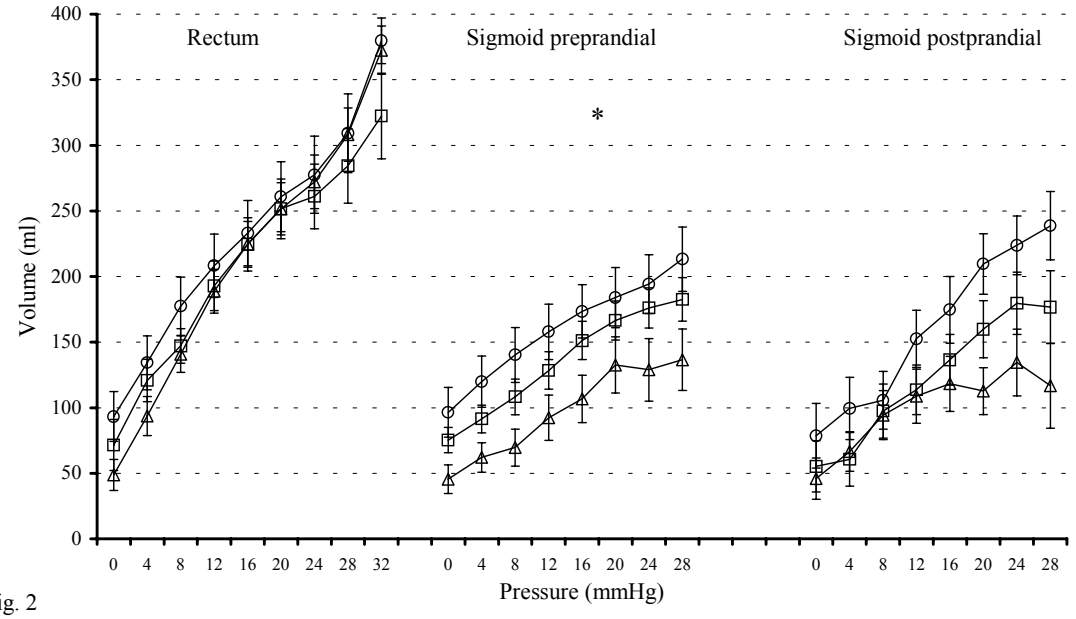
Rectum
Sigmoid preprandial
Sigmoid postprandial
*
Volume (ml)
Pressure (mmHg)

Fig. 2

Chapter 7

SUMMARY

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SUMMARY

Chapter 1 of this thesis is a general introduction in which the rationale for the research topics presented in this thesis is outlined. The available information on colonic motor and sensory functions in health, irritable bowel syndrome (IBS) and uncomplicated diverticular disease is summarized. The methods that can be used to evaluate motility and visceral perception are described and the relevant (patho) physiological results obtained with these tests are reported.

In IBS, recently developed techniques for prolonged recording of colonic motility in ambulant subjects have the potential to provide more insight into colonic motor function and its relationship with gastrointestinal symptoms. New pharmacotherapeutic options have emerged which aim to decrease visceral perception in IBS and to modulate colonic motility, but there is as yet very limited information on their effects on colonic function in IBS patients.

Our knowledge of the pathogenesis of asymptomatic (ADD) and symptomatic uncomplicated diverticular disease (SUDD) is still incomplete and the published results of studies on this subject are conflicting. The aim of our studies in these two groups of diverticular disease was to expand our knowledge of colorectal wall characteristics, visceral perception and motility, using state-of-the-art investigational techniques.

In **Chapter 2** a study is described in which a solid-state manometry catheter in the left colon was used to record motility patterns under physiological conditions during 24 hours in fully ambulant non-constipated IBS patients and matched healthy controls. The aim was to measure the response of left colonic phasic motility to physiologic stimuli, such as a meal and awakening, and to assess differences in the incidence and characteristics of high-amplitude propagated contractions (HAPCs) between IBS patients and healthy controls.

We showed that the descending colon in IBS patients has a decreased overall frequency of phasic contractions and motility index as compared to the sigmoid colon, whereas healthy controls did not show regional differences in left colonic motility. The IBS

patients had a lack of increase in the frequency of pressure waves and motility index in their descending colon in response to getting up or having a lunch, as compared to controls and as compared to their own sigmoid region.
In IBS patients the number of HAPCs was increased during the first half of the day. Clustered HAPCs were more frequently observed in IBS and these were found to be related to bowel movements whereas clusters were scarce and hardly related to bowel movements in controls. Furthermore, the HAPCs in IBS patients propagated more distally than did HAPCs in controls. These changes in HAPC incidence and characteristics may contribute to the higher stool frequency and softer stools that were reported by our non-constipated IBS patients.

Chapter 3 evaluates the effect of the 5-HT_3-antagonist alosetron on left colonic motility and stool characteristics in non-constipated IBS patients and matched healthy controls. Using a double-blind, randomized, crossover design and an ambulant manometry technique, 24-hour motility was studied on day 7 of treatment with alosetron 4 mg b.d., or placebo b.d. Pre- and postprandial phasic motility of the descending and sigmoid colon was studied. Alosetron increased contractile frequency in the sigmoid colon and the amplitude of contractions in the descending colon.
Alosetron increased the number of HAPCs in IBS patients during the second half of the day and prolonged the distance of HAPC propagation in the total study population, whereas no effects were found regarding HAPC duration, amplitude or propagation velocity. Paradoxically, stool frequency was decreased and stools became firmer during alosetron treatment.

In **Chapter 4** abdominal pain and HAPCs, in this chapter called high-amplitude propagated pressure waves (HAPPWs), were recorded during a prolonged, fully ambulatory, manometric study of the left colon in non-constipated IBS patients and healthy controls. The aim of the study was to quantify the association between pain episodes and HAPPWs, assessed by a modification of the symptom association

probability (SAP). An additional objective was to analyse HAPPW characteristics in IBS patients and healthy volunteers.
In the IBS patients, the incidence of HAPPWs was significantly higher than in healthy volunteers. During the 24-h study, 7 of the 11 IBS patients experienced 1-3 pain periods. Only 2 out of 10 controls experienced 1 pain period.
Four of the 7 IBS patients had SAP scores > 95% (96-99%), which implies that the probability that the association between HAPPWs and pain occurred by chance was less than 5%. The two control subjects who experienced abdominal pain had SAP values of 0 and 2%. A significant correlation was found between the duration of a pain period and the number of HAPPWs related to it. Pain-related HAPPWs occurred earlier after getting up and started at a more proximal level in the left colon than HAPPWs not related to pain. We conclude that an association between HAPPWs and pain episodes in IBS patients recorded under physiological conditions can be demonstrated and quantified.

Chapter 5 evaluates colonic and rectal periprandial tone and phasic motility in patients with ADD and SUDD and healthy controls. Using a dual barostat device, tone in the rectum and sigmoid colon was recorded simultaneously before and after a meal. Concurrently, four manometric pressure ports recorded phasic motility in the sigmoid colon. Rectal tone was not different between groups. In the sigmoid colon a trend towards a decreased volume was found in the SUDD group as compared to the ADD group. In the rectum and in the sigmoid colon a comparable postprandial increase in tone was found in the three groups. Phasic motility, expressed as area under the curve, was increased in the ADD group as compared to controls and SUDD group. Both SUDD patients and controls showed increased motility after the meal while the ADD group did not show this response. A negative correlation between sigmoid barostat volume and phasic motility was found in the SUDD group only. The differences in tonic and phasic motility in the sigmoid colon indicate that not only symptoms but also motility is a discriminating factor in SUDD and ADD.

In **Chapter 6** we investigated visceral perception and compliance of the colorectal wall in ADD, SUDD and healthy controls. Using a dual barostat device and stepwise intermittent isobaric distensions, sensations were scored and compliance curves obtained in both groups with uncomplicated diverticular disease and matched controls during the preprandial period in the rectum and during the pre- and postprandial period in the sigmoid colon. The SUDD group showed increased perception scores in the (non-diverticular) rectum as compared to controls and ADD, suggesting that SUDD patients might in fact be suffering from IBS. Increased perception in SUDD was also found pre- and postprandially in the sigmoid colon as compared to controls. No differences in perception score was found between ADD and controls. Neither in the rectum, nor in the sigmoid colon, differences between the three groups in the slope of the volume-pressure curves (dV/dP), i.e., compliance, was found. However, in the sigmoid colon, the preprandial volumes in SUDD patients were significantly lower than in the ADD patients. In the postprandial period a trend towards the same phenomenon was found. We conclude that hyperperception can be found in SUDD but not in ADD and this difference can not be explained by a change in wall compliance.

In answer to the questions posed in the introduction of this thesis:

1. Phasic motility of the left colon in non-constipated IBS patients is different from that in healthy controls in the sense that overall motility and the response to physiologic stimulants in the descending colon is less than in the sigmoid colon. In addition, the incidence of HAPCs is increased in IBS patients, HAPCs occur more frequently in clusters and propagate further distally in the sigmoid colon than in healthy subjects. These alterations may explain the higher stool frequency and softer stools reported by (non-constipated) IBS patients.

2. The 5-HT_3 -antagonist alosetron increases periprandial segmental left colonic motility and increases the incidence of HAPCs in IBS patients. Paradoxically, these effects are accompanied by a less frequent passage of firmer stools.

3. A temporal relationship between pain episodes and HAPPWs, as assessed by a symptom association probability score, was found in 4 of the 7 IBS patients who experienced pain episodes during the 24-hour recording period and in none of the 10 healthy controls.

4. SUDD patients tend to have a decreased sigmoid volume (higher tone) as compared to patients with ADD. Phasic motility is increased in ADD patients as compared to SUDD patients and healthy controls. These findings suggest that, apart from symptoms, motility factors discriminate between ADD and SUDD.

5. Patients with SUDD, in contrast to patients with ADD, show abnormal perception of distension, not only in the diverticular sigmoid colon but also in the unaffected rectum. This hyperperception is not due to abnormal colorectal wall compliance.

SAMENVATTING

Hoofdstuk 1 is een algemene inleiding waarin wordt uiteengezet waarom het in dit proefschrift beschreven onderzoek is uitgevoerd. Bestaande inzichten in de motorische en sensorische functies van het colon bij gezonde proefpersonen, bij patiënten met prikkelbaar darm syndroom (PDS) en bij patiënten met ongecompliceerde diverticulosis worden samengevat. De methoden die kunnen worden gebruikt om motorische en sensorische functies te meten worden beschreven en de resultaten die met deze onderzoeksmethoden werden verkregen bij gezonde vrijwilligers, bij PDS-patiënten en bij personen met ongecompliceerde diverticulosis worden weergegeven. Recent ontwikkelde technieken voor langdurige registratie van dikke darm motoriek bij volledig ambulante personen maken het mogelijk om meer inzicht te verkrijgen in de colon-motoriek en de relatie hiervan met symptomen bij patiënten met PDS. Recent werden nieuwe medicamenten ontwikkeld met als doel de verhoogde gevoeligheid van het maagdarm kanaal bij PDS te verminderen of de dikke-darm-motoriek te beïnvloeden. Tot nu toe is er echter slechts zeer beperkte informatie beschikbaar over het effect van deze medicamenten op de dikke-darm-functie. Onze kennis over de oorzaak van asymptomatische (ADD) en symptomatische ongecompliceerde diverticulosis (SUDD) is onvolledig en de gepubliceerde resultaten zijn vaak tegenstrijdig. Het doel van ons onderzoek verricht bij dezen twee groepen patiënten met diverticulosis was om de kennis te vergroten van de wandeigenschappen, perceptie en motoriek van de endeldarm en het (diverticuleuze) sigmoid, daarbij gebruik makend van de nieuwste onderzoeksmethoden op dit gebied.

In **hoofdstuk 2** wordt een onderzoek beschreven waarin een catheter met druk-opnemers in de linker helft van de dikke darm werd gebruikt om de drukpatronen van het colon gedurende 24 uur onder fysiologische omstandigheden te meten bij ambulante, niet-geconstipeerde PDS-patiënten. Een doel van dit onderzoek was om de reactie van het linker deel van de dikke darm op fysiologische prikkels, zoals het eten van een maaltijd of het ontwaken te bestuderen. Ook werd gekeken naar verschillen

tussen PDS-patiënten en gezonden in voorkomen en eigenschappen van de belangrijkste peristaltische golven van de dikke darm, de zogenaamde “high-amplitude propagated contractions” (HAPCs). Onze studie liet zien dat bij PDS-patiënten in het colon descendens minder motoriek is waar te nemen dan in hun eigen sigmoid. De gezonde vrijwilligers vertoonden een dergelijk verschil tussen twee regio’s van het linker colon niet. Als reactie op het ontwaken of het eten van een maaltijd vertoonden PDS-patiënten geen toename van de motoriek van het colon descendens terwijl deze respons wel aanwezig was bij de gezonden en in het sigmoid van beide groepen. Bij PDS-patiënten was het aantal HAPCs toegenomen tijdens de eerste helft van de dag. Snel opeenvolgende, gegroepeerde HAPCs kwamen vaker voor bij PDS-patiënten en gingen aan de stoelgang vooraf, terwijl gegroepeerde HAPCs bij gezonden zeldzaam waren en zelden voorafgingen aan de ontlasting. Tevens werden HAPCs bij PDS verder naar distaal, richting de endeldarm voortgeplant, dan bij gezonden. Deze veranderingen in HAPC-frequentie en -eigenschappen kunnen hebben bijgedragen aan de dunnere ontlasting en hogere frequentie van ontlasting zoals bij onze PDS-patiënten werd gevonden.

Hoofdstuk 3 evalueert het effect van de 5-HT_3-antagonist alosetron op de beweeglijkheid van het linker colon en het effect op ontlastingskarakteristieken bij niet-geconstipeerde PDS-patiënten en gezonde vrijwilligers. In een dubbelblind, gerandomiseerd, cross-over onderzoek werd van een draagbaar manometrisch systeem gebruik gemaakt om gedurende 24 uur de darm-motiliteit te meten op dag 7 van een behandeling met tweemaal daags 4 mg alosetron of placebo. De motoriek werd onderzocht in het colon descendens en sigmoid, voor en na de maaltijd. Alosetron verhoogde de frequentie van contracties in het sigmoid en de amplitude van contracties in het colon descendens. Bij PDS-patiënten verhoogde alosetron het aantal HAPCs gedurende de eerste helft van de dag en bij proefpersonen verlengde het de afstand waarover HAPCs werden voortgeplant. Er werd geen effect gezien op de duur van de HAPC, de amplitude of snelheid van propagatie. Paradoxaal genoeg nam de frequentie van ontlasting af en werd de consistentie van ontlasting harder tijdens behandeling met alosetron.

In **hoofdstuk 4** werden buikpijn en HAPCs, in dit hoofdstuk "high-amplitude propagated pressure waves" (HAPPWs) genoemd, geregistreerd tijdens een manometrisch onderzoek van het linker deel van de dikke darm bij ambulante PDS-patiënten en bij een controlegroep van gezonde personen. Het doel van het onderzoek was om de associatie tussen pijn perioden en HAPPWs te kwantificeren door gebruik the maken van een aangepaste "symptoom associatie waarschijnlijkheidsscore" (symptom association probability (SAP)). Een aanvullend doel van het onderzoek was om de eigenschappen van HAPPWs te analyseren bij PDS-patiënten en gezonde proefpersonen. In de PDS-groep was er een significant hoger aantal HAPPWs dan in de controle groep. Tijdens het 24-uurs onderzoek hadden 7 van de 11 PDS patiënten 1-3 pijnperioden. Slechts 2 van de 10 gezonden hadden ieder 1 pijnperiode. Vier van de 7 PDS patiënten hadden SAP scores > 95% (96-99%), wat betekent dat de kans dat de relatie tussen HAPPWs en pijn op toeval berustte kleiner was dan 5%. De twee gezonde proefpersonen die pijnklachten ondervonden hadden SAP scores van 0 en 2%. Er werd een significant verband aangetoond tussen de duur van een pijnperiode en het aantal bij die pijnperiode behorende HAPPWs. Pijn-gerelateerde HAPPWs kwamen vroeger op de dag voor en begonnen hoger op in de darm dan HAPPWs die niet pijn-gerelateerd waren. We concluderen dat bij patienten met PDS onder fysiologische omstandigheden een associatie tussen HAPPWs en pijnperioden kan worden aangetoond en gekwantificeerd.

In **hoofdstuk 5** worden de tonus in het rectum en de fasische motoriek en tonus van het sigmoid onderzocht bij patiënten met ADD, SUDD en bij gezonde vrijwilligers. Gebruik makend van een dubbele barostat werd de tonus tegelijkertijd gemeten in het rectum en in het sigmoid, voor en na een maaltijd. Op hetzelfde moment registreerden vier druk-sensoren de fasische motoriek van het sigmoid. De tonus in het rectum in de verschillende groepen was gelijk. Er werd een trend gevonden in de richting van een lager sigmoid-volume in de SUDD-groep, vergeleken met de ADD-groep. In rectum en in het sigmoid werd er een vergelijkbare toename gevonden van de tonus na de maaltijd

in alle drie de groepen. De fasische motoriek, uitgedrukt als “oppervlak onder de curve” (area under the curve (AUC)) was verhoogd in de ADD-groep vergeleken met de controle en de SUDD-groep. Zowel de SUDD-groep als de controle-groep vertoonde een stijging van de motoriek na de maaltijd terwijl de ADD-groep deze respons niet liet zien. Een negatieve correlatie tussen het volume en de motoriek van het sigmoid werd alleen in de SUDD-groep gevonden. De gevonden verschillen in tonus en motoriek in het sigmoid duiden erop dat niet alleen de klinische symptomen maar ook de motiliteit een onderscheidende factor vormen tussen SUDD en ADD.

In **hoofdstuk 6** onderzochten we de viscerale perceptie en compliantie van de wand van sigmoid en rectum bij ADD, SUDD en gezonde vrijwilligers. Gebruikmakend van een dubbele barostat en intermitterende, trapsgewijze isobare distensies, werd viscerale perceptie gemeten en compliantie-curves verkregen bij beide groepen met ongecompliceerde diverticulosis en de bij controle-groep, voor de maaltijd in het rectum en voor en na de maaltijd in het sigmoid. De SUDD-groep vertoonde een verhoogde perceptiescore in het (niet-diverticuleuze) rectum vergeleken met de controle-groep en met ADD, wat de suggestie wekt dat SUDD-patiënten in feite PDS-patiënten zouden kunnen zijn. Verhoogde perceptie in het sigmoid werd ook gevonden in de SUDD-groep, zowel voor als na de maaltijd, vergeleken met de controlegroep. De perceptiescore was niet verschillend tussen ADD-groep en controlegroep. Noch in het rectum, noch in het sigmoid, waren er verschillen tussen de groepen in de helling, d.w.z., compliantie, van de volume-druk curve (dV/dP). In het sigmoid waren de volumina bij de SUDD-patiënten voor de maaltijd significant lager dan bij de ADD-patiënten. In de periode na de maaltijd werd de zelfde trend gevonden. We concluderen dat een verhoogde perceptie kan worden gevonden bij SUDD maar niet bij ADD en dat dit verschil tussen groepen niet kan worden verklaard door een verandering in de compliantie van de wand.

Antwoorden op de vragen die in de introductie van dit proefschrift werden gesteld:

1. Fasische motoriek van het linker colon bij patiënten met PDS zonder constipatie is verschillend van die van een gezonde controlegroep in de zin dat de totale motoriek en de reactie op een fysiologische prikkel minder is in het colon descendens dan in het sigmoid. Daarnaast komen bij PDS-patiënten HAPCs en vooral gegroepeerde HAPCs vaker voor en planten HAPCs zich meer naar distaal voort in het sigmoid. Deze veranderingen zouden de hogere ontlastingsfrequentie en zachtere ontlasting bij niet-geconstipeerde PDS-patiënten kunnen verklaren.

2. Door de 5-HT_3 -antagonist alosetron neemt de beweeglijkheid rond de maaltijd in het linker colon toe en wordt de incidentie van HAPCs bij PDS-patiënten verhoogd. Het is paradoxaal dat deze effecten vergezeld worden door een lagere frequentie van steviger ontlasting.

3. Tijdens een 24-uurs drukregistratie werd een tijdsrelatie tussen pijnperioden en HAPPWs vastgesteld door gebruik te maken van een "symptom association probability score" bij 4 van de 7 PDS patiënten die pijnklachten hadden maar bij geen van de 10 controle-personen.

4. Patiënten met SUDD neigen tot lagere sigmoid-volumina (hogere tonus) vergeleken met patiënten met ADD. De fasische contracties in het sigmoid zijn toegenomen bij ADD vergeleken bij SUDD en de controle-groep. Deze bevindingen suggereren dat naast de klinische symptomen ook motiliteit een faktor is bij het onderscheid tussen ADD en SUDD.

5. Patiënten met SUDD laten, in tegenstelling tot patiënten met ADD, een abnormale gevoeligheid zien voor distensies in het diverticuleuze sigmoid, maar ook in het niet aangedane rectum. Deze verhoogde perceptie is niet een gevolg van een abnormale compliantie van de darmwand.

Chapter 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION and FUTURE PERSPECTIVES

The overall goal of this thesis was to gain more insight into two common gastroenterological disorders, irritable bowel syndrome (IBS) and uncomplicated diverticular disease, in which altered colonic motility and / or visceral perception are thought to play a role.

Research tools like prolonged ambulant manometry for assessment of phasic contractile activity and the barostat for measurement of tone, compliance and visceral perception have been used in the proximal gastrointestinal tract for years but only recently have these techniques found application in the human colon.
Studies using prolonged colonic manometry, performed since 1987, have provided important new information on colonic motility, such as on diurnal variations in phasic motility and on high-amplitude propagated pressure waves (HAPCs), also called high-amplitude propagated pressure waves (HAPPWs), that appeared to be responsible for major mass movements of colonic contents.[1] [2] However, most of these studies were performed in a laboratory setting using water-perfused catheters. Fully ambulant prolonged manometry studies, using solid-state catheters, are much more difficult to perform as consequence of frequent technical failure of electronic pressure transducers in the hostile environment of the colon, the frequency with which the catheter is dislocated by forceful propagated contractions and problems with perianal fixation of the catheter in these fully ambulant subjects.[3] In our studies, described in chapter 2, 3 and 4 of this thesis, we indeed experienced these technical problems leading to study failures, especially in the non-constipated IBS patients who had multiple bowel movements during the recording period. However, excellent support by the catheter manufacturer and use of catheter with sufficient rigidity to prevent it from curling up, reduced the number of our failures.

The method of colonic manometry used, allowed us to study phasic motility under near-physiological conditions, which had not been done before in non-constipated IBS

patients. The colonic motor abnormalities observed in these patients (higher frequency of HAPCs, more clustered HAPCs, and the HAPCs propagating more distally into the sigmoid colon , Chapter 2) might help to explain why non-constipated IBS patients complain of an increased defecation frequency and of softer stools. However, the relevance of the regional difference in left segmental motility that was found in IBS patients but not in controls is uncertain. Studies combining prolonged ambulant manometry with scintigraphic measurement of colonic transit may give more insight in the consequence of this regional motility difference.[3-5]

As confirmed in our studies, phasic colonic pressure waves often do not clearly propagate from one pressure sensor to the next. However, in our manometric catheters the pressure sensors or sideholes were 5 – 10 cm apart. Catheters equipped with multiple closely spaced pressure measuring ports (e.g. at 1-cm intervals) may give more insight into the propagation of pressure waves.[6] Ideally a multi-sensor solid-state catheter should be used that has an incorporated energy source, is fixated in the caecal region by a mucosal clip, ends in the rectum, and transmits its pressure signals wirelessly to a small data logger carried on a belt. Recording should be possible for several days. Analysis of manometric signals should be done with fully automated computerized analysis techniques for the detection of all presently known colonic motility patterns. Automated analysis prevents bias and saves much of the time required for visual analysis.[7]

In Chapter 3 we have shown that it is possible to perform a double blinded, randomized, crossover study using prolonged colonic manometry. However, highly motivated study subjects (and researchers) were needed to complete this inconvenient study. The 5-HT_3 -antagonist alosetron increased segmental motility in the left colon in the periprandial period studied and increased the number of HAPCs in IBS patients. Paradoxically this was accompanied by decreased stool frequency and firmer stools , suggesting delayed colonic transit , as was shown earlier by transit studies.[8] Alosetron may have normalized the decrease in segmenting pressure waves as was found in non-constipated patients in chapter 2. Combining the results of these two studies it can be suggested that, in non-constipated IBS patients, segmental motility is more important for left colonic transit than HAPCs.

In the year 2000, alosetron was withdrawn from the US market because of a high incidence of ischaemic colitis and severe constipation, resulting in many surgical interventions and 7 deaths. However, since June 2002, alosetron is back on the US market, under strict prescribing regulation. In constipation, phasic motility is characterized by a decreased number of HAPCs, unchanged fasting segmental motility and an insufficient postprandial increase.[6] [10] However, our study in IBS showed that alosetron leads to a decreased stool frequency and firmer stools as well as to an increase of left colonic segmental pressure waves and HAPCs. Therefore, it might be suggested that this increase of segmenting and propagated pressure waves and the firmer stool consistency brought about by alosetron, are able to cause ischaemic damage to the colonic mucosa in some IBS subjects with suboptimal blood supply. Future studies, using laser Doppler measurement of colonic tissue blood flow in combination with manometry, may shed more light on the mechanism for the development of ischaemic colitis in general and in IBS patients treated with alosetron in particular.[11]
In Chapter 4 our ambulant prolonged manometry technique was used to demonstrate the existence of statistically significant temporal relationships between pain episodes and HAPPWs in non-constipated IBS patients. When technical improvements would lead to reduction of costs and failure rates, this technique, in combination with the symptom association score (SAP) might be considered as a diagnostic tool in patients with unexplained episodic abdominal pain. The technique might also be used to study the origin of pain in patients with symptomatic uncomplicated diverticular disease. Furthermore, new IBS-targeted drugs that aim to decrease visceral perception might be assessed on the basis of their ability to reduce HAPPWs, pain periods and SAP scores.

The barostat has been used to study the human colon since 1991.[12] The barostat is considered to be the best tool for evaluation of colonic wall tone in vivo, and for measurement of study colonic wall compliance and visceral perception.[13]
In the study described in chapter 5 a dual barostat was used to measure rectal and sigmoid tone combined with manometric registration of phasic motility in the sigmoid colon. It was found that rectal tone is normal in diverticular disease while a tendency to a

decreased sigmoid volume was found in SUDD as compared to ADD and that phasic motility is increased in ADD as compared to SUDD and controls. These findings may suggest that ADD and SUDD develop by different pathophysiological mechanisms. In the study described in chapter 6 we used the barostat technique to show that patients with symptomatic uncomplicated diverticular disease (SUDD) but not patients with asymptomatic diverticular disease (ADD) have abnormal visceral perception, not only in the sigmoid colon but also in the rectum. Colorectal wall compliance in SUDD was similar to that in ADD. The results of our study raised the argument that patients with SUDD are in fact IBS patients who also happen to have diverticulosis. Future studies on perception and wall characteristics in SUDD patients as compared to age-matched patients with a long history of IBS without diverticula may resolve this issue. Until such studies have been performed it is recommended to exclude diverticular disease in studies on IBS. The combined results of chapter 5 and 6 may suggest that sigmoid hyperperception in SUDD is caused by an increased sigmoid tone. However, tone in the rectal area is normal whereas at this location also an increased visceral perception was found in SUDD.

Whereas colonic manometry and application of the barostat technique to the colon are invasive and require bowel preparation, it is to be expected that in the future new non-invasive techniques like magnetic resonance imaging (MRI) may be developed to a stage that they can be added to the armamentarium of investigators of colonic function.

The investigations described in this thesis not only have yielded new information on colonic function, but they have also made clear that the sensory and motor functions of the human colon are extremely difficult to study in vivo. Although it is more than likely that the development of new investigational techniques as well as refinement of existing techniques will facilitate further expansion of our knowledge of colonic function in health and disease in the near future, it is anticipated that progress in this area will be relatively slow.

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NAWOORD

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CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 22 april 1961 te Lisserbroek (Haarlemmermeer). In 1981 werd het VWO examen behaald aan het Fioretti College te Lisse. Aansluitend werd begonnen met de studie Geneeskunde aan de Universiteit van Leiden. In 1989 werd het artsexamen behaald. Vervolgens werd de dienstplicht vervuld bij de Koninklijke Marine. In deze periode werd ook het Amerikaanse artsexamen behaald. Hierna werd gedurende een jaar gewerkt als arts-assistent op de afdeling Interne Geneeskunde van het Bronovo Ziekenhuis te Den Haag. In 1991 werd begonnen met de opleiding Interne Geneeskunde in het Ziekenhuis Hilversum (opleider Dr. F. van Kersen). Dit werd in 1995 voortgezet in het Academisch Ziekenhuis Utrecht (opleider Prof. dr. D.W. Erkelens) en afgerond in 1998. In deze periode werd de opleiding gevolgd en klinisch onderzoek verricht op de afdeling Gastroenterologie (Prof. dr. G.P. van Berge Henegouwen) dat werd voortgezet na de registratie tot Internist. Sinds 1998 werkt hij in Het Diaconessenhuis Leiden.

Cees Clemens is de echtgenoot van Heleen Ceha en de trotse vader van Emma (1995) en Pieter (1997).