Motility and Endosonographic Studies in Patients with Anorectal Disorders

C.E.J. Sloots

Motility and Endosonographic Studies in Patients with Anorectal Disorders

Motiliteit en endoechografie studies bij patiënten met anorectale aandoeningen

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CHAPTER 1

GENERAL INTRODUCTION AND AIMS OF THE STUDY

This thesis consists of two parts. The first part describes rectal visceral sensitivity, compliance and motility in health and disease. The second part studies the anatomy and classification of cryptoglandular fistula and Crohn's disease associated fistula-in-ano by means of transanal endosonography.

Rectal visceral sensitivity and motility

The defecation process is a co-ordinated colorectal and anal motor action. A bowel movement consists of colonic contractions that proceed distally and increase rectal pressure. Simultaneously, the anal sphincters relax with the onset of the colonic contractions and remain relaxed until the bowel movement is expelled when a socially acceptable place is found.[1,2] When defecation cannot take place, the external sphincter contracts voluntarily and the rectum relaxes by increasing its compliance.[3,4] The studies in the first part of the thesis focus on the investigations of rectal visceral sensitivity and motility in health and constipation.

Rectal visceral sensitivity and compliance

Different methods have been used to test visceral sensitivity and compliance. Initially, latex balloons on a catheter connected with a syringe were used to perform volume-controlled distension. Later on, roller pomp and intraballoon pressure measurement were used to slowly distend the balloon and calculate compliance. In 1985, Azpiroz and Malagelada introduced the barostat consisting of a high-compliant polyethylene bag mounted on a catheter connected to a computer controlled distension pump.[5] With this system, volume-, pressure- or wall tension-controlled distension can be performed in an intermittent or continuous distension manner.[6,7] Rectal compliance can be measured inflating the intrarectal bag with a continuous pressure distension protocol and registering the intrabag volume. The volume curve has a sigmoidal shape (Figure 1). After an initial increase in pressure without volume increase, the volume steeply increases and a final increase in pressure without volume alteration (with the perception of pain and discomfort). In the first part of the compliance curve, the distension represents the muscular tone (active stretch) while the latter part of the curve represents the connective tissue and muscle (passive stretch).[8] Drugs (such as clonidine) influence dynamic compliance or active stretch but not passive stretch or the compliance at maximal tolerated pressure.[9] Rectal visceral sensitivity and

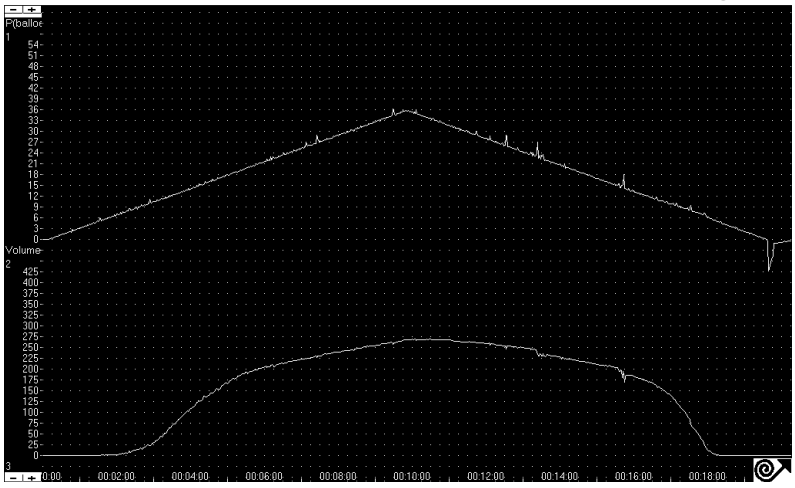

Figure 1

compliance are of interest in studying the awareness of rectal filling and the rectal storage function in physiology and pathophysiology.

Rectal motility

Rectal tone and phasic contractions of the bowel wall can be studied with the barostat or with colorectal manometry with a multiport assembly. In a wide hollow organ such as the rectum, manometry does not register the subtotal contraction.[10] Rectal tone and contractions are physiologically influenced. The colon relaxes during sleep and increases its tone on awakening and after a meal.[11] The response after ingestion of a meal starts prompt and is present in ascending, transverse, descending colon and in the rectum.[11-14] Studies of rectal tone and contractility give an impression of the propulsive function of the rectum in health and constipation.

Colonic transit time measurement

Colonic transit time (i.e. the period of transit of intraluminal contents throughout the colon) can be measured using radio-opaque markers. After ingestion of a set radio-opaque markers during 3 or 6 days, an abdominal film is taken on which the markers are counted (Figure 2).[15] Total colonic and segmental transit time can be calculated.[16] With this method the passage time of colonic contents can be measured to objectify complaints in constipation and the effects of drugs.

Figure 2

Functional Constipation

Functional constipation is a common complaint with a high variety in prevalence reported depending on the criteria used.[17] Different pathophysiological mechanisms are found in idiopathic constipation that could explain symptoms. Symptom complexes and anorectal and colonic motility test results are clustered in subtypes of idiopathic constipation. The generally used classification is slow transit constipation, pelvic floor dysfunction and constipation predominant irritable bowel syndrome.[18] Symptoms such as decreased stool frequency, laxative dependence, and a history of constipation since childhood can predict slow transit.
The term slow transit constipation generally refers to the patients with delayed colonic transit time and without an underlying systemic disorder or pelvic floor dysfunction.[18] Besides delayed colonic transit, decreased colonic motor activity after a meal or fewer high amplitude propagated contractions have been found.[19,20] Likewise, the term colonic inertia was introduced, which means that the colon is not responsive to a meal or a stimulant such as bisacodyl.[21]

Possibly, slow transit constipation represents a more generalised dysmotility disorder.[22]
Anismus (pelvic floor dyssynergia) is defined as an inappropriate contraction of the pelvic floor during straining, rather than relaxation.[24] Biofeedback training is the therapy of choice to improve symptoms of dyssynergic defecation such as straining and bowel frequency.[25,26]
In constipation predominant irritable bowel syndrome, bloating and pain are more prominent than decreased bowel frequency represented by an altered perception for rectal distension (visceral hypersensitivity).[23]

Rectocele

A rectocele or a posterior vaginal wall prolapse is a herniation of the anterior rectal wall into the vaginal lumen. Rectocele can develop due to a defect of the rectovaginal septum caused by vaginal childbirth or by excessive straining during defaecation. Patients with a rectocele can have defaecation disorders such as decreased bowel frequency in 8-41%, frequent straining in 22-53% and the need for digital support in 10-30%. Fifty percent of patients with a rectocele are bothered by their bowel function.[27-29] A rectocele can be diagnosed by digital vaginal and rectal examination. Defaecography can be helpful in confirming the diagnosis, however, physical findings are highly reliable.[30,31] Surgical treatment is considered the primary treatment in order to improve anatomy and symptoms.[28]

Transanal ultrasonography and fistula-in-ano

Transanal ultrasonography is a technique to visualise structures of the anal canal and rectum. The technique was derived from urology, where it was used for imaging of the prostate.[32] Transanal ultrasonography has been used in the diagnosis of various anorectal disorders. It is reliable in the staging and follow-up of rectal tumours.[33] Transanal ultrasonography has a proven value in assessment of faecal incontinence and perianal sepsis.[34]
Transanal ultrasonography is performed using a blind endoprobe connected to an ultrasound scanner. A rotating piezo-electric crystal in a water-filled rigid cone (1.7 cm diameter) is mounted on the top of the probe. Most used ultrasound frequencies are 7 and 10 MHz. With this system it is possible to obtain transverse images of the anorectal canal. The investigation is easy to perform with little patient inconvenience. Bowel preparation is not necessary for anal visualisation. One investigation can be performed in about 5 minutes.
Images obtained from transanal ultrasonography have been compared to anatomical preparations in order to establish basic ultrasound morphology.[35-37] Clearly visualised are the puborectalis muscle, the external and internal sphincters, the submucosal and pelvic floor structures around the sphincter complex. The puborectalis muscle is the point of orientation, as the proximal border of the sphincter complex. It appears as a V-shaped echogenic band, which slings posteriorly around the anal canal (Figure 3). The external and internal sphincters are shown when withdrawing the probe (Figure 4). The internal sphincter is a thin echolucent band of approximately 1-3 mm. It is

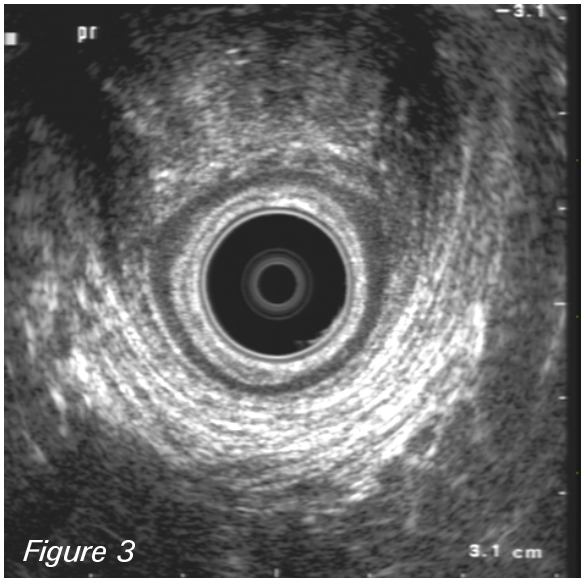

Figure 3

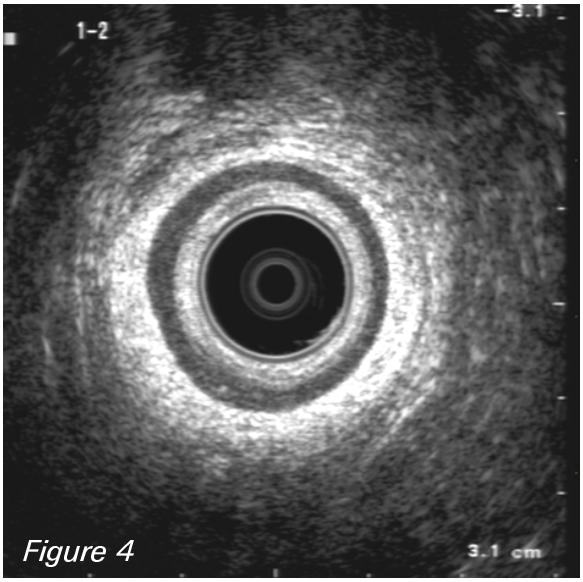

Figure 4

enclosed by the echogenic external sphincter, which is about 5-10 mm thick. The submucosal layer has a mixed echogenic aspect and is partly collapsed by the endoprobe. The mucosal layer can not be identified with the frequencies used, unless thickened. Other structures are identified such as the anococcygeal ligament, the transverse perineal muscles, the ischiocavernous muscles, the urethra and the pubic bones.[38-40]

Perianal sepsis or fistulas are feared because of recurrence and complications such as faecal incontinence. To reduce the risk of recurrence and postoperative incontinence, it is important to know the anatomic course of the perianal fistula before treatment. Proctological examination and probing of the fistula does not provide accurate assessment even as fistulography and computer tomography scanning. Transanal ultrasonography and magnetic resonance imaging (MRI) are accurate techniques to visualise fistula track and anal sphincter complex. Transanal ultrasound is moderate accurate in demonstrating fistula tracks.[41,42] A contrast agent such as hydrogen peroxide is needed to enhance accuracy to around 95% (Figure 5).[43-45]

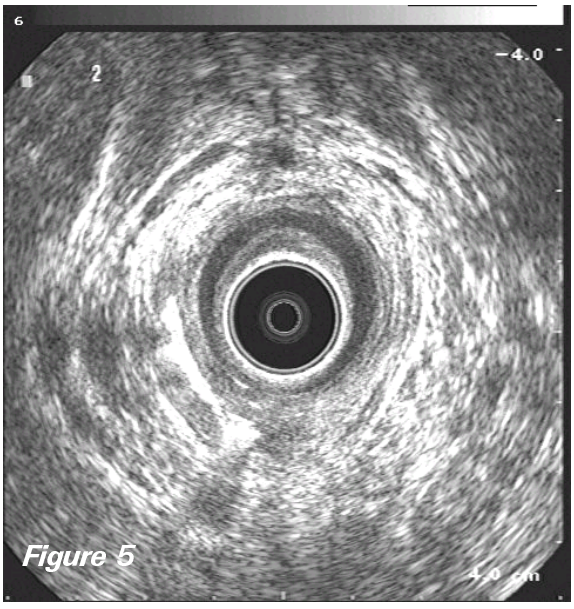

Figure 5

Transvaginal ultrasonography provides extra information about anovaginal fistulas and about the relation of perianal fistulas and the anovaginal septum.[46] The new three-dimensional endoanal sonography enhances interpretation and reviewing of images.[47] Moreover, transanal ultrasound can be performed in the operation room during surgery.

MRI with or without the use of endocoils is a competing technique to visualise anorectal disorders.[48-51] Because a prospective comparative study between

MRI and hydrogen peroxide enhanced transanal ultrasound has not yet been performed, it is not known which technique is superior. Depending on the local expertise and availability, a choice can be made.

AIMS AND OUTLINES OF THE INVESTIGATIONS

The aim of the studies in part 1 is to evaluate rectal visceral sensitivity and motility tests, e.g. rectal distension studies and colonic transit time measurement, in health and idiopathic constipation.
In our ano-rectal function laboratory rectal visceral sensitivity and compliance is measured using the water-inflated latex balloon method 'on routine'. Chapter 2 describes a retrospective study, which was performed to investigate the differences in rectal sensitivity and compliance in different patient groups compared to controls and to establish the clinical spin off of rectal compliance measurement.
A new technique, the barostat, has been promoted as a better instrument to determine visceral sensitivity and motility. In chapter 3, this technique is compared to the latex balloon system and different protocols were explored to test rectal visceral sensitivity and compliance such as pressure, volume or wall tension controlled continuous or intermittent distensions. Results of testing in healthy men and women are compared. With the barostat system, it is possible to design rectal tone. A tonic response can be triggered using a meal (postprandial rectal response). In chapter 4, two different caloric meals are compared in tone response and differences in tone response between healthy men and women are investigated. Smokers and coffee-users claim that these habits facilitate bowel movements. Chapter 5 contains a study in which this claim was tested using the rectal barostat in healthy controls.
Patients with idiopathic constipation are classified in slow transit, dyssynergic defecation and irritable bowel syndrome. However, recent studies show that these groups overlap. In chapter 6, patients with idiopathic constipation were subjected to rectal barostat testing to establish disorders in rectal sensitivity, compliance and the postprandial rectal response. Patients with a rectocele have disturbed defecation pattern in 50% of the cases. In Chapter 7, rectocele patients with disordered defecation were studied using anorectal manometry, rectal barostat and colonic transit time measurement to explore differences with healthy females and to evaluate the prognostic value of anorectal function tests for rectocele repair outcome.
Colonic transit time measurement using radio-opaque markers is a progressively used, easy to perform test to study the passage of intraluminal contents throughout the colon. Colonic transit time could be influenced by faecal impaction in patients with chronic constipation due to slow transit or dyssynergic defecation. In chapter 8, this was studied by comparing the colonic transit in an unprepared situation and in a situation after bowel cleansing.
Colonic transit time studies can be used to evaluate enterokinetic drugs such as prucalopride, a new 5-HT-4 agonist that stimulates bowel motility in healthy volunteers. Chapter 9 describes a double blind randomised cross-over study, which was performed to investigate the effects of prucalopride on colonic transit

time, anorectal function and complaints in patients with chronic constipation. Chapter 10 contains a review of the literature on modern study techniques of rectal and colonic motility.

In part two, the study of the anatomy of cryptoglandular and Crohn's disease associated fistula-in-ano using the transanal ultrasonography is described. Parks proposed a classification in four types for the anatomical track(s) of fistulas-in-ano.[52] This classification is generally used. However, it is still unknown how frequent these types occur in cryptoglandular fistulas and whether visualisation is necessary. In chapter 11, hydrogen peroxide enhanced transanal ultrasonography studies were reviewed to investigate the fistula tracks of never operated and recurrent cryptoglandular fistulas.
Fistula-in-ano is a feared complication in Crohn's disease. Surgical correction occurs frequently with recurrence and faecal incontinence. In chapter 12, the complex tracks of these fistulas are evaluated with hydrogen peroxide enhanced transanal ultrasonography studies and a new classification is proposed. Chapter 13 describes the effect of infliximab (a chimeric monoclonal antibody to human tumor necrosis factor (TNF-alpha) on complaints and fistula tracks of fistula-in-ano in patients with Crohn's disease.

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CHAPTER 2

RECTAL COMPLIANCE AS A ROUTINE MEASUREMENT
Extreme volumes have direct clinical impact, normal volumes exclude rectum as a problem

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Abstract

The clinical impact of rectal compliance and sensitivity measurement is not clear. The aim of this study was to measure the rectal compliance in different patient groups compared with controls and to establish the clinical effect of RC measurement.
Anorectal function tests were performed in 974 consecutive patients (284 men). Normal values were obtained from 24 controls. Rectal compliance measurement was performed by filling a latex rectal balloon with water at a rate of 60 ml per minute. Volume and intraballoon pressure were measured. Volume and pressure at three sensitivity thresholds, were recorded for analysis: first sensation, urge and maximal toleration. At maximal toleration, the rectal compliance (volume/pressure) was calculated. Proctoscopy, anal manometry, anal mucosal sensitivity and anal endosonography were also performed as part of our anorectal function tests.
No effect of age or gender was observed in either controls or patients. Patients with fecal incontinence had a higher volume at first sensation and a higher pressure at maximal toleration ($P=0.03$), the presence of a sphincter defect, low or normal anal pressures made no difference. Patients with constipation had a larger volume at first sensation and urge ($P<0.0001$ and $P<0.01$). Patients with a rectocele had a larger volume at first sensation ($P=0.004$). Patients with rectal prolapse did not differ from controls; after a rectopexy rectal compliance decreased ($P<0.0003$). Patients with inflammatory bowel disease had a lower rectal compliance, most pronounced in active proctitis ($P=0.003$). Patients with ileoanal pouches also had a lower compliance ($P<0.0001$). In the 17 patients where a maximal tolerated volume lower than 60 ml was found; 11 had complaints of fecal incontinence and 6 had a stoma. In 31 patients, a maximal tolerated volume between 60 and 100 ml was found; 12 patients had complaints of fecal incontinence and 6 had a stoma. Proctitis or pouchitis was the main cause for a small compliance. All 29 patients who had a maximal tolerated volume of more than 500 ml complained of constipation. No correlation between rectal and anal mucosal sensitivity was found.
Conclusion: Rectal compliance measurement with a latex balloon is easily feasible. In this series of 974 patients, some patient groups showed an abnormal rectal visceral sensitivity and compliance, but there was an overlap with controls. Rectal compliance measurement gave a good clinical impression about the contribution of the rectum to the anorectal problem. Patients with proctitis and pouchitis had the smallest rectal compliance. A maximal tolerated volume lower than 60 ml always led to fecal incontinence and a stoma should be considered for these patients. A maximal tolerated volume more than 500 ml was only seen in constipated patients and therapy should be given to prevent further damage to the pelvic floor. Values close or within the normal range rule out the rectum as an important factor in the anorectal problem of the patient.

Introduction

Rectal capacity, or compliance, is one aspect of anorectal function. The measurement of rectal compliance is generally performed with a latex balloon filled with air or water. This method is subject of discussion.[1-3] Critical remarks have been focussed on the size of the balloon in relation to the shape of the rectum, the extrarectal tissue, adaptation of the rectum and elasticity. Both methods and results differ amongst investigators. In addition, a completely different method has been introduced, with use of a barostat and a polyethylene balloon. This system provides more detailed information about visceral sensitivity and tone, but involves a cumbersome procedure.[4,5]
The aim of this study was to see whether direct conclusions could be drawn from a routine, rectal compliance and visceral sensitivity measurement with a compliant latex balloon in patients who were referred for anorectal function evaluation. A further purpose of the study was to assess whether there were differences between patient groups and healthy controls, how low and high maximal tolerable volumes were related to complaints and whether there was a correlation between rectal and anal sensitivity.

Patients and methods

Between 1991 and February 1999, 974 consecutive patients (284 men; 29 percent), with a mean age of 50 (standard deviation (SD) 20; range 8-98) years were referred for anorectal function evaluation. They all underwent a thorough medical history, digital examination, proctoscopy and anorectal function tests (rectal compliance measurement, anal manometry, anal sensitivity measurement) and anal endosonography. The patients were categorized into groups according to the reasons for referral or complaints (Table 1); if more than one complaint or diagnosis was present, they were categorized according to the most logical category. Patients were excluded if the referral was for reasons such as evaluation after sphincter reconstruction, hemorrhoidectomy, or surgery for other than a rectopexy or a second investigation in the course of their disease. All patients with constipation had barium enemas performed before referral, and no one had a megacolon. In patients suspected of having Hirschprung's disease large biopsies specimens were obtained for staining with acetylcholinesterase. Normal values for anorectal function tests and anal endosonograpy were obtained in 24 healthy volunteers (12 men), age 27, (SD 8; range 18-56) years.

Rectal compliance measurement

Anorectal function tests were performed with the patient lying in the left lateral position. A catheter with an external diameter of 2 mm and a terminal latex balloon 5 cm long in which a microtip transducer (type Hellige) is mounted was used. The microtip transducer was connected with the measuring system. The lumen of the balloon was connected to a roller-pump. The balloon was first inflated with air ten times to achieve a stable compliance of the balloon. The internal compliance of the balloon was then measured by filling the balloon with water of 37°C, 60 ml per minute, to a total of 200 ml, outside the patient. After

releasing the water the catheter was introduced in the rectum of the patient and the pump was started again. First rectal sensation (FS), urge (U) to defecate and maximal toleration (MT) were registered. At MT, the rectal compliance (volume/pressure) was calculated. Cut-off points for low maximal tolerated volume (MTV) were 60 ml and 100 ml, and for large MTV 500 ml.

Anal manometry, mucosal electrosensitivity and endosonography

A catheter with a diameter of 2 mm with two microtip transducers (Gaeltec ltd., Dunvegan, Scotland), 1 cm apart, and a terminal balloon that could be inflated, was connected to an electronic measurement system (GI-2000, MMS, Enschede, Holland). The catheter was calibrated at 37°C and set to zero outside the subject. The catheter was introduced until both microtips were placed in the rectum and were left to accommodate for several minutes. Then the catheter was connected to an automatic puller and was slowly withdrawn at a speed of 3 cm per minute. Two pressure profiles at rest were obtained. The maximum basal pressure (MBP) was recorded. The functional sphincter length was calculated by placing markers at the beginning and the end of the anal pressure profile. Next, the transducer tips were placed in the area of the MBP and the balloon in the rectum was inflated with 10 ml to elicit the distention reflex. A positive response was defined as a sharp decrease in basal pressure of at least 10 mmHg, followed by a slow recovery to the original pressure. This procedure was repeated with 20, 30, 40, 50 and 60 ml, until a reproducible reflex was obtained. The threshold volume was the lowest volume to induce the distention reflex. Then the catheter was introduced again until the beginning of the resting pressure. The catheter was pulled back by hand in steps of about 5 mm. The subject was asked to squeeze maximally at each level. The maximum squeeze pressure (MSP) was defined as the maximum increase in pressure above the resting pressure. Then the catheter was introduced again and the patients were asked to strain. This was performed with locations in the high, middle and low anal canal. The results were scored as relaxation, no response or contraction. High sphincter pressures were defined as MBP$>$40 and MSP$>$60 mm Hg, low sphincter pressures as MBP$<$30 and MSP$<$40.
A probe with two small electrodes was introduced in the anal canal. A constant current (square wave stimuli, 100 μsec, 5 pulses per second) was increased gradually from 1 to 20 mA until the threshold of sensation was indicated by the patient.
Endosonography was performed with an ultrasound scanner with a 360° rotating probe, a 7 -MHz transducer (focal range, 2 to 4.5 cm), covered by a hard sonolucent plastic cone (Brüel and Kjær, Naerum, Denmark). The probe was introduced into the rectum and slowly withdrawn. Serial radial images of 4, 3, 2 and 1 cm of the anal verge were taken. Defects of the internal and external sphincter were noted in a radial, clockwise manner with the 12 o'clock position anterior, and also in a longitudinal manner (proximal, distal, or full length).

Statistical analysis

Results were presented as mean, standard deviation (SD) and confidence interval (CI). Differences were compared using the Student's *t*-test. Correlation was calculated with the Pearson product moment correlation.

Results

No effect of age or gender on rectal sensitivity or compliance was observed in either controls or patients. The results of rectal sensitivity and compliance measurements are shown in Table 1. The results from the patients were compared with those from the controls.
Patients with fecal incontinence had a significant increase in volume at FS and an increase in pressure at MT ($P=0.03$). Grouping the incontinent patients according to the presence or absence of a sphincter defect and according to high or low anal pressures, did not change the results.
Patients with soiling ($P=0.04$) and patients with anal fissures ($P=0.03$) had a higher volume at MT compared with controls. Patients with constipation had a larger volume at FS and U ($P<0.0001$ and $P<0.01$). Hirschsprung's disease was excluded in all constipated patients. Patients with a rectocele had a higher volume at FS ($P=0.004$). Patients with a rectal prolapse did not differ from controls; however, after rectopexy, there was a significant increase in pressures at FS ($P=0.02$), U ($P=0.01$), MT ($P=0.03$) and consequently of compliance ($P<0.0003$). In patients with inflammatory bowel disease, the compliance was decreased significantly, most pronounced in patients with an active proctitis ($P=0.003$). In patients with an ileoanal pouch, all volumes were decreased ($P<0.001$) and all pressures increased ($P=0.01$) at FS, U and MT and subsequently compliance strongly decreased ($P<0.0001$). All pouches had some degree of pouchitis on both on endoscopy and histology.
In 17 patients, a MTV smaller than 60 ml was found (Table 2). Those without a stoma all had fecal incontinence. In 65 percent this was because of proctitis or pouchitis. In 31 patients an MTV between 60 and 100 ml was found (Table 3). Eighteen of 31 patients (58 percent) were fecal incontinent or had a stoma. The patients with proctitis or pouchitis received a stoma because of therapy-resistant inflammation and fecal incontinence. The two patients with a coloanal and ileoanal anastomosis had a stoma because of fecal incontinence. The two patients with an anal trauma had an injured, partially inflamed anorectal area and were still treated.
In 29 patients an MTV larger than 500 ml was found (Table 4); all had constipation and 24 percent also had fecal incontinence. Associated diseases were found in 21 (59 percent) patients. During straining, relaxation occurred in 18 (66 percent) and no response was seen in 11 (34 percent) of the patients. Correlation between FS and AS was significant neither for the whole group nor for the patients with fecal incontinence without a sphincter defect (neurogenic fecal incontinence).

	n	First Rectal Sensation		Urge		Maximal Toleration		COMP
		Volume (ml)	*Pressure (mmHg)*	*Volume (ml)*	*Pressure (mmHg)*	*Volume (ml)*	*Pressure (mmHg)*	*(ml/mmHg)*
Controls	24	73 (58-87)	23 (17-28)	167 (140-194)	29 (21-36)	230 (199-261)	39 (31-47)	7 (5.4-9.0)
Rectum								
Incontinence°	377	94 (87-100)*	23 (22-25)	178 (165-181)	34 (32-36)	237 (228-246)	46 (44-49)*	6.8 (5.9-7.6)
-incontinence-SD	196	94 (86-101)*	23 (21-25)	168 (158-177)	33 (30-36)	228 (216-239)	46 (43-49)*	6.0 (5.5-6.4)
-incontinence-no SD	181	98 (87-108)*	22 (20-24)	180 (167-192)	33 (30-35)	253 (238-268)	47 (44-51)*	6.4 (5.8-6.9)
-incontinence-low pressures	66	96 (83-109)*	22 (19-25)	172 (155-189)	32 (28-36)	232 (212-252)	45 (40-51)*	6.7 (5.5-7.8)
-incontinence-high pressures	53	88 (70-106)*	21(18-25)	174 (154-195)	32 (27-38)	260 (233-287)	49 (43-56)	6.3 (5.4-7.2)
Soiling	57	81 (64-98)	19 (17-22)	180 (159-201)	28 (24-33)	284 (255-313)*	45 (40-50)	7.2 (6.2-8.1)
Constipation	79	145 (124-166)*	25 (22-28)	220 (197-242)*	37 (31-43)	267 (243-292)	46 (40-52)	7 (6-8.6)
IBD-no proctitis	46	76 (61-90)	22 (18-27)	148 (125-171)	31 (26-36)	210 (177-243)	45 (39-51)	5.6 (4.5-6.7)
IBD- proctitis	22	77 (43-110)	20 (15-25)	152 (103-201)	34 (26-43)	197 (138-255)	47 (38-55)	4.5 (3.2-5.7)*
Fistula (no proctitis)	24	70 (52-88)	22 (17-27)	155 (126-184)	31 (24-37)	240 (196-285)	48 (41-56)	5.9 (4.4-7.5)
Fissure (no proctitis)	35	85 (60-110)	17 (13-20)	190 (149-230)	25 (19-31)	291 (249-333)*	37 (28-46)	10.1 (7.9-12.4)
Rectocele (not incontinent)	28	114 (91-136)*	24 (19-29)	205 (170-240)	33 (25-40)	251 (217-286)	39 (30-47)	8.4 (5.5-11.3)
Pain (no other diseases)	58	81 (66-96)	18 (15-20)	172 (151-193)	25 (21-28)	249 (224-275)	37 (32-41)	7.8 (6.9-8.8)
Rectal prolapse	36	84 (66-103)	16 (13-19)#	180 (154-207)	24 (19-29)#	277 (245-309)	38 (32-44)#	9.1 (7.1-11.1)#
Rectopexy	26	86 (67-105)	26 (18-33)#	165 (127-203)	37 (28-47)#	236 (195-277)	52 (41-64)#	5.4 (4.0-6.8)#
Pouch	16	29 (14-45)*	28 (20-35)*	77 (47-107)*	44 (36-52)*	99 (61-137)*	51 (41-62)*	2.5 (1-3.9)*

Table 1. Rectal compliance measurements in controls and patients, mean and 95% confidence interval.
SD = sphincter defect; low pressure: MBP < 30 and MSP < 40; high pressure: MBP > 40 and MSP > 60 mm Hg,
° incontinent patients without inflammatory bowel disease.
* $P < 0.05$ compared with controls, # $P < 0.01$ compared to each other.

Diagnosis	n	Incontinent	Stoma
All	17	11	6
Rectum			
Proctitis	6	3	3
-Crohn's disease	3	3	0
-Ulcerative colitis	2	0	2
-Radiation colitis	1	0	1
Rectum after anorectal surgery			
Pouchitis- J pouch	5	4	1
Colo-anal anatomosis	2	1	1
Ileo-anal anastomosis	2	1	1
Ripstein rectopexy	1	1	0
Anal atresia	1	1	0

Table 2. Characteristics of patients with Maximal Tolerated Volume < 60 ml.

Diagnosis	n	Incontinent	Stoma
All	31	12	6
Rectum			
Proctitis	13	4	3
-Crohn's disease	10	4	0
-Ulcerative colitis	3	0	3
Hemorrhoids	1	0	0
Intussusception/rectal prolaps	3	2	0
Rectum after anorectal surgery			
Pouchitis- J pouch	5	2	2
Ileoanal anastomosis	1	1	0
Rectopexy or vaginopexy	2	1	0
Anorectal trauma	3	1	2
Pain after anal surgery	3	1	0

Table 3. Characteristics of patients with Maximal Tolerated Volume between 60-100 ml.

Diagnosis	n
All	29
Constipation	29
Fecal incontinence	7
Hemorrhoids or mucosal prolaps	9
Fistula	4
Fissure	4

Table 4. Characteristics of patients with Maximal Tolerated Volume > 500 ml.

Discussion

Several methods of rectal compliance measurements are used currently. The latex balloon filled with air or water is a common used method. Considering the criticism about the shape and properties of the materials used,[1] care must be taken to describe the methods properly and to establish one's own normal values. As in other studies a considerable range and no effect of sex or age was observed in controls.[6-8] In patients with fecal incontinence, a higher first sensation threshold was found; this was also found in earlier reports.[9-12] This is probably because of autonomic neurogenic damage. In addition, we found an increased pressure at MT. This could indicate a decreased sensation for distension pressures and or a stiffer rectum in some patients.

Incontinent patients with a sphincter defect also had a higher FS and did not differ from patients without a sphincter defect (neurogenic fecal incontinence), indicating that a sphincter defect does not necessarily is the only cause of fecal incontinence. This again stresses that pudendal neuropathy plays an important role in all patients with fecal incontinence. Also, incontinent patients with anal pressures largely above the normal values, therefore good sphincters and good somatic innervation, did not differ from the patients with low anal pressures. Apparently diminished central awareness or behavior plays an important role in these patients with high anal pressures and not so much a diminished visceral sensitivity or MTV.

In patients with inflammatory bowel disease, especially with proctitis, the compliance was decreased. This was found before.[13-15] In patients with an ileoanal pouch, all of whom all had some degree of pouchitis, all threshold volumes were severely decreased, all pressures increased and compliance decreased. A reduced volume in pouches is well recognized in the literature[16-20] and is correlated to defecation frequency and fecal incontinence.

As a group, patients with fecal incontinence did not have a different MTV. However, an examination of our data on small rectal volumes shows that the 17 patients with an MTV smaller than 60 ml, if they did not have a stoma already, were all suffering from fecal incontinence. Volumes between 60 and 100 ml gave rise to complaints of fecal incontinence or led to a stoma in more than one-half of the patients. These figures are of importance when deciding on therapeutic goals such as conservative treatment for proctitis or pouchitis, reconstructive surgery or a stoma.

In patients with constipation or a rectocele, there was an increased volume at FS, probably due to the anatomic shape and or neurogenic damage caused by straining during evacuation, an effect seen in many patients. This is in contrast to an earlier study, were no differences were found in patients with a rectocele.[21]

A rectopexy leads to a smaller rectal volume, increased rectal pressures and a lower rectal compliance, which is explained by the obtained anatomical changes. This is in accordance with other studies.[22,23]

As a group, MTV of patients with constipation did not differ from controls. However, an MTV larger than 500 ml was seen exclusively in patients who were constipated, in whom 24 percent also had fecal incontinence. This suggests again that chronic constipation eventually will lead to an increased rectal volume, which by itself will interfere with a normal evacuation of stool. Then, excessive straining

and descent of the pelvic floor can subsequently lead to fecal incontinence by pudendal nerve damage during chronic straining.[24] Finding a large MTV in patients should always raise the question of chronic constipation, so that adequate advice can be given to prevent further damage to the rectum and pelvic floor.
The lack of correlation between rectal and anal sensitivity excludes anal sensitivity as a fast replacement test for the rectal sensitivity measurement. When focussing on patients with neurogenic fecal incontinence (no sphincter defects) there is also no correlation, showing that somatic and visceral nerve damage do not occur simultaneously.
Although more sophisticated measurements of rectal visceral sensitivity exist by means of the barostat, one should realize that that is additional investment, requires dedicated and well-educated personnel and is a cumbersome procedure. At the other hand, rectal compliance measurement with a simple latex balloon can give a good screening impression about the rectal compliance within 10 minutes with a direct clinical conclusion. Selected patients can always be referred for a complete Barostat procedure.

Conclusion

RC measurement with a latex balloon is easy feasible. RC measurement gives a good clinical impression about the contribution of the rectum in the anorectal problem. Some patient groups show abnormalities in rectal visceral sensitivity, but there is an overlap with controls. Patients with proctitis or pouchitis have the smallest volumes and compliance. An MTV smaller than 60 ml leads inevitable to fecal incontinence; more than one-half of the patients with a MTV between 60 and 100 ml have fecal incontinence. These figures are of importance in therapeutic strategy. Especially in patients with an MTV smaller than 60 ml, a stoma should be considered. Volumes larger than 500 ml are found only in constipated patients and should also lead to appropriated advice to avoid further damage to the pelvic floor. Therefore, extreme values in rectal sensitivity and compliance measurement have a direct obvious clinical effect. Values within or close to the normal range exclude the rectum as an important factor in the anorectal problem.

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CHAPTER 3

RECTAL VISCERAL SENSITIVITY IN HEALTHY VOLUNTEERS:
Influences of gender, age and methods

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Abstract

The barostat is a device that maintains a constant pressure within an air-filled polyethylene bag by means of a feedback mechanism. The system measures variations in rectal tone, by recording changes in the intrarectal pressure and volume. Different procedures, such as ramp distension or intermittent distension, are used to test visceral sensitivity and rectal wall compliance. It is not quiet clear which method is preferable and how the barostat measurements compare with those of the conventional latex balloon. In 28 healthy volunteers (11 males, mean age 36, range 22-67 years) rectal distension was performed in two ways:
1 Pressure-controlled distension by both intermittent and ramp distension, with measurement of Visual Analogue Scale (VAS, 0-5) at 8,12,16,20,24,28,32 and 36 mm Hg. Hysteresis (comparing area under the curve during deflation and inflation with ramp pressure distension) and compliance were calculated.
2 Volume-controlled distension, with registration of first sensation, urge to defecate and maximal tolerated distension. This procedure was compared to conventional water-filled latex balloon distension.
No differences were found between intermittent and ramp distension comparing VAS scores at the same pressures. Gender or age did not affect the VAS score. Males had larger volumes at the same pressures than females. Females had larger hysteresis than males. Older females had larger hysteresis than younger females. The pressure volume curves were S-shaped. Compliance at maximal tolerated distension (V/p) and maximal dynamic compliance ($\Delta V/\Delta p$) was higher in males than females. The polyethylene bag had higher MTV and MTP compared to the latex balloon. In conclusion, no differences were found in volumes, compliance and VAS between the intermittent and the ramp pressure controlled inflation, indicating potential for simplification of the procedure. Males had larger rectal volumes and compliances; females had more pronounced hysteresis. A systemic difference was found between distension with the water-filled latex balloon and with the air-filled polyethylene bag. This should be taken into account when interpreting results.

Introduction

Interest in visceral sensitivity of the rectum has increased because sensitivity can be altered in different conditions like irritable bowel syndrome,[1,2] constipation[3] and faecal incontinence.[4] Drugs,[5,6] a meal[7] or hyperglycemia[8] can influence visceral sensitivity. Several methods have been developed to measure rectal sensitivity. Rectal visceral sensitivity can be tested by using an air- or a water-filled latex balloon; high-compliance polyethylene bags in conjunction with a barostat; rectal endosonography;[9] or impedance planimetry.[10] The high-compliance barostat is increasingly used because of its presumed superiority in measuring visceral sensitivity.
The barostat system maintains a constant pressure within an air-filled bag by means of a feedback mechanism. The system measures variations in rectal tone by recording changes in the intrarectal pressure and volume.[11] Several studies have shown the reproducibility of distension studies with intermittent and ramp distensions in normal volunteers and IBS patients.[6,12-14]
Different procedures, like ramp distension or intermittent distension, have been used to test visceral sensitivity and rectal wall compliance.[15] So far, no method has been shown to be preferable and whether these methods are comparable or measure different aspects of rectal sensitivity is not clear. Also, the effect of age and sex has not been studied. Therefore, this study aimed to measure visceral sensitivity in healthy males and females of different ages using the two procedures (ramp and intermittent distension) with the barostat/polyethylene bag apparatus, and compare this method with the conventional latex balloon.

Materials and Methods

Healthy volunteers

Twenty-eight healthy volunteers (11 males, 17 females; mean age 36 years, range 26-66; body mass index 23 kg m^2, range 17-28) were recruited. They were divided in two age groups (young: 27 year, range 23-30; older: 42 year, range 30-66). Subjects presented to the unit after an overnight fast where they received an enema. After a digital examination, the barostat-bag was inserted in the rectum. The bag was unfolded with a pressure of 20 mmHg. The subjects were positioned on their backs, in 15° degrees.[15]

Barostat

An electronic barostat device (Synectics Visceral stimulator, Synectics medical, Stockholm, Sweden) was used. A flaccid polyethylene bag (maximal capacity 600-ml) was mounted on a catheter (diameter 5 mm) and fixated at both ends. After inflation, the bag became cylindrical with a length of 10 cm. The catheter was connected with the barostat with an inflation port and a pressure port. Maximal airflow was 38 ml per second. With a feedback mechanism, the barostat can regulate pressure or volume in the bag. Inflation can be accomplished by pressure or volume regulated distension. Pressure and volume

were continuously registered. Procedures were stopped if the safety value of the maximal volume of 600 ml or the pressure of 50 mmHg was exceeded or if the patient was unable to support the distension.

Procedures

Intermittent pressure distension. Intermittent rectal distension in a semi random staircase manner was performed at the pressures 8, 12, 20, 16, 32, 24, 36 and 28 mmHg. Pressure distension was continued one minute and followed by one-minute rest. After 30 seconds distension, the visual analogue scale (VAS) was scored. VAS score range varies from 0 to 5 (0,no feeling; 1,light sensation; 2, definitive sensation (beginning of urge to defecate); 3, normal urge to defecate; 4,strong urge to defecate; and 5, maximal tolerationof distension).

Continuous pressure distension. Continuous rectal distension was performed by ramp pressure-controlled inflation up to 36 mmHg over 10 minutes. The VAS score was registered at pressures 8, 12, 16, 20, 24, 28, 32 and 36 mmHg. Next, deflation was performed in 10 minutes to register hysteresis. Hysteresis was defined as the relative difference between the area under the pressure volume curve (AUC) in the descending and ascending part shown by the equation:[16] ([AUCdesc-AUCasc]/AUCasc)
Minimal distension pressure, defined as the pressure that was needed to inflate the rectal bag to 10 ml, was registered. Dynamic compliance was calculated as the increase in volume at a pressure step of 4 mmHg ($\Delta V/\Delta p$).

Continuous volume distension. Continuous rectal distension was performed by volume-controlled inflation at a rate of 30 mL minute^{-1} until maximal tolerated distension was reached. 'First sensation' volume and pressure (FSV, FSP), 'urge to defecate' volume and pressure (UV, UP) and 'maximal toleration' volume and pressure (MTV, MTP) were registered. Static compliance was measured at maximal tolerated distension (V/p).
Wall tension was calculated as pressure multiplied by the radius of the bowel (Lapace's law), whereas the rectum was assumed to be a cylinder.[6,13,17,18]

Latex balloon technique

A catheter of external diameter 2 mm with a 6-cm latex balloon fixed at the end was used. After filling, the balloon had a spherical shape. A microtip transducer (Hellige type) at the end of the catheter (inside the balloon) was connected with the measuring system (UD-2000, Medical Measurements Systems, Enschede, The Netherlands). The balloon was filled with water by a pump (50 mL minute^{-1}). Volume and pressure were continuously registered. First, the intrinsic compliance of the balloon was measured outside the subject. Next, the catheter was introduced into the subject's rectum and the procedure repeated. FSV, FSP, UV, UP, MTV and MTP were registered. Compliance was calculated at MTV and MTP. Corrections for the intrinsic balloon compliance were made.

Data and Statistical analysis

Results are presented as means with 95% confidence interval. Data were analysed in gender groups, and in age groups with the 30-year cut off point (young and older). Volume pressure curves and VAS-pressure curves were compared using the ANOVA method for repeated measurements in a quadratic model. The unpaired Student's *t*-test for normal log distribution was used to compare hysteresis and compliance between gender and age groups. The VAS scores were correlated with pressure, volume and wall tension by Pearson's correlation (R, correlation coefficient). The latex balloon distension was compared to the polyethylene bag distension with Pearson's correlation and with the method described by Bland and Altmann.[19]

Results

Intermittent and continuous distension showed no differences in VAS scores and volume pressure curves (Fig. 1). Males had larger volumes at the same pressures than females ($P=0.02$). VAS-scores were equal at the same pressures in males and females (Fig. 2). No significant difference was found between the age groups in VAS and volume/pressure.

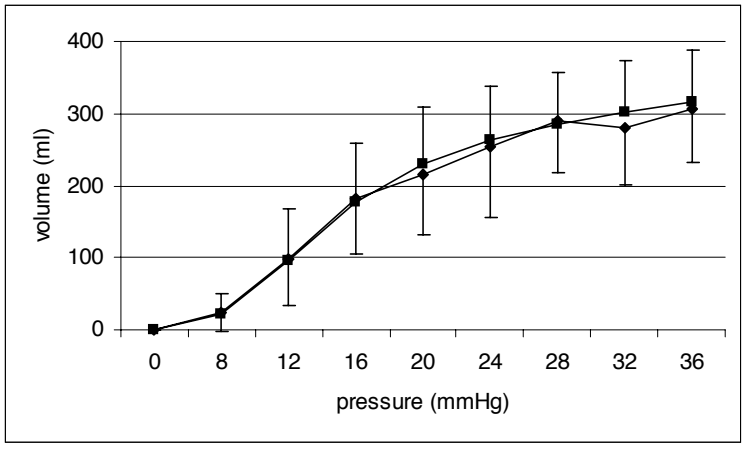

Figure 1. Volume-pressure curve with intermittent (■) and continuous (◆) distension (mean and sd).

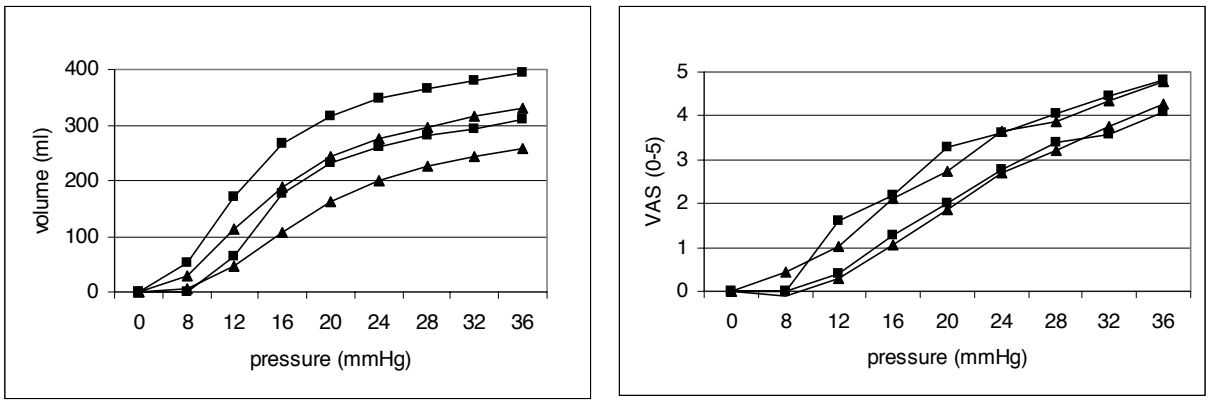

Figure 2. Volume-pressure and VAS-pressure curve in ramp distension. 95% confidence interval in males (■) and females (▲).

Hysteresis

Hysteresis was different between males and females (32%, CI 25-38 vs. 43%, 35-52; $P=0.05$) (Fig. 3). Hysteresis was different between the young and the older group in females (34%, CI 26-42 vs. 48%, CI 36-61; $P=0.037$). No relationship was found between hysteresis and maximal tolerated volume or pressure.

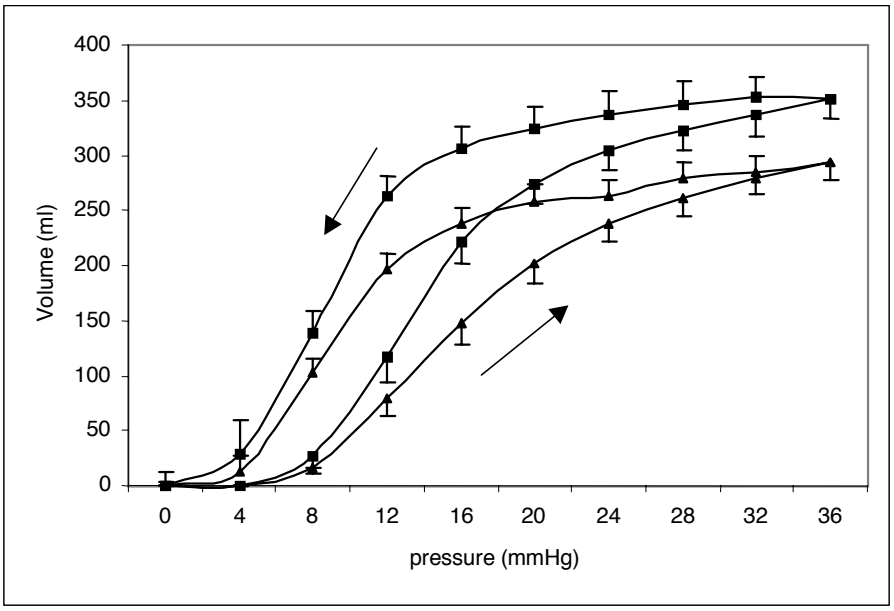

Figure 3. Volume-pressure curve during inflation and deflation part of the continue pressure distension showing hysteresis in males (■) and females (▲). In this figure is shown the difference between the slope of the inflation curve (arrow up) and the deflation curve (arrow down).

Compliance

All subjects had a S-shaped pressure volume curve. Dynamic compliance was calculated at a mean pressure 15.4 mmHg (CI 14.1-16.7). Dynamic compliance was higher in males (32 mL $mmHg^{-1}$, CI 25-39) than females (24 mL $mmHg^{-1}$ CI 19-28; $P=0.03$). Static compliance at maximal tolerated distension was also higher in males (10.3 mL $mmHg^{-1}$, CI 8.5-12.1) than in females (8.1 mL $mmHg^{-1}$, CI 6.8-9.5; $P=0.045$). There were no differences between dynamic and static compliance for the younger group (30 mL $mmHg^{-1}$, CI 23-36 vs. 9.4 mL $mmHg^{-1}$, CI 7.4-11.4) and the older group (24 mL $mmHg^{-1}$, CI 20-29 vs. 8.7 mL $mmHg^{-1}$, CI 7.4-10.1).

Wall tension

Wall tension was correlated with the VAS ($R=0.9$). Correlation between VAS and pressure ($R=0.9$) or volume ($R=0.8$) were of the same magnitude.

Minimal distension pressure.

Minimal distension pressure was 8.6 mmHg (7.7-9.4). No relationship was found between minimal distension pressure and sex or age, whereas a weak correlation was found with body mass index ($R=0.5$). VAS-scores were not influenced by differences in minimal distension pressure.

Continuous volume distension

The results of the continuous volume distension are shown in Table 1. Males had a significant higher FSP than women ($P=0.035$). There was a tendency for higher UP ($P=0.075$) and MTP ($P=0.18$) in males compared to females. FSV, UV and MTV tended to be higher in males than females ($P=0.12$, 0.14 and 0.6 respectively). No relationship was found between age and pressures or volumes.

	Polyethylene bag		Water-filled latex balloon	
	Male	Female	Male	Female
FSP (mmHg)	12 (10;14)*	15 (13;16)*	20 (11;29)	17 (12;21
FSV (ml)	139 (93;186)	128 (103;152)	116 (76;155)	102 (75;129)
UP (mmHg)	20 (17;23)	25 (21;29)	21 (13;30)	17 (11;23)
UV (ml)	275 (225;325)	231 (197;265)	182 (133;231)	159 (126;191)
MTP (mmHg)	36 (30;43)	41 (37;46)	32 (17;46)	24 (17;32)
MTV (ml)	364 (304;423)	322 (292;352)	280 (229;330)	239 (202;276)

Table 1. Continuous volume distension (* $P<0.05$).

Rectal distension with water-filled latex balloon

The results of the water-filled latex balloon distension are shown in Table 1. No significant differences were found between males and females in this test. However, males tended to tolerate higher volumes ($P=0.15$). No relationship was found between age and pressures or volumes.

Comparison between polyethylene bag and latex balloon.

MTV and MTP were larger with the polyethylene bag compared to the latex balloon (Table 1 and 2). Correlation coefficients for the volumes were moderate (FSV (R=0.50), UV(R=0.65) and MTV (R=0.64)) and poor to moderate for the pressures (FSP (R=0.20), UP (R=0.36) and MTP (R=0.63)).
The mean difference of the maximal tolerated volume between the balloons was 85.5 mL (CI 59- 111) and the mean difference of the maximal tolerated pressure is 11.4 mmHg (CI 6.8-16) (Fig 4).

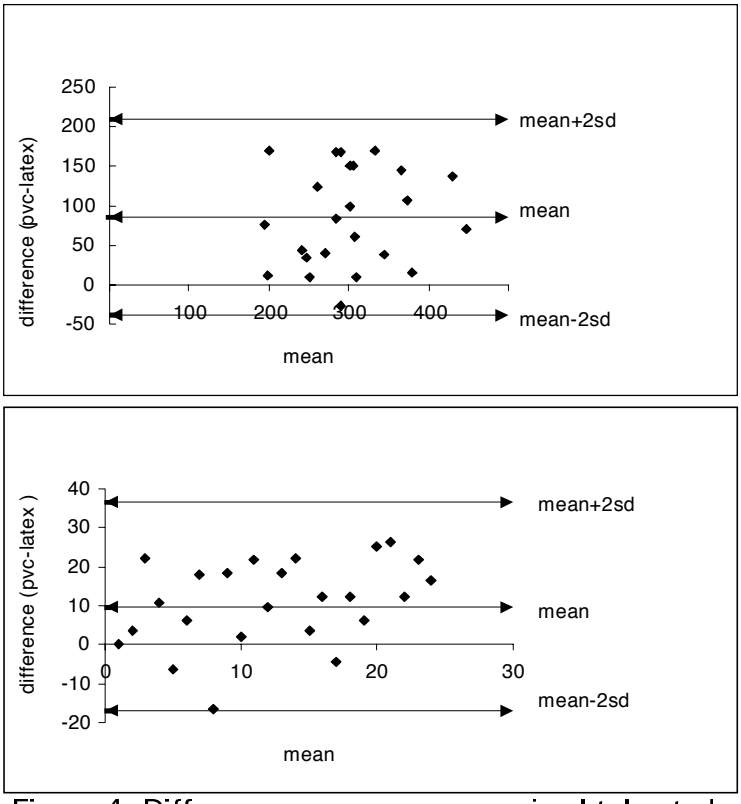

Figure 4. Difference versus mean maximal tolerated volume (above) and pressure (under) of the polyethylene bag and the latex balloon.

Discussion

In this study, we showed that visceral sensitivity is equal in males and females at given pressures, which is in concordance with the study of Malcolm *et al.*[20] In addition, we found that the equality of sensibility in males and females occurred despite the larger volumes in males.
This discrepancy suggests that pressure is the main parameter in sensitivity. Other studies support this concept. After prolonged distension with a constant pressure, the volume increased but the perception did not.[21] When the rectum is relaxed by glucagon, perception was changed in volume-controlled distension, but not in pressure-controlled distension.[6] Patients with rectal prolaps, who had lower volumes at distension pressures compared to controls, have equal perception.[22]
In recently published articles,[6,17,18] wall-tension is considered as an important parameter of gastric visceral sensitivity because it decreases variability in sensation scores. On comparing the following parameters: pressure; wall-tension; or volume, we could not find a decrease in variance in sensitivity score compared to tension. This suggest that wall tension is less important than pressure, which is in concordance with the study of Thumshirn *et al.*[18]
In this study, no difference was found between intermittent semirandom (phasic) and continuous (slow ramp) distension to determine visceral sensitivity in volunteers. Other studies in healthy volunteers also could not show differences between the methods of distension.[1,6] In contrast to this, Sun *et al.*[23] found that intermittent distension showed lower thresholds in a volume-controlled design.
In IBS patients, studies have been performed in which threshold levels of intermittent and continuous distension were compared. Some studies showed lower pain thresholds in intermittent distension compared to ramp distension despite similar compliance curves of both methods of distension.[3,12,24] Other authors could not find this difference between the distension methods[13,25] or are suggesting that perceptual alteration observed during ascending series of phasic distension is more related to hypervigilance of the subject towards aversive and potentially noxious visceral stimuli, which could explain the lower thresholds of IBS patients.[26]
A possible explanation for the discrepancy in visceral sensitivity between the intermittent distension and continuous distension may be found in the different tension receptors. Slow rectal distension is perceived by mucosal receptors of the sacral afferents, whereas rapid phasic distension may stimulate preferentially splanchnic afferents with receptive fields in deep muscular layers, serosa and mesentery and projecting to the lumbar cord.[12,25,27,28] In healthy volunteers, and with the methods we used, it is not possible to test these tension receptors separately.
Compliance can be defined as the capacity of the rectum to stretch (expand) in response to an imposed force.[15] In this study compliance was calculated at two levels. Dynamic compliance was calculated as the largest volume augmentation at a pressure step. Static compliance was calculated as the maximal tolerated volume related to the maximal tolerated pressure. Males had a larger compliance at both levels, such differences being caused by the larger volumes in males. In

the first part of the compliance curve, the distension represents the muscular tone (active stretch) while the latter part of the curve represents the connective tissue and muscle (passive stretch).[23,26] Drugs such as clonidine influence dynamic compliance or active stretch but not passive stretch or static compliance.[29] This model is supported by the mathematical model that Rao *et al.*[30] constructed using the rectal response to rapid and ramp inflation; the responses corresponding to submucous collagen, circular muscle and longitudinal muscle layers. It supports the perception of rectal sensations at lower strain levels and lower rates of inflation through the responds of a mechanoreceptor to circular muscle relaxation. First sensation is an anal canal sensation; urge distension occurs with the drop in tension of the circular smooth muscle; and maximal tolerated pressure is a physiological protection against damage. In our study, as in others, no difference in compliance could be found in respect to intermittent or slow ramp distension.[24] The clinical relevance of the compliance calculation is still doubtful.

Hysteresis was measured as relative difference in pressure-volume curve between the deflating and inflating areas and may be a parameter for adaptive properties of the rectal wall (smooth muscle relaxation).[16] In all subjects a hysteresis phenomena could be observed. Older females had a larger hysteresis than young females. In males, this difference in age could not be found. It could be possible that history of childbirth or a difference in pelvic anatomy attributes to this discrepancy in hysteresis, but a clear pathophysiological explanation is to be explored.

The best balloon to measure rectal compliance and sensitivity is still controversial.[31] A latex balloon can be filled with air or water and a correction for the compliance of the balloon must be made. The barostat system with the polyethylene bag is filled with air and can provide a constant pressure and volume regulation, which seems more sophisticated. *In vitro* the balloons are tested in 'artificial guts'. The latex balloon can expand under high pressures in a rigid tube whereas a polyethylene bag can not because of the attachment. In addition, a latex balloon first distends in volume without raise in pressure and has a more spherical shape. Both methods had difficulties in measuring compliance in *in vitro* pig gut. This was partly due to heterogeneous elastic properties along the length of the gut, and partly to internal compliance of the inflation apparatus.[32] In the study of Sun *et al.*, no difference could be shown in volume or sensation by using latex a balloon distended with water or with gas.[23] The thresholds of maximal toleration distension has a wide intrasubject range in repeated measures with the latex balloon.[1] Our study shows that with the flaccid air-filled polyethylene bag higher maximal tolerated distension can be reached. One explanation could be that the sensation of a water-filled balloon is different from that of an air-filled balloon, because of the weight. Another explanation could be that the latex balloon has a more spherical shape on distension while barostat balloon is more cylindrical. These differences could also count for the different thresholds between the balloon and bag.

Conclusions

Visceral sensitivity, measured with intermittent semirandom pressure distension and continuous pressure distension, is equal in healthy volunteers. Gender does not influence visceral sensitivity when it determined by pressure distension, however, males have larger volumes. Age does not influence the sensitivity thresholds. Pressure-volume curves are different in males and females due to the larger volumes in males, compliance is therefore larger in males. Older females have a larger hysteresis than males and young females. The air-filled high compliant polyethylene bag and the conventional water-filled latex balloon study have a systemic difference. These conclusions should be taken into account when interpreting results.

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CHAPTER 4

THE INFLUENCE OF GENDER, PARITY AND CALORIC LOAD ON THE GASTRO-RECTAL RESPONSE IN HEALTHY SUBJECTS.
A barostat study

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Abstract

The gastro-colonic response consists of a prompt increase in colonic tone after a meal. With the barostat and a high compliant air-filled bag, it is possible to measure rectal tone by recording changes in volume at a constant intrabag pressure. The aim of this study was to evaluate the gastro-rectal response in males and females as well as the effect of different caloric loads on the gastro-rectal response.
In 33 volunteers a barostat procedure during basal conditions and after a 600 kCal meal was performed. In 26 volunteers the procedure was repeated with a 1000 kCal meal. A meal response was defined as a decrease in volume of more than 10%. Phasic Volume Events (PVE) were defined as a 10% decrease in volume of 15-60 sec duration.
After a 600 kCal meal, the decrease of the volume after one hour was 28 ± 7% (mean ± sem $P<0.001$). A meal response was found in 64% of the subjects. Parous females had a diminished meal response compared with nulliparous females (2 ± 5% and 48 ± 11% $P<0.001$). After the 600 kCal meal, PVE's increased from 3 to 10 per hour ($P=0.001$).
In the 26 subjects, volume decrease was 40 ± 9% after a 1000 kCal meal and 20 ± 7% after the 600 kCal meal ($P=0.28$). In the high caloric meal, 18 subjects (69%) had a response versus 14 (54%) in the low caloric meal (NS). Enhancing the caloric load of the meal did not increase the amounts of PVE's.
Conclusions: A gastro-rectal response occurs in 64% of the healthy subjects after a 600 kCal meal. The gastro-rectal response can be measured to a similar extend in men and nulliparous women, however the response is significantly impaired in parous women. This is possibly due to neurogenic damage during childbirth. Increasing the caloric load did not increase the gastro-rectal response. Therefore, to study gastro-rectal meal response with the barostat a caloric meal of 600 kCal is sufficient and a correction for parity should be made when results are compared.

Introduction

Rectal motility and tone can be altered by stimuli such as a meal. The gastro-rectal response consists of a prompt increase in rectal tone after a meal.[1] In other regions of the colon, a similar response can be measured.[2] This gastro-colonic reflex is important in the process of defecation for the presentation of the fecal bolus to the rectum. If stool is propelled into the rectum from the more proximal colon and the rectum is in a state of increased tone, then a greater incremental pressure increase occurs, providing a heightening sensation and a prompt urge to defecate. In a fasting condition or during sleep, the rectum functions like a reservoir by decreasing its tone and stores the fecal bolus at low pressures.[3,4]
This mechanism in the process of defecation could play a role in the pathogenesis of a condition such as constipation. A blunted meal response and a relative paucity in motor events have been found in the rectum and in the rectosigmoid area, which could be restored after biofeedback therapy.[3,5,6]
Interest in the rectal tone is increased since the introduction of the barostat. With a flaccid polyethylene balloon, changes in volume, with a preset pressure, (tone) of a hollow organ like the rectum can be measured.[7] Until recently, measurements of rectal motor activity could only be assessed by intraluminal manometry. With the barostat, motility can be registered as well as the change in rectal tone whereas with manometry, rectal tone is not demonstrable, because the catheter has a weak contact with the bowel wall in a hollow organ.[8] With a manometry assembly rapid decreases in volume can adequately measured but slow decreases in volume do not relate to changes in manometrically recorded intraluminal pressure.[1]
Whether the gastro-rectal response is universal in males and females is unknown. In addition, the contribution of the caloric load of the meal is unclear, since in the literature different meals have been used. Therefore, we examined the gastro-rectal response in males and females as well as the effect of different caloric loads on the gastro-rectal response in healthy volunteers.

Materials and Methods

Healthy volunteers

Thirty-three healthy volunteers were recruited. The subjects' characteristics were 11 males (mean age 36 range 25-68 years), 11 parous females (mean age 41 range 29-59), 11 nulliparous females (mean age 24 range 20-30). The participants had normal bowel habits without a history of constipation nor a history of abdominal surgery. No one had ever taken laxatives. Written informed consent was obtained from all volunteers. Females who participated in the study were not pregnant nor menstruating. The study was approved by the Ethic Committee of our hospital. Subjects presented to the unit after a 12-hours fast and had bowel preparation with an enema. After a digital examination, the barostat-balloon was inserted in the rectum, just behind the

anal verge. The balloon was unfolded with a pressure of 20 mmHg and deflated. The subjects were positioned on their back, 15 degrees head down.[9]

Barostat

An electronic barostat device (Synectics Visceral stimulator, Synectics medical, Stockholm, Sweden) was used. A polyethylene bag (maximal capacity 600 ml) was mounted at the end of a tube (diameter 5 mm) and it was used after testing for leakage. The catheter was connected with the barostat with two connections, an inflation port and a pressure port for intrabag pressure measurement. With a pressure feedback mechanism, the barostat device can regulate pressure in the bag. Maximal airflow was 38 ml per second. Pressure and volume were registered continuously.

Procedure

An isobaric barostat procedure was conducted at 2 mmHg above minimal distension pressure (the pressure to unfold the balloon 10 ml). After 30 to 60 minutes of basal registration when a stable volume was reached, a liquid meal was given. In the first experiment, the meal consisted of 400 ml of Ensure plus® (600 kCal, 17% protein, 53% carbohydrates, 30% fat). In the second experiment, the meal consisted of 550 ml self-made milk shake (1000 kCal, 6% protein, 18% carbohydrate, 76% fat). After the meal, volume and intraballoon pressure was recorded for one hour. A meal response was defined as a more than 10% decrease in postprandial volume after one hour. Phasic volume events (PVE) were defined as 10% decrease in volume during 15-60 sec.[1,8,9]

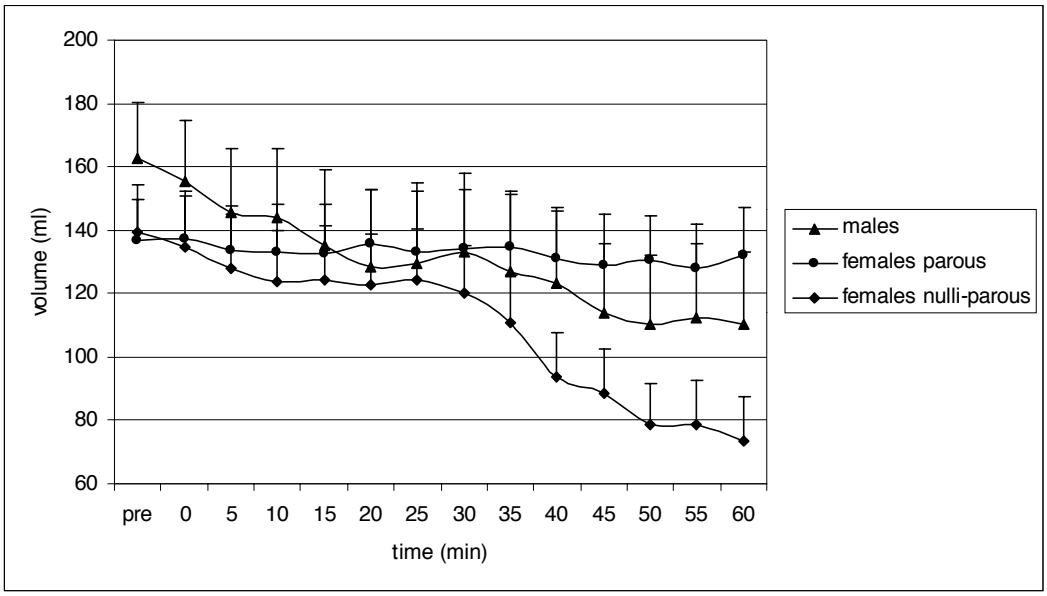
Data and Statistical analysis

Data were analyzed as mean volume over a 5-minute period. Results are presented as mean volume with standard error of the mean (SEM) or as percentages, relative to baseline volume. Pre- and postprandial data were compared using the ANOVA method for repeated measurements. Meal responses between males and females were compared using Fischer's exact test. Phasic volume events were calculated by the Polygram for Windows version 2.04 software (Synectics medical, Stockholm, Sweden) and reviewed by the investigator. Basal and postprandial phasic volume events were compared using the Student's *t*-test.

Results

First experiment.

Mean basal pressure was 10,6 ± 0,5 mmHg for males, 12,3 ± 0,6 mmHg for parous females and 11,3 ± 0,3 for nulliparous females (NS). Mean basal volume was 162 ± 18 ml for males, 136 ± 15ml for parous females and 139 ± 13 ml for nulliparous females (NS). After the 600 kCal meal, rectal volume was reduced to 105 ± 11 ml (28 ± 7%; $P=0.002$). The postprandial volume reduction was not different in males and females, however, parous females had a diminished meal response compared with nulliparous females (2% ± 5 versus 48% ± 11 $P<0.001$) (Figure 1 and 2). A meal response was found in 21 of the 33 subjects (64%). Nine (82%) males, three (27%) parous and nine (82%) nulliparous females responded ($P=0.03$).



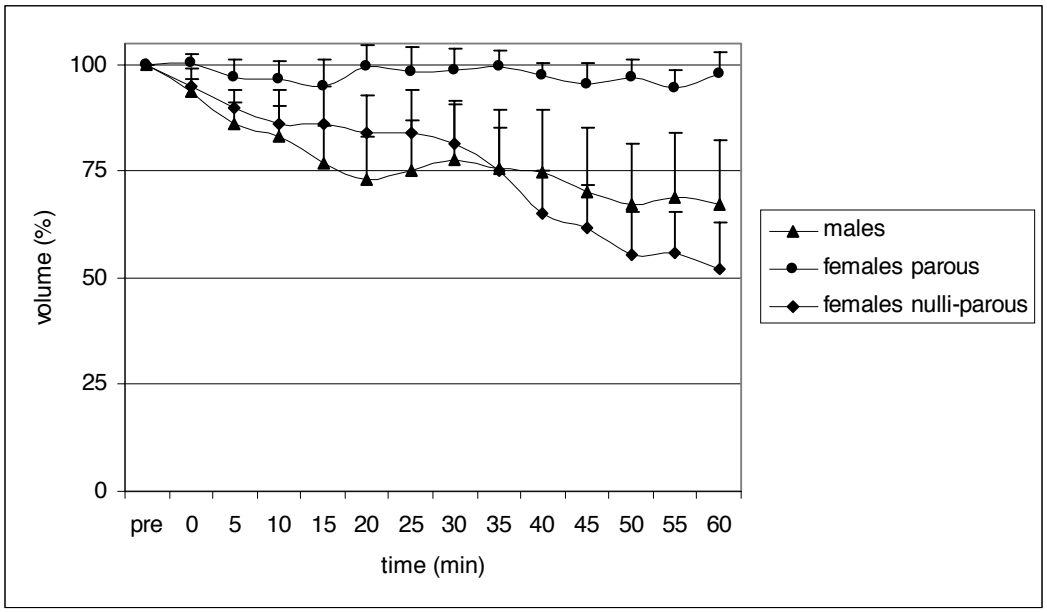


Figure 1 and 2: Response after 600 kCal meal; mean and SEM

Second experiment

The barostat procedure was performed with a 1000 kCal meal in 26 of the 33 subjects (of whom 12 did not respond in the 600 kCal meal test). Basal pressure and volume were 12.0 ± 0.4 mmHg and 118 ± 9 ml which were not significant lower than the first experiment ($P=0.37$ and 0.07 respectively). After the 1000 kCal meal, rectal volume was reduced to 74 ± 13 ml (39 ± 10 %; $P=0.008$). The volume reduction was not different between males (48 ± 19 %) and nulliparous females (51 ± 11 %), however, the meal response of the parous females (22 ± 15 %) tended to be lower ($P=0.078$) (Figure 3). A meal response was found in 18 of the 26 subjects (69%), 6 of the 7 males, 5 of the 10 parous females and 7 of the 9 nulliparous females (NS).

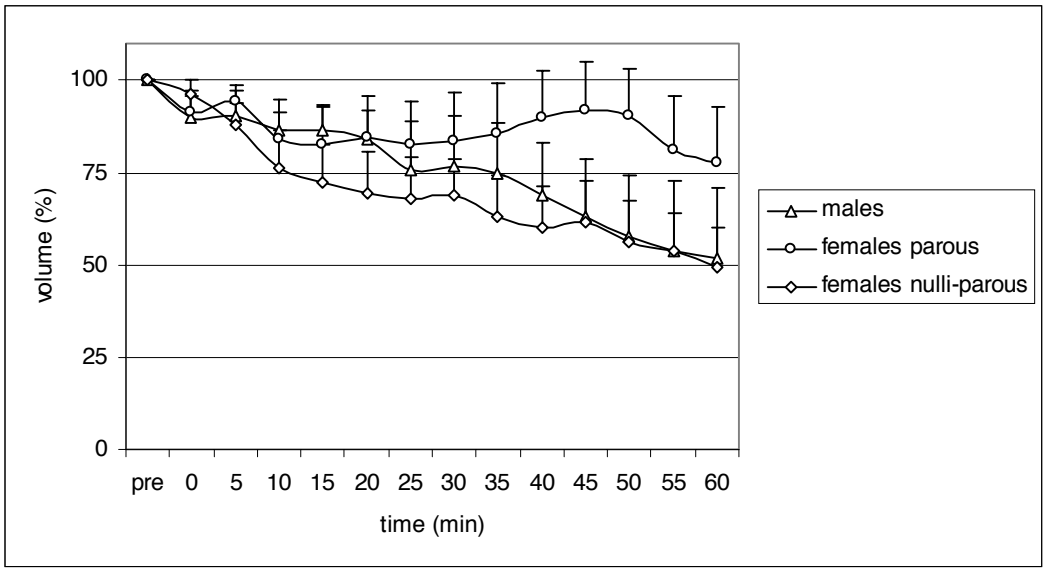


Figure 3: Response in % after 1000 kCal meal; mean and SEM

Comparison 600 kCal and 1000 kCal meal

In 26 subjects in whom the barostat procedure was performed with both the 600 and 1000 kCal meal, reduction in volume after the 600 kCal meal was 20 ± 7 % and after the 1000 kCal 40 ± 9 % ($P=0.28$). No significant difference was found between the 600 kCal and 1000 kCal meal in the postprandial volume when males (n = 7), parous females (n = 10) and nulliparous females (n = 9) were analyzed separately (Figure 4,5 and 6). After a 600 kCal meal, 14 of the 26 subjects (54%) had a response. After a 1000 kCal meal, 18 of the 26 (69%) patients had a meal response (NS). Two subjects who had a response after the 600 kCal meal, did not repeat the response after a 1000 kCal meal (2 parous females). Six subjects who did not had a meal response after a 600 kCal meal, had a response after the 1000 kCal meal (4 parous females, 1 male, 1 nulliparous female).

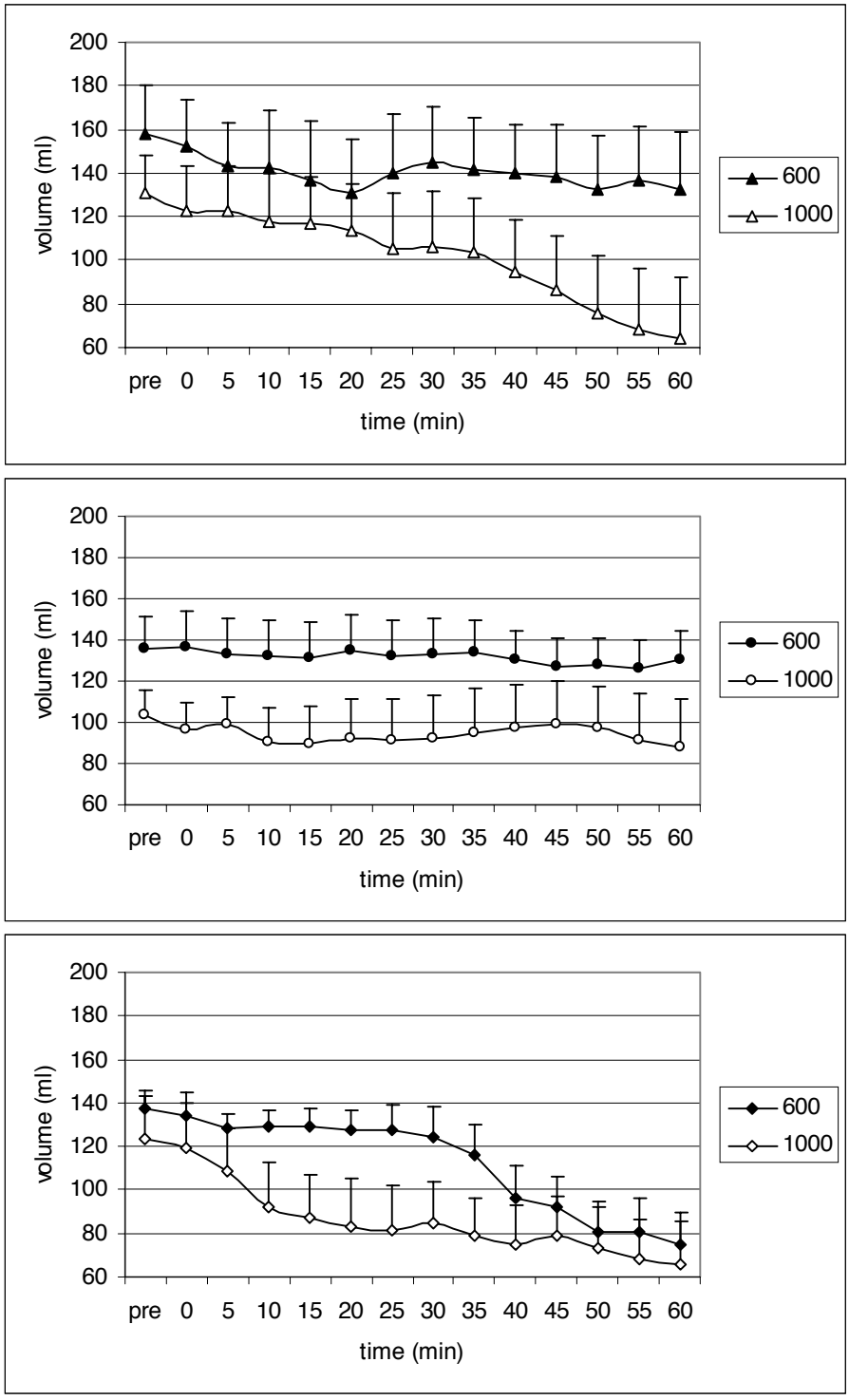


Figure 4-6: Response in males ($P=0.28$) on the upper graph; parous females ($P=0.85$) on the middle graph and nulliparous females ($P=0.58$) on the lower graph.

Phasic volume events

Experiment 1: Postprandial, an increase in PVE's was found (10 ± 1.8 times per hour versus basal 3.0 ± 0.9 times per hour; $P=0.001$). Experiment 2: Also with the 1000 kCal meal, a postprandial increase in PVE's was found (6 ± 1.3 times per hour versus basal 3.0 ± 1.3 times per hour; $P=0.019$).

Discussion

The gastro-colonic response is a contractile response that occurs throughout the colon after ingestion of a meal. This response is thought to play a role in the process of defecation in which a fecal bolus is presented at a state of increased tone and defecation urge occurs. Various authors have previously investigated the magnitude of this response, and reported a variation from 31 until 75% in postprandial volume reduction depending on the caloric load of the meal and the gender of the subjects (Table 1).[1,3,15,16,17] However, it remains unclear to what extend the response is influenced by the caloric load and the gender of the subject.

Author (reference)	*n (m/f)*	*Caloric load (kCal)*	*% fat*	*Pressure (mmHg)*	*Volume (ml)*	*Response (%)*
Lagier '99 (15)	12 (m)	1000	40	12.3 ± 4.5	123 ± 23	75 ± 14
Grotz '93 (3)	15 (10m,5f)	750	53		103 ± 4	65 ± 7
Bell '91 (1)	14 (5m,9f)	600/1000	Unknown		85 ± 6	41
Malcolm '97 (16)	25 (11m,14f)	1000	Unknown	6-10	Variate	31 ± 4
Leroi '99 (17)	13 (9m,4f)	1000	55	8.1 ± 6	155 ± 10	51 ± 8
Sloots '03	33 (11m,22f)	600	30	11.4 ± 0.3	146 ± 9	28 ± 7
	26 (7m,19f)	1000	76	12.0 ± 0.4	118 ± 9	39 ± 10

Table 1. Reported gastro-rectal response after a meal.

It is still in discussion why and how this reflex occurs. Not only a meal can provoke this response, also a gastric balloon filled with saline is able to enhance the rectal tone 'dose'-dependent.[10] This suggests that a mechanoreceptor is stimulated in the stomach. The direct onset of the response and the possibility of reduction of the response by anticholinergic drugs suggests a neural or neurohumoral pathway. Steadman et al. showed that 750 ml liquid meal (1000 kCal) caused a greater and more prolonged response than 750 ml of ingested water suggesting besides a gastric mechanoreceptor stimulus, a duodenal humoral stimulus.[11] Manometric studies showed that gastric balloon distension (100 until 300 ml water) gave a dose-related increase in rectosigmoid motility, which was abolished by atropine. Intraduodenal infusion of high fat solutions (in contrast to glucose or amino acids) provoked a colonic response. This response can only partly be blunted by atropine suggesting a more humoral mediated response.[12] Recently, the influence of a 5-HT-3 receptor on the gastro-colonic response has been explored. Antagonising this receptor inhibited both the mechanoreceptor-mediated gastrocolonic response as well as the duodenal humeral response suggesting a role for these receptors in the response.[13,14]
In our study, the gastro-rectal response during the 600 kCal experiment was not statistically significant different than that during the 1000 kCal experiment. The difference in caloric load between the two meals was mainly due to extra fat percentage (76 % versus 31 %). The meals had only a slight

difference in volumes (400 ml vs. 550 ml). This high caloric meal did not show an enhancement in gastro-rectal response, as has also been reported before in a smaller study.[1]
Table 1 shows results of other and our studies, which consistently suggest that the gastro-rectal response is lower in females than in males. We showed that this is mainly due to a lower response in parous women, whereas the response in nulliparous women does not differ from men. Apparently, the trauma of childbirth affects the efficacy of the gastro-rectal response, probably by damage of parasympathic and sympatic nerve endings and impairment of the neural reflex, comparable to the previously described damage to the pelvic floor innervation after straining during labour.[18] This hypothesis needs to be tested in the near future by a comparison with women who underwent caesarian section and controlled experiments before and after normal delivery.
Postprandially, an increase in frequency of phasic volume events was found what is in agreement with von der Ohe et al. who found this in the descending colon.[8] Other investigators could not find this difference in the rectum.[1] Phasic volume events are related to manometrically measured intraluminal pressure changes. Since they represent peristaltic waves in the colon and rectum, an increase in PVE's after a meal seems logic.
In conclusion, gastro-rectal response occurs in only 64% of the healthy subjects after a 600 kCal meal. The gastro-rectal response can be measured to a similar extend in men and nulliparous women, however the response is significantly impaired in parous women. This is possibly due to neurogenic damage during childbirth. Increasing the caloric load did not increase the gastro-rectal response. Therefore, to study gastro-rectal meal response with the barostat a caloric meal of 600 kCal is sufficient and a correction for parity should be made when results are compared.

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CHAPTER 5

HABITUAL STIMULATION OF DEFECATION: THE EFFECTS OF COFFEE USE AND NICOTINE ON RECTAL TONE AND VISCERAL SENSITIVITY

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Abstract

Coffee and cigarette use is believed to induce bowel movements. Aim of this study was to assess the effects of coffee and nicotine on rectal tone, compliance and sensitivity.
Healthy volunteers were recruited for the coffee (N = 8) and nicotine (N = 8) experiment. A flaccid bag, mounted on a catheter, was inserted in the rectum. After conditioning distension, continuous pressure distension (basal) was performed to register visceral sensitivity and compliance. After rectal adaptation, randomly on separate days, 280ml strong coffee or warm water or nicotine (2mg sublingual) or placebo was given. Rectal tone was measured for one hour. Continuous pressure distension was repeated.
Rectal tone increased 30 min after coffee (45%; P = 0,031) and after water (30%; P = 0,032), however, coffee and water were not significantly different. Rectal tone did not change significantly after nicotine (7%) or placebo (10%). Compliance and visceral sensitivity were not different between coffee and water or nicotine and placebo.
Conclusions: Coffee is a habitual stimulant of defecation by increasing rectal tone, however, warm water is also effective. Nicotine at this dose does not effect rectal tone. Coffee and nicotine does not influence sensitivity and compliance.

Introduction

Rectal tone can be influenced by pharmacological and physiological substances. The gastrorectal response is well documented consisting of a prompt increase of rectal tone after a meal.[1,2] The increased rectal tone and a heightening sensation can give a prompt urge to defecate. On the other hand, the rectum functions as reservoir by decreasing its tone for example during sleep.[3,4] Other habitual stimuli such as coffee[5,6] or cigarette smoking[7-10] could also exert their colorectal simulating function via direct alterations in rectal motility or sensibility.
Rectal visceral sensitivity can be tested reproducible using the barostat.[11,12] Rectal contractions and tone can be measured when a preset constant pressure is used to inflate the bag.[1,2] The barostat-method is superior to intraluminal manometry, since the manometry catheter has a weak contact with the bowel wall, and it only can adequately measure rapid large rectal contractions.[1,13]
In order to study the relationship between coffee or nicotine and the perception of physiologic sensations, we studied the effects of these compounds on rectal tone and visceral sensibility and compliance using the barostat in healthy subjects. The effect of coffee was investigated in a crossover design using moderate strong coffee and warm water. The effect of nicotine was tested using placebo-controlled nicotine sublingual tablets in a double-blind crossover setting.

Materials and Methods

Sixteen healthy volunteers were recruited by public advertisement. Eight volunteers (4 men, 4 women, 21-44 year old; Body Mass Index 22 range 18-29 kg/m^2) participated in the coffee experiment and eight non-smoking volunteers (1 man, 7 women, 18-25 year old; BMI 21 range 19-26 kg/m^2) in the nicotine experiment. The participants had normal bowel habits without a history of gastrointestinal disease or previous abdominal surgery. None of the volunteers used medication except all females used oral contraception. Four of the eight subjects in the coffee experiment were moderate coffee users (3-4 cups daily). Written informed consent was obtained from all volunteers. The study was approved by the Ethic Committee of our hospital.

Barostat

Subjects presented to the unit after an overnight fast for food and coffee. The subjects had bowel preparation with an enema. The barostat-balloon was inserted in the rectum, just behind the anal verge. The subjects were positioned supine, with 15 degrees Trendelenburg.[14] The barostat system consisted of the following: A flaccid polyethylene bag (maximal capacity 600ml) was fixated on a double-lumen catheter tube (diameter 5mm). After inflation, the balloon has a cylindrical shape with a length of 10cm. The catheter was connected with an electronic barostat device (Synectics Visceral stimulator, Synectics medical, Stockholm, Sweden) with two connections, an inflation port and a pressure port for intrabag pressure measurement. Maximal airflow was 38 ml per second. With a feedback mechanism, the barostat device can regulate pressure or volume in

the bag. Procedures were stopped if the safety value of the maximal volume of 600 ml or the pressure of 50mmHg was exceeded or if the patient was unable to hold the distension.

Procedures

1. Continuous volume distension (CVD)
Rectal volume controlled distension was performed at a rate of 30 ml per minute until maximal tolerated distension. This "conditioning" distension was performed in order to reduce and stabilize basal tone, to familiarize subjects with the procedure and enhance reproducibility.[11]
2. Continuous pressure distension (CPD)
Rectal distension was accomplished by ramp pressure controlled inflation until 36 mmHg in 10 minutes. Volume was registered continuously and visual analogue scale (VAS) was registered at pressure-steps of 4mmHg (VAS: 0 = no feeling, 1 = light sensation, 2 = clear feeling or beginning urge, 3 = normal urge to defecate, 4 = strong urge and 5 = maximal toleration). Then, deflation was performed in 10 minutes to register hysteresis. Hysteresis was being defined as the relative difference between the area under the pressure volume curve (AUC) in the ascending and descending part.[15] Minimal distension pressure (MDP; i.e. pressure to unfold the rectal bag until 10ml volume) was registered.
3. Rectal tone response
An isobaric barostat procedure was conducted at 2mmHg above MDP. After 30 to 60 minutes of basal registration, when a stable volume was reached, a stimulus was given (see further). After the stimulus, volume and intraballoon pressure were recorded for one hour. A response was defined as a more than 10% decrease in volume after one hour. Phasic volume event (PVE) was defined as 10% decrease in volume lasting 15-60sec.[1,13,14]
4. Continuous pressure distension was repeated one hour after intake of the stimulus.

Experimental design

In the coffee experiment, coffee or warm water was given to the subjects on separate days in a randomized crossover design. Fifteen grams of commercially available regular grounded coffee (Aroma Rood, Douwe Egberts Nederland B.V., Utrecht, The Netherlands) was used. This was (paper-) filtered with 300ml boiling water resulting in about 280ml of coffee (Caffeine content approx. 180mg). The coffee was drunk without additives. The control drink consisted of 280ml of warm water.[16]
In the nicotine experiment the subjects were given nicotine 2mg sublingual (Nicotinell® Microtab containing nicotine-ß-cyclodextrine, Pharmacia & Upjohn BV, Woerden, The Netherlands) or placebo in randomized order in a crossover design on separate days. Placebo consisted of tablets with comparable size and color. Subject and investigator were blinded for the medication. Nicotine tablets in the dose of 2mg mimics smoking of 2 cigarettes.

Data and Statistical analysis

Results are presented as means and standard error of the mean (SEM) or medians when appropriate. The isobaric procedure is presented as average volumes over 5 minutes periods. Basal volume was defined as the average of the volumes measured in the period 5 minutes before the administration of the stimulants. Phasic volume events were registered during the adaptation period before the stimulants and the hour thereafter by the Polygram for Windows version 2.04 software (Synectics medical, Stockholm, Sweden) and reviewed by the investigator. Volume- pressure curves, VAS-pressure curves and Volume-time curves were compared between coffee and water or between nicotine and placebo using the ANOVA method for repeated measurements.

Results

Coffee experiment

Basal rectal volume was not significantly different between the procedures with coffee (128 ± 14ml) and water (142 ± 16ml). Rectal volume decreased significantly starting at 30min from 126 ± 24 to 80 ± 28ml (45%) after coffee ($P = 0{,}031$) and from 142 ± 22 to 110 ± 30ml (30%) after water ($P = 0{,}032$). The response after coffee or water was not significantly different (Figure 1). Three subjects had no response at all after either coffee or water. Basal frequency of Phasic Volume Events (PVE's) did not differ between the procedures with coffee (3,7 ± 2,6 per hour) and water (4 ± 0,9 per hour). After coffee intake, PVE's increased with 2.3 ± 2.7 per hour (P = 0.4) and after water, PVE's decreased with 1.4 ± 1.3 per hour (P = 0.3). The change of PVE's did not differ between coffee and warm water (P = 0.08). Compliance, hysteresis and visceral sensitivity were not different after coffee or water, however, compared to basal measurement rectal sensitivity was impaired with both coffee and water ($P = 0{,}033$; Figures 2 and 3).

Nicotine experiment

Basal rectal volume did not differ for the nicotine (151 ± 16ml) and the placebo measurement (158 ± 25ml). Rectal volume did not change significantly after administration of nicotine (137 ± 19ml; 7%) or placebo (147 ± 35ml; 10%) (Figure 1). Two volunteers had only a response after nicotine and one after both nicotine and placebo. Basal amounts of PVE's did not differ between the nicotine (0 ± 0 per hour) and the placebo (1.1 ± 0.7 per hour). After nicotine, PVE's increased with 1,3 ± 0,5 per hour ($P = 0{,}06$) and after placebo with 1.2 ± 0.6 per hour ($P = 0{,}2$). The increase of PVE's did not differ between nicotine and placebo. Rectal visceral sensitivity, compliance and hysteresis were not statistically different after nicotine or placebo compared to basal ($P = 0{,}2$; Figure 4 and 5). Rectal visceral sensitivity was significantly lower after nicotine ($P = 0{,}012$) and placebo ($P = 0{,}034$) compared to basal.

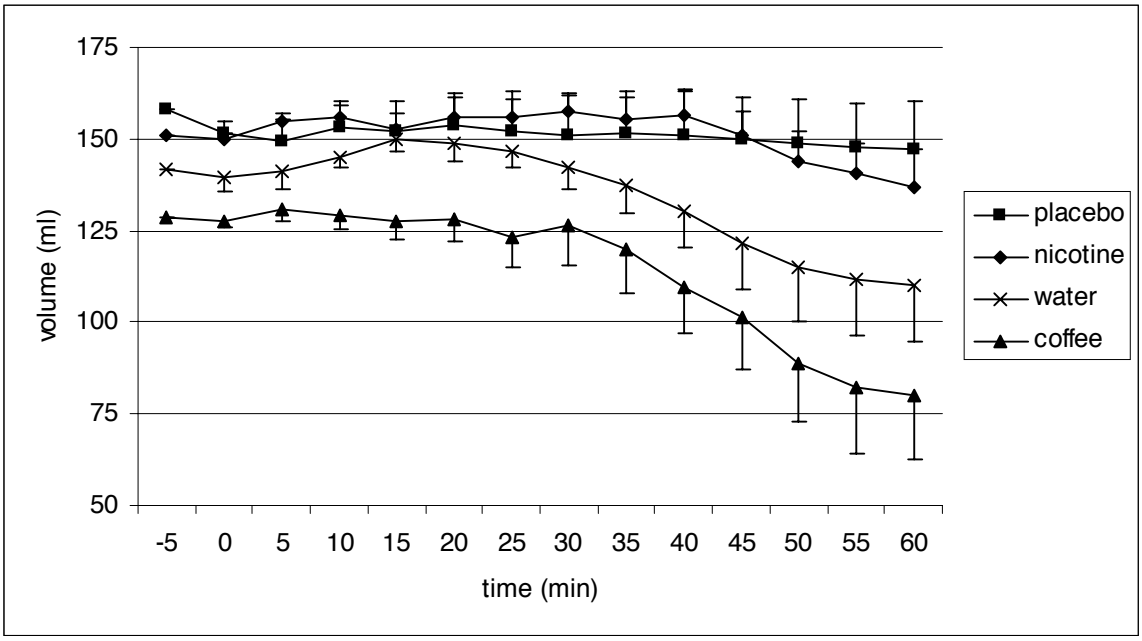

Figure 1. The decrease in rectal volume after coffee or water and nicotine or placebo intake at T=0. Means and SEM.

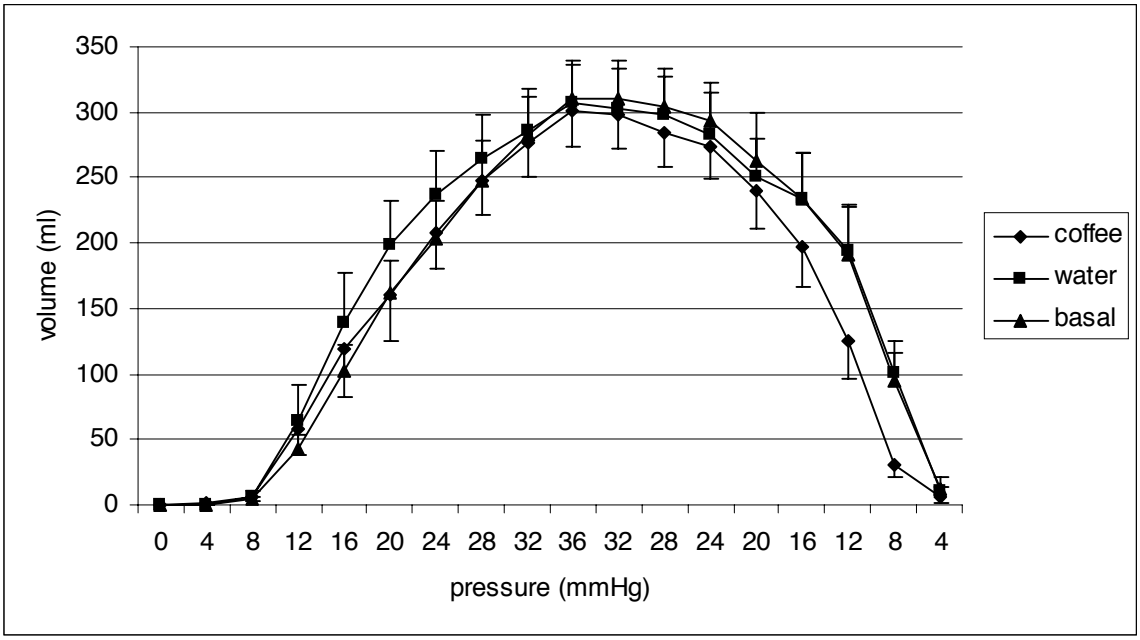

Figure 2. Rectal compliance during inflation and deflation under basal conditions and after coffee and water intake. Means and SEM.

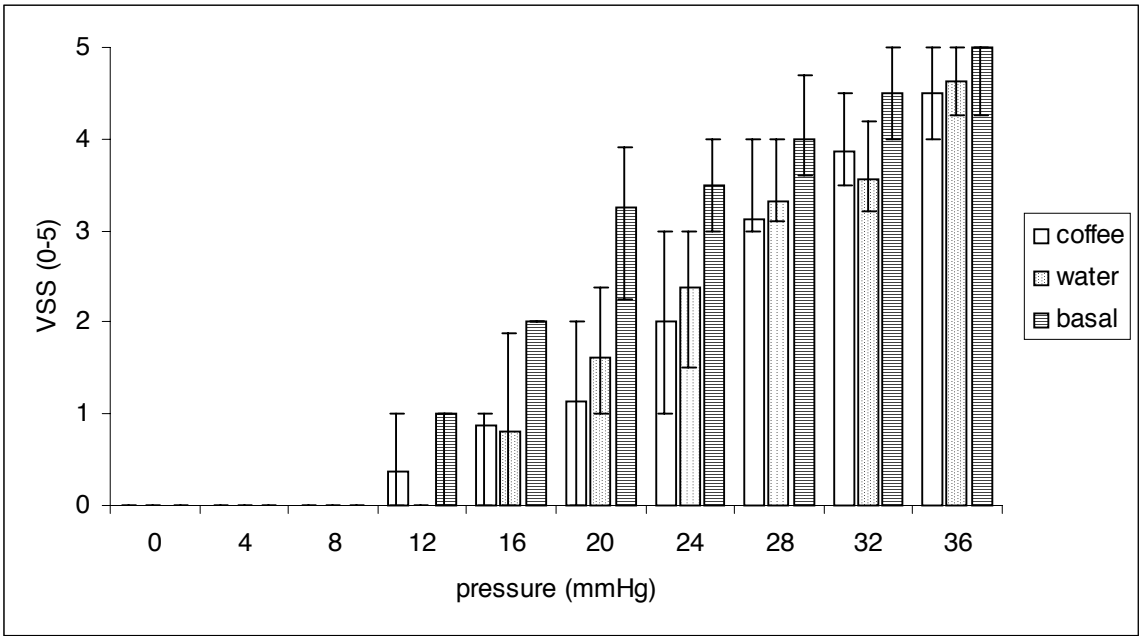

Figure 3. Rectal visceral sensitivity (VSS) during pressure controlled inflation under basal condition and after coffee and water intake. Medians and 25-75th centiles.

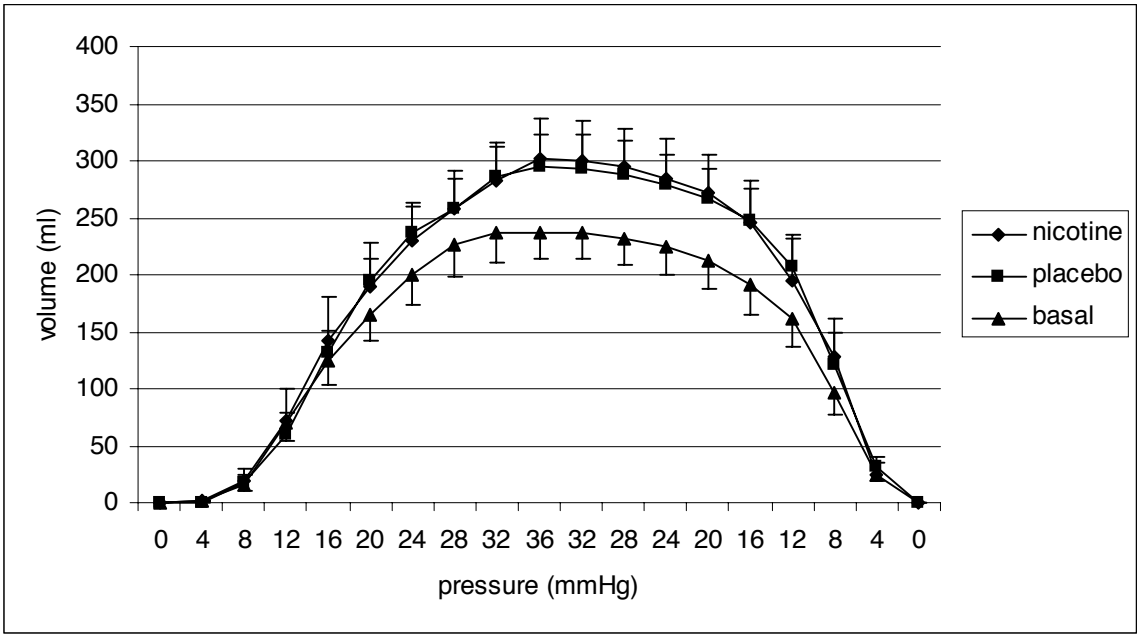

Figure 4. Rectal compliance during inflation and deflation under basal condition and after nicotine and placebo intake. Means and SEM.

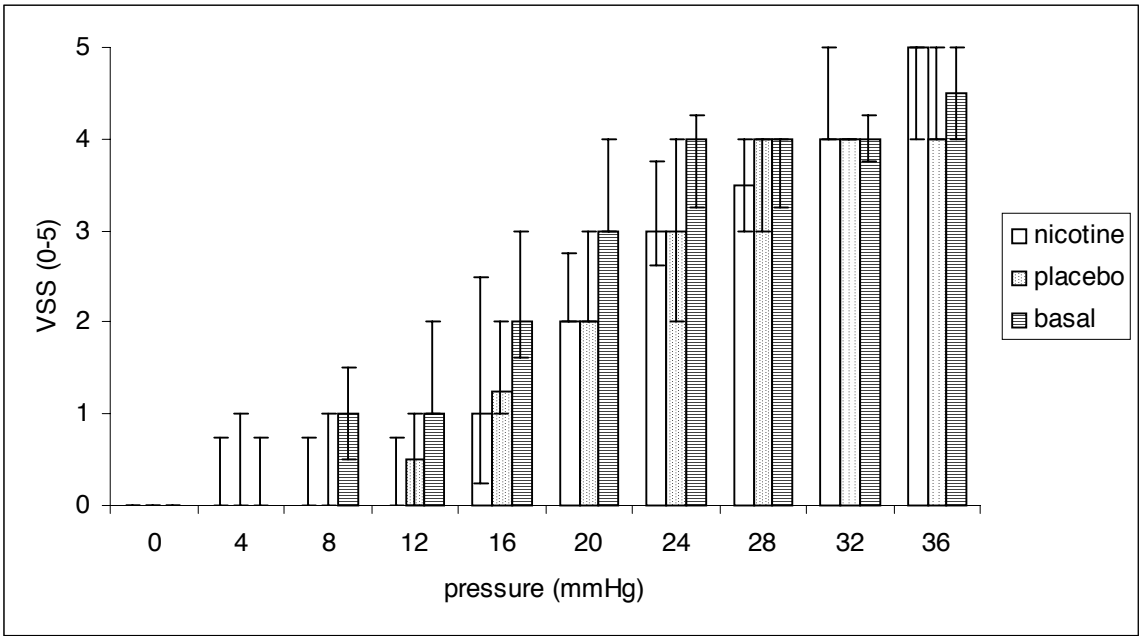

Figure 5. Rectal visceral sensitivity (VSS) during pressure controlled inflation under basal condition and after nicotine and placebo intake. Medians and 25-75th centiles.

Discussion

Coffee and smoking are generally believed to induce bowel movements. Caffeine, the compound which could cause the bowel stimulating effect of coffee, antagonises the adenosine receptors, which have an inhibitory effect on gastrointestinal motility.[17] However, other compounds of coffee can sort an effect on the gastrointestinal system.[18] Nicotine, the acting compound of smoking, releases of nitric oxide, which acts as a non-adrenergic non-cholinergic neurotransmitter and has more smooth muscle relaxing effects.[19] In this study, it was investigated whether rectal tone, compliance or visceral sensitivity are influenced by coffee use or smoking (by applying nicotine).
The present study demonstrated that the intake of 280ml coffee or warm water significantly increased rectal tone. The increase in rectal tone after coffee was larger than after water, however, this difference was not significant. Therefore, the increase in rectal tone after coffee is mainly due to gastric distension[20] comparable with the effect of water. The caffeine-compound of coffee had only a minor not statistically significant effect on rectal tone. A trend was found in the increase in Phasic volume events (PVE's), which correspond with rapid colonic contractions measured by intraluminal manometry.[1,13] Colonic manometry studies showed that caffeine increased colonic activity of the ascending colon in dogs.[21] In humans, distal colonic contractions increased after the intake of regular coffee and less after decaffeinated coffee, but not after hot water.[5,6] In our study, we did measure an effect from intake of water because we used the barostat system, which registers slow tone alterations that are not registered by intraluminal manometry. A trend was found in the increase of PVE's after coffee intake compared to water, which is in agreement with the findings of manometric studies.[5,6]

Coffee did not alter rectal visceral sensitivity or compliance compared to warm water intake. To our knowledge, the effect of coffee on colonic sensitivity has not been investigated before. Gastric perception and compliance was not influenced after coffee intake.[22]
To mimic the effects of smoking two cigarettes, nicotine was given in a 2mg dose. All subjects experienced side effects such as nausea and light-headedness within 10 minutes after application. The sublingual tablets dispersed in approximately 10 minutes. Nicotine did not influence rectal tone within one hour of application. A trend was found in increasing of the amount of PVE's after nicotine intake compared to basal. Compared to the placebo intake, the increase in PVE's was not different. This is in agreement with other studies which showed that an intracolonic solution of nicotine immediately decreased rectal resting pressure and pressure activity and that smoking of one cigarette had a biphasic effect on the distal colonic pressures.[7,9] Coulie et al. showed that low dose nicotine infusions (comparable to the nicotine tablets in our study) reduced colonic compliance but did not affect colonic phasic contractility or tone. A five times increased dose of nicotine induces an initial burst of colonic contractions, which subside with a sustained relaxation of the colon.[23] However, in non-smoking males transdermal nicotine application accelerated colonic transit of radio-opaque markers, which is not in agreement with the findings of barostat or manometric studies.[10] Rectal visceral sensitivity and compliance was not influenced by nicotine compared to placebo, which is in agreement with other authors.[8]
In our study, we found a significant decrease in rectal sensitivity after coffee, warm water, nicotine, and placebo compared to the basal measurement. Since sensitivity was also altered after placebo, other factors must be of influence. The rectum shows an adaptive response to continuous distension, which explains the gap between the area under the volume pressure curves after nicotine and placebo compared to the basal measurement.[24] In the coffee experiment, rectal tone was increased by coffee and warm water, abolishing this effect on rectal compliance. Furthermore, the subjects had nearly two hours of bed-rest during the rectal tone response procedure. Steadman et al. showed that during bed-rest at night rectal tone decreased and on waking the tone increased.[4] They did not study the effect of bed-rest on rectal sensitivity. In our study, subjects did not sleep during the experiments but over time with the procedure the bed-rest related relaxation could have contributed to a decrease of rectal sensitivity. This alteration in rectal sensitivity is an order effect, which makes comparison of visceral sensitivity and compliance measurements before and after a rectal tone response measurement unreliable to assess the effect of a compound.
In conclusion, coffee can be used as a habitual stimulant of defecation by increasing rectal tone, however, warm water intake is also effective. Nicotine intake (smoking) at this dose did not effect rectal tone. Coffee and nicotine had no influence on rectal visceral sensitivity.

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CHAPTER 6

RECTAL SENSORIMOTOR CHARACTERISTICS IN FEMALE PATIENTS WITH IDIOPATHIC CONSTIPATION WITH OR WITHOUT PARADOXICAL SPHINCTER CONTRACTION

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Abstract

Patients with idiopathic constipation are categorised into slow transit, pelvic floor dysfunction and irritable bowel syndrome, however, considerable overlap between these groups exists. Aim of this study was to establish abnormalities in patients with idiopathic constipation using rectal visceral sensitivity, compliance and motor function measurement and anal manometry.
Thirty female patients with idiopathic constipation and 22 female controls were investigated with rectal barostat and anal manometry. Visceral sensitivity and compliance were tested by intermittent and continuous pressure controlled distension. Patients were classified according to their sensations and compliance into normal, hypersensitive, stiff, insensitive or lax rectum. Postprandial Rectal Response (PRR) and Phasic Volume Events (PVE) were registered for one hour after a 600 kCal meal. Paradoxical Sphincter Contraction (PSC) was shown with manometry as a paradoxical increase of anal pressure during straining.
Abnormal rectal sensitivity or compliance was found in 90% of the patients with in 35% a lax, in 27% a hypersensitive, in 17% an insensitive and in 10% a stiff rectum. Both patients with constipation (11%; $P=0,042$) and controls (25%; $P=0,002$) showed a PRR, which was not significantly different ($P=0,12$). Nulliparous controls had significant higher PRR than parous controls, nulliparous and parous patients ($P=0,008$). Hypersensitive patients had lower PRR than other patients ($P=0,04$). Patients had less PVE's basal ($P=0,03$) and postprandial PVE's increased in both patients ($P=0,014$) and controls ($P<0,001$). PSC was found in 13 (43%) patients, who had higher sensitivity scores ($P=0,045$) than other patients. Rectal compliance or PRR were not different.
Conclusions: Patients with idiopathic constipation show in 90% an abnormality in rectal sensation or compliance. The postprandial rectal response was comparable between patients with constipation and controls, however, PVE's were diminished. The response was almost absent in parous patients and controls. Patients with paradoxical sphincter contraction had higher rectal sensitivity but with unaltered compliance and postprandial rectal response. The traditional subdivision of patients with idiopathic constipation in slow transit, pelvic floor dysfunction and irritable bowel syndrome seems to be an oversimplification and a more mixed population exists. Whether this could have implications in treatment of idiopathic constipation, should be investigated in future trials.

Introduction

Idiopathic constipation is characterised by infrequent bowel movements, hard stools, increased straining during defecation and the feeling of incomplete evacuation. These complaints are functional, a specific cause can not be found. Subtypes of idiopathic constipation have been proposed to explain symptom complexes and findings during anorectal and colonic motility tests. Patients with chronic constipation have been categorised in three groups: Slow transit, Pelvic floor dysfunction and Constipation predominant irritable bowel syndrome.[1] Idiopathic slow transit constipation describes a symptom complex with symptoms of decreased bowel frequency poorly responsive to fibre and laxatives and a delayed transit time without a megacolon. Other gastrointestinal manifestations include abdominal pain, bloating, malaise, nausea and difficult faecal expulsion.[2] The term slow transit constipation generally refers to the patients with delayed colonic transit time.[1] Besides delayed colonic transit, decreased colonic motor activity after a meal, fewer high amplitude propagated contractions (HAPC), uncoordinated phasic rectal activity or irresponsiveness to a meal or a stimulant such as bisacodyl were found.[3-6] Possibly, slow transit constipation represents a more generalised gastrointestinal dysmotility disorder.[7] Paradoxical sphincter contraction (anismus) is defined as an inappropriate contraction of the pelvic floor during straining, rather than relaxation.[8] Anal manometry, electromyography (EMG) or defecography can detect the paradoxical contraction of the anal sphincter.[9-11] Slow or normal transit can be found on colonic transit time studies.[12] Biofeedback training decreases straining and increases bowel frequency.[13] In constipation predominant irritable bowel syndrome (C-IBS), bloating and pain are more prominent than decreased bowel frequency represented by an altered perception for rectal distension (visceral hypersensitivity).[14,15] These patients with lower tolerance for balloon distension have high anxiety and depression scores.[16] Possibly, IBS patient have different processing of bowel perception in the brain since using the PET-scan during rectal distension perception of rectal painful distension was associated with activation of different areas in the brain.[17]
This classification according to their pathogenesis was meant to offer specific therapies. However, a mixture of characteristics occurs in constipated patients.[18] Patients with features of slow transit constipation can respond to biofeedback training and the absence of paradoxical sphincter contraction does not preclude benefit.[19] Patients with paradoxical sphincter contraction can show delayed colonic transit, even when the distal obstruction was removed.[20,21] Patients with IBS can show features of paradoxical sphincter contraction.[20]
Aspects of the defecation process can be disturbed in idiopathic constipation such as the responsiveness of the bowel towards stimuli, adequate perception of the distending rectum and relaxation of the pelvic floor. Slow transit constipation is caused by diminished colonic responsiveness to stimuli, pelvic floor dysfunction is due to paradoxical sphincter contraction and constipation predominant irritable bowel syndrome presents with altered sensitivity to rectal distension. The aim of this study was to investigate the postprandial rectal response, rectal sensitivity and compliance, and paradoxical sphincter contraction in patients with idiopathic constipation in order to come to a possible classification.

Patients and Methods

Subjects

Thirty female patients (median age 35 year; range 20-77) were included. All patients presented complaints of more than two of the following criteria for at least 6 months:

- less than two bowel movements per week
- lumpy and/or hard stools for more than 25% of the time
- sense of incomplete evacuation for more than 25% of the time
- straining at defecation for more than 25% of the time.[22]

All patients had less than two bowel movements per week and at least one of the other criteria. All patients were treated with laxatives and/or enemas, however, they felt their treatment was insufficient. Digital maneuvers were not reported. None of the patients presented alternating constipation and diarrhea. Abdominal pain or distension or bloating was not their main concern. None of the patients had a history of abdominal surgery. Colonoscopy was performed to exclude organic disease. According to the patients' clinicians, they were classified as idiopathic constipation and sent to our laboratory for evaluation. We performed rectal examination and anal manometry. Defecography was performed to exclude anatomical disorder when suspected, no significant rectal intussusception or enterocele were found. Colonic transit time measurement was performed to show slow transit, however in half of the included patients these tests were not reliable since patients could not stop using laxatives.
Twenty-two healthy female controls (median age 30 year and range 20-59) were recruited by advertising. The controls had normal bowel habits without history of constipation or abdominal surgery and did not use medication. Females who participated in the study were not pregnant. The protocol was approved by the local Ethics Committee and written informed consent was given by each subject.

Barostat

Subjects presented to the unit after an overnight fast. The subjects had bowel preparation with an enema. The subjects were positioned on their back with the head-lowered 15 degrees. The barostat-balloon was inserted in the rectum, just behind the anal verge. The barostat system consisted of the following: A flaccid polyethylene bag (maximal capacity 600ml) was fixated on a double-lumen catheter tube (diameter 5mm). After inflation, the balloon had a cylindrical shape with a length of 10cm. The catheter was connected with an electronic barostat device (Synectics Visceral stimulator, Synectics medical, Stockholm, Sweden) with two connections, an inflation port and a pressure port for intrabag pressure measurement. Maximal airflow was 38 ml per second. With a feedback mechanism, the barostat device can regulate pressure or volume in the bag. Procedures were stopped if the safety value of the maximal volume of 600 ml or the pressure of 50mmHg was exceeded or if the patient was unable to hold the distension.[23]

Procedures

The following procedures were performed in a standard order:
1. Conditioning distension: Rectal volume controlled distension was performed at a rate of 30 ml per minute until maximal tolerated distension. This 'conditioning' distension was performed in order to reduce and stabilise basal tone, to familiarise subjects with the procedure and enhance reproducibility.[24]
2. Intermittent pressure distension (IPD): Rapid rectal distension was performed in a semi-random staircase manner at the pressures 8, 12, 20, 16, 32, 24, 36 and 28 mmHg. Pressure distension was continued one-minute followed by one-minute rest. Volume and visceral sensitivity was registered after 30 seconds of adaptation. Visceral sensitivity (VSS) was scored from 0 to 5 (0 = no feeling, 1 = light sensation, 2 = clear feeling or beginning urge, 3 = normal urge (as they would go to the toilet), 4 = strong urge (as they would haste to the toilet) and 5 = maximal tolerated or pain). When unbearable pain was reported and the procedure had to be interrupted, only the next (lower) pressure was offered after which the following distensions were omitted.
3. Continuous pressure distension (CPD): Rectal distension was accomplished by pressure-controlled ramp inflation until 36mmHg in 10 minutes. Volume was registered continuously and sensitivity was registered at pressure steps of 4mmHg. Then, deflation was performed in 10 minutes to register hysteresis. Hysteresis was being defined as the relative difference between the area under the pressure volume curve (AUC) in the ascending and descending part ([AUCdesc-AUCasc]/AUCdesc).[25] Minimal distension pressure (MDP; i.e. pressure, which keeps the bag from being completely collapsed) was registered. Dynamic compliance was calculated as volume increase during pressure distension ($\Delta V/\Delta p$). Wall tension is considered an important parameter of visceral sensitivity to decrease variability in sensation-scores. Wall tension was calculated using Laplace's law (pressure * radius) regarding the balloon shape as a cylinder (volume is equal to $\pi * r^2 *$ length of cylinder).[26,27]
4. Postprandial rectal response (PRR): An isobaric barostat procedure was conducted at 2mmHg above MDP. After 30 to 60 minutes of basal registration when a stable volume was reached, a liquid meal was given consisting of 400 ml of Ensure plus® (600 kCal, 17% protein, 53% carbohydrates, 30% fat). After the meal, volume and intraballoon pressure was recorded for one hour. A meal response was defined as a more than 10% decrease in postprandial volume after one hour. Phasic volume events (PVE) were defined as 10% decrease in volume with duration of 15-60sec.[28,29]

Anal manometry

The maximal basal pressure (MBP), maximum squeeze pressure (MSP) and sphincter length (SL) were measured according to our methods as described previously.[30] To determine relaxation of the pelvic floor, the patients were asked to strain with the catheter in situ.[8,9,13] Paradoxical sphincter contraction (PSC) was defined as maximal basal pressure more than 60 mmHg and paradoxical increase of anal pressure during straining more than 10 mmHg.

Data and Statistical analysis

Results are presented as means with standard error of the mean (SEM). Volume pressure curves and VSS-pressure curves were compared in the groups using the ANOVA method for repeated measurements. Three groups of rectal sensitivity and rectal compliance were classified using the 95% confidence interval of the values of the controls. Rectal sensitivity was defined as hypersensitivity (VSS above 95% confidence interval of the controls: unable to hold distension until 36 mmHg in both the intermittent and the continuous distension), normosensitivity (VSS within the 95% CI) or hyposensitivity (VSS below the 95% CI). Rectal compliance was categorised in low, normal and high compliant after comparing the curve to the 95% CI of the controls. Rectal sensitivity and compliance were combined using the classification according to Prior et al.[31]

1. Normal rectum (normal sensitivity and compliance)
2. Hypersensitive rectum (low or normal compliance)
3. Stiff rectum (normosensitive and low compliance)
4. Insensitive rectum (hyposensitivity and normal or low compliance)
5. Lax rectum (normosensitivity or hyposensitivity and a high compliance).

Rectal volumes measured during the postprandial rectal response were analysed as mean volumes over 5-minute periods. Results are presented as mean volume with SEM or as percentages, relative to baseline volume. Pre- and postprandial data were compared using the ANOVA method for repeated measurements. Phasic volume events were calculated by Polygram 2.04 software (Synectics medical, Stockholm, Sweden) and reviewed by the investigator. Basal and postprandial phasic volume events were compared using the Student's *t*-test.

Results

Visceral sensitivity

The patients could be classified according to the 95% confidence interval of the controls in three sensitivity groups. Eight patients (25%) were found to be hypersensitive, sixteen (55%) were normosensitive and six patients (20%) had a hyposensitive rectum. Intermittent or continuous pressure distension did not reveal different sensitivity scores (Figure 1).

Compliance

Volume pressure curves were neither different between the continuous and the intermittent procedure in patients or controls nor different between hypersensitive, normo and hyposensitive groups and the controls. Also, static compliance was not different between the hyper-, normo and hyposensitivity patients. The patients could be classified according to the 95% confidence interval of the controls in three compliance groups (Figure 2). A low compliant rectum was found in 9 patients (30%), normal in 10 (33%) and high in 11 (37%). Table 1 shows the combination of the abnormalities of compliance and sensitivity. A rectal abnormality was found in 90% of the patients with 35% of the patients having a lax rectum.

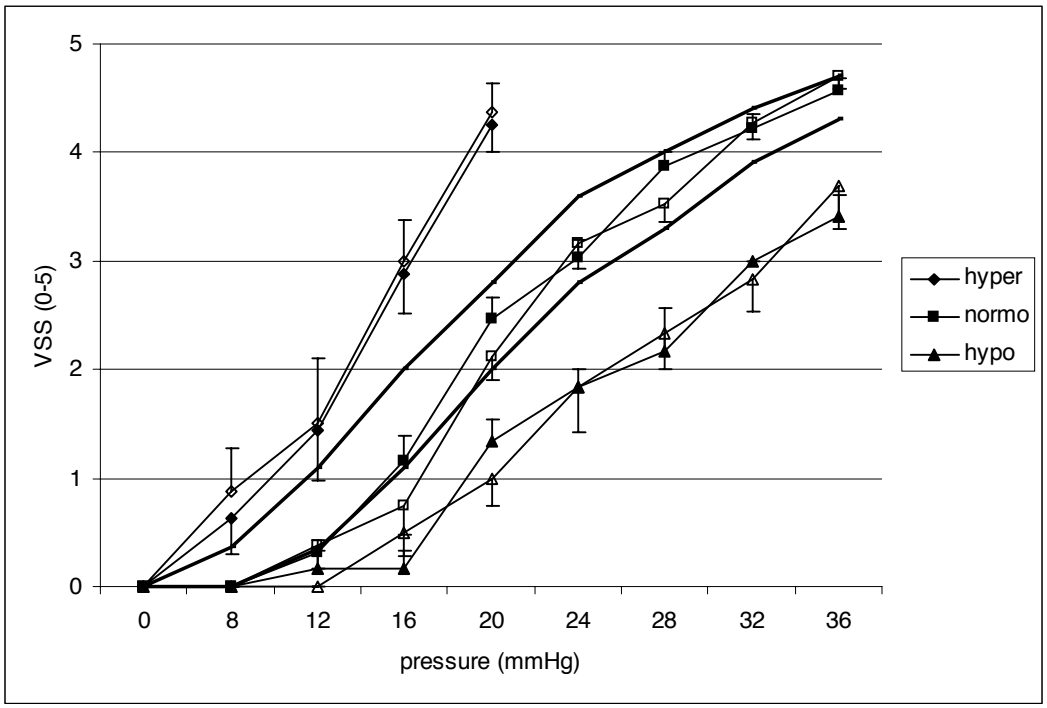

Figure 1. Line chart showing visceral sensitivity during intermittent pressure distension (IPD, closed symbols) and during continuous pressure distension (CPD, open symbols) in hypersensitive, normosensitive and hyposensitive patients compared to the 95% confidence interval of the controls (fat line).

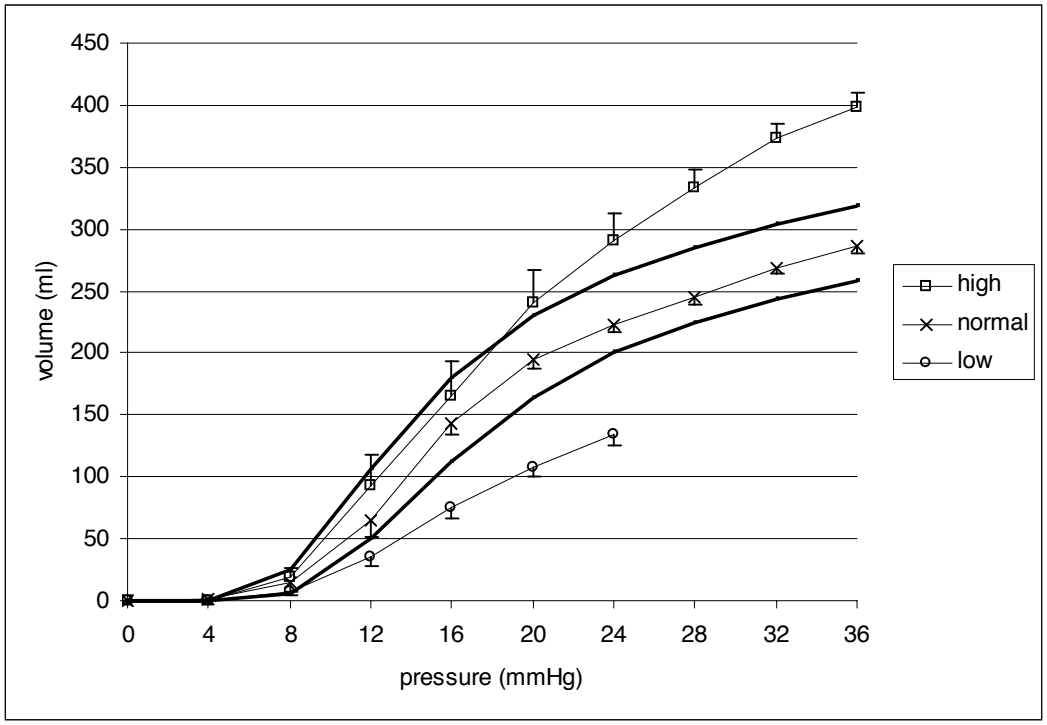

Figure 2. Line chart showing compliance curves during continuous pressure distension. The patients are divided in low, normal and high compliant and compared to the 95% confidence interval of the controls.

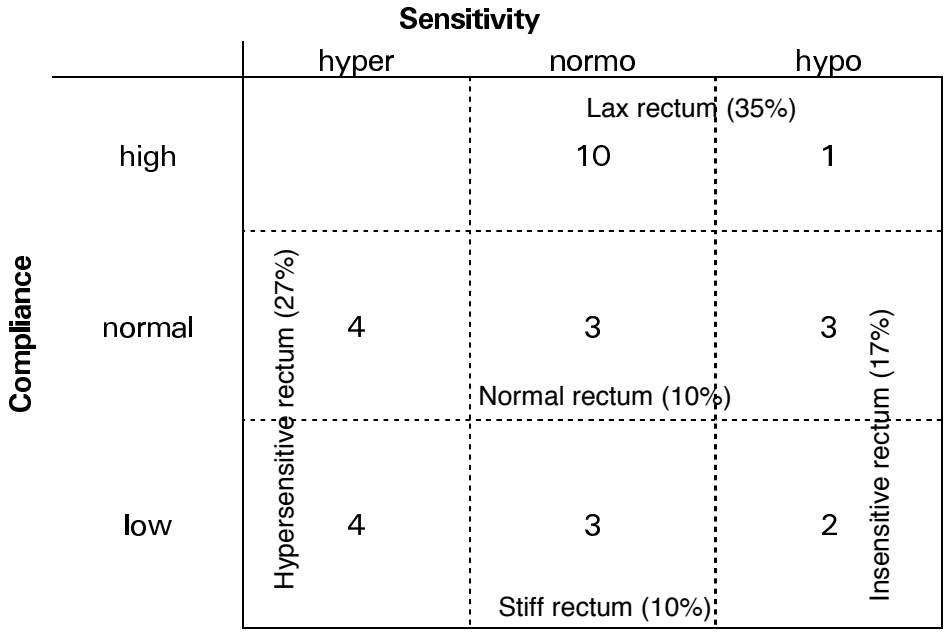

Table 1. Constipated patients characterised according Prior et al. [31]

When visceral sensitivity was expressed with wall tension as parameter, the difference in sensibility between patients and controls disappeared since patients tended to have lower volumes at the pressures (not significant). The sensitivity groups remained unaltered when VSS was expressed as wall tension instead of pressure. Hysteresis could not be assessed in patients with a hypersensitive rectum since the pressure of 36 mmHg was not reached. Hysteresis did not differ between patients with normosensitive (0,27 ± 0,03) and hyposensitive patients (0,30 ± 0,03) with constipation and controls (0,28 ± 0,02) (P=NS).

Postprandial rectal response

Basal pressure was not significantly different between patients (12,4 ± 0,4 mmHg) and controls (11,8 ± 0,3 mmHg). Rectal volume after the adaptation period was not significantly different between patients (160 ± 11 ml) and controls (138 ± 10ml; P=0,15). Postprandial volume decreased significantly to 144 ± 13 ml in patients (11%; P=0,042) and to 103 ± 12 ml in controls (25%; P=0,002). However, the decreased response in constipated patients was not significantly different from controls (P=0,12). Nulliparous controls had a significant lower postprandial volume (48%) than parous controls (2%), nulliparous (16%) and parous patients (4%) (P=0,008) (Figure 3). Hypersensitive patients (increase of 4%) had a significant (P=0,04) lower response than other patients. High adaptation volumes were found in patients with a lax rectum (210 ± 15 ml) or a normal rectum (176 ± 17 ml) compared to controls (138 ± 10 ml; P=0,01 and P=0,13) and patients with hypersensitive (122 ± 18 ml), stiff (124 ± 35 ml) or insensitive (115 ± 18 ml) rectums. Compliance did not influence the PRR (Figure 4).
Patients (0,4 ± 0,3 per hour) had significantly (P=0,03) less PVE's preprandial than controls (3,0 ± 1,1 per hour). Patients and controls showed an increase in PVE's postprandial (2,3 ± 0,5; P<0,001 vs. 8,5 ± 1,7 per hour; P=0,014 respectively).

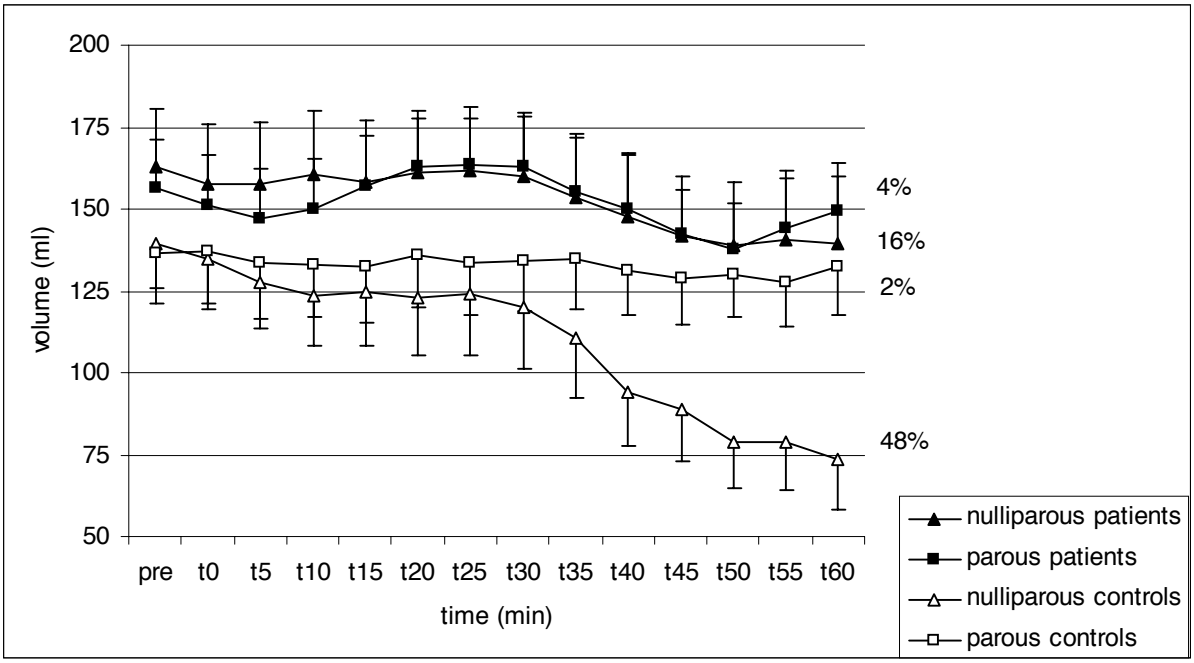

Figure 3. Line chart showing the postprandial rectal response in nulliparous and parous patients and controls. Parous controls, nulliparous and parous controls had lower PPR than nulliparous controls ($P=0{,}008$).

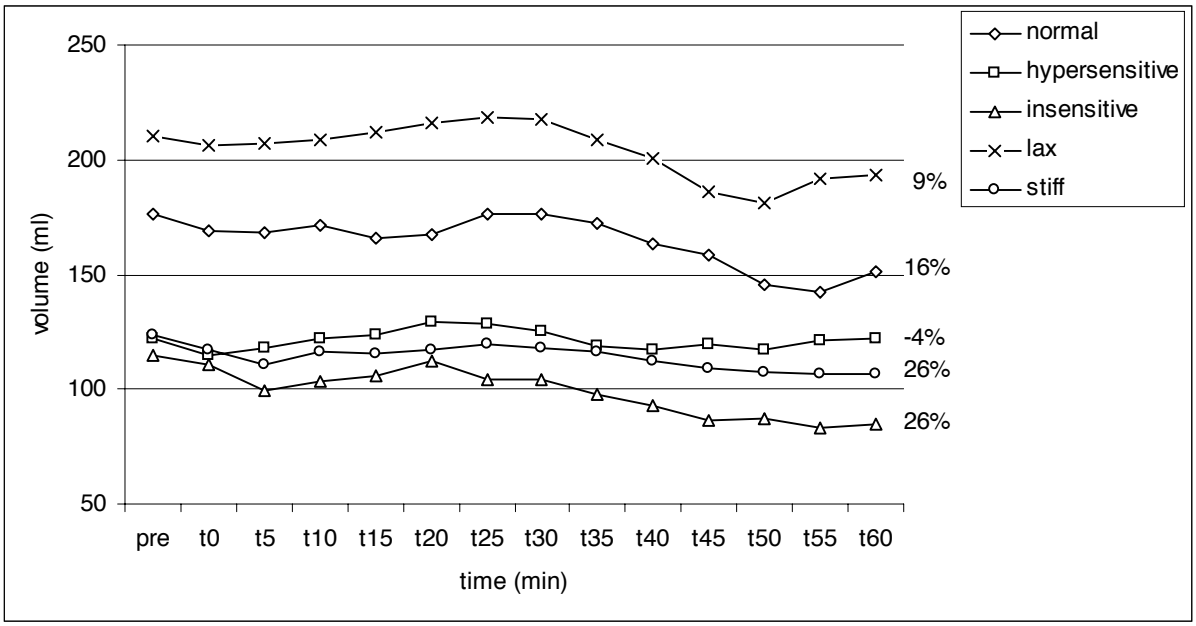

Figure 4. Line chart showing postprandial rectal response in patients with a normal rectum, hypersensitive rectum, insensitive rectum, lax rectum and a stiff rectum. Patients with a hypersensitive rectum had a significant lower response than the other patients ($P=0{,}04$).

Paradoxical sphincter contraction

Anal manometry showed mean resting pressure of 60 ± 17 mmHg and mean squeeze pressure of 64 ± 40 mmHg. PSC was found in 13 of the 30 patients (43%).
Patients with PSC had higher ($P = 0,045$) VSS than patients without PSC. PSC was present in 5/8 hypersensitive, 7/16 normosensitive and 1/6 hyposensitive patients ($P = 0,23$). Compliance and postprandial rectal response were not different between patients with PSC or without PSC.

Discussion

Internationally accepted criteria are used to define whether complaints of patients fulfil the syndrome of idiopathic constipation.[22] A subdivision can be made into slow transit constipation, pelvic floor dysfunction and constipation predominant irritable bowel syndrome (IBS-C). However, symptoms overlap presented by patients with chronic constipation and IBS. The Manning and later the Rome I and II criteria for IBS could not make a distinction on basis of symptoms.[14,32] We investigated patients with the postprandial rectal response, rectal sensitivity and compliance and paradoxical manometric response in order to make the traditional classification into these three groups. Doing so, we found that within that division, many other abnormalities were present.
Disturbances in rectal sensitivity have been found in patients with idiopathic constipation. In most reports, constipated patients have diminished sensitivity compared to controls.[33,34] However, after comparing the individual rectal sensitivity and the pressure volume curves of the constipated patients with the 95% confidence interval of the controls, patients could be classified into 5 separate groups following Prior et al. (Table 1).[31] Abnormal rectal sensitivity or compliance was found in 90% of the patients. A lax rectum with a high compliance and normal or low sensitivity was found in 35% accounting for the largest group. An unbearable painful sensation during distension for which the procedure was terminated occurred in 26% of the constipated patients. They had low or normal rectal compliance. These patients were classified as hypersensitive. Patients with a lax rectum had a rectal volume of more than 350 ml, which was considered an idiopathic megarectum.[35] Others have used the rectal diameter on lateral radiograph, which normally should be less than 6,5 cm (corresponding with 331 ml with a 10 cm long cylindrical balloon).[36] A megarectum can show thickening of the muscularis mucosa on pathological examination.[37] Whether this is the consequence or the cause of constipation remains unclear.
Pain to balloon inflation in the distal colon was first reported by Ritchie.[38] Mertz et al. stated that hypersensitivity is considered a biological marker of irritable bowel syndrome.[15] Hypersensitivity was described as a feeling of discomfort or pain preferentially during rapid balloon distension with normal thresholds for urge. IBS-C patients could present with a particular hypersensitive and increased rectal compliance.[15] Whether in IBS patients hypersensitivity is due to 'true' colonic irritation or a psychological perception deviation remains unknown. IBS patients also showed hypervigilance towards labelling a wide range of other visceral

stimuli.[39] Hypersensitivity in IBS patients can be a perceptual bias due to anxiety and somatization.[16,40] Progressively evidence is found that IBS patients have different processing of bowel perception on cerebral level.[17]
Patients with pelvic floor dysfunction can show abnormal visceral sensitivity. Rao et al. found that patients with obstructed defecation compared to non-obstructive defecation had increased volume threshold for first sensation but normal thresholds for desire or urge to defecate, which decreased significantly after biofeedback.[12,41] In contrast, we found that patients with PSC had higher rectal sensitivity but not different compliance compared to patients without PSC. Hypersensitivity was found in 38% of the PSC patients and hyposensitivity in 7%. This is in agreement with the study of Mertz et al. who found that 60% of the hypersensitive patients had paradoxical sphincter contractions.[20]
Different procedures were designed to study visceral sensitivity such as intermittent or continuous distensions. We did not find a difference in sensitivity scores between the intermittent and the continuous procedure, which is in agreement with studies in controls and in IBS patients.[40,42-44] Others showed that intermittent phasic distension elicited higher discomfort sensation in IBS patients than continuous ramp distension.[45,46] Several theories have emerged such as difference of mechanoreceptors, activation of neural reflexes and colonic contractions or extinction of response after repeated stimuli and hyperviligance towards visceral stimuli.[25,39,47,48]
Wall tension (p*r) has been promoted as a better parameter to measure rectal perception than pressure.[27,43] We calculated wall tension using Laplace's law regarding the balloon shape as a cylinder. The groups with different sensitivity, which were identified during the pressure distension, remained unaltered when wall tension was considered the parameter. Some critical remarks can be made with wall tension measurements. It was calculated with Laplace's law under assumptions that the wall of the viscus is infinitively thin, the balloon has a perfectly defined shape, and the pressure external to the viscus is evenly distributed.[49] MRI studies of the rectum during gradual balloon distensions showed that the lumen of the rectum does not behave as a rigid cylinder suggesting that wall-tension is not superior to pressure measurement.[50]
Paradoxical sphincter contraction (anismus) is a disturbed relaxation of the striated pelvic floor and anal musculature leading to a functional obstruction of defecation at the pelvic outlet.[8] Approximately 50% of patients with chronic constipation in a third referral centre have obstructive defecation.[10] An international working team defined diagnostic criteria for dyssynergic constipation consisting of 1. Criteria of functional constipation; 2. Evidence of manometric, EMG or radiological evidence; 3. Evidence of adequate propulsive forces during attempts of defecation; 4. Evidence of incomplete evacuation.[11] We defined pelvic floor dyssynergia in our population of constipated patients during anal manometric evaluation as maximal basal pressure more than 60 mmHg and paradoxical increase of anal pressure during straining more than 10 mmHg (PSC). Some remarks have to be made on the definition of pelvic floor dyssynergia. Paradoxical anal contraction occurs in healthy controls and patients with incontinence.[10,51] Overlap in demonstrating PSC between manometry, digital examination and defecography was shown to be very small (5%), suggesting that PSC was

primarily a laboratorium artifact.[51] However, in patients with incontinence the paradoxical increase during straining is a defensive mechanism to prevent loosing stools or air unwillingly. Controls can be embarrassed by the method of investigation. We conclude that paradoxical sphincter contraction consists of a high anal rest tone and a paradoxical increase during straining together with a heightened visceral sensitivity.
The colonic or rectal response to a meal has been established before.[52] A gastric phase (parasympatical) and a duodenal phase (neural and humoral) were found to play a role in mediating the response.[53,54] Using the barostat and a 600 kCal mixed liquid meal, we found in our constipated patients that the postprandial rectal response is comparable between patients with constipation and controls. Since parity influences the rectal response as we demonstrated before, nulliparous patients had a lower rectal response compared to nulliparous controls.[55] The response between parous patients and parous controls were not different. PSC did not influence the postprandial rectal response. Patients with rectal hypersensitivity had no response at all.
Conflicting studies were reported on the postprandial rectal tone response in constipated patients. Some investigators found a blunted response to a meal in patients with chronic constipation and in patients with a Slow-transit and outlet obstruction patients.[56-58] One study could not find differences in postprandial rectal tone between patients with slow transit, constipation predominant IBS and controls.[59] In addition, we found that hypersensitive constipated patients had the lowest response. Constipated patients had fewer phasic volume events (PVE's) than controls, both pre- and postprandial. Phasic volume events recorded by the barostat occur simultaneously with phasic events recorded with colonic manometry.[29] The postprandial rectal response is diminished in patients with constipation, however, the complexity of the response and the heterogeneous population studied influences the results and conclusions.
In conclusion, 90% of the patients with idiopathic constipation show an abnormality in rectal sensation or compliance, which can be classified as lax (35%), hypersensitive (27%), insensitive (17), stiff (10%) or normal (10%). The postprandial rectal response was comparable between patients with constipation and controls, however, PVE's were diminished. The postprandial rectal response was almost absent in parous patients and controls. Patients with paradoxical sphincter contraction had higher rectal sensitivity but with unaltered compliance and PPR. The traditional subdivision of patients with idiopathic constipation in slow transit, pelvic floor dysfunction and irritable bowel syndrome seems to be an oversimplification and a more mixed population exists. Whether this could have implications in treatment of idiopathic constipation, should be investigated in future trials.

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CHAPTER 7

RECTOCELE REPAIR IMPROVES EVACUATION AND PROLAPSE COMPLAINTS INDEPENDENT OF ANORECTAL FUNCTION AND COLONIC TRANSIT TIME

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Abstract

Evacuation disorders associated with a rectocele can be improved by rectocele repair. Aim of our study was to investigate whether anorectal function test results change after rectocele repair.
Fourteen patients with a 2nd or 3rd degree rectocele and an evacuation disorder were treated by posterior colporrhaphy and evaluated pre- and postoperatively (after 8 months range 3-14) using questionnaires, anal manometry and endosonography, rectal barostat testing, and colonic transit time measurement with radio-opaque markers. Results from female controls were used for comparison.
Preoperatively, rectocele patients had high maximal basal sphincter pressures, large sphincter lengths, low maximal squeeze pressures with an anal sphincter defect in 7 and low visceral sensitivity scores compared to controls. Postprandial rectal responses (more than 10% decrease in postprandial volume after one hour) were found in 3/14 patients compared to 2/11 parous (NS) and 9/11 nulliparous controls (P = 0,005). After repair, a rectocele of 2nd degree was found in four patients. Questionnaire scores were decreased for straining (P = 0,008), evacuation disorder (P = 0,004), manually support (P = 0,001) and protrusion (P = 0,005). Overall patient satisfaction with the operation scored 8,25 (range 3-10). Defecation frequencies and stool consistencies were unaltered. Anal pressures, rectal compliance-curves, visceral sensitivity and colonic transit times were unaltered after the rectocele repair.
Conclusions: Rectocele repair improved complaints of evacuation disorder and protrusion, however, defecation frequency and stool consistency were not influenced. Anorectal function was unaltered after rectocele repair. Selection of patients for rectocele repair should be performed based on evacuation and protrusion complaints, anorectal function or colonic transit time measurements have a limited role.

Introduction

A rectocele or a posterior vaginal wall prolapse is a herniation of the anterior rectal wall into the vaginal lumen. Rectocele development is due to a defect of the rectovaginal septum caused by vaginal childbirth or by excessive straining during defecation. Patients with a rectocele have defecation disorders such as decreased bowel frequency in 8-41%, frequent straining in 22-53% and the need for digital support in 10-30%. Fifty percent of patients with a rectocele are bothered by their bowel function.[1,2,3] Surgical treatment is considered the primary treatment in order to improve anatomy and symptoms. Rectocele repair (posterior colporraphy) corrects the posterior vaginal wall topography in 75-100%.[2,4,5,6] Complaints of constipation improve in 45-60%.[2,4,6]
Anorectal function tests or colonic transit time measurement may select the patients who will benefit from the procedure. In this study, it is investigated whether anorectal function tests and colonic transit time reflect the complaints of evacuation and constipation occurring in rectocele patients and whether results of these tests change after rectocele repair.

Patients and Methods

In the period between September 1998 and June 2000 consecutive patients with an evacuation disorder associated with a rectocele were included in this study. Patients were evaluated using questionnaires, anal manometry, endoanal ultrasonography, rectal barostat procedure, postpandial rectal response (only preoperative), and colonic transit time measurement. Written informed consent was obtained from all subjects. The study was approved by the Medical Ethical Committee of the Vrije Universiteit Medical Centre.

Questionnaires

Pre and postoperative symptoms were evaluated using a questionnaire with the following items: average defecation frequency per week, stool consistency, straining, incomplete evacuation, manual support of the pelvic floor or vaginal wall, complaints of protrusion (feeling of a lump, worsening in the afternoon, backpain), dyspareunia, faecal incontinence and urinary incontinence. These items were scored using a five point scale (none-light-moderate-severe-very severe). Overall score for bowel habits and patient satisfaction with the repair were noted on a 10-cm visual analogue scale (VAS).

Rectocele

The degree of rectocele defect was measured clinically by the operating gynaecologist with reference to the relatively fixed point of the hymen as grade 1 when the protrusion of the posterior vaginal wall did not come as far as the hymen, grade 2 when the hymenal edge was clearly reached, grade 3 outside the hymenal edge and grade 4 for very severe types of rectocele outside the hymenal boundary during straining.[7,8,9]

Anal manometry and endoanal ultrasonography

The maximal basal pressure (MBP), maximum squeeze pressure (MSP) and sphincter length (SL) were measured according to our methods described previously.[10] Endoanal ultrasonography was performed using a diagnostic ultrasound system (type 3535, Bruel and Kjaer, Naerum, Denmark) with a 7 Mhz rotating endoprobe (type 1850, focal range 2 to 4,5 cm) covered by a water-filled hard sonolucent cone (diameter 1.7 cm), producing a 360º view. The endoprobe was introduced into the rectum and serial radial images as well as video recordings were made of the distal part of the rectum, the puborectalis muscle and the anal canal. A sphincter defect was seen as a hypoechoic interruption in the sphincter complex.[11]

Barostat

An electronic barostat device (Synectics Visceral stimulator, Synectics medical, Stockholm, Sweden) was used to measure rectal visceral sensitivity, compliance, and postprandial rectal response. Rectal visceral sensitivity was measured using an intermittent semi random pressure distension at the pressure steps 8, 12, 20, 16, 32, 24, 36 and 28 mmHg with registration of visceral sensitivity score (VSS) ranging from 0 to 5 (0 = no feeling, 1 = light sensation, 2 = clear feeling or beginning urge, 3 = normal urge, 4 = strong urge and 5 = maximal toleration). Rectal compliance was measured using a continuous pressure distension of the bag up to 36 mmHg in 10 minutes and VSS was registered. Next, deflation was performed in 10 minutes to register hysteresis. Continuous volume distension was performed until maximal tolerated distension. First sensation volume and pressure, urge volume and pressure, and maximal toleration volume and pressure were registered.[12]
Postprandial rectal response was performed at a pressure of 2 mmHg above minimal distension pressure (the pressure to unfold the balloon 10 ml). After 30 to 60 minutes of basal registration when a stable volume was reached, a liquid meal (400 ml of Ensure plus® containing 600 kCal; 17% protein, 53% carbohydrates, 30% fat) was given. After the meal, volume and intraballoon pressure were recorded for one hour. A postprandial rectal response was defined as a more than 10% decrease in volume after one hour.[13]

Colonic transit time

The colonic transit time was measured using the radio-opaque marker technique. Subjects ingested one capsule daily containing ten radio-opaque markers during 6 days (distribution: P&A Mauch, CH-4142 Münchenstein, Switzerland). An abdominal X-ray was performed on the seventh day. Colonic transit time and the segmental transit times of the right colon, left colon and rectosigmoid were calculated by counting the markers in the regions and multiply with 2,4 hours as described previously.[14,15]

Surgical procedure

Posterior colporraphy and perineorraphy was performed as suggested by Nicholls and Randall[9], conform the Bullard modification. Vicryl® 2/0 was used as suturing material. At the discretion of the surgeon the pubococcygeus muscle-bellies were approximated with one or two stitches of Vicryl® 0 or not at all before closing the posterior vaginal wall.

Data analysis and statistics

The Mann-Whitney-U-test was used to compare patients with controls and the Wilcoxon-paired-signed-rank-test to compare preoperative and postoperative data. Visceral sensitivity, compliance curves and postprandial rectal response-curves were compared with an ANOVA method for repeated measurements in a quadratic model.

Results

Fourteen patients were included with the following characteristics: median age 51 year (range 38-71); there were 13 patients who had had a vaginal delivery (median 2 range 1-5), one patient had never been pregnant and 8 patients had a previous hysterectomy. Five patients presented with a 2nd degree rectocele and nine patients with a 3rd degree. Results were compared with normal values from healthy females who were investigated previously in our department.[12,13,16]
A classical posterior colporrhaphy (rectocele repair) was performed in all patients, in two in combination with enterocele repair, in two with Manchester type of repair and in one with hysterectomy and overlapping anterior anal sphincter repair.
After 8 months (range 3-14) all patients were seen for post-operative evaluation. Digital examinations revealed that the rectocele was absent in ten patients (70%), reduction of the rectocele in three patients (21%) from 3rd to 2nd degree, and unaltered in one (2nd degree rectocele).

Questionnaires

The results of the questionnaires are shown in Table 1. Preoperatively, all patients reported difficulty in evacuation with straining and manual support, which significantly improved after the rectocele repair. Four patients (30%) still had complaints of protrusion and difficult evacuation with manual support after the repair, two with a demonstrable rectocele. Defecation frequency was less than 3 times a week and stool consistency was hard to very hard in six patients, which remained unaltered in four. Six patients continued to use laxatives. Faecal and urine incontinence scores remained unaltered after the repair for the whole group. In one patient, severe faecal incontinence improved but the urine incontinence remained unaltered. Three patients complained of dyspareunia persisting after surgery. One patient complained of aspecific pelvic floor pain post-operatively. VAS for bowel habits improved significantly and overall

satisfaction with the repair was high. Four patients scored low (<6) on overall satisfaction because of ongoing constipation in one, dyspareunia in two and recurrence in one.

	Before Repair	After Repair	*P* value
Protrusion*	4 (3-5)	1 (1-4)	0.005
Incomplete evacuation*	4 (1-5)	2,5 (1-5)	0.004
Manual support*	4 (3-5)	1 (1-4)	0.001
Straining*	3 (1-5)	2,5 (1-4)	0.008
Defecation frequency#	7 (2-7)	7 (3-14)	NS
Stool consistency*	3,5 (3-5)	3,5 (2-5)	NS
Faecal incontinence*	1 (1-4)	1 (1-3)	NS
Urine incontinence*	1,5 (1-5)	1,5 (1-4)	NS
VAS bowel habits$	7,5 (0-9,5)	3 (0-10)	0.035
VAS satisfaction†		8,25 (3-10)	

Table 1. Results of the questionnaires before and after rectocele repair. Visual analogue scale (*: 0 = none; 5 = very severe; # per week; $: 0 = no complaint; 10 = could not be worse; †: 0=not at all; 10=very satisfied), Median and range. NS= not significant.

Anal manometry and endoanal ultrasonography

Rectocele patients had high anal maximal basal pressures and sphincter length compared to controls (Table 2). Ten patients had a maximal basal pressure of more than 60 mmHg. Maximum squeeze pressure was lower in rectocele patients compared to controls. After the rectocele repair, anal pressures were unaltered. Seven patients (50%) had an anterior external sphincter defect. One patient had restoration of continence after overlapping anterior anal sphincter repair with a reduction of the sphincter defect but the maximal squeeze pressure was unaltered.

Manometry	Controls	Before Repair	After Repair
Maximal basal pressure	52 (30-75)	70 (30-100) #	70 (20-100)
Maximal squeeze pressure	65 (35-80)	30 (15-100) $	30 (10-60)
Sphincter length	3,0 (1,7-4,8)	4,6 (3,0-6,8) ‡	5,0 (3,0-6,5)
Colonic transit time			
Right	14 (3,6-28,8)	10 (0-60)	8 (0-38)
Left	6,6 (0-18)	10 (0-60)	11 (0-62)
Rectosigmoid	17 (8,4-28,8)	14 (2-36)	13 (0-46)
Overall	39 (22,8-62,4)	42 (5-125)	41 (10-115)

Table 2. Results of anal manometry and colonic transit time in controls, patients before and after rectocele repair. Median and range. (MBP = Maximal basal pressure, MSP = Maximal Squeeze pressure, SL = Sphincter Length). # *P*=0,046; $ *P*=0,01; ‡ *P*=0,002. Rectocele patients versus controls.

Rectal visceral sensitivity and compliance (Figure 1-2)

Visceral sensitivity and compliance was not different between the intermittent and continuous procedure. The volume-pressure-curve was not different between rectocele patients and controls nor pre and postoperative or during

inflation and deflation (Figure 1). Individually, 11 patients had a deviant rectal compliance or visceral sensibility compared to the 95% confidence interval of the controls according to Prior et al.[17] A lax rectum (a high compliance and a low or normal sensitivity) was found in 6 patients, a stiff rectum (low compliance and a normal sensitivity) in 2 patients, an insensitive rectum (normal compliance and a low sensitivity) in 3 patients and a normal rectum (intact compliance and sensitivity) in 3 patients. None had a hypersensitive rectum (normal or low compliance and hypersensitivity). Rectocele repair did not change visceral sensitivity (Figure 2). Continuous volume distension revealed only a higher first sensation pressure in rectocele patients compared with controls (P=0,001).

Postprandial rectal response (Figure 3)

Preprandial pressure and volume was not significant different between patients (13 ± 0,6 mmHg and 138 ± 18 ml) and parous controls (12 ± 0,6 mmHg and 136 ± 15 ml). In nulliparous controls pressure was lower (11 ± 0,3 mmHg; P=0,03) but volume was not (139 ± 13 ml; P=0,5). Rectocele patients had an impaired postprandial rectal response compared to nulliparous controls (P =0,02) but not to parous controls (NS). Three rectocele patients (21%) had a response compared to 2 parous controls (18%) and to 9 nulliparous controls (82%).

Colonic transit time

Two patients had an overall colonic transit time of more than 70 hrs. Rectosigmoid transit time was not delayed in rectocele patients compared to controls. Overall colonic transit time and rectosigmoid transit time were not different after the rectocele repair (Table 2).

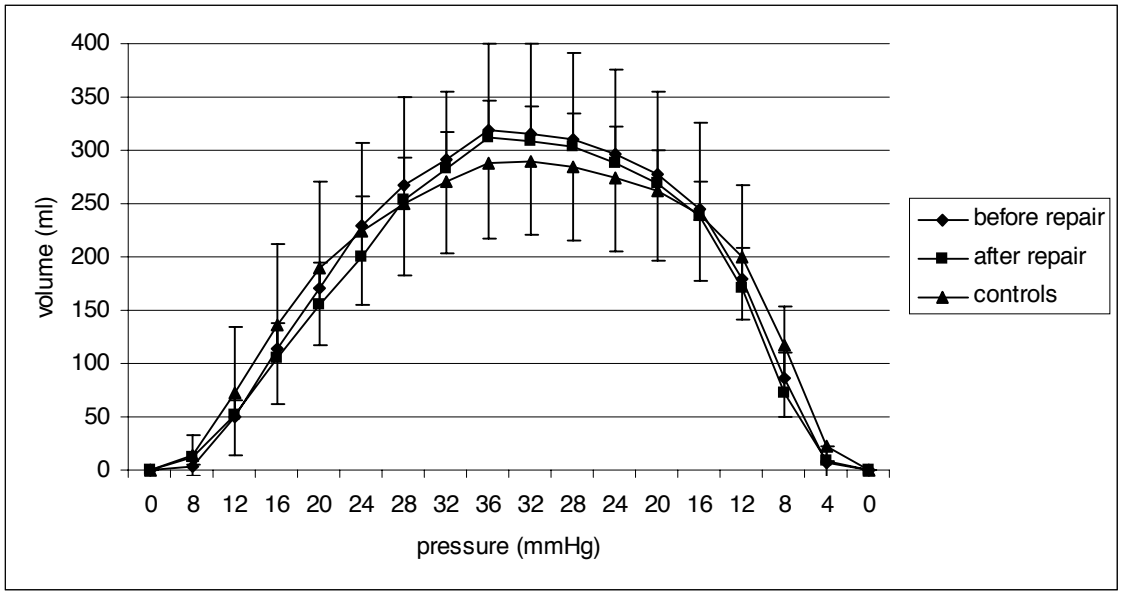

Figure 1. Line chart showing rectal compliance during inflation and deflation in rectocele patients before and after repair and in controls (means and sem). Hysteresis was not different between patients before and after rectocele repair and controls.

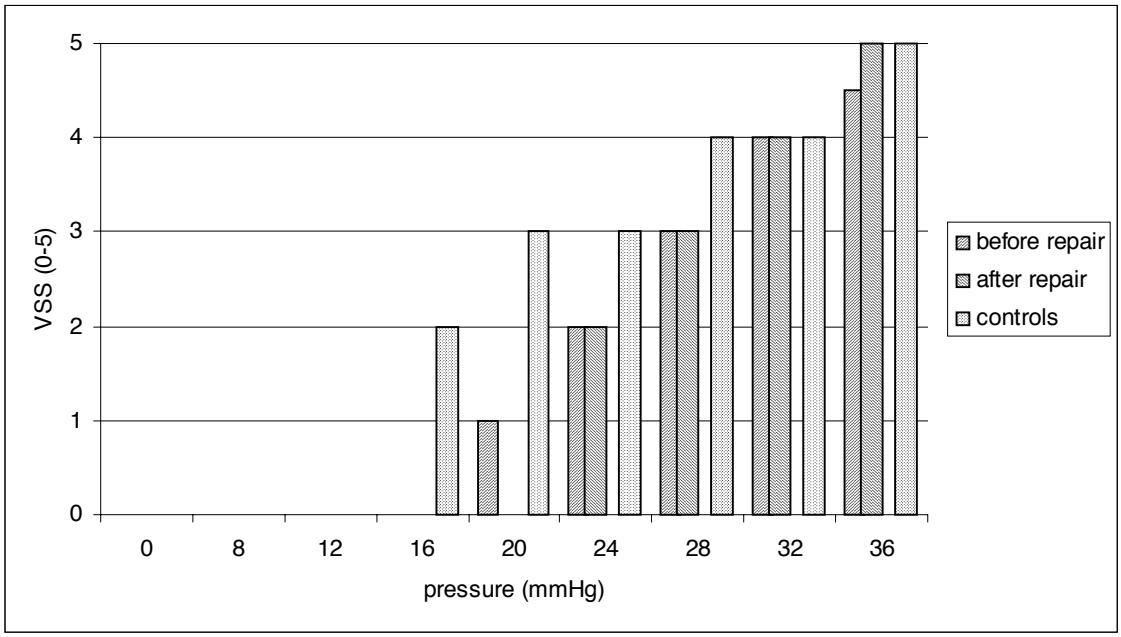

Figure 2. Line chart showing visceral sensitivity in rectocele patients before and after rectocele repair and in controls (Medians). VSS was lower in rectocele patients (P=0,001).

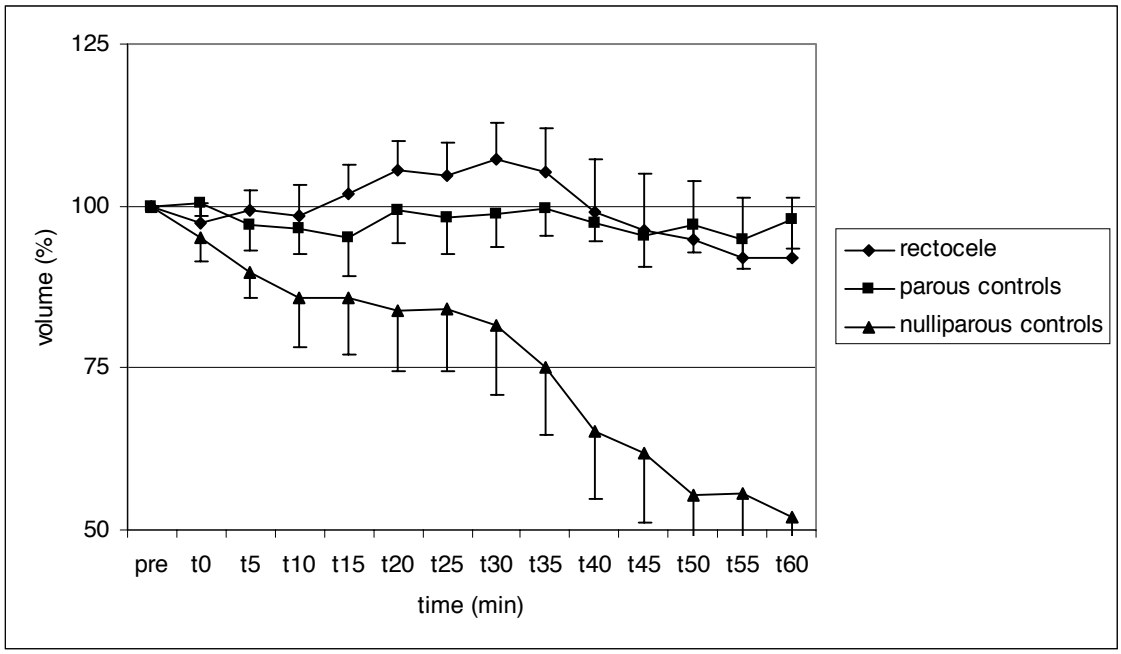

Figure 3. Line chart showing postprandial rectal response in rectocele patients and in parous and nulliparous controls (mean and sem).

Discussion

Rectocele repair is a commonly performed procedure to improve complaints of constipation, evacuation disorder and protrusion. In our study, evacuation disorder consisting of complaints of severe straining with defecation and manually support on perineum or digitally via the vagina, improved in all patients. However, 15% had minor evacuation complaints despite an effective repair and

15% had continuing evacuation complaints with a persisting rectocele. Defecation frequency and stool consistency did not improve after rectocele repair and patients continued using laxatives postoperatively. Rectocele repair improved evacuation even in patients with decreased stool frequency, which is in agreement with the study of others.[2,18]

Rectocele is often associated with dyspareunia, in large series percentages have been reported as high as 26-67%.[2,3,6] Improvement or cure was found in about 50% of these patients after rectocele repair.[3,6] Dyspareunia is a major postoperative complication associated with levator muscle plication[4] In our study, three patients (21%) presented dyspareunia preoperatively which persisted after the repair. One not sexually active patient complained of a-specific pelvic floor pain, possibly due to firm levator muscle plication. If rectocele repair is performed, a compromise must be found between the restoration of the pelvic floor and vaginal defect and conservation of sexual function.

Colonic transit time measurement reflects the passage of colonic intraluminal contents. Two patients had an increased colonic transit time before rectocele surgery suggesting impaired colonic function and motility. Other patients had a colonic transit time within the normal range. Rectosigmoid transit time was not delayed in our group of rectocele patients despite of the fact that all patients complained of disturbed evacuation, which is in agreement with earlier reports.[19,20] Some authors suggest that patients with a delayed transit have a poor outcome after rectocele surgery[21] or that a delayed colonic transit time is a criterion to exclude from rectocele repair.[2] We put forward from our data that colonic transit remains unaltered after repair. Patients with delayed transit can benefit from a rectocele repair since evacuation complaints were improved. Before surgery is performed, this should be discussed with patients.

Anal basal pressures and sphincter lengths were higher in rectocele patients compared to controls. High anal pressures could be caused by paradoxical sphincter contraction (dyssynergic defecation). The relationship between rectocele and paradoxical sphincter contraction is suggested by anorectal function testing[22-24] and by the benefit from biofeedback treatment in 16-50%.[25,26] It is still in discussion whether the outcome of rectocele repair is impaired by the presence of paradoxical sphincter contraction.[27] Unfortunately, it is unclear how accurate patients with a rectocele and paradoxical sphincter contraction can be diagnosed. Defecography shows puborectalis contraction during straining[26], but also anorectal manometry [24], a balloon expulsion test or an electromyogram[22,25] indicate paradoxical sphincter contraction. It is unknown whether these tests differentiate between paradoxical sphincter contraction and disturbed evacuation caused by an alteration of the anterior rectal wall topography. The bulging posterior vaginal wall changes the pelvic floor in defecography, obstructs balloon expulsion, or changes pelvic floor assessment with electromyography. In our laboratory, we measured paradoxical sphincter contraction using anal manometry. We found it extremely difficult to objectify paradoxical sphincter contraction in a patient with a ballooning perineum or with a prolapsing rectocele. High basal anal pressure and sphincter length are signs of paradoxical sphincter contraction, however, it also results from disturbed pelvic

floor anatomy, or from excessive straining and formation of hemorroidal tissue. On the other hand, if paradoxical sphincter contraction was present, improvement of evacuation after rectocele repair was not expected
Maximal squeeze pressure was diminished in rectocele patients, which was caused by a less functioning external sphincter due to scarring in 50% of the patients after a complicated vaginal delivery. Other authors did not find differences in anal pressure between rectocele patients and controls.[29,30] In our study, continence, sphincter pressures and endoanal ultrasonography images were unaltered after the rectocele repair with a vaginal approach. After a repair with a transanal approach (possibly due to the use of anal retractors) decline in continence and sphincter pressures was described.[29-31] Therefore, a transvaginal repair caused minimal deterioration of anal sphincter function in patients who often have already external sphincter damage.
Rectal compliance and maximal distension thresholds were not different between rectocele patients and healthy controls, which is in agreement with an earlier study.[28] Rectal sensitivity, however, was diminished in rectocele patients compared with controls. Differences are mainly found at the beginning of the pressure distension curve and at first sensation pressure threshold. Rectocele repair did not change compliance curves and rectal sensitivity. Other authors who used transanal approach of the rectocele, found a discrete decrease in maximal tolerated volume three to six months postoperatively[29-31], which increased to preoperative values after one year.[29] Possibly, the decrease in MTV can be explained from direct plication of the rectal wall during transanal surgery in contrast to the vaginal approach.
Postprandial rectal response was less frequent in rectocele patients suggesting decreased rectal motility compared to nulliparous controls (but not to parous controls). This diminished rectal motility (and sensitivity) may be caused by damage of the rectal sensory afferents after prolonged straining during defecation or during childbirth.[13] Furthermore, hysterectomy causes disturbance of rectal motility, which was performed previously in eight patients.[32]
In our study, the diagnosis of rectocele was confirmed during digital vaginal and rectal examination by the operating gynaecologist. The classic classification was used to describe the extension of the posterior vaginal wall prolapse. Defecography was not performed, because on the one hand, it can be helpful in confirming the diagnosis of rectocele but on the other hand, it does not alter management, since physical findings are highly reliable.[33,34] Even when defecography criteria were met (such as anterior bulge outside the line of the rectal wall more than 2 cm occurring during resting and pushing), the rectocele might be totally asymptomatic[35] and defecography did not predict outcome after repair.[5] Moreover, the investigation can cause embarrassment and the irradiation exposure is significant.
In conclusion, rectocele repair improved complaints of evacuation disorder and protrusion, however, neither defecation frequency, stool consistency and laxative use were influenced. Rectocele patients were characterised by high basal anal pressure and sphincter-length, low squeeze pressure, obstetric external sphincter damage in 50%, low visceral sensitivity with a normal rectal compliance, decreased rectal motility and normal or delayed overall colonic

transit time measurement. After rectocele repair neither anorectal function nor colon transit were altered and therefore the prognostic value of anorectal function tests seems limited. Selection of patients for rectocele repair should be performed based on evacuation and protrusion disorder, and not on anorectal function or colonic transit time.

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CHAPTER 8

EFFECT OF BOWEL CLEANSING ON COLONIC TRANSIT IN CONSTIPATION DUE TO SLOW TRANSIT OR EVACUATION DISORDER

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Abstract

Colon transit time measurement with radio-opaque markers is a method of studying the passage of luminal contents throughout the colon. Overall colon transit time (CTT) as well as segmental transit times (right (RTT), left (LTT) and rectosigmoid (RSTT)) can be calculated. We hypothesise that CTT is influenced by fecal impaction when the rectum is emptied infrequently. The aim of this study is to investigate the effect of bowel cleansing on colonic transit time in patients with chronic constipation.
In 25 women (age 41 year; range 20-65) with constipation according to Thompson criteria, CTT measurement was performed in an unprepared situation and repeated after cleansing with 4 litres of Klean-Prep®. Ten healthy female volunteers (age 41 year; range 27-57) were used as controls.
In constipated patients, CTT decreased from median 70 h (range 10-130) to 48 h (5-94) in the cleansed state ($P<0.001$). A shortening of transit time was found in all three segments. In 10 patients with ST (CTT$>$ 86 h), CTT decreased from 110 h (range 94-130) to 86 h (38-94) ($P<0.001$). Five of the ten patients with ST before bowel cleansing had a CTT below 86 h after cleansing. In female controls, uncleansed CTT and RSTT shortened from 39 h (23-62) and 17 h (8-29) to 29 h (17-48) and 10 h (0-20) after bowel cleansing ($P=0.058$ and $P=0.046$).
Conclusions: Colonic intraluminal contents have a substantial effect on colonic transit. In female controls, bowel cleansing shortened rectosigmoid transit. Women with constipation had faster transit in the cleansed state, however, the distribution of markers was not altered. Despite the effect of bowel cleansing on CTT, it seems unnecessary to prepare the bowel in clinical practice because the differentiation of patients between slow transit constipation and outlet obstruction is not changed. However, because in an infrequent defecation pattern the influence of fecal impaction is considerable, CTT should be applied with care for critical clinical decisions in the treatment of constipation.

Introduction

Colonic transit time (CTT) measurement with the use of radio-opaque markers is a method for investigating the passage of colonic intraluminal contents throughout the colon. CTT correlates with the pattern of defecation [1-3] and it is comparable to the transit time measured with scintigraphic studies.[1,4] Overall colonic transit time can be measured by counting the radio-opaque markers on the plain abdominal radiograph. Patients are categorised as having 'slow transit constipation' if overall colonic transit time is delayed. Segmental transit times can be calculated after counting the markers in the colonic regions. Different methods are used to describe the distribution of the radio-opaque markers on the radiograph. The most practical subdivision is into three segments: right sided area, left-sided area and rectosigmoid area.[5] With this subdivision, it is possible to identify an accumulation of markers in the rectosigmoid region, which could direct to an 'outlet obstruction'.[6-8] CTT measurement with radio-opaque markers is progressively used in clinical practice because it is easy to perform with little patient inconvenience. CTT objectifies the complaints of patients with constipation[9] and it is a useful criterion to select patients for surgery[10,11] and for the evaluation of new entero-kinetic drugs.[12,13]
Only a few data are available on the influence of fecal impaction on CTT. The CTT was influenced substantially in an irregular defecation pattern when healthy subjects willingly retained stools. Mainly rectosigmoid transit and by reflex mediation right colonic transit is increased.[14] In constipated patients, the distribution of markers was altered when CTT is measured after bowel preparation with a light laxative.[15] It is not clear if delayed colonic transit in patients with obstructive defecation is attributable to retained faeces in the rectum, or to a coexistent disorder of colonic motor function. We hypothesized that colonic cleansing would normalize colonic transit when the latter was attributable to retained faeces in the rectum, as opposed to a colonic motility disorder. Therefore, we measured colonic transit in an uncleansed and in a cleansed state both in patients with constipation and in healthy females.

Patients and Methods

Subjects

Twenty-five consecutive female patients (age 41 year; range 20-65) were included for Experiment 1. All had constipation according to the Thompson criteria[16] consisting of two of the following criteria for at least 6 months: less than two spontaneous bowel movements in a week (without laxatives) or 25% hard stools or 25% sensation of incomplete evacuation or 25% straining. None of the patients had previous abdominal surgery other than a hysterectomy (in 7). All patients used laxatives.
Ten healthy females (median age 41 year; range 27-57) were recruited by advertising for Experiment 2. The participants had normal bowel habits without history of constipation or abdominal surgery. The volunteers did not use medication. Females who participated in the study were not pregnant. The

protocol was approved by the local Ethics Committee of the 'Vrije Universiteit' Medical Centre and written informed consent was given by each subject.

Study design

Experiment 1: Patients with constipation ingested a capsule with 10 radio-opaque markers at 8.00 h daily on 6 consecutive days. On the seventh day, a plain abdominal radiograph was performed. After a washout period of 10 days, 4 litres of Klean-Prep® was ingested the day before the subjects took the first of the markers. The subjects ingested again the markers on six consecutive days and a plain abdominal radiograph was performed on the seventh day.
Experiment 2: The subjects ingested two capsules with 10 radio-opaque markers, at 8.00 hours and at 20.00 hours daily for 3 consecutive days. On the fourth day a plain abdominal radiograph was performed. After a washout period of 10 days, 4 litres of Klean-Prep® was ingested the day before the subjects took the first set of markers for the second colonic transit time measurement. Throughout the study period, the volunteers were asked to register the defecation frequency and stool consistency in a diary.

Colonic transit time measurement

Colonic transit time (CTT) measurement was assessed by means of a modified radio-opaque marker technique using gelatine capsules containing 10 radio-opaque polyurethane markers consisting of 40% barium sulphate (distribution: P. & A. Mauch, CH-4142 Münchenstein, Switzerland). Overall CTT was calculated by counting the total of markers on the plain abdominal radiograph. Segmental CTT was calculated using the number of markers in the three segments identified according to Arhan et al.[5] The central point was the fifth lumbar vertebra. The right colon segment was the part between the line over the right pelvic outlet ring and the line over the spinal processes of the lumbar vertebra. The left colon segment was the part between the line over the spinal processes of the lumbar vertebra and the left pelvic rim, the distal part was the rectosigmoid area. In the determination of the segments, the configuration of the air in the bowel was taken into account.
To calculate the transit time the modified Metcalf formula was used.[17] As the subjects ingested ten radio-opaque markers daily during 6 days in experiment 1 and 10 markers, twice daily, during 3 days in experiment 2, the overall colonic transit time was calculated accordingly:

$$CTT = {}^{1}/_{N} * \sum_{i=1}^{i} Ni\ [\tfrac{1}{2}(t_{i+1} - t_{i-1})]$$

Where CTT = the overall colonic transit time; N = total number of a particular markers given; i = number of capsules taken; Ni = number of markers of a particular type present on the film; and ½(ti + 1 - ti-1) = time interval between successive intakes of markers.
This formula was summarised in the 6-days-method (patients):

$$CTT = 2.4 * Ni \text{ (in hours)}$$

And in the 3-days method (controls):

CTT = 1.2*Ni (in hours)

Segmental transit time was calculated in a similar way as the overall CTT. Slow transit constipation was defined as more than 86 hrs, which is the upper limit of the 95 percentile of the CTT in 84 females using the same method.[18] Outlet obstruction was defined as more than 50% of the markers in the rectosigmoid area.[15]

Bowel cleansing

For bowel cleansing, 4 litres of the osmotic laxative Klean-prep® was ingested within 4-6 hours. One litre Klean-prep® contained 17.6 mmol (59 g) macrogol 3350 (polyethylene glycol), 125 mmol sodium, 10 mmol potassium, 40 mmol sulphate, 35 mmol chloride, 20 mmol hydroxycarbonate and 49.4 mg aspartame. All healthy subjects produced clear fluids after cleansing. All patients with constipation produced fluids after intake of the solution; however, not all had clear fluids. Bowel cleansing solution was well tolerated by all subjects.

Anorectal function

The maximal basal pressure was measured according to our methods as described previously.[19] To determine relaxation of the pelvic floor, the patients were asked to strain with the catheter in situ.[20,21] Pelvic floor dyssynergia was defined as a maximal basal pressure of more than 60 mmHg and paradoxical increase of anal pressure during straining of more than 10 mmHg.

Data analysis and statistics

Results are presented as median and range because the distribution of the data was non-parametric. Mann-Whitney-*U*-test was used to compare data in normal situation. Wilcoxon-Paired-Signed-Ranks-test was used to compare data in basal situation and after bowel cleansing.

Results

Healthy females

Throughout the study period, reported stool consistency and frequency remained constant. Loose stools and an increased frequency were only reported during the use of the cleansing solution until the following evening. The first day after the cleansing stools normalised.
In the uncleansed state, overall CTT and rectosigmoid transit time (RSTT) were 39 h (range 3-62) and 17 h (8-29). After bowel cleansing, RSTT decreased to 10 h (0-20) ($P=0.046$) and overall CTT tended to decrease to 29 h (17-48) ($P=0.058$). Only in 1 of the 10 subjects an increase in overall CTT was found after cleansing (Fig.1a-d).

Patients with constipation

In the uncleansed state overall colonic transit time was 70 hrs (range: 10-130) (Fig.2a-d). Slow transit (ST) was found in 10 patients and 15 patients had a transit within the normal range. Overall colon transit time after bowel cleansing was significantly shorter (48 h range: 5-94; $P<0.001$) than in the uncleansed state. A small increase of overall CTT in the cleansed state was found in 3/25 patients. A decrease in transit was found in all colonic segments. The overall colonic transit time in ST patients decreased from 110 to 86 h ($P=0.005$). This difference in CTT was larger in ST patients than in normal transit patients (-26 h vs. -12 h; $P=0.004$). Five ST patients in the uncleansed situation had a transit within the normal range after bowel cleansing. However, when the upper limit of the range of cleansed CTT in the female controls (more than 48 hrs) was applied to form the criterion for ST, only one patient with ST in the uncleansed state did not have ST in the cleansed state. Two patients without ST in the uncleansed state had ST in the cleansed state. In our group, 6 patients met the outlet obstruction criteria in the unprepared CTT. However, in the cleansed state 5/6 still fulfilled this criterion and 1 new patient could be added.

Pelvic floor dyssynergia

Ten patients had manometric signs of pelvic floor dyssynergia. Of these patients, one had outlet obstruction, one had slow transit and two had combined slow transit and an outlet obstruction (>50% of the markers in the rectosigmoid region). RSTT was not significantly different between the patients with pelvic floor dyssynergia (20.4 h 2.4 – 86) and the patients without pelvic floor dyssynergia (28.8 h 0-65). Overall CTT in uncleansed state was 61 h (10-130) and shortened in the cleansed state to 38 h (12-94) ($P=0.001$). RSTT decreased to 18 h (0-60) after cleansing ($P=0.059$). The distribution of the markers was not altered. After cleansing, the proportion of patients with outlet obstruction was not altered. One patient who had slow transit in the uncleansed state (122 h), had a dramatically decreased overall transit time after cleansing (48 h) and in one patient transit time (67 h) did not change after cleansing.

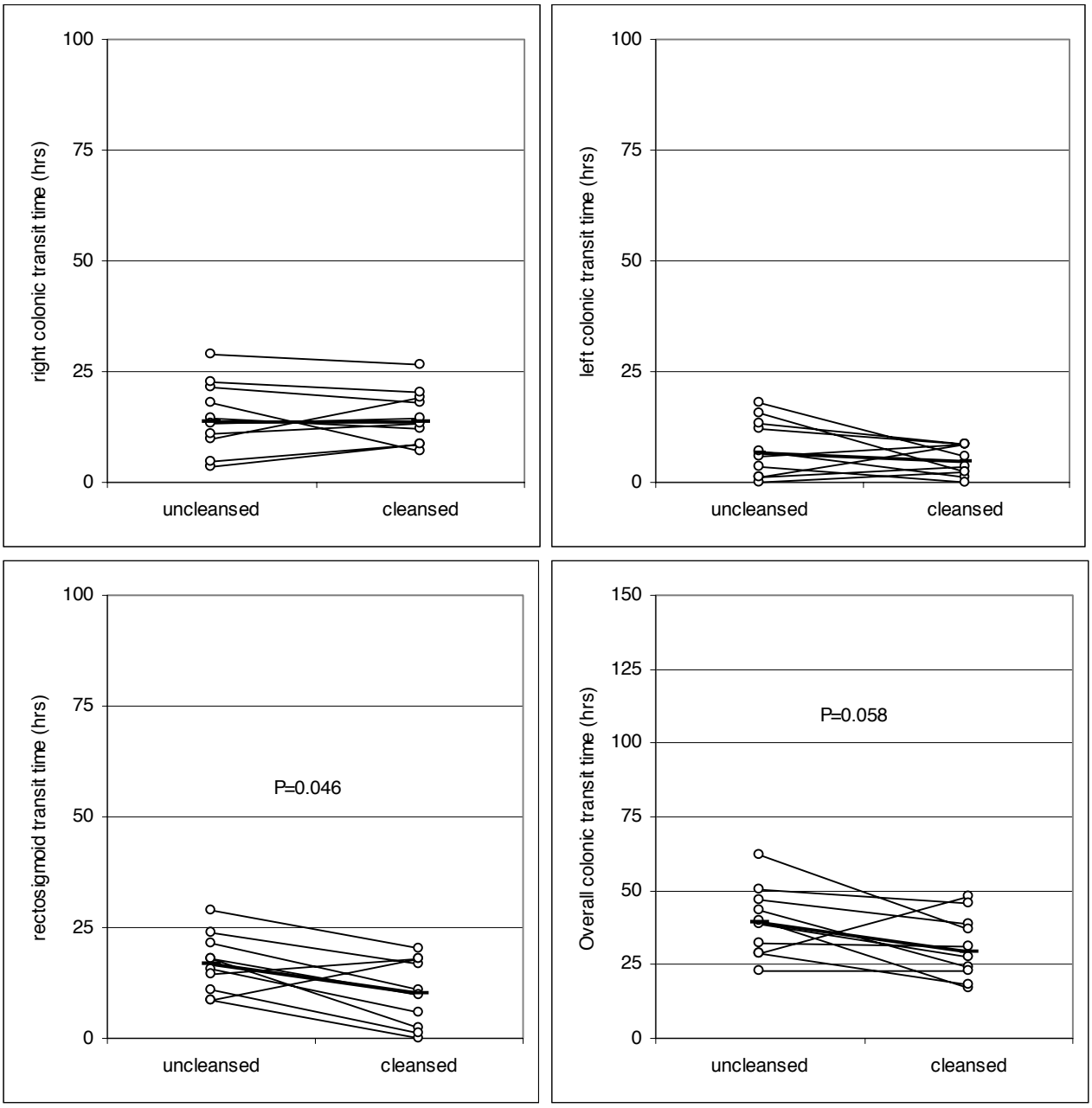

Figure 1A-D. Colonic transit time in healthy females in the uncleansed situation and after bowel cleansing. Median values are plotted as bold lines.

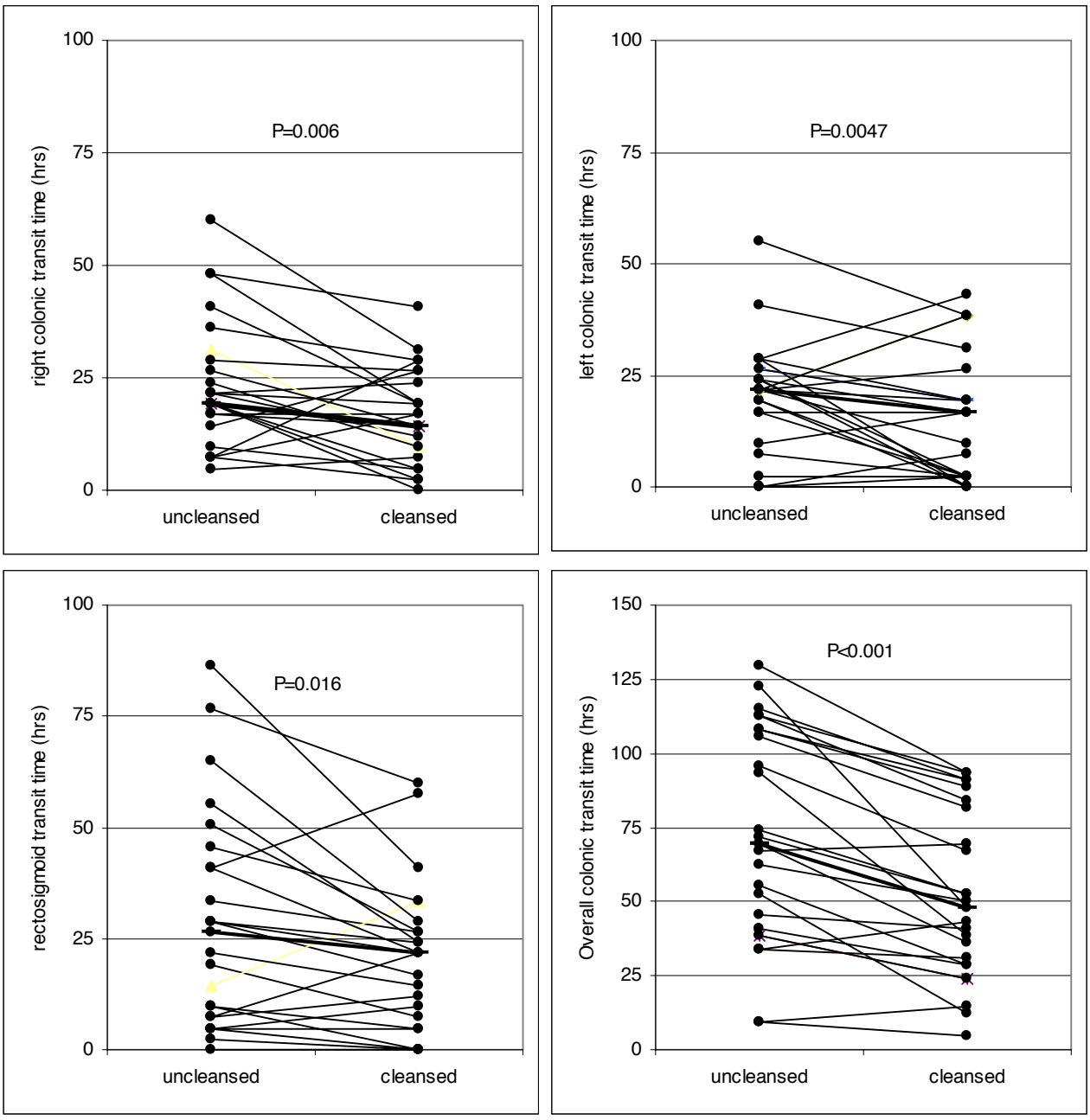

Figure 2A-D. Colonic transit time in constipated patients, uncleansed and after bowel cleansing. Median values are plotted as bold lines.

Discussion

This study was performed to confirm the hypothesis that fluctuations in the filling state of the colon substantially influence CTT measurement. As strict clinical conclusions are drawn from CTT, it is important to know whether CTT can differ for example after an very large bowel movement occurring once every week, which is often claimed by patients with constipation. Furthermore, it is not clear if delayed colonic transit in patients with obstructive defecation is attributable to retained faeces in the rectum, or to a coexistent disorder of colonic motor function. We hypothesized that colonic cleansing would normalize colonic transit when the latter was attributable to retained faeces in the rectum,

as opposed to a colonic motility disorder. Our study showed that bowel cleansing decreased CTT substantially in constipated patients. In 50% of the patients with slow transit, transit time decreased to the normal range in the cleansed state. However, cleansing the bowel in controls decreased rectosigmoid transit time significantly and a trend was found in a decrease of overall CTT. Therefore, we conclude that the upper limit of the cleansed CTT values in controls (e.g. 48 hrs) should be used to determine the cut-off point for detection of slow transit. Only one patient, who had slow transit in the uncleansed state (> 86 h), had transit within the normal range for the cleansed state (< 48 h). Therefore, if slow transit was found with a CTT measurement in an uncleansed state, this was mainly due to decreased colonic function. Faecal impaction played a role in delay of CTT, however, when this impaction was resolved, still delay in transit was found.

Faecal impaction in the distal colon would be expected in patients with pelvic floor dyssynergia. Pelvic floor dyssynergia patients are unable to expel stools through paradoxical sphincter contraction and thus are bothered by obstructive defecation.[20] In agreement with other studies,[22] we found that in these patients rectosigmoid delay (outlet obstruction) in the uncleansed state was not more usual than in patients without pelvic floor dyssynergia. Furthermore, the overall transit time was shortened in the cleansed state, but the rectosigmoid transit was not particularly decreased. We expected that slow transit was secondary to faecal impaction in an outlet disorder and the 'true level of obstruction' would be found after washing-out the fecal mass. We could not confirm this in our study. Some remarks have to be made on the definition of pelvic floor dyssynergia. Rao et al.[23] showed that paradoxical anal contraction occurs in subjects without constipation. Ten of 45 healthy subjects showed an obstructive pattern during anorectal manometry and four were unable to expel a 50cc water-filled balloon. Voderholzer et al.[22] evaluated paradoxical sphincter contraction (PSC) in patients with constipation, patients with incontinence and controls using digital examination, anal manometry, defecography and radio-opaque marker transit measurement. In the patients 41% of the constipated, 25% of the incontinence showed manometric paradoxical sphincter contraction, as did 22% of the controls. The overlap of manometry, digital examination and defecography was very small (5%). It was concluded that PSC was primarily a laboratory artefact. However, in patients with incontinence the paradoxical increase during straining is a defensive mechanism to prevent loosing stools or air unwillingly. Controls can be embarrassed by the method of investigation.

Only one study is published about bowel preparation and colonic transit time. Bergin and Read[15] performed a study in 25 constipated patients (22 females) in whom colonic transit time was measured unprepared and 3 days after purging with 20 mg picosulfate. The overall CTT was unchanged, but the distribution of the markers in the colon was altered; the markers accumulated more distally were suggestive for an outlet obstruction. The authors concluded that the accumulation of faeces in the rectum under normal condition caused a distribution pattern similar to colon inertia. Removal of this fecal 'mass' enabled the markers to progress to the true obstruction. In contrast, we did not find different distribution patterns of the markers. Our patients had lower transit times in the cleansed state but the distribution appeared to be similar. Firstly, we

used bowel cleansing in order to empty the colon rigorously before measuring the second CTT. Secondly, the subjects started directly with the marker intake the day after the bowel cleansing. Finally, we studied both constipated patients with 'normal' CTT as well as with slow transit.
In all healthy subjects, 4 litres of Klean-Prep® cleared the colon of faeces and resulted in watery stools. The first day after bowel cleansing, stools normalised. On the days, in which the patients took the capsules, they produced normal stools, therefore a direct effect of the laxative on the CTT measurement seems unlikely. Klean-prep® was not always able to clean the bowel fully in constipated patients, some reported they still had coloured but watery stools. But they all passed a large quantity of stools and faecal impaction was absent. The production of watery stools stopped after one day and a direct effect of the cleansing on the CTT is unlikely.
Various methods are described to measure CTT. Single[5,15] or multiple markers[24] are used with one[15,18] or more abdominal radiographs at different intervals.[5,8,17] Methods over 3[8,15,17,24] or 6 days[6,18] have been performed and different formulae have been used to calculate the transit time[25], even different lines to determine the segments.[5,15,26] Therefore, normal values (upper limit of 95% confidential interval) range from 68 to 113 h in the literature.[6,8,17] We used a six-day method with a single marker and single radiograph technique to study constipated patients. The upper limit of the range of uncleansed CTT in female controls was 62 hrs in our study. However, the definition of slow transit constipation (more than 86 hrs) was used according to Meier et al. who studied 86 females using the same method.[18] Outlet obstruction was defined as more than 50% of the markers in the rectosigmoid area according to Bergin & Read.[15] We used a 3-day method in controls because we expected that the CTT would be shortened to less than 24 hrs and thus most markers were expelled before the radiograph was taken. The calculation of CTT would be less accurate if a 6-day method was used.[12]
In the interpretation of the results of this study, we presumed that CTT with the use of radio-opaque markers is reproducible in constipated patients. However, to our knowledge, a reproducibility study using an adequate analysis has never been published. Bouchoucha et al.[8] explored reproducibility in 28 patients with irritable bowel syndrome who twice underwent a CTT measurement, each a month apart. Results of the two measurements were found to be similar with correlation coefficients in the range of r = 0,6. However, in this comparative study two different methods of CTT were used (multiple marker-single X-Ray and single marker-multiple X-Ray), and subjects were patients with irritable bowel syndrome and not patients with constipation. Knowles et al.[27] performed colon transit time measurement in 16 IBS patients a month apart during placebo treatment in a trial. Test-retest reliability was good for overall colonic transit time ($r = 0.71$), but was lower for segmental transit time (ranging from $r = 0.5$ for RTT and LTT to 0.3 for RSTT). In patients with an irregular defecation pattern CTT measurement may be less reproducible as this test is influenced by several factors such as intra-subject variability in defecation pattern and the relative short period of measurement. However, such a reproducibility study still has to be performed in constipated patients.

In conclusion, colonic intraluminal contents have a substantial effect on colonic transit. In female controls, bowel cleansing shortened colonic transit time, and this was most pronounced in the rectosigmoid area. Women with constipation had faster transit in the cleansed state, but the distribution of markers was not changed. Despite the effect of bowel cleansing on CTT, it seems unnecessary to prepare the bowel in clinical practice because the differentiation of patients between slow transit constipation and outlet obstruction is not changed. Because in an infrequent defecation pattern the influence of fecal impaction is considerable, results of CTT measurement should be applied with care when used in critical clinical decisions for the treatment of constipation.

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CHAPTER 9

EFFECTS OF PRUCALOPRIDE ON COLONIC TRANSIT, ANORECTAL FUNCTION AND BOWEL HABITS IN PATIENTS WITH CHRONIC CONSTIPATION

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Abstract

There is a need for better-tolerated drugs to normalize bowel function in chronic constipation. Prucalopride is a highly selective, specific, serotonin$_4$ receptor agonist with enterokinetic properties. Aim of this study was to evaluate the effects of prucalopride on bowel function, colonic transit and anorectal function in chronic constipation patients.
Twenty-eight patients were enrolled in this double-blind, placebo-controlled, cross-over study (prucalopride 1 mg $n = 12$; 2 mg $n = 16$). Patients kept a bowel function diary. Colonic transit times (CTT) and anorectal function (anal manometry, rectal sensitivity and rectal compliance) were assessed.
Prucalopride (1 mg) compared to placebo significantly increased the mean number of spontaneous complete, spontaneous, and all bowel movements per week. Prucalopride (1 mg) significantly decreased the percentage of bowel movements with hard/lumpy stools and straining and increased the urge to defecate. Prucalopride (1 and 2 mg) decreased mean total CTT 12.0 h (42.8 h vs. placebo 54.8 hrs; $P = 0.074$). No statistically significant effects were found in any of the anorectal function parameters. Prucalopride was well tolerated. There were no clinically relevant changes in standard safety parameters.
Conclusions: Prucalopride significantly improves stool frequency and consistency, the urge to defecate and may decrease CTT in patients with chronic constipation.

Introduction

Constipation is a very common gastrointestinal disorder.[1–4] However, many patients who present with constipation have no obvious dietary, systemic or local structural causes for their symptoms, i.e., they have idiopathic or functional constipation.[5]

The treatment of chronic functional constipation is a challenge, since current treatments, such as dietary adjustments and laxatives, do not always improve patients' symptoms, particularly those with a long history of constipation. Increased dietary fibre and laxatives can result in significant bloating, flatulence and distension,[6] or may be insufficient to improve the complaints of patients. There is therefore a need for more effective and better-tolerated treatments that normalize bowel motility.

Functional constipation is often associated with impaired colonic motility. Moreover, in some patients with severe functional constipation, there is a decrease in the frequency and duration of high amplitude propagating contractions (the human equivalent of giant migrating contractions)[7] and an associated reduction in the number of mass movements.[8] Delayed colonic transit can be measured adequately using radio-opaque markers. In such patients, a reasonable therapeutic approach would appear to be to stimulate intestinal motility.[9]

Prucalopride is a novel, highly selective, specific serotonin$_4$ (5-hydroxytryptamine$_4$, 5-HT$_4$) receptor agonist with enterokinetic properties.[9–11] Stimulation of 5-HT$_4$ receptors facilitates cholinergic and non-adrenergic, non-cholinergic (NANC) excitatory neurotransmission,[12] and this mechanism has been proposed to explain the enterokinetic properties of prucalopride.[13] Preclinical studies have shown that prucalopride stimulates the peristaltic reflex[14] and dose-dependently enhances the occurrence of giant migrating contractions in the colon of a canine model,[15] which suggest that it might be suitable for the treatment of disorders associated with dysmotility of the small or large bowel. Studies with prucalopride in healthy volunteers showed that it increased stool frequency and improved stool consistency, and shortened colonic transit time (CTT),[10,11] but did not alter anorectal function.[11]

The aim of this study was to evaluate the efficacy and tolerability of prucalopride (1 or 2 mg) on bowel function, gastrointestinal transit time and anorectal function in patients with chronic functional constipation.

Materials and methods

This single-centre, randomized, double-blind, placebo-controlled, cross-over trial was conducted between May 1996 and June 1998. It was performed in accordance with Good Clinical Practice and the Declaration of Helsinki, and Ethics Committee approval was granted before commencement. Written informed consent was obtained from all patients before entry to the trial.

Patients

Male and female patients aged 18–70 years with a history of chronic functional constipation (see definition below), which was causing disability, with the patient's occupational, social and recreational activities governed by constipation and efforts to attain relief, and who had experienced poor results with routine laxatives and diet counselling, were eligible for inclusion. Patients also had to have a normal inhibition pattern of the external anal sphincter during straining. Constipation was defined according to the Thompson criteria[1] as: ≥ 2 of the following criteria for at least 6 months: ≤ 2 spontaneous bowel movements (a bowel movement was considered spontaneous if it was not preceded within the previous 24 hours by the intake of a laxative); lumpy (scyballae) and/or hard stools for ≥ 25% of the time; sense of incomplete evacuation for ≥ 25% of the time; straining at defaecation for ≥ 25% of the time.
Exclusion criteria included: drug-induced constipation; secondary causes of constipation (e.g. endocrine, metabolic or neurological disorders); previous abdominal surgery (except hysterectomy, surgery for Meckel's diverticle, appendectomy, cholecystectomy, inguinal hernia repair, splenectomy, nephrectomy or fundoplication) or anismus thought to be the primary cause of constipation. Patients with megacolon or megarectum; known or suspected organic disorders of the large bowel (e.g. obstruction, carcinoma, or inflammatory bowel disease) or active proctological conditions thought to be responsible for the constipation were also excluded. As were patients who were pregnant, breast feeding, not using acceptable methods of birth control or who had known illnesses or conditions that might interfere with adequate assessment of the investigational drug.

Study design

All medication, except those drugs specified below, had to be stopped at least 14 days before the study. During the 2-week run-in period patients' bowel habits were documented and their constipation confirmed. Patients were instructed not to change their diet and fibre intake during the trial, and were also asked to avoid hot/spicy foods. Alcohol was not permitted during the study.
Concomitant treatment with agents known to influence bowel habit (e.g. anticholinergics, prokinetics, calcium-, ferrous-, bismuth-, magnesium- or aluminium-containing compounds) or laxatives (except rescue medication – see below) was not allowed. Patients receiving oral contraceptives, tricyclic agents or calcium-channel blockers were required to continue treatment at the same dose for the duration of the study.
Rescue medication (bisacodyl, standard dose 15 mg) was allowed if ≥ 3 days elapsed without a bowel movement. If this dosage was insufficient, an increase in dose was allowed. However, if this did not result in stools then tap water or phosphate enemas could be used.
After the run-in period patients were randomized to two treatment groups. Group 1 received prucalopride 1 mg or placebo, while Group 2 received prucalopride 2 mg or placebo in a cross-over design, which consisted of five, 2-week periods:

run-in (i.e. no treatment); prucalopride (1 or 2 mg) or placebo; wash-out (i.e. no treatment); placebo or prucalopride (1 or 2 mg); run-out (i.e. no treatment).

Efficacy assessments

The primary efficacy parameter was transit time, which was measured during the second week of each treatment period according to a modified Metcalf method.[16] Patients swallowed 10 radio-opaque markers with their breakfast on 6 consecutive days (days 8–13 of each treatment period) and those markers remaining in the colon on day 14 were counted via a single abdominal X-ray. The X-ray was used to calculate mean or total colonic transit time (MCTT), and segmental transit times of the right colon (RCTT) and left colon (LCTT) and rectosigmoid (RSTT).[17] The basic formula for calculating MCTT is:

$$\text{MCTT} = \sum_{i=1}^{6} n_i [(t_{(i+1)} - t_i)]/N$$

where n_i = number of markers of a particular shape present on film (i = 1, 2, 3, 4, 5, 6), N = number of markers of each shape taken (N = 10 for all types), t_i = is the time of intake of marker i (i = 1, 2, 3, 4, 5, 6) and t_7 ($t_{(i+1)}$ for i = 6) is the time of the abdominal X-ray. Assuming $(t_{(i+1)} - t_i)$ = 24 hours for all i, and N = 10, the formula can be simplified to:

$$\text{MCTT} = 2.4 \sum_{i=1}^{6} n_i = 2.4\, n$$

For segmental transit times (RCTT, LCTT and RSTT), the same formula was applied by counting the number of markers in each segment.
The total intestinal transit time was calculated by counting the number of differently shaped markers in the first stool on day 14.[18]
Secondary efficacy parameters measured were diary parameters and anorectal function tests.
Patients kept daily diaries for the entire 10-week study, in which they recorded: date and time of each bowel movement, stool consistency (lumpy, hard, normal, loose or watery) urgency (yes or no, if yes patients recorded the number of times per day) straining (none, a little, much), sensation of incomplete evacuation (yes or no) and severity of abdominal pain (none, mild, moderate, severe). Patients also recorded whether each bowel movement was spontaneous (i.e. not induced by a laxative within the previous 24 hours) and complete (i.e. associated with a sense of complete evacuation).
Patients were also asked to note time and date of marker intake in their diaries, but it appeared that many patients neglected to do so. For that reason the investigator conducted a blind review of all x-rays, after the trial was over. This review showed that, even if time and date of intake had not been recorded, the patients had taken their markers. It was therefore decided to include all x-rays in the CTT analysis.
The review also revealed that two X-rays deviated from the others in that all markers of the last 4–6 intakes were located together in the right colon, indicating that the patient had taken the markers altogether shortly before the X-ray was

made. The two X-rays, which appeared to belong to different patients in the prucalopride 2 mg/placebo group, were excluded from the final CTT analysis. All anorectal function tests were performed on the last day of each treatment period. Maximal basal pressure (MBP), maximum squeeze pressure (MSP) and anal sensitivity were measured according to methods developed in our laboratory and reported previously.[19,20] Volumes and pressures of rectal sensitivity, e.g. first sensation, urge to defecate and maximal tolerated volume were recorded.[19]

Safety and tolerability

Standard laboratory safety tests were performed at the start and end of the study and after each treatment period. Blood pressure, heart rate and ECG recordings were measured at the start of the study and 3 hours after drug administration on day 14 of each treatment period. Adverse events were monitored throughout the trial.

Statistical analysis

Because this was a pilot efficacy study, exploratory statistical analysis was used. All statistical tests were two-tailed and interpreted at the 5% level of significance. The placebo and active treatment periods were compared using analysis of variance, including fixed effects for period and treatment and a random patient effect. In addition, the placebo and active treatment periods were compared using Koch's non-parametric analysis for two-period cross-over designs.

RESULTS

Patients

Of the 28 patients randomized to receive treatment (prucalopride (1 mg)/placebo group $n = 12$; prucalopride (2 mg)/placebo group $n = 16$), three discontinued treatment prematurely because of adverse events during prucalopride treatment in the first period, and one was uncooperative with continuing treatment after the first period (placebo); all four patients were in the prucalopride 2 mg/placebo group.
The patients' demographic data and clinical characteristics are summarized in Table 1. History of constipation did not differ in the two dose treatment groups except that the duration of constipation was longer in the prucalopride (1 mg) sequences (Group 1; 23.6 years for prucalopride-placebo and 20.0 years for placebo-prucalopride) than in either of the prucalopride (2 mg) sequences (Group 2; 16.3 years and 11.6 years, respectively for prucalopride-placebo and placebo-prucalopride). Compliance with the study medications was excellent during each treatment period in both groups (all median capsule intakes 7.0 per week).

Variable	Group 1 (n = 12)	Group 2 (n = 16)
Gender (% female)	92	88
Age (years)	42.4 (4.61)	37.5 (3.63)
Weight (kg)	66.6 (2.79)	62.5 (3.06)
Height (cm)	168.0 (2.34)	167.4 (1.80)
History of constipation		
Duration (years)	19.9 (5.04)	14.3 (2.32)
Age at first consultation (years)	28.3 (4.72)	26.8 (4.43)
Previous 6 months		
Time between stools (days)	6.3 (1.16)	7.6 (1.27)
Frequency of BMs (number/week)	2.0 (0.51)	3.9 (1.32)
Laxative use (%)	100	100
Inadequate therapeutic effect (%)	100	94

Table 1. Baseline demographics and clinical characteristics of study population. All values are expressed as mean ± SEM, except where indicated. BM = bowel movement

Colonic transit time

Colonic transit times were analyzed in 25 patients, i.e. 20 patients with 2 observations and 5 patients with only 1 observation. The results for these patients are shown in Table 2 and Figure 1. The estimated MCTTs were 10.8 hours shorter after prucalopride (1 mg) compared with placebo (37.0 vs. 47.8 h) and 15.2 hours shorter after prucalopride (2 mg) vs. placebo (48.4 vs 63.5 h). None of the differences were statistically significant. MCTT measured during placebo treatment was higher in Group 2 than in Group 1. When both prucalopride and placebo groups were combined, the estimated mean total MCTT was 12.0 hours shorter with prucalopride than with placebo (42.8 vs. 54.8 h; P = 0.074) (Figure 1).

	Group 1		
	Prucalopride 1 mg (n = 12)	Placebo (n = 12)	**Difference**
MCTT (h)	37.0 (14.6–59.5)	47.8 (26.0–69.6)	**-10.8 (-30.3–8.8)**[1]
RCTT (h)	10.4 (2.7–18.0)	15.2 (7.7–22.7)	**-4.8 (-10.5–0.9)**
LCTT (h)	11.3 (-2.6–25.3)	18.6 (5.2–32.0)	**-7.3 (-23.4–8.9)**
RSTT (h)	14.6 (2.9–26.3)	14.0 (2.5–25.5)	**+0.6 (-6.0–7.1)**
	Group 2		
	Prucalopride 2 mg (n = 12)	Placebo (n = 13)	**Difference**
MCTT (h)	48.4 (23.0–73.7)	63.5 (37.6–89.5)	**-15.2 (-39.1–8.7)**[2]
RCTT (h)	14.5 (2.7–26.4)	16.1 (4.0–28.2)	**-1.6 (-12.5–9.2)**
LCTT (h)	13.1 (2.3–23.8)	20.1 (9.2–31.1)	**-7.1 (-16.6–2.5)**
RSTT (h)	21.5 (10.0–32.9)	27.0 (15.4–38.7)	**-5.6 (-14.0–2.8)**

Table 2. Colonic transit times (LS means; 95% CIs) in the second week of treatment with prucalopride 1 or 2 mg or placebo
MCTT = mean total colonic transit time, RCTT = right colonic transit time, LCTT = left colonic transit time, RSTT = rectosigmoidal transit time. LS means and p values obtained from cross-over mixed model, including factors for sequence, period and treatment. [1]P = 0.24, [2]P = 0.18

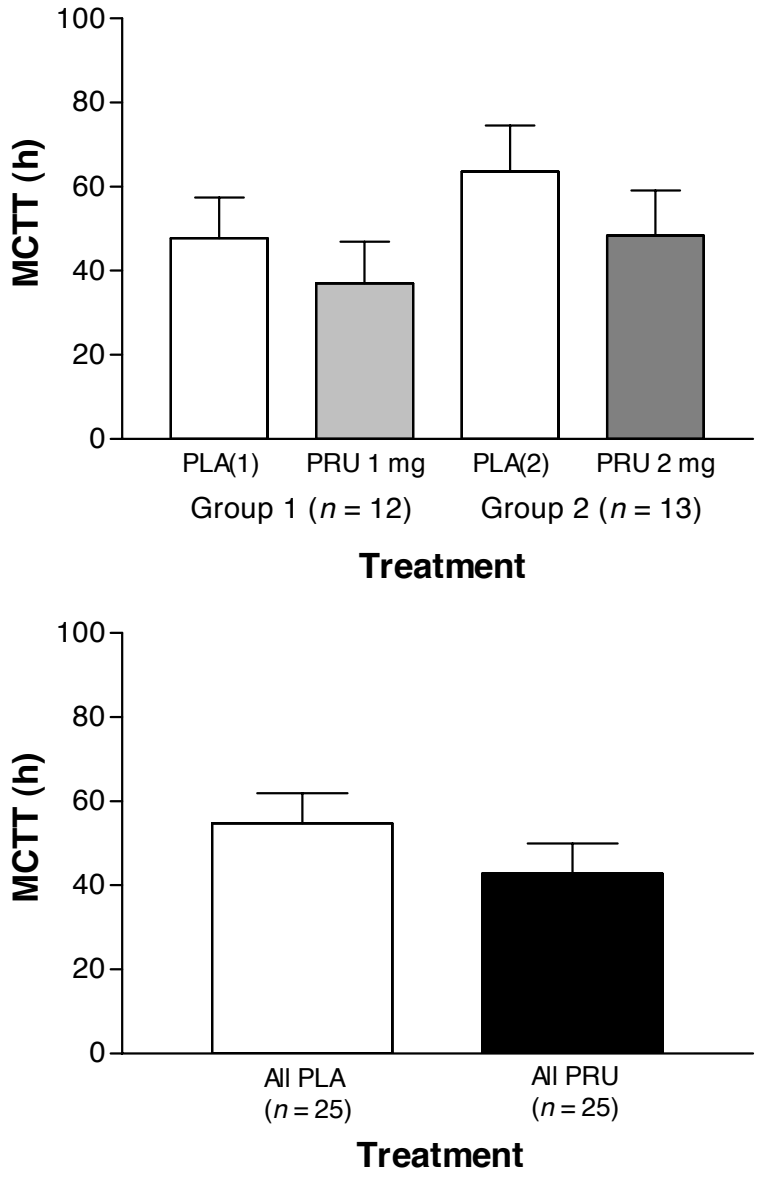

Figure 1. Estimated mean colonic transit times (MCTT; LS means ± SEM).
PRU prucalopride. PLA placebo.

Diary

Changes in bowel habit after treatment with prucalopride (1 or 2 mg) or placebo are shown in Table 3. Treatment with prucalopride (1 mg) resulted in a significant ($P \leq 0.05$) increase in the frequency of spontaneous complete, spontaneous and all bowel movements per week compared with placebo. Similar increases were not seen in the prucalopride (2 mg) group. Prucalopride (1 mg) also significantly ($P \leq 0.05$) decreased the percentage of bowel movements associated with hard/lumpy stools, increased the percentage of bowel movements with little/much straining and increased the urge to defecate. The changes with prucalopride (2 mg) were smaller than those with 1 mg and were not statistically significant compared with placebo.

	Group 1			Group 2		
	Prucalopride 1 mg (*n* = 12)	Placebo (*n* = 12)	*P*	Prucalopride 2 mg (*n* = 12)	Placebo (*n* = 13)	*P*
Average number of bowel movements/week						
SCBMs	2.6 (1.13–4.16)	1.2 (0.39–1.95)	0.011	2.0 (0.37-3.59)	1.7 (-0.25–3.63)	NS
SBMs	8.1 (5.21–11.07)	5.3 (3.36–7.33)	0.026	6.3 (3.66–9.02)	5.8 (1.38–10.16)	NS
All BMs	8.8 (5.73–11.96)	5.6 (3.70–7.43)	0.028	6.9 (4.35–9.45)	7.0 (2.71–11.29)	NS
Consistency of BMs						
Normal (%)	34.4 (19.8–49.0)	30.9 (13.3–48.5)	NS	31.1 (15.2–47.0)	37.8 (22.3–53.3)	NS
Hard/lumpy (%)	18.8 (4.1–33.5)	50.4 (30.1–70.8)	0.011	22.7 (4.7–40.7)	40.4 (18.0–62.8)	NS
BMs with little/much straining (%)	66.3 (44.9–87.7)	81.9 (65.9–97.9)	< 0.046	87.0 (75.5–98.6)	90.3 (77.4–103.2)*	NS
Urge to defecate (no./week)	6.9 (4.0–9.8)	4.7 (2.9–6.6)	0.035	10.1 (4.0–16.3)	8.5 (2.6–14.3)	NS
Sense of complete evacuation (%)	35.0 (17.7–52.3)	34.0 (10.0–58.0)	NS	29.4 (9.5–49.3)	41.0 (14.2–67.8)	NS
Time to first BM (hr/min)	8:43 (-1:04–18:31)	19:04 (-1:55–40:04)	NS	22:50 (1:20–44:21)†	38:25 (4:27–72:22)	NS

Table 3. Bowel habit parameters (means; 95% CIs) after 2 weeks' treatment with prucalopride 1 or 2 mg or placebo. S = spontaneous (i.e. not induced by a laxative within the previous 24 hours), C = complete (i.e. associated with a sense of complete evacuation) bowel movement; BM = bowel movement; NS = not significant; * = *n* = 11; † = *n* = 14; *P* values obtained from mixed model.

	Group 1		Group 2	
	Prucalopride 1 mg (*n* = 12)	Placebo (*n* = 12)	Prucalopride 2 mg (*n* = 12)	Placebo (*n* = 13)
MBP (mmHg)	61.3 (52.0–70.6)	64.7 (55.1–74.2)	70.8 (55.8–85.9)	65.4 (51.7–79.0)
MSP (mmHg)	66.3 (44.1–88.4)	64.6 (37.2–92.0)	59.6 (33.2–86.0)	50.8 (30.5–71.0)
FSV (mL)	130.8 (87.6–174.0)	141.9 (88.6–195.2)	105.7 (65.9–145.4)	120.8 (79.4–162.3)
FSP (mmHg)	31.6 (13.9–49.2)	21.5 (14.7–28.3)	20.2 (12.4–27.9)	22.5 (13.9–31.1)
Urge volume (mL)	234.8 (173.9–295.8)	233.2 (176.9–289.4)	204.0 (156.7–251.3)	213.5 (164.6–262.3)
Urge pressure (mmHg)	37.1 (23.8–50.3)	38.1 (22.7–53.5)	30.3 (17.6–42.9)	33.8 (22.7–44.9)
MTV (mL)	272.8 (201.9–343.6)	225.7 (151.6–299.9)	249.4 (200.4–298.5)	257.9 (208.5–307.4)
MTP (mmHg)	46.8 (30.6–62.9)	42.9 (28.1–57.7)	40.6 (22.9–58.3)	41.8 (30.4–53.3)
AS (mA)	4.7 (3.6–5.7)	5.1 (3.7–6.5)	3.5 (2.6–4.4)	4.7 (3.2–6.1)

Table 4. Anorectal function (means; 95% CIs) in the second week of treatment with prucalopride 1 or 2 mg prucalopride or placebo. MBP = maximum basal pressure, MSP = maximum squeeze pressure, FSV = first sensation volume, FSP = first sensation pressure, MTV = maximum tolerable volume, MTP = maximum tolerable pressure, AS = anal sensitivity

AE reported in ≥ 2 patients during treatment	Group 1		Group 2	
	Prucalopride 1 mg (*n* = 12)	Placebo (*n* = 12)	Prucalopride 2 mg (*n* = 15)	Placebo (*n* = 13)
Headache*	3	3	4	1
Abdominal pain*	1	2	4	1
Nausea	2	2	2	0
Diarrhoea	1	0	2	0
Flatulence*	1	1	2	0
Treatment withdrawals due to AEs	0	0	3	0

Table 5. Incidence of adverse events (AEs) during treatment with prucalopride 1 or 2 mg or placebo. *1 patient experienced the AE during treatment with placebo and prucalopride 1 mg

Anorectal function

No statistically significant changes were found in any of the parameters of anal manometry, anal sensitivity, and rectal compliance after treatment of prucalopride (1 or 2 mg) compared with placebo (Table 4).

Safety and tolerability

Prucalopride (1 or 2 mg) was generally well tolerated with an adverse event profile similar to placebo. Most adverse events were mild or moderate in severity and resolved spontaneously. The most frequent adverse event was headache, which was reported by six prucalopride and three placebo patients, and by one patient during both placebo and prucalopride (1 mg) treatment (Table 5). Other adverse events reported by more than 2 patients during treatment were abdominal pain, nausea, diarrhoea, and flatulence. Three patients in the prucalopride (2 mg) group withdrew from treatment because of adverse events, which were predominantly gastrointestinal in nature (diarrhoea and headache $n = 1$; abdominal pain, diarrhoea, flatulence, malaise and nausea $n = 1$; and headache and sensation of oedema (swollen hands, feet and face) $n = 1$). All these patients recovered after stopping the trial medication. No deaths or serious adverse events were reported during the study. There were no clinically relevant changes in any of the standard laboratory or cardiovascular parameters measured.

DISCUSSION

The frequency of constipation in the population is not precisely known. Depending on the definition used, prevalence is reported varying from 2% to 4% for infrequent stools and from 10% to 16% for excessive straining.[21–23] In nursing homes frequencies seem to be higher: up to 20%.[24] Depending on the population studied and the definition used, it has been estimated that up to 15% of the normal population has symptoms associated with functional constipation, while 5–10% may experience outlet delay. However, the true prevalence may be even higher as many patients do not consult their doctors.[23,25,26]

The results of this double-blind, placebo-controlled, cross-over study confirm the safety and efficacy of prucalopride (1 or 2 mg) in the treatment of chronic functional constipation. Because the study population was predominantly female and had a long history of not responding to laxatives or dietary counselling, it therefore reflected the normal population of patients with severe functional constipation.[6]

As it was not clear from previous studies in healthy volunteers, which had used doses 1 and 2 mg,[10,11] whether the effects of prucalopride on colonic transit were dose dependent; both doses were evaluated in this study. In the first study[10] no dose dependency was found, but in the second[11] the effects of prucalopride on gastrointestinal motility were dose-dependent, with the 2 mg dose having the greater effects. A study in healthy volunteers has shown that prucalopride (single and once-daily dosing with 1–6 mg) has a well-characterized, predictable, dose-proportional, pharmacokinetic profile with rapid, oral absorption. Furthermore prucalopride is not associated with food interactions as concomitant food intake had no significant effects on its oral bioavailability ($> 90\%$).[27,28] Since prucalopride has a long elimination half-life, approximately 24 h, once-daily administration was used in our study.

Although both doses of prucalopride (1 and 2 mg) decreased colonic transit time in our study, the differences were not statistically significant compared with placebo. However, despite randomization, the MCTT during placebo treatment for the prucalopride (2 mg) group was considerably longer than that with prucalopride (1 mg), which may have affected the result with active treatment. In addition, because the transit studies were conducted during the second week of each treatment period, this may not have allowed sufficient time for prucalopride to show its full beneficial effects; most other published studies have involved at least 4 weeks' treatment.[29–31] The additional analysis, in which all patients with two valid MCTT assessments (both prucalopride and placebo), resulted in an overall 24% reduction (14 h) with prucalopride (1 and 2 mg) compared with placebo ($P = 0.057$). This is consistent with previous studies in patients with chronic constipation,[29,30] which demonstrated that 4 weeks of once-daily prucalopride (0.5–4 mg) improved colonic transit.

In our study, prucalopride (1 mg) resulted in significant improvements in the average weekly number of bowel movements (spontaneous complete, spontaneous and all), stool consistency, the need to strain at defaecation and the urge to defaecate compared with placebo. Significant changes were not seen with prucalopride (2 mg), but this may have been influenced by the relatively high frequency of bowel movements in this group of patients during placebo treatment.

Anorectal function (anal sphincter pressures, anorectal sensitivity and rectal compliance) was unaffected by prucalopride in the present study. Similar results have been found in studies in healthy volunteers.[10,11] However, another study in patients with chronic constipation showed that 4 weeks of prucalopride (1 mg) significantly enhanced several parameters (both of distension and electrical stimulation) of rectal visceral sensitivity compared with placebo.[32]

Prucalopride was generally well tolerated in our study. The majority of adverse events were mild to moderate in severity and there were no clinically relevant changes in blood biochemistry, urinalysis, blood pressures, heart rate or electrocardiogram. The most common adverse event with prucalopride was transient headache, which was reported by 29% of the prucalopride patients compared with 17% receiving placebo. Other adverse events experienced by prucalopride patients were mainly gastrointestinal in nature (abdominal cramps, diarrhoea, nausea and flatulence) and reflected the colonic effects expected from a drug with enterokinetic properties.[10,11] The adverse event profile with prucalopride in our study was similar to that observed in previous studies in healthy volunteers [9,10,33,34] and patients with chronic constipation.[29–31]

In conclusion, once-daily administration of prucalopride was safe and effective for the treatment of patients with chronic functional constipation. Prucalopride (1 mg) significantly improved stool frequency and consistency and reduced the need to strain at defaecation. The results suggest that it may also decrease MCTT in these patients. Although improvements with prucalopride (2 mg) were not always statistically significant compared with placebo, this probably reflects the refractory nature of the long-standing constipation in this patient population. Because treatment with prucalopride was also generally well tolerated it therefore has potential in the management of chronic constipation.

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CHAPTER 10

RECTAL VISCERAL SENSITIVITY, COMPLIANCE AND MOTILITY MEASUREMENT IN HEALTH AND FUNCTIONAL DISORDERS. A REVIEW

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Abstract

The defaecation process is a complex mechanism. Colorectal motor function, visceral sensitivity, compliance and tone are closely co-ordinated with pelvic floor function. Disturbances in these modalities may lead to functional complaints. Modern colorectal function tests are reviewed with attention focused on methodology, aspects of functional disorders and influence of treatment.
Visceral sensitivity, compliance, tonic response and phasic contractility can be investigated with a barostat system. A barostat system consists of a high compliant polyethylene bag and a feedback controlled computerised inflation device and is progressively used besides latex balloon inflation systems. Different protocols are described such as intermittent or continuous distensions. Whether distinct sensations are measured remains in discussion. Pressure-controlled inflation is preferable to volume-controlled or wall tension-controlled, since pressure-controlled is independent of the shape of the bowel. The compliance curve (volume pressure curve) is S-shaped and is indicative of the viscoelasticity of the gut. Barostat measurements are reproducible. Results are influenced by gender, age and body mass index. Certain drugs also influence visceral sensitivity.
Colorectal motility can be measured using manometry or barostat. Colorectal motility is physiologically stimulated on awaking postprandially (gastrocolonic response) and by drugs. Furthermore, radio-opaque markers or scintigraphic markers can be used to measure colonic transit (CTT). Overall as well as segmental CTT can be calculated although the use of the latter is disputed. Women have longer colonic transit than males.
Diarrhoea and Constipation predominant Irritable Bowel Syndrome (IBS) are related to hypersensitivity during colonic distension. IBS seems more than just a bowel disorder since alterations at cerebral level have been found. In IBS patients, an increase of colonic motor action is found. Functional constipation is subdivided in slow transit, pelvic floor dysfunction and constipation predominant IBS, however considerable overlap exists. Patients with longstanding constipation have decreased visceral sensitivity and some have a megarectum. Hypersensitivity is found in 25-60% of patients with constipation depending on the criteria used for constipation. Colonic motor function is decreased in constipated patients both fasting or after a meal. Whether subgroups in constipation differ is not clear. Colonic transit time measurement in constipated patients is used to objectify complaints. Whether rectosigmoid delay refers to pelvic floor dysfunction is subject to discussion. CTT can be used to evaluate the influence of drugs.
Colonic sensitivity and motor function studies are described in patients with faecal incontinence, rectocele, rectal prolapse, radiation proctitis and inflammatory bowel disease.
In conclusion, a variety of tests comprising visceral sensitivity, compliance, tonic response and phasic contractility (barostat), colorectal motility (barostat or manometry), colorectal transit (radio-opaque or scintigraphic markers) can demonstrate abnormalities in patients with colorectal disorders. However, a

substantial overlap with healthy controls exists. Most research has been focussed on functional constipation and IBS.

Introduction

The defaecation process is a co-ordinated colorectal and anal motor action. A bowel movement, which can be stimulated by a meal, awakening or medication such as bisacodyl, consists of colonic contractions that proceed distally and increase rectal pressure. Simultaneously, the anal sphincters relax with the onset of the colonic contractions and remain relaxed until the bowel movement is expelled when a socially acceptable place is found.[1,2] When defaecation cannot take place, the external sphincter contracts voluntarily and the rectum relaxes by increasing its compliance. [3,4] Different aspects of the transport, sensation and evacuation of a bowel movement can be studied. Rectal and colonic sensation is important for the subject to be aware of the time of defaecation. Adequate transport to the rectum and evacuation from the rectum must be performed with only minor straining and with a relaxation of the pelvic floor when an appropriate location is found. The methods to study the process of defaecation will be reviewed both in health and functional disorders.

Colorectal function tests in health

Visceral sensation and compliance

Different methods have been used to test visceral sensitivity and compliance. Initially, latex balloons on a catheter connected with a syringe were used to perform volume-controlled distension. Later on, roller pomp and intraballoon pressure measurement were used to slowly distend the balloon and calculate compliance. In 1985, Azpiroz and Malagelada introduced the barostat consisting of a high-compliant polyethylene bag mounted on a catheter connected to a computer controlled distension pump.[5] With this system, volume-, pressure- or wall tension-controlled distension can be performed in an intermittent or continuous distension manner.

Different systems and balloons

Rectal visceral sensitivity and compliance measurement is most commonly performed using distension balloons. Other techniques are described such as rectal endosonography and impedance planimetry but these techniques did not reach a wide public of users.[6,7] The materials that can be used to create distension balloons are latex (from a condom) or polyethylene (from a sandwich bag). Initially, latex balloons were used in combination with a water pump or with a syringe filled with air.[8-10] The use of water or gas to distend the balloon did not influence the measured compliance or sensation.[9] Latex because of its stiffness influences the results of compliance measurement and the intraballoon pressure values have to be corrected for the internal balloon compliance.[11] Furthermore, because of its spherical shape, in-vitro the latex balloon expands

under high pressures in a rigid tube.[12] Therefore, polyethylene bags are more appropriate since its internal compliance is nearly zero and it does not expand in a rigid tube.[5,12,13] The difference in results using a flaccid air-filled bag or a water-filled latex balloon is considerable. With the barostat bag higher maximal tolerated distension can be reached. Furthermore, the values of the intraballoon pressures, which were measured using the latex method, were less reliable than with the barostat system. An explanation is suggested that the sensation of a water-filled balloon is different from an air-filled, as it weights heavier. The latex balloon has a more spherical distension while barostat balloon distends cylindrical. The latex balloon has to be corrected for its internal compliance, which alters with using it repeatingly. Therefore the pressure values are less reliable.[13,14]
Accurate compliance measurement of the rectum is not only disturbed by the type of balloon but also by the characteristics of the rectum itself. In vitro studies showed that balloon distension have difficulties in measuring compliance in 'in vitro' pig gut with inhomogeneous and different elastic properties along his length partly because of internal compliance of the inflation apparatus.[12] MRI studies showed that during inflating the rectal balloon the rectal ampulla distends first and then the balloon expands cranially.[15] Therefore, expansion of the balloon poorly fits to a cylindrical model and the intrarectal position of the balloon influences compliance measurement.

Intermittent or continuous distension

Different distension protocols are described to measure rectal visceral sensitivity. In phasic or intermittent distensions, the intrarectal bag fills rapidly followed by a plateau phase after which the balloon is deflated. Repeated distensions can be presented with increasing pressures or volumes (staircase) or with a randomised height of distension. In continuous or ramp distension the bags fills gradually with a preset velocity until a limit.[16] Theoretically, slow and rapid distension can stimulate different mechanoreceptors. Slow rectal distension is perceived by mucosal receptors of the sacral afferents, whereas rapid phasic distension may stimulate preferentially splanchnic afferents with receptive fields in deep muscular layers, serosa and mesentery, projecting to the lumbar cord.[17] This hypothesis is supported by the following findings. Rectal thresholds are elevated in slow ramp distension but not in intermittent distension after application of topical lidocaine that blocks the mucosal receptors.[18,19] Patients with spinal cord injury only notice sensations during intermittent distension by stimulating projections to the lumbar cord.[18] Slow ramp distension but not rapid distension could inhibit the RIII reflex (a spinal reflex elicited by electrical stimulation of a sensory nerve and recorded from a flexor muscle in the ipsilateral limb) suggesting a different recruitment of receptors.[19,20] IBS patients score higher discomfort sensations during intermittent phasic distension than during continuous ramp distension.[9,18,21-24] However, other theories have emerged to explain the difference between sensations during continuous or intermittent distension. Intermittent distension reduces colonic compliance due to activation of neural reflexes and colonic contractions whereas in slow distension the colon

can adapt to the distending balloon.[24-27] Furthermore, repeated noxious sigmoid distension changes the sensory descriptors of controls and causes hypervigilance towards aversive and potentially noxious visceral stimuli.[28,29] Other authors did not find differences in sensations between continuous or intermittent distension methods in controls or in IBS patients.[14,30-35]
The most practical way in performing colonic distension studies is to use a continuous pressure distension protocol to assess visceral sensitivity and compliance. When specifically visceral sensation is tested in IBS patients an intermittent protocol could be used with only 3 to 4 distension periods. This would greatly reduce patient's inconvenience.

Wall tension

Distrutti et al. advocate wall tension as an important parameter of visceral sensitivity. They designed a tensostat in order to distend the rectum wall tension-controlled.[31,36] Wall tension is calculated using Laplace's law (pressure * radius) regarding the balloon shape as a cylinder (volume is equal to $\pi * r^2 *$ length of cylinder).[31,37] The use of wall tension as the parameter of sensitivity has some limitations. Wall tension was calculated using Laplace's law under assumptions that the wall of the viscus is infinitively thin, the balloon has a perfectly defined shape, and the pressure external to the viscus is evenly distributed. However, the dynamic shape of the barostat bag does not follow the geometric forms such as a sphere or a cylinder, which makes an accurate calculation of the wall tension difficult or impossible.[38] Furthermore, variance in sensitivity score did not decrease if gastric or rectal sensitivity was expressed as wall tension compared to pressure or volume.[14,25,37] The sensation remains unaltered during the adaptive response of the rectum to constant pressure distension in which volume increases and thus the wall tension.[39] This suggests that wall tension is not a better parameter to determine sensations than pressure.

Compliance

The compliance curve or pressure volume (P-V) curve has an S-shape. The curve consists of an initial steep increase in pressure (with the first sensation threshold), plateau phase in which volume mainly increases (with the sensation of wind) and a final rapid ascent of pressure (with the perception of pain and discomfort).[9] Åkervall et al. showed that in the beginning of the curve internal sphincter inhibition occurred at the first sensation threshold, and at the inflection point of the curve external sphincter excitation occurred at the threshold of urge to defecate.[26] Rao et al. constructed a mathematic approach to rectal sensation and compliance. First sensation at the beginning of the compliance curve is not a 'true' rectal sensation but an anal canal sensation occurring when the balloon comes in contact with the anal mucosa. Urge distension in the steep part of the curve is related to the drop in rectal circular smooth muscle tension, and longitudinal smooth muscle drop is inflation rate dependent, possibly for a rate detecting mechanism that is in some way related to different patterns of circular

muscle relaxation. By in vitro validation maximal toleration at the last phase of the curve is a physiological protection mechanism associated with tetanic smooth muscle contraction in order to protect against irreversible damage.[40] Interesting points on the P-V curve are the early increase of volume (minimal distension pressure), the inflection point (dynamic compliance i.e. the highest volume increase at a pressure step) and maximal tolerated distension level. In the first part of the compliance curve, the distension represents the muscular tone (active stretch) while the latter part of the curve represents the connective tissue and muscle (passive stretch).[9] Drugs such as clonidine influence dynamic compliance or active stretch but not passive stretch or the compliance at maximal tolerated pressure.[41] In the assessment of the effect of stimuli on the rectal compliance, the pressure volume curve should be regarded and not only the compliance on the maximal toleration threshold.
Hysteresis is another indicative of viscoelasticity. Hysteresis is defined as the relative difference between the area under the pressure volume curve (AUC) in the descending and ascending part.[14,24,42] Hysteresis is a feature of the compliance and the resilience of the rectum. However, its clinical relevance is not yet clear.

Reproducibility

Measurements of rectal visceral sensitivity and compliance are reproducible using the latex balloon.[9,25,30,43,44] A wide intersubject variation is found in controls using the latex balloon, even a variation in maximal tolerated volume from 58-908ml.[8,10,14,30] Therefore, discrimination with pathological conditions is difficult. Day-to-day variation in sensory thresholds is large using the latex balloon method, however, no systematic trend is found, indicating that the variation was related to each subject rather than the method. Maximal tolerated volume has the best reproducibility.[43] Reproducibility using the barostat system with a polyethylene bag is better than the latex distension system for sensations as well as for compliance curves.[14,24,25,44] Results of visceral sensitivity and compliance measurements alter on repeated distensions on a single day.[30] After a first distension, the following distensions remain stable. Therefore, a conditioning distension is suggested before determining sensitivity and compliance.[25]

Physiological and pharmacological influences of colonic and rectal sensitivity and compliance

Conflicting studies are published about the influence of gender on rectal sensitivity and compliance. One study using air-filled latex balloon distension showed that rectal thresholds tended to be higher in men, however, in the age group above 60 years rectal compliance was higher in women than in men.[43] Others could not confirm this.[45] Using polyethylene bag distension, visceral sensitivity was equal in males and females at given pressures.[14,46] Compliance-curve and compliance at maximal tolerated distension were higher in men than in women.[14] Others could not find gender differences in rectal or colonic

compliance.[26,47] Aged subjects (86 years) compared to young subjects (26 years) have lower pressures at the thresholds for first sensation, urge to defecate and pain. Compliance was not different.[48] Rectal sensitivity was not different between the phases of the menstrual cycle in female subjects.[49] Body mass index (BMI) influenced P-V curves during inflation, mostly in the onset of the curve.[24] Gender-matched controls should be used to compare barostat results. Correction for age is necessary if a large difference in age is expected. BMI has an effect at the level of minimal distension. Table 1 shows the influence of physiological stimuli and drugs on visceral sensitivity and compliance.

Physiological stimuli		Sensitivity	Compliance
Meal [50-52]		+	+/=
Hyperglycemia [53,54]		+/-	+/=
Hypocapnic hyperventilation [55]		+	
Mental stress [56]		+	
Active relaxation [56]		-	
Coffee [57]		=	=
Nicotine	Low dose [57-59]	=	=/+
	High dose [59]		-
Yohimbine [41,46]		+	=
Clonidine [41,46]		-/=	+/=
Octreotide [60,61]		-	=
Intrarectal lidocain [60]		-	
Ondansetron [34]		=	-
Fentanyl (mu opioid-preferring) [62]		-	=
Glucagon [46]		=	=
Nitroglycerin [46]		=	=
Phenylephrine [41]		=	
Rotidrine [41]		=	
Neostigmine [63]		=	
Atropine [63]		=	
SB-207266 (5HT4 receptor antagonist) [64]		=	=
Amitryptiline [65]		=	=

Table 1. Influence of colorectal sensitivity and compliance in healthy subjects
+ Increase in visceral sensitivity or compliance; = no effect on visceral sensitivity or compliance;
- Decrease in visceral sensitivity or compliance

Colorectal motor function and transit

Rectal and colonic contractions are studied using several techniques. In the seventies, measurement of myoelectrical activity was performed by clipping electrodes to the bowel wall. Later on, colonic and rectal manometry gained more and more interest, which was enhanced by 24-hrs ambulatory manometry.

In the late eighties and nineties, the barostat with the use of a highly compliant bag was used to study tone as well as phasic contractions of the bowel wall. Barostat tracings and colonic manometry overlap in about 80%. The number of Phasic Volume Events in barostat tracings (PVE e.g. temporarily decrease in bag volume) is about 0,9 to 2,9 times greater than the number of phasic events (manometric peaks). High amplitude propagated contractions (HAPC) are associated with a sustained reduction in barostat volume, which lasts longer than the typical PVE. The most plausible explanation is that in a wide hollow organ such as the rectum, manometry does not register the subtotal contraction, which are registered with the barostat.[66] Bowel contractions registered with manometry or barostat do not always include movement of scintigraphic markers or radio-opaque markers. Gradual postprandial movement of intraluminal contents is registered together with non-propagating colonic motor activity. Propagating contractions are associated with rapid movement of the tracers.[67]

Physiological and pharmacological influences of colorectal motility

Colonic motor function is lower during the night and increases approximately 3-fold in activity on awakening according to ambulatory 24-hour manometry data. Ingestion of a meal causes an increase in motor activity during the following two hours. Most common motor action patterns are simultaneous pressure waves, propagating pressure waves and specialised propagating pressure waves (sort of HAPC) that continue in 30% to the anus and occur mostly after meals or on awakening. Infrequently retrograde waves are seen.[68] The colon relaxes during sleep and increases its tone on awakening and after a meal, which is shown by colonic barostat studies.[69] Physical activity stimulates propulsive action.[70] An intensity-dependent decrease in the colonic pressure activity occurs during exercise, but after the exercise the number and amplitude of propagated waves increase.[71] Colonic motor function shows a circadian rhythm. The colon is quiet during the night, but becomes active on awakening, after a meal and after exercise. Table 2 and 3 give an overview of the drugs tested on fasting colorectal tone and phasic activity.

Peristaltic reflex

The colonic peristaltic reflex can be studied using multiballoon assemblies. The peristaltic reflex consists of an orad contraction and a caudad relaxation.[85] Others described a biphasic caudad response consisting of first a relaxation and then a contraction.[73] Peristaltic reflex of sigmoid and rectum have been studied using two balloon assemblies. Step-wise distension of the rectosigmoid shows an immediate contraction of the rectosigmoid and the rectal balloon, and a relaxation of the internal and external sphincter.[86] Distension with a distally placed rectal balloon increases proximal rectal tone in healthy volunteers.[87] In contrast, another study showed that rectal distension caused an increase in colonic bag volume and a decrease in phasic contractions.[88]

Tone increase	No effect	Tone decrease
Cholinergic		
• neostigmine (cholinesterase inhibitor) [72]	• edophronium (anticholinesterase agent) [74]	• atropine [74]
• bethanechol (muscarin receptor agonist) [73]		
Adrenergic		
• yohimbine (alpha-2 antagonist) [41,46]	• phenylephrine (selective alpha-1-agonist) [41]	• clonidine (alpha-2-agonist) [41,46]
	• rotidrine (selective beta-2-agonist) [41]	
Other		
• coffee [57]	• nicotine [57,59]	• nicotine high dose [59]
• hypocapnic hyperventilation [55,75.76]	• eucapnic hyperventilation [55,75,76]	• glucagon [46,72]
	• hyperglycemic clamping [73,77]	• nitroglycerin (NO donor) [46]
		• morphine [74]

Table 2. Influences on fasting colonic tone in healthy subjects

Stimulation	No effect	Inhibition
Cholinergic		
• neostigmine (cholinesterase inhibitor) [72,78]		• atropine [74]
Adrenergic		
• propanolol (unselective beta blocking agent) [79]	• yohimbine [41]	
• metoprolol (beta-1-selective blocking agent) [80]	• phenylephrine (selective alpha-1-agonist) [41]	
• clonidine (alpha-2-agonist) [41]	• rotidrine (selective beta-2-agonist) [41]	
Other		
• morphine (inhibited by naloxone) [74,78]		
• hypocapnic hyperventilation [75]	• eucapnic hyperventilation [75]	• nicotine [59,83,84]
• coffee [57,81,82]	• nicotine [57]	

Table 3. Influences on fasting phasic activity in healthy subjects

Gastrocolonic response

The term gastrocolonic response is not a correct term because not only gastric stimulation evokes colonic and rectal motor action but also the entry of nutrients in the duodenum. The gastrocolonic response starts prompt after ingestion of a meal.[89] The response is present in ascending, transverse, descending colon and in the rectum and the increase in tone is strongest in the sigmoid colon.[69,72,90,91] A meal increases colonic tone and myoelectrical activity and induces simultaneous and retrograde pressure waves.[69,89,92] This propagating and non-

propagating colonic motor activity corresponds with antero- and retrograde movement of intraluminal contents.[67]
Whether a *cephalic phase* exists, is still in debate. Rogers et al. showed that food discussion, smell of food and sham feeding increased colonic motor action but the sight of food did not.[93] In contrast, Sun et al. could not show a cephalic phase on the colon myoelectrical spike activity after sham feeding.[78] The existence of a *gastric phase* is clearly shown using gastric balloon distension, which causes a volume dependent increase in rectosigmoid motility within 60-90 sec.[85,94] Also, ingestion of water causes an increase in sigmoid tone, however, not as strong and perpetually as a 1000 kCal liquid meal of the same volume.[69] The parasympathetic system plays a major role in the regulation of the gastric phase since the anticholinergic drugs clinidium bromide or atropine can inhibit it.[78,94,95] However, atropine also effects fasting colonic tone and motility.[96] A *duodenal phase* was already suggested by Holdstock et al. since the entry of food in the upper small intestine is important for the response in patients after total gastrectomy.[97] The *duodenal phase* is modulated by the parasympathetic system since atropine partly blunted the response after intraduodenal lipid infusion.[89,94] A *proximal colon phase* is suggested by Tomlin et al. who found a temporally relationship of the late increase in rectosigmoid motility after a meal to the second rise in breath hydrogen. Therefore, the late postprandial rectosigmoid response might be generated by chemical or mechanical stimulation of the proximal colon.[98] Intestinal continuity seems to be a prerequisite for the gastrocolonic response since intraduodenal lipid infusion causes an increase in motility of the colon when the luminal flow is restored after a loop ileostomy but not when the ileostomy was present.[99]

Inhibition	No effect
anticholinergic drugs • atropine [89,94,96] • clinidium bromide [78,95]	adrenergic drugs [41,46] • clonidine (alpha-2-agonist) • yohimbine (alpha-2-antagonist) • phenylephrine (selective alpha-1-agonist) • rotidrine (selective beta-2-agonist)
serotinergic antagonists • ondansetron (5HT3 antagonist) [102] • granisetron (5HT3 antagonist) [85]	cholecystokinin mediators • CCK-octapeptide or caerulin [94,96,104] • loxiglomide (CCK-A antagonist)[104]
others • mebeverine [103] • naloxone [78] • hyperglycemic clamping [73]	others • gastrin [89] • glucagon (rectal muscle relaxant) [46] • nitroglycerin (NO donor) [46] • SB-207266, a 5HT4 receptor antagonist [64] • euglycemic, hyperinsulinemic clamping [73]

Table 4. Influences on the postprandial colonic response in healthy subjects

The caloric load of the meal is of importance to elicit a gastrorectal response. Early studies showed that a 350 kCal meal could not stimulate the colon, but a 1000 kCal meal did.[89] Others could not find differences between a 600 and a 1000 kcal meal on the gastrorectal response.[72,100] Fat compared to protein or carbohydrate is the predominant stimulus of colonic response, which is modulated by protein or amino acids.[85,92,94,101]
Table 4 shows the effects of compounds tested on the gastrocolonic response.

Colonic transit

Colonic transit time (CTT) can be measured using radio-opaque markers or scintigraphic markers. Both methods measure the transit of intraluminal contents throughout the colon. A comparative study showed that central mass of markers and isotope progression was not different, however, the transit of markers was systematically more rapid than the progression of isotopes.[105] Furthermore, both transit of radio-isotopes and radio-opaque markers are slower in subjects with hard stools.[106] Comparable colonic transit time measurements can be performed using radio-isotopes or radio-opaque markers. Since the latter method is easier to perform with little patient inconvenience, this method is reviewed.

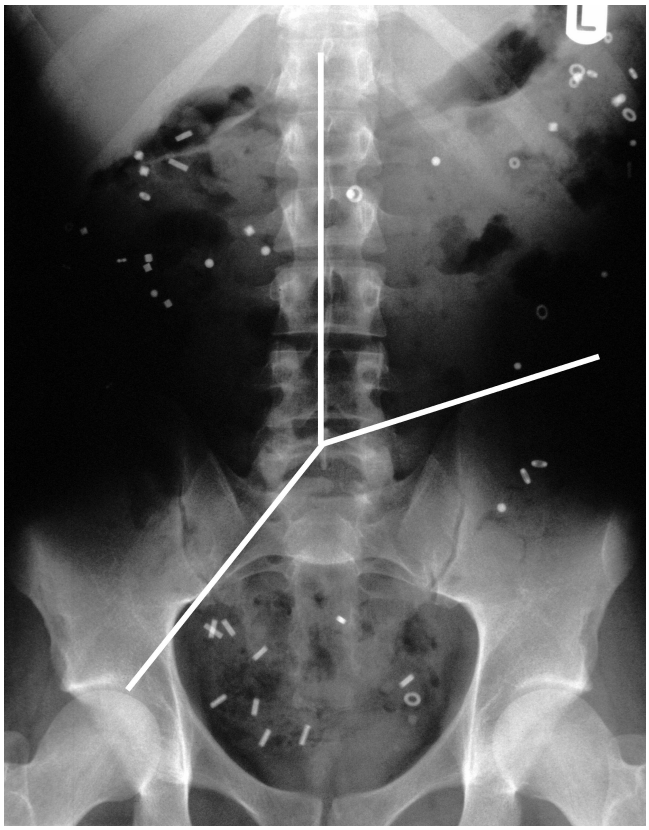

Figure 1. Example of an abdominal film showing radio-opaque markers.

A large variety of methods are described to measure CTT. The concept always is similar. Originally, the subjects ingested one set of markers followed by multiple abdominal films. To minimise radiation exposure, Metcalf et al. showed that multiple sets of marker ingestion followed by one abdominal compared well to the single set and multiple radiograph technique.[107] Bouchoucha et al. showed that at least six days of marker ingestion and single abdominal radiograph should be performed to reach a steady state (Figure 1).[108]
Using the following formula colonic transit time can be calculated [107]:

$$CTT = {}^{1}/_{N} * \sum_{i=1}^{i} Ni\ [½(t_{i+1} - t_{i-1})]$$

CTT = Overall Colonic Transit Time; N = Total number of a particular markers given; i = Number of capsules taken; Ni = Number of markers of a particular type present on the film; $½(t_{i+1}-t_{i-1})$ = Time interval between successive intakes of markers.

This formula can be summarised in 6-days-method with ingestion of markers and the following abdominal film on the seventh day at the same times:
CTT = 2,4*Ni (in hours)

This formula is criticised because it underestimates colonic transit times for a number of reasons; 1. The steady state may not be reached 2. In patients with diarrhoea the interval of marker ingestion may be too large, 3.The markers are ingested in a bolus and not continuously. A new formula to calculate CTT was designed using kinetic coefficients in a three-compartment model showing a systematical difference.[109] This latter formula is very complex compared to the above-mentioned formula and is not presented.
Segmental CTT can be calculated using the amount of markers in colonic segments. Arhan et al. described a method in which three segments are identified.[110] Central point is the fifth lumbar vertebra. Right colon segment is the part between the line over the right pelvic outlet ring and the line over the spinal processes of the lumbar vertebra. The left colon segment is the part between the line over the spinal processes of the lumbar vertebra and the left pelvic rim, the distal part is the rectosigmoid area. In the determination of the segments, the configuration of the air in the bowel is taken into account.
Reproducibility of CTT measurement is acceptable when overall transit times are concerned, however, moderate reproducibility is found for segmental transit times. In IBS patients correlation coefficients in the range of r = 0,6 were found.[108] In another study, correlation was r=0.71 for overall colonic transit time and r=0.5 for right and left colonic transit time and 0.3 for rectosigmoid transit time.[111]

Influence of gender, age, physical activity, stress and drugs on CTT

Women have longer colonic transit time compared to men.[106,107,112,113] The reason for this difference is unclear. Several studies suggest the influence of gender hormones, however, evidence is still not given. Longer rectosigmoid transit time was found during the luteal phase compared with the follicular phase.[112] Other studies could not confirm these findings.[106,114,115] CTT is not different between females taking contraceptives or postmenopausal women compared to other women.[114,115]
The effect of age on CTT is still in debate. Adults and children do not show different overall CTT but segmental analysis reveals a relative stagnation in the rectosigmoid area of children.[110] Other studies did not find differences between young and elderly.[107,116]
CTT is not increased after sports.[117-119] Stress is of influence on colonic transit time since stress-free controls have shorter transit then those who claim that their bowel habits are modified by stress.[108]
Colonic transit time is influenced by colonic intraluminal contents. Alteration of colonic transit times was found when this was measured after preparation with bowel cleansing compared to the uncleansed state. Healthy males had a delay of transit. But both healthy and constipated females had an acceleration of colonic transit after bowel cleansing.[120]

Alcohol shortens colonic transit time.[121] The effect of smoking is unclear. CTT in non-smoking men is shorter than in smoking men.[112] However, application of nicotine accelerates colonic transit of radio-opaque markers and isotopes compared to baseline.[59,122]
Bulk-forming agents, senna and lactulose have an accelerating effect on colonic transit.[123-126] Loperamide and dihydrocodeine delay colonic transit.[125,127] Serotinergic antagonists such as ondansetron (5HT3 receptor antagonist) and SB-207266 (5HT4 receptor antagonist) delay colonic transit whereas 5HT4 receptor agonists such as prucalopride and tegaserod shorten colonic transit time.[64,128-131]

Functional disorders of the colon and rectum

Irritable bowel syndrome

Irritable bowel syndrome compromises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation. Recently, the Rome II multinational working team defined diagnostic criteria for functional gastrointestinal disorders (Appendix).[132] These criteria are developed out of earlier publications such as the Manning criteria and the Rome I criteria.[133,134] Criticism on the new Rome II criteria comprises exclusion of subgroups based on predominant bowel dysfunction, leaving out of postprandial exacerbation of symptoms, and not encompassing functional painless diarrhoea associated with urgency, borborygmi and incomplete evacuation.[135] Further, the IBS population is subject to developing definitions in which functional test results still not are included. Since the defecation process is disturbed in IBS patients, colonic and rectal function tests revealed abnormalities both in visceral sensitivity and motility.

Visceral sensitivity and compliance

Already in 1973, Ritchie reported that patients with IBS are hypersensitive to sigmoid balloon distension.[136] For the first time a complaint related pathophysiological feature was found in these patients without abnormalities on physical, chemical, radiological or endoscopical tests. From here, other authors have proceeded in investigating hypersensitivity in IBS patients. Swartbrick et al. showed that IBS patients had different pain referral.[137] Mertz et al. stated that hypersensitivity is considered a biological marker of irritable bowel syndrome since 94% of the patients have altered visceral perception in the form of lowered thresholds for aversive sensations (discomfort), increased intensity of sensations, or altered viscerosomatic referral. They described hypersensitivity as feeling of discomfort or pain preferentially during rapid balloon distension.[22] However, in other studies continuous colonic distension could also elicit hypersensitivity.[18,33-35] Both diarrhoea predominant and constipation predominant IBS patients and children with IBS can show hypersensitivity to balloon distension.[22,139,140] Hypersensitivity becomes more obvious postprandially.[52] IBS

hypersensitivity is not limited to the colon. IBS patients manifest hypersensitivity to jejunal balloon distension and an overlap is suggested with dyspepsia patients.[141,142] IBS patients are sensitive to mechanical distension but not to electrical bowel wall stimulation. Sensitivity to somatic stimulation is decreased and thus hypersensitivity is typically visceral predominant. [141]
Rectal sensitivity and compliance measurement is used to classify IBS patients. Mertz defined three subgroups. One group is younger and has rectal hypersensitivity and a hypertensive and hyperreactive anal sphincter. The group is notable symptomatically for a higher prevalence of diarrhoea and a higher bowel frequency. A second group has normal sensitivity to rapid distension and hyposensitivity to rapid phasic distension and is predominantly constipated. The third group has the greatest degree of rectal hypersensitivity and shows elevated rectal compliance; symptomatically, they report the greatest number of primary symptoms, are most likely to report their condition as severe, and are predominantly constipated.[22] Another classification is proposed by Prior et al. They identified five different abnormal rectal subgroups: 1. Normal rectum (normal sensitivity and compliance), 2. Sensitive rectum (low sensation thresholds, normal or low rectal compliance), 3. A stiff rectum (normal or low thresholds, high pressures) 4. Insensitive rectum (high sensation thresholds, normal or high pressure) or 5. A lax rectum (low pressures and normal to high volumes needed to produce rectal sensations). A sensitive rectum was a particular feature of IBS-D (57%) compared to IBS-C (7%).[139] This classification of patients seems to be preferable.[33]
It is not clear whether hypersensitivity in IBS patients is a 'true' colonic irritation or the hypersensitivity is due to an abnormality in colonic perception. Compared to IBS patients, patients with colonic irritation due to mild ulcerative colitis do not report comparable hypersensivity.[143] IBS patients tend to label visceral stimuli in negatively affected terms and score higher on anxiety in psychological tests especially those who show hypersensivity. [29,35,139,144-6] Furthermore, after a period of acute gastro-enteritis hypersensitivity is found both in patients who developed IBS complaints and patients who did not.[145] Pain sensitivity is not biological marker but a psychological marker in IBS patients.[144] An alteration on cerebral level is supported by functional anatomical studies. Cerebral Evoked Potentials studies revealed that IBS patients compared to controls have shorter latency and larger amplitude of the responses after rectal electrical stimulation and therefore, a state of afferent hypersensitivity is present.[147] PET-scanning showed that perception of rectal painful distension is associated with the activation of the anterior cingulate cortex in controls. However, in IBS patients, not the anterior cingulate cortex but the left prefrontal cortex is activated.[148] Rectal painful distension is associated with more intensive activation of the Anterior Cingulate Cortex (ACC) on fMRI studies.[149] Visceral hypersensitivity in IBS patients can be elicited with rectal balloon distension and more evidence suggest that different processing on cerebral level is responsible for the altered sensation instead of a disordered bowel wall function. Subjects with anxiety disorder or a previous life event are more prone to develop symptoms related to rectal hypersensitivity. Several drugs that influence hypersensitivity were tested in IBS patients (Table 5).

	Hypersensitivity	Compliance
Serotinergic drugs		
Ondansetron (5HT-3 antagonist) [34]	=	-
Alosetron (5HT-3-antagonist) [150]	=	+
Granisetron (5HT3 antagonist) [138]	↓	=
Opioid agonists		
Fedotozine (kappa-agonist) [151]	↓	=
Fentanyl (mu opioid-preferring) [62]	↓	=
Oxytocin [152]	↓	=
Other		
Octreotide [61,153]	↓	=
Neostigmine [23]	=	-
Glucagon [23]	=	+
Lidocain (intraluminal) [18]	=	
Hypnotherapy [154]	↓	

Table 5. The effects of drugs on colorectal hypersensitivity and compliance in IBS
decrease (↓) or no effect (=) on hypersensitivity;
increase (+), no effect (=), or decrease (-) in compliance

Motility

IBS patients have increased colonic phasic motility during fasting and postprandially.[104,138,155-157] Different patterns in manometric alterations have been recognised. Higher amplitude of intraluminal pressure activity pre and postprandially [155], prolonged postprandial increase in colonic spike activity and motor activity[157,158], and increased frequency and amplitude of high amplitude propagated contractions (HAPC) [156], occur in IBS patients. Both IBS-D and IBS-C have higher activity than controls.[159] In contrast, two studies did not show an increased postprandial response: in IBS-D and in children with IBS.[140,160] The abnormal postprandial response in IBS patients is reduced by clinidium (anticholinergic) [157], octylonium bromide and nifedipine (smooth muscle relaxants by interfering with calcium ion mobilisation) [158,161] and granisetron (5HT3 antagonist). [138] These compounds could play a role in reducing the postprandial symptoms of IBS patients.

Functional Constipation

Functional constipation is a common complaint with a high variety in prevalence reported depending on the criteria used.[162] The appendix shows the commonly used criteria. Different pathophysiological mechanisms cause the symptoms of idiopathic constipation. Therefore, subtypes of idiopathic constipation cluster symptom complexes and anorectal and colonic motility test results. The generally used classification is slow transit constipation (with a delayed colonic transit), pelvic floor dysfunction (with disturbed rectal evacuation tests) and constipation predominant irritable bowel syndrome (with normal transit and evacuation tests).[166-8] Overlap consists between the subgroups. Symptoms such

as decreased stool frequency, laxative dependence, and a history of constipation since childhood can predict slow transit. Symptoms such as backache, normal stool frequency, heartburn, and a history of anorectal surgery, are associated with pelvic floor dysfunction . More than 60% of constipated patients fulfil the Manning criteria for IBS.[169] Patients with IBS can show pelvic floor dysfunction.[166,167] Patients with pelvic floor dysfunction can show delayed colonic transit, even when the distal obstruction was removed.[120,166,167,]
Originally, idiopathic slow transit constipation, a term introduced by Preston and Lennard-Jones, partly based on the Arbuthnot Lane's clinical observations is a syndrome consisting of symptoms of decreased bowel frequency poorly responsive to fibre and laxatives and a delayed transit time without a megacolon.[170,171] Other gastrointestinal manifestations include abdominal pain, bloating, malaise, nausea and difficult faecal expulsion. The term slow transit constipation generally refers to the patients with delayed colonic transit time without an underlying systemic disorder or pelvic floor dysfunction.[168] Besides delayed colonic transit, decreased colonic motor activity after a meal or fewer high amplitude propagated contractions (HAPC) have been found.[172,173] Likewise, the term colonic inertia was introduced, which means that the colon is not responsive to a meal or a stimulant such as bisacodyl.[174] Possibly, slow transit constipation represents a more generalised dysmotility disorder.[175-177]
Pathologically identifiable changes were found in the myenterical plexus in severe idiopathic constipation.[178] A higher frequency of inclusion bodies presence in both layer of the muscularis propria is found in both slow transit constipation due to Chagas' disease and after pelvic surgery possibly as a result of denervation.[179] Furthermore, slow transit constipation is associated with a decreased cell volume of the interstitial cells of Cajal.[180] These histological changes could be the cause or the consequence of chronic constipation.
In constipation predominant irritable bowel syndrome, bloating and pain are more prominent than decreased bowel frequency represented by an altered perception for rectal distension (visceral hypersensitivity; e.g. lower than 95% confidence interval of normal controls).[22] Criteria and pathophysiological mechanism are described in the IBS section.
Anismus (pelvic floor dyssynergia) is defined as an inappropriate contraction of the pelvic floor during straining, rather than relaxation.[181-183] New diagnostic criteria were formulated by the Rome II international working team (Appendix 1).[165] The paradoxical contraction of the anal sphincter can be detected with anal manometry[183-184], electromyography (EMG) or defecography. Differentiation from neurological disorders can be made by EMG testing since an intact muscle apparatus and nerve supply is present.[196] Anismus is frequently observed in sexually abused women.[187]
Biofeedback training is the therapy of choice to improve symptoms of dyssynergic defecation such as straining and bowel frequency. Furthermore, biofeedback improves colonic transit time, evacuation of isotope markers, the anorectal angle during straining and the paradoxical contraction of the sphincter muscles and rectal sensations in around 80% of the patients.[188-191] Besides biofeedback with the use of a visual display is also muscular training using personal instruction and encouragement successful in the treatment of

dyssynergic defecation.[192] Some scepsis has been shown towards the phenomena of anismus or dyssynergic defecation. Controls can show paradoxical contraction of the pelvic floor or difficulty in expelling a water-filled balloon.[184,193] The overlap between manometry, digital examination and defecography to demonstrate paradoxical sphincter co-ordination is limited (5%).[193] Furthermore, myectomies of the anal sphincter or botulinum toxin injection in order to the treat the spastic anal sphincter do not improve complaints of anismus , which suggests that not only a spastic anal sphincter but a more complex mechanism is causing of anismus.[194,195] Patients with features of slow transit constipation can respond to biofeedback training and the absence of paradoxical pelvic floor contraction during straining also does not preclude benefit.[196]

Visceral sensitivity and compliance

Visceral sensitivity is decreased in patients with longstanding severe idiopathic constipation.[197-199] Especially slow transit constipation is related to lower rectal sensations. [200,201]
The term 'idiopathic megarectum' was introduced to describe large, insensible rectums. A megarectum has a volume of more than 320 ml in women and 440 ml in men or a diameter on lateral radiograph of more than 6,5 cm.[202-203] Approximately 30% of patients with idiopathic constipation have a megarectum. The majority of these patients report normal sensations during rectal pressure distension.[33] Pathological examination of muscle strips of a megarectum reveal smooth muscle hypertrophy, which may cause the functional abnormality.[204] Megarectum is occurring frequently in patients with constipation. Whether this is the consequence or the cause of constipation remains unclear.
Depending on the definition 25-60 % of the constipated patients show rectal hypersensitivity or sigmoidal hypersensitivity.[33,166.167,205] When hypersensitivity is present in constipated patients, constipation predominant irritable bowel syndrome (IBS-C) can be put forward.[139]
Patients with dyssynergic defecation show increased or decreased rectal sensations depending on the criteria used to define the pelvic floor dysfunction. An increased volume threshold for first sensation with normal thresholds for desire or urge was found. These alterations were normalised after biofeedback.[183,190,206] Patients with paradoxical straining during manometry have higher visceral sensitivity scores compared to constipated patients without pelvic floor dysfunction.[33] Another study showed that rectal sensitivity is blunted or absent in a majority of patients with obstructed defecation after pelvic surgery. Rectal compliance was normal. [207]

Motility

Constipation is associated with disturbance in colonic and rectal motor function leading to impaired propulsive action. Constipated patients have a reduction of contractions in the left colon and a paucity of HAPC (contractile waves of >50mmHg) which are of lower amplitude.[173,208,209] Slow transit constipation

patients show less fasting and postprandial motor action and a smaller increase in sigmoid contractions after awakening.[209] Rectal wall tone response to a meal, neostigmine or glucagon is blunted in constipated patients.[211] Slow transit and outlet obstruction constipation patients have lower colonic tone and motor responses to a meal than normal transit constipation and controls. Increase of HAPC is not different but phasic contractions after a meal are lower in the slow transit and the outlet obstruction group.[212] Patients with obstructed defecation and delayed colonic transit have a blunted postprandial rectal response in contrast to patients with normal transit.[213] Biofeedback training corrects the decrease in postprandial colonic tone response in patients with an evacuation disorder.[206] In contrast, Penning et al. found that postprandial rectal tone response was not different between slow transit, constipation predominant IBS and controls.[201] Furthermore, postprandial rectal tone response is comparable between patients with constipation and controls, however, since parity diminishes the rectal response, nulliparous patients have lower rectal response than nulliparous controls.[100] Constipated patients have fewer fasting and postprandial phasic volume events (PVE's).[33] Constipation is associated with less colorectal motor action reflecting in diminished phasic activity and phasic volume events, and in a decrease in rectal tone response.

Colonic transit time

Colonic transit time studies are performed in order to objectify complaints and to confirm slow transit in functional constipation patients. This can be used to select patients for treatment.[214] It was suggested that CTT could be used to establish the localisation of obstruction, which is not supported by recent literature.
Since patients do not report their stool frequency with great reliability, CTT can objectify constipation. However, CTT correlates closely with stool weight ($R = 0,53$) and not to stool frequency.[215] To date, a CTT reproducibility study in constipated patients has never been performed. Segmental transit times and especially rectosigmoid transit time has been believed to show obstructed defecation or pelvic floor dysfunction.[216,217] However, some studies do not support these findings. Patients with a rectocele, enterocele, descending perineum syndrome or dyssynergic defecation are found equally among slow transit and rectosigmoid delayed patients.[120,193,218-220] Furthermore, accumulation of faeces in the colon can cause a delay in colonic transit. When this faecal mass is removed prior to measuring CTT using a laxative, the overall CTT remains unchanged, but the markers accumulate more distally suggestive of an outlet obstruction.[221] Bowel cleansing accelerates overall colonic transit both in health as well as in slow transit constipation and pelvic floor dysfunction without segmental transit change. An effect of the total removal of the faecal contents does not reveal a distal obstruction.[120]
Colonic transit time measurement is used to assess the effects of therapy. Polyethylene glycol (PEG) electrolyte solution, cisapride (a 5HT3 antagonist and 5HT4 agonist), prucalopride (a 5HT4 receptor agonist) treatment shortens CTT in constipated patients.[222-224] Neither naloxone (opioid antagonist) nor nalmefene (a

stronger opioid antagonist than naloxone) shorten CTT in idiopathic constipation.[225]

Other disorders

Faecal incontinence

Patients with complaints of faecal incontinence show lowered [226,227] or normal rectal compliance [228]. Lowered rectal compliance causes urgency.[229] This is most prominent when the capacity of the rectum is lower than 100 ml for example in proctitis. However, in idiopathic faecal incontinence these extreme low values of rectal capacity are seldom found.[8] Patients with faecal incontinence were found to have normal [227,228] or disturbed rectal sensitivity.[226,229-231] Rasmussen et al. found an increased rectal sensitivity and compliance both in idiopathic and traumatic incontinence.[226] Siproudhis et al. found that incontinence patients have blunted rectal perception compared to controls. Incontinence patients with normal anal sphincter function have lower rectal compliance compared to incontinence patients with sphincter dysfunction.[227,230] Speakman et al. found that first sensation and urge volume was higher in neurogenic incontinence (prolonged pudendal nerve latencies) compared to patients with an anatomically disrupted sphincter but intact pudendal latency and controls. Maximal toleration volume, rectal compliance and rectal sensation to electrical stimulation were not different.[231] Salvioli et al. found that initial perception pressures were lower and urgency and maximal tolerated distension were normal. Rectal compliance was not different from controls. However, a reduced compliance was associated with a reduced rectal sensitivity and urgency.[229] The disturbed sensitivity can have implications for the close relationship between the perception of rectal distension, external anal sphincter contraction and transient internal sphincter relaxation. Patients with faecal incontinence, impaired rectal sensation but normal sphincter pressures show a disturbed relationship between rectal sensation and anal contraction. Internal sphincter relaxation occurs before the sensation is perceived and external sphincter contraction is delayed or absent.[3] In faecal incontinence, more important mechanisms are sphincter contractile function and the defecation pattern. Rectal sensitivity and compliance are of importance when extreme low values are found. In idiopathic faecal incontinence, low volumes at first threshold could be due to increased awareness, but the rectal capacity and maximal tolerated distension are within the normal range.

Rectocele

Rectal compliance and maximal distension threshold are not different between rectocele patients and healthy controls.[220,232] However, rectal sensitivity is diminished most prominent in the beginning of the pressure distension curve and at first sensation pressure threshold in rectocele patients compared to controls. Compliance curves and rectal sensitivity did not change after transvaginal repair. Transanal repair of the rectocele causes a discrete decrease in maximal tolerated

volume three to six months postoperatively. [233-235] After one year maximal tolerated volume increases to preoperative values.[233] Possibly, the decrease in MTV can be explained from direct plication of the rectal wall during transanal surgery in contrast to the vaginal approach.

Rectal prolapse, solitary ulcer syndrome

Patients with a full rectum prolapse, anterior mucosal prolapse or solitary rectal ulcer have lower rectal volumes at the thresholds desire for defecate and maximal tolerated volume compared to controls. This could be due to alteration in compliance or perception.[236] Rectal prolapse patients suffering from incontinence have adequate rectal perception but rectal adaptation volumes (compliance) is lower.[230]

Radiation proctitis

Patients with a chronic radiation injured rectum have a reduction of rectal compliance.[237-239] Histology suggests that smooth muscle hypertrophy and myenteric plexus damage are contributory.[237] Threshold volumes for perception of rectal distension are lower in the radiated patients who experienced faecal urgency.[239]

Inflammatory bowel disease

Patients with ulcerative colitis in the active phase have increased sensitivity and lower rectal distension volumes for first sensation, desire to defecate and maximal tolerated distension compared to the quiescent phase. Rectal compliance is decreased in both active and quiescent phase. The frequency and urgency of defecation and faecal incontinence may be due to a hypersensitive, hyperactive and poorly compliant rectum.[240-243] Compared to controls, ulcerative colitis patients with mild inflammation of the distal colon have higher discomfort thresholds.[143] Crohn's disease patients with ileitis terminalis without rectal disease have higher rectal pressure thresholds for discomfort compared to controls. Autonomic responses (skin conductance response) are decreased in all Crohn patients. This lowered sensation to rectal distension and autonomic responses can be explained by the endogenous pain inhibition due to the chronic visceral inflammation.[244]
Active ulcerative colitis causes a decrease in motor function both fasting and postprandially.[59,243,245,246] In mild or quiescent colitis fasting colonic phasic pressure activity is increased, but postprandial colonic tone response is reduced.[59] Gastrointestinal transit is not fastened in UC patients. Gastric emptying is normal, mouth-to-caecum transit is slower in patients with ulcerative colitis and whole gut transit is within normal ranges.[243] Alterations of the interstitial cells of Cajal were found in patients with severe ulcerative colitis, which could explain the decrease in colonic and rectal motor function.[247] Therefore, diarrhoea in UC seems not to be caused by a motility problem.

Conclusions

Research on colorectal motility comprises visceral sensitivity, compliance, tonic response and phasic contractility (barostat), colorectal motility (barostat or manometry), colorectal transit (radio-opaque or scintigraphic markers) tests. Methodology of these tests is subject to discussion and optimal performance still has to be evolved. However, colorectal function tests can adequately be used to study physiology and pathophysiology. Influences of physiological mechanisms and drugs have been subject for investigations. Abnormalities have been shown in functional colorectal disorders, however, a substantial overlap exists between health and disease and among the disorders. Most research has been focussed on functional constipation and IBS.

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Appendix. Criteria of functional colorectal disorders

Irritable bowel syndrome criteria

Rome II criteria [132]
At least 12 weeks or more, which need not to be consecutive, in the previous 12 months of abdominal pain or discomfort that has 2 or 3 features:
- Relief with defecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in form (appearance) of stool

Constipation criteria

Thompson criteria [163]
more than two of the following criteria for at least 6 months:
- less than 2 bowel movements per week
- lumpy and/or hard stools for more than 25% of the time
- sense of incomplete evacuation for more than 25% of the time
- straining at defecation for more than 25% of the time.

Rome I [164]
Two or more criteria:
- two or fewer bowel movements per week at least 25% of the time
- sensation of incomplete evacuation at least 25% of the time
- lumpy or hard stools at least 25% of the time
- straining at defecation at least 25% of the time

Rome II criteria [132]
At least 12 weeks, which need to not be consecutive, in the preceding 12 months of two or more of:
- straining in > ¼ defecations
- lumpy or hard stools in > ¼ defecations
- sensation of incompete evacuation in > ¼ defecations
- sensation of anorectal obstruction/blockade in > ¼ defecations
- manual maneuvers to facilitate > ¼ defecations (e.g., digital evacuation, support of the pelvic floor)
- <3 defecations/week

Loose stools are not present, and there are insufficient criteria for IBS

Diagnostic criteria of dyssynergic constipation [165]
- Criteria of functional constipation
- Manometric, EMG or radiologic evidence for inappropriate contraction or failure to relax the pelvic floor during repeated attempts to defecate
- Evidence of adequate propulsive forces during attempts of defecation
- Evidence of incomplete evacuation

CHAPTER 11

ASSESSMENT AND CLASSIFICATION OF NEVER OPERATED AND RECURRENT CRYPTOGLANDULAR FISTULAS-IN-ANO USING HYDROGEN PEROXIDE ENHANCED TRANSANAL ULTRASOUND

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Abstract

Classification and visualization of fistula-in-ano is used to determine surgical treatment according to the type of fistula, predict the recurrence rate and incontinence risk, and compare the results of treatment published in literature. Hydrogen peroxide enhanced transanal ultrasound (HPUS) with the peroxide introduced through the external opening of the fistula gives a clear and accurate visualization of the track in relation to the sphincters. The aim of this study was to review never operated and recurrent cryptoglandular fistulas-in-ano visualized with the aid of HPUS in order to establish the anatomical differences. Eighty-one patients with never operated (48) or recurrent (33) cryptoglandular fistulas-in-ano were assessed by clinical examination and HPUS. Never operated fistulas were single track, trans- or inter-sphincteric fistulas in 80%. In 15%, the tracks were sinus with no connection to the pectinate line. Two patients (5%) had transsphincteric fistulas with a ramification. No supra or extrasphincteric fistulas were found in the never operated fistula group. In the recurrent fistula patients, 57% had a single trans or intersphincteric track, 15% of the patients had a single track supra or extrasphincteric fistula and 27% had a ramified fistula. Conclusions: All never operated cryptoglandulair fistulas-in-ano were inter- or trans-sphincteric. An extra track was found in 5%. Recurrent fistulas-in-ano were supra or extrasphincteric in 15% and ramified in 27%. Therefore, never operated fistulas-in-ano do not require any special investigation before surgical treatment. However, before treating recurrent fistulas, visualization by HPUS is recommended to detect supra or extrasphincteric fistulas or ramification.

Introduction

Classification of fistulas-in-ano is used to determine (surgical) therapy, make a prognosis concerning recurrence and fecal incontinence, and compare the results published in the literature. In 1976 Parks presented a classification of fistulas-in-ano which is still universally used today.[1] He proposed dividing the fistulas anatomically in inter, trans, supra and extrasphincteric fistulas. This anatomical classification was determined during the operation by the direction of the probe introduced into the track in relation to the anal canal and the amount of sphincter mass divided during surgery. However, pathogenesis of the fistulas was not taken into account in this classification.
Since a different pathophysiology exists for each of these different fistulas, it is clear that anatomical spread and localization may be different as well. A better understanding of this relation will permit a more simple classification in order to facilitate a practical surgical approach. Hydrogen peroxide enhanced transanal ultrasound (HPUS) is an excellent method to classify perianal fistulas and it correlates well with surgical findings as we and others have demonstrated.[2-5] In addition, HPUS is more accurate than endosonography without HPUS and digital examination.[5] Also, HPUS can visualize complex fistulas which helps to direct the surgeon to the difficult branches. The aim of this study is to determine the differences in fistula tracks between the never operated and recurrent fistulas and to make recommendations about the need for preoperative imaging.

Patients and methods

Patients

Eighty-one patients with fistula-in-ano (65 males and 16 females; mean age 46 years range 22 to 79) were assessed by history, physical examination, probing of the fistula track, proctoscopy and HPUS. In patients with a recurrence, Crohn's disease was excluded by patients history, physical examination, enteroclysis and endoscopy.

Physical examination

The perineal region was inspected for visualization of the external opening and digital examination was performed with careful probing of the fistula track. During the digital examination, the presence of the internal opening (induration) was recorded as well as the palpation of the tip of the passing probe in the anal canal.

Proctoscopy

Proctoscopy was performed to exclude proctitis and anal malignancy, and to evaluate the internal opening of the fistula.

Hydrogen peroxide enhanced ultrasound (HPUS)

Hydrogen peroxide (HP) enhanced ultrasound was used involving a diagnostic ultrasound system (type 3535, Bruel and Kjaer, Naerum, Denmark) with a 7 Mhz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a water-filled hard sonolucent cone (diameter 1.7 cm), producing a 360º view. The endoprobe was introduced into the rectum and serial radial images as well as video recordings were made of the distal part of the rectum, the puborectalis muscle and the anal canal. A fistula track could be seen as a tube-like hypoechoic image. A sphincter defect was seen as a hypoechoic interruption in the sphincter complex. After conventional US was performed, HP 3% was introduced into the fistula track with a flexible intravenous cannula (Venflon (R), Ohmeda, Helsinborg, Sweden). Hereafter US was repeated as described previously. By infusion of HP, which generated the formation of small air bubbles, the hypoechoic fistulous track turns bright hyperechoic. The comparison of images with and without HP identified the course of the fistula and its extensions and allowed to make a distinction between active fistulas and fibrotic tissue common in previously operated patients. The site of the internal opening, secondary extensions of the fistula and the presence of defects in one or both sphincters were also carefully recorded. The evidence of the internal opening was defined as a hypoechoic (conventional US) or echoic (HPUS) breach at the level of the submucosa (Figure 1).

Classification

The tracks were classified in single track or branched.[6] The relation to the sphincters was classified according to Parks classification[1] into four main groups:

- Intersphincteric, in which the track ramifies only in the intersphincteric plane and finally to the skin;
- transsphincteric, where the track passes from the intersphincteric plane through the external sphincter complex at varying levels into the ischiorectal fossa;
- suprasphincteric, in which the track passes in the intersphincteric plane over the top of the puborectalis muscle, then downwards again through the levator plate to the ischiorectal fossa;
- extrasphincteric, in which the track passes from the perineal skin, through the ischiorectal fat and levator muscles into the rectum at another level than the pectinate line and outside the external sphincter complex altogether.

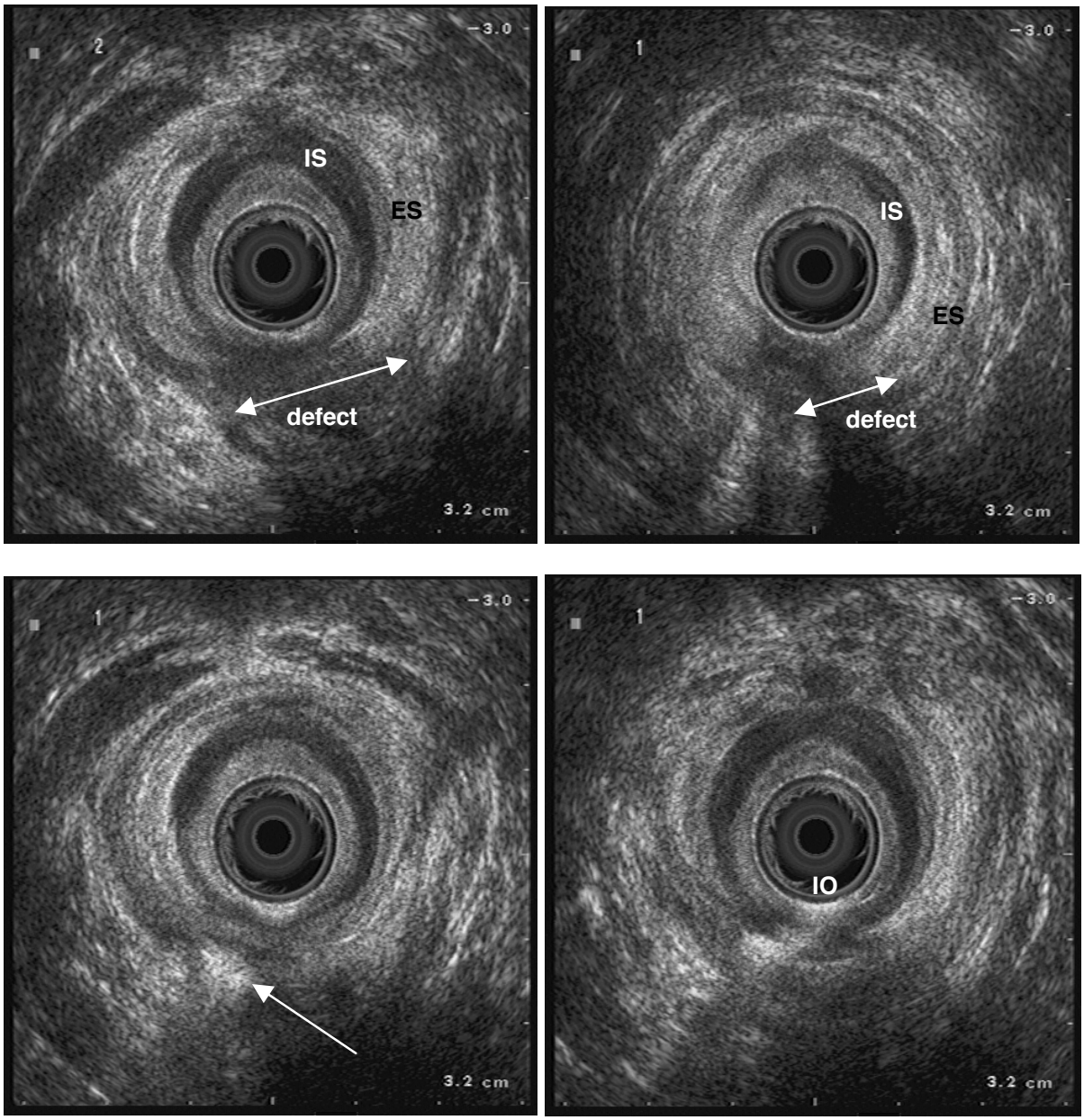

Figure 1A-D: Transanal ultrasound showing a recurrent transsphincteric fistula. 1A (Top Left) Endosonography without hydrogen peroxide shows a defect as a dark area clock-wise from 5 until 7 hours posteriorly in external anal sphincter (ES) and internal anal sphincter (IS) and 1B (Top Right) more caudally . 1C (Down left) After injection of hydrogen peroxide via the external opening the fistula-in-ano becomes visible (arrow) as a bright hyperechoic lesion and 1D (Down right) the internal opening (IO) can be detected.

Results

Never operated fistula-in-ano

Forty-eight patients had a never operated fistula (with the exception of simple abscess drainage). Eighty percent had a single track fistula, 32 of which were transsphincteric (66%) and seven (15%) intersphincteric fistulas. In seven (15%), the fistulas appeared to be sinus without a connection with the anal canal. Two patients (5%) were found to have a double track, one transsphincteric with an

intersphincteric track up to the supralevator space and the other patient a transsphincteric track with a horseshoe extension. No supra or extrasphincteric fistulas were found in the never operated group. (Table 1)
Twenty-five out of 32 transsphincteric fistulas developed after spontaneous abscess-drainage, while in seven the abscess was surgically drained. In only two of the seven patients with an intersphincteric fistula the fistula formed after a spontaneous abscess drainage. Moreover, the transsphincteric fistula with an intersphincteric track up to the supralevator space occurred after extensive abscess drainage.

Recurrent fistula-in-ano

Thirty-three patients had a recurrent fistula-in-ano (Table 1). The fistula was recurrent after fistulectomy in 10 patients, fistulotomy in 11, mucosal advancement flap technique in two and a seton technique in three patients. The seven other patients had already undergone two or more operations.
Nineteen patients (57%) had a single inter- or transsphincteric track. Single track supra- or extra-sphincteric fistulas were found in five patients (15%), all following a 'laying open' fistulotomy. The other nine patients had a fistula with more than one track (27%). Six fistulas were inter- or transsphincteric, two had a horseshoe branch and four had a supralevator branch. Three of the other nine were found to be extrasphincteric fistula, two with a horseshoe extension and one with a supralevator branch.

All Fistula (57)

Never operated (48)

- 32 single transsphincteric
- 7 single intersphincteric
- 7 sinus
- 2 branched
  - 1 transsphincteric with horseshoe extension
  - 1 transsphincteric with intersphincteric supralevator extension

Recurrent (33)

- 16 transsphincteric
- 3 intersphincteric
- 5 supra- or extrasphincteric
- 9 branched
  - 6 trans- or intersphincteric
    - 2 with horseshoe extension
    - 4 with supralevator extension
  - 3 extrasphincteric
    - 2 with horseshoe extension
    - 1 with supralevator extension

Table 1. Description of the fistulas and the extensions.

Discussion

The cryptoglandular concept is currently the most widely supported theory about the aetiology of never operated fistulas-in-ano. Development of an intersphincteric abscess seems to be the first stage after the inflammation of one of the glands of Morgagni. This gland abscess situated in the intermuscular (intersphinteric) space has been called the cryptoglandular abscess. The anal glands can be localized cephaled, caudal or penetrating into the external sphincter. From here, the abscess can further develop intersphincterically and in some cases extend through some part of the external sphincter.[1,6-12] Morgan and Thompson suggested that the intersphincteric abscess could follow the terminal fibroelastic conjoint longitudinal tendon septal fibres that transverse the external sphincter to reach the ischiorectal fossa.[13] Parks based his classification on this theory, the examination of patients during surgical intervention by probing and the amount of sphincter mass divided.[1] Parks did not distinguish between never operated and recurrent fistulas in his classification.

As early as 1978, Eisenhammer[14] in his series of 800 patients, did not find the supra or extrasphincteric variations in never operated cryptoglandular fistula. Eisenhammer claimed that the cryptoglandular abscess/fistula never invades the supralevator space and is always inter or transsphincteric, except for the recurrent cryptoglandular fistula which may extend its track(s) through the supralevator space. These findings were confirmed during surgical treatment in studies of Fucini and other groups.[15-18]

Hydrogen peroxide enhanced transanal ultrasound (HPUS) can confirm these important basic concepts since it is an excellent method to classify perianal fistulas and correlates well with surgical findings (95%) as we and others demonstrated.[2-5] In addition, we have demonstrated that there was an additional value of HPUS of 33% over endosonography without HPUS and 58% over digital examination.[5] In a large study of 180 patients, the fistula track and internal opening could be found with great accuracy with HPUS.[5] Limitations of the technique include exact localization of the internal opening making use of accurate criterions, loss of resolution due to air in the rectal ampulla, bubbling in the anal canal due to the injected hydrogen peroxide and the use of different transducers (e.g. a 7 mHz transducer reveals more about the sphincter complex, whereas a 10 mHz tranducer reveals more about the submucosa). However, in experienced hands it is a rapid, simple and well-tolerated technique, which provides highly accurate information about the fistula track and the sphincter integrity before surgery.

A comparison between the endosonographic and surgical findings was not made in the present study since HPUS is proven to be a reliable technique in the above referenced articles, in our series some patients refused surgery and in the operated patients not all fistula tracks were explored prospectively during the surgery. Magnetic Resonance Imaging (MRI) with or without endocoil is a competitive technique to HPUS to visualize adequately fistula tracks. Until now, both techniques have not been compared directly but accuracy rates are comparable depending on the technique used and the type of fistula track analyzed.[19-22] The decision to use one of the visualization techniques should depend on the hospital's expertise and the accessibility of the diagnostic tool.

Presuming the diagnostic accuracy of HPUS and MRI are equal, HPUS seems more attractive considering costs.
In our study, in which we visualized the fistula tracks with HPUS, we found that never operated cryptoglandular fistulas-in-ano are trans or intersphincteric fistula. A ramification was only found in two out of 48 patients. One patient had a horse-shoe extension and another had a supralevator branch. In the latter patient, extensive abscess drainage had been performed before. It was only in the recurrent group that supra and extrasphincteric tracks were found. Similar conclusions were drawn in studies in which the fistula tracks were delineated during surgery.[14-18]
In conclusion, a never operated cryptoglandular fistula does not require any special investigation and can be treated by the standard surgical treatment. In recurrent fistulas, it is crucial to be informed about the fistula track because 43% of the fistulas are ramified or extended above the supralevator plane. Therefore, we advise hydrogen peroxide enhanced transanal ultrasound before treatment of the recurrent fistula.

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CHAPTER 12

ASSESSMENT AND CLASSIFICATION OF FISTULA-IN-ANO IN PATIENTS WITH CROHN'S DISEASE WITH HYDROGEN PEROXIDE ENHANCED TRANSANAL ULTRASOUND

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Abstract

Crohn's disease is well known for its perianal complications, among which fistulas-in-ano are the most common abnormalities. Fistulas-in-ano in Crohn's disease tend to be complex and have a high recurrence rate. Therefore, the role of surgery is generally more conservative. Hydrogen peroxide enhanced transanal ultrasound has proved to be superior to physical examination, fistulography, CT and conventional ultrasound in demonstrating the fistula tract. This study examined the fistula tracks in patients with Crohn's disease.
Forty-one patients with Crohn's disease and fistulo-in-ano were investigated using physical examination, sondage of the fistula, proctoscopy and transanal ultrasound. Hydrogen peroxide was infused via a small catheter into the fistula. The main track and the ramification of the fistula were classified according to the anatomical Parks' classification.
Only 9 (22%) patients had a single inter- or transsphincteric fistula. In 5 (12%) patients a single supra or extrasphincteric fistula (high fistula) was found, in 14 (34%) more than one fistula track (ramified) and in 13 (32%) an anovaginal fistula. Thus, 78% of patients had a surgically difficult to treat fistula. In the ramified fistula, the main track follows the Parks' classification but ramifications can have a bizarre pattern, which is not in agreement with this classification. Optimal documentation by means of hydrogen peroxide enhanced transanal ultrasound is therefore mandatory before surgery or before other therapies such as anti-TNF-treatment.

Introduction

Perianal complications occur frequently in Crohn's disease. Perianal lesions, including maceration of the perineal skin, skin tags and fissures, ulcers, anal stenosis and perianal fistulas and abscesses, are found in approximately 30-40% of the patients with Crohn's disease.[1,2] Fistulas-in-ano occur in 6-34% of the patients with Crohn's disease[3] and are the most commonly detected perianal lesions.[4] These fistulas lead to chronic complaints and are a source for abscess formation. Treatment of these fistulas-in-ano can be medical or surgical. Medical treatments include antibiotics, immunomodulators or newer compounds such as anti-TNF. Surgical treatment consists of lay-open fistulotomy, mucosa advancement, seton drainage, fecal diversion, or finally proctocolectomy. Both surgical and medical treatment are frequently complicated by recurrence. It is important before treating fistula-in-ano in Crohn's disease to be informed about the track, extensions and ramifications of these fistulas. Many fistula tracks are complex and therefore the sphincter complex will be damaged during surgery and the recurrence rate is high afterwards.

The most often used anatomical classification to describe the track of fistula-in-ano is that of Parks et al.[5] Parks et al. formulated their classification based on probing and laying open the fistula during surgery. Obtaining accurate assessment with this method is often not possible before or without surgery. Moreover, fistulas in Crohn's disease are known to be complex and do not fit into this classification.[6] New techniques have been introduced to visualize the anatomical relation between sphincters and fistula track. Transanal ultrasound clearly visualizes the sphincter tissue and the defects caused by fistula or surgery [7,8] and the combined use of hydrogen peroxide (HPUS) as a contrast agent makes transanal ultrasound highly accurate (95%) in demonstrating the fistula track. It is superior to surgery and to digital examination and transanal ultrasound without the use of hydrogen peroxide. Moreover, this microbubble containing contrast agent has also been used in hydrogen peroxide enhanced ultrasound fistulography in assessing enterocutaneous fistulas.[9] HPUS has proved to be superior than physical examination, fistulography, Computer Tomography and conventional ultrasound in demonstrating the fistula track found at surgery.[10]

The aim of the study was to document the fistula tracks in patients with Crohn's disease using HPUS applying the Parks et al. classification to describe the anatomical fistula track and the ramifications and to examine whether a new kind of classification would be more appropriate.

Materials and methods

Patients

Forty-one consecutive patients with Crohn's disease (33 women, mean age 38 years, range 24-69) with complaints of fistula-in-ano were evaluated on the proctology ward. Evaluation of the patients consisted of medical history, physical examination and sondage of the fistula, proctoscopy, and HPUS. Biopsy specimens underwent pathological examination confirmed proctitis. Table 1 shows the surgical history and the use of immunosuppressive drugs.

Hydrogen Peroxide enhanced transanal UltraSound (HPUS)

HPUS was performed using a Diagnostic Ultrasound System (type 3535, Brüel and Kjær, Naerum, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2-4.5 cm) covered by a water filled hard sonolucent cone (diameter 1.7 cm), producing a 360° view. The endoprobe was introduced into the rectum and serial radial images as well as video recordings were taken of the distal part of the rectum, the puborectalis muscle and the anal canal. The fistula track appeared as a tubelike hypoechoic lesion. A sphincter defect was seen as a hypoechoic interruption in the sphincter complex. After conventional ultrasound (US) was performed, 3% hydrogen peroxide was introduced into the fistula track with a flexible intravenous cannula (Venflon®, Ohmeda, Helsingborg, Sweden). Conventional ultrasound was then repeated as described above. The infusion of HP generated the formation of small air-bubbles and changed the fistula track from hypoechoic to bright hyperechoic. Comparison of images with and those without HP identified the track of the fistula and its extensions and allowed distinction between active fistulas and fibrotic tissue in previously operated patients. The site of the internal sphincter opening, ramification of the fistula, and the presence of the defects in one or both sphincters were also recorded carefully. The evidence of the internal opening being present was defined as a hypoechoic (conventional ultrasound) or echogenic (HPUS) breach at the level of the submucosa.[10] Transvaginal ultrasound was also performed in anovaginal or anterior fistulas; hydrogen peroxide was introduced via the external opening or the fistula opening in the introitus. [11]

The following classification is used at our unit for HPUS classification:

a) Single inter- or transsphincteric track
b) Single high track (supra- or extrasphincteric fistula)
c) Ramified fistula
d) Anovaginal fistula

The main track of the ramified fistula were classified in relationship to the sphincters according to Parks et al.[5] into:

1. Intersphincteric in which the fistula ramifies only in the intersphincteric plane
2. Transsphincteric where the fistula passes from the intersphincteric plane through the external sphincter complex at varying levels into the ischiorectal fossa.
3. Suprasphincteric where the track passes in the intersphincteric plane over the top of the puborectalis muscle, then downwards again through the levator plate to the ischiorectal fossa and finally to the skin.
4. Extrasphincteric where the track passes from the perianal skin, through the ischiorectal fat and levator muscles into the rectum, outside the external sphincter complex altogether.

Submucous fistulas are fistula where the track is subsphincteric and does not involve nor pass the sphincter complex. Anovaginal fistula have an extension toward the vaginal introitus. The complexity of the fistula tracks was

examined in relation to the biopsy-proven inflammation of the rectum (proctitis) and the activity of the inflammatory bowel disease or the use of prednison.

Results

There was no clear relationship between the complexity of the fistula and the absence of proctitis or the use of immunosuppressive drugs. (Table 1).

Single low fistula:

Five intersphincteric and four transsphincteric fistulas compromised the single low fistula. In one patient a recurrent transsphincteric fistula was found which occurred after a gracilis transplant for an anovaginal fistula and an ostomy and subtotal colectomy.

Single high fistula:

One extrasphincteric fistula was recurrent after fistulectomy, and another occurred after an extensive surgical history with pouch surgery and gracilis transplant in which the fistula towards the pouch and the transplant remained.

Ramified fistula:

Only a single patient had a recurrent transsphincteric fistula which ramified in horse-shoe shaped anterior pattern after multiple fistulectomy. The main tracks and ramifications are presented in Table 2. An example of a ramified fistula visualized with HPUS is given in Fig. 1.

Anovaginal fistula:

Two anovaginal fistulas were recurrent after previous fistula surgery. One single track and one complex transsphincteric anovaginal fistulas were recurrent after rectal mucosa advancement flap repair. Anovaginal fistulas are summarized in Table 3. An example of an anovaginal fistula visualized with HPUS is given in Fig. 2.

	n	%	M/F	Ileocecal surgery	Ostomy	STC/IAP	Rec	Proctitis		Prednison use		Imuran use	
								n	%	*n*	%	*n*	%
Single low track	9	22	3/6	1	3	1/1	1	7	77	4	44	1	11
Single high track	5	12	1/4	0	0	1/1	2	5	100	1	20	1	20
Ramified	14	34	4/10	5	2	2/0	1	7	50	7	50	6	42
Anovaginal	13	32	0/13	4	3	4/0	2	7	54	5	38	5	38
Total	41	100	8/33	10	8	8/2	6 (14%)	26	63	17	41	13	31

Table 1. Description of the fistula track, recurrences, proctitis, and prednison use in the four types of fistula. (*STC* subtotal colectomy; *IAP* Ileoanal pouch anastomosis, *Rec* recurrence after previous fistula surgery).

Main track	n	Ramification
Not classified	1	submucous web of fistula tracks without connection with the anal canal
Intersphincteric	2	1 intersphincteric horse-shoe shaped to anterior 1 multiple external fistula endings in web with the main track continuous with the supralevator space
Transsphincteric	8	2 supra or extrasphincteric branch 6 extrasphincteric horseshoe-shaped to anterior
Suprasphincteric	1	subsphincteric web with multiple external fistula endings
Extrasphincteric	2	1 fistula with two separate external fistula endings on 6 and 9 o'clock which communicated via an extrasphincteric horseshoe-shaped bridge 1 fistula with two horseshoe branches anterior and posterior continuous with the supralevator space

Table 2. Fistula-in-ano with ramifications (without anovaginal fistulas); main track was classified according to Parks et al.[5]

Anovaginal fistula	n	Ramification
Transsphincteric	3	none
Transsphincteric	2	ramified through the septum towards the perineum ramified around the vaginal introitus towards the perineum
Suprasphincteric	5	none
Suprasphincteric	3	one with two external fistula defect with a subcutaneous junction with a branch suprasphincteric and a branch towards the rectovaginal septum which ends in the vagina one with a branch to the perineal skin via the rectovaginal septum one with a supralevator branch and a contralateral horseshoe-shaped branch

Table 3: Anovaginal fistula (n = 13) and the ramifications

Ref	*n*	Subm	Inter	Trans	Low	Supra	Extra	High	Ramified	AV	Unclass	Visualisation
Marks et al.[13]	125[a]				46 (37)		2 (2)		25 (20)	33 (26)	19 (15)	Surgery
Hobbiss Schofield[14]	26				22 (85)			1 (1)			3 (11)	Surgery
Williams et al.[15]	64[b]	17 (27)	19 (30)	21 (33)	57 (90)	5 (8)	1 (1)	6 (9)	1 (1)			Surgery
Bayer and Gordon[6]	28		9 (32)	10 (36)	19 (68)				9 (32)			Surgery
Halme Sainio[16]	35	8 (23)	1 (3)	9 (26)	18 (52)			17 (48)				Surgery
McKee Keenan[17]	70				34 (48)			19 (27)			17 (24)	Surgery
Makowiec et al.[18]	90	22 (24)	4 (4)	29 (32)	55 (60)	1 (1)	5 (6)	6 (7)	14 (16)	15 (17)		US, MRI, surgery
This study	41		5 (12)	4 (10)	9 (22)	2 (5)	3 (7)	5 (12)	14 (34)	13 (32)		HPUS

Table 4. Review of literature in classification of fistula-in-ano in Crohn's disease. (n = number of fistulas; low; submucous (subm), intersphincteric (inter), and transsphincteric (trans) fistulas; High suprasphincteric, (supra) and extrasphincteric (extra) fistula; AV Anovaginal fistulas; unclass unclassified; paracentheses percentage).

[a]125 fistula were described in 112 patients

[b]64 fistula in 55 patients.

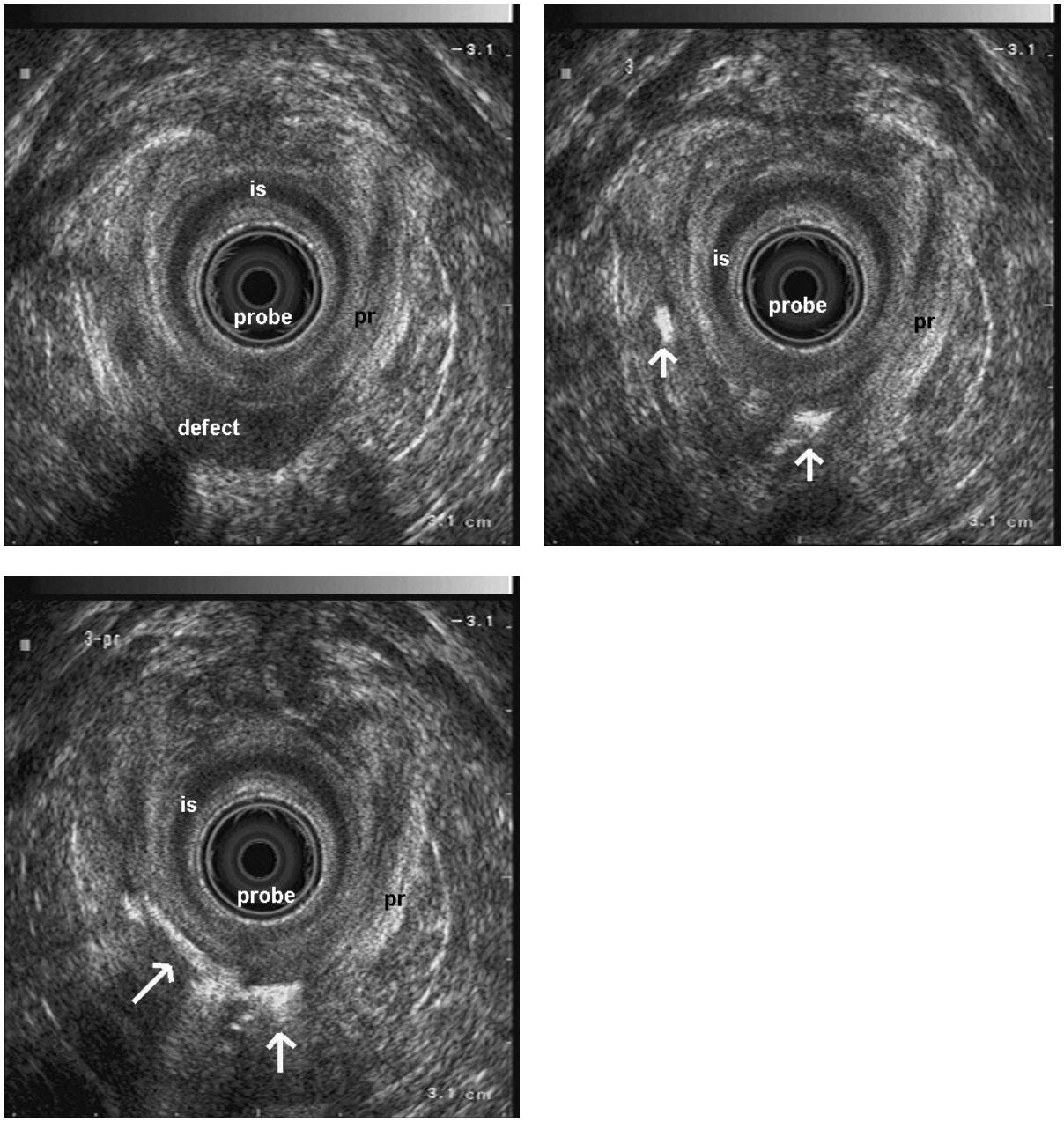

Figure 1A-C: Hydrogen peroxide enhanced transanal ultrasound shows complex fistula track in a patient with multiple external fistula openings: A) Defect is shown in puborectalis muscle (PR) suggestive for a fistula track. B,C After hydrogen peroxide is indwelled in the fistula via the external opening B, an extrasphincteric fistula (arrows) is visualized which is connected with horse-shoe shaped branch (arrows) at the level of the puborectalis muscle (PR) and with continuous branches above the levator plate C. IS internal sphincter.

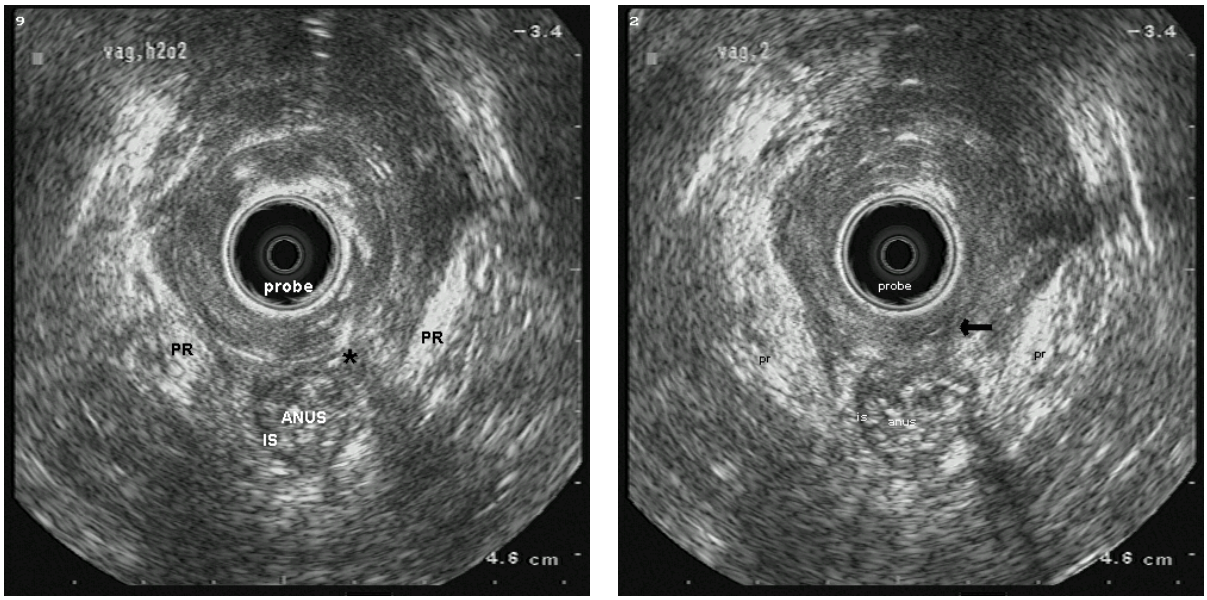

Figure 2 A) Transvaginal ultrasound shows a defect in the rectovaginal space suggestive for a fistula (Arrow). B) After injecting hydrogen peroxide in the fistulaopening which is located in the vaginal introitus, an anovaginal fistula is visualized with the fistula opening at the level of the puborectalis muscle (Asterisk). The probe is situated in the vagina, and the anus shows dorsally. IS internal sphincter; PR puborectalis muscle.

Discussion

A different pathogenesis is suggested in perianal fistulas associated with Crohn's disease than that in those without this association. The basic primary lesion in the anus is ulceration of the mucosa as a typical painless midline fissure resulting in low or intersphincteric fistulas. A second lesion is a penetrating cavitating ulcer that leads to fistulous abscess. These cavitating ulcers may be high or low depending on the level of cavitating ulcer in relation to the anorectal ring and will lead to high, complicating fistulas. Anterior ulcers in the female cause anovulval or vaginal fistulas if low and rectovaginal if high. Hughes proposed a classification of fistulas in low/superficial (e.g., perianal, anovulval or anoscrotal, intersphincteric and anovaginal) and high/complex (e.g., blind supralevator, high direct (anorectal), high complex, rectovaginal and ileoperinal). This is part of the PeriAnal Crohn's Disease index (PACD) in combination with classification of anal ulceration and stricture.[12]
Several studies have classified perianal fistulas in patients with Crohn's disease during surgery (Table 4). In a review from St. Mark's Hospital of 125 fistulas associated with Crohn's disease, 15 percent remained unclassified.[13]; low fistulas, rectovaginal fistulas and ramified fistulas occurred in fairly equal amounts. Hobbiss and Schofield[14] observed almost only low fistulas (85%). Williams et al.[15] reported principally (73%) recurrent perianal fistulas, and no ramifications were noted. Bayer and Gordon[6] classified 28 patients during surgery and had difficulties finding the connection with the anal canal; ramified fistulas were found in 32%. Halme and Sainio[16] reported a high percentage (48%) of supra- and extrasphincteric fistulas, but they did not describe the ramifications. McKee and Keenan[17] found 50% low fistulas; no ramification

was given. In the series described above low fistulas (subcutaneous, inter and transsphincteric) occurred in 28-89% of the patients with perianal fistulas, as found during surgery.
Remarkably, only one study has used visualization techniques to classify the fistulas associated with Crohn's disease. Makowiec et al.[18] investigated ninety patients proctologically and endosonographically (without hydrogen peroxide). When the anatomical fistula type was not clear, magnetic resonance imaging (MRI) was performed. In the patients who were operated on, exploration was performed during surgery. This study reported a large percentage of blind ischiorectal (submucosal) tracks. High fistulas were found in 7% and ramified fistulas occurred in 16%. These high fistulas and ramified fistulas have low healing and high recurrence rates especially if the internal opening is undetected.
Visualizing the fistula track by HPUS we found that single track, inter- or transsphincteric fistulas-in-ano accounted for only 22% of the patient with Crohn's fistulas. Supra or extrasphincteric fistulas accounted for 12% of the fistulas in our population, and 34% were ramified making the fistula track complex. In the complex fistulas the Parks et al. classification can be useful for describing the main track but not in the ramifications. Using HPUS we observed only 22% low fistulas while Makowiec et al.[18] reported 66% low fistulas, both with the limitations of a cross-sectional study. The wide differences in findings may have been caused by the selection of patients for surgery, treatment bias, and the progressiveness of the disease.
Fazio[19] classified fistulas as simple or complex, with simple fistulas being easy to diagnose and treat with fistulotomy without loss of anorectal function whereas complex fistulas are more difficult to treat because of underlying disease or already impaired anorectal function. This is the simplest clinical classification, but it does not account for the quality of sophisticated new visualization techniques. With HPUS we can distinct four kinds of fistulas: low fistulas (e.g., single track subsphincteric, intersphincteric and transsphincteric fistulas), high fistulas (e.g., suprasphincteric and extrasphincteric fistulas), ramified fistulas, and anovaginal fistulas. Different therapies should be applied in each kind of fistula. Whereas low fistulas can be treated by fistulotomy, in high fistulas this is not recommended. High fistulas can be treated by advancement flap closure; however, ramified fistulas tend to recur and drainage can be archived with seton placement. Anovaginal fistulas need more sophisticated surgery such as transanal or transvaginal flap repair, or tissue interposition.[20] Low fistulas can be treated by surgery with a good chance of healing (80%); however, in ramified fistulas a more medical treatment such as anti-inflammatory drugs is advocated or in progressive disease a protective loop ileostomy.[3,15]

The anatomical path of the fistulas predicts outcome of medical or surgical treatment. Spontaneous fistula healing can occur in 50% of the cases within 2 years. However, 44-60% have a recurrence or development of a new fistula depending on the treatment, the condition of the rectal mucosa, and the anatomical track of the fistula. Low track fistulas have a better outcome than high fistulas or anovaginal fistulas, in which after healing of the fistula, symptoms of incontinence and pain can persist.[17,18] Anal involvement in Crohn's disease is probably best managed by a combination of an aggressive

physician and a conservative surgeon.
In our study we found no relationship between the complexity of the fistulas and proctitis or the use of immunosuppressive drugs. Other series report a moderate relationship between large bowel disease and perianal disease.[6] In contrast to our study, Halme and Sainio found rectal involvement to be associated with high fistulas, while low fistulas were related to a healthy rectum; fistula track was differentiated during surgery, but unfortunately no information was given about ramification.[16] Three other studies reported a relationship between anal complications and rectal Crohn's disease.[21] Likewise, healing rates were better when fistulas were treated without rectal involvement.[17,18]
In conclusion, only 22% of the fistulas were single inter- or transsphincteric fistula in our population of patients with Crohn's disease. Suprasphincteric, extrasphincteric, ramified or anovaginal fistulas were found in 78%. Main track of the fistula-in-ano in Crohn's disease follows the Parks et al.[5] classification, but ramifications can have a completely different pattern which is not in agreement with this classification. A more clinically relevant classification is proposed in which four kinds of Crohn's disease associated fistulas-in-ano are described (e.g., low fistulas, high fistulas, ramified fistulas and anovaginal fistulas). The complexity of the fistula requires optimal documentation by means of HPUS before surgery or when other therapies are carried out such as anti tumor necrosis factor treatment.

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CHAPTER 13

ENDOSONOGRAPHIC EVIDENCE OF PERSISTENCE OF CROHN'S DISEASE ASSOCIATED FISTULAS AFTER INFLIXIMAB TREATMENT, IRRESPECTIVE OF CLINICAL RESPONSE

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Abstract

Infliximab has been reported to improve fistulizing Crohn's disease. Moreover, prompt healing of mucosal ulcers has been described. Whether fistulas disappear or remainders of fistulas persist is unknown. This study documents fistulous tracts before and after infliximab therapy by means of hydrogen peroxide enhanced endosonography

Eight patients with perianal, vaginal or perineal fistulas were treated with a triplet of infliximab 5mg/kg infusions. At baseline, and at Week 4 after the last infusion, fistulas were documented by local inspection, digital examination, and hydrogen peroxide enhanced anal or vaginal endosonography.

Patients with vaginal or perineal fistulas did not respond clinically to therapy, whereas patients with perianal fistulas improved considerably. However, in all patents, remainders of fistulous tracts were demonstrated by endosonographic techniques.

CONCLUSIONS: Short-term treatment of Crohn's disease associated fistulas with infliximab does not induce disappearance of fistulous tracts, irrespective of therapeutic response.

Introduction

Perianal fistulas constitute one of the major challenges in treatment of Crohn's disease, occurring in 10% - 33% of affected patients.[1,2] These fistulas rarely respond to medical or surgical treatment. Antibiotics may have short-term efficacy, although this has never been documented in controlled studies.[3] Immunomodulatory drugs may improve the course of fistulizing disease, but response rates are disappointing.[4-6] Infliximab, a chimeric monoclonal antibody to human tumor necrosis factor (TNF)-α, has recently been shown to be effective in patients with chronic active Crohn's disease. This clinical improvement after infliximab therapy in patients with refractory chronic active Crohn's disease is accompanied by significant healing of endoscopic lesions and disappearance of the mucosal inflammatory infiltrate.[7,8] Unfortunately, relapse of disease after a prior response to infliximab is usual.[9] In patients with fistulizing Crohn's disease, a favorable therapeutic response has been reported in 60 to 70 percent of patients after three infliximab infusions at baseline, Week 2 and Week 6, lasting for about three months.[10] The significant healing of mucosal inflammation seems contradictory to the relapsing tendency of Crohn's disease. Improvement of fistulas has only been assessed by external findings and clinical scores in patients with fistulous Crohn's disease.
Endosonographic imaging of the perianal lesions provides excellent information about the local anatomy, the presence of perianal fistulas and other abnormalities, especially when the resolution of the images is enhanced by hydrogen peroxide.[11] Also, local inflammatory changes can be assessed reliably.[12] These endosonographic findings correlate well with surgical findings.[11,13] We report the anatomic findings in patients with perianal or vaginal fistulizing Crohn's disease who were treated with infliximab to evaluate treatment response in relation to local inflammatory changes.

Patients and methods

Patients

Eight patients were included, all with Crohn's disease, complicated by longstanding vaginal or perianal fistulas, refractory to a wide range of medical and surgical therapies. These patients from a third-line referral clinic were enrolled in a compassionate use program with the chimeric monoclonal anti-TNF-α antibody infliximab. Four patients had perianal fistulas, three had rectovaginal fistulas and one had a fistula from the perineum to the cavum Douglasi. Crohn's disease was diagnosed based on typical clinical, histopathologic, radiologic and endoscopic findings. Patient characteristics and baseline therapy are described in Table 1. Prior to therapy, patients were screened by physical examination, routine laboratory analysis and endoscopy. Four patients used ciprofloxacin. The patients without current maintenance treatment were treated with immunosuppressives in the past, but this treatment was discontinued because of adverse events or refractory disease.

Patient No./site	Age and gender	Years of CD	History	Treatment
1 V	28F	9	• 1993, subtotal colectomy + pouch • 1995, enterocutaneal fistula, followed by fistulectomy/pouchectomy • 1996, abscess in cavum Douglasi fistulizing to vagina • 1998, correction of fistula by M gracilis plasty into pelvis, complicated by enterocutaneal fistula left upperleg, and recurrence of fistula	-
2 V	28F	13	• 1992, ileocoecal resection • 1994, perianal fistula • 1999, diverting ileostomy, perianal and rectovaginal fistulas	AZA steroids
3 V	51F	20	• 1989, rectovaginal fistula	-
4 Pe	30F	9	• 1994, perianal fistulas • 1995, subtotal colectomy, complicated by rectovaginal fistula • 1996, ileostomy • 1997, proctectomy	-
5 PA	36F	12	• 1993, perianal fistula, and diverting ileostomy • 1994, diversion colitis • 1998, reanastomosis, followed by relapse of perianal fistulas	-
6 PA	38M	15	• 1986, ileocoecal resection • 1991, entero-enteral fistula , resection neoterminal ileum • 1998, liverabscess • 1999, perianal fistulas	AZA steroids
7 PA	40M	19	• 1984, perianal fistula • 1985, subtotal colectomy / ileostomy	AZA
8 PA	38F	13	• 1990, perianal fistula / anal stenosis	local steroids

Table 1. Patient characteristics and Crohn's disease history
Patient 1-3 suffered from rectovaginal fistulas (V), patient 4 had a perineal fistula (Pe). Patients 5-6 had perianal fistulas (PA). F = female, M = male, AZA = azathioprine.

Methods

The perianal region was examined by local inspection, digital examination, proctoscopy and conventional photography.
Anal endosonography was performed using a Diagnostic Ultrasound System (type 3535, Brüel and Kjær, Naerum, Denmark) with a 7 MHz rotating endoanal probe (type 1850, focal range 2-4.5 cm) covered by a water filled hard sonolucent cone (diameter 1.7 cm), producing a 360^0 view. Hydrogen peroxide was used as a contrast agent to demonstrate the anatomy of fistulous tracts.[11,12,14] In females,

vaginal endosonography was performed optionally in case of pain, and of stenosis, or to obtain additional information.[15]
Perianal fistulas were classified according to Parks et al.[16]: whether the primary tract was intersphincteric, transsphincteric, suprasphincteric or extrasphincteric. In addition, secondary extensions were described, such as horseshoe, supralevatory, or infralevatory (including superficial subcutaneous extensions, for example to the scrotum). Rectovaginal fistulas were described separately. The presence of rectal involvement was based on a combination of endoscopic and histological findings.

Treatment protocol

Infliximab (Remicade®, Schering Plough, Brussels, Belgium) was administered in a dose of 5 mg/kg as a two-hour intravenous infusion at baseline, at Week 2 and at Week 6. Concomitant therapy was continued and steroids were tapered when possible.
Treatment response was evaluated by the treating physician. A fistula was considered to be closed when it did no longer drained despite local compression. The fistula was considered to be non-responsive when the production of the fistula did not change, and intermediate responsive when the drainage was significantly reduced.
The patients were reevaluated at Week 10 after baseline, *i.e.*, four weeks after the third infusion with infliximab. Reinfusion of another triplet with infliximab intravenously was allowed after established therapeutic response.

Results

Rectovaginal fistulas and perineal-cavum Douglasi fistula

Three patients (numbers 1, 3, and 4 in Table 2) did not respond at all, whereas in one patient with a vaginal fistula (number 2) a decrease of fistulous discharge was noted. Retreatment with another triplet of infliximab infusions of the latter patient did not provide further improvement. Anal endosonography showed unaltered sphincter defects and persistent fistulas. Local and endosonographic findings in the examined patients are described in Table 2.

Perianal fistulas

In one patient (number 7 in Table 3), fistulas closed completely, and in the other three patients (numbers 5,6 and 8) more than 50% of fistulas closed and fistulous discharge decreased greatly. In addition, these patients experienced a higher level of daily activities because of a feeling of increased energy within a few days time. The therapeutic benefit lasted for an average of 10 weeks in three patients. They needed another triplet of infusions. An extended therapeutic benefit was noted in two of these patients. In the third patient, the fifth infusion of infliximab induced drug-induced lupus-like arthritis and further infliximab therapy was withdrawn. The fourth patient had ongoing therapeutic benefit.

Local and endosonographic findings in the examined patients are described in Table 3.
Figure 1 shows a favorable clinical response to infliximab (Patient 7 in Table 3). Figure 2 depicts ultrasonographic findings in this patient with a transsphincteric fistula, whereas Figure 3 shows another patient with a transvaginal fistula, nonresponsive to infliximab (Patient 3 in Table 2).

Adverse events

Adverse events occurred in 6 out of 8 patients. These consisted of non-productive coughing in two patients, nausea in two patients, general malaise and myalgia in one patient and exanthema in another patient. One patient had transient conjunctivitis and later arthritis, probably as a result of drug-induced lupus and one patient developed a pyoderma, mainly localised in the face in areas with pre-existent eczema. Serious adverse experiences did not occur.

Technique	Findings at Baseline	Findings After Treatment
patient 1; vaginal fistula		
External	scars perineum, one fistula opening	*identical external and endosonographic findings*
endo*vagina* / H_2O_2	defect of IAS and EAS fistulous tract to postsurgical remainings of rectal cavity	
patient 2; vaginal fistula		
external	one draining fistula opening, anal stenosis	*one nonproducing fistula opening unaltered*
endo *vaginal*	rectovaginal fistula through anterior IAS, EAS, and PRM. Pararectal fistulous tract,	
H_2O_2	with fluid-filled cavity. not performed	*fistulous tract with midsphincteral split; tracts towards anus and perforating the vaginal septum*
patient 3; vaginal fistula		
external	Vulvar fistula; perineal skintag; rectal stenosis with fissura	*identical*
endo	Lateral and anterior defects of IAS, EAS and PRM	*unaltered*
H_2O_2	not performed	*fistulous tract from vulva through septum to rectum (Figure 3).*
patient 4; perineal fistula to cavum Douglasi		
external	no fistula opening visible	*identical external and endosonographic findings*
endo	defects of IAS, EAS and PRM	
H_2O_2	No external fistula opening	

Table 2. Perianal and endosonographic findings in three patients with recto-vaginal fistulas, and one patient with perineal-cavum Douglasi fistula

Technique	Findings at Baseline	Findings After Treatment
patient 5		
External	two draining fistulas	*fistulas closed, perianal scar*
Endo	defects of IAS, EAS and PRM	*identical defects, small fluid-filled cavity at level of PRM*
H_2O_2	pararectal, horseshoe shaped fistulous tract with extrasfincteric split at level of PRM, horseshoe shaped; no interior opening.	*no fistula opening.*
patient 6		
External	scars at perineum, rectal stenosis; two fistula openings perianal.	*identical*
endo	defects of IAS, EAS and PRM.	*identical*
H_2O_2	transsfincteral fistulous tract towards M supralevator level; no internal opening.	*one fistula opening closed; identical fistulous tract.*
patient 7		
External	three fistulas, one subcutaneous nodule	*two fistulas, one closed. Anal fissure (Figure 1).*
endo	two defects EAS	*identical*
H_2O_2	communicating fistulous tracts with IAS opening at level of PRM	*one opening closed, fistulous tract identical (Figure 2).*
patient 8		
external	7 fistulous tracts from perineum, 5 draining	*identical, but discharge decreased; 2 out of 7 fistulous tracts open.*
endo*vagina*		*identical*
l	multiple defects dorsal of IAS and EAS	*identical appearance*
H_2O_2	7 communicating fistulous tracts; 4 to right, and 3 to left nates	

Table 3. Perianal and endosonographic findings in patients with perianal fistulas IAS internal anal sphincter, EAS external anal sphincter, PRM puborectal muscle.

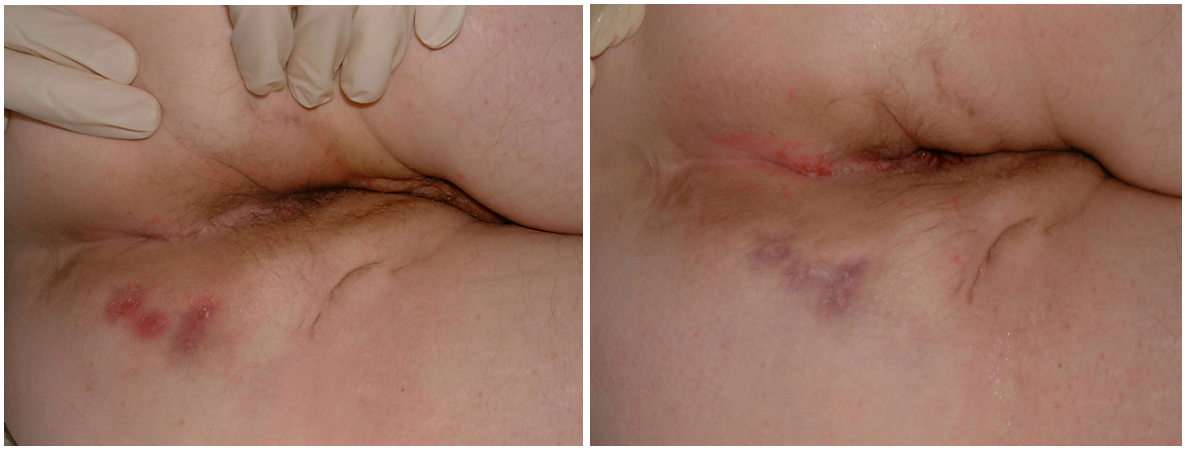

Figure 1. Reduction of inflammation after administration of Infliximab in patient 7.

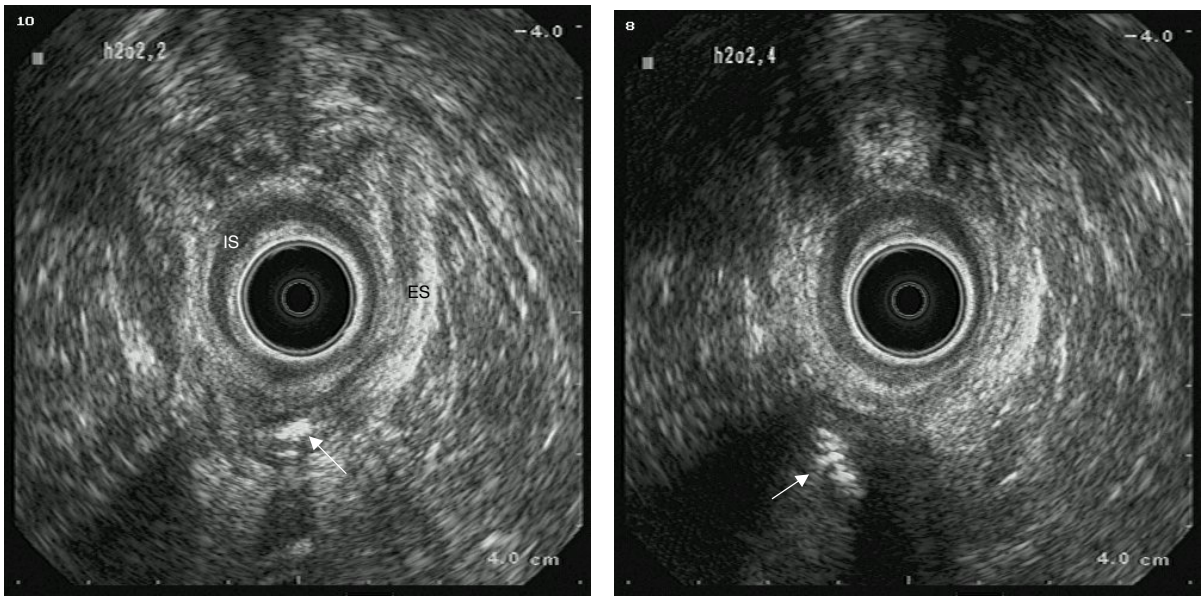

Figure 2. Transanal ultrasonography with peroxide introduced via the external fistula opening in patient 7 showing a transsphincteric fistula (arrow left picture) with a supralevetor extension (arrow right picture). IS internal sphincter; ES external sphincter.

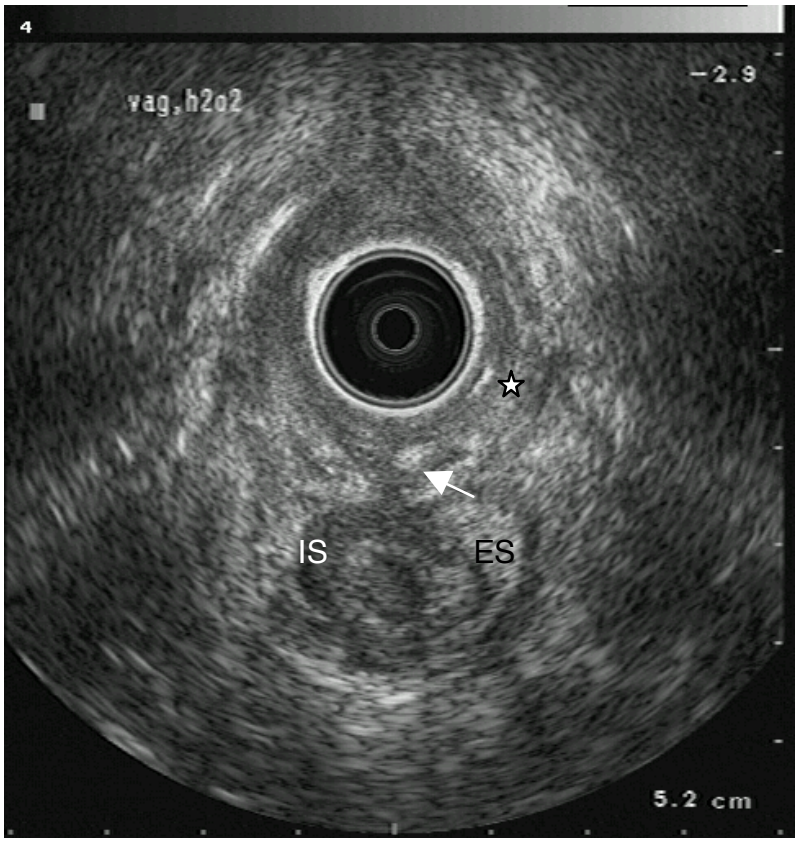

Figure 3. Transvaginal ultrasonography with hydrogen peroxide infused via the fistulaopening in the introitus (astriks) showing a transsphincteric anovaginal fistula (arrow) in patient 3. IS internal sphincter; ES external sphincter

Discussion

Therapeutic efficacy of infliximab in patients with fistulizing Crohn's disease seems to be dependent on the nature of the fistulous tracts: in Crohn's disease complicated by vaginal fistulas, a disappointing lack of efficacy was found in all four patients, whereas in Crohn's disease associated perianal fistulas, significant improvement of complaints was noted.

Reports concerning the efficacy of infliximab in treatment of vaginal fistulas are sparse. Controlled studies are not available. This subgroup of patients however may have a less favorable response to infliximab, as compared with the results reported in patients with perianal fistulas.[17,18] A clear explanation of this poor therapeutic response is lacking. It may be due to the specific anatomical site; rectovaginal fistulas penetrate the thin rectovaginal septum, devoid of extensive vascularisation or abundant muscle tissue. Even in patients without Crohn's disease rectovaginal fistula are often refractory to treatment. Conservative treatment can be expected to fail. Surgical therapy is difficult and requires often an interponate to prevent recurrences.[19] Another explanation may be that rectovaginal fistulas may have a different pathogenesis that is less characterized by TNF-alpha mediated inflammatory changes. For example, two patients had prior local rectal surgery, which may be complicated by formation of fistulas.

Patients with perianal fistulas who participated in this study responded favorable to treatment, as has been documented before.[10] The increase in daily activities and improvement of wellbeing that patients who respond characteristically experience may indicate that decrease of serum TNF-α plays a pivotal role.

Endosonographic images in patients with rectovaginal fistula, and the one with a perineal fistula were unaltered. This was not unexpected because a clinical response was lacking too. Surprisingly, even in patients with perianal fistula who had significant clinical improvement, the pictures were almost identical. The endosonographic differences concerned mainly closure of external fistula opening(s) and collapse of the particular side-branch, connected to the fistula opening. The fistula tract was invariable present. This may explain the recurrence: although inflammation was suppressed by infliximab, local disease activity could persist due to concomitant infection in the remnants of the fistula tracts. In this respect, fistulizing perianal Crohn's disease differs from other forms of chronic active Crohn's disease, where healing of ulcers occurs shortly after treatment with infliximab.[7,8]

In conclusion, the findings of this study show that the anatomic substrate of fistulas complicating Crohn's disease do not disappear irrespective of the clinical response to infliximab. This finding indicates that long-term prolongation of infusions with infliximab can be expected, once infliximab is started as a therapy for fistulas complicating Crohn's disease. The demonstrated persistence of fistulous tracts after infliximab therapy may necessitate a different therapeutic approach than drug therapy only. One could postulate that a long-term treatment with infliximab, combined with restorative surgery, may improve outcome.

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CHAPTER 14

SUMMARY AND CONCLUSIONS

Summary

Chapter 1 contains the aims of the thesis. This thesis consists of two parts. In part one, the study of rectal visceral sensitivity, compliance and motility in health and disease is described. In part two, the study of the anatomy of cryptoglandular and Crohn's disease associated fistulas-in-ano using the transanal ultrasonography is described.

Part 1. Rectal visceral sensitivity and motility.

Chapter 2 consists of a retrospective study of latex balloon rectal compliance measurement, which was performed to establish the differences in rectal sensitivity and compliance in different patient groups compared to controls and to establish the clinical effect of rectal compliance measurement. In 974 consecutive patients rectal compliance measurement was performed with a water-filled latex balloon. Volume and intra-balloon pressure were registered. At three sensitivity thresholds, volume and pressure were noted for analysis: first sensation, urge and maximal toleration. At maximal toleration, the rectal compliance (Volume/pressure) was calculated. Rectal compliance measurement with a latex balloon is easily feasible. Some patient groups show an abnormal rectal visceral sensitivity and compliance, but there is an overlap with controls. Rectal compliance measurement gives a good impression about the contribution of the rectum to an anorectal problem. Patients with proctitis and pouchitis have the smallest rectal compliance. A maximal tolerated volume less than 60 ml always leads to faecal incontinence and a stoma should be considered. A maximal tolerated volume more than 500 ml is only seen in constipated patients and therapy should be given to prevent further damage to the pelvic floor. Values close to or within the normal range rule out the rectum as an important factor in an anorectal problem of the patient.

Chapter 3 describes the use of a new technique, the barostat, for testing of rectal sensitivity and compliance. The barostat is a device that maintains a constant pressure within an air-filled polyethylene bag (sandwich bag) by means of a feedback mechanism. The system measures variations in rectal tone, by recording changes in the intrarectal pressure and volume. Different procedures, such as ramp or intermittent distension, are used to test visceral sensitivity and rectal wall compliance can be calculated. The study was performed to establish possible differences between the ramp and intermittent distension, between the barostat method and the conventional latex balloon method and the effect of gender and age. Therefore, 28 healthy persons, 11 men and 17 women, were subjected to barostat procedure consisting of continuous and intermittent pressure rectal distension with registration of Visual Analogue Scores (VAS). Furthermore, a continuous volume distension was performed in order to compare with the results of the latex balloon distension. Compliance curves and hysteresis (comparing area under the pressure volume curve during deflation and inflation with ramp pressure distension) were calculated. The different distension procedures did not influence VAS or the S-shaped compliance curve. Males had

larger volumes at the same pressures and larger compliance than females, however, VAS was not different. Hysteresis was smaller in males. Older females had larger hysteresis than younger females. A systemic difference was found between distension with the water-filled latex balloon and with an air-filled polyethylene bag. Since the intermittent and continuous procedures were not different in VAS or compliance curve, a simplification of the procedure is suggested. Men and women are different in their rectal characteristics, which means that gender-matched controls should be used.

Chapter 4 studies the gastro-rectal response that consists of a prompt increase in colonic tone after a meal. With the barostat system, it is possible to measure rectal tone by recording changes in volume at a constant intrabag pressure. The gastro-rectal response was defined as a 10% decrease in volume within the first hour after ingestion of the meal. In this study the gastro-rectal response was evaluated in 33 healthy volunteers (11 males 11 women without childbirth and 11 women with childbirth). In addition, the effect of different caloric loads (600 kCal or 1000 kCal) was studied. A gastro-rectal response occurred in 64% of the healthy subjects after a 600 kCal meal. The gastro-rectal response was to a similar extend in men and nulliparous women, however, the response was significantly impaired in parous women. This could be due to neurogenic damage after childbirth. Increasing the caloric load did not increase the gastro-rectal response. Therefore, to study gastro-rectal meal response with the barostat a caloric meal of 600 kCal is sufficient and a correction for parity should be made when results are compared.

Chapter 5 presents a study in which the claim of smokers and coffee-users is investigated that these habits facilitate bowel movements. The effect of coffee and nicotine on rectal tone and sensitivity was studied in two groups of 8 healthy volunteers using the rectal barostat. After a continuous volume distension and continuous pressure distension with registration of compliance and visceral sensations, an isobaric procedure was performed. After 30 min of adaptation, 280 ml strong coffee or warm water was given in one experiment (randomly on separate days) and 2 mg sublingual nicotine or placebo in a second experiment, followed by 60 min of volume registration. Continuous pressure distension was repeated. Rectal tone increased significantly after coffee (45%) and warm water (30%) intake, however, the differences between both were not significant. This suggests that the increase in tone is an effect from the gastric volume load, and in a minor extent due to the caffeine-compound of coffee. Neither nicotine nor placebo influenced rectal tone. After coffee, warm water, nicotine, and placebo, rectal sensitivity was decreased suggesting that other factors were of influence (such as two hours of bed-rest).

Chapter 6 outlines the study in which 30 women with idiopathic constipation are subjected to rectal barostat testing. Their results are compared to 22 healthy women. Patients with idiopathic constipation are categorised into slow transit, pelvic floor dysfunction and irritable bowel syndrome, however, considerable overlap between these groups exists. Aim of this study was to establish

abnormalities in rectal function in women with idiopathic constipation using rectal visceral sensitivity, compliance and motor function measurement (postprandial response, PPR) and anal manometry. Paradoxical Sphincter Contraction (PSC) was demonstrated with anal manometry as a paradoxical increase of anal pressures (>10 mmHg) during straining. Abnormal rectal sensitivity or compliance was found in 90% of the patients with in 35% a lax (normo- or hyposensitive, high compliance), in 27% a hypersensitive (hypersensitive, low or normal compliance), in 17% an insensitive (hyposensitive, normal or low compliance) and in 10% a stiff rectum (normosensitive, low compliance). The PPR was not significantly different between patients with constipation and controls, however, PVE's were diminished in patients. The PPR was almost absent in parous patients and parous controls, and in patients with rectal hypersensitivity. Patients with PSC had higher rectal sensitivity but with unaltered compliance and PPR. The traditional subdivision of patients with idiopathic constipation in slow transit, pelvic floor dysfunction and irritable bowel syndrome seems to be an oversimplification and a more mixed population exists. Categorisation based on rectal characteristics is possible in a lax, hypersensitive, insensitive and a stiff rectum.

Chapter 7 describes anorectal function tests in patients with a rectocele and a disturbed defecation pattern scheduled for surgery. Anorectal function was studied in these patients to explore differences with healthy females and to establish the prognostic value of anorectal function tests for rectocele repair outcome. Patients were evaluated before and after a posterior colporrhaphy using questionnaires, anal manometry, rectal visceral sensitivity and compliance measurements, postprandial rectal response (only pre-operative) and colonic transit time measurement using radio-opaque markers. Five patients had a 2nd degree and nine a 3rd degree vaginal wall prolapse. Rectocele patients had high maximal basal pressures and large sphincter lengths, low maximal squeeze pressures and lower sensitivity scores than controls. The rectal compliance curves were similar. Postprandial rectal responses in rectocele patients similar to parous controls were diminished compared to nulliparous controls. After repair (8 months range 3-14), gynaecological examination showed a rectocele of 2nd degree in four patients. Straining, rectal evacuation, manual support of the pelvic floor during straining and protrusion were improved, however, defecation frequencies and stool consistencies were unaltered. Anal pressures, compliance-curves, visceral sensitivity and colonic transit times were unaltered after the rectocele repair. This study shows that rectocele repair improved complaints of evacuation disorder and protrusion, however, defaecation frequency, stool consistency and laxative use were not influenced. Anorectal function test results remained unaltered after rectocele repair. Therefore, selection of patients for rectocele repair should be performed based on evacuation and protrusion complaints, instead of the results of anorectal function or colonic transit time.

Chapter 8 studies the effect of colonic intraluminal contents on colon transit both in 10 healthy women and in 25 women with constipation. Colonic transit time measurement using radio-opaque markers is a progressively used and easy

to perform test to study the passage of intraluminal contents throughout the colon. Overall colon transit time (CTT) as well as segmental transit times (right (RTT), left (LTT) and rectosigmoid (RSTT)) can be calculated. Colonic transit time could be influenced by faecal impaction in patients with chronic constipation due to slow transit or dyssynergic defecation. This was studied by comparing the colonic transit in an unprepared situation and in a situation after bowel cleansing. Colonic intraluminal contents have a substantial effect on colonic transit. In female controls, bowel cleansing shortened rectosigmoid transit. Women with constipation, due to slow transit or dyssynergic defecation, also showed faster transit in the cleansed state, however, the distribution of markers was not altered. Despite of the bowel cleansing effect on colonic transit time, it seems unnecessary to prepare the bowel in clinical practice because the differentiation of patients between slow transit constipation and outlet obstruction is not changed. However, because in an irregular defecation pattern the influence of faecal impaction is considerable, CTT should be applied with caution when critical clinical decisions are made in the treatment of constipation.

Chapter 9 Prucalopride is a new 5-HT-4 agonist that stimulates bowel motility in healthy volunteers. A double blind randomised cross-over study was performed to investigate the effects of prucalopride (1mg and 2 mg daily) on colonic transit time, anorectal function and complaints in 28 patients with chronic constipation. Prucalopride 1 mg compared to placebo significantly increased the mean number of bowel movements per week and improved consistency of the stools and straining. There was a tendency of decreased mean total CTT with Prucalopride compared to placebo ($P = 0.074$). No statistically significant effects were found in any of the anorectal function parameters. From this study, prucalopride seems to be safe and effective in improving bowel habits and colonic transit time of patients with chronic functional constipation and therefore has potential in the management of chronic constipation.

Chapter 10 is a review of the current literature on rectal function tests. A variety of tests, comprising visceral sensitivity, compliance, tonic response and phasic contractility (barostat), colorectal motility (barostat or manometry), colorectal transit (radio-opaque or scintigraphic markers), can demonstrate abnormalities in patients with colorectal disorders. However, a substantial overlap with healthy controls exists. Most research has been focussed on functional constipation and IBS.

Part 2. Anal endosonography and fistula-in-ano

Chapter 11 studies the generally used Parks' classification (inter, trans, supra and extra sphincteric) to describe the anatomical track of fistulas-in-ano in cryptoglandular disease. The frequency in which these types occur and whether visualisation is necessary is still unknown. Hydrogen peroxide enhanced transanal ultrasound (HPUS) is a well-established technique to demonstrate fistula tracts and correlates very well with findings during surgical exploration. Therefore, HPUS images were reviewed to investigate the fistula track in never

operated (n = 48) and recurrent (n = 33) cryptoglandular fistulas. All never operated cryptoglandular fistulas-in-ano were inter or transsphincteric. An extra track was found in 5%. Recurrent fistulas-in-ano were supra or extrasphincteric in 15% and ramified in 27%. Therefore, never operated fistulas-in-ano do not require any special investigation before surgical treatment. However, before treating recurrent fistulas, visualisation by HPUS is recommended to detect supra or extrasphincteric fistulas or ramification.

Chapter 12 describes the anatomical track of Crohn's disease associated fistula-in-ano. These fistulas are feared since surgical correction occurs frequently with recurrence and faecal incontinence. This study was performed to document the fistula tracks in forty-one patients with Crohn's disease using hydrogen peroxide enhanced transanal ultrasonography studies. Only 22% of the patients appeared to have single inter- or transsphincteric fistula. In 12% of the patients single supra or extrasphincteric fistula (high fistula) was found. 34% of the patients showed ramified fistula (more than one fistula track) from which the main track follows the Parks' classification but these ramifications had a bizarre pattern, which is not in agreement with this classification. An anovaginal fistula was found in 32%. Thus, 78% of patients had a surgically difficult to treat fistula. Therefore, optimal documentation by means of hydrogen peroxide enhanced transanal ultrasound is mandatory before surgery or before other therapies such as anti-TNF-treatment.

Chapter 13 Infliximab (a chimeric monoclonal antibody to human tumor necrosis factor, TNF-alpha) is a new compound to treat Crohn's disease. The effect of three infusions of infliximab (5mg/kg) is studied in an open label trial in eight patients with Crohn's disease associated fistula-in-ano using hydrogen peroxide enhanced transanal ultrasound. Patients with vaginal or perineal fistulas did not respond clinically to therapy, whereas patients with perianal fistulas improved considerably. However, in all patients, remainings of fistulous tracts were demonstrated by endosonographic techniques.
Therefore, short-term treatment of Crohn's disease associated fistulas with infliximab does not induce disappearance of fistulous tracts, irrespective of clinically therapeutic response. Probably, infliximab is more effective in combination with other therapies such as antibiotics or surgery.

Conclusions and recommendations

Part 1. Rectal visceral sensitivity and motility.

Rectal visceral sensitivity and compliance measurements are of importance in patients with benign rectal disorders. The water-filled latex balloon technique to distend the rectum is an easy to perform method to detect crude dysfunction of the rectal perception and compliance. It gives a quick impression whether the rectum causes complaints of faecal incontinence (a maximal tolerated volume of less than 100 ml) or whether the rectum is part in a constipation syndrome (maximal tolerated volume of more than 500ml).

Compared to the new technique, the barostat, there is a systematic difference in results. The barostat consists of a highly compliant bag and a distension device with a feedback mechanism. With this apparatus it is possible to perform different procedures such as ramp or intermittent distensions, or pressure, volume, or wall tension controlled distensions. However, in healthy controls, no differences were found between the ramp and intermittent distensions in compliance or visceral sensitivity. Pressure was a better parameter for visceral sensitivity than volume or wall tension. Therefore, it seems reasonable to perform only a single distension method, ramp or intermittent, pressure controlled in order to study compliance and visceral sensitivity. Males and females have different compliance and therefore gender-matched controls should be used in studies.
Since the barostat can provide a constant pressure in the bag, rectal tone can be measured as changes of volume in course of time. Also, phasic volume events (PVE; volume decreases during 15-60 seconds) as representative of peristaltic waves can be measured. A 600 kCal or a 1000 kCal meal equally increases rectal tone and PVE's. Males and nulliparous females show a gastro-rectal response, however, in parous females this response was absent, possibly due to neurogenic damage during childbirth. Coffee use increases rectal tone even as warm water, however nicotine in the dose of 2mg does not influence rectal tone. Visceral sensitivity is not altered after coffee or nicotine in this setting.
Patients with idiopathic constipation can be classified according to their rectal characteristics in lax, hyposensitive, hypersensitive, stiff or normal. In our population, most frequent were lax and hypersensitive. Hypersensitivity is a biological marker of Irritable bowel syndrome (IBS), however, is also present in constipated patients. The gastro-rectal response is decreased in constipated patients, even in nulliparous constipated patients.
Anorectal function in patients with a rectocele and constipation is characterized by a high rest pressure and long sphincter length together with diminished squeeze pressures. Postprandial tone response is absent in these (parous) patients. Rectocele repair (posterior colporraphy) improves complaints of protrusion and rectal evacuation. Anorectal function and colonic transit were not altered after surgery. Rectal visceral sensitivity and compliance measurement can obtain a place in clinical practice when specific medical treatment is selected for rectal hypersensitivity. The gastro-rectal response is not clinically useful since this response is already absent in parous females. Rectocele patients should be selected on complaints of evacuation and protusion and not on anorectal function or colonic transit time.
Colonic transit time measurement with radio-opaque markers gives an impression about the transit of intraluminal contents through the colon. Colonic contents influence transit time since it is accelerated after bowel cleansing. Both women with slow transit as well as women with dyssynergic defecation show shortening of colonic transit time after bowel cleansing. In women with an irregular defecation pattern, colonic transit time measurement can be influenced by colonic intraluminal contents (impaction), which make this test less reliable. Colonic transit time can be used as a parameter to study effectiveness of enterokinetic drugs. Prucalopride (a 5-HT4-agonist) improves bowel habits and

colonic transit in patients with idiopathic constipation without effecting anorectal function test results.

Part 2. Anal endosonography and fistula-in-ano.

Hydrogen peroxide enhanced transanal ultrasonography is a well-established technique to visualize fistula tracks. In patients with cryptoglandulair disease without prior operation, fistula tracks were inter and transsphincteric, and ramification occurred in only 5%. In recurrent fistula, however, the tracks were complex in 42% and therefore requesting visualisation before surgical treatment. Crohn's disease associated fistulas always require visualisation before surgical treatment since 78% is complex. In Crohn's disease associated fistula, Infliximab treatment improves complaints of fistula-in-ano, but not of anovaginal fistulas. Fistula tracks were still present when visualized using hydrogen peroxide enhanced transanal ultrasound.

SAMENVATTING EN CONCLUSIES

Samenvatting

Hoofdstuk 1 bevat het doel van dit proefschrift. Het proefschrift bestaat uit twee delen. In het eerste gedeelte wordt de rectale viscerale sensitiviteit, compliantie en motiliteit bij gezonden en patiënten beschreven. Het tweede gedeelte beschrijft de anatomie van cryptoglandulaire en Crohnse fistels, onderzocht met anorectale endoechografie.

Deel 1. Rectale viscerale sensibiliteit en motiliteit.

Hoofdstuk 2 bestaat uit een retrospectieve studie van verschillende patiëntengroepen naar de resultaten van rectale compliantie meting met behulp van de latex ballon. Het doel was om de verschillen in rectale sensitiviteit en compliantie tussen verschillende patiëntengroepen en gezonden te bekijken en om de klinische relevantie van de rectale compliantie meting te bepalen. In 974 achteropeenvolgende patiënten werd rectale compliantie meting verricht met een door water opgevulde latex ballon. Volume en druk werden genoteerd als de patiënt de volgende drempels aangaf: eerste gevoel, aandrang en maximaal verdraagbaar. Op het niveau van maximaal verdraagbaar werd de compliantie berekend (Volume/druk). Rectale compliantie meting met een latex balloon is eenvoudig. Enkele patiëntengroepen tonen abnormale rectale viscerale sensitiviteit en compliantie, echter, er is een overlap met gezonden. Rectale compliantie meting geeft een goede klinische impressie over het aandeel van het rectum in het functionele anorectale probleem. Patiënten met proctitis en pouchitis hebben de kleinste compliantie. Een maximaal verdaagbaar volume van minder dan 60 ml leidt altijd tot fecale incontinentie. Bij deze patiënten zou een stoma zou overwogen moeten worden. Een maximaal verdraagbaar volume van meer dan 500 ml wordt slechts gezien bij patiënten met obstipatie. Deze patiënten zouden behandeld moeten worden om verdere schade aan de bekkenbodem te voorkomen. Waarden dicht of binnen het normale bereik sluiten het rectum uit als belangrijkste oorzaak van de klachten.

Hoofdstuk 3 beschrijft het meten van rectale sensitiviteit en compliantie middels een nieuwe techniek, de barostat. De barostat is een apparaat dat binnen een gesloten systeem een met lucht gevuld polyethylene zakje (boterhamzakje) op een constante druk kan houden door een feedback mechanisme. Het systeem meet variaties in rectale tonus door registratie van veranderingen in druk en volume. Verschillende protocollen zoals continue of intermitterende distensie worden gebruikt om viscerale sensibiliteit en compliantie te bepalen. Deze studie werd verricht om te bekijken of er verschillen zijn tussen de barostat methode en de hiervoor genoemde latex ballon methode, tussen de continue en intermitterende procedures, alsmede het effect van leeftijd en geslacht. Hiervoor werden 28 gezonde mannen (11) en vrouwen (17) onderworpen aan een barostat meting bestaande uit een continue en intermitterende drukgestuurde rectale distensie met registratie van de viscerale sensibiliteit (VAS). De continue volumegestuurde distensie registratie met de barostat werd vergeleken met de latex ballon methode. Compliantie en hysteresis (quotiënt van de oppervlakte

onder de druk-volume-curve tijdens deflatie en inflatie) werden berekend. De verschillende inflatie protocollen gaven geen verschil in de gerapporteerde viscerale sensitiviteit of the S-vormige compliantie curve. Mannen hadden grotere volumina bij de drukken en een grotere compliantie dan vrouwen, echter, de viscerale sensitiviteit was niet verschillend. Hysteresis was kleiner bij mannen. Oudere vrouwen hadden een grotere hysteresis dan jongere vrouwen. Er was een systematisch verschil tussen de barostat met de hoog compliante lucht opgeblazen ballon en de methode met de water gevulde latex ballon. Omdat beide distensie procedures niet verschillen in resultaat kan worden volstaan met een van beide. Mannen en vrouwen verschillen wat betreft hun rectale karakteristieken, hetgeen betekent dat bij het vergelijken van resultaten, voor geslacht gepaarde controle waarden moeten worden gebruikt.

Hoofdstuk 4 bestudeert de gastro-rectale reflex welke bestaat uit een directe toename in tonus van het rectum na een maaltijd. Met het barostat systeem is het mogelijk om rectale tonus te meten door registratie van veranderingen in volume bij een constante druk in de ballon. De gastro-rectale respons wordt gedefinieerd als een afname van meer dan 10% in volume binnen een uur na inname van de maaltijd. In deze studie werd de gastro-rectale respons geëvalueerd bij 33 gezonde vrijwilligers (11 mannen, 11 vrouwen zonder en 11 vrouwen met kinderen). Daarnaast werd het effect van verschillende calorische maaltijden (600 of 1000kCal) bestudeerd. Een gastro-rectale respons werd gevonden in 64% van de proefpersonen na een 600kCal maaltijd. De gastro-rectale respons was even groot in mannen en nullipara vrouwen, echter bij vrouwen met kinderen was de respons significant afgenomen. Mogelijk komt dit door neurogene beschadiging tijdens de bevalling. Een hogere calorische waarde van de maaltijd leidde niet tot een grotere respons. Daarom lijkt een 600kCal maaltijd voldoende bij het bestuderen van de gastro-rectale respons met de barostat. Bij het vergelijken van resultaten zou gecorrigeerd moeten worden voor pariteit.

Hoofdstuk 5 presenteert een studie waarin de stelling van rokers en koffie-drinkers wordt getoetst dat deze gewoonten de stoelgang bevorderen. Het effect van koffie en nicotine op de rectale tonus en viscerale sensibiliteit werd bestudeerd bij twee groepen van acht gezonden met behulp van de barostat. Na continue volume distensie en continue druk distensie met registratie van compliantie en viscerale sensibiliteit, werd een isobare procedure verricht. Na 30 minuten adaptatie, werd er in het koffie experiment 280 ml sterke koffie of warm water (gerandomiseerd op verschillende dagen) en in het nicotine experiment 2 mg nicotine als sublinguaal tablet of placebo gegeven, gevolgd door 60 minuten van registratie. Hierna werd de continue druk distensie herhaald. Rectale tonus nam significant toe na koffie (45%) en na warm water (30%), echter de verschillen tussen beide waren niet significant. Dit suggereert dat de toename in tonus een effect is van het volume van de dranken in de maag en in mindere mate een gevolg is van de cafeïne in de koffie. Nicotine noch placebo beïnvloedde de rectale tonus. Na koffie, warm water, nicotine en placebo was de rectale sensibiliteit verminderd. Dit suggereert dat andere

factoren van invloed waren bijvoorbeeld de twee uur durende bedrust tijdens het onderzoek.

Hoofdstuk 6 bevat de studie waarin 30 vrouwen met idiopatische obstipatie worden onderzocht met de rectale barostat. De resultaten worden vergeleken met 22 gezonde vrouwen. Patiënten met idiopathische obstipatie worden ingedeeld in slow transit, bekkenbodem disfunctie en prikkelbaar darm syndroom (IBS). Er bestaat aanzienlijke overlap tussen de drie groepen. Doel van de studie was om te onderzoeken of patiënten met idiopathische obstipatie een abnormale rectum functie hebben door de rectale viscerale sensibiliteit, compliantie, postprandiale rectale respons met de barostat te meten. Paradoxale aanspanning van de anale sphincter (PSC) werd aangetoond met anale manometrie als een paradoxale toename van de anale druk (> 10 mmHg) tijdens persen. Abnormale rectale sensibiliteit of compliantie werd gevonden bij 90% van de patiënten met in 35% een lax (normosensitief of hyposensitief en hoge compliantie), in 27% hypersensitief (hypersensitief, lage of normale compliantie), in 17% insensitief (hyposensitief, normale of lage compliantie) and in 10% een stijf rectum (normosensitief, lage compliantie). Patiënten met obstipatie en gezonden hadden een vergelijkbare postprandiale rectale respons, echter PVE's waren verminderd bij de patiënten. De postprandiale rectale respons was vrijwel afwezig bij multipara patiënten en multipara gezonden en bij patiënten met rectale hypersensibiliteit. Patiënten met PSC hadden een hogere rectale sensibiliteit maar een normale compliantie en postprandiale rectale respons. De traditionele onderverdeling van patiënten met idiopathische obstipatie in slow transit, bekkenbodem disfunctie en IBS lijkt een te eenvoudige weergave; patiënten lijken een meer gemengde indeling te hebben. Er kan een indeling worden gemaakt op basis van de rectale karakteristieken in een lax, hypersensitief, insensitief, stijf en een normaal rectum.

Hoofdstuk 7 beschrijft de rectale functie bij patiënten met een rectocele waarbij de indicatie tot operatie gesteld werd wegens prolapsklachten en een verstoorde stoelgang, namelijk een evacuatieprobleem. Daarnaast werd gekeken naar eventuele preoperatieve prognostische factoren voor een goed operatieresultaat en naar een eventuele veranderde postoperatieve anorectale functie. Veertien patiënten werden geëvalueerd voor en na een posterieure colporrhaphie middels vragenlijsten, anale manometrie, rectale viscerale sensibiliteit en compliantie meting, postprandiale rectale respons (preoperatief) en colon transit tijd meting met radiopake markers. Vijf patiënten hadden een tweede graads en negen een derde graads vagina achterwand prolaps. Rectocele patiënten hadden een relatief hoge rustdruk en langer sfinctertraject, een lage knijpkracht, en een lagere sensibiliteit scores dan gezonde controles. De rectale compliantie was niet verschillend. De postprandiale rectale respons was minder in rectocele patiënten vergeleken met gezonde nullipara, maar gelijk met gezonde multipara. Na de operatie (8 maanden, range 3-14) werd bij gynaecologisch onderzoek een tweedegraads rectocele gevonden bij 4 patiënten. Persen, rectale evacuatie, manueel ondersteunen van de bekkenbodem en verzakkingsklachten waren verbeterd, in tegenstelling tot de defecatiefrequentie en de

ontlastingsconsistentie. Anale drukken, compliantie-curve, viscerale sensibiliteit en colon transit tijden waren niet veranderd na de operatie. Deze studie toont aan dat een rectocele repair klachten van evacuatie en verzakking verbetert maar geen effect heeft op de defecatie frequentie, ontlastingsconsistentie en het gebruik van laxeermiddelen. Resultaten van anorectale functie testen waren niet veranderd na de operatie. Selectie van patiënten met een rectocele voor een operatie zou moeten gebeuren op basis van verzakkings en evacuatie klachten maar niet op basis van anorectale functie of colon transit tijd.

Hoofdstuk 8 bestudeert het effect van coloninhoud op de colon transit bij 10 gezonde vrouwen en 25 vrouwen met obstipatie. Colon transit tijd meting met behulp van radiopake markers wordt steeds meer gebruikt en is makkelijk toepasbaar voor het meten van de passage van coloninhoud door de darm. Gehele colon transit tijd en segmentele transit tijd (rechter colon, linker colon en rectosigmoid) kan worden bepaald. De colon passage tijd zou beïnvloed kunnen worden door fecale impactie bij patiënten met chronische obstipatie door slow transit of bekkenbodem disfunctie. Dit werd bestudeerd door de colon passage tijd te vergelijken in een onvoorbereide situatie en in een situatie na darmlavage. Darminhoud heeft een substantieel effect op de passage. Bij de gezonde vrouwelijke vrijwilligers werd de rectosigmoid passage tijd verkort. Vrouwen met obstipatie, door slow transit of bekkenbodem disfunctie, hadden snellere passage na lavage, echter de distributie van de markers was onveranderd. Ondanks het effect van lavage op de colon passage tijd, lijkt het niet nuttig de darm voor te bereiden in de praktijk omdat de differentiatie tussen slow transit en uitgangsobstructie niet verandert. Voor klinische beslissingen moet de colon transit tijd met voorzichtigheid gebruikt worden omdat bij een onregelmatige stoelgang de invloed van fecale impactie aanzienlijk is.

Hoofdstuk 9: Prucalopride is een nieuwe 5-HT-4 agonist die de darm motiliteit stimuleert bij gezonden. In een dubbel-blinde gerandomiseerde cross-over studie werd het effect van prucalopride (1mg of 2mg per dag) op de klachten, anorectale functie en colon passage tijd van patiënten met obstipatie geëvalueerd. Prucalopride in de 1mg dosis, vergeleken met placebo, verbeterde het defecatie patroon, ontlastingsconsistentie en persen. Prucalopride, vergeleken met placebo, gaf een trend tot versnelling van de colon passage tijd ($P = 0{,}074$). Er werden geen statistisch significante verschillen gevonden bij de resultaten van de anorectale functie testen. Prucalopride is een veilig en effectief middel om de stoelgang en de colon passage tijd te verbeteren bij patiënten met chronische obstipatie en kan daarom een rol gaan spelen in de behandeling van deze aandoening.

Hoofdstuk 10 geeft een overzicht van de literatuur over rectale functie testen. Een verscheidenheid aan testen, zoals viscerale sensitiviteitsmeting, compliantie, tonische respons en fasische contractiliteit (barostat), colorectale motiliteit (barostat en manometrie), colorectale transit (radiopaque of scintigrafische markers) kunnen afwijkingen aantonen bij patienten met colorectale afwijkingen.

Het meeste onderzoek is gericht op functionele obstipatie en het prikkelbare darm syndroom.

Deel 2 Anale endoechografie en fistula-in-ano

Hoofdstuk 11 bestudeert de algemeen gebruikte Parks classificatie (inter, trans, supra en extrasfincterisch) om het anatomisch verloop van cryptoglandulaire fistula-in-ano te beschrijven. Het is onbekend in welke frequentie deze typen voorkomen. Transanale echografie met waterstof peroxide is een bewezen techniek om fistels af te beelden en correleert goed met de bevindingen bij chirurgische exploratie. Daarom werden anale echografie afbeeldingen bekeken om het verloop bij nooit geopereerde (N = 48) en recidief (N = 33) cryptoglandulaire fistels te bestuderen. Alle fistels die nooit tevoren waren geopereerd hadden een inter of transsfincterisch verloop. Een vertakking werd gevonden in 5%. Recidief fistels waren in 15% supra of extrasfincterisch en in 27% vertakt. Om deze reden is het niet noodzakelijk om fistels, die niet eerder zijn geopereerd, te visualiseren voordat de operatie plaatsvindt. Echter, bij recidief fistels is het aanbevolen deze eerst te visualiseren middels transanale echografie met waterstofperoxide om supra of extrasfincterische fistels of vertakkingen te ontdekken.

Hoofdstuk 12 beschrijft het anatomische verloop van fistula-in-ano bij de ziekte van Crohn. Deze fistels worden gevreesd omdat chirurgische behandeling gepaard kan gaan met recidief en fecale incontinentie. Deze studie werd verricht om het fistel verloop bij 41 patiënten met de ziekte van Crohn middels transanale echografie met waterstofperoxide te documenteren. Slechts 22% van de patiënten bleek een enkelvoudige inter of transsfincterische fistel te hebben. In 12% van de patiënten werd een enkelvoudige supra of extrasfincterische fistel (hoge fistel) gevonden. 34% van de patiënten hadden een vertakte fistel (meer dan één fistelgang) waarvan de hoofdtak de classificatie volgens Parks volgt, doch de vertakking een bizar verloop had, welke niet in overeenstemming was met de classificatie. Een anovaginale fistel werd gevonden in 32%. Dus, 78% van de patiënten hadden een fistel welke chirurgisch moeilijk te behandelen is. Optimale documentatie door middel van transanale echografie met waterstof peroxide is aanbevolen voor de behandeling middels chirurgie of medicamenteus zoals anti-TNF-therapie.

Hoofdstuk 13: Infliximab (een chimerische monoclonaal antilichaam tegen humaan tumor necrosis factor (TNF-alpha) is een nieuw middel om de ziekte van Crohn te behandelen. Het effect van 3 infusen met infliximab (5mg/kg) werd bestudeerd in een open label onderzoek bij 8 patiënten met fistula-in-ano bij de ziekte van Crohn met behulp van transanale echografie met waterstof peroxide. Patiënten met vaginale of perineale fistels hadden geen klinische verbetering na de behandeling, waarvan patiënten met perianale fistels aanzienlijk verbeterden. Echter, bij alle patiënten werden resten van de fistelgangen aangetoond middels echografie. Daarom, korte termijn behandeling van fistula-in-ano bij de ziekte van Crohn met infliximab geeft geen verdwijning van de fistelgangen, ongeacht het

klinische effect. Wellicht is de behandeling van infliximab meer effectief in combinatie met andere therapieën zoals antibiotica of een operatie.

Conclusies en aanbevelingen.

Deel 1. Rectale viscerale sensibiliteit en motiliteit.

Rectale viscerale sensibiliteit en compliantie zijn van belang bij patiënten met benigne rectale aandoeningen. De watergevulde latex ballon techniek voor het distenderen van het rectum is een eenvoudige methode om grove afwijkingen in rectale perceptie en compliantie te ontdekken. Het geeft een snelle indruk of het rectum fecale incontinentie (een maximaal tolerabel volume van minder dan 100 ml) veroorzaakt of wanneer het rectum deel is van een obstipatie syndroom (maximaal tolerabel volume van meer dan 500 ml).
Vergeleken met een nieuwe techniek, de barostat, is er een systematisch verschil in resultaten. De barostat bestaat uit een zeer compliante ballon en een distensie apparaat met een terugkoppelingsmechanisme. Met dit apparaat is het mogelijk om verschillende procedures zoals continue of intermitterende, druk, volume of wandspanning gestuurde distensies uit te voeren. In gezonde vrijwilligers werden er geen verschillen gevonden tussen continue en intermitterende distensies wat betreft compliantie of viscerale sensibiliteit. Druk was een betere parameter voor viscerale sensibiliteit dan volume of wandspanning. Het lijkt daarom redelijk om één drukgestuurde distensie methode te verrichten bij het bestuderen van viscerale sensibiliteit en compliantie. Mannen en vrouwen hebben verschillende complianties en daarom zouden voor geslacht vergelijkbare controles moeten worden gebruikt.
Daar de barostat een constante druk in de ballon kan geven, kan met het systeem tonus worden gemeten (veranderingen in volume in de tijd). Ook fasische volume veranderingen (PVE; volume afname gedurende 15-60 seconden) kunnen worden gemeten als een representatie van peristaltische golven. Een 600 kCal en een 1000 kCal maaltijd geven een gelijke toename van rectale tonus en PVE's. Mannen en nullipara vrouwen hebben een gastro-rectale respons in tegenstelling tot multipara vrouwen waarbij de respons afwezig is, mogelijk door neurogene schade tijdens de bevalling. Zowel koffie als warm water inname geeft een toename van rectale tonus, maar nicotine in de dosis van 2mg beïnvloedt de rectale tonus niet. Koffie en nicotine lijken in deze studie geen invloed te hebben op de rectale sensibiliteit en compliantie.
Patiënten met idiopatische obstipatie kunnen worden ingedeeld in een lax, een hyposensitief, een hypersensitief, een stijf of een normaal rectum aan de hand van de rectale eigenschappen. In onze populatie kwamen het lax en het hypersensitieve rectum het meest voor. Hypersensitiviteit is een biologisch kenmerk van prikkelbaar darm syndroom (IBS), welke echter ook voorkomt bij patiënten met obstipatie. De gastro-rectale respons is verminderd bij patiënten met obstipatie.
Anorectale functie bij patiënten met een rectocele en obstipatie wordt gekenmerkt door een hoge rustdruk en grotere sfincterlengte alsmede een

verminderde knijpkracht. De gastro-rectale respons is afwezig bij deze patiënten. Rectocele herstel (vagina achterwandplastiek) verbetert klachten van verzakking en rectale evacuatie. Anorectale functie en colon passage tijd veranderden niet na de ingreep. Rectale viscerale sensibiliteit en compliantie meting kunnen een plaats verwerven bij de klinische beoordeling van patiënten met obstipatie wanneer er een specifieke behandeling is voor rectale hypersensibiliteit. De gastro-rectale respons is niet klinisch bruikbaar omdat deze respons verminderd is bij gezonde multipara. Rectocele patiënten zouden geselecteerd moeten worden voor operatie op klachten van evacuatie en verzakking en niet op anorectale functie of colon passage tijd.
Colon passage tijd met radiopake markers geeft een indruk over de passage van darminhoud door het colon. Colon inhoud beïnvloedt de colon passage tijd aangezien er een versnelling optreedt na darmlavage. Zowel patiënten met slow transit obstipatie als patiënten met bekkenbodem disfunctie hebben een verkorting van de colon passage tijd na darmlavage. Bij patiënten met een irregulair defecatie patroon, kan de colon passage tijd meting verstoord worden door darminhoud (fecale impactie) wat deze test minder betrouwbaar maakt. Colon passage tijd kan als een parameter worden gebruikt om de werkzaamheid van enterokinetische medicijnen te testen. Prucalopride (een 5HT-4 agonist) verbetert de stoelgang en de colon passage tijd bij patiënten met obstipatie zonder de anorectale functie te beïnvloeden.

Deel 2. Anale endoechografie en fistula-in-ano.

Transanale echografie met gebruik van waterstofperoxide als een contrast medium is een bewezen techniek om fistelgangen te visualiseren. Bij patiënten met cryptoglandulaire ziekte zonder een eerdere fisteloperatie zijn de fistelgangen inter- en transsfincterisch, met slechts in 5% een vertakking. Bij recidief fistels zijn de fistelgangen in 42% complex. Deze recidieven vereisen derhalve visualisatie voor chirurgische therapie. Fistels bij de ziekte van Crohn vereisen altijd visualisatie voor chirurgische therapie omdat 78% een complex verloop heeft. Infliximab verbetert klachten van fistula-in-ano bij de ziekte van Crohn maar niet van anovaginale fistels. Echter, de fistelgangen zijn nog steeds zichtbaar bij transanale echografie met waterstofperoxide.

NAWOORD

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CURRICULUM VITAE

Cornelius Emmanuel Johannes Sloots (Pim) was born in Venray on 25th of August 1970. He graduated from grammar school (Gymnasium β, Boschveld College, Venray) in 1988. From 1988 to 1996 he attended medical school in Nijmegen. During his medical training he was student assistant at the department of anatomy, he followed a scientific internship on the gastroenterology department of the University Medical Center Nijmegen and he was student doctor in the Designated district hospital 'Teule' in Biharamulo, Tanzania. He was member of the Medical Society SO.DA.NO.GO.
After graduation from medical school he was surgical resident at the Hospital Walcheren in Vlissingen and at the University Hospital in Maastricht. In 1998 he started as clinical investigator at the department of gastroenterology, Vrije Universiteit Medical Center, Amsterdam, and he continued at the department of gastroenterology and hepatology, Erasmus Medical Center, Rotterdam.
In 2001 he started his surgical training at Máxima Medical Center, Veldhoven (Dr. F.A.A.M. Croiset van Uchelen), which he will continue at the University Medical Center Nijmegen (Prof. Dr. R.P. Bleichrodt).