Slow Transit Constipation

Aspects of Diagnosis and Treatment

ERIK LUNDIN
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Abstract

Oral 111-Indium-DTPA colonic scintigraphy was used to assess segmental transit in 23 patients with slow transit constipation (STC) and 13 controls. The transit time did not differ between patients and controls in the right colon, whereas the patients had a consistent delay from the transverse colon and distally ($P<0.05–0.001$). Two individual patients had a delay in the right colon.

Twenty-eight patients underwent a left- ($n=26$) or a right-$n=2$ hemicolecotomy for STC, after evaluation including colonic scintigraphy. Twenty-three patients ($80\%$) were satisfied with the outcome after a median of 50 months. The median stool frequency increased from one to seven per week ($P<0.001$). The number of patients with bloating, excessive straining and painful defecation decreased ($P<0.05$). The laxative use decreased ($P<0.01$) and faecal continence was unchanged. A blunted rectal sensation correlated to a poor outcome.

Fifty constipated patients with slow colonic transit and 28 controls were investigated with anorectal manovolumetry. Anal resting pressure was lower ($P<0.05$), and squeeze pressure tended to be lower ($P=0.09$) in patients. Rectal sensation was not different between groups, although ten patients had a threshold for filling sensation above the 95th percentile of controls. The rectal compliance was increased in patients ($P<0.05–0.01$).

Total and segmental colonic transit was assessed with radio-opaque marker study and scintigraphy in 35 constipated patients, and related to normal values. Twenty-seven of 31 female patients had a prolonged total transit time on marker study, and 26 on scintigraphy. Of those 31 patients, 29 had prolonged segmental transit only in one or two segments on marker study. The two methods gave a similar result, except in the descending colon ($P<0.05$). However, the results varied considerably for individual patients.

In conclusion, patients with STC often benefit from a segmental colonic resection, following assessment including scintigraphy. Anorectal physiology testing may predict surgical results.

Keywords: colostomy, constipation, radio-opaque markers, rectal compliance, rectal sensation, scintigraphy, segmental colonic resection, segmental colonic transit, sphincter pressure

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urn:nbn:se:uu:diva-5770 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-5770)
To my family

and in memory of Maria Racutanu
List of Papers

This thesis is based on the following papers, which are referred to in the text by the roman numerals given below (I–IV):


III Lundin E, Graf W, Karlbom U. Anorectal physiology in the decision making before surgery for slow transit constipation. Submitted.


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### Abbreviations

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<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>GC</td>
<td>Geometric centre</td>
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<tr>
<td>GITT</td>
<td>Gastrointestinal transit time</td>
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<tr>
<td>5-HT</td>
<td>Serotonin, 5-Hydroxytryptamine</td>
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<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
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<tr>
<td>$^{111}$In-DTPA</td>
<td>111-Indium diethylene triamine pentaacetic acid</td>
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<tr>
<td>IRA</td>
<td>Ileo-rectal anastomosis</td>
</tr>
<tr>
<td>RAIR</td>
<td>Recto-anal inhibitory reflex</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<td>STC</td>
<td>Slow transit constipation</td>
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<td>SW</td>
<td>Slow wave</td>
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Introduction

Background

Constipation is one of the most common gastrointestinal complaints. The prevalence of constipation ranges from two to approximately 20 percent in the western world depending on its definition. It is more common in women than in men and increases with age in the adult population. In a population-based Swedish study, it was found that 5.7% of women and 2.1% of men, aged 31 to 76, were constipated “often” or “always” and the numbers being constipated “sometimes” were 14.2% and 6.1% respectively (Walter et al. 2002).

The patients present with a variety of symptoms. Infrequent defecation and hard stools are usually attributed to slow colonic transit, whereas a feeling of blocked stool passage, incomplete emptying, excessive straining and manual manoeuvres to facilitate emptying usually are considered symptoms of obstructed defecation (or outlet obstruction). These symptoms (some or all) are often included when constipation is defined, e.g. by the Rome II criteria (Thompson et al. 1999), Table 1. Abdominal pain and bloating, painful stool passage, nausea and malaise are common complaints (Preston and Lennard-Jones 1986). For patients with chronic constipation these symptoms often have a substantial impact on general wellbeing and social life (Glia and Lindberg 1997).

Table 1. The Rome II criteria for functional constipation

| At least 12 weeks, which do not have to be consecutive, in the preceding 12 months of 2 or more of: |
| 1. Straining in >1/4 defecations |
| 2. Lumpy or hard stools in > 1/4 defecations |
| 3. Sensation of incomplete evacuation in > 1/4 defecations |
| 4. Sensation of anorectal obstruction/blockade in > 1/4 defecations |
| 5. Manual manoeuvres to facilitate > 1/4 defecations (e.g. digital evacuation, perineal support) |
| 6. < 3 defecations/week |

Loose stools are not present and there are insufficient criteria for the irritable bowel syndrome

Constipation is not a disease, but a symptom. It may be a manifestation of colonic diseases, such as an obstructing tumour, stricture or a colonic volvulus. Hirschsprung’s disease (megacolon), caused by an aganglionic seg-
ment in the anorectal junction with variable extent proximally, is an example of a rare cause of organic constipation. Extracolonic causes of constipation include metabolic, endocrine, neurological and psychiatric diseases. Diet habits and lifestyle are important for gastrointestinal function and there are numerous pharmaceutical agents that may cause constipation, *Table 2.*

Functional constipation is usually classified as; slow transit constipation (STC), obstructed defecation, a combination of those two, or being related to the irritable bowel syndrome (IBS). A study including 1009 patients with severe chronic constipation and an anatomically normal colon showed, after physiological and radiological studies, that 13 % had STC, 25% obstructed defecation and 3% a combined pathology. Fifty-nine percent had normal results of investigations and were classified as having IBS (Nyang et al. 1997). The corresponding figures in another study were: 21%, 24%, 20% and 35% respectively (Glia et al. 1998). Thus, slow colonic transit occurs in a relatively small group of constipated patients over all.

Table 2. Extracolonic causes of constipation*

<table>
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<tr>
<th>Diet and habits</th>
<th>Endocrine, metabolic and collagen disease</th>
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<tr>
<td>Inadequate fibre intake</td>
<td>Diabetes mellitus</td>
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<tr>
<td>Immobilisation/Lack of exercise</td>
<td>Hypothyroidism</td>
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<td>Ignoring the call to stool</td>
<td>Hypercalcemia</td>
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<td>Dehydration</td>
<td>Pregnancy</td>
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<td></td>
<td>Hypokalemia</td>
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<td></td>
<td>Uraemia</td>
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<td>Psychiatric disease</td>
<td>Amyloidosis</td>
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<td>Depression</td>
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<td>Psychosis</td>
<td>Scleroderma</td>
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<td>Anorexia nervosa</td>
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<tr>
<td>Neurological disease</td>
<td>Pharmacological causes</td>
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<td>Cerebrovascular disease</td>
<td>Opiates</td>
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<td>Parkinson's disease</td>
<td>Antidepressants</td>
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<td>Multiple sclerosis</td>
<td>Antacids</td>
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<td>Central nervous system malignancies</td>
<td>Calcium antagonists</td>
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<td>Cauda equina lesions</td>
<td>Cholestryramine</td>
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<td></td>
<td>Antiparkinsonians</td>
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<td></td>
<td>Anticonvulsants</td>
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*Examples of extracolonic causes*
Physiology

The colon is innervated through an extrinsic (autonomic nervous system) and an intrinsic (enteric nervous system) pathway. The extrinsic system consists of sympathetic and parasympathetic supply. The sympathetic supply to the proximal colon, including part of the transverse colon (embryological midgut), derives from the coeliac and superior mesenteric plexuses. The parasympathetic supply derives from the vagus nerve. Animal studies have shown that the parasympathetic vagal supply also affects the distal colon, although it has quantitatively less effect in that segment (Dapoigny et al. 1992). The nerves follow the arterial supply of the superior mesenteric artery.

The distal transverse colon, the descending- and the sigmoid colon receives its sympathetic supply from the inferior mesenteric and the superior hypogastric plexuses. The sympathetic supply to the rectum is derived from the inferior hypogastric plexus. The parasympathetic innervation to the left colon and rectum (embryological hindgut) comes from the pelvic splanchnic nerves (S2-S4). They merge with the respective plexus (to follow the arterial supply) but also enter the colonic wall in the region of the recto-sigmoid junction to form the intramural (ascending-) nerves of the colon. They lie in the plane of the myenteric plexus and run in oral and caudad directions. The ascending nerves of the colon extend along 60–80 percent of the colonic length (Knowles et al. 2001).

The external anal sphincter is innervated by the pudendal nerve (S2-S4). The internal anal sphincter has sympathetic supply from the inferior hypogastric plexus and parasympathetic supply from the pelvic splanchnic nerves.

The parasympathetic motor neurons are cholinergic and the sympathetic neurons adrenergic. In general, parasympathetic stimuli increase bowel motility and secretion, and relax the internal anal sphincter, whereas sympathetic stimuli have the opposite effect. Apart from motor stimuli, the extrinsic nervous system also conduct sensory information through afferent parasympathetic and sympathetic nerves (Goyal and Hirano 1996). They are sensitive to distension and certain chemical intraluminal stimuli (se below). Thus, distension of the distal colon may inhibit the motility of the proximal colon, or even proximal gastrointestinal tract, through intestinal reflexes (Knowles et al. 2001).

The intrinsic (enteric) colonic nervous system consists mainly of two major nerve plexa; the myenteric (Auerbach’s) plexus and the submucosal (Meissner’s) plexus. The myenteric plexus is situated between the outer longitudinal and the inner circular muscle layer, and the submucosal plexus between the inner circular muscle and the muscularis mucosae. The intrinsic nervous system continues down into the internal anal sphincter.
Some of the more important neurotransmitters in the enteric nervous system are; acetylcholin, tachykinins (including substance P) and enkephalins, which are likely to be excitatory, and nitric oxide, vasoactive intestinal peptide and neuropeptide Y, which are likely inhibitory (Costa et al. 1996, Porter et al. 1998). Serotonin (5-HT) is believed to act in interneurons in the enteric nervous system (Gershon 2004).

A spontaneous activity of the colon, independent of the extrinsic nervous system, can be registered by electromyography as slow waves (SW). The source of colonic SW is a special plexus at the submucosal surface of the circular muscle layer consisting of the interstitial cells of Cajal. The interstitial cells of Cajal are thus suggested to act as pacemaker cells in the generation of autorhythmicity of the gut muscle.

An increase in intestinal intraluminal pressure causes a local propulsive activity through the peristaltic reflex. This is initiated by release of 5-HT from large numbers of enterochromaffin cells in the mucosa. 5-HT responsive primary afferent neurones transfer the information to interneurons and motoneurons of the enteric nervous system. The action is stopped by re-uptake of 5-HT by the enterocytes (Gershon 2004). Different subclasses of 5-HT receptors in the bowel mediate signals to the extrinsic sensory nerves and central nervous system (5-HT3) and to intrinsic excitatory nerves (mainly 5-HT4).

The patterns of motility in the colon can be summarised as; rhythmic and tonic segmenting contractions, with the latter forming the haustral rings, and rhythmic peristaltic contractions, which in the right colon (at least in many species) are thought to be retrograde, and in the left colon antegrade (Christensen 1994). Furthermore, there are the mass movements, which are strong peristaltic contractions that move the faeces forward. They occur after eating and at intervals of several hours.

Defecation is a partly voluntary and partly involuntary process. Rectal filling is percepted by mechanoreceptors in the anorectal area. A reflex relaxation of the internal sphincter, the recto-anal inhibitory reflex (RAIR), takes place and the person experiences the need to defecate. If defecation is not convenient, the external anal sphincter contracts and the internal sphincter will thereafter regain its tone. When emptying takes place, both sphincters and the puborectalis muscle relax and the anorectal angle decreases. Abdominal pressure is raised and peristaltic contractions of the rectum, as well as the colon help to expel the faeces (Lubowski et al. 1995).

Aetiology and pathophysiology

Severe chronic constipation is a condition most commonly seen in women. The cause of STC is largely unknown and it is often referred to as idiopathic. The clinical presentation of the patients is heterogeneous and it is generally
accepted that there may be several different mechanisms behind functional constipation. Young women with onset of constipation in childhood or adolescence constitute one group. They typically present with infrequent defecation, absence of call to stool and abdominal bloating and discomfort. A family history of constipation has been found in more than 50 percent of patients, which may suggest a genetic aetiology (Chaussade et al. 1989, Knowles et al. 1999b).

Other patients relate onset of constipation to events such as childbirth (MacDonald et al. 1997) or pelvic surgery. Constipation following anterior resection (Rasmussen et al. 2003), rectopexy (Dolk et al. 1990a, Siproudhis et al. 1993) and hysterectomy (van Dam et al. 1997) has been reported. The mechanism is suggested to be damage to the autonomic pelvic nerves (Knowles et al. 2001). They lie in immediate proximity to the rectum, uterine cervix, posterior part of the bladder and within the uterine broad ligament in women, and to the rectum, seminal vesicles, prostate and the posterior part of the bladder in men (Williams et al. 1989). Constipation has been reported to follow radical hysterectomy (Possover and Schneider 2002), whereas simple hysterectomy, for benign disorders, (Altman et al. 2004) did not affect colonic function. This would be logical, since more extensive pelvic surgery would increase the risk of nerve damage.

In some patients with adult onset of constipation no preceding event can be identified. Mechanisms such as autoimmunity or infection as causes of neuronal injury have been discussed (Knowles et al. 2001). A recent finding of ganglionitis with intraepithelial lymphocytosis and mild chronic mucosal inflammation in biopsies from patients with STC (Lindberg et al. 1999) may support these theories.

Scintigraphic transit studies have shown the same patterns of abnormal colonic transit in patients with STC since childhood and those with onset after a pelvic event (Scott et al. 2001). This may point in the direction of a dysfunction in the autonomic nervous system. Extra intestinal functional disorders are also common. Urological, especially bladder symptoms have been described to be more frequent in patients with STC (Preston and LeNard-Jones 1986). Furthermore autonomic and sensory dysfunction in the lower limbs, similar to that in diabetic patients with constipation, has been described (Knowles et al. 1999b).

Functional disturbances in the upper gastrointestinal tract are not uncommon in STC. Findings of delayed gastric emptying (Hemingway and Finlay 2000), antroduodenal abnormalities on manometry (Bassotti et al. 1996) and prolonged oro–caecal transit time (Penning et al. 2000) indicate that STC may be part of a pan-enteric motility disorder.

Abnormalities in the enteric nervous system have been reported in several studies. Reduced numbers of neurones or ganglia in the myenteric plexus or neuronal structures in the circular muscle have been found (Krishnamurthy et al. 1985, Porter et al. 1998, He et al. 2000, Wedel et al. 2002). Other stud-
ies have shown similar morphological abnormalities with a segmental distribution along the colon (Schouten et al. 1993, Yu et al. 2002).

Several neurotransmitters have been described to be increased or decreased in patients with STC. The results, however, are sometimes contradictory. Decreased levels of tachykinins and enkephalins in the circular muscle have been found, whereas the levels of vasoactive intestinal peptide, neuropeptide Y and nitric oxide were equal to controls (Porter et al. 1998). Another study showed increased levels of vasoactive intestinal peptide, neuropeptide Y and substance P (tachykinin) in the bowel wall or myenteric plexus (Sjölund et al. 1997). In vitro studies have shown that the colon in STC is more strongly innervated by nitric oxide with an enhanced nitric oxide induced relaxation (Mitolo-Chieppa et al. 1998, Tomita et al. 2002). The contractile response in vitro to acetylcholine and tachykinins has been shown to be reduced (Mitolo-Chieppa et al. 1998, Mitolo-Chieppa et al. 2001), although another study failed to demonstrate any deficiency in acetylcholine content in STC patients (Porter et al. 1998). Other neurotransmitters, such as motilin and calcitonin gene-related peptide (Dolk et al. 1990b) have also been found in altered levels.

In recent years, attention has been drawn to the pacemaker cells of colonic slow waves; the interstitial cells of Cajal. These cells may be found in each layer of the colonic wall. A consistent finding in several studies is a decreased number of the interstitial cells of Cajal in the sigmoid- (He et al. 2000), as well as the entire length of the colon (Lyford et al. 2002, Yu et al. 2002).

Abnormalities of the neuroendocrine system have also been described in STC. Increased numbers of 5-HT containing cells (Lincoln et al. 1990, Sjölund et al. 1997), as well as decreased numbers of 5-HT and enteroglucagon containing cells (El-Salhy et al. 1999) have been found in the colonic mucosa. Furthermore, altered levels of somatostatin, enteroglucagon and pancreatic glucagon in blood have been seen (van der Sijp et al. 1998).

The above described abnormalities of enteric neuronal morphology, neurotransmitters and gastrointestinal hormones may be involved in the pathophysiology of STC. However, there is little or no evidence as to whether they represent primary or secondary pathological disturbances.

A prolonged segmental colonic transit time has been proposed to be the effect of obstructed defecation (Kuijpers 1990). This is supported by a study where stool frequency was decreased and recto-sigmoid and right colonic transit time prolonged by voluntarily suppressed defecation (Klauser et al. 1990). Continuous rectal distension has also been demonstrated to delay gastric emptying (Coremans et al. 2004) and duodeno–caecal transit (Kellow et al. 1987) probably through visceral reflex pathways. Thus, obstructed defecation may be a cause of delayed colonic transit in some patients.

Since most patients with chronic constipation are women, alterations in sex hormones have been discussed as an aetiological factor. Although a pro-
longed transit time has been found during pregnancy, the physiological changes in hormone levels of the menstrual cycle do not seem to alter colonic transit time (Degen and Phillips 1996, Müller-Lissner et al. 2005).

Long term use of stimulant laxatives has been considered to impair colonic function. Findings such as colonic redundancy, dilatation and loss of haustral folds on barium enema have been termed "the cathartic colon". Of these findings, only loss of haustral folds was confirmed in a recent study (Joo et al. 1998). Recent reviews conclude that there is no evidence that currently used laxatives are harmful to colonic function or may be addictive (Knowles and Martin 2000, Müller-Lissner et al. 2005).

Psychiatric disorders are not uncommon in patients with STC (Nylund et al. 2001). It has been suggested that some types of constipation are psychological responses to life stresses (Devroede et al. 1989). However, an aetiological relationship to STC is contradicted by findings of more psychological abnormalities in patients with normal transit constipation than in those with STC (Chattat et al. 1997). A relationship with a history of sexual abuse has been reported in patients with lower functional digestive disorders, including constipation as well as diarrhoea (Leroi et al. 1995). This association has generally been considered in patients with IBS or obstructed defecation. In contrast, a recent study found no differences with respect to previous sexual abuse in patients with idiopathic constipation, IBS, organic colon disease or controls, and questions such a relationship (Hobbis et al. 2002).

Finally, although factors such as a diet poor in fibre, a low fluid intake and lack of physical exercise may influence gastrointestinal function, there is no evidence that they are the cause of STC (Müller-Lissner et al. 2005).

Evaluation

Organic colon disease, such as obstructing tumours or strictures should be ruled out before further evaluation of functional constipation is indicated. Non colonic causes of constipation including endocrine- or metabolic disease as well as pharmacologically induced constipation should be excluded. This can usually be done by a thorough history, simple blood chemistry and a clinical examination. Furthermore, before extensive examinations are performed, treatment with dietary measures, bulking agents or mild laxatives should be inadequate.

Evaluation of symptoms is important to assess the type and severity of constipation, although symptoms are usually not specific enough to fully characterise the disorder (Koch et al. 1997). Questionnaires may be useful in the assessment, as well as follow-up of patients (Österberg et al. 1996), and make it possible to create symptom scoring systems (Agachan et al. 1996).

The complete work-up of chronic constipation usually includes colonic transit time measurement, defecography, anorectal manometry (or mano-
volumetry) and electromyography (EMG) of the pelvic floor. These tests provide important information regarding the pathology in individual patients, which may influence the choice of treatment (Halverson and Orkin 1998) (Glia et al. 1998).

Colonic transit measurement
Radio-opaque marker study is a widely used method to measure the total colonic transit time and to diagnose STC. Most methods also give crude estimates of segmental colonic transit. Techniques with ingestion of radio-opaque markers and several abdominal radiographs (Martelli et al. 1978, Arhan et al. 1981, Chaussade et al. 1989) or a single radiograph (Metcalf et al. 1987, Abrahamsson et al. 1988) have been described, Figure 1.

*Figure 1.* Radio-opaque marker study for a patient with prolonged segmental transit time in the ascending and the recto-sigmoid colon. Single abdominal X-ray on the seventh day, after ingestion of ten ring shaped markers daily during six days.
Scintigraphic methods with radio-isotope tracers are also used. After the early techniques were described with intubation of the caecum to deposit the tracer (Krevsky et al. 1986, Kamm et al. 1988b, Krevsky et al. 1989), clinically more feasible methods where the tracer is ingested, have been developed (Roberts et al. 1993, van der Sijp et al. 1993, Notghi et al. 1994, McLean et al. 1995). As compared to radio-opaque markers, scintigraphic methods may have the advantages that the colon can easier be outlined and frequent scans can be obtained without increasing the radiation dose, Figure 2. The main clinical purpose of assessing segmental transit in patients with STC would be to select patients for segmental colonic resection (see next section). This would require from any method of transit study that it can clearly distinguish between right- and left-sided colonic delay.

Figure 2. Segmental colonic transit scintigraphy for a patient with right-sided colonic delay. First image for positioning of the patient. The following are geometric mean images collected by 2 h, 6 h, 24 h, 2 days, 3 days, 6 days, 7 days and 8 days respectively, after ingestion of $^{111}$In-DTPA.

Studies comparing radiological and scintigraphic methods have previously shown good correlation for colonic transit (Stivland et al. 1991, van der Sijp et al. 1993, Degen and Phillips 1996). However, different methods have not been compared with respect to the transit time in each colonic segment related to normal values. Furthermore, it is not known whether scintigraphy
adds significant information to that obtained by radio-opaque marker study (e.g. Abrahamsson’s method), affecting the choice of surgical treatment.

Both radiological (Metcalf et al. 1987, Abrahamsson et al. 1988) and scintigraphic (Degen and Phillips 1996, Madsen et al. 2003) studies have shown that healthy females have longer colonic transit times than men. The effect of age on colonic transit is less clear, but elderly subjects have been shown to have longer transit times than the young and middle aged (Madsen et al. 2003). In another study middle aged women had slower colonic transit than young women (Graff et al. 2001). Various methods to measure colonic transit differ in the way transit time is defined and calculated, resulting in a variation in the numerical reference values (Wagener et al. 2004). Thus, normal values, for the method in use, are required.

Anorectal function

Defecography by video technique demonstrates anatomical and physiological abnormalities, such as rectocele, enterocele, rectal inussusception or prolapse and paradoxical puborectalis contraction. These findings are common in constipated patients. Defecography may also give an estimate of rectal emptying, and findings such as a rectocele or paradoxical puborectalis contraction correlate to an impaired rectal evacuation (Karlbom et al. 1999).

By anorectal manovolumetry, sphincter pressures and rectal sensory thresholds may be measured. The RAIR can be demonstrated and rectal compliance assessed. The results may provide diagnostic information. For example, absence of the RAIR would suggest Hirschsprung’s disease. Published results of anorectal physiology studies in constipated patients are not consistent. Low (Read et al. 1986, Bassotti et al. 1994) and normal (Roe et al. 1986, Waldron et al. 1988, Varma and Smith 1988) anal resting pressures as well as reduced (Waldron et al. 1988, Varma and Smith 1988, Bassotti et al. 1994) and normal (Rasmussen et al. 1993) rectal sensation have been reported. Moreover, low (Rasmussen et al. 1993), normal (Roe et al. 1986, Sloots and Felt-Bersma 2003) and high (Varma and Smith 1988) rectal compliance and an altered recto-anal reflex response (Waldron et al. 1988) have been found. The varying results may be due to different selection of patients. Age and gender may also affect the results (Åkervall et al. 1990). A study analysing symptoms of constipation has shown that infrequent defecation seemed to be related to alterations in anorectal physiology, whereas symptoms of obstructed defecation did not (Karlbom et al. 2004). Slow colonic transit as an inclusion criterion in a study of anorectal physiology might help to elucidate abnormalities in patients who may be candidates for surgical therapy for STC.

EMG may be registered in the external anal sphincter and the puborectalis muscle. It can demonstrate a paradoxical contraction in these muscles on straining. Paradoxical puborectalis contraction on EMG is associated with
impaired rectal emptying and is considered to cause obstructed defecation (Karlbom et al. 1998).

Upper gastrointestinal function

Evaluation of upper gastrointestinal function may be done if a pan-enteric motility disorder is suspected. Patients with STC frequently show abnormalities when examined with antroduodenal manometry (Bassotti et al. 1996). These alterations, however, may be relatively mild and antroduodenal motility generally well preserved (Penning et al. 2000). Oro-caecal transit time, as measured by hydrogen breath test, is often prolonged in patients with STC (Penning et al. 2000).

Gastric emptying may be studied by scintigraphic methods. Delayed gastric emptying has been demonstrated in patients with STC (Hemingway and Finlay 2000, Mollen et al. 2001).

Treatment

Patients with severe STC usually respond poorly or not at all to fibres and bulking agents. They are thus dependent on stimulant laxatives or enemas, Table 3. A surgical option for these patients that has been widely used is colectomy and ileo-rectal anastomosis (IRA) (Kamm et al. 1988a, Yoshioka and Keighley 1989, Wexner et al. 1991, Lubowski et al. 1996, Nyam et al. 1997). The success rate varies between 50 and 90 % after at least three years follow-up. A number of patients, however, experience postoperative side effects such as diarrhoea, faecal incontinence and frequent stools. Postoperative diarrhoea has been reported in up to 30 % and faecal incontinence in approximately 15 % (Kamm et al. 1988a, Redmond et al. 1995, Christiansen and Rasmussen 1996, Lubowski et al. 1996). Furthermore, studies have shown poorer results of IRA in patients with reduced rectal sensation (Åkervall et al. 1988a, Pluta et al. 1996). Both anal and rectal function thus seems to be of importance when surgical treatment for STC is considered. The morbidity following IRA, e.g. small bowel obstruction, is not negligible. At a median follow up of 11 years a frequency of operation for small bowel obstruction of 25 percent has been reported (Nylund et al. 2001).

A limited colonic resection may be a way to treat STC and avoid the side effects related to IRA. There are a few reports on segmental colectomy based on segmental transit studies (Kamm et al. 1991, de Graaf et al. 1996, You et al. 1998) but this treatment has not been generally accepted. In the studies by de Graaf et al. and You et al. the method used to diagnose segmental slow transit was radio-opaque marker study. Assuming that scintigraphy may possibly be a more accurate method to assess segmental colonic transit in
STC, there is a need to evaluate the functional outcome of segmental resection based on the results of scintigraphy.

Whether coexisting obstructed defecation should be treated before IRA is performed for STC has been under debate. Some authors have not been able to find any difference in outcome between patients with untreated obstructed defecation and those with isolated STC (Kamm et al. 1988a, Lubowski et al. 1996). Other authors have excluded patients with coexisting obstructed defecation (Wexner et al. 1991), or chosen to treat obstructed defecation before IRA (Nyam et al. 1997), and argue that IRA should only be performed in patients with a normal rectal function.

Impaired upper gastrointestinal function may also influence the functional results after IRA negatively in patients with STC (Redmond et al. 1995).

Table 3. Pharmacological treatment for constipation

<table>
<thead>
<tr>
<th>Type</th>
<th>Generic substance</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulking agents</td>
<td>Ispaghula</td>
<td>Lunelax</td>
</tr>
<tr>
<td></td>
<td>Crude fibre</td>
<td>Fiberform</td>
</tr>
<tr>
<td></td>
<td>Sterkulia</td>
<td>Inolaxol</td>
</tr>
<tr>
<td>Osmotic laxatives</td>
<td>Laktitol</td>
<td>Importal Ex-Lax</td>
</tr>
<tr>
<td></td>
<td>Laktulos</td>
<td>Duphalac</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laktipex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactulos Pharmacia</td>
</tr>
<tr>
<td></td>
<td>Magnesium oxide</td>
<td>Salilax</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glygol</td>
<td>Movicol</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Bisacodyl</td>
<td>Dulcolax</td>
</tr>
<tr>
<td></td>
<td>Sodium picosulphate</td>
<td>Cilaxoral</td>
</tr>
<tr>
<td></td>
<td>Sagrada extract</td>
<td>Emulax</td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>Pursennid Ex-Lax</td>
</tr>
<tr>
<td>Ememas</td>
<td>Bisacodyl</td>
<td>Toilax</td>
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<td></td>
<td>Lauryl sulphate</td>
<td>Mikrolax</td>
</tr>
<tr>
<td></td>
<td>Sodium docusate</td>
<td>Klyx</td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td>Resulax</td>
</tr>
<tr>
<td>Suppository</td>
<td>Carbon dioxide producing</td>
<td>Relaxit</td>
</tr>
</tbody>
</table>

Available on the Swedish market 2004
Gut directed biofeedback retraining has been shown to decrease symptoms and increase stool frequency in patients with pelvic floor abnormalities as well as slow colonic transit (Chiotakakou-Faliakou et al. 1998). Biofeedback has also been shown to improve colonic transit (Emmanuel and Kamm 2001).

Sacral nerve stimulation, previously used for urinary bladder dysfunction and for faecal incontinence, has recently been tried on a small number of patients with constipation, including STC (Kenefick et al. 2002). Improvement regarding symptoms, stool frequency, anorectal function and transit time was seen. Future studies may reveal the effectiveness of this method.

An appendicostomy for antegrade enema was first described by Malone et al. (Malone et al. 1990). Although an antegrade continent enema procedure may be a more attractive option than a permanent stoma, only about 50 percent of patients with STC have had a satisfactory long term outcome, and revision procedures are very common (88 %) (Lees et al. 2004).

In recent years, new prokinetic drugs have been developed. Prucalopride, a highly selective 5-HT4 receptor agonist, has been demonstrated to increase stool frequency and decrease stool consistency and straining in patients with severe constipation (Sloots et al. 2002, Coremans et al. 2003). Furthermore, prucalopride has reduced whole gut transit and improved rectal sensation (Emmanuel et al. 2002). Tegaserod, a partial 5-HT4 receptor agonist, has also increased stool frequency and provided relief from other symptoms of chronic constipation (Johanson 2004, Kamm et al. 2005). Other drugs that target the same receptors are being developed as well (Nagakura et al. 1999). However, to date none of these selective, prokinetic drugs are available on the Swedish market.
Aims of the thesis

- To evaluate a scintigraphic method, feasible in clinical practice, to assess segmental colonic transit with special reference to right- or left-sided delay. Another aim was to evaluate the method with respect to inter-observer variation in the interpretation of the scans.

- To prospectively evaluate functional outcome and patient satisfaction after segmental colonic resection for STC, following a thorough assessment including segmental colonic scintigraphy.

- To assess anorectal physiology, including parameters that may affect the outcome of surgery, in constipated patients with prolonged colonic transit time compared to healthy subjects.

- To compare a radiological and a scintigraphic method to assess colonic transit, with respect to total and segmental transit time in patients with STC.
Material and methods

Subjects

The patients in Study I–IV were all consecutive patients, referred to the Department of Surgery at the University Hospital (Akademiska Sjukhuset) of Uppsala, who fulfilled the inclusion criteria of the respective study.

Paper I

Twenty-three patients (19 women and 4 men, median age 51 years, range 22-78) were included in the study and underwent 111-Indium diethylene triamine pentaacetic acid (111In-DTPA) segmental colonic scintigraphy. Inclusion criteria were constipation symptoms and a prolonged colonic transit time on radio-opaque marker study. The median (range) symptom duration was 20 (1-50) years. Thirteen control subjects (11 women and 2 men, median age 47 years, range 38-54) without any history of constipation, systemic disease or medication affecting gastrointestinal transit were recruited from the hospital staff. The patients were evaluated by barium enema, radio-opaque marker study, anorectal manovolumetry, EMG and video defecography before the scintigraphic examination. A coexisting obstructed defecation had been treated with biofeedback in 11 patients (Karlbom et al. 1997) and with transanal repair of a rectocele in 2 patients (Karlbom et al. 1996).

Paper II

Twenty-eight patients (26 women and 2 men, median age 52 years, range 32-79) with intractable constipation underwent segmental colectomy between 1993 and 1999. The median (range) symptom duration was 17 (1-50) years. Symptoms included infrequent defecation, hard stools, excessive straining, abdominal pain and bloating. All patients had tried dietary measures and laxatives with inadequate effect. The preoperative evaluation included anorectal manovolumetry, EMG, video defecography, radio-opaque marker study and segmental colonic scintigraphy. The gastrointestinal transit time, as measured by radio-opaque markers, exceeded the normal range in all but two patients. These two patients had a transit time close to the upper limit of the normal range and symptoms typical of STC. The patients in this series were found to have a marked delay in either the left or the right colon.
on the scintigraphic study. A coexisting obstructed defecation was primarily treated with biofeedback in ten patients, with transanal repair of a rectocele in four, and with anorectal myectomy in one patient. The symptomatic relief of these procedures was unsatisfactory, indicating that slow transit was a major or contributing cause of symptoms.

Paper III
Fifty consecutive patients (43 women and 7 men, median age 49 years, range 22-86) with idiopathic constipation and a prolonged colonic transit time were investigated by anorectal manovolumetry. The median (range) duration of constipation was 10 (0.5-50) years. The median (range) stool frequency with the use of laxatives was 1 (0-7) per week. No patient had radiological signs of megarectum or a history of inflammatory bowel-, connective tissue-, or neurological disease. Nine patients had previously had a hysterectomy and two patients a suture rectopexy. The onset of constipation was not related to surgery in any patient, although one had aggravated symptoms after rectopexy. The evaluation included radio-opaque marker study and video defecography. Twenty-eight control subjects (23 women and 5 men, median age 50 years, range 25-75) were recruited from patients undergoing minor surgery not involving the anorectal area and from the hospital staff. Abdominal or defecation symptoms were denied by all.

Paper IV
During the period of 1991–2003 a total of 85 patients with severe constipation underwent both radio-opaque marker study and 111In-DTPA segmental colonic scintigraphy. Seventy-seven patients had a prolonged or borderline prolonged total colonic transit time on marker study, and were considered for the present study. Thirty-five were finally included in the study after exclusion of patients with a history of colonic resection or a stoma (n=11), a documented change in symptoms (n=5) or treatment of obstructed defecation between investigations (n=14), and study results either missing or of inadequate quality (n=12). The 35 patients (31 women and 4 men, median age 47 years, range 17-75) had symptoms consistent with STC, i.e. predominating infrequent defecation. The median (range) time between the radiological and the scintigraphic investigation was 4 (1-27) months.

For the scintigraphic study, 13 healthy individuals (11 women and 2 men, median age 47 years, range 38-54) without any symptoms of constipation, systemic disease or medication affecting gastrointestinal transit were recruited from the hospital staff and served as a control group. For the radiological study, reference values from the original description of the method were used (Abrahamsson et al. 1988).
Clinical evaluation and follow-up

All patients were evaluated with digital examination and rigid proctoscopy. A barium enema or colonoscopy was performed in most patients to exclude structural colonic abnormalities. Exceptions were young patients without any signs of organic disease. Metabolic causes of constipation, such as hypothyroidism or diabetes mellitus, were excluded by standard blood tests. A criterion for further evaluation was that the patients had tried dietary measures and bulking agents for approximately three months with inadequate effect.

A validated questionnaire (Österberg et al. 1996) was used in the assessment of the patients (Study I-II). It included 49 questions regarding symptoms associated with constipation, anal incontinence, previous anorectal surgery and obstetric history. This questionnaire was also used in the follow-up of patients after surgery (Study II). In addition the patients were asked to rate the result of the operation as either excellent, good, fair or poor, and to state whether they would recommend the operation to a relative with the same symptoms.

Radio-opaque marker study (I-IV)

The method described by Abrahamsson et al. was used (Abrahamsson et al. 1988). The patients ingested ten ring-shaped markers daily at the same hour for six consecutive days. On the seventh day a plain abdominal radiograph was obtained (Figure 1). The patients kept their usual diet and social activities but no laxatives or enemas were allowed during the study period.

In healthy individuals, as well as in constipated patients, a steady state between ingested and excreted markers is reached within seven days. The distribution of markers on the radiograph depends on segmental transit time.

The total gastrointestinal transit time (GITT) in days was defined by the formula: \((M + 5) / 10\), where \(M\) is the number of retained markers on the radiograph. Segmental colonic transit times were calculated as: \(M_{\text{segm}} / 10\), where \(M_{\text{segm}}\) is the number of markers in the respective segment. The defined segments were: 1, the ascending colon including the hepatic flexure, 2, the transverse colon, 3, the descending colon including the splenic flexure and 4, the recto-sigmoid colon.

The upper 95th percentile of the GITT in healthy subjects is 4.7 days in women and 2.8 days in men. Since the transit time through the upper gastrointestinal tract is short, GITT mainly reflects the colonic transit time. The corresponding values for segmental transit time is 1.3 days for the ascending-, 0.7 days for the transverse-, 2.3 days for the descending-, and 1.3 days for the recto-sigmoid colon in women and 1.0, 0.5, 1.2 and 1.3 days respectively in men.
Segmental colonic scintigraphy (I-II, IV)

Ten millilitres of 15 MBq $^{111}\text{In}$-DTPA, suspended in saline, was ingested. Using a gamma camera (Siemens PHO-Gamma LFOV, Erlangen, Germany or Maxxus (dual-head), GE Medical Systems, Milwaukee, Wisconsin, USA), anterior and posterior scans were obtained in the supine position. Assessment of uptake was performed on calculated geometric mean values from the anterior and the posterior scan. The images were collected after 1, 2, 3, 6 and 24 hours, and then every 24 hours until the radioactive tracer had been evacuated. Using a customised software program (Hermes software package, Nuclear Diagnostics, Hägersten, Sweden), radionuclide decay was corrected for and the colon was outlined by adding the sequential scans.

The regions of interest (ROI) were defined and drawn for each subject as follows: ROI 1, caecum and half of the ascending colon; ROI 2, distal half of the ascending colon including the hepatic flexure; ROI 3, right half of the transverse colon; ROI 4, left half of the transverse colon; ROI 5, splenic flexure including the overlapping proximal part of the descending colon; ROI 6, distal part of the descending colon; ROI 7, sigmoid colon and ROI 8, rectum, Figure 3. The total number of registered counts in each composed image was normalised to 100 and the percent activity in each ROI calculated.

Figure 3. The eight regions of interest at colonic transit scintigraphy. © 2004 Blackwell Publishing Ltd. Colorectal Disease, 6, 499–505.
The subjects were instructed to keep their usual diet but no laxatives or enemas were allowed during the registration period. The week before and during the investigation period each patient kept a diary where bowel movements, diet, medication and activities were registered. The progression of the geometric centre (GC) of tracer over time, as described by Krevsky et al. (Krevsky et al. 1986), and the percent activity in different segments at different time points were calculated. The inter-observer variation in the interpretation of the scans was evaluated by comparing the number of counts at six, 24 and 96 hours in the eight ROIs, as drawn by two independent observers (Study I).

Video defecography (II-III)

Video defecography was performed as previously described by Karlbom et al. (Karlbom et al. 1999). A semisolid barium contrast was instilled in the rectum and the small bowel was outlined by oral contrast taken one hour before the study. Video radiographs were taken from the left lateral view at rest and while squeezing and straining to evacuate the contrast medium. Ano-rectal angles, signs of paradoxical puborectalis contraction, rectocele, enterocele, circular intussuception, and contrast leakage were registered. The rectal evacuation rate was evaluated by computer based area calculation. The area of the lower eight cm of the rectum with homogenous contrast was calculated (pixels) at rest, after the initial evacuation (i.e. first strain) and after the total evacuation period, and the evacuation rate was expressed as percent evacuated area per second.

Anorectal manovolumetry (II-III)

A method originally described by Åkervall et al. was used (Åkervall et al. 1988b). The anal pressures were measured using an endotracheal tube connected to a pressure transducer. The cuff was filled with 2.5 ml of water at body temperature. A thin walled highly compliant polyethylene bag with a maximal volume of 500 ml was used as a rectal balloon. A plastic catheter was led through the endotracheal tube and connected to the rectal balloon thereby allowing simultaneous measurements of anal pressures and rectal volumes. Isobaric rectal distension pressures were generated, by creating a difference in height between two water reservoirs.

Anal resting- and squeeze pressures and the frequency and amplitude of SW and ultra slow waves were registered. The rectal volume was recorded after 4, 18 and 60 seconds at each 5 cm H$_2$O pressure increment (5-40) and at 50 and 60 cm H$_2$O. The subjects were instructed to report the first perception of filling, urge and pain. The rectal compliance (ml/cm H$_2$O) was calcu-
lated after 4, 18 and 60 seconds at different pressure levels as well as at the thresholds of the different subjective sensations. The threshold for eliciting the RAIR and the amplitude of the reflex was registered. The recovery to resting pressure after eliciting the RAIR was noted after 30 and 60 seconds and expressed as percent of the reflex amplitude.

Our routines for performing the investigation have previously been described in detail (Holmberg et al. 1995).

Electromyography (II)

EMG was recorded with hook electrodes in the external anal sphincter and the puborectalis muscles. The EMG amplitude (mV) was registered at rest and while straining and squeezing in the left lateral and sitting positions and while expelling a balloon (Foley catheter Ch 18 filled with 40 ml of water at body temperature). A strain/squeeze index (100 x strain amplitude/squeeze amplitude) was calculated from the EMG measurements for the external anal sphincter and the puborectalis muscle, in the two positions and at balloon expulsion. A mean value of the five indices exceeding 50 was considered as paradoxical activity (Karlbom et al. 1998).

Surgical procedures (II)

The anastomosis in left hemicolectomy was made between the mid-transverse colon and the upper rectum at the level of the sacral promontory. In right hemicolectomy, it was made between the distal ileum and the mid-, to distal transverse colon. In some patients a suture rectopexy was performed together with the left hemicolectomy. The indications for rectopexy were rectal prolapse or intra anal intussusception on defecography, together with symptoms (incomplete rectal emptying, faecal incontinence, rectal pain).

Statistics

Non parametric statistical methods were used. The Mann Whitney U test was used to compare groups (Study I-IV). Correlation was studied by the Spearman Rank correlation test (Study I, III-IV). Fisher's exact test was used to analyse differences in proportions (Study III). Treatment effects were evaluated using Wilcoxon’s matched pairs test for numerical values and McNemar’s test for categorical answers (Study II). McNemar’s test was also used to compare different methods (Study IV). Presented data are median (and range) unless otherwise stated. All P-values are two-tailed, and a P-value below 0.05 was considered as statistically significant.
STATISTICA software was used for the calculations (StatSoft, Tulsa, Oklahoma, USA).

Ethics
Approval for the studies was obtained from the Ethics Committees for Clinical Research (Study I-IV) and for Radiation Safety (Study I) at the University of Uppsala.
Results

Paper I

Comparison of the scintigraphic results in patients and control subjects

According to diaries, the patients had a median (range) of 4.5 (0-30) stools during the week before the study, with the use of laxatives and/or enemas. During the study period when no laxatives or enemas were allowed, the patients had a median (range) of 3.0 (0-50) stools weekly, compared to 8.0 (5-21) for controls.

The position of the geometric centre (GC) for patients did not differ from controls during the first 24 hours. After 24 hours, when the GC had reached the transverse colon, there was a consistent delay for patients throughout the investigation ($P<0.05$–$0.001$), *Figure 4*.

*Figure 4.* Geometric centre of tracer for constipated patients and control subjects (mean value). NS, not significant. *$P<0.05$*. **$P<0.01$**. ***$P<0.001$**. Mann–Whitney U test. © 2004 Blackwell Publishing Ltd. Colorectal Disease, 6, 499–505.
When comparing the GC of the subgroup of patients that had been treated for coexisting outlet obstruction before the scintigraphic study with the patients who had an isolated STC, there was no significant difference at any time point (all $P>0.20$).

Curves illustrating percent radioactivity over time showed that the patients had an increased retention of the radioactive tracer in the left (ROI 4–6) and recto-sigmoid colon (ROI 7–8), whereas the transit pattern in the right colon did not differ from the controls, Figures 5–7.

The median (range) number of days to evacuate the tracer was $>9.0$ (5–13) for patients and $4.5$ (3–8) for controls ($P<0.001$). For social reasons some patients with long transit times ended the investigation before the tracer was completely evacuated.

Figure 5. Percentage radioactivity in the right colon (ROI 1–3) for constipated patients, control subjects (mean value) and two individual patients with right-sided delay. © 2004 Blackwell Publishing Ltd. Colorectal Disease, 6, 499–505.

Individual patients

Although the scintigraphic transit pattern in the right colon (ROI 1–3) was similar to the controls for most patients, two patients showed a marked delay in that segment, Figure 5. In the left colon (ROI 4–6) they had a relatively rapid transit, Figure 6. One of the two patients had a rapid transit through the recto-sigmoid colon, whereas the other patient accumulated the tracer in a redundant sigmoid colon, Figure 7.
Figure 6. Percent radioactivity in the left, including the descending colon (ROI 4–6) for constipated patients, control subjects (mean value) and two individual patients with right-sided delay. © 2004 Blackwell Publishing Ltd. *Colorectal Disease*, 6, 499–505.

Figure 7. Percentage radioactivity in the recto-sigmoid colon (ROI 7–8) for constipated patients, control subjects (mean value) and two individual patients with right-sided delay. © 2004 Blackwell Publishing Ltd. *Colorectal Disease*, 6, 499–505.
Inter-observer variation

The inter-observer variation in the interpretation of the scans was assessed comparing each ROI. The $R$-values were generally higher in the proximal colon and showed somewhat lower values more distally, Table 4. Only for ROI 8 at six hours, there was no significant correlation. When dividing the colon into three segments, the right (ROI 1–3), the left (ROI 4–6) and the recto-sigmoid colon (ROI 7–8), respectively, the $R$-values exceeded 0.7 ($P<0.001$) with the exception of ROI 7–8 at six hours where the $R$-value was 0.58 ($P<0.01$), Table 5.

Table 4. Inter-observer variation of regions of interest (ROI). $R$-values at 6, 24 and 96 hours after ingestion of $^{111}$In-DTPA

<table>
<thead>
<tr>
<th></th>
<th>6 hours (n=19)</th>
<th>24 hours (n=27)</th>
<th>96 hours (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI 1</td>
<td>0.90</td>
<td>0.94</td>
<td>0.84</td>
</tr>
<tr>
<td>ROI 2</td>
<td>0.95</td>
<td>0.91</td>
<td>0.93</td>
</tr>
<tr>
<td>ROI 3</td>
<td>0.90</td>
<td>0.81</td>
<td>0.87</td>
</tr>
<tr>
<td>ROI 4</td>
<td>0.89</td>
<td>0.86</td>
<td>0.87</td>
</tr>
<tr>
<td>ROI 5</td>
<td>0.94</td>
<td>0.91</td>
<td>0.63**</td>
</tr>
<tr>
<td>ROI 6</td>
<td>0.52*</td>
<td>0.72</td>
<td>0.57**</td>
</tr>
<tr>
<td>ROI 7</td>
<td>0.52*</td>
<td>0.62</td>
<td>0.68</td>
</tr>
<tr>
<td>ROI 8</td>
<td>0.12 NS</td>
<td>0.40*</td>
<td>0.62**</td>
</tr>
</tbody>
</table>

NS, not significant. *$P<0.05$. **$P<0.01$. All other values $P<0.001$. Spearman Rank correlation test

Table 5. Inter-observer variation of groups of regions of interest (ROI), the right-left- and recto-sigmoid colon respectively. $R$-values at 6, 24 and 96 hours after ingestion of $^{111}$In-DTPA

<table>
<thead>
<tr>
<th></th>
<th>6 hours (n=19)</th>
<th>24 hours (n=27)</th>
<th>96 hours (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right colon (ROI 1–3)</td>
<td>0.86</td>
<td>0.98</td>
<td>0.76</td>
</tr>
<tr>
<td>Left colon (ROI 4–6)</td>
<td>0.95</td>
<td>0.96</td>
<td>0.83</td>
</tr>
<tr>
<td>Recto-sigmoid colon (ROI 7–8)</td>
<td>0.58**</td>
<td>0.73</td>
<td>0.83</td>
</tr>
</tbody>
</table>

**$P<0.01$. All other values $P<0.001$. Spearman Rank correlation test
Paper II

Clinical outcome

After segmental colonic resection, there were no deaths in hospital or within 30 days, and no major complications that necessitated reoperation. One patient had a prolonged postoperative ileus. The median (range) postoperative hospital stay was seven (4-30) days.

The operation was considered a failure in five patients because each finally required further surgery. Three of these patients underwent surgery before follow-up; one had a colostomy, one an appendicostomy and one patient underwent several operations without resolving the constipation. The latter patient was finally diagnosed with gastrointestinal pseudo-obstruction. Two patients had recurrent constipation, with gradual onset of symptoms after six and 12 months. These patients, one of whom reported a fair, and the other a poor result at follow-up, later had an IRA.

Six patients were subsequently readmitted to hospital. Two underwent surgery for small bowel obstruction and one had a repair of an incisional hernia.

Functional outcome

After a median (range) follow-up of 50 (16-78) months, the result of the operation was considered as good or excellent by 17 patients and fair by seven patients. Four patients reported a poor result. Twenty-three patients would recommend the operation to a relative, Table 6.

Table 6. Global outcome of segmental colonic resection for slow transit constipation as rated by 28 patients, and number of patients recommending the operation

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of patients</th>
<th>No. recommend op.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Good</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Fair</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Poor</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients who underwent further surgery before follow-up, due to unsuccessful results (n=3), were considered to have a poor result and not to recommend the operation.

The median (range) stool frequency increased from one (0-7) to seven (0-63) per week \( (P<0.001) \). Twenty of 25 patients had a postoperative stool frequency between three per day and three per week. A reduction was seen in the number of patients with excessive straining \( (P=0.041) \) as well as the percentage of time spent straining at defecation \( (P=0.025) \). The incidence of bloating and painful defecation was reduced \( (P=0.021 \) and \( P=0.013 \) respectively) whereas the proportion of patients with abdominal pain was unchanged, Table 7.
Table 7. Functional outcome of segmental colonic resection in 25 patients with slow transit constipation

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>Follow-up</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency (per week)*</td>
<td>1.0 (0-7)</td>
<td>7.0 (0-63)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>14</td>
<td>=0.074‡</td>
</tr>
<tr>
<td>Bloating</td>
<td>24</td>
<td>18</td>
<td>=0.021‡</td>
</tr>
<tr>
<td>Excessive straining</td>
<td>19</td>
<td>13</td>
<td>=0.041‡</td>
</tr>
<tr>
<td>Percentage time straining*</td>
<td>88.5 (10-100)</td>
<td>52.5 (0-100)</td>
<td>=0.025†</td>
</tr>
<tr>
<td>Painful defaecation</td>
<td>13</td>
<td>5</td>
<td>=0.013‡</td>
</tr>
</tbody>
</table>

Values are numbers of patients or *median (range). †Wilcoxon's matched pairs test. ‡McNemar's test.

The number of patients with hard stools decreased from 12 to three \((P=0.016)\) and the number with normal stool consistency increased from one to seven \((P=0.041)\). Furthermore, the use of laxatives and enemas decreased.

Table 8. The median (range) symptom index at follow-up was 4.5 (0-10), compared with 6.5 (3-11) before surgery \((P<0.001)\).

Faecal continence improved in eight patients and deteriorated in five. The Miller incontinence score increased from a median of 1.0 to 3.0 \((P=0.46)\). One patient, who underwent left hemicolectomy, developed diarrhoea after operation with about nine loose stools daily.

Table 8. Use of medication for constipation in 25 patients before and after segmental colonic resection for slow transit constipation

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>Follow-up</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No laxatives / enemas</td>
<td>0</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bulking agents</td>
<td>16</td>
<td>5</td>
<td>0.006</td>
</tr>
<tr>
<td>Motor stimulants</td>
<td>14</td>
<td>3</td>
<td>0.010</td>
</tr>
<tr>
<td>Enemas, all types</td>
<td>15</td>
<td>3</td>
<td>0.002</td>
</tr>
<tr>
<td>Combination of laxatives</td>
<td>15</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are numbers of patients. \(^*\)McNemar's test.

Correlation to outcome

The median (range) preoperative stool frequency was 0 (0-0.5) per week in those whose operation failed and one (0-7) in patients who had a successful outcome \((P<0.001)\). The median (range) percentage of time spent straining at defecation was 100 (95-100) and 82 (10-100) percent respectively \((P=0.042)\). There were no differences between the patients who had a successful outcome and those who did not with respect to other preoperative symptoms, the patients' age at onset of constipation (before or after 30 years of age), previous surgery or primary treatment of obstructed defecation.

All five patients whose operation failed had impaired rectal sensory function, with distension pressure thresholds for sensation of filling as well as
urge, exceeding the normal range on preoperative manovolumetry. Among the 23 patients with successful outcome, four had impaired rectal sensation \((P<0.001)\), Table 9. There was no difference in anal pressures or the threshold pressure required to elicit the RAIR. The initial rate of rectal evacuation on defecography was lower in patients whose operation failed than in the other patients \((P=0.025)\), Table 9. The median strain-squeeze index on EMG was within the normal range in both groups, and the gastrointestinal transit time did not differ between the groups, Table 9.

Of the two patients with a right colonic delay identified on scintigraphy, treated with a right hemicolecctomy, one had a fair result and recommended the operation and the other one was among the early failures. The two patients with a marginally prolonged transit time had an excellent and a fair outcome, respectively, and both recommended the operation. Of the six patients who had a rectopexy with left hemicolecctomy, three had a good or excellent result and three had a fair outcome; all six recommended the operation.

Table 9. Results of preoperative evaluation in relation to outcome of surgery

<table>
<thead>
<tr>
<th></th>
<th>Failed operation ((n=5))</th>
<th>Successful operation ((n=23))</th>
<th>(P^{**})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manovolumetry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold pressure for rectal filling sensation* ((\text{cm} \text{H}_2\text{O}))</td>
<td>50 (30-60)</td>
<td>20 (5-35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Threshold pressure for urge to defaecate† ((\text{cm} \text{H}_2\text{O}))</td>
<td>&gt;60</td>
<td>35 (20-60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Defaecography‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial rectal evacuation rate</td>
<td>1.9 (0-3.4)</td>
<td>5.2 (0-11.4)</td>
<td>=0.025</td>
</tr>
<tr>
<td>Total rectal evacuation rate</td>
<td>1.6 (0-2.5)</td>
<td>2.6 (0.5-8.3)</td>
<td>=0.15</td>
</tr>
<tr>
<td><strong>Electromyography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain / squeeze index§</td>
<td>3.0 (0-52)</td>
<td>21.5 (0-118)</td>
<td>=0.11</td>
</tr>
<tr>
<td><strong>Radio-opaque marker study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transit time (days¶)</td>
<td>5.4 (5.0-6.3)</td>
<td>5.9 (4.2-6.5)</td>
<td>=0.38</td>
</tr>
</tbody>
</table>

Values are median (range). *Normal range 10-25 cmH\(_2\)O (maximum measurement 60 cmH\(_2\)O). †Normal range 20-50 cm H\(_2\)O (maximum measurement 60 cmH\(_2\)O). ‡Percent area evacuated / sec. calculated for 5 failures and 16 successes. §Normal value \(
=4.7\) days for women and \(=2.8\) days for men. **Mann-Whitney \(U\) test.

Paper III

Anal manometry (Sphincter function)

Anal resting pressure was lower in patients compared to controls: median (range) 54 (22-130) vs. 68 (35-100) cm H\(_2\)O \((P=0.03)\), and 12 patients had pressures below the 5\(^{th}\) percentile of controls. Maximal squeeze pressure tended to be lower in patients than in controls: 147 (53-382) vs. 177 (65-423) cm H\(_2\)O \((P=0.09)\).
Ultra slow waves were an unusual finding, 2 patients and 4 controls showed this variation in resting pressure, whereas SW were seen in most subjects (76 of 78). The frequency of SW differed between patients and control subjects. The median frequency in patients was 9 (0-12) per minute, compared to 12 (6-17) in controls ($P<0.001$). In all, 22 patients (44 %) were outside the 5th–95th percentile of controls in at least one of the above analysed sphincter function parameters.

Rectal volumetry (Rectal function)

The thresholds for filling sensation: median (range) 15 (5-60) vs. 20 (10-25) cm H$_2$O ($P=0.52$), for urge: 30 (15->60) vs.30 (15-60) cm H$_2$O ($P=0.49$), and for pain: 50 (25->60) vs. 50 (25->60) cm H$_2$O ($P=0.85$), did not differ between patients and controls. In the pressure interval of 5-60 cm H$_2$O, all patients and all controls perceived filling. Six patients did not experience urge and 16 patients did not feel pain. The corresponding figures for control subjects were 0 and 7 respectively ($P=0.08$, $P=0.61$). However, ten patients had a threshold for filling sensation above the 95th percentile of controls. In a similar way, nine patients had a threshold for urge above the 95th percentile of controls. In all, 12 patients were outside the 5th–95th percentile of the control group regarding rectal sensation.

Rectal compliance was consistently higher in patients in the pressure interval 5-35 cm H$_2$O, Figure 8. There was a significant difference at all time points measured (4, 18, and 60 seconds, $P=0.04$–0.001).

![Figure 8](image_url)

*Figure 8.* Rectal compliance at 60 seconds in constipated patients with slow colonic transit and control subjects. *$P<0.05$. **$P<0.01$. Mann–Whitney $U$ test.*
Recto-anal inhibitory reflex.

The threshold for, and the maximal amplitude of the RAIR, did not differ between the groups, Table 10. In one patient the reflex could not be elicited, but when re-examined with a larger balloon, the reflex was seen. The recovery of anal resting pressure after eliciting the reflex was reduced in patients in the pressure interval 10-50 cm H$_2$O ($P=0.05$–<0.001), Table 10.

Table 10. Quality of the recto-anal inhibitory reflex (RAIR) in constipated patients with slow colonic transit and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=50)</th>
<th>Controls (n=28)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold for the RAIR</td>
<td>10 (5-50)</td>
<td>15 (10-25)</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximal RAIR amplitude</td>
<td>38 (10-100)</td>
<td>35 (13-80)</td>
<td>0.54</td>
</tr>
<tr>
<td>Reflex at 15 cm H$_2$O of rectal distension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAIR amplitude</td>
<td>18 (0-75)</td>
<td>14 (0-50)</td>
<td>0.14</td>
</tr>
<tr>
<td>Recovery 30 sec (%)</td>
<td>45 (0-100)</td>
<td>57 (0-100)</td>
<td>0.03</td>
</tr>
<tr>
<td>Recovery 60 sec (%)</td>
<td>45 (14-140)</td>
<td>53 (0-137)</td>
<td>0.05</td>
</tr>
<tr>
<td>Reflex at 25 cm H$_2$O of rectal distension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAIR amplitude</td>
<td>27 (0-64)</td>
<td>30 (10-75)</td>
<td>0.51</td>
</tr>
<tr>
<td>Recovery 30 sec (%)</td>
<td>42 (0-140)</td>
<td>60 (14-150)</td>
<td>0.001</td>
</tr>
<tr>
<td>Recovery 60 sec (%)</td>
<td>41 (0-110)</td>
<td>66 (0-150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reflex at 35 cm H$_2$O of rectal distension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAIR amplitude</td>
<td>31 (0-110)</td>
<td>34 (7-70)</td>
<td>0.21</td>
</tr>
<tr>
<td>Recovery 30 sec (%)</td>
<td>27 (0-225)</td>
<td>47 (28-119)</td>
<td>0.002</td>
</tr>
<tr>
<td>Recovery 60 sec (%)</td>
<td>20 (0-150)</td>
<td>60 (0-158)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are median (range) cm H$_2$O unless otherwise stated. Mann–Whitney U test.

Relationships to other data

Male patients had higher resting pressure: median (range) 84 (55-100) vs. 50 (22-130) cm H$_2$O ($P=0.01$), and squeeze pressure: 261 (185-362) vs. 125 (53-284) cm H$_2$O ($P<0.001$), than female patients. Otherwise, there were no differences according to gender. There was no correlation between physiological variables and age, symptom duration or age at onset of symptoms (data not shown). Rectal size (lateral area of the rectum on defecography) did not correlate to rectal compliance ($R=-0.06$–0.16, $P=0.29$–0.99).

Of the two patients operated on with rectopexy, one had no deviations in sphincter or rectal parameters whereas the other had clearly elevated thresholds for rectal sensation. A previous hysterectomy did not influence anorectal physiology (data not shown). Twenty-two patients had a colonic transit time of more than 6 days (retaining more than 90 percent of the markers) and were analysed as a subgroup. Rectal compliance was higher in the interval 5-50 cm H$_2$O in these patients compared to other patients, Table 11. Otherwise there were no physiological differences between the subgroups.
Table 11. Rectal compliance in subgroups of constipated patients with slow colonic transit

<table>
<thead>
<tr>
<th>Rectal compliance (ml/cm H2O)</th>
<th>GITT&gt;6 days (n= 22)</th>
<th>GITT&lt;6 days (n= 28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 cm H2O of rectal distension</td>
<td>7.0 (2.0-12.6)</td>
<td>4.9 (1.7-10.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>25 cm H2O of rectal distension</td>
<td>6.8 (1.8-9.9)</td>
<td>4.7 (1.7-9.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>35 cm H2O of rectal distension</td>
<td>6.1 (2.0-9.1)</td>
<td>5.1 (1.9-7.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

GITT, gastrointestinal transit time. Values are median (range). Mann–Whitney U test.

Paper IV

Ninety percent of the female control subjects had evacuated the radioactive tracer completely by day eight. Thus, the upper normal limit for the total transit time on scintigraphy was 8 days. The normal segmental transit time was below 1 day for the ascending-, below 2 days for the transverse-, below 5.5 days for the descending- and below 3 days for the recto-sigmoid colon. Figure 9 shows the median value, the 10th and the 90th percentile of the GC-curve for the female controls. By day five, half of the controls had evacuated the tracer.

Figure 9. Progression of the geometric centre (GC) of tracer for 11 female control subjects on scintigraphy. ROI, region of interest.
Of the 31 female patients, 27 had a prolonged total colonic transit time on the radio-opaque marker study and 26 (missing data on one patient) on the scintigraphic study.

Table 12 illustrates the pattern of prolonged segmental transit time on the radiological marker study. Fourteen patients had a prolonged transit time in one segment, 15 patients in two segments and one patient in three segments. None of the patients had a prolonged transit time in all four segments. A prolonged transit time in the ascending colon was found in 11 patients, in the transverse colon in 13 patients, in the descending colon in 6 patients and in the recto-sigmoid colon in 17 patients. Seven patients had a prolonged transit time in two non-adjacent segments.

Table 12. Segmental distribution of radio-opaque markers in 31 constipated female patients

<table>
<thead>
<tr>
<th>Colonic segment</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal in all segments</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged in one segment</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>2</td>
</tr>
<tr>
<td>TC</td>
<td>3</td>
</tr>
<tr>
<td>DC</td>
<td>0</td>
</tr>
<tr>
<td>RS</td>
<td>9</td>
</tr>
<tr>
<td>Prolonged in two segments</td>
<td></td>
</tr>
<tr>
<td>AC TC</td>
<td>4</td>
</tr>
<tr>
<td>AC DC</td>
<td>1</td>
</tr>
<tr>
<td>AC RS</td>
<td>3</td>
</tr>
<tr>
<td>TC DC RS</td>
<td>2</td>
</tr>
<tr>
<td>TC RS</td>
<td>3</td>
</tr>
<tr>
<td>DC RS</td>
<td>2</td>
</tr>
<tr>
<td>Prolonged in three segments</td>
<td></td>
</tr>
<tr>
<td>AC TC DC</td>
<td>1</td>
</tr>
<tr>
<td>AC TC RS</td>
<td>0</td>
</tr>
<tr>
<td>AC DC RS</td>
<td>0</td>
</tr>
<tr>
<td>TC DC RS</td>
<td>0</td>
</tr>
</tbody>
</table>

AC, ascending colon. TC, transverse colon. DC, descending colon. RS, recto-sigmoid colon.

The progression of the GC for female patients and controls on scintigraphy is illustrated in Figure 10. By six hours, at which time the GC had reached the end of the ascending colon, there was no significant difference between groups. However, from 24 hours and onward, representing the transit from the middle transverse colon and distally, the progression of the GC was slower for the patient group ($P < 0.05 - 0.001$).

Table 13 shows the number of patients with a prolonged or a normal, total and segmental transit time as measured by radio-opaque markers and scintigraphy. There was no significant difference between the two methods except
in the descending colon, where more patients were diagnosed with a prolonged transit time by scintigraphy than by marker study \( (P=0.02) \). Comparison of the methods with respect to recto-sigmoid transit time could not be made, since the GC did not pass the segment in a considerable number of patients.

**Figure 10.** Progression of the geometric centre (GC) of tracer for 31 female patients and 11 female control subjects on scintigraphy. Median values for groups. ROI, region of interest. NS, not significant. \*\( P<0.05 \), \**\( P<0.01 \), \***\( P<0.001 \). Mann–Whitney U test.

**Table 13.** Results of radio-opaque marker studies and scintigraphy in 31 constipated female patients. Prolonged or normal transit time as identified by the respective method

<table>
<thead>
<tr>
<th>Method</th>
<th>Prolonged Radiol</th>
<th>Prolonged Scint</th>
<th>Normal Radiol</th>
<th>Normal Scint</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>17</td>
<td>=0.11</td>
</tr>
<tr>
<td>TC</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>=0.77</td>
</tr>
<tr>
<td>DC</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>12</td>
<td>=0.02</td>
</tr>
<tr>
<td>TOT</td>
<td>23</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>=0.68</td>
</tr>
</tbody>
</table>

Figures are numbers of patients. Radiol, gastrointestinal transit time on marker study. Scint, transit time of geometric centre. AC, ascending colon. TC, transverse colon. DC, descending colon. TOT, total colonic transit time. Mc Nemar’s test.

Agreement in the results of the radiological and the scintigraphic study was seen in 20 patients in the ascending colon (\( n=30 \)), in 16 patients in the transverse colon (\( n=28 \)), in 16 patients in the descending colon (\( n=30 \)) and
in 24 patients for total colonic transit (n= 30), Table 13. In the recto-sigmoid colon there was agreement in eight out of the 12 patients where comparison could be made (data not shown).

There was a significant correlation between the GITT and the position of the GC at ten days ($R = -0.46$, $P=0.02$) when tested for all 35 patients (the four men included). At all other time points, there was no significant correlation ($R = -0.12– -0.41$, $P= 0.06–0.52$).
General discussion

Constipated patients

Patients with chronic constipation can usually be characterised as having STC, obstructed defecation, a combined STC and obstructed defecation, or the IBS, based on symptoms, radiological, and physiological investigations. In the present studies, all patients had slow colonic transit, as diagnosed by radio-opaque marker study, which excludes patients with IBS. Thus, STC was defined as the clinical entity with constipation symptoms and a prolonged GITT. This group is most likely heterogeneous, comprising different aetiologies of STC. Obstructed defecation has been proposed to be one cause of STC (Kuijpers 1990). In the present material, those patients were considered to belong to the mixed group, i.e. with combined STC and obstructed defecation. However, it is possible in theory that a patient with a severe recto-sigmoid stasis due to outlet obstruction, could have a prolonged GITT without having a motility disorder of the colon. In such a case, biofeedback treatment should lead to a normalised transit time together with improvement in symptoms.

The GITT was slightly below the 95th percentile of healthy controls in a few cases in Study II (n=2) and Study IV (n=4), however, those patients had the clinical picture of STC. A coexisting obstructed defecation had been treated with biofeedback before entering Study I and II. The symptomatic relief was unsatisfactory, why the patients were further evaluated with scintigraphy. In Study IV, treatment of obstructed defecation between the radiological and the scintigraphic transit investigation was an exclusion criterion. The study thus includes patients from both the STC and the mixed group, although the symptoms of obstructed defecation were not so severe, as to warrant biofeedback before further evaluation. Study III focused on patients with STC as possible candidates for a colonic resection. A previous study comparing subgroups of constipated patients based on clinical presentation showed that infrequent defecation was related to alterations in anorectal physiology, whereas symptoms of obstructed defecation were not (Karlbom et al. 2004). Thus, coexisting symptoms of obstructed defecation was not an exclusion criterion in Study III.
Aspects of evaluation and diagnosis

All patients in the present studies underwent a minimum evaluation by radio-opaque marker study, defecography, EMG and anorectal manovolumetry. Radio-opaque marker study is a widely used method to diagnose STC. Measurement of the colonic transit time may occasionally be the only way to differ between STC and constipation predominant IBS. Radio-opaque marker study may also give a crude estimate of segmental colonic transit (see below).

Defecography shows anatomical and some physiological abnormalities in the anorectal area. A rectocele and a paradoxical puborectalis contraction are both associated with a lower evacuation rate (Karlbom et al. 1999), and are common causes of obstructed defecation.

EMG was used to diagnose paradoxical contraction of the external sphincter or puborectalis muscle. A strain/squeeze index exceeding 50 percent was a criterion to offer the patient biofeedback retraining for obstructed defecation. If a patient suffers from faecal incontinence in addition to constipation, the electrophysiological study may also include single fibre EMG of the external anal sphincter and measurement of pudendal nerve terminal motor latency to diagnose neurological damage.

Evaluation of anorectal physiology by means of manovolumetry usually does not help in finding the cause of constipation in individual patients. However, the results may have a predictive value for the outcome of surgical therapy.

Study III showed several alterations in sphincter function in patients with slow colonic transit. A reduced anal resting pressure, a lower grade of recovery following the RAIR and a lower frequency of SW indicate an impaired function of the internal anal sphincter. There was also a tendency towards lower squeeze pressure in the patient group, and overall 44 percent of the patients were outside the 5th to 95th percentile of controls in at least one of the analysed sphincter parameters. Some of these patients would most likely be at risk of faecal incontinence if they would undergo a colectomy for constipation (see next section). The finding of a lower anal resting pressure is consistent with the study by Read et al. (Read et al. 1986) who examined 14 women with STC. Other studies did not find any difference in resting pressure between constipated patients and controls. This may be explained by patients with a normal transit time being included (Waldron et al. 1988), or by transit time not being assessed (Varma and Smith 1988). Another explanation may be that the control subjects were older than the patients (Roe et al. 1986, Varma and Smith 1988), since anal pressure has been shown to decrease with age in normal subjects (Åkervall et al. 1990).

STC is a motility disorder of unknown aetiology, sometimes associated with a dysfunction of the upper gastrointestinal tract (Bassotti et al. 1996). Abnormalities of the internal sphincter are not surprising, since this sphincter is an extension of the colonic smooth muscle. Another finding in the patients
with slow colonic transit was a significantly increased rectal compliance as compared to controls. This may be related to a lower tone in the rectal wall smooth muscle, which would also be congruent with a colonic motility disorder. Furthermore, the subgroup of patients with a transit time exceeding six days had a significantly higher rectal compliance, as compared to the patients with a more moderately prolonged transit time. This finding suggests an association between the degree of colonic motility dysfunction and the severity of anorectal disturbances.

Rectal sensation did not differ between the patient group and the controls. However, a quarter of the patients had rectal sensory thresholds exceeding the 95th percentile of controls. A blunted rectal sensation has been found to be associated with poorer functional results after colectomy for STC (Åkervall et al. 1988a, Pluta et al. 1996). An impaired rectal sensation can be improved with biofeedback treatment (Rao et al. 1997, Battaglia et al. 2004). Thus, preoperative biofeedback may possibly have a favourable impact on the functional outcome of surgery, although this requires further studies.

Total colonic transit time is usually expressed as oro-anal transit time or GITT. Since the transit time in the upper gastrointestinal tract is short, as compared to the colonic transit time, this estimate reflects well colonic transit. In order to minimise the radiation exposure, marker studies by single X-ray techniques are commonly used (Metcalf et al. 1987, Abrahamsson et al. 1988). Since the first radiological methods were described, scintigraphic techniques to assess colonic transit have been developed.

The scintigraphic technique described in Study I was evaluated with respect to right- or left sided colonic delay in patients with STC. The results showed a significantly delayed transit in the left colon for the patient group, whereas there was no difference as compared to controls as long as the GC was within the right colon. However, by analysing percent activity curves, two patients with a transit delay in the right colon, followed by a relatively rapid transit in the left colon could be identified. One of the two patients had a rapid transit throughout the recto-sigmoid colon, whereas the other accumulated the tracer in a redundant sigmoid colon.

About half of the patients initially had a coexisting obstructed defecation, which had been treated before the scintigraphic study. The GC curve did not differ at any time between these patients and the patients with an isolated STC. Thus, the transit pattern was not affected by remaining evacuation difficulties.

The accuracy of colonic transit scintigraphy depends on a correct delineation of the respective segments. The intra-individual correlation between two observers who independently drew the colonic ROIs was lower in the distal colon. This may be due to the mobility of the sigmoid colon, making it more difficult to identify. However, the correlation was generally good, except for ROI eight by six hours, i.e. before the tracer had reached the caecum. This variability may be due to whether the observer had corrected for the little
activity emitted from bowels nearby, or not. When comparing the three larger segments, used to identify transit patterns for individual patients, the correlation was highly significant.

Study IV compared a single X-ray radio-opaque marker method (Abrahamsson et al. 1988) with scintigraphy to assess total and segmental colonic transit. Comparison was difficult due to the different dynamics of the two methods. In the radiological study, the marker was administrated intermittently for several days and one picture taken, whereas in the scintigraphic study, the radioactive tracer was ingested once and several scans collected, usually during ten to 13 days. Furthermore, most radiological or scintigraphic methods, differ in the way transit time is defined and calculated, resulting in a variation in the numerical reference values (Wagener et al. 2004). The present methods could be compared for female patients by using existing normal values for the radiological study, and by defining corresponding values for the scintigraphic study. In view of the limited size of the scintigraphic control group, the 90th percentile was chosen instead of the 95th as the upper normal limit.

On radio-opaque marker study a prolonged transit time was seen in one segment in 14 out of 31 female patients and in nine of these the delay was in the recto-sigmoid colon. The latter finding probably reflects that the material included patients with coexisting obstructed defecation. However, in the 15 patients with prolonged transit in two segments, any combination of segments occurred in approximately the same number of patients. This may indicate a methodological error (see below) since the pathophysiology behind all these different patterns of delayed transit is difficult to explain. A prolonged transit in three or four segments was very uncommon, a finding which may have implications in the choice of surgical treatment (colectomy or segmental resection). The scintigraphic study also showed a segmental delay in most patients, since the progression of the GC differed between patients and controls only in the transverse colon and distally.

When compared with respect to prolonged or normal transit time, we could not show any significant difference between the two methods in the ascending colon, the transverse colon, or for the total colonic transit (Table 13). In the descending colon, however, 16 patients had a prolonged transit time on scintigraphy, as compared to six on radio-opaque marker study.

It was not possible to calculate the transit time for the GC in the recto-sigmoid colon in the patient group. Toward the end of a study little tracer remains and it is spread out in the distal colon after bowel movements. Consequently, the GC never reaches the end of the eighth ROI unless all tracer is completely evacuated, which was not the case in several patients. Patients with functional outlet obstruction might be easier identified by the radio-opaque marker study. However, this diagnosis is usually based on electromyography or defecography.
The radiological- and the scintigraphic investigations were not done simultaneously in the present study. Previous studies have addressed the intra-individual variation between repeat studies, and shown a good correlation for the total colonic transit time in healthy subjects and constipated patients (Abrahamsson et al. 1988, Degen and Phillips 1996, Nam et al. 2001, Sadik et al. 2003). Furthermore, a study of transit time in 25 constipated female patients, before and after bowel cleansing, showed that although the total transit time was reduced, the segmental distribution of markers was not altered (Sloots and Felt-Bersma 2002).

Radiological and scintigraphic techniques have previously been compared in constipated patients. One study (Stivland et al. 1991) found a significant correlation of transit in a large segment; the combined ascending and transverse colon. Another study (van der Sijp et al. 1993) compared the progression of the centre of mass (equal to GC) for markers, using a dual x-ray technique, and radioisotope, and showed that there was no significant difference between groups of patients at any time.

Unlike previous studies, we have compared transit in each segment in relation to controls. Although we were not able to demonstrate significant differences between the two methods (except for transit in the descending colon), there was a considerable variation in the results for individual patients, which is in agreement with the study by van der Sijp (van der Sijp et al. 1993). This variability may be due to either the properties of the respective method, or an intra-individual variation in colonic function.

In the absence of a "gold standard" for segmental colonic transit studies, the results of Study IV did not prove that one method is superior to the other. However, the radiological method is associated with several possible sources of error. If the different sets of markers are not ingested at the correct time point, the calculated GITT, and especially the segmental transit time will be inaccurate. The radioisotope tracer, on the other hand, is ingested under supervision of the laboratory staff. Whether a colonic mass movement occurs just before or after the single X-ray, will also highly affect the result. Furthermore, the colonic segments are often difficult to identify on a single radiograph, where the colon can only be outlined by its gas content, faeces, and the retained markers. Patients with chronic constipation often have a redundant colon (Joo et al. 1998), and deciding to which segment markers belong may be very difficult due to overlapping of mobile segments, such as the caecum, the transverse- and the sigmoid colon. On colonic transit scintigraphy, the entire colon can easier be outlined by superposing the consecutive scans. The dynamic sequence of images makes it easy to identify overlapping segments, although it may still be difficult to calculate the number of counts, if the tracer is within two overlapping segments at the same time of image collection.

It could be argued that a prolonged transit time in a segment does not necessarily mean an impaired motility within that segment, but rather an
effect of stasis from a distal functional obstruction. With respect to this, there is probably no difference between the radiological and the scintigraphic method. Segmental transit studies by existing techniques can not give a very detailed picture of segmentally impaired motility. However, with the intention to select patients for a segmental or subtotal colectomy, it is usually enough to differ between prolonged and normal transit in larger colonic segments.

In view of the variability of the results for individual patients, it seems wise to do a repeat transit study before surgery is embarked on. Improved results of subtotal colectomy have also been reported for patients where a prolonged total colonic transit time was confirmed by a second radio-opaque marker study (Nam et al. 2001). If a segmental colonic resection is considered, it is the authors' policy to do a radio-opaque marker study as a primary investigation, and to let it be followed by a scintigraphic study to verify the results.

Aspects of surgical treatment
Some patients with intractable STC can not get symptom relief by less than a surgical intervention. Success rates of IRA range from 50 to almost 100 percent. The varying results probably depend on both selection of patients and how a successful outcome is defined. For most healthy individuals a stool frequency of more than three per day, which is often the result of IRA, may not be acceptable. However, patients with a history of severe constipation for many years may accept the inconvenience of several loose stools daily, as opposed to their previous inability to pass stools. The situation is different if diarrhoea or faecal incontinence occurs following surgery. These disabling symptoms have been reported in up to 30 and 15 percent respectively after IRA (Kamm et al. 1988a, Redmond et al. 1995, Nylund et al. 2001, Glia et al. 2004), and have been found to correlate to a lower quality of life score (FitzHarris et al. 2003). Other consequences of this major operation are complications, such as intestinal obstruction, seen in up to 25 percent (Nylund et al. 2001).

Surgery for STC does not address the cause of constipation, but aims at reducing symptoms by removing a poorly functioning colon. This should be done with a minimum of adverse effects. Several aspects suggest that the motility dysfunction in STC has a segmental distribution. The right and left colon has different embryological origin, i.e. the right colon derives from the mid gut, and the left colon from the hind gut. Thus, the right colon has its parasympathetic nerve supply mainly from the vagus nerve, whereas the left colon is supplied by the pelvic splanchnic nerves (S2-S4). A disorder of the pelvic nerves has been suggested to be the cause of STC (Knowles et al. 2001). Abnormalities of the enteric nervous system have also been found
with a segmental distribution (Schouten et al. 1993, Yu et al. 2002). Furthermore, scintigraphic studies have identified different patterns of segmental slow transit, such as a delay in the right colon (Krevsky et al. 1989, Stivland et al. 1991), in the transverse colon and splenic flexure (Roberts et al. 1993) or a more distal delay in the left or recto-sigmoid colon (Kamm et al. 1988b, Krevsky et al. 1989, Stivland et al. 1991, Roberts et al. 1993).

Segmental colonic resection has been tried in order to minimise the side effects of IRA. To date, there are few studies reporting the outcome of segmental resection for STC (de Graaf et al. 1996, You et al. 1998). In these studies, radio-opaque markers were used to assess segmental transit time.

Study II addressed the outcome of segmental colonic resection in 28 patients with STC, resistant to medical therapy and treatment of coexisting obstructed defecation. The preoperative evaluation included assessment of segmental colonic transit with scintigraphy. Twenty-three patients out of 28 (80 %) were satisfied with the results. The stool frequency increased to a median of one per day among the 25 patients followed for a median of 50 months, and was achieved without laxatives, or with only bulking agents in 19 of these patients. One patient had postoperative persisting diarrhoea, but the median incontinence score did not change significantly. Similar to after IRA, bloating and abdominal pain remained common symptoms after surgery.

All five patients whose operation failed had an impaired rectal sensory function on preoperative manovolumetry, whereas only four of the 23 patients with a successful outcome had impaired rectal sensation. Thus, a blunted rectal sensation seems to correlate to a poorer outcome after segmental resection, which has also been reported after IRA (Åkervall et al. 1988a, Pluta et al. 1996). However, a more recent study reporting the results at a median of 11 years after IRA did not find any correlation between rectal sensation and outcome (Nylund et al. 2001). A possible explanation could be that the predictive value of rectal sensation decreases with longer follow-up. The success rates of IRA also appears to decrease with time (Knowles et al. 1999a) and these findings may be due to the progressive nature of STC. Of the five patients with an unfavourable outcome, two had received biofeedback retraining for obstructed defecation. The other three had not, since the indication for biofeedback did not include blunted rectal sensation in the present study. It is possible that their outcome could have been improved by preoperative biofeedback. However, whether treatment of blunted rectal sensation improves the outcome of surgery for STC has not been investigated.

There were no differences in outcome between the patients previously treated for obstructed defecation, either with biofeedback or repair of a rectocele, and those with isolated STC. This suggests that coexisting obstructed defecation should not exclude patients from resection, provided that it has been treated before surgery. Biofeedback retraining has been shown to de-
crease symptoms and increase stool frequency in patients with pelvic floor abnormalities as well as slow colonic transit (Chiotakakou-Faliakou et al. 1998). In a recent study, biofeedback has also been shown to improve colonic transit (Emmanuel and Kamm 2001). These findings suggest that biofeedback should be tried before surgery in the majority of patients with intractable STC, including those with coexisting obstructed defecation, blunted rectal sensation, and possibly those with an isolated colonic motility disorder.

Upper gastrointestinal motility was not preoperatively assessed in the present study. One patient with a poor result was later diagnosed with gastrointestinal pseudo-obstruction. The outcome of IRA has also been reported to be poor for patients with a generalised intestinal dysmotility, as compared to those with an isolated colonic dysfunction (Redmond et al. 1995). However, the value of different findings of disturbed gastric and small bowel function is not entirely clear. Although abnormalities on antro-duodenal manometry are found in patients with STC (Bassotti et al. 1996), these findings may be of minor nature (Penning et al. 2000). Gastric emptying can be delayed by voluntary suppressed defecation (Tjeerdema et al. 1993), and rectal distension (Coremans et al. 2004). Delayed gastric emptying has also been improved, or returned to normal in some patients after IRA (Hemingway and Finlay 2000). Gastrointestinal pseudo-obstruction is a severe form of generalised motility disorder. A colonic resection in such patients is of little or no benefit, and may be associated with a considerable morbidity. However, the clinical picture of gastrointestinal pseudo-obstruction is usually different from STC, whereas the manometric abnormalities are less obvious (Spiller 1999). Upper gastrointestinal testing may still be advocated if a patient is suspected to have a severe pan-enteric motility disorder.

Based on the present studies, it is suggested that a primary evaluation of patients with severe chronic constipation is done by means of radio-opaque marker study, defecography, anorectal manovolumetry and EMG. Patients with evidence of obstructed defecation may usually be treated with biofeedback retraining or repair of a rectocele. If they are not improved and have a slow colonic transit on marker study, they can be further evaluated by scintigraphy in order to identify a segmental colonic dysfunction. When a segmental slow transit is diagnosed, the patients may be offered a left, or in a few cases a right hemicolecotomy.
Conclusions

- At examination with $^{111}$In-DTPA segmental colonic scintigraphy, the majority of patients with STC had a left-sided delay of colonic transit. A few patients with a right-sided delay could be identified. The different colonic segments could be accurately identified. The method is therefore a potential tool to select patients for a left-, or in a few cases a right hemicolectomy for STC.

- Segmental colonic resection, based on a thorough evaluation of anorectal and colonic function, including $^{111}$In-DTPA segmental colonic scintigraphy, can be done with a successful outcome in the majority of patients. A median stool frequency of one per day and a significant reduction in laxative use was achieved, after a median follow-up of 50 months. The proportion of patients with bloating and excessive straining was significantly reduced and faecal continence was unchanged. A blunted rectal sensation correlated to a poor outcome. The results suggest that a segmental resection may be a better option than IRA for selected patients with STC.

- Anorectal manovolumetry revealed several abnormalities related to the internal anal sphincter in patients with slow colonic transit. Rectal compliance was increased in these patients and a quarter of the patients also had a reduced rectal sensation. These findings are of importance when surgical therapy is considered, since they provide prognostic information. Considering the risk of faecal incontinence following IRA, a segmental resection may be a better alternative for this group of patients, in which impaired sphincter function is common.

- Both radio-opaque marker study and $^{111}$In-DTPA segmental colonic scintigraphy showed that the majority of patients with slow colonic transit had a segmental colonic transit delay. With exception of the descending colon, the two methods gave a similar result of segmental transit. However, the results varied considerably for individual patients. These differences could be due to either different properties of the respective method, or an intra-individual variation in colonic transit. Since scintigraphy has some advantages, it is reasonable to confirm the result of a marker study with segmental colonic scintigraphy when surgery is considered for STC.
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