

# AN ASSESSMENT OF INVESTIGATIONS FOR EVACUATORY DYSFUNCTION

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***AN ASSESSMENT OF INVESTIGATIONS  
FOR EVACUATORY DYSFUNCTION***

by

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## ABSTRACT

Normal defecation is a complex physiological act that requires proper co-ordination between several organs and is heavily influenced by various extrinsic factors like diet. Difficulty in evacuation can lead to constipation. Chronic constipation affects a significant proportion of the population and poses a significant medical and economic burden to any country. Common investigations for chronic constipation were evaluated with a systematic review and clinical studies.

Systematic review of anorectal manometry (ARM), the balloon expulsion test (BE) and fluoroscopic evacuation proctography (EP) for constipation showed wide variation in the diagnostic yield of these tests along with significant variation in test methodology and data interpretation. A proctographic study involving healthy volunteers confirmed that a range of so-called structural abnormalities can exist in health. Constipation is often a symptomatic diagnosis. Symptoms incorporated within the Rome III criteria, one of the most widely used diagnostic criterion for constipation, were unable to reliably predict the final proctographic diagnosis in a cohort of constipated patients. Agreement between ARM, BE and EP for the diagnosis of subtypes of constipation was assessed prospectively in consecutive patients satisfying the Rome III criteria for functional constipation. Despite strict adherence to the Rome III criteria, agreement between recommended investigations was poor. The final diagnosis was influenced by the choice of investigation.

Chronic constipation is an enigmatic disorder. The confusion is further compounded by a lack of consensus on investigation protocols and the absence of a recognized 'gold standard' test. In order to identify the elusive 'gold standard', and hence reach a consensus, large and well-designed studies that can assess the clinical utility of these investigations are urgently required.

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Finally, I would also like to thank all the patients and volunteers who consented to take part in these studies, particularly for their compliance during prolonged investigation.

*To my family*

# STATEMENT OF ORIGINALITY

I, Somnath Palit, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

The recruitment of healthy volunteers and the subsequent investigation in chapter 3 was performed by other members of the gastro-intestinal physiology unit. The author was responsible for data analysis and subsequent dissemination of results in a later publication. Most of the patients included in chapter 4 were assessed by other members of the gastro-intestinal physiology unit as part of a routine clinical referral. The author was responsible for re-analysing all investigations along with data collection and analysis.

20 of 100 patients in chapter 5 were investigated by another member of the gastro-intestinal physiology unit. The author was responsible for all other patients, including re-analysing all investigations, data collection and analysis.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

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Signature: [Somnath Palit]

Date: 22/02/2015

# PUBLICATIONS

Some of the results presented in this thesis have already been published, in part, in the following journals:

## PAPERS

1. **Palit, S.**, Lunniss, P. J. & Scott, S. M. 2012. The physiology of human defecation. *Dig Dis Sci*, 57, 1445-64.
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## ABSTRACTS

1. **Palit, S.**, Thin, N. N., Knowles, C. H. & Scott, S. M. 2011. Prospective comparison of balloon expulsion, anorectal manometry and evacuation proctography for the diagnosis of rectal evacuatory disorder. *Gastroenterology*, 140, S-609.
2. **Palit, S.**, Thin, N. N., Knowles, C. H., Scott, S. M. & Lunniss, P. J. 2012. Prospective comparison of balloon expulsion, anorectal manometry and evacuation proctography for the diagnosis of evacuatory dysfunction. *British Journal of Surgery*, 99,S4, 6-40.
2. Brokjaer, A., Scott, S. M., **Palit, S.** & Zarate, N. 2012. Assessment of Anorectal Function in Asymptomatic Volunteers Using a New High Resolution Manometric Recording System. *Gastroenterology*, 142, S-904.
3. **Palit, S.**, Thin, N. N., Knowles, C. H., Scott, S. M. & Lunniss, P. J. 2012b. Prospective comparison of balloon expulsion, anorectal manometry and evacuation proctography for the diagnosis of evacuatory dysfunction. *Neurogastroenterology & Motility*, 24,S2, 111.

## PRESENTATIONS TO LEARNED SOCIETIES

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2. Prospective comparison of balloon expulsion, anorectal manometry and evacuation proctography for the diagnosis of rectal evacuatory disorder. **Palit, S.**, Thin, N. N., Knowles, C. H., Scott, S. M., Lunniss, P.J. The Royal Society of Medicine (RSM) short papers meeting London, UK, November 2011.
3. Prospective comparison of balloon expulsion, anorectal manometry and evacuation proctography for the diagnosis of rectal evacuatory disorder. **Palit, S.**, Thin, N. N., Knowles, C. H., Scott, S. M. & Lunniss, P. J. Society of Academic and Research Surgeons (SARS) meeting, Nottingham, UK, January 2012.
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## ABBREVIATIONS

- ACG - American college of gastroenterology  
ANOVA - Analysis of variance  
ARA - Ano-rectal angle  
ARM - Ano-rectal manometry  
BE - Balloon expulsion test  
BE<sub>50</sub> - Balloon expulsion test (using 50 mls of water)  
BE<sub>DDV</sub> - Balloon expulsion test using a volume sufficient to elicit a sustained defecatory urge  
BET - Balloon expulsion test  
CARA - Central ano-rectal angle  
CI - Confidence interval  
DD - dyssynergic defecation  
EAS - external anal sphincter  
ED - Evacuatory dysfunction  
EMG - Electromyography  
EP - Evacuation proctography  
EPD - Excessive pelvic floor descent  
FDD - Functional defecation disorder  
HAPC - High amplitude propagated contraction  
IAS - Internal anal sphincter  
IBS - Irritable bowel disease  
IBS - C - Irritable bowel disease constipation predominant  
IBS - D - Irritable bowel disease diarrhoea predominant  
ICC - Interstitial cells of Cajal  
IP - Impaired propulsion  
LAPC - Low amplitude propagated contraction  
MC - Motor complex  
Med. Recto - Medium rectocele  
Meg. R - Megarectum  
NA - Not applicable  
Nob. ARWP - Non-obstructive anterior rectal wall prolapse  
Nob. Ent/Sig - Non-obstructive enterocele or sigmoidocele

Nob. Int - Non-obstructive intussusception  
Ob. ARWP - Obstructive Anterior rectal wall prolapse  
Ob. Ent/Sig - Obstructive enterocele or sigmoidocele  
Ob. Int - Obstructive intussusception  
PARA - Posterior ano-rectal angle  
PCL - Pubo-coccygeal line  
PRISMA - Preferred reporting items for systematic reviews and meta-analysis  
PS - Propagated sequence  
R&D - Research and development  
RAIR - Recto-anal inhibitory reflex  
RED - Rectal evacuatory disorder  
rIGLE - Rectal intraganglionic laminar endings  
RMC - Rectal motor complex  
SD - Standard deviation  
Sig. Recto - Significant rectocele  
STC - Slow transit constipation  
TURP - Trans-urethral resection of prostate  
TVT - Trans-vaginal tape  
US - Ultrasound  
VIP - Vasoactive intestinal peptide

## THESIS STRATEGY

The primary goal of this research was to assess the common investigations for evacuatory dysfunction. The studies that I have performed, along with the results, are presented in this thesis.

The thesis starts with an in-depth review of the physiology of human defecation. Like any other organ, it is crucial to have a good understanding of relevant colonic and anorectal physiology in order to appreciate the associated problems. The second half of the introductory chapter is a review of the epidemiology and aetiopathogenesis of chronic constipation.

The investigations assessed are: anorectal manometry, the balloon expulsion test and evacuation proctography. Although there are methodological variations for all these tests, this is most obvious with proctography. Previously published methodology and consensus statements have been followed in this thesis for performance and interpretation of normative data for manometry and balloon expulsion tests. The neo-stool consistency used for evacuation proctography in our unit is slightly different from previously published literature. I have therefore established the normative values for evacuation proctography in healthy volunteers (performed according to our test protocol) in the third chapter. These values have been used in the subsequent chapters.

The fourth chapter presents the results of a study where the symptom profile and proctographic abnormalities of 500 consecutive chronically constipated patients were assessed. The main aim of this study was to define the frequency of symptoms and

proctographic abnormalities in this cohort, and to assess whether specific proctographic abnormalities could be predicted from the usual symptom repertoire.

In the penultimate chapter, 100 constipated patients underwent anorectal manometry, the balloon expulsion test and evacuation proctography. One of the most widely accepted diagnostic criteria for chronic constipation was followed strictly to assess the 'yield' and the diagnostic agreement between these investigations.

In the final chapter I have summarised the key findings of all my studies and identified some areas for future research.

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**Statement of contribution for chapter 1:** All parts of the following chapter was researched and written by myself.

# 1

## *Introduction*

### **1A The Physiology of Human Defecation**

#### **1A.1 INTRODUCTION**

Continence and defaecation are inextricably linked, with common anatomical, physiological and neurological bases. However, although continence is ultimately dependent upon sphincteric function (as long as anal pressure is greater than rectal pressure, continence is maintained) and the ability to appropriately 'sense' the nature of rectal contents, defaecation appears to be a much more complex process. Normal defaecation involves a well orchestrated activity of the distal colon, the rectum, the pelvic floor muscles and the anal sphincters, which are coordinated by the integration of the somatic, autonomic and the enteric nervous system and is heavily modulated by a number of reflexes and also by the higher centres in the brain. Disordered defaecation and incontinence are both associated with significant economic and personal burdens (Cook et al., 2009). Rational directed management of the individual constipated patient is suboptimal (Johanson and Kralstein, 2007), primarily because our understanding of defaecation is incomplete; this may reside in a combination of lack of appropriate investigative tools, over-reliance on acceptance of various mechanisms believed to contribute to defaecation through received wisdom, lack of focussed research, and lack of consensus over what constitutes 'normal'. Understanding of the processes involved in normal defaecation in humans is fundamental to the management of patients presenting with symptoms of constipation.

#### **1A.2 FREQUENCY OF NORMAL DEFECATION**

Infrequency of defaecation is often used to define constipation. A community questionnaire survey involving more than 1800 volunteers found that the most common bowel pattern was



once a day in both sexes, but this pattern was present in only 40% of men and 33% of women (Heaton et al., 1992); another 7% of men and 4% of women had a regular twice or thrice daily bowel habit (Heaton et al., 1992). Inquiring the bowel symptoms of 1455 adults, Connell *et al*, (Connell et al., 1965) found that over 99% had between 3 motions per day to 3 motions per week. Similar findings was reported by Hardy *et al*, in a study involving 440 nurses (Hardy, 1945). Based on these studies, it is generally accepted that in adults, the 'normal' frequency ranges between a maximum of three times per day to a minimum of three times per week (Schaefer and Cheskin, 1998). However, less than three motions per week has been considered normal if this is not associated with discomfort (Abyad and Mourad, 1996). It is important to note that patients' perception of what is 'normal' and what is constipation can differ from their clinicians (Sandler et al., 1990, Herz et al., 1996). While clinicians often define constipation by decreased stool frequency or weight, patients tend to define it in terms of disordered function (e.g. need to strain) and passage of hard stool (Sandler and Drossman, 1987).

In children, the frequency of bowel movements decreases with age; the decline occurs during the first 3 years and is most rapid from the first months postpartum (Fontana et al., 1989). By the age of 4, bowel frequency is equivalent to that of adults (Weaver, 1988). The average frequency of defaecation in children is 6.3+/- 1.3 times per week (range: 4-9 per week) (Corazziari et al., 1985). The frequency of high amplitude propagating contractions (HAPCs), which have been linked to colonic mass movements (see below), is significantly higher in young children when compared to children older than 4 years of age (Di Lorenzo et al., 1995); this correlates with the increased number of bowel movements observed in young children (Di Lorenzo et al., 1995).

### **1A.3 FACTORS INFLUENCING EVACUATION**

#### **1A.3.1 INFLUENCE OF PSYCHO-BEHAVIOURAL FACTORS AND VOLUNTARY SUPPRESSION OF DEFAECATION**

There is now increasing recognition that a variety of psycho-behavioural factors can affect gastrointestinal function. Influence of psychological trait on bowel habit has long been appreciated (Drossman, 2011), and several studies have shown that the incidence of constipation is higher in patients with psychological impairment (Wald et al., 1989, Nehra et al., 2000, Dykes et al., 2001) or a history of traumatic life events including sexual and physical abuse (Leroi et al., 1995, Drossman et al., 1995). The influence of mental state, such as short-term anxiety and stress also impact on bowel habit. Furthermore, it is well known that stool 'withholding' behaviour, often triggered by an instinct to avoid painful evacuation, is one of the main causes of defaecatory dysfunction in children (Loening-Baucke, 1993b, Borowitz et al., 2003, Khanna et al., 2010). Two separate studies have reported that up to 97% of constipated children display stool withholding behaviour (Partin et al., 1992, Loening-Baucke, 1993a). Other associated findings were the presence of a rectal / abdominal mass and a history of earlier painful defaecation (Partin et al., 1992, Loening-Baucke, 1993a, Borowitz et al., 2003). There is evidence that constipation and painful defecation not only precede toileting refusal (Blum et al., 2004), but also help in maintaining this behaviour (Blum et al., 1997, Whitehead et al., 2009), which manifests as 'retentive posturing' where toddlers hold an erect posture and forcefully contract their gluteal and pelvic floor musculature (Loening-Baucke, 1993a) until the defaecatory urge disappears due to rectal accommodation. It is hypothesised that stool in the rectum gradually hardens and becomes more difficult to evacuate causing a vicious cycle that can ultimately lead to chronic rectal distension (Benninga et al., 2004). Ignoring the defaecatory urge may be a conscious decision, or an unconscious automatic habit of the child resulting from altered or diminished brain processing of urge sensations due to loss of attention (Scott et al., 2011). Such 'conditioning' behaviour has also been reported in adults (Richards et al., 2010), many of

whom display toilet avoidance behaviour due to pain, or to the lack of the 'sanctum' of one's private lavatory (Kamm, 2006). In a seminal study, Klauser *et al* compared frequency of defaecation and colonic transit in 12 healthy male volunteers during a two-week study where one week of normal defaecation and one week of voluntary suppression of defaecation followed each other in a randomised order (Klauser *et al.*, 1990). Voluntary suppression of defaecation led to decrease in stool frequency, stool volume and increases in total colonic and recto-sigmoid transit times, a finding which suggests that constipation can be "learned" (Klauser *et al.*, 1990).

Appropriate toilet training also appears necessary for normal defaecation. Improper training has been implicated as a cause of constipation in children. Studies have shown that toilet training is now initiated at an older age than it was in the past (Bakker and Wyndaele, 2000). In the 1940s, toilet training was usually started before 18 months of age, whereas today, training often starts between 21 and 36 months, and only 40 - 60% children complete toilet training by the age of 3 (Taubman, 1997, Schum *et al.*, 2001). One study reported that girls develop toileting skills earlier than boys (Schum *et al.*, 2002). Lack of successful toilet training by 42 months of age is associated with toileting refusal behaviour (Taubman, 1997). Toilet training is initiated and completed significantly earlier in urban areas as compared to rural areas (Aziz *et al.*, 2011). Race and income are independent predictors of the age at which parents believe they should initiate toilet training; Caucasians and higher income group parents are more likely to start toilet training at a later stage as compared to other races and lower income groups (Horn *et al.*, 2006). Parents play a key role in toilet training; they need to provide the direction, motivation and positive reinforcement in addition to setting aside time and having patience during the process (Anon, 1999).

### **1A.3.2 INFLUENCE OF POSTURE ON DEFAECATION**

The defaecatory position that a subject assumes is dictated by a number of factors, including the type of toilet available (if available), physical and mental ability, and cultural factors. In

Western countries, sitting on a toilet seat (commode) is common, whereas in Africa and Asia squatting is the preferred position.

Using defaecography (simulated defaecation of a neostool under continuous fluoroscopic screening), it has been demonstrated that the anorectal angle becomes more obtuse (opens up) with increasing hip flexion, making evacuation easier (Tagart, 1966). In a study which compared the time and sense of satisfactory rectal emptying in 3 postures (sitting on a standard Western commode; sitting on a similar commode with a 10 cm stool under the subjects' feet, effectively lowering the height of the commode; and in the squatting posture), it was found that evacuation was quickest and afforded a more complete sense of bowel emptying in the squatting posture and was most difficult on the standard Western type commode (Sikirov, 2003). As expected, other studies have shown that evacuation is also easier when sitting compared to lying (Barnes and Lennard-Jones, 1985, Rao et al., 2006). The latter of these studies also showed, perhaps not surprisingly, that compared to the sitting posture, the frequency of dyssynergia (uncoordinated pelvic floor activity) during evacuation was greater when lying down (Rao et al., 2006).

### **1A.3.3 INFLUENCE OF COLONIC TRANSIT, VOLUME AND CONSISTENCY OF STOOL**

Stool volume and consistency are directly related to gastrointestinal (GI) transit time (Degen and Phillips, 1996a). Co-ordinated colonic motor activity drives transit, and hence the rate at which colonic contents are delivered to the rectum, as well as the physical and chemical nature of the faeces itself.

As a general rule (though not absolute), loose stools are associated with rapid GI / colonic transit, (Davies et al., 1986, O'Donnell et al., 1990) whereas constipation may be associated with slow GI transit and reduced motility (Bharucha, 2008). Degen and Phillips, who assessed transit in 32 healthy volunteers with scintigraphy and radio-opaque markers (Degen and Phillips, 1996a) concluded that hard stools correlated significantly with slower

intraluminal movement and loose stool with faster transit. Other studies have reported that constipation may be associated with greater levels of (uncoordinated) contractile activity in the pelvic colon in comparison to patients with diarrhoea (Connell, 1962). Intuitively, reduced colonic motor activity, and hence delayed transit should allow greater water absorption from intra-luminal contents, desiccating the stool and reducing volume, resulting in harder motions that are more difficult to expel. In a study investigating constipated children, Benninga *et al* found a significant association between the presence of a palpable rectal mass and a colonic transit time of >100 hrs (Benninga *et al.*, 1996); these children suffered from nocturnal 'overflow' faecal soiling. Conversely, increased and co-ordinated motor activity can deliver larger quantities of more liquid faecal material into the rectum, which may overpower the continence mechanism. In constipated patients, stool form correlates well with whole gut (O'Donnell *et al.*, 1990) and colonic transit (Saad *et al.*, 2010). In constipated subjects, a mean Bristol stool form (O'Donnell *et al.*, 1990) of <3 (indicating hard stools, ranging from pellet-like or, 'nuts', to sausage- or snake-like, with cracks on its surface) is specific and sensitive for the diagnoses of delayed whole gut and colonic transit (Saad *et al.*, 2010). This relationship may be absent in healthy individuals (Saad *et al.*, 2010). In contrast to stool form, frequency of defaecation is poorly correlated with whole gut or colonic transit (O'Donnell *et al.*, 1990, Saad *et al.*, 2010), in that true slow transit is *usually* associated with infrequency, but frequent bowel actions does not imply fast transit i.e. a constipated patient may revisit the toilet repeatedly (Dinning *et al.*, 2011). Likewise, in children, stool frequency has been shown to correlate with total gastrointestinal transit time, but not all children with prolonged transit have reduced bowel frequency (Corazziari *et al.*, 1985).

Very few studies have compared the effect of stool volume or form on evacuation. Bannister *et al* demonstrated that evacuation of small hard spheres mimicking pellet-like stool required more effort (measured as longer time and higher intrarectal pressures) than the expulsion of a compressible 50 ml balloon, used as a surrogate of soft stool (Bannister *et al.*, 1987b). In a more recent study (Rao *et al.*, 2006), only 4% of subjects were unable to expel a silicone

stool-substitute in the sitting position, while 16% were unable to expel a 50 cc balloon. Moreover, balloon expulsion time was significantly longer than expulsion of the stool substitute.

#### **1A.3.4 INFLUENCE OF DIET AND INTRALUMINAL CONTENTS**

Ingestion of a meal is regarded as the most potent physiological stimulus influencing colonic / gastrointestinal transit and motor activity. A meal-induced increase in colonic motor activity is more pronounced in the transverse / descending colon than the recto-sigmoid colon (Ford et al., 1995a, Rao et al., 1998b, Rao et al., 2000). Studies performed around 35 years ago, showed that overall colonic response to a meal is excitatory and follows a biphasic pattern, with a first peak of activity seen within the first 10 to 50 minutes and a second peak occurring within 70 and 90 minutes of having a meal (Snape et al., 1979, Battle et al., 1980a, Wright et al., 1980). A fatty meal stimulates colonic motor activity (Snape et al., 1979, Wright et al., 1980, Renny et al., 1983, Rao et al., 2000) to a greater extent than a carbohydrate-rich (Wright et al., 1980, Rao et al., 2000) or a protein-rich meal (Wright et al., 1980). However, fatty meals also stimulate retrograde colonic activity which may result in a net decrease in colonic transit (Rao et al., 2000). The stimulatory effect of a carbohydrate-rich meal has a more rapid onset than that of a fatty meal (Rao et al., 2000) but is shorter lived. Ingestion of a protein and amino acid-rich meal actually inhibits colonic motor activity (Battle et al., 1980a, Wright et al., 1980). Likewise, alcohol has been shown to have an inhibitory effect on recto-sigmoid motility (Berenson and Avner, 1981, Bouchoucha et al., 1991). Patients in whom the colonic intraluminal contents have a high osmotic load (e.g. bile salt malabsorption and lactose intolerance) have a rapid colonic transit (Rao, 2004). It should be noted that the effect of dietary components on colonic motor functions using contemporary methodologies (pancolonic manometry / scintigraphy) has not been reproduced.

Although it is generally agreed that an increase in dietary fibre intake is beneficial for constipation (Williams and Bollella, 1995, Loening-Baucke et al., 2004, Castillejo et al.,

2006), there have been concerns about the adverse effects of a high fibre diet in children, including a resultant lowering of calorie intake (Heaton, 1973, Stevens et al., 1987, Levine et al., 1989), increased faecal energy loss (Stevens et al., 1987, Williams and Bollella, 1995) and decreased bioavailability of minerals (Haghshenass et al., 1972). Dietary fibre intake can also lead to excessive gas formation resulting in abdominal bloating and cramping, though it has been reported that if fibre content in diet is increased gradually rather than acutely, excessive gas formation can be reduced (Anderson et al., 1994).

### **1A.3.5 INFLUENCE OF AGE AND GENDER**

Age and gender are also known to effect evacuation (Mugie et al., 2011); epidemiological studies indicate that the incidence of constipation is characterised by 2 peaks - one during early childhood and the second after the age of 60 - 65 (see below). In childhood constipation, one study has shown that half of the affected children develop constipation within the first year of their life (Del Ciampo et al., 2002), with transition from breast milk to formula feeding being proposed as the possible cause (Iacono et al., 2005). Other studies have reported a peak incidence between 3 - 5 years (Issenman et al., 1987, Loening-Baucke, 2005, Ip et al., 2005, van den Berg et al., 2006). The second peak, occurring in geriatric patients (Sonnenberg and Koch, 1989a, Sandler et al., 1990) has been variously attributed to aging with consequent loss of tissue elasticity (Bannister et al., 1987a), increased evidence of neuropathy with age (Bartolo et al., 1983a), pelvic floor weakness and laxity (Bartolo et al., 1983a), reduced mobility and polypharmacy (Chatoor and Emmanuel, 2009).

With regard to gender, incidence of childhood constipation is reported to be similar between boys and girls (Corazziari et al., 1985, Sonnenberg and Koch, 1989b, de Araujo Sant'Anna and Calcado, 1999), or slightly higher in boys (van Ginkel et al., 2003). However in adults, constipation is much more common in women (Sonnenberg and Koch, 1989a, Heaton et al., 1992, Sandler et al., 1990, Stewart et al., 1999). It is not clear why this change occurs.

However, gender specific differences in pathophysiologic mechanisms and the increased incidence of constipation in association with pregnancy and delivery have been implicated (van Ginkel et al., 2003). Colonic transit time is faster in males compared to females (Meier et al., 1995, Degen and Phillips, 1996b), and females are also more likely to pass hard stools, (Heaton et al., 1992, Degen and Phillips, 1996a) perhaps making them more susceptible to constipation (Heaton et al., 1992). Increased perineal descent, reflecting a less supportive pelvic floor (likely a consequence of parity), has been noted in elderly females compared to younger females, and a study found decreased ability among both sexes to evacuate 18 mm spheres with advancing age (Bannister et al., 1987a). Other possible causes for a female preponderance of constipation in adult population include the influence of female hormones (Heaton et al., 1992), the menstrual cycle (Hinds et al., 1989, Turnbull et al., 1989, Celik et al., 2001, Fukuda et al., 2005), parity and childbirth, pelvic floor function (Kepenekci et al., 2011) and pelvic surgery (e.g. hysterectomy) (Johanson et al., 1989).

#### **1A.3.6 OTHER INFLUENCES**

There are several other important factors that influence the ability to defecate, not least intact cognition (Veugelers et al., 2010) and mobility (Dukas et al., 2003, Chien et al., 2011), as evidenced by studies of the institutionalised (Kinnunen, 1991), as well as fluid intake (Veugelers et al., 2010, Chien et al., 2011) and access to sanitation (Vernon et al., 2003, Lundblad and Hellstrom, 2005). Cultural and lifestyle factors are likely to have major influence, but obviously are more difficult to study.

Circulating hormones (like somatostatin) and humoral factors (like Substance P, vasoactive intestinal peptide, Peptide YY and cholecystokinin.) are also known to be important as they can influence gastrointestinal motility that underscores efficient defaecation (Battle et al., 1980b, Goyal and Hirano, 1996, Tzavella et al., 1996, Cortesini et al., 1995, El-Salhy et al., 1999, McCrea et al., 2008). Secondary constipation is a well known consequence of



systemic disorders including diabetes, hypothyroidism, hypercalcemia, several forms of myopathies and neuropathies.

Additionally, in patients with intractable constipation a reduction in the number of interstitial cells of Cajal (He et al., 2000, Wedel et al., 2002b, Hasler, 2003, Sabri et al., 2003), which are regarded as intestinal pacemakers (Huizinga et al., 1995, Ward and Sanders, 2001), morphological changes or reduction in number of ganglia and/or glial cells (Wedel et al., 2002b, Wedel et al., 2002a, Bassotti et al., 2006), and an abnormal nerve fibre density in the circular muscle layer (Hutson et al., 2004) have all been identified. The mechanistic significance of such findings is however unclear.

#### **1A.4 THE PHASES OF DEFAECATION**

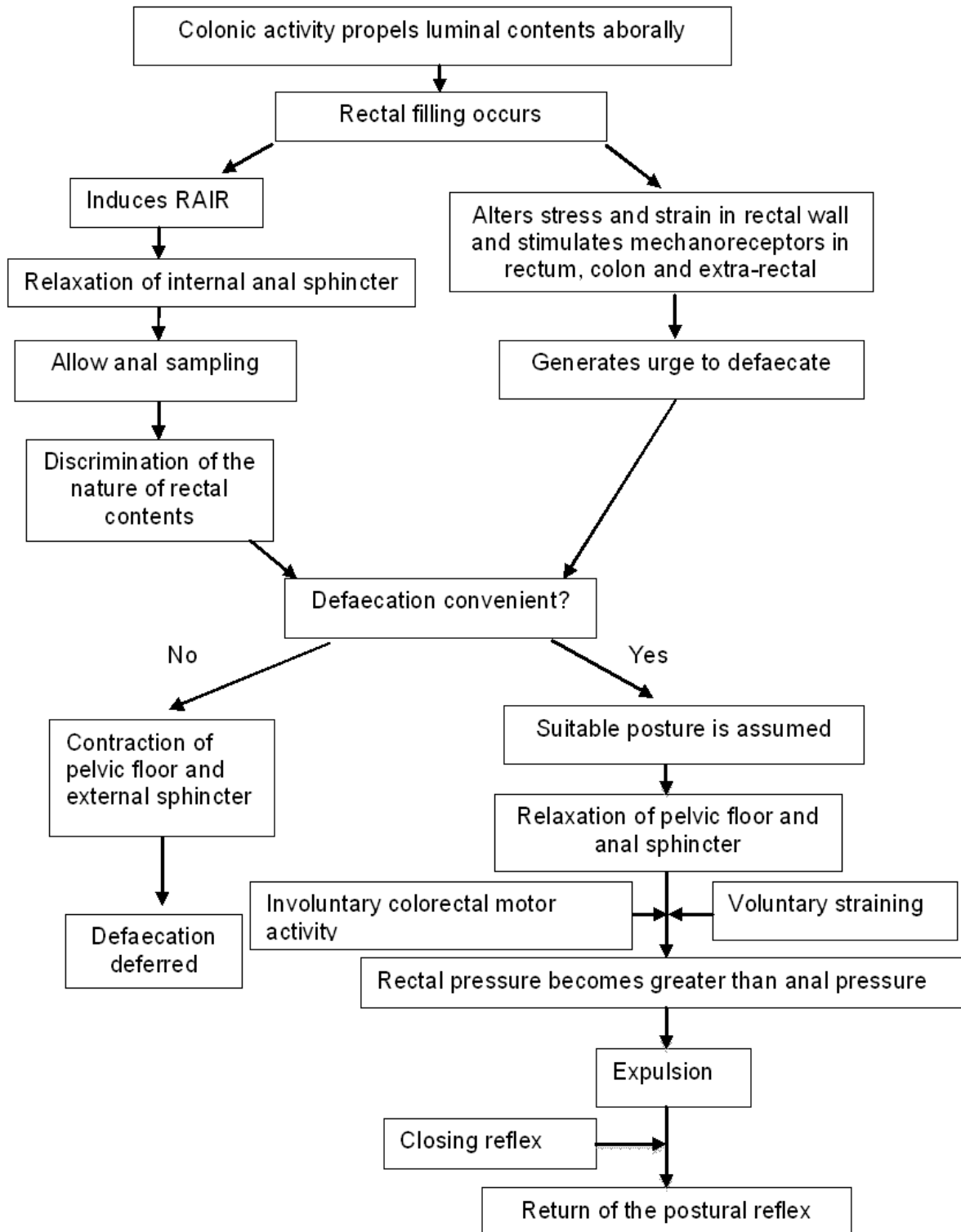
The multiple factors that ultimately result in defaecation are best appreciated by describing four temporally and physiologically fairly distinct phases: (1) the basal phase; (2) a pre-defaecatory phase, leading to generation of a defaecatory urge; (3) the expulsive phase, during which evacuation occurs; and finally, (4) termination of defaecation (Figure. 1A.1). The key events occurring during each phase is summarized in Table 1A.1.

##### **1A.4.1 THE BASAL PHASE**

Prior to the events that specifically lead up to defaecation, a comprehension of normal colorectal motor functions is required, during what may be regarded as a 'basal phase'.

###### **1A.4.1.1 Colonic motor activity**

Colonic functions relevant to normal defaecation include: absorption of water from intraluminal contents; net antegrade propulsion of colonic contents at an adequate rate; and temporary storage of faeces until convenient to expel them. After delivery of chyme from the terminal ileum into the caecum, luminal contents are transported distally while gradual



**Figure 1A.1:** Flowchart to show the principal events occurring during defaecation

		<b>Basal phase</b>	<b>Pre-expulsive phase</b>	<b>Expulsive phase</b>	<b>Termination of defaecation</b>
<b>Colon</b>	Physiological changes	<ul style="list-style-type: none"> <li>• Antegrade, retrograde and non-propagated contractions occur</li> </ul>	<ul style="list-style-type: none"> <li>• Increase in amplitude and frequency of PS</li> <li>• PS site of origin shifts distally and then proximally</li> </ul>	<ul style="list-style-type: none"> <li>• HAPC often temporally associated with expulsion</li> </ul>	<ul style="list-style-type: none"> <li>• No significant activity</li> </ul>
	Physiological effects	<ul style="list-style-type: none"> <li>• Colonic contractions propel the faecal bolus distally</li> </ul>	<ul style="list-style-type: none"> <li>• Leads to colonic mass movements and rectal filling</li> </ul>	<ul style="list-style-type: none"> <li>• Facilitates faecal expulsion</li> </ul>	
<b>Rectum</b>	Physiological changes	<ul style="list-style-type: none"> <li>• RMCs occur</li> </ul>	<ul style="list-style-type: none"> <li>• Receptive relaxation occurs in response to rectal filling</li> <li>• Rectal stretching stimulates mechano-receptors.</li> </ul>	<ul style="list-style-type: none"> <li>• Rectal contractions may occur</li> </ul>	<ul style="list-style-type: none"> <li>• No significant activity</li> </ul>
	Physiological effects	<ul style="list-style-type: none"> <li>• RMCs help to keep the rectum empty</li> </ul>	<ul style="list-style-type: none"> <li>• Rectum functions as a temporary reservoir of faeces</li> <li>• Stimulation of mechanoreceptors generate rectal filling sensation</li> </ul>	<ul style="list-style-type: none"> <li>• Increases the intrarectal pressure which is aided by straining</li> </ul>	
<b>Pelvic floor</b>	Physiological changes	<ul style="list-style-type: none"> <li>• Remains contracted due to postural reflex</li> </ul>	<ul style="list-style-type: none"> <li>• Remains contracted due to the postural reflex</li> </ul>	<ul style="list-style-type: none"> <li>• Pelvic floor relaxes</li> </ul>	<ul style="list-style-type: none"> <li>• Forceful contraction of puborectalis occurs</li> </ul>
	Physiological effects	<ul style="list-style-type: none"> <li>• Aids continence</li> </ul>	<ul style="list-style-type: none"> <li>• Aids continence</li> </ul>	<ul style="list-style-type: none"> <li>• Straightens the ARA</li> <li>• Pelvic floor to descends assuming a funnel shape</li> </ul>	<ul style="list-style-type: none"> <li>• Increases the acuity of anorectal angulation aiding continence</li> </ul>
<b>Anal sphincters</b>	Physiological changes	<ul style="list-style-type: none"> <li>• Sphincters remain contracted to preserve continence</li> </ul>	<ul style="list-style-type: none"> <li>• At lower levels of rectal filling RAIR occurs, at higher levels sustained IAS relaxation occurs</li> <li>• External sphincter stays contracted</li> </ul>	<ul style="list-style-type: none"> <li>• Relaxation of anal sphincters</li> <li>• Conjoint longitudinal muscles of the anal sphincter are contracted</li> </ul>	<ul style="list-style-type: none"> <li>• Voluntary contraction of the external sphincter</li> <li>• Relaxation of conjoint longitudinal muscles</li> </ul>
	Physiological effects	<ul style="list-style-type: none"> <li>• Aids continence</li> </ul>	<ul style="list-style-type: none"> <li>• Allows sampling while preserving continence</li> </ul>	<ul style="list-style-type: none"> <li>• Intra-anal pressure drops and anal canal shortens</li> </ul>	<ul style="list-style-type: none"> <li>• Anal pressure rises and anal canal elongates</li> </ul>
<b>Overall effect</b>		<ul style="list-style-type: none"> <li>• Propulsion of intraluminal contents</li> </ul>	<ul style="list-style-type: none"> <li>• Rectal filling leading to generation of call to stool</li> <li>• Sampling of rectal contents</li> </ul>	<ul style="list-style-type: none"> <li>• Expulsion of rectal contents due to pressure gradient</li> </ul>	<ul style="list-style-type: none"> <li>• Closure of anal canal.</li> </ul>

**Table 1A.1:** A summary of the physiological events during each phase of defaecation

RMC – rectal motor complex; PS: propagated sequences; HAPC: high amplitude propagated contraction; RAIR: rectoanal inhibitory reflex; ARA: anorectal angle. (References in text)

desiccation and mixing occurs making them progressively more solid (Scott, 2003). This transport is facilitated by complex colonic motility patterns.

Colonic motor activity shows a circadian pattern, in that it increases after awakening, (Rao et al., 2001b) and is higher during the day compared to the night (Christensen, 1985, Narducci et al., 1987, Rao et al., 2001b, Dinning et al., 2010b). Colonic activity also increases after meals (see above) (Bampton et al., 2001, Rao et al., 2001b, Dinning et al., 2010b). Patients with constipation may lack the nocturnal suppression of colonic activity (Dinning et al., 2008b) and exhibit reduced colonic responses to food (Leroi et al., 2000, Herve et al., 2004, Rao et al., 2004b, Dinning et al., 2008b), as well as lack the spatio-temporal organisation of colonic contractile patterns (Dinning et al., 2010a).

Colonic motor functions can simplistically be subdivided into 'transit' (i.e. intra-luminal movement), measured clinically either by radio-opaque marker studies, colonic scintigraphy, or more recently by wireless telemetric capsule methods (Camilleri et al., 2008, Dinning and Di Lorenzo, 2011, Rao et al., 2011), or 'contractile activities', the sum of which underlies the shift in intra-luminal content. This is best measured by intraluminal manometry (Scott, 2003). Although colonic manometry still remains a research tool in adults, it been used to influence clinical management in highly selected paediatric cases (Di Lorenzo et al., 1992, Rudolph and Winter, 1999, Martin et al., 2001, Pensabene et al., 2003).

From transit studies the upper limit of normal colonic transit time has been determined to be around 70 -72 hours in adults (Spanish, 1998, Dinning et al., 2009b). Colonic transit is faster in children (Weaver, 1988), being reported as less than 57 hours (Corazziari et al., 1985, Bautista Casasnovas et al., 1991, Zaslavsky et al., 1998, Gutierrez et al., 2002). 'Slow transit' refers to a clinical condition likely resulting from ineffective colonic propulsion. Abnormalities of colonic transit are often expressed as segmental (right colonic, left colonic or recto-sigmoid delay) or pan colonic in nature (Stivland et al., 1991, Diamant et al., 1999,

Dinning et al., 2009b). Whether evacuatory dysfunction influences distal colonic transit delay is debatable (Dinning et al., 2009b). It has been suggested that acute rectal distension inhibits colonic contractility by means of an inhibitory recto-colonic reflex (Law et al., 2002). McLean *et al* showed a correlation between proctographically confirmed evacuatory dysfunction and distal colonic transit delay (McLean et al., 1995). Preferential retention of markers in the rectosigmoid area is often regarded as being a result of obstructed defaecation (Longstreth et al., 2006). However, a more recent study (Zarate et al., 2008a), in which 196 patients with slow transit constipation underwent a radio-opaque marker test, proctography and scintigraphy, found that evacuatory dysfunction is not associated with a specific pattern of transit delay and scintigraphy alone cannot predict the presence or absence of evacuatory dysfunction.

Colonic motor activity is characterized by brief (phasic) contractions and also sustained (tonic) contractions (best measured with a barostat) (Camilleri et al., 2008). Phasic contractions are further classified as propagating or non-propagating contractions, or sequences, based on whether or not they propagate along the colon. Non-propagated contractions appear to be the most common event, and can occur as isolated, seemingly random contractions or in 'bursts' (Narducci et al., 1987, Scott, 2003). They have a frequency of between 2 - 4 cycles per minute (Brookes et al., 2009) and amplitude of between 5 - 50 mm Hg (Rao et al., 2001b). The duration of these contractions can either be short (<15 seconds) or long (15 - 60 seconds) (Spriggs et al., 1951, Sarna, 1991, Scott, 2003). 'Bursts' of non-propagated pressure activity, lasting 3 minutes or more can also occur (Scott, 2003). These contractions can either be rhythmic (occurring at frequencies of 2 - 3 cycles/min or 6 - 8 cycles/min) or arrhythmic (Narducci et al., 1987, Scott, 2003). A recent study using high resolution manometry with 1 cm sensor spacing (as opposed to majority of colonic manometries which have traditionally been performed with recording sites spaced 10 cm or more apart) indicates that manometric pressure patterns often propagate for less than 10 cm (Dinning et al., 2009a), which indicates propagated activity may have been previously

'mislabelled' as non-propagated activity (Brookes et al., 2009, Dinning et al., 2014). Although the role of non-propagated activity in luminal transport is not fully understood (Brookes et al., 2009), it is thought to aid mixing of intraluminal contents by local propulsion (Garcia-Olmo et al., 1994, Bassotti et al., 2005) and retropulsion (Cook et al., 2000) of the faecal bolus.

Propagated colonic activity can be retrograde (oral propagation) or antegrade (aboral propagation). Retrograde colonic activity is thought to be less frequent than antegrade activity (Rao et al., 2001b, Dinning et al., 2008b), and appears mostly confined to the proximal colon (Cook et al., 2000). The frequency of retrograde propagated activity may be higher in patients with constipation than in healthy individuals (Dinning et al., 2008b) indicating that the ratio between retrograde and propagated contractile activity may be an important pathophysiological mechanism of delayed colonic transit.

Among propagated sequences, there are sets of propagated pressure waves that are distinct by virtue of their elevated amplitude. These waves, known as high amplitude propagated contractions (HAPCs), have been widely and variably defined (Bampton et al., 2000, Scott, 2003), but typically have amplitudes >100 mmHg (Bassotti and Gaburri, 1988, Cook et al., 2000, Bharucha, 2007). In adults, HAPCs occur, on average, 5 – 6 times a day (range 2 – 24) (Scott, 2003), whereas the frequency of HAPCs is significantly greater in children younger than 4 years of age (Di Lorenzo et al., 1995) which likely correlates to the increased number of bowel movements in infants / toddlers. Although HAPCs can originate anywhere in the colon, they do so mostly in the proximal colon and then migrate distally for a variable distance (Cook et al., 2000, Rao et al., 2001b, Bampton et al., 2001, Dinning et al., 2010b). The distance of propagation correlates with the proximity of the site of origin to the caecum (Cook et al., 2000, Bampton et al., 2001, Dinning et al., 2010b). One study found that only a third of the HAPCs reached the anus, the remainder terminating at the rectosigmoid region (Rao et al., 2001b). HAPCs are often temporally associated with defaecation (Bampton et al., 2000, Rao et al., 2001b, Bassotti et al., 2003) or passing flatus

(Rao et al., 2001b). They help in propulsion of the faecal bolus (Cook et al., 2000) and are the manometric equivalent of 'mass movements' noted radiologically (i.e. a rapid shift of a considerable volume of intraluminal content) (Ritchie et al., 1971, Torsoli et al., 1971). Frequency of HAPCs is often reduced in patients with constipation (Bassotti et al., 1988, Leroi et al., 2000, Bassotti et al., 2003, Hagger et al., 2003, Herve et al., 2004, Rao et al., 2004b, Dinning et al., 2008b, Dinning et al., 2009b), and this is often the most consistent motor abnormality described in such patients.

The majority of colonic propagated activity is characterized by low amplitude propagated sequences (PSs; or low amplitude propagated contractions: LAPCs). These typically have an amplitude <50 mmHg (Bassotti et al., 1995), occur 40 – 120 times in a 24 hour period, (Cook et al., 2000, Bassotti et al., 2001, Rao et al., 2001b) and propagate for distances <22.5 cm (Bampton et al., 2001). Studying the relation between frequency of PSs and constipation, some authors have found a reduced frequency in obstructed defaecation (Dinning et al., 2008b) and slow transit constipation (Hagger et al., 2003); others have found no difference (Bassotti et al., 2003). In healthy individuals, propagating sequences display a spatio-temporal or 'regional linkage' (where two consecutive PSs, originating from different colonic regions overlap)(Dinning et al., 2009c, Dinning et al., 2010b). The significance of this finding lies in the fact that although a single PS does not span the entire length of the colon, a series of 'regionally linked' PSs can. This linkage has been found to be absent in patients with constipation (Dinning et al., 2009c, Dinning et al., 2010a).

A study using high frame-rate scintigraphy and proximal colonic manometry found that >93% of antegrade and retrograde PSs were associated with movement of luminal contents (Dinning et al., 2008a). Additionally, there was no difference in amplitude or velocity between the PSs that were associated with shift of luminal contents and those that were not. However, only 45% of antegrade flow episodes were associated temporally with a PS. Thus while most PSs result in propulsion / retropulsion, a significant amount of luminal

displacement of contents can occur without it. Similar results were obtained from another study (Cook et al., 2000) in which 28% of luminal movements were associated with a PS, 32% with a non-propagated activity and 40% with no discernible associated pressure event. However, distance of luminal movement was highest when associated with a PS. Cook *et al* also found a significant correlation between the site of origin of a PS and its propulsive activity: 86% of PS originating in the caecum or ascending colon were propulsive compared to only 30% of those originating at or distal to the hepatic flexure (Cook et al., 2000).

The sigmoid colon primarily exhibits cyclical bursts of contractions (though they also occur throughout the rest of the colon), called motor complexes (MC) or 'periodic colonic motor activity'; these may be important in modulating the delivery of faecal material into the rectum. These motor complexes typically have amplitudes of 15 – 60 mm Hg, last 3 – 30 min and recur at 80 – 90 min intervals (Kumar et al., 1989). By conventional manometry, up to 70% of these are non-propagating, approx. 18% propagate aborally, and 15% migrate orally (Rao et al., 2001b). Another feature of the sigmoid colon is that when distended, it contracts, with concomitant relaxation of the recto-sigmoid junction; this mechanism likely facilitates progression of faeces into the rectum (Shafik, 1996). The presence of a sphincter between the sigmoid and the rectum (the recto-sigmoid sphincter of O'Beirne)(Ballantyne, 1986) has long been debated. Although the evidence of a convincing anatomical sphincter is lacking, a high-pressure zone with unique contractile properties (in response to sigmoid and rectal distension / contraction) has been shown in the distal sigmoid, which supports the idea of a physiological sphincter (Ballantyne, 1986, Wadhwa et al., 1996, Shafik et al., 1999, Shafik, 1999). The role of the recto-sigmoid junction in normal defaecation is still unclear.

#### **1A.4.1.2 Rectal motor activity**

Rectal motor activity, like the sigmoid, is characterised by recurrent motor complexes. The frequency of rectal motor complexes appear unaffected by meal intake (Rao et al., 2001b). The role of these motor activities is not fully understood (Brookes et al., 2009). However,



rectal motor complexes are seen to propagate in a retrograde direction (Rao and Welcher, 1996); it has thus been postulated they help to keep the rectum empty by acting as a 'braking mechanism' to untimely flow of colonic contents (Rao and Welcher, 1996). It has been proposed that rectal motor activity may be used as a marker of enteric neuromotor function as their presence is independent of intact extrinsic innervation (Kumar et al., 1989, Spencer, 2001, Scott, 2003). In healthy volunteers, during the basal phase, the rectum remains mostly empty (Truelove, 1966) or can contain a variable amount of faeces without conscious awareness (Halls, 1965).

#### **1A.4.1.3 Pelvic floor and puborectalis activity**

At rest, the levator ani, the puborectalis and the external anal sphincter remain in a state of continuous contraction. This reflex is known as the postural reflex (Porter, 1962), and it helps to support the weight of the pelvic viscera. The reflex is maintained through the lower lumbar and sacral spinal cord (Porter, 1962).

In relation to defaecation, among the pelvic floor muscles, the puborectalis is probably the most relevant. It originates from the posterior surfaces of the pubis, passes around the anorectal junction inferolaterally and decussates with its fibres from the opposite side to form a sling behind the anorectal junction. The puborectalis derives its nerve supply from direct branches of the anterior roots of S3 and S4 (Snooks and Swash, 1986, Madoff et al., 2004, Rao, 2004, Bajwa and Emmanuel, 2009).

At rest, the contractile traction of puborectalis maintains the anorectal angle (angle between the long axis of the rectum and the long axis of the anal canal) at approximately 90 degrees (Mahieu et al., 1984). While this angulation helps in preservation of continence (Bartolo et al., 1983b), increased acuity has been related to obstructed defecation (Bartolo et al., 1985, Bannister et al., 1986).

#### **1A.4.1.4 Anal canal activity**

At rest, the anal canal remains closed to preserve continence. The anal sphincter complex is extremely dynamic, and is influenced by a variety of reflexes and modulation by higher centres in such a way that rather than acting as a passive barrier, it provides an airtight seal at all times except when the subject wants to pass flatus or defecate (Lunniss and Scott, 2007).

The anal canal is normally closed by the tonic activity of the internal and external anal sphincters, together with the anal cushions. The internal anal sphincter (IAS) is chiefly responsible for continence at rest (Frenckner, 1975), and is predominantly composed of slow-twitch, fatigue-resistant smooth muscles. Electromyographic study of the IAS demonstrates a constant activity at rest (Ustach et al., 1970, Hancock, 1976, Pedersen and Christiansen, 1989), which is unaffected by respiration or administration of a general anaesthesia (Wankling et al., 1968). The contribution of the IAS to anal canal tone is debated, but has been reported as being as much as 85% at rest, 65% during constant rectal distension and 40% after sudden rectal distension (Frenckner and Euler, 1975). Other studies estimate a lesser influence, in that approximately 55% of resting anal tone is due to IAS activity (Lestar et al., 1989). The external anal sphincter (EAS) is also in a state of constant tonic activity at rest, (Floyd and Walls, 1953) and this generates approximately 30% of the basal resting anal tone (Lestar et al., 1989). The anal vascular cushions, including the superior haemorrhoidal plexus, contribute to approximately 15% of the resting anal tone, (Lestar et al., 1989) but importantly provide the 'hermetic seal' which cannot be achieved by sphincteric muscle tone alone.

Integral to the dynamic nature of anal canal activity is the intermittent, transient relaxation of the internal anal sphincter, which allows descent of distal rectal contents into the upper anal canal, endowing a subconscious or conscious perception of their physical nature. This so-called "sampling reflex" occurs approximately 7 times per hour (Miller et al., 1988b) in

healthy control subjects, but less frequently in patients with incontinence (Miller et al., 1988a). This reflex can be reproduced under laboratory conditions, where rectal distension causes reflex relaxation of the internal anal sphincter (in this case known as the 'recto-anal inhibitory reflex': RAIR), as well as contraction of the external anal sphincter.

*In vivo*, the consequence of the sampling reflex is a drop in upper anal canal pressure, so that rectal pressure becomes greater than or equal to mid anal pressure (Miller et al., 1988b). Lower anal canal pressure, however, remains virtually unchanged, (Duthie and Bennett, 1963) and overall, maximal intra-anal pressure remains higher than intra-rectal pressure to preserve continence (Haynes and Read, 1982). The net effect of this pressure change is to briefly expose the anal sensory area to the rectal contents so that sampling can occur (Duthie and Bennett, 1963, Miller et al., 1988b). The reflex is controlled by the enteric nervous system (Frenckner, 1975, Meunier and Mollard, 1977, Beuret-Blanquart et al., 1990), with a degree of regulation from the sacral cord (Meunier and Mollard, 1977) and is absent in patients suffering from Hirschsprung's disease (Meunier et al., 1978).

The anal canal epithelium is lined by highly sensitive nerve endings derived from sensory, motor and autonomic nerves, in addition to the enteric nervous system (Rao, 2004). The anal sensory area contains specialised sensory end organs, including Krause end bulbs, Golgi Mazzoni bodies, genital corpuscles, Meissner's corpuscles and Pacinian corpuscles (Duthie and Gairns, 1960). It is important to note, however, that this information was derived from studies performed over 50 years ago, using techniques which may now be regarded as outdated. Few other data are available. Slowly adapting afferents that remain silent in basal conditions, but are sensitive to circumferential stretch exist in the IAS of guinea pigs (Lynn and Brookes, 2011). Lynn *et al* also demonstrated that in guinea pigs, rectal nerve axons to the IAS predominantly end in extensive varicose arrays within the circular muscle (Lynn and Brookes, 2011). Mechanotransduction sites were strongly associated to these varicose arrays (Lynn and Brookes, 2011).

## **1A.4.2 THE PRE-EXPULSIVE PHASE**

During this phase, specific motor events occur, which culminate in an awareness by the subject of an urge to defecate, the 'call to stool'.

### **1A.4.2.1 Origin of the defaecatory urge**

In order to achieve normal defaecation, the importance of a defaecatory urge cannot be overemphasised. The voluntary process involved in defaecation *starts* with a sensation of 'call to stool'. Although our knowledge on the origin of this urge has increased significantly in the last few decades, the precise location of the receptors responsible and contribution of the organs involved are still debated. It is likely that the colon, rectum, anus, extra-rectal tissue and the puborectalis may all contribute to varying degrees (see below).

#### 1A.4.2.1.1 Role of the colon

In healthy subjects, there is a close relationship between HAPCs and urge to evacuate, a relationship that is often absent in patients with constipation (Dinning et al., 2004). In a study in volunteers, it was shown that out of 27 instances of perceived urge to defecate, 26 were associated with a propagated sequence, of which 62% were associated with HAPCs (Bampton et al., 2001). This study also showed that propagated sequences were more likely to result in urge during the one hour pre-expulsive phase (as compared to the basal phase), and that sequences that propagated further were more likely to result in an urge. During the pre-expulsive phase, propagated sequences often start as unperceived colonic contractions in the proximal colon, and migrate distally while increasing in amplitude to become a 'full blown' HAPC, that is then associated with an urge to defecate (Bampton et al., 2000). It is feasible that increased colonic activity seen during the pre-expulsive phase leads to movement of colonic contents distally, which in turn stimulates distal colonic (or perhaps rectal) afferents (Bampton et al., 2000), possibly by distension, resulting in sensory perception. However, balloon distension of the colon in healthy individuals typically results in a colicky or 'windy' pain rather than the usual defaecatory urge (Goligher and Hughes, 1951,

Ford et al., 1995b). Goligher *et al* reported that performing balloon distension of the terminal colonic segment in patients with colostomies typically resulted in periumbilical or suprapubic pain rather than the typical 'rectal-type' sensation associated with an urge to defecate (Goligher and Hughes, 1951). Although these studies prove the importance of the colon in generation of urge, they also serve to highlight that it is probably not the principal organ involved.

#### 1A.4.2.1.2 Role of the rectum, the pelvic floor and the extra-rectal tissues

The rectum is regarded as the primary site of origin of the defaecatory urge. Gradual distension of the rectum produces a graded sensory response starting with an initial awareness of filling (Meunier et al., 1976). With continued distension, this is followed by a constant sensation (likened to the desire to pass wind), that is replaced by a sustained urge to defecate, and finally by a sense of discomfort and an intense urge to defecate as the maximal tolerable volume / pressure is reached (Sun et al., 1990, Broens et al., 1994, Broens and Penninckx, 2002). Rectal-type sensation similar to a desire to defecate can be elicited by distension of the bowel up to 15 cm from the anal verge, whereas distension above this level typically leads to a colonic-type sensation similar to wind pain or suprapubic pain (Goligher and Hughes, 1951). In patients with residual rectum following colectomy (and colorectal anastomosis), balloon distension below the suture line results in a normal defaecatory urge (Goligher and Hughes, 1951). In another surgical study, following a unique procedure in which the anorectum was mobilised on its neurovascular pedicle and transposed to the anterior abdominal wall to preserve intestinal length in patients with short bowel syndrome, balloon distension through an abdominal wall stoma provoked sensation of pelvic filling (Williams et al., 1996).

In support of an extra-rectal origin of urge sensation, it has been shown that defaecatory desire can be provoked by stimulating nerve endings and stretch receptors in pelvic floor muscles including the puborectalis, and from structures adjacent to the rectum (Scharli and

Kiesewetter, 1970). It has also been shown that anaesthetising the rectal wall with Lignocaine has no effect on perception if rectal distension is rapid (although the threshold for perception is increased if distension is gradual) (Lembo et al., 1994). Additionally, in patients following rectal excision and colo-anal anastomosis, it has been observed that a sense of impending defaecation is preserved. (Simonsen et al., 1976, Lane and Parks, 1977) and that this is dependent upon the location of the colonic stump within the pelvis (Goligher and Hughes, 1951). A study of filling sensations in patients who had undergone restorative proctocolectomy with pouch-anal anastomosis concluded that neorectal filling thresholds were comparable to normal individuals (Broens and Penninckx, 2002). However, the nature of sensation in these patients appeared different from their sense of call to stool prior to surgery (Goligher and Hughes, 1951, Simonsen et al., 1976, Lane and Parks, 1977). This led Abercrombie *et al* (Abercrombie et al., 1996) to suggest that the receptors are likely located in the rectal wall and that after rectal excision, patients adapt to new sensations and associate them to a sense of impending defaecation.

In summary, based on these observations, it can be concluded that both the rectum and the pelvic floor have a role in the generation of normal filling sensation, and also in the urge to defecate.

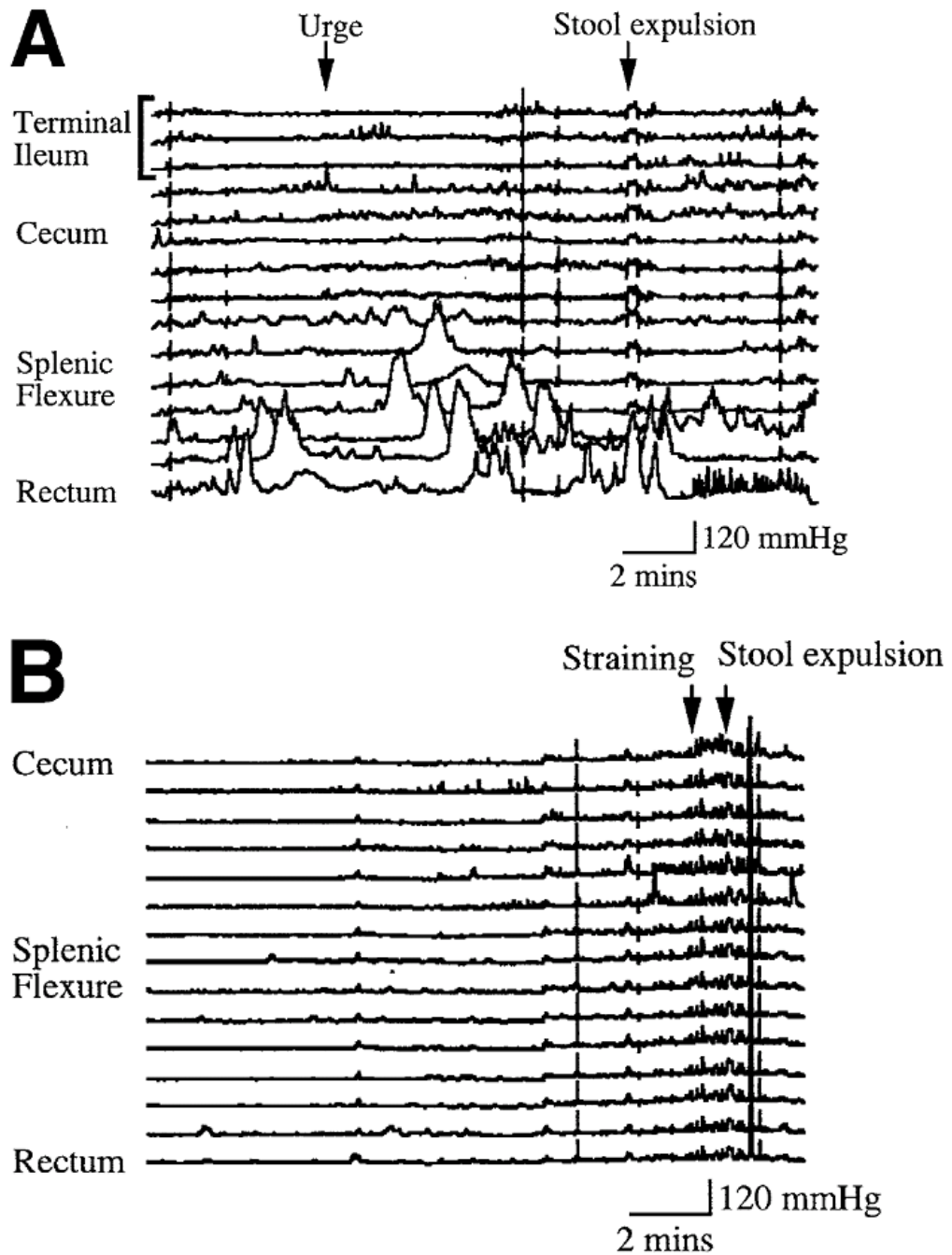
#### 1A.4.2.1.3 Role of the anal canal

Although intact anal canal sensation is essential for 'sampling' of faecal contents, whether it directly contributes to the generation of a defaecatory urge is unclear. Goligher *et al* studied the nature of defaecatory urge in healthy volunteers and in a series of patients who had undergone colectomy with a variable length of anorectum left *in situ* (Goligher and Hughes, 1951). In healthy volunteers, inflation of a balloon in the anal canal led to a sensation of stool escaping from the anus rather than a typical defaecatory urge. This work also showed that in patients with a colo-anal anastomosis, where the anal canal distal to the mucocutaneous junction was preserved, balloon distension most commonly elicited a sense of 'wind' or

perineal or sacral discomfort, and rarely a very vague sensation akin to rectal stimulation (Goligher and Hughes, 1951). Thus the anus informs the subject in a direct somatic way of the contents impinging upon it.

#### **1A.4.2.2 Colonic motor activity (up to 1 hour before defaecation)**

During the pre-expulsive phase, there is a distinct change in colonic motor activity characterised by a progressive, time-dependent increase in the frequency and amplitude of propagated sequences (Bampton et al., 2000, Dinning et al., 2004). This is absent in constipated patients (Figure 1A.2) (Dinning et al., 2004, Dinning et al., 2008b). Between 60 minutes to 15 minutes before defaecation, there is distal shift in the site of origin of PSs, which move from the transverse colon or splenic flexure towards the descending colon (Bampton et al., 2000, Dinning et al., 2004). However, this pattern reverses in the final 15 minutes preceding defaecation, when a retrograde shift in the site of origin of PS occurs (Figure 1A.2) (Bampton et al., 2000, Dinning et al., 2004, Dinning et al., 2010b). Little is known about the initiating stimulus, mechanism, or function of this organised migration in the site of origin of these PSs, but it has been hypothesised that it may be due to the effect of long colo-colonic reflex pathways (Bampton et al., 2000); during the initial phase of antegrade migration, movement of luminal contents distally may stimulate distal colonic afferents, which in turn may initiate progressively retrograde PSs as well as a sensation of urge (Bampton et al., 2000).



**Figure 1A.2:** Pancolonc manometric tracings during defaecation. In a healthy volunteer (A), stool expulsion is preceded by several PSs. The site of origin of each subsequent PS is seen to originate from a site more proximal than the preceding sequence. Such activity is absent in a constipated patient (B). (*Kindly reproduced with permission from Gastroenterology 2004; 127:49-56 (Dinning et al., 2004)*)



#### **1A.4.2.3 Rectal sensorimotor activity**

During this phase, rectal filling occurs. Impaired (blunted) perception of rectal distension, or rectal hyposensitivity, is often associated with an attenuated 'call to stool' and constipation (Baldi et al., 1982, Meunier, 1986, Shouler and Keighley, 1986, De Medici et al., 1989, Wald et al., 1989), with or without overflow incontinence (Wald and Tunuguntla, 1984, Hancke and Schurholz, 1987, Lubowski and Nicholls, 1988, Sun et al., 1990, Hoffmann et al., 1995). Conversely, rectal hypersensitivity, reflecting increased perception of distension, is associated with a heightened sense of urge, allied to faecal urgency, with or without incontinence (Farthing and Lennard-jones, 1978, Sun et al., 1992, Williams et al., 2001, Chan et al., 2005b).

Responding appropriately to the 'call to stool' appears fundamental to normal defaecation. Furthermore, normal functioning of rectal afferent nerves and normal rectal wall biomechanical properties appear critically important for perception of rectal fullness and ultimately a defaecatory urge (Gladman et al., 2006). It is postulated that habitual suppression of the defaecatory urge may lead to attenuation of the call to stool resulting in rectal faecal impaction and secondary dilation, potentially culminating in a megarectum (Harraf et al., 1998, Mertz et al., 1999, Mimura et al., 2002, Di Lorenzo and Benninga, 2004). Nevertheless, the clinical importance of impaired peripheral sensation in children has been questioned (Scott et al., 2011). Although earlier studies reported that larger rectal distension volumes were needed to trigger rectal sensation in constipated children (Meunier et al., 1979, Molnar et al., 1983), more recent studies found no difference in sensory function in children with functional constipation when compared to healthy volunteers (Voskuil et al., 2006, van den Berg et al., 2008), although rectal compliance (stretch response to an imposed force) was greater (i.e. the rectum was more lax) in constipated individuals. Alternatively, megarectum may be secondary to other disordered neuromuscular dysfunctions (Gattuso et al., 1997, Gattuso et al., 1998, Lunniss et al., 2009a). Whether idiopathic megarectum is a primary or secondary phenomenon is unknown (Mimura et al.,

2002), but it is likely that psychological (Ringel et al., 2004), behavioural and neurophysiological factors may all play a part (Mimura et al., 2002).

In consideration of the perception of rectal filling, it has been postulated that *in vivo*, the incoming faecal bolus, likely transported by PS activity, deforms the rectal wall, altering stress and strain, and thus activating mechanoreceptors that then induce reflex rectal contractions (Denny-Brown and Robertson, 1935, White et al., 1940). The amplitude of the rectal contraction increases with higher rectal volumes (Haynes and Read, 1982). It has been proposed in some studies that rectal sensation does not occur unless accompanied by rectal contractions (Sun et al., 1990, Corsetti et al., 2004). Furthermore, the duration of rectal contractile activity correlates well to the duration of rectal sensation (Sun et al., 1990). Reduced rectal contractility has been reported in constipated patients (Waldron et al., 1988, Vasudevan et al., 2006). Rectal sensation, and by implication contraction of the rectum, is also an important determinant of reflex external anal sphincter contraction (Sun et al., 1990) and hence maintenance of continence (Read and Read, 1982).

In order to evaluate whether volume, pressure or weight of rectal contents provides the main trigger for rectal sensation, Broens *et al* compared the sensation generated by inflating a rectal balloon with 60 mls of air, water and mercury (Broens et al., 1994). The study demonstrated a constant relationship between level of rectal sensation and the pressure in the rectal balloon. Sensation levels were independent of both the weight and the volume of the rectal contents. They concluded that rectal sensation is sensitive to intrarectal pressure changes which triggers tension-activated stretch receptors (Broens et al., 1994). However more recent studies suggest that rectal wall deformation rather than intrarectal pressure is the direct stimulus, since mechanoreceptors are stimulated by circumferential strain and shearing forces that cause deformations in rectal wall morphology (Gregersen and Kassab, 1996, Petersen et al., 2003, Gladman et al., 2009), which may be secondary to intraluminal pressure changes (Petersen et al., 2003).

Our understanding of the morphology of visceral afferent nerve endings potentially responsible for generation of rectal sensation is far from complete, (Zagorodnyuk et al., 2010) and most of our knowledge is based on animal studies. In the myenteric ganglia of the guinea pig rectum, specialized nerve terminals with branched, flattened lamellar endings, called rectal intraganglionic laminar endings (rIGLEs), have been identified as mechanotransduction sites of low threshold, stretch-sensitive mechanoreceptors (Lynn et al., 2003, Olsson et al., 2004). Their density decreases significantly proximally along the distal gut (Lynn et al., 2003). Functionally, rIGLEs are probably independent of the enteric nervous system since they have been shown to function normally in the rectums of piebald lethal mice devoid of any enteric ganglia (Spencer et al., 2008). In addition, medium-to-high threshold mechanoreceptors sensitive to local compression and stretch are present in close association with intramural and extramural blood vessels of major viscera including the colon (Song et al., 2009).

It has been shown that rectal sensation is preserved after bilateral pudendal nerve block (Frenckner and Euler, 1975, Chan et al., 2005a). However, low spinal anaesthesia (L5 – S1) abolishes rectal sensation, which is then perceived only as a vague abdominal discomfort at higher levels of rectal filling. Rectal sensation, including abdominal discomfort, is fully abolished by high spinal anaesthesia (T6 – T12) (Frenckner and Ihre, 1976). This shows that the sacral outflow plays a key role in the perception of rectal sensation while the thoracolumbar outflow has a lesser role. It has also been shown that the sense of rectal distension is impaired in patients with bilateral excision of sacral nerve roots (preserving S1 – 2 bilaterally) (Gunterberg et al., 1976). The importance of the lower sacral cord and the S3 nerve root in particular is emphasised by the preservation of bowel and bladder function by preserving at least one S3 nerve root during sacral resection (Todd et al., 2002).

Current neuroanatomical thinking indicates that rectal sensation does not depend on the integrity of the pudendal nerves (Frenckner and Euler, 1975), but spinal afferents travel in

parallel with the sympathetic and sacral parasympathetic pathways from the rectum, in nerves passing in the lateral ligaments, through the pelvic plexus and the pelvic splanchnic nerves (*nervi erigentes*) to reach the sacral segments of the spinal cord, with the majority of the sensory information entering the S3 and S4 nerve roots (Gunterberg et al., 1976, Todd et al., 2002). However, a proportion of rectal sensory information is conveyed via lumbar afferents which run from the inferior mesenteric ganglion into the hypogastric nerves, down through the pelvic ganglia, entering the rectum via the rectal nerves. This pathway is probably responsible for the perception of abdominal discomfort associated with rectal distension (Frenckner and Ihre, 1976).

Integrity of afferent neuronal pathways can be assessed using cerebral evoked potentials (Loening-Baucke and Yamada, 1993, Garvin et al., 2010), whereas efferent pathways can be evaluated using motor evoked potentials (Remes-Troche et al., 2011); alterations have been suggested in patients with colorectal dysfunction. By measuring cerebral evoked potentials in response to rectal balloon distension, Loening-Baucke *et al* found that children with chronic constipation and encopresis have significantly prolonged latencies suggestive of a defect in the afferent pathway from the rectum (Loening-Baucke and Yamada, 1995). Such findings have recently been reproduced in constipated adults with rectal hyposensitivity (Burgell et al., 2013). Other than integrity of the afferent pathway, evoked potentials may also depend on the degree of stimulation from surrounding structures (Loening-Baucke and Yamada, 1993), the differences in cortical neuronal orientation or volume, the state of myelination of the nerves, and type and diameter of nerve fibres constituting the pathway (Hobday et al., 2002).

In addition to rectal afferent nerve function, rectal wall biomechanical properties are central to governing rectal sensitivity. The healthy rectum is compliant i.e. it can accommodate increases in volume with little change in pressure (Bajwa and Emmanuel, 2009). This allows the rectum to distend in response to incoming faecal material, a phenomenon known as

adaptive relaxation, (Gladman et al., 2005), which enables it to serve as a temporary storage organ (i.e. its 'reservoir' function). Rectal distensibility depends on both passive and active properties of its walls (Liao et al., 2008). Passive mechanical distension (stress relaxation) depends on the viscoelastic properties of the rectal wall (Gladman, 2005), which is influenced by its collagen content and the state of contraction of the smooth muscle fibres within it (Gregersen and Kassab, 1996, Lunniss et al., 2009a). Active distension occurs by adaptive relaxation (Gladman et al., 2005), which is influenced by neuron-controlled smooth muscle relaxation (Liao et al., 2008). It is also influenced by the properties of the extrarectal tissues (Madoff et al., 1990). In healthy subjects, gradual balloon distension causes an initial phase of rapid increase in rectal cross sectional area, followed by a slow increase until a steady state is reached (Dall et al., 1993). Circumferential rectal wall tension shows a linear increase, and rectal compliance a non-linear decrease with increasing distension pressure (Dall et al., 1993). If the distending stimulus persists, it is possible that the rectal wall may continue to relax (Musial and Crowell, 1995), to an extent that a loss of urge to defecate occurs (Chan et al., 2001).

In studying a group of patients with constipation and rectal hyposensitivity to simple balloon distension, Gladman *et al* found that a subgroup of these patients had increased rectal capacity and / or compliance (i.e. excessive laxity) with normal rectal mucosal electrosensitivity (used as a direct measure of afferent nerve function), while another subgroup had normal wall biomechanical properties, but a significantly elevated rectal mucosal electrosensitivity threshold (Gladman et al., 2005, Gladman et al., 2009). Thus hyposensitivity can result from: a) abnormal rectal wall properties where afferent nerve function may be intact (i.e. a secondary disorder due to inadequate stimulation) or b) from impaired afferent function (i.e. a primary disorder) (Gladman et al., 2006), which can occur at any level of the pathway from receptor to higher centres of the central nervous system (Gladman et al., 2006).

#### **1A.4.2.4 Pelvic floor activity**

As in the basal phase, the pelvic floor continues to remain in a state of continuous contraction, thus preserving continence. When a defaecatory urge occurs, and if defaecation is not convenient, the external anal sphincter and the pelvic floor muscles including puborectalis can be further voluntarily contracted (Goligher and Hughes, 1951, Porter, 1962). This increases the acuity of the anorectal angle, elevates the pelvic floor, and lengthens the high pressure zone of the anal canal (Wester and Brubaker, 1998). Whether such activity actually results in retropulsion of rectal contents into the sigmoid is unknown.

#### **1A.4.2.5 Anal canal activity**

Whether there is a change in frequency (or characteristics) of the sampling reflex during the pre-expulsive phase is unknown. However, personal human experience teaches that with increased rectal filling, there is increased anal and conscious awareness of intra-luminal contents. Broens *et al*, who studied anal canal relaxation allied to rectal filling sensation showed that at a filling volume which elicited a constant sensation, the upper anal canal diameter was 3.2 cm; this increased to 4 cm and 4.4 cm at urge and maximum tolerable volumes respectively (Broens et al., 2002). Thus, with increasing rectal filling, the voluntary muscles acting to preserve continence (i.e. occlusion of the distal anal canal) play an increasingly important role.

#### **1A.4.3 THE EXPULSIVE PHASE**

Facilitated by the sampling reflex, and in the presence of a defaecatory urge, if a conscious decision to evacuate is made, rectal contents and a variable quantity of colonic contents are evacuated during this phase. Efficacy of expulsion may be influenced by additional voluntary straining and assumption of an appropriate posture. The final common path is affected by an elevation in intra-rectal pressure and relaxation of the pelvic floor and anal canal. Even in the healthiest of subjects, it is important to note that voluntary suppression of defaecation may be overcome by the physical nature and volume of stool.

#### **1A.4.3.1 Colonic activity**

During defaecation, a variable portion of the colon, as well as the rectum, empties (Lubowski et al., 1995). A scintigraphic study of defaecation in 11 healthy volunteers showed that the mean percentage of segmental evacuation was: right colon 20%, left colon 32% and rectum 66% (Lubowski et al., 1995). In healthy adults, 35 – 40% of all HAPCs in a day occur during or immediately preceding defaecation (Rao et al., 2001b, Dinning et al., 2010a), and virtually all episodes of defaecation are associated with HAPCs. (Herbst et al., 1997, Bampton et al., 2001); this is compatible with the radiological concept of mass movement (Ritchie et al., 1971, Torsoli et al., 1971). Performing simultaneous scintigraphy and left colonic and anal manometry during defecation in a healthy volunteer, Kamm *et al* showed an equivalent propulsive pattern to swallowing, i.e. colonic (*cf.* oesophageal body) peristaltic wave with simultaneous anal (*cf.* lower oesophageal) sphincter relaxation (Kamm et al., 1992).

#### **1A.4.3.2 Rectal activity**

Logic would dictate that in order for rectal contents to be evacuated, intra-rectal pressure must exceed anal canal pressure. Accordingly, it is widely accepted that normal defaecation is associated with an increase in intra-rectal pressure (Bharucha et al., 2006, Rao et al., 2009) and a necessary relaxation of the anal canal resulting in decreased anal pressure. Straining during evacuation raises intra-pelvic and hence intra-rectal pressure. Intuitively, simultaneous rectal contractions would likely augment evacuation, but whether this is true or not has not been clearly demonstrated (Brookes et al., 2009). One group reported no appreciable rise in intra-rectal pressure in relation to intra-pelvic pressure during evacuation (MacDonald et al., 1993), and suggested that evacuation is not accompanied with rectal contraction. Others have suggested that the rectum can contract during evacuation (Ito et al., 2006). It is probable that evacuation is effected by both voluntary straining and cooperative colorectal contractions; the relative contribution of each likely depends on circumstances, such as volume and consistency of the stool (Bharucha, 2006a), and behavioural and cultural influences (including the timing of attempted defaecation in relation

to onset of the defaecatory urge). One study showed that subjects who displayed stronger rectal contractile activity in response to rectal filling needed to strain less and had larger amplitude rectal contractions during evacuation ('rectal-contraction-type' evacuators), in contrast to 'strain-type' evacuators, in whom rectal contractile activity during filling and during evacuation were proportionally less (Ito et al., 2006).

#### **1A.4.3.3 Pelvic floor activity**

During this phase, there is reflex inhibition of pelvic floor tonic activity (Enck and Vodusek, 2006). How this is mediated is not entirely clear. Muscle spindles have been found in the human pelvic floor (Panu et al., 1995), and it has been suggested that increased abdominal pressure (stretch stimulus) although initially excitatory to the pelvic floor, becomes inhibitory when prolonged beyond a critical level (Porter, 1962). More recently it has been suggested that higher centres modulate pelvic floor reflex pathways, and that there may be a 'gating mechanism' that allows or prevents stimuli from various sources (like increased intra-abdominal pressure and pelvic organ distension) to excite or inhibit the motor neurons (Enck and Vodusek, 2006). Adequate pelvic floor relaxation is essential for effective evacuation, failure of which is a recognised cause of disordered defaecation (i.e. pelvic floor dyssynergia, or dyssynergic defaecation) (Rasmussen, 1994, Wester and Brubaker, 1998, Rao et al., 2004a, Bharucha et al., 2006, Lunniss et al., 2009a). Relaxation of the pelvic floor coupled with high intra-abdominal pressure causes it to descend, (Bartolo et al., 1985) assuming a funnel shape with the tip of the funnel located at the anorectal junction. The anorectal angle straightens due to relaxation of the puborectalis part of the pelvic floor; such straightening of the angle is also helped by the posture assumed during defaecation, which usually involves a degree of hip flexion.

#### **1A.4.3.4 Anal canal activity**

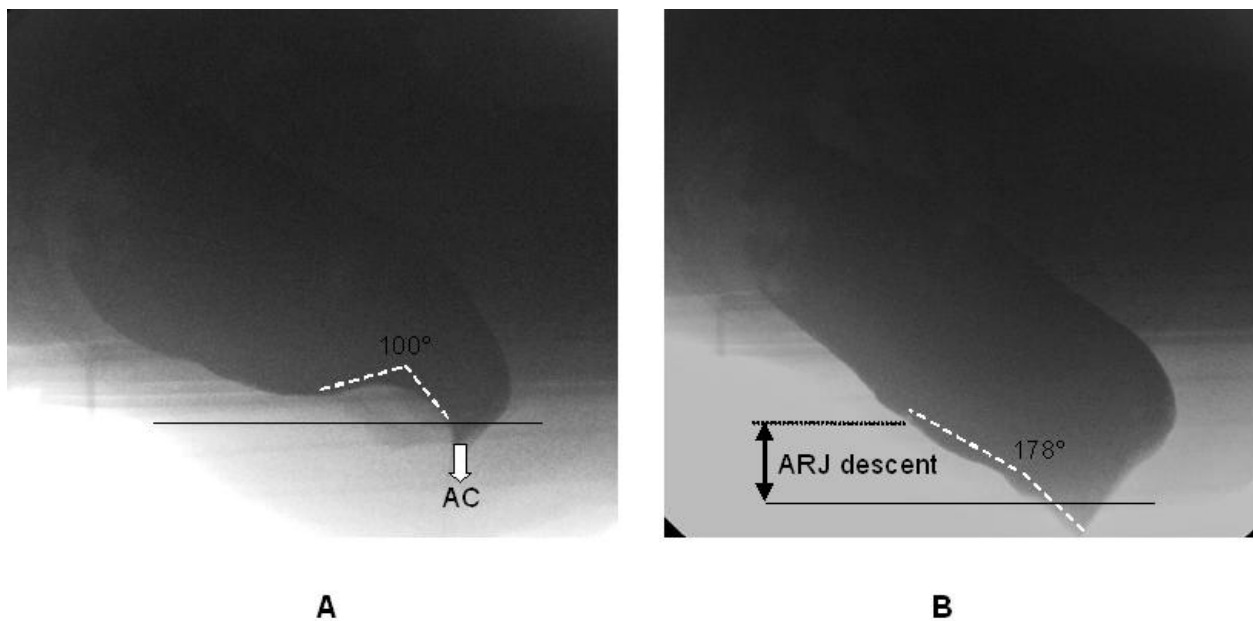
During the expulsive phase, anal canal relaxation occurs. Inadequate relaxation of the anal sphincter is also a recognised cause of pelvic floor dyssynergia (Rao et al., 2004a, Bharucha



et al., 2006, Longstreth et al., 2006, Lunniss et al., 2009a), seen in both adults and in children. It has been suggested that infants with constipation fail to coordinate the increased intra-abdominal pressure with adequate pelvic floor relaxation (Rasquin-Weber et al., 1999). In fact they may even inappropriately contract their external anal sphincter during defaecation (Meunier et al., 1979, Loening-Baucke and Cruikshank, 1986, Wald et al., 1987, Loening-Baucke, 1989); whether this behaviour is primary or secondary to chronic faecal retention is unclear. Dyssynergic defaecation is often screened by the balloon expulsion test (Minguez et al., 2004). A study by Loening-Baucke *et al* reported that chronically constipated children who were unable to expel a rectal balloon were less likely to recover after conventional laxative treatment (Loening-Baucke and Cruikshank, 1986). In a separate study, balloons of 30 ml, 50 ml and 100 ml were used, and it was reported that failure to expel the 100 ml balloon (but not smaller volume balloons) within 1 min correlated with treatment failure (Loening-Baucke, 1989). Another study by the same group found that children with functional constipation and encopresis who were able to expel the rectal balloon were twice as likely to respond to treatment (Loening-Baucke, 1996). Nevertheless, the ability of the balloon expulsion test to predict response was only slightly better than by chance (Loening-Baucke, 1996).

Internal anal sphincter relaxation occurs involuntarily in response to rectal distension and the relaxation is proportional to the intra-rectal pressure (Ustach et al., 1970, Frenckner, 1975). After assuming a posture convenient for defaecation, the subject strains by contracting the abdominal muscles and diaphragm against a closed glottis (Valsalva manoeuvre). This is associated with relaxation of the external anal sphincter. It has been suggested that the levator plate (that inserts into the posterior aspect of the rectum) and the longitudinal muscles of the anus contract simultaneously during evacuation. The resultant force vector is directed posteriorly and downwards resulting in the opening of the anorectal angle (Petros and Swash, 2008) (Figure 1A.3). This is facilitated by contraction of the pubococcygeus muscle that 'splints' the perineal body, effectively tensing the anterior wall of the anal canal,

allowing only the posterior wall to move backwards (Petros and Swash, 2008). Contraction of the conjoint longitudinal muscles of the anus also causes flattening of the anal vascular cushions (Loder et al., 1994) and shortening of the anal canal (Brookes et al., 2009). The incoming faecal bolus possibly further flattens the vascular cushions by direct compression (Loder et al., 1994). All these changes, occurring simultaneously, probably decrease the anal canal pressure to a value lower than the intrarectal pressure resulting in a pressure gradient from the rectum to the outside. Expulsion occurs and continues due to high intrarectal pressure, augmented by straining. It has been postulated that once defaecation starts, sensory input from the anus maintains the propulsive activity until the rectum is empty (Lynch et al., 2000, McCrea et al., 2008). This is probably due to a spinal reflex since rectal emptying, once initiated, is nearly complete even in patients with spinal injury (Lynch et al., 2000).



**Figure 1A.3:** Normal evacuation proctogram images during defaecation. At rest (A), the posterior anorectal angle (dotted white line) measures 100°; the level of the anorectal junction (ARJ) is marked by the solid black line; and the site of the closed anal canal (AC) is represented by the white arrow. During expulsion (B), the anorectal angle opens to 178°, the anorectal junction descends, and the anal canal opens.

#### **1A.4.4 TERMINATION OF DEFAECATION**

This phase begins under semi-voluntary control (the sense of complete rectal emptying, with cessation of those manoeuvres aimed at increasing intra-pelvic pressure), and thence by involuntary contraction of the external anal sphincter and pelvic floor, which closes the anal canal and reverses the pressure gradient towards the rectum. When traction is applied to the anus and then released (likened *in vivo* to passage of stool), the external sphincter shows a momentary increase in activity that tends to close the canal. This reflex is known as the 'closing reflex' (Porter, 1962, Nyam, 1998, Bajwa and Emmanuel, 2009, Brookes et al., 2009) and is important at the end of defecation to provide the internal sphincter, which is no longer inhibited by rectal distension, time to recover its tone (Nyam, 1998). This reflex seems to be cortically modulated since it is impaired in patients with spinal injury (Porter, 1962). Once straining ceases and intra-abdominal pressure falls, the postural reflex in the pelvic floor is reactivated (Porter, 1962), resulting in contraction of the puborectalis which increases its traction on the anorectal junction, returning the angle to its basal state. Simultaneous relaxation of the conjoint longitudinal muscle elongates the anal canal and allows the anal cushions to passively distend, resulting in full closure of the anal canal.

#### **1A.5 CONCLUSION**

In conclusion, defaecation is a complex process that is influenced by a number of conscious and subconscious events. The contribution of higher centre influences is perhaps best exemplified by the contrasting defaecatory habits of man and higher mammals, in whom a socially convenient time and place for the act predominate, over lower species in whom such habits are absent. Although defaecation may be divided into various phases, and the various components contributing to those phases are identifiable, understanding of the coordinated interplay between the brain, the spinal cord, peripheral nerves and end organs (colon, rectum, anus and extraintestinal pelvic muscles) remains limited. Our knowledge of motor activity in particular has seen major advances recently, but there remain significant gaps in our understanding of other processes. Research into combined modality assessment under

ideal physiological circumstances is fundamental to further comprehension of evacuatory function and dysfunction which, along with other 'functional bowel diseases' have significant impact on quality of life.

# **1B Definition, epidemiology, classification and pathophysiology of constipation**

## **1B.1 DEFINITION**

Constipation is a general term that embraces a range of conditions where a subject is dissatisfied with their defaecation (Lunniss et al., 2009a). There is no universally agreed definition of constipation (Lembo and Camilleri, 2003, Vrees and Weiss, 2005, Cook et al., 2009, Rao and Meduri, 2011). Patients with constipation often complain of infrequent bowel movements (usually fewer than three motions a week) (Connell et al., 1965), hard stools that are difficult to pass, a need to strain excessively (or a need for manual manoeuvres to pass stool), a sense of incomplete bowel movement and excessive time spent on the toilet. Others may describe even more diverse symptoms such as general discomfort, nausea, lethargy or back pain (Johanson and Kralstein, 2007). Patients and doctors often have different perception about what constitutes 'constipation' (Herz et al., 1996). Moreover, self-reported constipation is often subjective and is also influenced by social customs (see below) (Stewart et al., 1999). Clinicians often use the frequency of defecation, stool weight, colonic transit studies and other anorectal physiology investigations to diagnose constipation (Ashraf et al., 1996). With regard to the former, constipation is traditionally defined as fewer than 3 bowel motions per week (Connell et al., 1965, Lopez Cara et al., 2006). However, in an epidemiological survey in the United States involving 10,018 respondents, 9% reported fewer than 3 motions per week and 11% reported 3 or more weeks with fewer than 3 motions a week (Stewart et al., 1999). By contrast, 38% in the same study reported a frequent sense of incomplete evacuation, 24% reported regular unsuccessful attempts at bowel movement and 20% reported abdominal pain / bloating or a sense of outlet blockage. Bowel infrequency has also been shown to be a less common symptom than defaecatory difficulty (especially straining) in other general population studies (Pare et al., 2001) and in

patient cohorts with well-defined chronic constipation (Pare et al., 2001, Johanson and Kralstein, 2007).

Because of the variation in perception of constipation, consensus criteria have been proposed by experts to aid diagnosis, evidence based management and further research. One of the most widely used diagnostic criteria, the Rome criteria, has been proposed by an international panel of experts and is presently in its third iteration (Rome III) (Longstreth et al., 2006) (with the IV<sup>th</sup> iteration due in 2016). Rome III defines functional constipation solely on symptoms, by the presence of 2 or more of the following six symptoms in at least 25% of defecations (over the last 3 months with symptom onset at least 6 months prior to diagnosis and only in the absence of sufficient criteria to diagnose IBS): hard stools, straining, sensation of incomplete evacuation, sensation of anorectal blockage, the use of manual manoeuvres during evacuation, and infrequent bowel movements (<3 movements per week) (Table 1B.1). The Rome III criteria recognises subgroups of functional constipation based on symptoms and physiological tests which would imply that the experts consider symptoms alone to be inadequate to identify subtypes of functional constipation in clinical practice. The other widely accepted diagnostic criterion has been proposed by The American College of Gastroenterology (ACG) Chronic Constipation Task Force. They have defined constipation as unsatisfactory defecation characterised by infrequent stools, difficult stool passage or both at least for previous 3 months. Difficult stool passage includes: straining, hard/lumpy stool, difficulty in passing stool, incomplete evacuation, prolonged time to stool, or the need for manual manoeuvres to pass stool (ACG, 2005) (Table1B.2).

**Table 1B.1:** Rome III criteria for functional constipation (Longstreth et al., 2006)

*Diagnostic criteria\**

1. Must include *two or more* of the following:
    - a. Straining during at least 25% of defecations
    - b. Lumpy or hard stools in at least 25% of defecations
    - c. Sensation of incomplete evacuation for at least 25% of defecations
    - d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
    - e. Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
    - f. Fewer than three defecations per week
  2. Loose stools are rarely present without the use of laxatives
  3. Insufficient criteria for irritable bowel syndrome
- \* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Table 1B.2:** American College of Gastroenterology Chronic Constipation Task Force criteria (ACG, 2005)

Unsatisfactory defecation characterized by infrequent stool, difficult stool passage, or both

Difficult stool passage includes:

- Straining
- Hard/lumpy stool
- Difficulty passing stool
- Incomplete evacuation
- Prolonged time to stool
- Need for manual manoeuvres to pass stool

Symptoms must be reported for at least 3 months

## 1B.2 EPIDEMIOLOGY OF CONSTIPATION

Constipation is one of the most common chronic disorders of the digestive tract (Johanson et al., 1989) affecting between 2% and 35% of the general population (Johanson et al., 1989, Frexinos et al., 1998, Stewart et al., 1999) depending on the criteria used. Similar prevalence rates of 0.7% to 29.6% have been reported for constipation in the paediatric literature (van den Berg et al., 2006). Systematic review and meta-analysis of general adult population studies, excluding convenience sampling and using a mix of self-reporting and specific diagnostic criteria yielded a pooled prevalence of 14.0% (Suarez and Ford, 2011). In the United States alone, constipation accounted for approximately 2.5 million physician visits a year in the late 80's (Sonnenberg and Koch, 1989b) and tertiary care for constipation was estimated to cost an average of US\$2,752 per patient in the United States in the late 90's (Rantis et al., 1997). A recent systematic review found that in the US, the estimated cost of management of chronic constipation can vary between US\$1,912 - \$7,522 per patient per year depending on whether they are treated in the community or as an inpatient (Nellesen et al., 2013). A recent UK cohort study of 3.8 million patients in primary care has provided further information (Shafe et al., 2011). In this cohort, 1.3% patients per annum consulted their general practitioner for symptoms of constipation. This figure remained constant over a 5 year period and included all common causes e.g. pregnancy and drug-induced constipation. The wide range of prevalence estimates for constipation reported in epidemiological studies is likely secondary to the variation of the definition used for constipation and the method used for the survey (Higgins and Johanson, 2004).

Comparing the prevalence of constipation in the same individuals, Pare *et al* reported a prevalence of 27.2% using self-report, 14.9% with Rome I and 16.7% with Rome II (Pare et al., 2001). Similarly, Garrigues *et al* reported a prevalence of 29.5% using self report, 19.2% using Rome I and 14% using Rome II (Garrigues et al., 2004). One of the largest population studies to assess the prevalence of self-reported constipation used data from over 800,000 respondents in the US from a mail survey questionnaire distributed between 1959-1960 by



the American Cancer Society. They observed a prevalence of 18.5% in men and 33.7% in women (Hammond, 1964) with a combined prevalence of 27.1% (Higgins and Johanson, 2004). Other studies have reported a prevalence rate ranging from 3.4% to 35% for self-reported constipation (Everhart et al., 1989, Sandler et al., 1990, Harari et al., 1996, Chiarelli et al., 2000, Haug et al., 2002, Walter et al., 2002, Siproudhis et al., 2006)

Studies that have diagnosed constipation using symptoms other than the Rome criteria vary greatly in their definition of constipation; prevalence rates vary from 4.3% to 31.7% (Higgins and Johanson, 2004, Peppas et al., 2008). In a population group made up of 835 white adults between the age of 30 - 64 years, Talley *et al* reported a chronic constipation prevalence rate of 17.4% where constipation was defined as the presence of hard stool and straining greater than 25% of time and/or less than 3 motions a week (Talley et al., 1991). Using a similar population, but fewer number (690 compared to 835) according to the Rome I criteria, Talley *et al* reported a prevalence of 19% for functional constipation and 11% for outlet obstruction (Talley et al., 1993). Conversely, Drossman *et al* observed a prevalence rate of 3.6% for functional constipation, again using the Rome I criteria (Drossman et al., 1993). Studies using the Rome II criteria for diagnosis of constipation have reported prevalence rates of 14% to 30.7% (Stewart et al., 1999, Pare et al., 2001, Garrigues et al., 2004, Howell et al., 2006).

Most studies have reported a higher prevalence of constipation in women than in men with female :male ratio ranging from 1.01 to 3.77(Hammond, 1964, Everhart et al., 1989, Sandler et al., 1990, Talley et al., 1991, Talley et al., 1993, Harari et al., 1996, Stewart et al., 1999, Pare et al., 2001) with a median of 2.2 (Higgins and Johanson, 2004). This ratio is much more pronounced in patients with chronic idiopathic constipation attending tertiary care (Preston and Lennard-Jones, 1986, Knowles et al., 2003). There is an increased prevalence of constipation among non-Caucasians, with non-white : white ratios between 1.13 to 2.89 (Everhart et al., 1989, Sandler et al., 1990, Drossman et al., 1993, Stewart et al., 1999) with a median of

1.41 (Higgins and Johanson, 2004). Similarly, subjects with lower income have a significantly higher rate of constipation than subjects with higher income (Higgins and Johanson, 2004). An inverse relationship between the years of education and prevalence of constipation has been reported mostly by studies involving self-report constipation, but in studies using Rome criteria to define constipation, the difference is less apparent (Higgins and Johanson, 2004). Some studies have also reported an increasing trend towards constipation with increasing age (Hammond, 1964, Johanson et al., 1989, Sandler et al., 1990, Harari et al., 1996) and a meta-analysis has confirmed this relationship (Suarez and Ford, 2011).

### **1B.3 CLASSIFICATION**

Constipation is broadly divided into primary (idiopathic) constipation and secondary constipation (Jamshed et al., 2011). Secondary constipation is a result of a definite systemic or local cause. Some selected causes of secondary constipation are listed in Table 1B.3. Primary or idiopathic constipation can be further subdivided into three categories: normal transit constipation, slow transit constipation and evacuatory disorders (Lembo and Camilleri, 2003, Jamshed et al., 2011). There is however a significant overlap between these groups. Ragg *et al* investigated 541 patients with chronic constipation and found that 53% had outlet obstruction, 5% had isolated slow transit constipation, 29% had co-existent outlet obstruction and slow transit and 12% had normal transit constipation (Ragg et al., 2011).

**Normal transit constipation:** this is an ill-defined condition in which stool passes through the intestine at a normal rate and frequency of bowel motions and evacuation are normal, but the patients perceive that they are constipated (Lembo and Camilleri, 2003). Patients often experience abdominal pain and bloating, and may have psychosocial issues (Wald et al., 1989, Ashraf et al., 1996). Symptoms usually respond to dietary fibres and laxatives (Voderholzer et al., 1997b).

**Slow transit constipation:** normal colonic transit time is less than 72 hours (Anon, 1998, Lembo and Camilleri, 2003, Dinning et al., 2009b). In patients with slow transit constipation,

the colonic transit time is prolonged which is can be confirmed by a colonic transit study (in reality most methods actually determine a prolonged whole gut transit time). As an isolated phenomenon, this is most commonly observed in young women with constipation dating

**Table 1B.3:** Secondary causes of constipation

Drugs

- Opiates
- Anti parkinson medications
- Iron supplements
- Diuretics
- Anticholinergics
- Antipsychotics
- Antidepressants

Neurological

- Parkinson's disease
- Multiple sclerosis
- Spinal cord injury
- Autonomic neuropathy

Metabolic

- Hypothyroidism
- Diabetes
- Chronic renal failure
- Hypercalcemia
- Hypokalemia

Psychological

- Psychological/physical/sexual abuse
- Affective disorders
- Eating disorders

Structural

- Obstructing tumour
- Stricture

Congenital

- Hirschsprung's disease
- Imperforate anus
- Anal atresia

Others

- Pregnancy
- Chaga's disease
- Dehydration
- Amyloidosis
- Scleroderma
- Pregnancy

from early childhood and is associated with infrequent bowel motion (once a week or fewer), bloating and abdominal discomfort or pain (Preston and Lennard-Jones, 1986).

**Evacuatory disorders:** Evacuatory disorders are characterised by difficulty in evacuating the stool once it reaches the rectum (Lembo and Camilleri, 2003, Jamshed et al., 2011). Nomenclature is not standardized and variable terms such as anismus, pelvic floor dyssynergia, defaecatory disorders, obstructed defaecation syndrome, spastic pelvic floor syndrome and functional faecal retention in children are also used to describe this condition. Common causes include functional abnormalities of the anal sphincter or pelvic floor and dynamic structural abnormalities such as rectocele, intussusception and excessive perineal descent (Lunniss et al., 2009b).

#### **1B.4 ETIOPATHOGENESIS OF CONSTIPATION**

Defecation is a complex process that involves integration of somatic and visceral muscle function with sensory information with control from local, spinal and central nervous system. This is further influenced by multitude of factors, most importantly by the nature of the hindgut contents, the speed at which it is delivered and the ability of the hindgut to sense and accommodate these contents (Lunniss and Scott, 2007). Disruption to the normal defaecatory process due to problem anywhere from the central nervous system down to the anal sphincters can result in constipation. For the sake of simplicity alone, the pathogenesis of constipation has been described here considering colonic, rectal, pelvic floor and central causes separately although many patients with constipation have problems that often involve more than one of these organs simultaneously either primarily or as a knock-on effect (Dinning et al., 2009b).

##### **1B.4.1 COLONIC CAUSES OF CONSTIPATION**

Normal colonic functions include absorption of water from intraluminal contents, propulsion of contents at an adequate rate and storage of faeces, particularly in the sigmoid colon, until convenient to evacuate (Palit et al., 2012). Colonic motility problems, abnormalities in colonic

reflexes and lack of normal response to physiological stimulus may all lead to constipation and can be directly recorded using pan-colonic manometric methods (Dinning et al., 2008b, Dinning and Di Lorenzo, 2011), or indirectly with transit studies such as radio-opaque markers.

#### **1B.4.1.1 Abnormality in colonic motility**

1B.4.1.1.1 High amplitude propagated contractions (HAPC) are primarily responsible for major luminal transit (Cook et al., 2000) and facilitate defaecation (Bampton et al., 2000). Several studies have shown a reduced frequency of HAPCs in patients with slow transit constipation (Bassotti et al., 1988, Knowles et al., 2001, Bassotti et al., 2003, Hagger et al., 2003, Herve et al., 2004). However, a study of children with slow transit constipation found that the frequency of HAPCs may be normal suggesting an alternate pathogenesis may be involved in children (King et al., 2008).

1B.4.1.1.2 Low amplitude propagating contractions- in patients with slow transit constipation, some studies have reported a decrease in the frequency of low amplitude propagated sequences (Rao et al., 2004b, King et al., 2008) while others have reported a normal frequency when compared to healthy controls (Bassotti et al., 2003). A change in regional frequency has also been reported with one study reporting a decrease in the transverse colon (Dinning et al., 2009b) while another reported an increase in the sigmoid colon (Dinning et al., 2004).

1B.4.1.1.3 Lack of regional linkage between colonic propagated sequences -studies in healthy adults have shown that a series of two to three colonic propagated sequences may be linked in an organised spatio-temporal manner in such a way that although a single propagated sequence does not span the length the colon, collectively a series of linked propagated sequences do. This 'regional linkage' is absent in constipated patients (Dinning et al., 2009c).

### **1B.4.1.2 Colonic reflexes**

It is known that mechanical stimulation of the rectum (e.g. through faecal retention or impaction) can inhibit activity of more proximal portions of the GI tract such as the stomach (Qian et al., 2002) and colon (Bampton et al., 2002, Rao et al., 1998a, Mollen et al., 1999) through long inhibitory recto-intestinal reflexes. Indeed, voluntary suppression of evacuation can lead to a prolongation of total and regional intestinal transit time indicating that constipation can be 'learned' (Klauser et al., 1990).

### **1B.4.1.3 Lack of response to physiological and chemical stimulus**

1B.4.1.3.1 Response to eating-there is normally an increase in the frequency of HAPCs after a meal (Bampton et al., 2001, Rao et al., 2001b). This response is often absent in patients with constipation (Leroi et al., 2000, De Schryver et al., 2003, Herve et al., 2004, Rao et al., 2004b).

1B.4.1.3.2 Response to awakening - colonic motor activity normally increases upon awakening and decreases upon sleeping (Bampton et al., 2001, Rao et al., 2001b). Some studies have reported that the increase in colonic activity after awakening is absent or reduced in patients with constipation (Rao et al., 2004b, King et al., 2008) while others have found no significant difference compared to healthy controls (Bassotti et al., 1998, Dinning et al., 2004). Similarly, some studies have shown no difference in nocturnal suppression of colonic motor activity in constipated patients when compared to controls (Hagger et al., 2003, Rao et al., 2004b, King et al., 2008), while others have reported an absence of nocturnal suppression (Dinning et al., 2004). It has been suggested that the lack of diurnal variation may reflect a neuropathic cause of constipation (Rao et al., 2004b).

1B.4.1.3.3 Response to chemical agents - intravenous injection of cholinergic agonists like edrophonium (Bassotti et al., 1993) and rectal infusion of chenodeoxycholic acid (Dinning et al., 2005) increase the frequency of HAPC in healthy controls. This response is absent in constipated patients (Bassotti et al., 1993, Dinning et al., 2005). These may signify

abnormality in the cholinergic (Bassotti et al., 1993) or recto-colonic pathways(Dinning et al., 2005).

#### **1B.4.2 RECTAL CAUSES OF CONSTIPATION**

Normal rectal function is reliant on its biomechanical properties, structural integrity and an intact nerve supply (Lunniss et al., 2009a). Thus sensory-motor dysfunction and abnormalities of the rectal wall may all lead to disordered evacuation.

**1B.4.2.1 Rectal sensory dysfunction** -blunting of rectal sensation (rectal hyposensation) has been reported in up to 68% of patients with constipation (defined as infrequency of, and/or obstructed defecation) (Gladman et al., 2006). Rectal hyposensitivity as a cause of constipation was first postulated in 1940 in a study investigating patients with neurogenic hindgut dysfunction(White et al., 1940) and has gained more support recently (Read et al., 1986, Shouler and Keighley, 1986, Gladman et al., 2003a, Gladman et al., 2007). It is often the only demonstrable abnormality found in physiologic testing in constipated patients (Meunier, 1986, Gladman et al., 2003b). Although generally assumed to be secondary to impaired afferent nerve function (Gladman et al., 2006), rectal hyposensitivity can also occur secondary to structural and biomechanical abnormalities in the rectal wall (Gladman et al., 2009) which may result in inadequate stimulation of the rectum.

**1B.4.2.2 Rectal motor dysfunction** -isolated rectal hypocontractility has been reported in patients with constipation (Waldron et al., 1988). Assessment of rectal phasic activity using manometry and tonic activity using barostat are often used for assessment of rectal motor activity (Scott, 2003, Scott and Gladman, 2008). Some studies using barostat to evaluate patients with evacuatory dysfunction have reported blunting or absence of the expected increase in rectal tone after rectal distension, application of Bisacodyl or ingestion of a meal (Schouten et al., 1998, Gosselink et al., 2000, Gosselink and Schouten, 2001), particularly in patients with prolonged transit time. Constipated patients with normal transit may have a

reduction in the frequency and amplitude of rectal motor complexes (Bassotti et al., 1994). In patients with slow transit constipation on the other hand, an increase in the frequency of rectal motor complexes has been reported (Rao et al., 2001a) - it has been suggested that in these patients an excessive uncoordinated rectal phasic activity possibly impedes stool transport and may contribute to the pathogenesis of slow transit (Rao et al., 2001a).

**1B.4.2.3 Rectal biomechanical dysfunction** -rectal compliance is used as a measure to assess biomechanical properties of the rectal wall. It is the pressure/volume relationship observed during rectal distension (Whitehead and Delvaux, 1997, Azpiroz et al., 2002) and reflects the ability of the rectum to distend. Some studies have reported an increased compliance in patients with constipation (Gladman et al., 2005, van den Berg et al., 2008) while others have reported a normal compliance, particularly in patients with evacuatory dysfunction (Gosselink et al., 2001). A more compliant rectum distends more in response to an imposed pressure, a property that is influenced by the amount of collagen content in the rectal wall and the state of rectal smooth muscle activity (Gregersen and Kassab, 1996). It also depends on the elastic *versus* viscous properties of the rectal wall and the mobility of surrounding pelvic organs to allow for the rectum to expand - rectal fibrosis, pelvic irradiation and chronic inflammation may all produce a relatively rigid rectal wall (Azpiroz et al., 2002) incapable of significant distension.

**1B.4.2.4 Rectal structural abnormalities**- imaging simulated defecation in a laboratory setting using fluoroscopic evacuation proctography and more recently with magnetic resonance proctography may demonstrate structural abnormalities of the rectum, often associated with impaired evacuation (rate and/or percentage of evacuation). Frequently observed abnormalities include rectal intussusception (Shorvon et al., 1989, Mellgren et al., 1994) which can often occlude the lumen and obstruct evacuation (Faccioli et al., 2010), rectocoeles and enterocoeles (Mellgren et al., 1994). Although it is unclear why these structural abnormalities develop, it is possibly linked to a weakness of the supporting



structures of the rectum (Petros and Swash, 2008) particularly as a result of pregnancy, child birth, ageing or from years of straining (Lunniss et al., 2009a). It is unclear exactly how rectoceles, rectal prolapse or descending perineal syndrome lead to evacuatory dysfunction, but it has been ascribed to a dissipation of force vectors (Capps, 1975, D'Hoore and Penninckx, 2003). It should however be noted that although clinicians often ascribe symptoms to these structural changes, studies have shown little correlation between various structural abnormalities and symptoms of constipation (Savoie-Collet et al., 2003, Dvorkin et al., 2005)

#### **1B.4.3 CONSTIPATION DUE TO PELVIC FLOOR DISORDERS**

Normal defecation requires a coordinated increase in rectal pressure and associated relaxation of the pelvic floor and anal canal (*cf.* chapter 1A). It was initially thought that inadequate relaxation of the sphincter complex due to hypertrophy or paradoxical spasm of the puborectalis or the anal sphincters (Wasserman, 1964, Preston and Lennard-Jones, 1985) caused pelvic floor disorders. However, it is now believed that the anal sphincter muscle is unlikely to be the sole culprit (Rao, 2008) since there is minimal benefit after sphincter myomectomy or sphincter paralysis with Botulinum toxin injection (Pinho et al., 1989). Some patients with pelvic floor dysfunction fail to generate an adequate rectal pressure (Rao et al., 1998c), while others may demonstrate a paradoxical contraction or inadequate relaxation of the anal canal (Rao et al., 1998c). Although inadequate rectal propulsive / expulsive effort and inadequate anal sphincter relaxation have historically been placed in the same 'diagnostic bucket' of dyssynergic defecation (Minguez et al., 2004, Rao et al., 1998c, Suttor et al., 2010), ROME III criteria have separated them into two distinct and mutually exclusive diagnostic entities viz. impaired rectal propulsion and dyssynergic defecation (Longstreth et al., 2006), based on the fact that patients with impaired propulsion form a distinct manometric sub-group among dyssynergic patients (Rao et al., 2004a, Halligan et al., 1995b). It has however been argued that

it is likely that these patients often have a global disorder (MacDonald et al., 1991) and lack the normal synergism or coordination between the rectum, the pelvic floor and the anal canal (Rao et al., 1998c). Some of the studies included in the subsequent chapters of this thesis have closely followed the ROME III criteria for diagnosis of functional defecation disorders and its subtypes. (The diagnostic criteria used in the subsequent chapters are presented in table 1B.4). At the other end of the spectrum of pelvic floor dysfunction are patients with descending perineal syndrome. In these patients, the perineum balloons below the bony outlet of the pelvis on straining. It may result from childbirth/trauma of pregnancy, pudendal neuropathy or from repeated straining to evacuate (Times and Reickert, 2005). Although it was believed that descending perineal syndrome led to stretch related pudendal neuropathy eventually leading to faecal incontinence (Henry et al., 1982), more recent studies have failed to demonstrate a link between descending perineal syndrome and pudendal neuropathy (Jorge et al., 1993a, Ryhammer et al., 1998).

**Table 1B.4:** Diagnostic criteria for functional defecation disorders, dyssynergic defecation and impaired propulsion (based on ROME III criteria) used in subsequent chapters

**Functional defecation disorder (FDD)**

1. Using ARM: BOTH impaired anal relaxation (<20% sphincter relaxation) and inadequate propulsive force (intra-rectal pressure <45 mm Hg) (Bharucha et al., 2006)
2. Using EP: any 2 of:
  - a. abnormal expulsion amount (<35%) OR abnormal expulsion time (>134 secs) (*cf.* chapter 3)
  - b. inadequate sphincter relaxation - i.e. maximal anal canal width <.5 cm (*cf.* chapter 3) /persistent puborectalis impression (Jorge et al., 1993b)
  - c. abnormal expulsion amount OR time AND impaired pelvic floor movement (<3 cm) (Halligan et al., 1995b, Bharucha et al., 2006)
3. Using ARM +/- BE<sub>50</sub>: any 2 of:
  - a. impaired balloon evacuation (failed BE<sub>50</sub>)
  - b. impaired anal relaxation on ARM
  - c. inadequate propulsive force on ARM
4. Using ARM +/- EP: any one of:
  - a. FDD on ARM (as per criteria above)
  - b. FDD on EP (as per criteria above)
  - c. abnormal expulsion amount OR time (EP) AND impaired anal relaxation (ARM) OR insufficient rectal pressure increase on ARM
  - d. inadequate sphincter relaxation (EP) AND inadequate propulsive force (ARM)
  - e. impaired anal relaxation (ARM) AND abnormal expulsion amount OR time (EP) AND impaired pelvic floor movement (EP)
5. Using EP +/- BE<sub>50</sub>: any one of:
  - a. FDD on EP (as per criteria above)
  - b. impaired balloon expulsion (BE<sub>50</sub>) AND inadequate sphincter relaxation (EP)
  - c. impaired balloon expulsion (BE<sub>50</sub>) AND abnormal expulsion OR abnormal time (EP) AND impaired pelvic floor movement (EP)
6. Using ARM +/- BE +/- EP: (using the criteria above)  
FDD on: ARM, or EP, or ARM +/- BE, or ARM +/- EP, or EP +/- BE

**Impaired Propulsion (IP)**

1. Using ARM: On bearing down, maximal intrarectal pressure <45 mm Hg (Bharucha et al., 2006)
2. Using EP: Abnormal expulsion amount OR time AND pelvic floor descent <3 cm (Halligan et al., 1995b, Bharucha et al., 2006).

**Dyssynergic Defaecation (DD)**

1. Using ARM: Impaired anal relaxation AND *adequate* increase in intra-rectal pressure (i.e.  $\geq 45$  mmHg) (Bharucha et al., 2006)
2. Using EP: Impaired sphincter relaxation AND no proctographic evidence of IP (according to the criteria above) (Bharucha et al., 2006)

**Structural abnormalities**

- On EP: Significant structural abnormality (*cf.* chapter 3)

#### **1B.4.4 ABNORMALITIES IN THE BRAIN-GUT AXIS**

The CNS can influence GI functions by hard wiring (autonomic nervous system), neuro-endocrine (hypothalamo-pituitary adrenal axis) and immune modulation. Animal studies have shown that colonic response to stress may be mediated by corticotrophin releasing factor via hypothalamic and efferent autonomic pathways (Gue et al., 1991). Such an inhibitory mechanism may explain why psychological trauma is often associated with altered bowel function (Kamm, 2006). Depression, anxiety and traumatic life events like sexual and physical abuse are more common in women with severe constipation (Drossman et al., 1995, Kamm, 1997, Mason et al., 2000, Olden and Drossman, 2000, Drossman, 2011). It is known from studies in healthy volunteers that transit can be delayed at will (Klauser et al., 1990) suggesting behavioural factors may also influence constipation. This may be the mechanism involved in constipation arising from toilet avoidance behaviour often seen in young children or in frequent travellers like aircrews (Kamm, 2006). Further support to the importance of the brain-gut axis is shown by improved bowel function in patients after behavioural treatment to be associated with improved rectal mucosal blood flow (Emmanuel and Kamm, 2001), which is a marker of the cerebral autonomic efferent nerve supply to the large bowel (Emmanuel and Kamm, 2000).

#### **1B.5 HISTOLOGICAL CHANGES SEEN IN CONSTIPATION**

Many histological abnormalities have been described in the colon of patients with chronic constipation. Although our understanding of a cause and effect relationship of these changes to constipation is rudimentary, they nonetheless merit mention.

*Abnormality in the enteric nervous system / neuroendocrine system-* the neuroendocrine system of the gut broadly consists of endocrine cells mostly scattered along the mucosal surface and enteric nervous system including peptidergic, serotonergic and nitrergic neurones located along the bowel wall (El-Salhy, 2003). Interstitial cells of Cajal also play a vital role in the enteric nervous system by generating smooth muscle electrical slow waves that are required for normal colonic motility and transfer of signal between nerve and

muscles - they are hence regarded as pacemaker cells of the gastro-intestinal tract (Huizinga et al., 1995, Ward and Sanders, 2001).

Patients with slow transit constipation have a decrease in the number of interstitial cells of Cajal (He et al., 2000, Lyford et al., 2002, Tong et al., 2004). There is a reduction in the number of neurones in the myenteric plexus of patients with slow transit constipation (Krishnamurthy et al., 1985, Schouten et al., 1993, Wedel et al., 2002a). Pancreatic polypeptide, peptide YY and neuropeptide Y regulate intestinal motility and absorption of water and electrolytes (El-Salhy, 2002). In patients with constipation, the levels of these peptides have been variously reported to be low or high (Sjolund et al., 1997, Peracchi et al., 1999, Mollen et al., 2000, Penning et al., 2000). In the large gut of patients with slow transit constipation serotonergic neurone density has been reported to be reduced (Penning et al., 2000) or increased (Peracchi et al., 1999). Substance P and vasoactive intestinal peptide (VIP) levels are also increased or decreased in patients with slow transit constipation (Koch et al., 1988, Dolk et al., 1990, Cortesini et al., 1995, Tzavella et al., 1996, Porter et al., 1998, Peracchi et al., 1999). Other studies have reported that large intestines of patients with slow transit constipation are more densely innervated with neurones secreting the inhibitory neurotransmitter nitric oxide (Bult et al., 1990, Tomita et al., 2002). Similarly, in patients with slow transit constipation, plasma levels of cholecystinin have been shown to be high (Sjolund et al., 1997, Mollen et al., 2000) and motilin levels low (Preston et al., 1985, Sjolund et al., 1986, Mollen et al., 2000). It has been suggested that patients with idiopathic slow transit constipation have a disturbed neuroendocrine system in general, but the nature of disturbance varies between individuals. Thus patients with idiopathic slow transit constipation have been aptly described by El-Salhy (El-Salhy, 2003) as a homogenous group with a disturbed neuroendocrine system who are heterogeneous considering the nature of the disturbance.

**Statement of contribution for chapter 2:** In the following systematic review, the literature search, qualitative scoring of the studies, analysis and write-up was performed by me. Decision regarding which study to include when two or more published studies seemed to have used the same data-set were taken by my supervisors Dr Scott and Professor Knowles.

# **2** *Systematic Review of Balloon Expulsion Test, Anorectal Manometry and Fluoroscopic Evacuation Proctography for Chronic Constipation*

## **2.1 INTRODUCTION**

Constipation is a common condition that affects around 14% of the adult population (Stewart et al., 1999, Soares and Ford, 2011) and poses a significant economic and social burden (Rantis et al., 1997, Shafe et al., 2011). Although there is no consensus on the definition of constipation (Lembo and Camilleri, 2003), the Rome III criteria (Bharucha et al., 2006) are probably the most widely used diagnostic criteria. Although such criteria diagnose constipation based on symptoms alone, specific subtypes of constipation i.e. dyssynergia, and impaired propulsion are diagnosed on the basis of clinical investigations. A number of investigations exist, of which the balloon expulsion test, anorectal manometry and fluoroscopic evacuation proctography are the most widely used. The protocols, methodology and interpretation of these tests can vary significantly between institutions (Bharucha et al., 2013b) which makes it difficult to compare results.

The last systematic literature review of these investigations was performed a decade ago (Rao et al., 2005), and predates the Rome III criteria. In the last decade, the technology driving these investigations and our understanding of them has evolved along with diagnostic algorithms. A contemporary systematic review of the results of the balloon expulsion test, anorectal manometry and fluoroscopic proctography in patients with constipation is thus merited.

## **2.2 METHODS**

### **2.2.1 SEARCH STRATEGY**

The online database of PUBMED and MEDLINE was searched for relevant manuscripts published as full text articles in English between 1975 and 2014. The search terms used were 'balloon expulsion', 'anorectal manometry', 'defaecography' and 'evacuation proctography'. These search terms have been used in a similar systematic review in the past (Rao et al., 2005). We limited our search to studies involving adults presenting with symptoms of constipation. Since there is no consensus definition for constipation (Lembo and Camilleri, 2003, Vrees and Weiss, 2005, Cook et al., 2009, Rao and Meduri, 2011), we screened all studies where the authors reported the patients to be constipated. Abstracts were screened first to select potentially relevant articles which were then assessed for suitability. Their bibliographies were also reviewed. Literature search and screening of studies were performed by myself. This systematic review was performed following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidance.

### **2.2.2 SELECTION CRITERIA**

Only studies reporting: a) the results from patients with unselected chronic constipation (did not have an established diagnosis of dyssynergia, impaired propulsion, slow transit constipation or other causes of chronic constipation); b) where patients underwent either the balloon expulsion test and/or anorectal manometry and/or fluoroscopic evacuation proctography; c) that reported the rate of abnormal finding (for manometry, we excluded studies that did not report either dyssynergia or impaired rectal propulsion); d) that were reported in English language were included. Studies were excluded if they: a) included only patients with a specific subtype of chronic constipation or where patients had received bio-feedback or surgery prior to the investigation(s); b) recruited less than 20 patients.

Quality of all studies meeting the inclusion criteria were assessed and each study was scored, as described in table 2.1 - using previously described study characteristics (Rao et



al., 2005) and validated methodology (Lijmer et al., 1999, Cash et al., 2002). Only studies with a methodological score of 3 or more were included (Cash et al., 2002, Rao et al., 2005). Of these studies, there was one example of duplicate publication using the same series of patients (Ratuapli et al., 2013b, Ratuapli et al., 2013a) - the publication with the greater number of patients was thus included (Ratuapli et al., 2013b). Discrepancies regarding individual study inclusion, data extraction and interpretation were resolved by consensus with senior authors prior to final analysis.

A flow chart showing the number of studies assessed for each investigation is presented in Figure 2.1.

There were significant methodological differences between the studies, which precluded a meta-analysis. Data for frequency of abnormality for each investigation is hence presented here in a tabular form.

**Table 2.1:** Assessment of methodological quality for studies [Adapted from (Lijmer et al., 1999, Cash et al., 2002, Rao et al., 2005)]

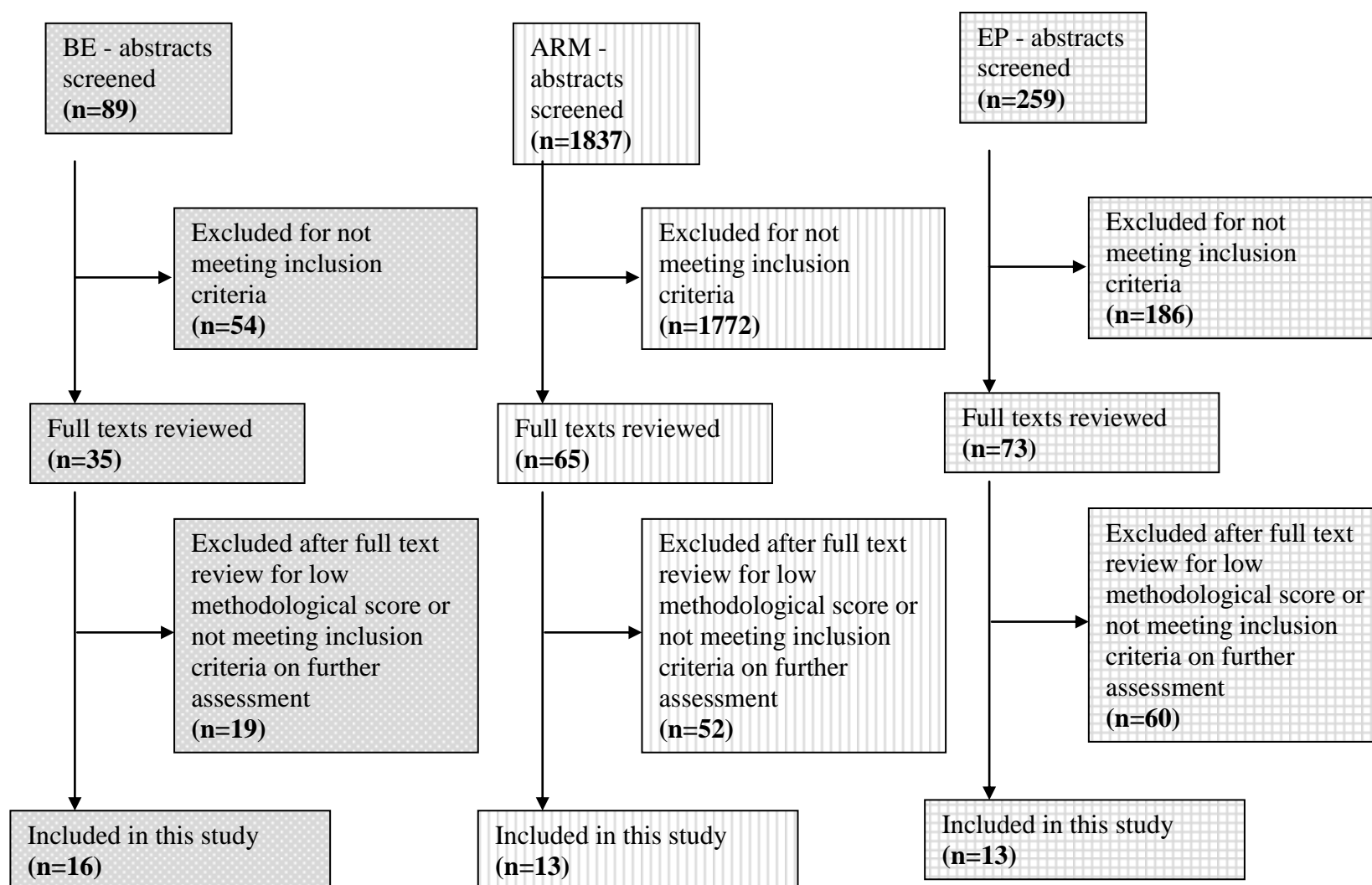
<b>Study Characteristic</b>	<b>1 point</b>	<b>0 point</b>
Population	Clinical	Case control
Verification	Compared to reference test	No comparison to reference test
Blinding	Blinded	Not blinded
Patient selection	Consecutive	Non-consecutive
Data collection	Prospective	Retrospective
Test details	Sufficient details provided	Insufficient details
Details of reference test	Sufficient details provided	Insufficient details
Details of study population	Sufficient details provided	Insufficient details

Where possible, the following data were extracted from included studies:

a) studies involving balloon expulsion testing: average age of subjects; gender ratio; position of test (left lateral vs. sitting); time (or traction) allowed for expulsion; percentage of subjects unable to expel the balloon.

b) studies involving anorectal manometry: average age of subjects; gender ratio; percentage of subjects with dyssynergia and impaired propulsion.

c) studies involving proctography: average age of subjects; gender ratio; percentage of patients with dyssynergia; rectocele; intussusceptions; enteroceles; sigmoidoceles; other structural abnormalities such as prolapse; excessive pelvic floor descent.



**Figure 2.1:** Systematic review flow chart (BE = balloon expulsion test; ARM = anorectal manometry; EP = evacuation proctography)

## **2.3 RESULTS**

### **2.3.1 BALLOON EXPULSION TEST**

Out of a total of 89 studies, 16 met the inclusion criteria. The methodological scores of these studies are presented in Table 2.2, and a summary of the findings of these studies are presented in Table 2.3. A total of 1920 patients with chronic constipation were evaluated by these 16 studies combined. Although most of the studies were performed with the patient in a sitting position, one (Bharucha et al., 2005) was done with the patient in a left lateral position and one (Barnes and Lennard-Jones, 1985) was done with the patient in either position. The balloon volume used in the studies also varied between a minimum of 10 mls (Halligan et al., 1995b) to maximum of an individualised volume sufficient to elicit a sustained desire to defecate (Schouten et al., 1997, Minguez et al., 2004). Most studies used 50 mls (Barnes and Lennard-Jones, 1985, Bannister et al., 1986, Rao et al., 1998c, Rao et al., 2004a, Bharucha et al., 2005, Suttor et al., 2010, Tantiphlachiva et al., 2010, Bordeianou et al., 2011, Lee et al., 2013, Ratuapli et al., 2013b, Chiarioni et al., 2014), two studies (Glia et al., 1998, Hicks et al., 2013) used 60 mls. In the study by Minguez *et al* (Minguez et al., 2004) the mean volume of water required to reach a sensation of sustained desire to defecate was  $185 \pm 69$  mls (range, 100–300 mls). For studies performed in the sitting position, the time allowed to expel the balloon before the test was deemed abnormal was 1 minute (Minguez et al., 2004, Suttor et al., 2010, Tantiphlachiva et al., 2010, Lee et al., 2013), 3 minutes (Rao et al., 2004a, Ratuapli et al., 2013b) or 5 minutes (Bannister et al., 1986, Rao et al., 1998c, Bordeianou et al., 2011, Hicks et al., 2013, Chiarioni et al., 2014). For the study performed in the left lateral position the test was considered abnormal if the patient failed to evacuate the balloon with 100g traction (Bharucha et al., 2005). In this study, 44% patients who failed the balloon expulsion test required 188–470 g traction to expel the balloon, and 56% could not expel the balloon despite 586 g of external rectal traction which was the upper limit tested in the procedure. Two studies (Schouten et al., 1997, Hicks et al., 2013) used air to fill the balloon while the others used water. Among the studies assessed, the rate of abnormal balloon expulsion test varied between 17% (Suttor et al., 2010) to 79%

(Bharucha et al., 2005). Among control subjects, the rate of a failed balloon expulsion test varied from 0% to 16% (Barnes and Lennard-Jones, 1985, Bannister et al., 1986, Rao et al., 1998c, Bharucha et al., 2005, Ratuapli et al., 2013b, Chiarioni et al., 2014).

### **2.3.2 ANORECTAL MANOMETRY**

Out of a total of 1837 articles - 13 articles met the inclusion criteria. The methodological scores of these studies are presented in Table 2.4, and a summary of these studies are presented in Table 2.5. A total of 1210 patients with chronic constipation were evaluated by these studies but there were significant differences in methodology and interpretation of test results, hence a meta-analysis could not be performed. Among the studies included, only one used either HRAM or traditional manometry (Lee et al., 2013), all other studies were performed with traditional manometry. All studies were performed in the left lateral position. There was considerable variation in what constituted manometric evidence of dyssynergia, with some studies using the Rome II criteria (Whitehead et al., 1999), some using a lack of anal relaxation during straining (Murad-Regadas et al., 2010, Suttor et al., 2010) while another study diagnosed dyssynergia if anal residual pressure was more than anal resting pressure (Tantiplachiva et al., 2010) (residual pressure was defined as the difference between the baseline pressure and the lowest (residual) pressure within the anal canal, when the subject was bearing down) (Rao et al., 1999). Although according to Rome III criteria (Bharucha et al., 2006) a diagnosis of impaired rectal propulsion and dyssynergic defecation would seem mutually exclusive, some authors have considered the former to be a 'sub-type' of dyssynergic defecation (Rao et al., 2004a) and have presented their rates of dyssynergia as such (Minguez et al., 2004, Suttor et al., 2010). Among the studies included, the rate of dyssynergia among patients with constipation varied between 22% (Minguez et al., 2004) to 100% (Suttor et al., 2010). The study involving the largest number of constipated patient reported a dyssynergia rate of 87% (Tantiplachiva et al., 2010). The rate of impaired propulsion was reported separately by only one study (Rao et al., 2004a) and it was present in 24% of patients.

**Table 2.2:** Methodological scores for selected studies on balloon expulsion

Study	Population	Verifica tion	Blind ing	Patient selection	Data collection	Test details	Details of reference test	Population details	Score
(Chiarioni et al., 2014)	1	1	0	1	1	1	1	1	7
(Ratuapli et al., 2013b)	1	0	0	0	1	1	0	1	4
(Lee et al., 2013)	1	0	0	0	0	1	0	1	3
(Hicks et al., 2013)	1	0	0	0	1	1	0	1	4
(Bordeianou et al., 2011)	1	1	0	1	1	1	1	1	7
(Tantiphlachiva et al., 2010)	1	0	0	1	1	1	0	1	5
(Suttor et al., 2010)	1	0	0	1	1	1	0	1	5
(Bharucha et al., 2005)	1	0	0	0	1	0	0	1	3
(Rao et al., 2004a)	1	0	0	0	1	1	0	1	4
(Minguez et al., 2004)	1	0	0	1	1	1	0	1	5
(Rao et al., 1998c)	1	0	0	1	1	1	0	1	5
(Glia et al., 1998)	1	0	0	1	1	1	0	1	5
(Schouten et al., 1997)	1	0	0	0	1	1	0	1	4
(Halligan et al., 1995a)	1	0	0	1	1	1	0	1	5
(Bannister et al., 1986)	1	0	0	1	1	1	0	1	5
(Barnes and Lennard- Jones, 1985)	1	0	0	1	1	1	0	1	5

**Table 2.3:** Summary of articles included for the balloon expulsion test

Study	Patients (n)	Contr ols (n)	Avg. age	Gender F/M	Balloon volume used	Positio n	Time allowed (min)	% abnormal patients	% abnormal controls
(Chiarioni et al., 2014)	286	40	44	260/26	50 mls water	Sitting	5	48	0
(Ratuapli et al., 2013b)	295	62	-	295/0	50 mls water	Sitting	3	24	3
(Lee et al., 2013)	104		49	-	50 mls water	Sitting	1	48	
(Hicks et al., 2013)	239		52	239/0	60 mls air	Sitting	5	61	
(Bordeianou et al., 2011)	123		50	118/7	50 mls water	Sitting	5	47	
(Tantiplachiva et al., 2010)	209		41	191/18	50 mls water	Sitting	1	45	
(Suttor et al., 2010)	25		49	25/0	50 mls water	Sitting	1	17	
(Bharucha et al., 2005)	52	41	40	41/0	50 mls water	Left lateral	Traction >100 g	79	10
(Rao et al., 2004a)	100		53	80/20	50 mls water	Sitting	3	42	
(Minguez et al., 2004)	130		38	124/6	Water until DDV (mean 185 mls)	Sitting	1	25	
(Rao et al., 1998c)	35	25	44	30/5	50 mls water	Sitting	5	57	16
(Glia et al., 1998)	134		52	112/22	60 mls water	Sitting	-	23	
(Schouten et al., 1997)	49		47	45/4	Air until DDV	Sitting	-	67	
(Halligan et al., 1995b)	74			65/9	10 mls water	Sitting	-	53	
(Bannister et al., 1986)	34	27	32	34/0	50 mls water	Sitting	5	25	0
(Barnes and Lennard-Jones, 1985)	31	15	-	30/1	50 mls water	Sitting/l ying	-	64	7
<b>Summary [median† (range)]</b>	<b>1920‡</b>	<b>210‡</b>	<b>47 (32-53)</b>	<b>1689/118‡ (14:1)*</b>	<b>50 mls (10 - DDV)</b>	<b>Sitting §</b>	<b>3 (1 - 5)</b>	<b>47.5 (17-79)</b>	<b>5 (0-16)</b>

(DDV = desire to defecate; † median denotes median of medians (or averages), not true median; ‡ these represent total numbers; \* represents gender ratio; § this represents mode)

**Table 2.4:** Methodological scores for selected studies on anorectal manometry

Study	Population	Verification	Blinding	Patient selection	Data collection	Test details	Details of reference test	Population details	Score
(Lee et al., 2013)	1	1	0	0	0	0	0	1	3
(Tantiphlachiva et al., 2010)	1	0	0	1	1	0	0	1	4
(Suttor et al., 2010)	1	0	0	1	1	1	0	1	5
(Murad-Regadas et al., 2010)	1	1	0	0	1	0	0	0	3
(Rao et al., 2004a)	1	0	0	0	1	1	0	1	4
(Minguez et al., 2004)	1	1	0	0	1	1	1	1	6
(Vaizey and Kamm, 2000)	1	0	0	1	1	1	0	0	4
(Rao et al., 1998c)	1	0	0	1	1	1	0	1	5
(Glia et al., 1998)	1	0	0	1	1	1	0	1	5
(Rao and Patel, 1997)	1	0	0	1	1	1	0	1	5
(Wexner and Jorge, 1994)	1	0	0	1	1	1	0	1	5
(Ger et al., 1993)	1	0	0	1	1	1	0	1	5
(Wald, 1986)	1	0	0	1	1	1	0	1	5



**Table 2.5:** Summary of articles included for anorectal manometry

Study	Patients (n)	Controls (n)	Avg. age	Gender F/M	% DD patients	% DD controls	% IP patients
(Lee et al., 2013)	107		49	100/7	60		
(Tantiphlachiva et al., 2010)	209		41	191/18	87		
(Suttor et al., 2010)	25		49	25/0	100 with or without IP		
(Murad-Regadas et al., 2010)	49		24-78	49/0	39		
(Rao et al., 2004a)	100		53	80/20	46		24
(Minguez et al., 2004)	130		38	124/6	22 with or without IP		
(Vaizey and Kamm, 2000)	20		-	-	65		
(Rao et al., 1998c)	35	25	44	30/5	51	16	
(Glia et al., 1998)	134		52	112/22	44		
(Rao and Patel, 1997)	69		45	54/15	48		
(Wexner and Jorge, 1994)	180		60	138/42	75		
(Ger et al., 1993)	116		60	81/35	63		
(Wald, 1986)	36	36	24-84	28/8	30	-	
<b>Summary [median† (range)]</b>	<b>1210‡</b>	<b>61‡</b>	<b>49 (24-84)</b>	<b>1012/178 ‡ (5.6:1)*</b>	<b>51 (22-100)</b>	<b>16 §</b>	<b>24 §</b>

(DD = dyssynergic defaecation; IP = impaired rectal propulsion; † median denotes median of medians (or averages), not true median; ‡ these represent total numbers; \* represents gender ratio; § these represent mode)

### 2.3.3 EVACUATION PROCTOGRAPHY

Out of a total of 259 studies, 13 met the inclusion criteria. The methodological scores of these studies are presented in Table 2.6, and a summary of these studies are presented in Table 2.7. A total of 1196 patients with symptoms of chronic constipation were evaluated by these studies. Dissimilarities in methodology and data interpretation precluded a meta-analysis. All studies included used a fixed volume of neostool as compared to an individualised volume. Volume of neostool used varied between a minimum of 120 mls (Beer-Gabel et al., 2004, Halligan et al., 1995b) to a maximum of 300 mls (Martellucci and Naldini, 2011, Vitton et al., 2011). The small bowel (Karl bom et al., 1999, Beer-Gabel et al., 2004, Martellucci and Naldini, 2011, Vitton et al., 2011) and vagina (Murad-Regadas et al., 2009, Martellucci and Naldini, 2011, Vitton et al., 2011) were opacified in some studies. Criteria for diagnosing dyssynergia on proctography varied between studies: prominent puborectalis impression (Karl bom et al., 1999, Murad-Regadas et al., 2009), failure to open the anorectal angle on straining (measured using either posterior or central anorectal angles) (Schouten et al., 1997), or a combination of both - prominent puborectalis impression with failure to open the anorectal junction on straining (Martellucci and Naldini, 2011) - were used. The rate of dyssynergia varied between 6% (Martellucci and Naldini, 2011) to 52%(Halligan et al., 1995b). Schouten *et al* reported a rate of 13% using the posterior anorectal angle and 25% using the central anorectal angle in the same cohort of patients. The incidence of rectocele of any depth varied between 9% (Wald et al., 1990a) to 87.5%(Vitton et al., 2011). In a study involving 54 constipated women, Martellucci *et al*(Martellucci and Naldini, 2011) found smaller rectoceles to be more common than larger rectoceles: 27.8% had rectocele <2cm deep, 22% had rectoceles 2-4cm deep and 14.8% had rectoceles deeper than 4 cm in antero-posterior depth. Incidence of intussusception varied from 3% - 74%(Turnbull et al., 1988, Wald et al., 1990a, Halligan et al., 1995b, Glia et al., 1998, Prokesch et al., 1999, Karl bom et al., 1999, Beer-Gabel et al., 2004, Perniola et al., 2008, Murad-Regadas et al., 2009, Martellucci and Naldini, 2011, Vitton et al., 2011). The study by Martellucci *et al* reported that 27.8% patients had a recto-

rectal intussusception, 13% had recto-anal intussusception and 9.3% had an external intussusception (prolapse). The incidence of enterocele and sigmoidocele varied between 16% (Murad-Regadas et al., 2009) to 21% (Beer-Gabel et al., 2004, Vitton et al., 2011). Excessive pelvic floor descent was reported by 2 studies at 53.7% (Murad-Regadas et al., 2009) and 73.2% (Vitton et al., 2011). While Murad-Regadas *et al* (Murad-Regadas et al., 2009) diagnosed excessive descent if the anal canal descended by >4cm on straining, Vitton *et al* (Vitton et al., 2011) diagnosed it if the anorectal junction was >2 cm below the pubococcygeal line at rest or >3cm below it on straining. The incidence of rectal prolapse varied between 9% (Martellucci and Naldini, 2011) to 17% (Prokesch et al., 1999). Comparing evacuation rates between constipated patients and healthy subjects, Karlbom *et al* (Karlbom et al., 1999) reported that constipated patients emptied a smaller area of their rectum and took almost twice as long to evacuate when compared to healthy volunteers (who completed evacuation at a median of 19 seconds; range 8 - 54 seconds). They concluded that the percentage of area evacuated and initial and total evacuation rates were all significantly lower in constipated patients than in the control subjects.

## 2.4 DISCUSSION

This systematic review has found that the rate of dyssynergia in patients with chronic constipation can range between 22 - 100% (median 51%) when diagnosed with manometry, between 6-52% (median 26%) when diagnosed with fluoroscopic defaecography and between 17-79% (median 47.5%) when balloon expulsion is used to screen for the condition. Such 'investigation dependant' variability in the rates of dyssynergia has been reported by another systematic review (Videlock et al., 2013). Such differences may be partly explained by test performance (see below). The rate of dyssynergic defecation reported in this review is similar to other systematic reviews (Rao et al., 2005, Videlock et al., 2013). Most of the manometry studies included in this review were performed with water perfused systems. It will be interesting to see if the rate of dyssynergia changes with the use of novel high resolution and 3D manometry.

**Table 2.6:** Methodological scores for selected studies on evacuation proctography

Study	Population	Verification	Blinding	Patient selection	Data collection	Test details	Details of reference test	Population details	Score
(Vitton et al., 2011)	1	0	1	1	1	1	0	1	6
(Martellucci and Naldini, 2011)	1	0	0	1	1	1	0	1	5
(Murad-Regadas et al., 2009)	1	0	0	0	0	1	0	1	3
(Perniola et al., 2008)	1	0	1	0	0	1	0	1	4
(Beer-Gabel et al., 2004)	1	1	1	0	0	1	1	1	6
(Prokesch et al., 1999)	1	0	0	0	1	1	0	1	4
(Karl bom et al., 1999)	1	0	0	1	1	1	0	1	5
(Karl bom et al., 1998)	1	0	0	1	1	1	0	1	5
(Glia et al., 1998)	1	0	0	1	1	1	0	1	5
(Schouten et al., 1997)	1	0	0	0	1	1	0	1	4
(Halligan et al., 1995b)	1	0	0	1	1	1	0	1	5
(Wald et al., 1990a)	1	0	0	0	1	1	0	1	4
(Turnbull et al., 1988)	1	0	0	1	1	1	0	1	5

**Table 2.7:** Summary of articles included for evacuation proctography

Study	Patients (n)	Age	Gender F/M	DD (%)	Rectocele (%)	Intussusception (%)	Ent./ Sig. (%)	Others
(Vitton et al., 2011)	56	51	56/0		88 (>2cm)	59	21 (Ent)	EPD 73% (>2cm below PCL at rest or >3 cm below it on straining)
(Martellucci and Naldini, 2011)	54	59	54/0	6	64 (any size), 28 (<2cm); 22 (2-4cm); 15%(>4cm)	50 (overall); 28 Recto-rectal; 13 recto-anal	18 (Ent)	Prolapse 9%
(Murad-Regadas et al., 2009)	255	-	255/0	27	33 (>2cm)	65	16 (Sig)	EPD 54% (>4cm descent of anal canal)
(Perniola et al., 2008)	31	53	31/0		80 (>1cm)	74		
(Beer-Gabel et al., 2004)	33	58	33/0		54	58	21 (Ent)	Prolapse 15%
(Prokesch et al., 1999)	30	44	25/5	13		33		Prolapse 17%
(Karl bom et al., 1999)	215	51	192/23	25	53 (>2cm)	52 (>0.6cm)	26	
(Karl bom et al., 1998)	171	51	152/19	29				
(Glia et al., 1998)	134	52	112/22	36	27	37		
(Schouten et al., 1997)	49	47	45/4	13 (PARA); 25 (CARA)				
(Halligan et al., 1995b)	74		65/9	52	77	32		
(Wald et al., 1990a)	36	24-84	28/8	25	9	40		
(Turnbull et al., 1988)	58	19-75	52/6	17	56	3		
<b>Summary [median † (range)]</b>	<b>1196‡</b>	<b>51 (24-84)</b>	<b>1100/96‡ (11.4:1)*</b>	<b>25 (6-52)</b>	<b>55 (9-88)</b>	<b>50 (3-74)</b>	<b>19.5 (16-26)</b>	<b>Prolapse 15 (9-17)</b>

(DD = dyssynergic defaecation; Ent. = enterocele; Sig. = sigmoidocele; EPD = excessive pelvic floor descent; PCL = pubococcygeal line; PARA - Posterior anorectal angle; CARA - central anorectal angle; † median denotes median of medians (or averages), not true median; ‡ these represent total numbers; \* represents gender ratio)

Constipation is more common in women, with a median female: male ratio of approximately 2.2:1 (Higgins and Johanson, 2004). Among the studies included in this review, the female: male ratio for patients undergoing investigations is approximately 10:1. This would suggest women are much more likely to need investigation. The reason for this discrepancy is not entirely clear but could be influenced partly by willingness to seek help or progress in symptoms due to innate anatomical and hormonal differences between the genders.

The balloon expulsion test is a simple and cheap investigation that can be performed easily in the outpatient setting without need for specialist equipment. However, due to the nature of the test itself it does not provide a diagnosis *per se*. There were significant differences in methodology for performing the balloon expulsion test among the articles included in this study. Most were performed in the sitting position, but the time allowed to evacuate the balloon varied widely. Chiarioni *et al* assessed balloon expulsion test, manometry and EMG in 286 consecutive constipated patients to determine the upper limit of normal expulsion time (Chiarioni et al., 2014). If BET >1minute was considered abnormal, the positive predictive values for detecting dyssynergia on ARM and EMG were 68% and 65% respectively. For BET >2 minutes they were 77% and 76% for ARM and EMG respectively. Similarly the negative predictive values for diagnosis of dyssynergia on ARM and EMG as predicted by BET >1 minute were 81% and 97%. For BET >2 minutes these were 80% and 95% for ARM and EMG respectively. Based on their findings they proposed that the upper limit for balloon expulsion test should be 2 minutes. A relatively low positive predictive value (57%) for diagnosis of dyssynergia using the balloon expulsion test has also been reported in another study when proctography is used as the comparing investigation (Bordeianou et al., 2011). Another study by Minguéz *et al* reported a specificity of 89%, sensitivity of 87%, a negative predictive value of 97% and a positive predictive value of 64% for the diagnosis of dyssynergia using the

balloon expulsion test (Minguez et al., 2004). In this study ARM and fluoroscopic defaecography were used to diagnose dyssynergia retrospectively. Other studies have however reported that a significant proportion of patients with manometric, proctographic or electromyographic evidence of dyssynergia were able to expel a balloon (Dahl et al., 1991, Schouten et al., 1997, Rao et al., 2004a). Factors associated with an inability to expel a balloon can be a high anal canal pressure at rest or during evacuation, a low intra-rectal pressure during evacuation or a combination of both (Ratuapli et al., 2013b), impaired rectal propulsion (Chiarioni et al., 2014), acute anorectal angling during evacuation (Halligan et al., 1995a), or even a significant rectocele (Hicks et al., 2013) which being a structural abnormality, is not investigated using the balloon expulsion test *per se*. The investigation is also influenced by the fact that it is performed in the left lateral position, which is not a physiological position to defecate and can increase the rate of dyssynergia (Kamm et al., 1992, Rao et al., 2006). Other factors that are more difficult to quantify e.g. patient embarrassment can also influence the outcome. Balloon expulsion test can be abnormal in up to 16% of healthy subjects (Rao et al., 1998c) which undermines its use as a diagnostic tool. For the above reasons the balloon expulsion test should not be used in isolation to diagnose dyssynergia (Bharucha et al., 2013a). There is no consensus on the optimal position for the test although intuitively, the sitting position may be more physiological. Schouten *et al* (Schouten et al., 1997) reported moderate agreement between the test performed in the left position and sitting position. In their study, Chiarioni *et al* (Chiarioni et al., 2014) reported excellent agreement between balloon test performed 30 days apart in a cohort of constipated patients (in only 6 out of a 286 patients the test was discordant when performed a month later).

Anorectal manometry allows measurement of rectal and anal canal pressures and 'anorectal coordination' during attempted evacuation. Normally during attempted

evacuation, there is a rise in intra-rectal pressure associated with a decrease in the anal canal pressure. The 'term' impaired rectal propulsion, a condition where the patient does not generate enough rectal pressure to affect evacuation, is relatively new and was proposed in the Rome III criteria (Bharucha et al., 2006). The concept of impaired propulsion however, has been around for slightly longer (Rao et al., 1997, Rao et al., 1998c, Rao et al., 2004a) but it has traditionally been regarded as a subtype of dyssynergic defecation and some studies have presented their data for dyssynergia and impaired rectal propulsion together (Minguez et al., 2004, Suttor et al., 2010). Although several studies included in this review were performed after the Rome III criteria was published, only one (Rao et al., 2004a) presented the rate of impaired propulsion (24%). Despite consensus opinion on what should be considered abnormal in manometry (Rao et al., 2002, Bharucha et al., 2006), there were significant differences in data interpretation within the studies. Rao *et al* (Rao et al., 2004a) assessed 100 constipated patients, 53 of whom underwent a repeat manometry 1 month after the original manometry. They found good inter-measurement agreement between the manometry with 51 of the 53 tests showing the same abnormality on repeat testing. Ninety-five percent of patients (118 with constipation and 71 with faecal incontinence) assessed in a study by Vitton *et al* (Vitton et al., 2013) comparing water perfused manometry and 3D high resolution anorectal manometry showed a dyssynergic pattern. Similarly high rates of dyssynergia have also been reported in other studies (Wexner and Jorge, 1994, Tantiphlachiva et al., 2010). The reason for such a high rate of dyssynergia is not entirely clear, but it has been recommended that manometry should not be used in isolation to diagnose dyssynergia and that it should be combined with other tests like the balloon expulsion test or colonic transit or defaecography (Rao et al., 2005, Bharucha et al., 2013a).



Like the other investigations for functional constipation, evacuation proctography also suffers from a lack of consensus on methodology and test interpretation. No two studies evaluated in this review, except where they came from the same institution, used the same methodology for the test and interpretation of results. Although data-pooling was not possible in our review, it is clear that the rate of dyssynergia is lower with proctography - median 26% (6-52% among the studies included in this review) when compared to manometry, median 51% (22-100% among the studies in this review). This is in line with previous reports (Vidlock et al., 2013). It is not entirely clear why this may be, but it may be partly due to the position in which these tests are performed and the state of rectal fullness. Manometry is performed in the left lateral position with an empty rectum, whereas proctography is performed in the sitting position with a full rectum. Sitting position is inherently a more physiological position for defecation compared to the left lateral position (Kamm et al., 1992, Rao et al., 2006). It has also been shown that the rate of dyssynergia on manometry is significantly less when the rectum is full (Rao et al., 2006). The rate and degree of evacuation during proctography can be very variable (Halligan and Bartram, 1995) and should be interpreted with caution. Intuitively, using a thick neo-stool will prolong evacuation time when compared to thin 'nearly liquid' neo-stool. Proctography is the most commonly used dynamic investigation of constipation that can diagnose structural abnormalities. Whether such structural abnormalities are the cause or effect of chronic constipation is debated (Hicks et al., 2013). The presence or absence of structural abnormalities does not seem to influence the outcome of biofeedback therapy for dyssynergia (Gilliland et al., 1997, Thompson et al., 1999) and these structural 'abnormalities' are also present in healthy subjects (*cf.* chapter 3), although to a less marked degree. Also, it has been reported that the presence of structural abnormalities may not influence rectal evacuation during proctography (Halligan et al., 1995b). In contrast, there are many studies that report significant improvement in symptoms after surgical correction of these structural abnormalities

in carefully selected group of patients (Kuijpers and Bleijenberg, 1990, Graf et al., 1996, Boccasanta et al., 2004, Renzi et al., 2008, Isbert et al., 2009, Samaranayake et al., 2010). It is logical to assume that a large rectocele, an obstructing recto-anal intussusception or other significant structural abnormality has the potential to alter the mechanics of normal evacuation significantly, but more studies with robust design are required to define the significance of these abnormalities.

Although there are several guidelines on investigations for chronic constipation (Bharucha et al., 2006, Bove et al., 2012, Bharucha et al., 2013a), there is often no agreement between suggested investigations e.g. the Association of Italian Gastroenterologists and the Italian Society of Colorectal Surgeons advise defaecography as a first line investigation for chronic constipation (Bove et al., 2012) whereas the American Gastroenterology Association only advise defaecography in patients where manometry and the balloon expulsion test are discordant (Bharucha et al., 2013a). Such differences are partly down to the lack of a gold standard investigation and significant variation in methodology and interpretation of tests (Bharucha et al., 2013b). Moreover, it has been shown that there is very poor diagnostic agreement between common investigations for constipation (Schouten et al., 1997, Palit et al., 2011). Hence selection of investigation algorithm is often decided according to local preferences as is evident from a recent systematic review of dyssynergia (Videlock et al., 2013) which found that majority of studies using defaecography were from Europe and from surgical departments, whereas the majority of studies using manometry were from USA and from the gastroenterologists.

The balloon expulsion test is a simple office based screening test for impaired evacuation. It does not provide a diagnosis and cannot test structural abnormalities responsible for evacuatory dysfunction. It can be argued that anorectal manometry is

not strictly a test of evacuation but rather tests for recto-anal co-ordination. Like the balloon expulsion test, it does not provide information regarding structural abnormalities. Proctography on the other hand uses ionising radiation, but it is a dynamic test of evacuation and provides information regarding structural abnormalities and dyssynergic defecation. It is also more physiological than the other two tests since it is performed in the sitting position with a full rectum.

In conclusion, there is significant heterogeneity among common tests for evacuatory dysfunction which is partly driven by lack of consensus on what should be considered 'abnormal'. A lack of gold standard investigation further compounds the issue, ultimately leading to differences between experts regarding selection of investigation and diagnostic algorithm. There is a need for large well designed studies to evaluate the diagnostic yield, utility and agreement between tests in order to work towards a gold standard test and also to identify predictors of response to surgery or biofeedback.

**Statement of contribution for chapter 3:** The recruitment of healthy volunteers, the subsequent investigation and its analysis and data collection were performed by other members of the GI Physiology Unit - more specifically by Mr Chetan Bhan, Mr Derek Boyle, Dr Mark Scott and Professor Marc Gladman. The data-analysis, write-up of this chapter and the associated publication (Palit et al., 2014) were done by me.

# 3

## *Evacuation Proctography: A Reappraisal of Normal Variability*

### **3.1 INTRODUCTION**

Evacuation proctography (EP) was originally described in the 1950s, but popularised in the 1980's (Mahieu et al., 1984) concomitant with increasing interest in functional anorectal disorders. In patients with symptoms of evacuatory dysfunction (ED), proctography has been deemed clinically useful (Bove et al., 2012) because it assesses dynamic changes in rectal wall morphology, as well as function associated with evacuation (Lunniss et al., 2009a). EP thus has advantages over simple balloon expulsion testing or manometry. However, interpretation of EP imaging in symptomatic patients is reliant both on robust normative data and appreciation of the individual clinical context. Previous EP studies in asymptomatic subjects are limited by unrepresentative subject demographics, bias through mode of recruitment, or test methodology, and the literature has only limited information on patterns of defaecation and evacuatory efficiency in asymptomatic subjects (see below).

### **3.2 AIM**

The aim of this study was to prospectively study asymptomatic volunteers to determine normal ranges for measured and derived variables of EP that could be used subsequently in clinical practice.

### **3.3 MATERIALS AND METHODS**

Adult volunteers were recruited (between July 2008 to November 2009) from adverts placed within Barts and the London NHS Trust and Queen Mary University of London (Ethics approval: City Health Authority REC: P/97/338). Volunteers were remunerated for reasonable travel expenses and to compensate for loss of earnings during the study. Potential participants were screened for coexistent gastrointestinal (GI) disease by means of a

comprehensive departmental questionnaire (*cf.* appendix), which includes validated incontinence and constipation scores (Vaizey et al., 1999, Knowles et al., 2000), as well as medical and obstetric histories. Any subject with a history of faecal incontinence, constipation, gastrointestinal disease, chronic neurological or collagen vascular disease, BMI  $\geq 30$ , or scores above published thresholds of normality for incontinence and constipation (0 and 6, respectively)(Vaizey et al., 1999, Knowles et al., 2000) were excluded. Subjects unable to communicate in English were also excluded. Parity was not an exclusion criterion. All subjects gave informed consent prior to the investigation.

### **3.3.1 EVACUATION PROCTOGRAPHY TECHNIQUE**

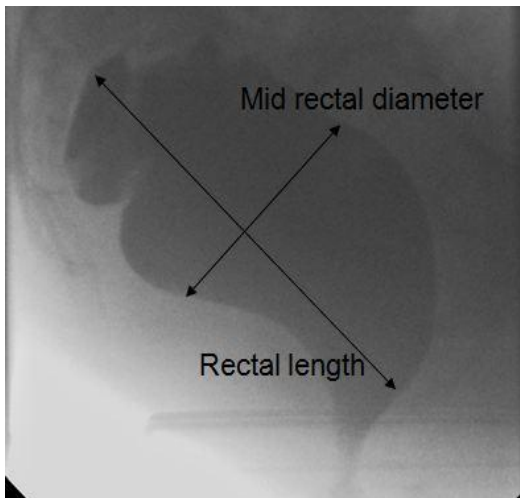
The technique used was based on that described by Mahieu (Mahieu et al., 1984) with modification (Zarate et al., 2008b). In the left-lateral position, synthetic stool consisting of a mixture of barium sulphate, porridge oats, and water (in 1:2:1 ratio by volume) was inserted into the rectum via a large bore syringe until a strong, sustained desire to defecate was achieved i.e. an individualised (Lopez et al., 1998, Chan et al., 2001, Minguez et al., 2004) rather than a fixed volume (Bartram et al., 1988b, Goei et al., 1989, Freimanis et al., 1991b) was used. Subjects were then seated upright on a radiolucent commode upon a fluoroscopic X-ray table (Siemens Axiom Iconos, Bracknell, Berkshire, UK). A lateral image was taken at rest and again while the subject performed a 'squeeze' manoeuvre. The subject was then, under continuous lateral fluoroscopic screening, instructed to expel the rectal contents until they believed evacuation to be complete or felt unable to empty any further neostool. All fluoroscopic examinations were recorded and stored on a recordable DVD player (DVR-7000, Pioneer, CA, USA). To allow accurate measurement of images on DVD, a metal wire of known length was measured at various magnifications within the fluoroscopic field; these measurements were subsequently used to calibrate an imaging software tool (Image J, National Institute of Health, Bethesda, USA). *Post hoc* analyses of dimensions and areas were performed on still DVD images.

### **3.3.2 MEASUREMENTS**

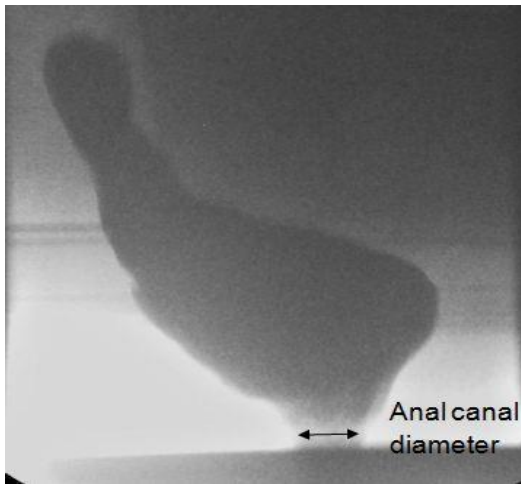
#### **3.3.2.1 Anorectal dimensions**

Rectal length was determined by measuring a line drawn from the most proximal level of rectal contrast (Figure 3.1a) to the level of the upper anal canal during the rest phase. The mid-rectal diameter was measured by drawing a line between the anterior and posterior walls of the rectum bisecting the midpoint of the line drawn to measure the rectal length at 90° (Gladman et al., 2007).

Rectal volume was calculated from rectal capacity, which was defined as the volume of neostool instilled to reach a strong sustained desire to defecate. The anal canal diameter was determined by measuring the maximum transverse distance between the anterior and posterior walls of the lower anal canal at the peak of evacuation (Figure 3.1b).



**Figure 3.1a:** Proctographic still demonstrating rectal length and diameter measured at rest

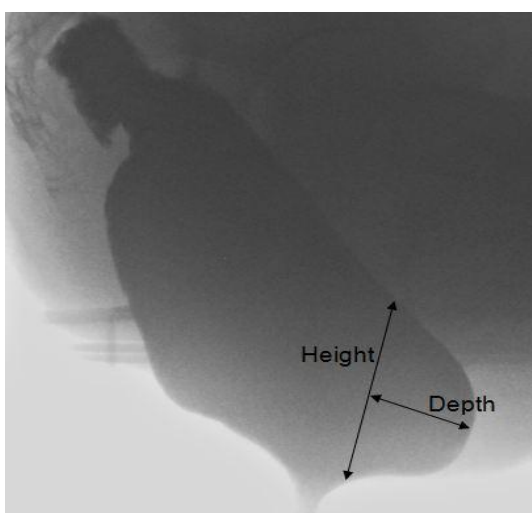


**Figure 3.1b:** Proctographic still demonstrating the anal canal diameter measurement

### 3.3.2.2 Rectal wall morphology

The following well-described morphologies were recorded:

**3.3.2.2.1 Rectocoele:** defined as an anterior bulge beyond the line of the anterior rectal wall evident during maximal evacuatory effort. The height was measured as the length of a line running across the 'mouth' of the rectocoele, and the depth as the length of a line running perpendicularly from the line across the mouth to the apex of the bulge (Figure 3.2a) (Shorvon et al., 1989). In addition, the amount of contrast retained within the rectocoele, as a percentage of total contrast instilled was calculated using the image software tool.



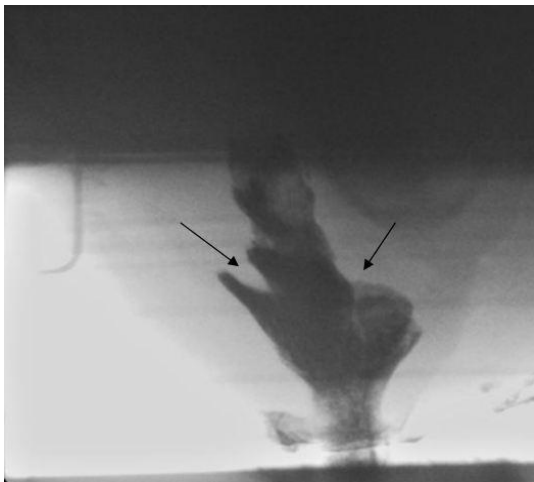
**Figure 3.2a:** Proctographic still demonstrating rectocoele with dimensions measured



3.3.2.2.2 Rectal intussusception: defined as an infolding of the rectal wall (Figure 3.2b);

specific note was made of:

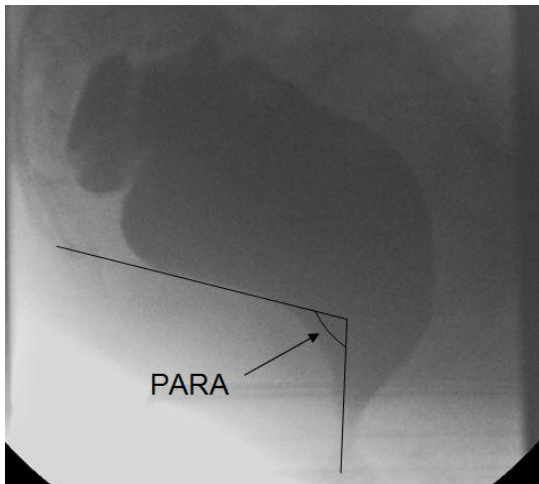
- i. whether it was anterior, posterior or circumferential;
- ii. the 'take off' point(s), defined as distance from the anorectal junction; and
- iii. Shorvon grade (grades 1 and 2: mucosal; 3: full thickness with only one wall involved; 4: circumferential but recto-rectal; 5: impinging on the internal anal orifice; 6: intra-anal; and 7: prolapse beyond the anal verge) (Shorvon et al., 1989).



**Figure 3.2b:** Proctographic still demonstrating a rectal intussusception

#### 3.3.2.2.3 Anorectal angles

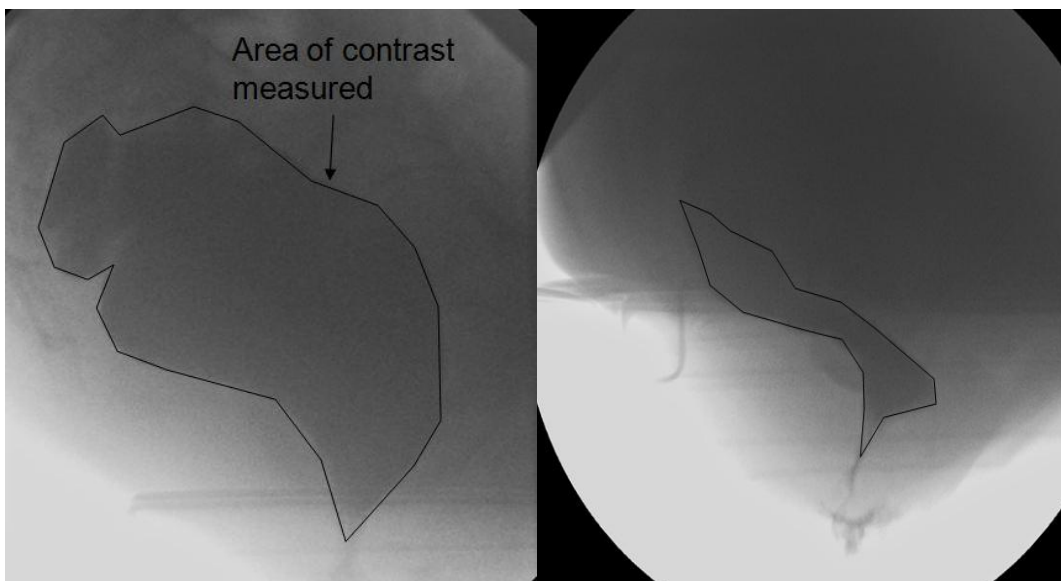
The posterior anorectal angle (PARA) (Shorvon et al., 1989) was defined as the angle between a tangential line drawn along the posterior edge of the rectal ampulla just proximal to the impression of the puborectalis and a line drawn along the axis of the anal canal (Figure 3.3). The angle was measured during rest, squeeze and maximum evacuatory effort. Proportions of subjects who had the anticipated directional change (decrease with squeeze and increase with maximum evacuatory effort compared to rest) were determined (Mahieu et al., 1984).



**Figure 3.3:** Proctographic stills demonstrating the method of measuring the posterior anorectal angle (PARA).

### 3.3.2.3 Evacuatory efficiency

Each procedure was timed from the commencement of evacuatory effort to completion. The number of distinct expulsive attempts required was noted. The area of contrast within the rectum gave a measure of rectal 'area' at rest (Figure 3.4a), and at end evacuation (Figure 3.4b) from which percentages of contrast evacuated were calculated, a modification of the technique that has been shown to correlate well with the measured weights of evacuated contrast (Ting et al., 1992).



**Figure 3.4 a & b:** Proctographic stills demonstrating the method of measuring the area of rectal contrast a) at rest at the beginning of evacuation, and b) at the end of evacuation.

#### **3.3.2.4 Descriptive patterns of evacuation**

All proctograms were reviewed, to determine if subjects could be grouped into stereotypical patterns of evacuation. Particular attention was paid to the number of expulsive attempts required to empty the rectum, speed of opening of the anal canal, and a subjective impression of global evacuatory efficiency.

#### **3.3.3 ASSESSORS**

Proctographic examinations were performed by several clinical research fellows, appropriately trained and experienced in the procedure, and with the appropriate radiation protection certification. Measurements, morphologies and subjective grading of evacuation pattern were determined by colorectal surgical trainees who were also employed as research fellows in our GI Physiology Unit.

#### **3.3.4 STATISTICAL ANALYSIS**

Formal sample size calculation could not be performed due to lack of previously published studies on healthy volunteers using the methodology used in this study. Given that the main aim of the study was to derive normative data for use in clinical practice, data for main variables were grouped separately by gender. For all variables, normality testing (Shapiro-Wilk) was performed. Normal ranges are expressed as means and standard deviations or 95% confidence intervals. Tests of equality of means between male and females were performed using unpaired t-tests. Categorical findings were compared using  $\chi^2$  test. Categorical inter-rater agreements (for the presence of rectocele and intussusception) were assessed using kappa statistics, and levels of agreement between observers for anorectal angle measurements were assessed using Bland-Altman statistics. To compare evacuatory patterns, ANOVA was used with Dunn's post-test analysis. All analyses were performed using proprietary software (Stata V10.0, Stata Corp., Texas, USA; Prism<sup>®</sup> 5.0, GraphPad Software, Inc., San Diego, CA, USA).  $P < 0.05$  was taken to indicate statistical significance.

### **3.4 RESULTS**

Forty-six subjects (28 female; parity: 11 nulliparous, 17 parous [median parity 1, range 0 – 3]), overall median age 41 years (range 21 – 63) were recruited. All subjects tolerated the procedure well with no complications. Mean radiation dose delivered was 0.6 mSv (effective dose 0.1 – 1.0 mSv), equivalent to approximately 3 months of annual UK background exposure (calculated by Clinical Physics department). All proctograms were analysed fully with respect to the variables sought. Derived normal ranges for these variables are shown in Table 3.1.

#### **3.4.1 ANORECTAL DIMENSIONS**

A mean of 221 mls (SD=72 mls) of radio-opaque neostool was instilled. Rectal length was similar between males and females, but mid-rectal diameter was significantly greater in males (6.2 cm [SD=1 cm]) than females (5.1 cm [SD=0.9 cm];  $P=0.0007$ ). There was no effect of age on rectal diameter ( $P=0.91$ ,  $r=0.02$ ). The mean anal canal diameter during evacuation was 1.7 cm (SD=0.6 cm). It was 1.9 cm (SD=0.6) in men and 1.6 cm (SD=0.6 cm) in females ( $P=0.096$ ).

#### **3.4.2 RECTAL WALL MORPHOLOGY**

##### **3.4.2.1 Rectocoele**

Rectocoeles were noted in 26/28 females (93%). Mean depth was 2.5 cm (SD=0.7 cm) and mean height 3.4 cm (SD=1.5 cm) with no significant difference between incidence ( $P=0.146$ ) or depth (2.6 vs. 2.4 cm,  $P=0.519$ ) between nulliparous and parous females. There was also no correlation between depth and age ( $P=0.2$ ,  $r=0.25$ ). Of all females with a rectocoele, contrast was retained within the rectocoele in 18 (69%) at the end of evacuation (median percentage contrast within the rectocoele, as a percentage of the total contrast instilled, was 21% [range 0-100]).

**Table 3.1:** Proctographic measurements

Variables	Overall	Male	Female	P value (M vs. F)
<b>Demographics</b>				
Number	46	18	28	NA
Age (median [range])	41 [21 - 63]	38 [21 - 58]	43 [21 - 63]	0.17
Parity	-	-	11 nulliparous 17 parous	
<b>Anorectal dimensions (cm)</b>				
Rectal length	11.0 ( $\pm$ 1.6)	10.6 ( $\pm$ 1.6)	11.3 ( $\pm$ 1.6)	0.15
Mid rectal diameter	5.5 ( $\pm$ 1.0)	6.2 ( $\pm$ 1)	5.1 ( $\pm$ 0.9)	<b>0.0007</b>
Neostool volume* (mls)	221 ( $\pm$ 72)	195 ( $\pm$ 56)	229 ( $\pm$ 73)	0.194
Anal canal diameter	1.7 ( $\pm$ 0.6)	1.9 ( $\pm$ 0.6)	1.6 ( $\pm$ 0.6)	0.096
<b>Rectal wall morphology</b>				
Rectocele (numbers)	26 (56%)	0	26 (93%) 9/11 nulliparous, 17/17 parous: P=0.146	NA
Rectocele depth (cm)	-	0	2.5 ( $\pm$ 0.7); 2.6 ( $\pm$ 0.7) nulliparous 2.4 ( $\pm$ 0.7) parous P=0.519	NA
Intussusception (numbers)	9 (20%)	4 (22%)	5 (18%) 4/11 nulliparous 1/17 parous P=0.06	0.366
<b>Anorectal angles (degrees)</b>				
PARA resting	108 ( $\pm$ 12)	106 ( $\pm$ 13)	110 ( $\pm$ 11.5)	0.283
PARA squeeze	96 ( $\pm$ 14)	95 ( $\pm$ 15)	97 ( $\pm$ 13)	0.642
PARA max straining	132 ( $\pm$ 12)	129 ( $\pm$ 12)	134 ( $\pm$ 12)	0.199
$\Delta$ PARA rest-squeeze	-12( $\pm$ 11)	-11 ( $\pm$ 13)	-13 ( $\pm$ 9)	0.603
$\Delta$ PARA rest-max evacuatory effort	23 ( $\pm$ 16)	23 ( $\pm$ 16)	23 ( $\pm$ 16)	0.988
Failure to close PARA on squeeze (n)	4 (9%)	3 (17%)	1 (4%)	0.067
Failure to open PARA on straining (n)	3 (6%)	1 (6%)	2 (7%)	0.427
<b>Evacuatory efficiency</b>				
Total % evacuated	68 ( $\pm$ 17)	71 ( $\pm$ 17)	65 ( $\pm$ 18)	0.257
Time for total evacuation	113 (95%CI: 92 - 134)	88 (95%CI: 63 - 113)	128 (95%CI: 98 - 158)	0.056
Type 1 evacuation (n)	18 (40.5%)	10 (55.6%)	8 (44.4%)	<b>0.036</b>
Type 2 evacuation (n)	9 (19.6%)	2 (22.2%)	7 (77.8%)	0.129
Type 3 evacuation (n)	19 (41.3%)	6 (31.6%)	13 (68.4%)	0.196

Values are mean  $\pm$  SD unless otherwise stated. \* Data from n=11 M and 21 F

### **3.4.2.2 Rectal intussusception**

Intussuscepta were seen in 5 (18%) female subjects (4 nulliparous, 1 parous) and 4 (22%) males; these involved the posterior wall only in 4 but were circumferential in 5. No subject had isolated anterior rectal wall intussusception. All five females had a coexistent rectocele. The median distance of the 'take off' point from the anorectal junction was 4 cm (range 2.5–4.6 cm) anteriorly and 5.9 cm (3–9.9 cm) posteriorly. All intussuscepta were of grades 3 or 4 (i.e. full-thickness recto-rectal). The median posterior wall infolding length was 1.5 cm (range 0.7–2.6) and anterior wall infolding length was 1.6 cm (range 0.7–2.1). No intussusception resulted in complete occlusion of the rectal lumen, nor had an effect on evacuatory function, measured as either percentage evacuated (mean intussusception 68% vs. no intussusception 67%,  $P=0.94$ ), or time taken for the major evacuatory attempt (mean intussusception 47secs vs. no intussusception 52secs;  $P=0.72$ ).

There was complete agreement ( $\kappa = 1.0$ ) for the diagnosis of rectocele and intussusception between 2 observers.

### **3.4.2.3 Anorectal angles**

Anticipated angle changes (Mahieu et al., 1984) i.e. decrease with squeeze and increase with maximum evacuatory effort, were seen in 42/46 (91%) and 43/46 (93%) subjects respectively. There was no gender variation in measured ARAs. There were good levels of inter-observer agreement (e.g. for resting PARA: mean difference  $-0.6^\circ$  [95% limits of agreement:  $-17$  to  $+16^\circ$ ]; for squeeze PARA: mean difference  $+1.0^\circ$  [95% limits of agreement:  $-20$  to  $+22^\circ$ ]).

### **3.4.3 EVACUATORY EFFICIENCY**

Mean total evacuatory time was 88 sec (CI: 63 – 113) in males and 128 sec in females (CI: 98 – 158;  $P=0.056$ ). The mean total percentage evacuated was 71% in males (SD=17; CI:

63 – 80) and 65% in females (SD=18; CI: 58 – 72;  $P=0.26$ ). Among all subjects, an average of 68% (SD=17) instilled contrast was expelled by end of evacuation.

### 3.4.4 DESCRIPTIVE PATTERNS OF EVACUATION

All 46 subjects were qualitatively categorised into 3 patterns of evacuation:

*Type 1* (n = 18, 8 female) - rapid opening of the anorectal angle and widening of the anal canal; majority of neostool expulsion occurred in one relatively rapid and well defined evacuatory attempt.

*Type 2* (n = 9, 7 female) - evacuation occurred in frequent, but short (pulsatile) expulsive attempts with small volumes of contrast passed at each attempt.

*Type 3* (n = 19, 13 female) - evacuation characterised by a steady and constant, but slow expulsion.

Median number of expulsive attempts was 2 (range 1-12). The pattern of evacuation was strongly associated with evacuatory efficiency (Table 3.2), with Type 1 evacuators expelling neostool most efficiently across all parameters of emptying.

**Table 3.2:** Measures of evacuatory efficiency by pattern.

Variable	Evacuation types (mean[SD])			P value
	Type 1 (n=18)	Type 2 (n=9)	Type 3(n=19)	
Total % evacuated	78 ( $\pm$ 28)	56 ( $\pm$ 40)	64 ( $\pm$ 28)	<b>0.002</b>
Total evacuation time (secs)	58 ( $\pm$ 58)	130 ( $\pm$ 134)	156 ( $\pm$ 134)	<b>&lt;0.0001</b>

### 3.5 DISCUSSION

This study has demonstrated that evacuatory efficiency and dynamic morphological changes can vary greatly in health, but probably not in relation to parity (at least in asymptomatic volunteers). Hence, the presentation of normal ranges based on results obtained from this

study can be segregated on the basis of gender alone. Normative values derived from our data (mean +/- 2SD or 95% CI) are presented in table 3.3. Based on these data, it is reasonable to suggest that: (1) expulsion of <35% neostool and/or evacuation lasting >134 seconds may reflect impaired evacuation; (2) failure to open the anorectal angle during defecation is very uncommon in health; (3) the maximal normal mid rectal diameter  $\leq 8.2$  cm in men and  $\leq 6.9$  cm in women; (4) the demonstration of a rectocele <4.0 cm in depth at end evacuation should not be considered abnormal; smaller rectoceles, irrespective of the degree of 'trapping' are almost omnipresent in females; (5) the presence of a rectal intussusception impinging upon and occluding the anal canal, or involving an isolated anterior rectal wall prolapse only, is an abnormal finding.

**Table 3.3:** Normative values for evacuation proctography

Variable	Male	Female	Overall	P value (M vs. F)
Mid rectal diameter (cm)	$\leq 8.2$	$\leq 6.9$	$\leq 7.5$	<b>0.0007</b>
Anal canal diameter (cm)	$\geq 0.7$	$\geq 0.4$	$\geq 0.5$	0.096
% evacuation	$\geq 37$	$\geq 29$	$\geq 34$	0.257
Evacuatory time (secs)	$\leq 113$	$\leq 158$	$\leq 134$	0.056

Previous studies of EP reporting anatomical findings amongst asymptomatic individuals are sparse in the literature and have been limited by three main factors. Subject enrolment has usually been of younger males and young nulliparous females (Shorvon et al., 1989), whereas the majority of patients referred for clinical investigation are middle-aged, parous women (Lunniss et al., 2009a). Secondly, recruitment of 'asymptomatic' patients from a pool who have had normal lower gastrointestinal investigations (Goei et al., 1989) cannot be considered equivalent to asymptomatic volunteers. Finally, most studies have used a protocol in which a fixed volume of barium paste is instilled into the rectum (Goei et al.,



1989, Freimanis et al., 1991a), rather than an individualised volume needed to yield a strong, sustained desire to defecate. Use of an individualised volume is important, as sensation is a key component to evacuation (Gladman et al., 2006). Indeed, it has been shown that ability to evacuate during tests of defaecatory function is improved with greater (or individualised) volumes (Chan et al., 2001, Minguez et al., 2004). Previously reported normative evacuation parameters - 75-100% evacuation within 30 seconds (Halligan et al., 1995a) or evacuation percentage ranging between 12.5 - 100% (Freimanis et al., 1991) were not reproducible in our study. This may again be the result of our 'thicker' neo-stool consistency and individualised volumes of neo-stool used. Diameter of the anal canal reported in our study is comparable to other studies (Goei et al., 1985, Halligan et al., 1995a), but none of the previous studies provide cut-off values for mid-rectal diameter and 'significant rectocoeles' for comparison.

Determination of rectal length may be of limited usefulness or accuracy (as radiological discrimination between the distal sigmoid and proximal rectum is difficult), but may prove relevant, for example, when assessing evacuation following rectopexy or in patients with suspected megarectum. The diagnosis of megarectum continues to be debated (Gladman et al., 2007), but a rectal diameter greater than 8.2 cm in adult men and 6.9 cm in women (Table 3.1) should prompt further investigations.

The results indicate that the presence of an anterior rectocoele is a normal finding in women, since it was observed in 93% of female subjects, regardless of parity. In females, due to the presence of vagina, there is a relative lack of support to the anterior rectal wall which predisposes them to rectocoeles. This may also explain why the presence of rectocoele was not related to parity. Furthermore, the data suggest that only rectocoeles of 4.0 cm or above should be considered truly abnormal with regard to size, though it is accepted that smaller rectocoeles may be clinically important in some patients (Siproudhis et al., 1992). The percentage of the total neostool at the end of evacuation trapped within the rectocoele was

highly variable (0 – 100%), confirming a previous study that evacuatory difficulties should not necessarily and solely be attributed to this finding (Halligan and Bartram, 1995). The findings do, however, contrast to some studies of asymptomatic subjects using MR proctography (Schreyer et al., 2012), and may be due to differences in subject position, volume and nature of neostool instilled, and image resolution. They also contrast with studies of symptomatic parous females where pelvic floor injuries have been described using various imaging methods (Viton et al., 2011).

Rectal intussusception has been reported in asymptomatic individuals (Goei et al., 1989, Shorvon et al., 1989). In the present study, 20% of asymptomatic subjects had a full-thickness rectal intussusception (grade 3 or 4), but the presence of an intussusception did not affect the rate or completeness of evacuation.

The method of measurement (Shorvon et al., 1989, Yang et al., 1994) and significance (Penninckx et al., 1991, Halligan et al., 2001) of anorectal angles are controversial, with little standardisation. The results for PARA measurements from this study are similar to those reported (Shorvon et al., 1989), but the direction of angle change (i.e. increase associated with attempted evacuation), is probably of more clinical utility. This was found in 93% of subjects when PARA was used. Using a standardised method for measuring the ARA, which is reliable and consistent (Choi et al., 2000), there was no disagreement in the direction of angle change during evacuation. However, approximately 7% of the volunteers in this study showed an unexpected directional change in PARA during evacuation. By comparison, up to 16% of volunteers are unable to expel an intra-rectal balloon during the balloon expulsion test (Rao et al., 1999, Dedeli et al., 2007, Ratuapli et al., 2013b), and an even higher number of healthy subjects (up to 22%) are found to have abnormal anorectal muscular co-ordination on manometry (Rao et al., 1998c, Rao et al., 1999). Thus, it is reasonable to suggest that such a pattern should prompt further investigations for dyssynergia.

Evacuatory efficiency in asymptomatic subjects has usually been derived from studies involving patients where small numbers of healthy volunteers have acted as a control group (Ting et al., 1992, Karlbom et al., 1999). The present study has demonstrated a wide range of percentages evacuated in asymptomatic volunteers, contrary to previous reports which suggest a mean evacuation of 82+/-15% of contrast (Bartram et al., 1988a). With respect to time taken to evacuate, again, the results from this study demonstrate a much wider range than previously reported. This might be due to individualised volumes instilled per subject (rather than using a standardised volume) although this has not been formally tested.

Patterns of evacuation have not been previously reported; this study demonstrates that in normality there are three patterns of evacuation, of which one (Type 1) was qualitatively and quantitatively more rapid and more efficient (Table 3.2). It must be remembered that these 3 evacuatory patterns are described in asymptomatic volunteers with no evacuatory dysfunction; nevertheless, they could be used as comparators when assessing EPs obtained from symptomatic subjects.

This study has some limitations. Comparable data for healthy volunteers using this methodology to guide sample size were not available. It must be acknowledged that an overall sample size of 46 is probably insufficient to yield adequate levels of statistical power when considering the correlation of morphological abnormalities with age or parity. Some centres routinely opacify the small bowel prior to proctography (Maglinte and Bartram, 2007) while others don't (Halligan et al., 1995b). In this study opacification was not used in order to keep the study protocol simple, but this may have impacted on the ability to diagnose enterocoeles. A radio-opaque vaginal tampon was also not used since it may splint the rectovaginal septum and thus reduce the yield for rectocoele and possibly intussusception (Archer et al., 1992). Although anorectal angles were measured to look for dyssynergia in this study, presence of a persistent puborectalis impression or inadequate pelvic floor excursion, which may signify the presence of dyssynergia (either in isolation or in

association with poor evacuation) (Jorge et al., 1993b, Halligan et al., 1995b, Bharucha et al., 2006) were not evaluated. The influence of subject weight and height on normal evacuation is still not well understood, but such ponderal data were not recorded. Finally, it is a limitation of proctography in general that the quality or magnitude of the effort allied to an expulsive attempt is impossible to quantify. Nevertheless, it must be acknowledged that proctography has advantages over other tests of evacuatory dysfunction in being a dynamic test of evacuation that can identify both structural and functional disorders. Provisions of normal ranges for variables of EP were sought in this study, for EP to be clinically useful to determine whether an individual patient undergoing this investigation is deemed to have normal or abnormal measures of rectal evacuation.

In conclusion, the normal ranges generated by this study can be applied clinically for subsequent disease comparison. These data should, of course, be placed within the context of clinical assessment and the results of other physiological tests of anorectal function.

**Statement of contribution for chapter 4:** Most of the patients included in this study were assessed by other members of our GI Physiology Unit as a routine clinical referral. The clinical history and evacuation proctography were performed by those clinicians as part of their assessment. I have reanalyzed the proctograms of all the patients included in this study. The data-analysis and the chapter write-up has also been done by me. My supervisors, in particular Professor Knowles has double-checked the statistical analysis.

# 4

## *Can ROME III symptoms for functional constipation predict proctographic abnormalities?*

### 4.1 INTRODUCTION

Chronic constipation is a common condition that effects a significant proportion of the general population (Higgins and Johanson, 2004, Peppas et al., 2008) and can result in considerable impairment to quality of life (Irvine et al., 2002). In patients in whom laxatives fail to relieve symptoms, a battery of specialised tests may be recommended (Wald et al., 2014). Although the cost of managing constipation varies from country to country, it can pose a significant burden to health systems. A recent systematic review found that in the US, the estimated cost of management of chronic constipation can vary between US \$1,912 - \$7,522 per patient per year depending on whether they are treated in the community or as an inpatient (Nellesen et al., 2013). These findings have been confirmed by a recent study that was conducted to assess the healthcare costs associated with chronic constipation in the Swedish population (Bruce Wirta et al., 2014).

Functional constipation can be diagnosed using the Rome criteria (Longstreth et al., 2006) on the basis of pattern of symptoms alone. The presence of two or more of six listed symptoms in at least 25% of defecations (over the last 3 months with symptom onset at least 6 months prior to diagnosis and only in the absence of sufficient criteria to diagnose IBS) is required for diagnosis: hard stools, straining, sensation of incomplete evacuation, sensation of anorectal blockage, the use of manual manoeuvres during evacuation, and infrequent bowel movements (<3 movements per week). The Rome III criteria also recognises subgroups of functional constipation based on symptoms and physiological tests (Bharucha et al., 2006), which implies that experts consider symptoms alone to be inadequate to identify subtypes of functional constipation in clinical practice.

Although several studies have investigated the correlation between symptoms of constipation and a broad diagnosis (i.e. slow transit constipation, disordered defecation or 'normal transit' constipation) (Grotz et al., 1994, Koch et al., 1997, Halverson and Orkin, 1998, Glia et al., 1999, Xin et al., 2014), there have been no studies to methodically assess the correlation between symptoms and the subgroups of functional constipation (as diagnosed using the Rome III criteria), or particularly to the presence of any structural anatomical rectal abnormalities that may account for obstructive defecation. A strong association between a specific symptom and a particular pathology might be relevant to rationalising the use of expensive physiologic tests.

Evacuation proctography is a dynamic test of evacuation that can identify functional and structural causes of chronic constipation (*cf.* chapter 3). In a study designed to assess the utility of manometry, balloon compliance, proctography, colonic transit study and electromyography and Pudendal nerve terminal motor latencies in patients with constipation, Halverson *et al* found that transit time and proctography were the two most useful investigations (Halverson and Orkin, 1998). Proctography done for obstructed defecation syndrome has been regarded as 'the benchmark against which to test newer modality' by in a recent consensus statement (Bove et al., 2012). They advised that for these patients, transit study remains the first line investigation followed by X-ray defaecography.

## **4.2 AIMS AND HYPOTHESES**

The aims of this study were:

- (1) to describe symptom profiles and proctographic findings in a large cohort of patients with Rome III defined functional constipation, and
- (2) to determine whether any of the six common constipation symptoms described in the Rome III criteria predict specific structural and functional proctographic abnormalities.

The following broad hypothesis was tested:

Rome-reported symptoms have greater incidence in patients with abnormal vs. normal proctograms (i.e. individual symptom associations would result in odds ratios  $\geq 1.0$  at the 0.05 significance level).

#### **4.3 MATERIAL AND METHODS**

The study was conducted as a retrospective clinical service evaluation study. The R&D department at Barts NHS Trust were contacted to discuss the need for ethical approval prior to the study. It was advised that since the study has been designed as a service evaluation study, no formal ethical approval will be needed.

Five hundred ( $n = 500$ ) consecutive cases were selected from patients referred to the Gastrointestinal Physiology Unit, Royal London Hospital (now Barts Health NHS Trust) for investigation of their symptoms of chronic constipation between November 2009 and November 2011. The number of 500 was for pragmatic reasons. All patients are routinely sent a departmental questionnaire (*cf.* appendix) to be filled at home prior to their appointment.

**Inclusion criteria:** Patients were included if they satisfied all the following criteria:

- a) Fully completed the functional constipation specific Rome III criteria symptoms of the departmental questionnaire
- b) Satisfied the Rome III criteria for functional constipation, and
- c) Subsequently underwent evacuation proctography.

**Exclusion criteria:** Patients were excluded if they were  $<16$  yrs at the time of the investigation, or had irritable bowel syndrome according to the ROME III criteria.

A total of 2612 cases were screened retrospectively of which 500 consecutive patients meeting the inclusion criteria were included in this study. The main reason for exclusion was incomplete completion of the Rome III specific questions needed for diagnosis of functional constipation.



#### **4.3.1 QUESTIONNAIRE**

This includes questions for assessment of constipation, faecal incontinence and irritable bowel syndrome. The questions relevant for diagnosis of constipation along with the allowed responses are presented in the appendix. It was departmental policy to electronically transcribe completed questionnaires into a Microsoft Excel file using Kofax Scanning Software (Data Capture Solutions Ltd, Slough, Berkshire, UK). Relevant data were then extracted from the excel file. Symptoms tested in predictive analyses were bowel infrequency (< 3 motions per week), passage of hard stool (>25% of time), patients requiring manual manoeuvres to aid emptying on >25% of attempts, patients experiencing a sense of incomplete evacuation (>25% of time), patients feeling a sense of outlet obstruction / blockage (>25% of time) and a need to strain (>25% of time).

#### **4.3.2 EVACUATION PROCTOGRAPHY TECHNIQUE**

Fluoroscopic evacuation proctography was performed as described previously (chapter 3) using barium, water and oats mixture with the patient sitting on a radio-lucent commode. Neostool was instilled until the patient developed a sustained desire to defecate. Previously established departmental normative values were used to differentiate between normal and abnormal proctogram (Table 3.3, chapter 3). Amount of neostool expelled or retained at the end of evacuation were estimated visually. In keeping with the Rome III criteria (Bharucha et al., 2006), a functional defecation disorder was diagnosed when the patient had any 2 of: a) inadequate expulsion (amount OR time), b) inadequate anal sphincter relaxation, or c) inadequate expulsion (amount OR time) with pelvic floor descent of <3 cm (Halligan et al., 1995b, Bharucha et al., 2006). Similarly, impaired propulsion was diagnosed when the patient had inadequate expulsion (amount OR time) with pelvic floor descent of <3 cm (Halligan et al., 1995b, Bharucha et al., 2006). Again, based on Rome III criteria (Bharucha et al., 2006), dyssynergic defaecation was diagnosed when the patient had inadequate anal sphincter relaxation but did not have evidence of impaired rectal propulsion (as per criteria

above). According to previously established normative values (*cf.* chapter 3, table 3.3), structural abnormalities were considered 'significant' if the patient had a rectocele >4 cm in antero-posterior depth, any obstructive pathology (obstructive intussusception, isolated anterior rectal wall prolapse, enterocele) or megarectum (mid rectal diameter >8.2 cm in men or >6.9 cm women). 'Obstructive pathology' was defined as a pathology that caused obstruction of neostool expulsion. Intussuscepta were graded according to the Shorvon scale (Shorvon et al., 1989). A rectocele was defined as any anterior bulge beyond the line of the anterior rectal wall evident during maximal evacuatory effort, and the depth of a rectocele was measured as the length of a line running perpendicularly from the line across the expected anterior rectal wall to the apex of the bulge (Palit et al., 2014). Although only rectoceles >4 cm in depth were considered to be significant, the number of patients with rectoceles of any depth was also noted. All proctograms were re-analysed by me.

#### **4.3.3 STATISTICAL ANALYSIS:**

Symptoms included in the Rome III criteria for diagnosis of functional constipation were extracted from the questionnaire. Responses were then graded using a binary category (0= patient did not complain of the symptoms / experiences it <25% of time; and 1 = experiences the symptom >25% of time) in accord with suggested Rome III criteria analysis. For bowel frequency, responses were coded as 1 = the patient had <3 bowel motions per week and 0 = the patient had  $\geq 3$  motions per week. It is accepted that an alternative way to analyse these data would have been to interpret questionnaire responses as ordinal variables however this has an implicit assumption that these have a natural linearity i.e. the difference between 0 & 1 is for instance the same as the difference between 2 & 3. A further alternative would be to consider each value of the scale as 'dummy' indicator variables. This method would treat all scale responses as individual categorical variables. Subsequent exploratory regression analyses could then be used to determine best cut-off threshold for each symptom with subsequent dichotomous recoding (0 or 1). This approach was not undertaken because: first, the Rome III criteria recommend predetermined thresholds of abnormality at 25% and

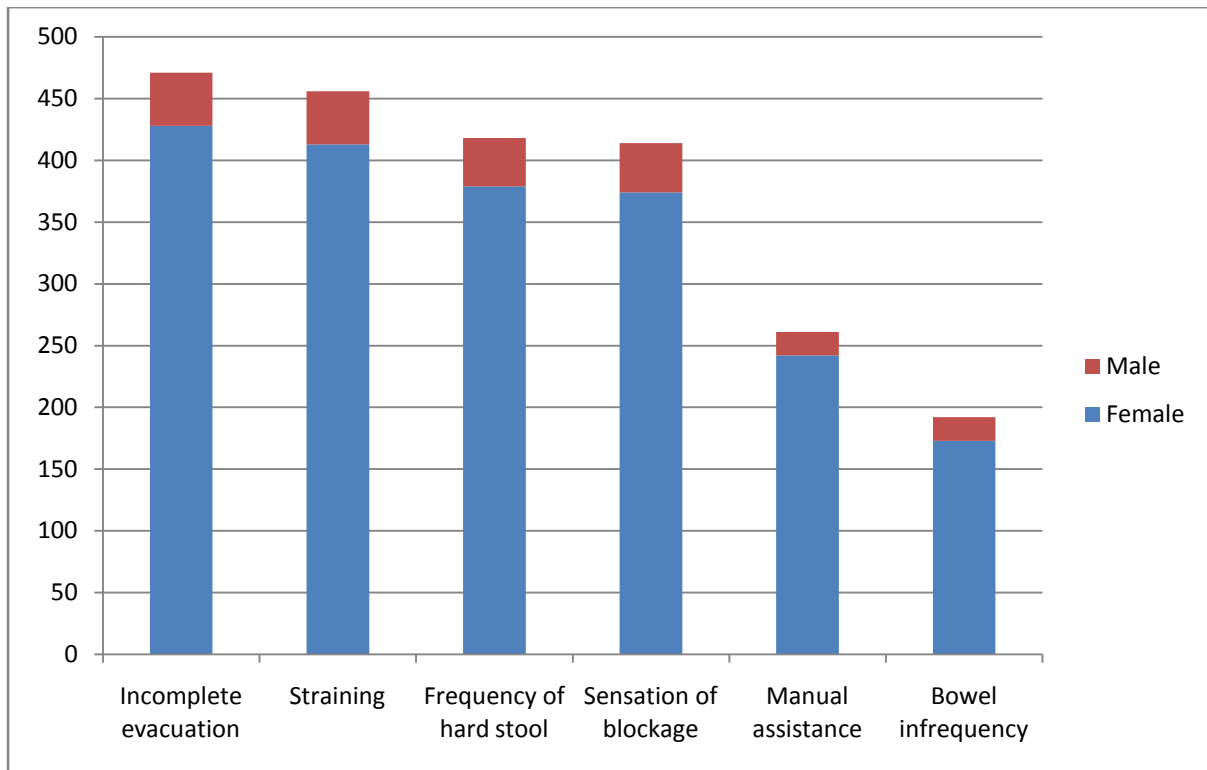
using any other cut-off would counter the over-riding aim of this study (to determine the utility of Rome III specific symptoms in predicting proctographic abnormalities); and secondly because such analyses are unwieldy and deemed superfluous when it was clear that basic exploratory analyses yielded largely negative associations. Proctographic abnormalities were also coded dichotomously: 0 = normal and 1 = abnormal. Abnormalities coded on this basis were: the presence or absence of a functional defecation disorder (FDD), impaired propulsion (IP), dyssynergic defecation (DD), significant rectocele, obstructive intussusception, obstructive isolated anterior rectal wall prolapse, obstructive enterocele/sigmoidocele and megarectum. Predictive associations were analysed using logistic regression using the proctographic findings as the dependant variable and symptoms as the independent variable. Univariate exploratory analyses were used to develop subsequent multivariate models. Data were presented as regression coefficients, significance (p value of <.05 was used as cut-off) and odds ratio with 95% confidence interval. Analysis was performed using IBM SPSS (version 20) software for Microsoft Windows.

#### **4.4 RESULTS**

Of the 500 cases, 452 (90.4%) were women and 48 (9.6%) were men. All patients met the Rome III criteria for functional constipation. Median age was 51 years (range 15 - 84 years).

##### **4.4.1 FREQUENCY OF SYMPTOMS**

Among the six symptoms used in the Rome III criteria, a sense of incomplete evacuation was the most common (figure 4.1). It was reported by 471 patients (94.2%); followed by straining (n=456; 91.2%); frequent passage of hard stool (n= 471; 83.6%); sense of outlet obstruction (n=414; 82.8%); and need for manual manoeuvres (n=261; 52.2%). Infrequent bowel movement was the least frequent symptom, reported by only 192 patients (38.4%) patients. There was no association between gender and any symptom  $\chi^2$  test.



**Figure 4.1:** Stacked bar diagram showing the frequency of individual symptoms

Sub-analysis of overall response for the each constipation-relevant question, broken down by sex, is presented in clustered bar diagrams (Figures 4.2a- 4.2f). Approximately 25% of females and 35% males reported opening their bowels 3 times a day or more which may represent repeated toilet visits driven by a sense of incomplete evacuation. Approximately 20% females and 30% males reported that they needed >30 minutes to evacuate; a further 10% females and 20% males needed between 20-29 minutes. Approximately 25% females and 35% males reported that they always experienced a sense of outlet obstruction. A further 34% of females and 30% males reported suffering outlet obstruction more than half the time.

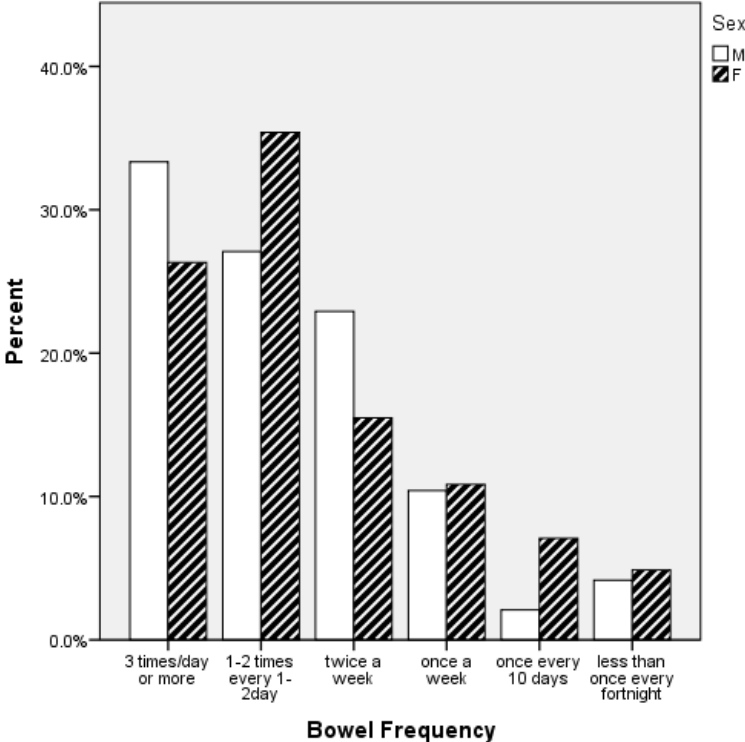


Figure 4.2a: Clustered bar diagram showing the frequency of bowel motions for each gender

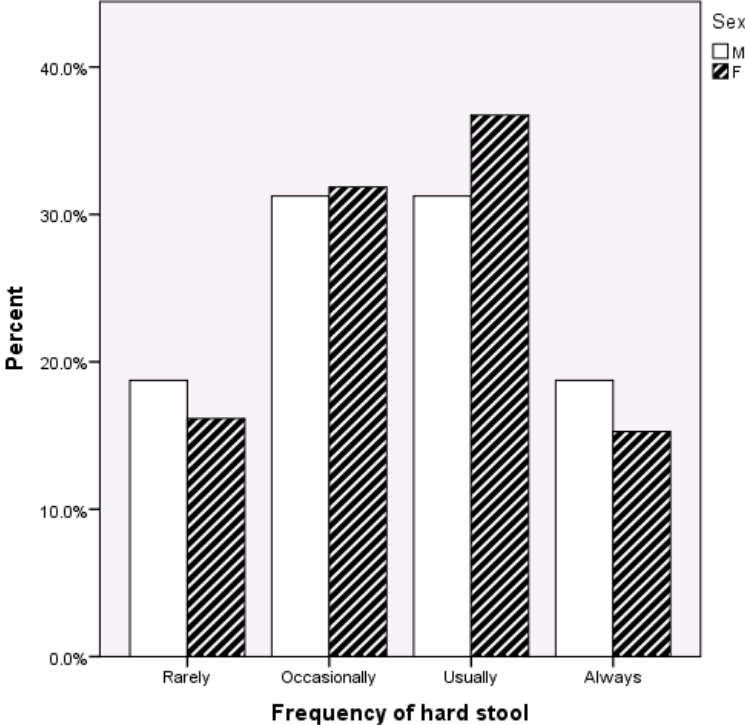


Figure 4.2b: Clustered bar diagram showing the frequency of hard stool for each gender

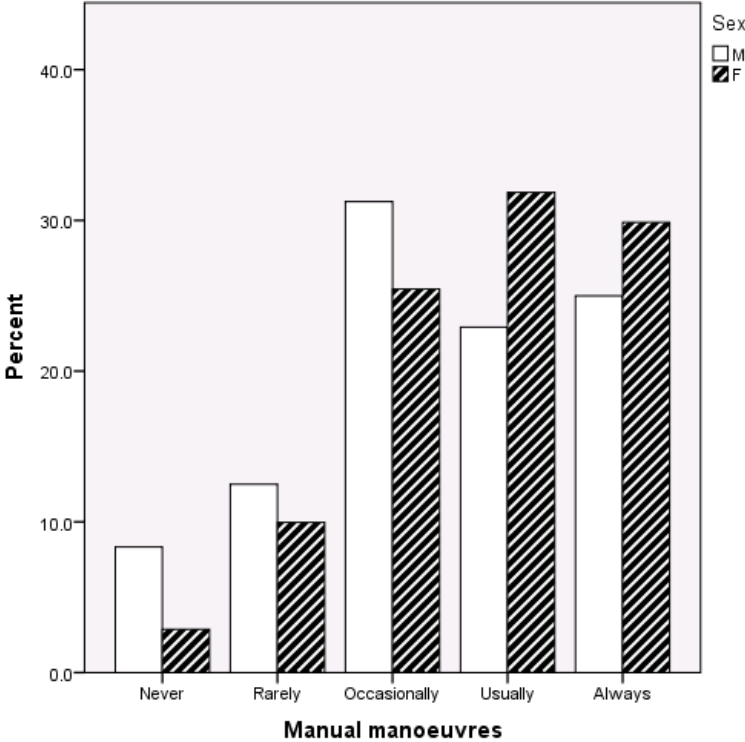


Figure 4.2c: Clustered bar diagram showing the frequency of manual manoeuvres for each gender

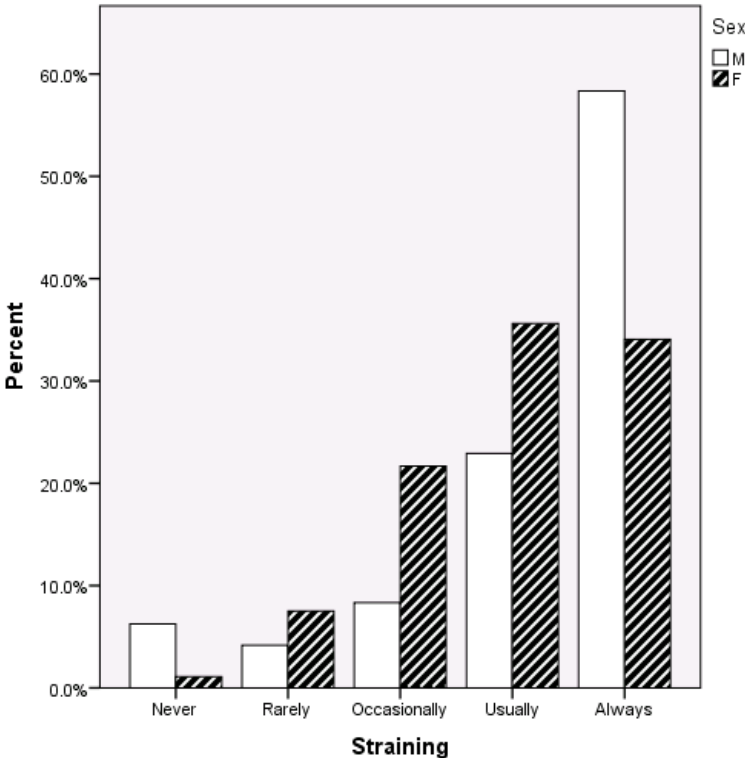
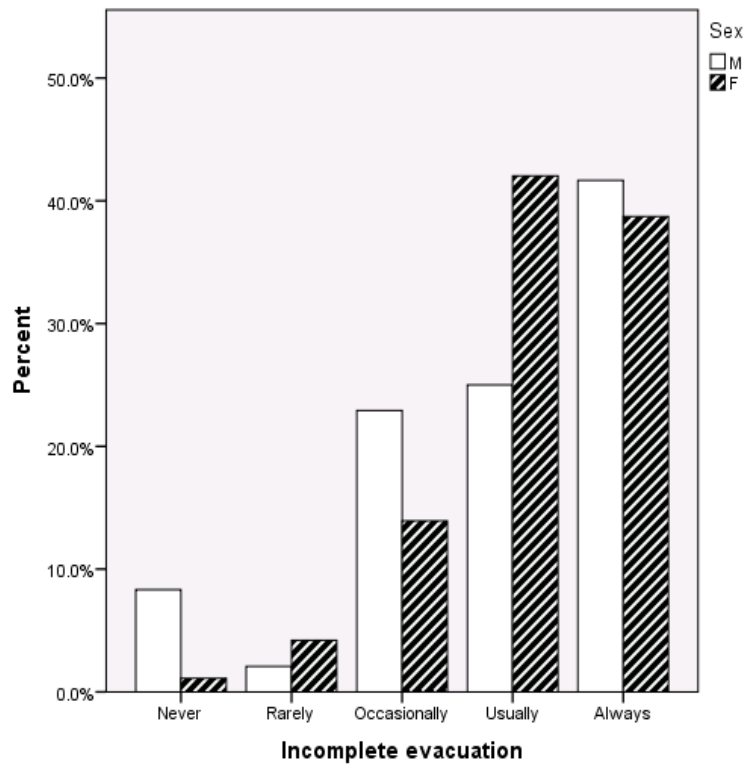
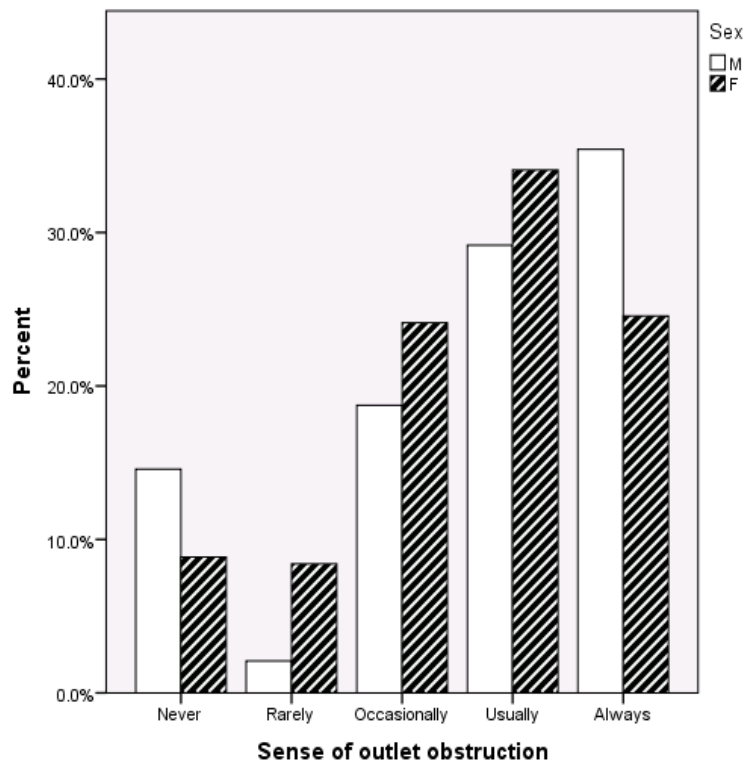


Figure 4.2d: Clustered bar diagram showing the frequency of straining for each gender



**Figure 4.2e:** Clustered bar diagram showing the frequency of incomplete evacuation for each gender



**Figure 4.2f:** Clustered bar diagram showing the frequency of outlet obstruction for each gender

#### 4.4.2 FREQUENCY OF PROCTOGRAPHIC ABNORMALITIES

Proctography was abnormal in 308 (61.6%) patients (275 females and 33 males i.e. 60.8% of all female and 68.8% all male patients) (Table 4.1). Of the abnormal proctograms, 186 patients (37.2%) (173 F; 13 M) had significant structural abnormalities alone, 49 patients (9.8%) (39 F, 10 M) had functional abnormalities alone and 24 patients (4.8%) (22 F, 2 M) had significant structural and functional abnormalities. A further 49 patients (9.8%) (41 F, 8 M) had poor evacuation only with no demonstrable structural or functional abnormality. Overall 7.4% of patients (37 of 500) had a megarectum. 158 patients (31.6%) had insignificant findings (rectocele <4 cm or non-obstructive pathologies) and were regarded as normal. A further 34 patients (6.8%) had a completely normal proctography i.e. no structural or functional abnormalities detected.

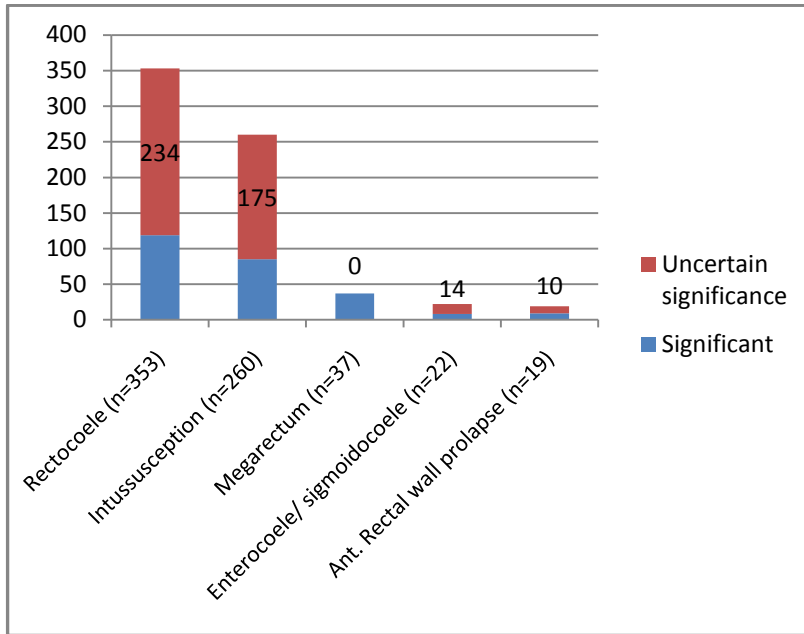
**Table 4.1:** Frequency of abnormal proctographic findings

<b>Proctographic findings</b>	<b>Overall</b>	<b>Female</b>	<b>Male</b>	<b>P-value</b>
Abnormal EP	308	275	33	0.28
Functional abnormality	73	61 (22.2%)	12 (36.4%)	0.07
FDD	34	26 (9.5%)	8 (24.2%)	<b>0.01</b>
DD	69	58 (21.1%)	11 (33.3%)	0.11
IP	4	3 (1.1%)	1 (3%)	0.35
Isolated poor evacuation	49	41 (14.9%)	8 (24.2%)	0.09
Significant structural abnormality	210	195 (70.9%)	15 (45.5%)	<b>0.004</b>
Significant rectocele	119	119 (43.2%)	0 (0%)	<b>&lt;0.001</b>
Obstructing intussusception	85	77 (28%)	8 (24.2%)	0.65
Megarectum	37	30 (10.9%)	7 (21.2%)	0.08
Obstructing anterior rectal wall prolapse	9	9 (3.3%)	0 (0%)	0.29
Obstructing enterocele / sigmoidocele	8	8 (2.9%)	0 (0%)	0.32



Among the 73 patients who had a functional abnormality on proctography (EP), 34 (26 F, 8 M) satisfied the Rome III criteria for diagnosis of functional defecation disorder (FDD), 69 patients (58 F, 11 M) satisfied the Rome III criteria for dyssynergic defaecation and 4 patients (3 F, 1 M) satisfied the criteria for impaired propulsion. Functional defecation disorder was more commonly seen in males (24.2% vs. 9.5%;  $p=0.01$ ).

Figure 4.3 shows the frequency of all observed structural abnormalities. 353 patients (70.6%) had a rectocele of >2 cm depth, of whom 119 patients (23.8%) had a significant rectocele (>4 cm in depth). A rectocele was not seen in any male patients. An intussusception was seen in 260 patients (52%). 85 patients (17%, 77 F, 8 M) had an obstructive intussusception. Megarectum was seen in 37 patients (7.4%, 30 F, 7 M). Isolated anterior rectal wall prolapse was present in 19 patients of which 9 were seen to obstruct evacuation (1.8%) and were hence considered significant. An enterocele or sigmoidocele was present in 22 (4.4%) patients, of whom 8 (1.6%) had an obstructing enterocele / sigmoidocele. Significant (obstructing) anterior rectal wall prolapses, enteroceles and sigmoidoceles were seen only in female patients. There was a significant overlap among various structural and functional abnormalities (table 4.2). Significant structural abnormalities were more common in females than males (70.9% vs. 45.5%;  $p=0.004$ ) mainly as a consequence of the prevalence of rectoceles only in females (119 vs. 0%,  $P<0.0001$ ).

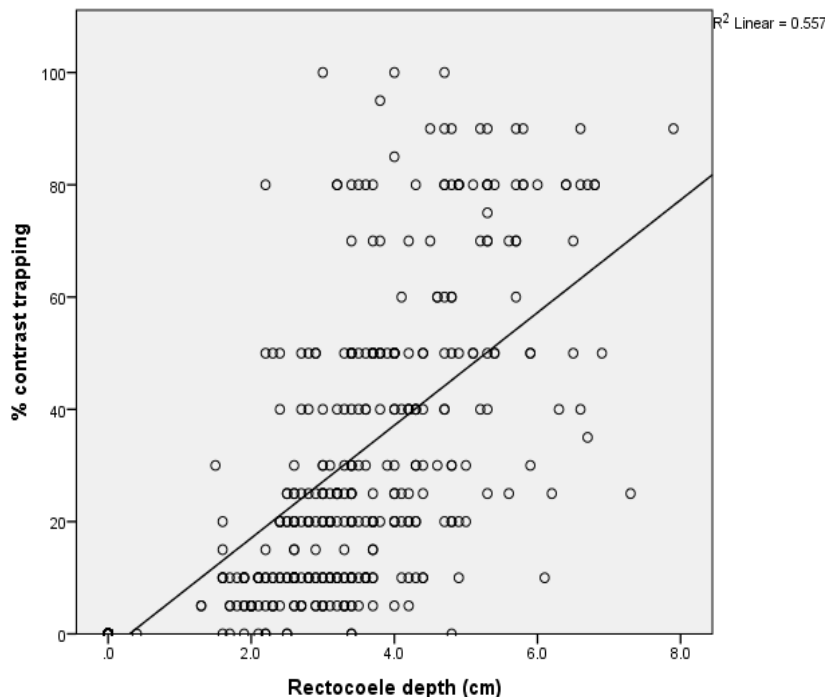


**Figure 4.3:** Frequency of all structural abnormalities (significant and of uncertain clinical significance) seen during proctography. Rectocoeles were included only if they were >2 cm in antero-posterior diameter.

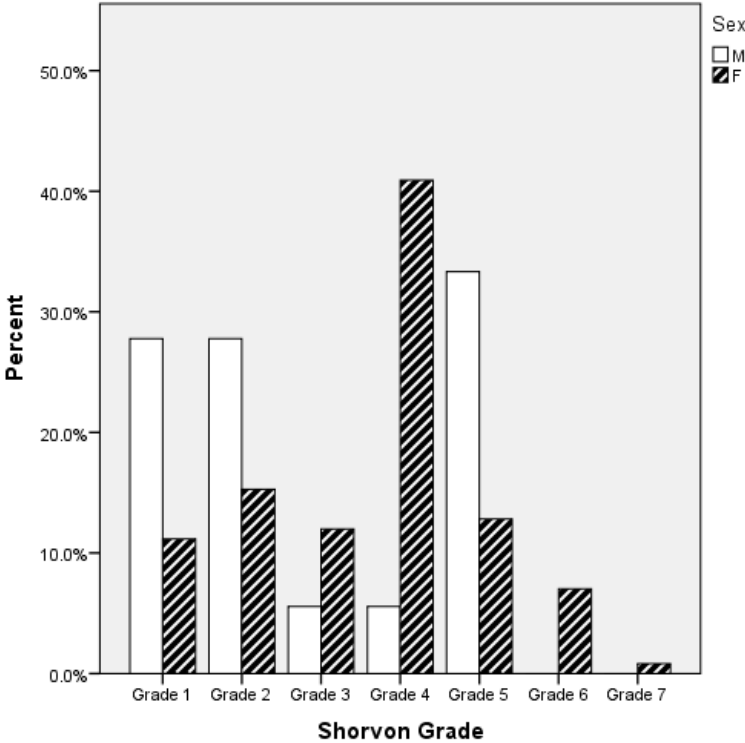
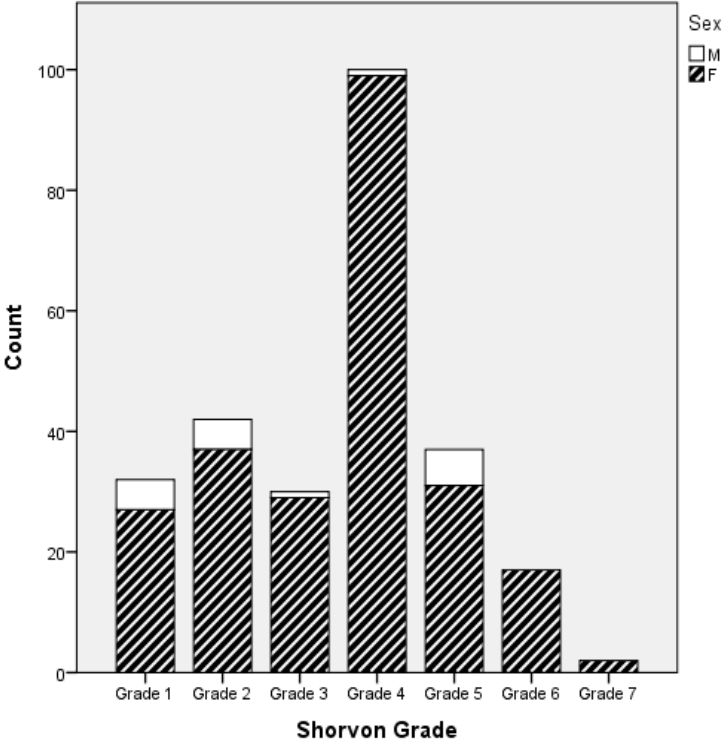
**Table 4.2:**Overlap between proctographic abnormalities. FDD = functional defecation disorder, IP = impaired propulsion, DD = dyssynergic defecation, Sig. Recto = significant rectocele, Med. Recto = medium rectocele (2.1-4cm in AP depth), Ob. Int = obstructive intussusception, Nob. Int = non-obstructive intussusception, Meg. R = megarectum, Ob. ARWP = obstructive anterior rectal wall prolapse, Nob. ARWP = non-obstructive anterior rectal wall prolapse, Ob. Ent / sig = Obstructive enterocele / sigmoidocele, Nob. Ent / sig = non-obstructive enterocele / sigmoidocele.

	IP (4)	DD (69)	Sig. Recto (119)	Med. Recto (207)	Ob. Int (85)	Nob. Int (175)	Meg. R (37)	Ob. ARWP (9)	Nob. ARWP (10)	Ob. Ent / sig (8)	Nob. Ent / sig (14)
FDD (34)	4 (0.8%)	30 (6%)	1 (0.2%)	10 (2%)	0	0	2 (0.4%)	1 (0.2%)	0	0	1 (0.2%)
IP (4)		0	0	0	0	0	1 (0.2%)	0	0	0	0
DD (69)			12 (2.4%)	24 (4.8%)	7 (1.4%)	6 (1.2%)	4 (0.8%)	2 (0.4%)	1 (0.2%)	0	3 (0.6%)
Sig. Recto (119)				0	28 (5.6%)	42 (8.4%)	12 (2.4%)	3 (0.6%)	5 (1%)	4 (0.8%)	6 (1.2%)
Med. Recto (207)					30 (6%)	80 (20%)	12 (2.4%)	6 (1.2%)	5 (1%)	3 (0.6%)	5 (1%)
Ob. Int (85)						0	4 (0.8%)	0	0	0	0
Nob. Int (175)							9 (1.8%)	0	2 (0.4%)	1 (0.2%)	3 (0.6%)
Meg. R (37)								0	2 (0.4%)	1 (0.2%)	2 (0.4%)
Ob. ARWP (9)									0	1 (0.2%)	0
Nob. ARWP (10)										0	0

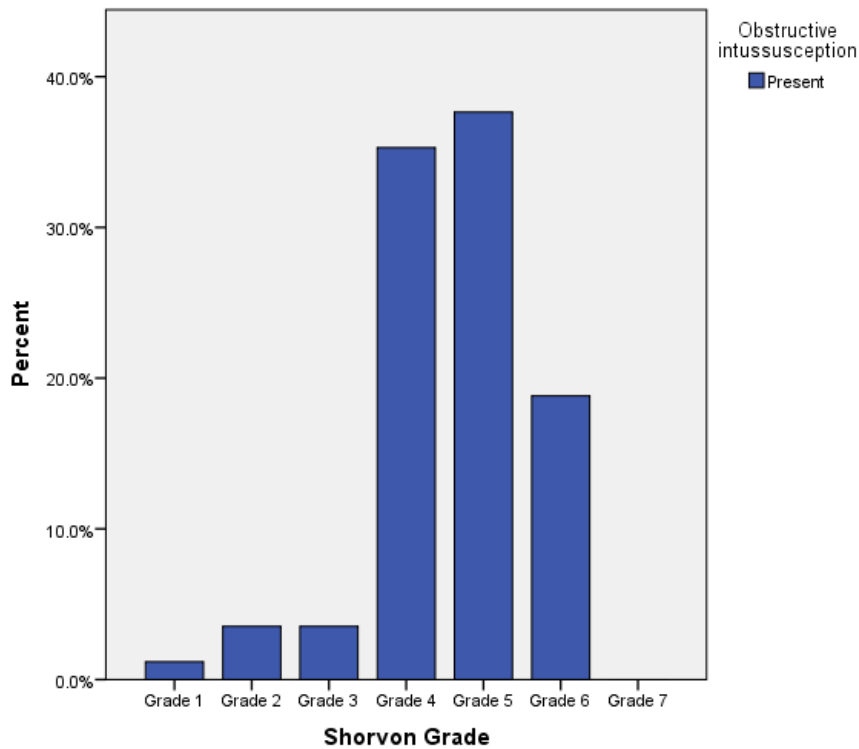
Analysis of all patients with rectocele (including those >2 cm but <4 cm in size) showed that median rectocele depth was 2.9 cm with median 10% retention of contrast (visual estimation as a percent of the total contrast instilled). Spearman's rank correlation test revealed a strong and significant correlation between rectocele depth and the percentage of contrast trapped ( $r_s = .861$ ;  $p < 0.0001$ ; Figure 4.4). When intussusceptions were graded according to Shorvon grade, grade 4 intussusception was most frequent (100 patients, 99 F, 1 M) followed by grade 2 (42 patients, 37 F, 5 M). Only 2 patients (both females) had a grade 7 intussusception (rectal prolapse) and both were non-obstructive. The frequency of individual Shorvon grades categorised by gender and presence of obstruction are presented in figures 4.5 a and b respectively. Obstructive intussusceptions (n=85) were most commonly caused by Shorvon grade 5 intussusceptions (n= 32, 37.6%), followed by grade 4 (n=30, 35.3%) and grade 6 (n=16, 18.8%) (figure 4.5a-b).



**Figure 4.4:** Scatter plot of rectocele depth and percentage of contrast (as a proportion of that originally instilled) trapped in the rectocele at the end of evacuation.



**Figure 4.5a:** Stacked bar diagrams to show the frequency of various grades of intussusception (Shorvon grade) (Shorvon et al., 1989) sub-categorised by gender



**Figure 4.5b:** Histogram to show the grades (Shorvon grade) of obstructive intussusception (Shorvon et al., 1989) as a % of all obstructive intussusceptions

#### 4.4.3 PREDICTION OF PROCTOGRAPHIC ABNORMALITIES FROM SYMPTOMS

Frequencies of functional constipation related Rome III specific symptoms and major proctographic abnormalities are presented in table 4.3.

Results of regression analysis of major proctographic findings and functional constipation related Rome III symptoms are presented in tables 4.4a - 4.4g. For the diagnosis of functional defecation disorder (FDD) and dyssynergic defecation (DD) the only significantly predictive symptom in logistic regression analysis was passing motions <3 times per week ( $p=.002$  and  $p=.006$  for FDD and DD respectively). None of the symptoms reached significance for the diagnosis of impaired propulsion.

**Table 4.3:** Percentage of functional constipation related Rome III specific symptoms in patients for a given proctographic finding

Symptoms vs. proctographic findings	Functional defaecation disorders (n=34)	Dyssynergic defaecation (n=69)	Impaired propulsion (n=4)	Significant structural abnormality (n=210)	Significant Rectocele (n=119)	Obstructive intussusception (n=85)	Megarectum (n=37)	No significant proctographic abnormality (n = 192)
Straining	30/34 (88.2%)	63/69 (91.3%)	4/4 (100%)	195/210 (92.9%)	112/119 (94.1%)	76/85 (89.4%)	35/37 (94.6%)	170/192 (88.5%)
Hard stool	28/34 (82.4%)	56/69 (81.2%)	4/4 (100%)	184/210 (87.6%)	100/119 (84%)	75/85 (88.2%)	33/37 (89.2%)	152/192 (79.2%)
Incomplete evacuation	32/34 (94.1%)	66/69 (95.6%)	4/4 (100%)	201/210 (95.7%)	115/119 (96.7%)	82/85 (96.5%)	35/37 (94.6%)	176/192 (91.7%)
Blockage	32/34 (94.1%)	62/69 (89.9%)	4/4 (100%)	178/210 (84.8%)	102/119 (85.7%)	67/85 (78.8%)	32/37 (86.5%)	150/192 (78.1%)
Manual Manoeuvres	14/34 (41.2%)	32/69 (46.3%)	2/4 (50%)	124/210 (59%)	71/119 (59.7%)	42/85 (50.6%)	25/37 (67.6%)	93/192 (48.4%)
<3 motions /week	22/34 (64.7%)	37/69 (55.2%)	1/4 (25%)	75/210 (35.7%)	40/210 (33.6%)	28/85 (32.9%)	14/37 (37.8%)	65/192 (33.9%)

For significant structural abnormalities, need for manual manoeuvres and passage of hard stool were the only symptoms that achieved statistical significance ( $p=.009$  and  $p=.04$  respectively). Multivariate analysis using these 2 symptoms showed significance only for manual manoeuvres ( $p=.015$ ; table 4.4h). None of the Rome III symptoms could reliably predict the presence of a significant rectocele, an obstructive intussusception or a megarectum.

**Table 4.4a:** Results of univariate logistic analyses for prediction of functional defaecation disorders

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Functional defaecation disorders	Straining	.351	.529	1.42	.476 - 4.234
	Hard stools	.095	.839	1.1	.440 - 2.746
	Incomplete evacuation	.016	.983	1.016	.231 - 4.466
	Sensation of Blockage	-1.258	.089	.284	.067 - 1.209
	Manual Manoeuvres	.477	0.186	1.611	.795 - 3.267
	Bowel motion <3times/wk	-1.161	<b>.002</b>	.313	.151 - .649

**Table 4.4b:** Results of univariate logistic analyses for prediction of dyssynergic defaecation

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Dyssynergic defaecation	Straining	-.015	.974	.985	.4 - 2.4
	Hard stools	.197	.556	1.218	.632 - 2.347
	Incomplete evacuation	.345	.580	1.412	.416 - 4.799
	Sensation of Blockage	-.687	.1	.503	.222 - 1.141
	Manual Manoeuvres	.271	.298	1.311	.787 - 2.18
	Bowel motion <3times/wk	-.722	<b>.006</b>	.486	.291 - .811



**Table 4.4c:** Results of univariate logistic analyses for prediction of impaired propulsion

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Impaired propulsion	Straining	-16.476	.998	0	0
	Hard stools	-16.563	.997	0	0
	Incomplete evacuation	-16.443	.998	0	0
	Sensation of Blockage	-16.573	.997	0	0
	Manual Manoeuvres	.089	.930	1.093	.153 - 7.82
	Bowel motion <3times/wk	-1.584	.172	.205	.021 - 1.987

**Table 4.4d:** Results of univariate logistic analyses for prediction of significant structural abnormality

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Significant structural abnormality	Straining	-.368	.268	.692	.361 - 1.327
	Hard stools	-.527	<b>.04</b>	.59	.357 - .977
	Incomplete evacuation	-.503	.222	.604	.27 - 1.356
	Sensation of Blockage	-.241	.323	.786	.487 - 1.268
	Manual Manoeuvres	-.476	<b>.009</b>	.621	.434 - .889
	Bowel motion <3times/wk	.197	.294	1.217	.843 - 1.757

**Table 4.4e:** Results of univariate logistic analyses for prediction of significant rectocele

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Significant rectocele	Straining	-.543	.203	.581	.252 - 1.34
	Hard stools	-.042	.884	.959	.548 - 1.679
	Incomplete evacuation	-.703	.201	.495	.169 - 1.453
	Sensation of Blockage	-.283	.336	.754	.424 - 1.34
	Manual Manoeuvres	-.397	.063	.673	.443 - 1.021
	Bowel motion <3times/wk	.271	.219	1.311	.851 - 2.019

**Table 4.4f:** Results of univariate logistic analyses for prediction of obstructive intussusception

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Obstructive intussusception	Straining	.251	.524	1.286	.594 - 2.785
	Hard stools	-.454	.208	.635	.313 - 1.288
	Incomplete evacuation	-.603	.332	.547	.162 - 1.851
	Sensation of Blockage	.315	.288	1.371	.766 - 2.453
	Manual Manoeuvres	.134	.572	1.144	.717 - 1.825
	Bowel motion <3times/wk	.285	.257	1.33	.812 - 2.178

#### 4.5 DISCUSSION

In this study most of the patients were middle aged with significantly higher number of females (female: male ratio of approximately 10:1), which is similar to the gender ratio seen previously (*cf.* chapter 2). Of the 6 symptoms incorporated in the Rome III criteria for diagnosis of functional constipation, a sense of incomplete evacuation was the commonest (94.2%) followed by straining (91.2%). Bowel infrequency (passing less than 3 motions per week) was the least common complaint. Statistically, there was no gender based difference in symptoms.

**Table 4.4g:** Results of univariate logistic analyses for prediction of megarectum

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Megarectum	Straining	-.557	.454	.573	.133 - 2.466
	Hard stools	-.514	.345	.598	.206 - 1.737
	Incomplete evacuation	-.08	.915	.923	.211 - 4.04
	Sensation of Blockage	-.305	.538	.737	.279 - 1.949
	Manual Manoeuvres	-.695	.056	.499	.245 - 1.017
	Bowel motion <3times/wk	.026	.942	1.026	.515 - 2.046

**Table 4.4h:** Results of multivariate logistic analyses for prediction of significant structural abnormality

Abnormality	Symptom	Regression Coefficient	Significance (p value)	Odds ratio	95%CI for odds ratio
Significant structural abnormality	Hard stools	-.475	.067	.622	.374 - 1.033
	Manual Manoeuvres	-.447	<b>.015</b>	.639	.446 - .918

Most proctographic abnormalities seen in this study were due to structural abnormalities; in fact 'significant' structural abnormalities were nearly 3 times as common as functional abnormalities (68% vs. 23.7%) in patients satisfying the Rome III criteria for functional constipation. Interestingly, structural abnormalities were significantly more common in females (70.9% vs. 45.5%;  $p=0.004$ ), and functional defecation disorder was more common in males (24.2% vs. 9.5%;  $p=0.01$ ). The reason for higher prevalence of structural abnormality in females may be partly explained by the fact that rectocele was only seen in female patients. A significant proctographic abnormality was noted in 61.6% patients (308 of 500). A significant rectocele was the commonest abnormality and was present in nearly 24% of patients. This was followed by an obstructing intussusception (17%), dyssynergia (14%), megarectum (7.4%) and functional defecation disorder (6.8%). Similar to previous reports, (Mellgren et al., 1994, Ragg et al., 2011) several patients had more than one

abnormality to explain their symptoms. In this study, roughly a third of the patients with any significant structural abnormality had another coexisting structural abnormality. Overlap between significant structural and functional abnormality was marginally less frequent with roughly 10% of patients with significant structural abnormality also having a functional abnormality (usually dyssynergia).

Defecating less than 3 times per week was the only symptom to reach statistical significance for functional defaecation disorders and dyssynergic defaecation. None of the Rome III symptoms could reliably predict individual structural abnormalities. For significant structural abnormalities in general, a need for manual manoeuvres to aid evacuation reached statistical significance in multivariate analysis. Interestingly, for all above symptoms that reached significance, the regression coefficients were negative and odds ratio was  $<1$ , which would suggest that patients complaining of these symptoms are *less likely* to have the proctographic abnormality in question. The reason for such negative association between symptoms and proctographic abnormalities is not clear from our data. Bowel infrequency and the need for manual manoeuvres were the 2 least commonly encountered symptoms in this. This coupled to the fact that both these symptoms are negative predictors for more than one abnormality (FDD and DD in case of bowel infrequency; and structural abnormalities in general in the case of manual manoeuvres) undermines their clinical utility as diagnostic tools. In general Rome III specific symptoms were of limited utility in predicting individual proctographic abnormalities and based on the results of this study, the null hypothesis could not be rejected.

Unlike this study, previous studies assessing correlation of symptoms with the cause of constipation have focused mostly on the broader types of constipation viz. slow transit constipation or pelvic floor dysfunction as a whole as opposed to the subtypes of pelvic floor dysfunction. The study by Grotz *et al* concluded that clinical symptoms cannot be used to identify subgroups of chronic constipation although they found that a sensation of anal

blockage was associated with pelvic floor dysfunction (Grotz et al., 1994). A higher prevalence of backache and bowel infrequency in patients with pelvic floor dysfunction has been reported by another study (Glia et al., 1999). Karlbom *et al* reported an association between a large rectocele and the need for manual manoeuvres (Karlbom et al., 1995) whereas Halverson *et al* reported an association between rectocele and pelvic outlet obstruction type symptoms (Halverson and Orkin, 1998). A study by Koch *et al* found that although a sense of incomplete evacuation had a good sensitivity for disordered defecation, and sense of outlet obstruction and need for manual manoeuvres had a good specificity, none of the symptoms had an acceptable sensitivity and specificity to be of diagnostic value (Koch et al., 1997). Most studies, including this study, have a limited 'symptom repertoire' to diagnose constipation. Whether a handful of volunteered symptoms are enough to discriminate between the subtypes of constipation is debatable. As highlighted in Pescatori's iceberg diagram (Pescatori et al., 2007), constipation is often associated with a variety of occult disorders that are often not part of a regular constipation questionnaire but can have significant influence on the symptomatology and management of constipation.

Constipation is usually defined using symptoms. The traditional definition of constipation is based on bowel infrequency (Connell et al., 1965, Whitehead et al., 1989, Lopez Cara et al., 2006). Similar to previous reports (Stewart et al., 1999, Ragg et al., 2011), bowel infrequency was the least common constipation symptom among the patients in this study. In contrast, many patients with constipation, and obstructed defecation in particular, often report multiple attempts at evacuation driven by a sense of incomplete evacuation from a previous failed attempt. It is therefore advisable to avoid using only bowel infrequency as sole diagnostic criteria for constipation. The commonest symptoms in constipation in this study were a sense of incomplete evacuation and excessive straining which is similar to previous reports (Koch et al., 1997, Glia et al., 1999). The frequency of symptoms in this study differ slightly from another recent study that has also reported the frequency of symptoms in 174 patients fulfilling the Rome III criteria for functional constipation (Xin et al.,

2014). Xin *et al* have reported straining as the commonest symptom present in 92% patients (similar to this study), followed by bowel infrequency in 75% patients (*c.f.* 38% in this study), hard stool (71% vs. 84% in this study), sense of incomplete evacuation (69% vs. 94% in this study), sense of outlet obstruction (52% vs. 83% in this study) and finally the need for manual manoeuvres has been reported as the least common symptom (18.4% vs. 52% in this study). The reason for these differences, although not very obvious, may be due to differences in demographics and cultural factors between the two groups studied.

Evacuation proctography is a dynamic test of evacuation which can identify both functional and structural abnormalities, and is useful during the initial work-up of patients with chronic constipation (Bove *et al.*, 2012). As a first line investigation for functional constipation, this supports the use of proctography over balloon expulsion test or manometry which are currently recommended first (Bharucha *et al.*, 2013a), but are unable to diagnose structural abnormalities.

This study has a few limitations. It was performed as a retrospective study. Since the primary aim of was to evaluate the predictive power of symptoms included in the Rome III criteria, only patients who met the Rome III criteria and had fully filled in all the Rome specific questions in the questionnaire were included. This was done to prevent a response bias but unfortunately it means that the study suffers from a selection bias. Although proctography was performed under strict departmental protocol by several practitioners who had been appropriately trained in the procedure, the studies were performed by more than one clinician. Also a colonic transit was not performed in all the patients hence a proportion of the patients in this study are likely to have co-existent slow transit constipation.

This study also has several strengths. This is probably the first study that uses widely recognised diagnostic criteria for patient selection and diagnosis. It is also the largest study of its kind. Although previous studies have assessed correlation between symptoms and

pelvic floor dysfunction as a whole, none of them have assessed it for the subtypes of pelvic floor dysfunction. Although several practitioners performed the proctography, they were all analysed by a single clinician.

In conclusion, although some symptoms are associated with particular proctographic abnormalities, none of the symptoms evaluated had significant predictive capacity to be of use clinically. Based on the frequency of symptoms in this cohort of constipated patients it is inadvisable to use bowel infrequency in isolation as a diagnostic criterion for constipation. Sense of incomplete evacuation and straining are much more common in patients with constipation. In this series, significant structural abnormalities were more common in women and functional defecation disorder was more common in men. The data suggests that in patients fulfilling the Rome III criteria for functional constipation, significant structural abnormalities are much more frequent than functional abnormalities. Since structural abnormalities cannot be diagnosed by balloon expulsion test and manometry, algorithms that do not incorporate routine use of a dynamic test of evacuation are likely to miss these abnormalities. This study supports the recent Italian consensus (Bove et al., 2012) which advises the use of proctography (along with colonic transit time) as first line investigation for patients with chronic constipation.

**Statement of contribution for chapter 5:** 20 of 100 patients included in the subsequent chapter have been investigated by another member of our GI Physiology Unit (Mr Noel Thin). I have assessed all the other patients myself. The data collection, analysis and write-up has been done by me.



# 5 *Diagnostic Disagreement between Tests of Defaecatory Function: A Prospective Study of 100 Constipated Patients*

## 5.1 INTRODUCTION

Constipation is common, with a worldwide prevalence of approximately 14% (Peppas et al., 2008, Mugie et al., 2011). Among patients who do not have an underlying organic cause for their symptoms, assessments of colonic transit and defaecatory function are used to classify patients into 3 categories: slow colonic transit, disordered evacuation, and those in whom test results are normal (i.e. normal transit and evacuation). Rectal evacuation can be evaluated *directly* by means of the balloon expulsion (BE) test, and also by proctography (defaecography), using either fluoroscopy, scintigraphy (Hutchinson et al., 1993), or magnetic resonance imaging (Brandao and Ianez, 2013). Alternatively, the assessment of rectoanal pressures and motor coordination during simulated evacuation (the 'push' manoeuvre) by anorectal manometry (ARM) provides an *indirect* test of evacuation. A recent systematic review of dyssynergic defecation found that BE and ARM are more widely used in the United States, whereas radiological techniques are more commonly employed in Europe and Asia (Videlock et al., 2013). Overall, these tests suggest that poor evacuation may result from disturbed function (e.g. failure to effectively increase intra-rectal pressure or adequately relax the anal canal / pelvic floor on attempted defecation) (D'Hoore and Penninckx, 2003, Lembo and Camilleri, 2003, Rao et al., 2005, Bharucha, 2007, Bharucha et al., 2013a), and / or secondary to 'mechanical' (structural) obstructive features (e.g. an occlusive intussusception, large rectocele) (D'Hoore and Penninckx, 2003, Bove et al., 2012, Piloni et al., 2013).

The BE test has been recommended as a screening test (Minguez et al., 2004, Bharucha and Wald, 2010), because it simple, inexpensive, and reasonably sensitive and specific for identifying impaired evacuation when compared to other methods (Fleshman et al., 1992,

Minguez et al., 2004). The BE test is generally performed after inflating the balloon to a fixed volume, typically 50 ml (Rao et al., 2005). Alternatively, the balloon can be inflated until patients report the urge to defecate (Minguez et al., 2004). However, the BE test does not identify obstructive anatomical abnormalities of the pelvic floor that may be amenable to surgical repair (Holley, 1994, van Dam et al., 1997, Felt-Bersma and Cuesta, 2001, D'Hoore and Penninckx, 2003, Bharucha et al., 2013b). While proctography assesses both evacuatory ability and anatomical features, it suffers from limitations (Diamant et al., 1999, Bharucha et al., 2006, Rao and Meduri, 2011, Bharucha et al., 2013a). In addition to cost and radiation exposure, some “abnormalities” (e.g. small rectocoeles and minor rectal intussusception) are common in asymptomatic control subjects (*cf.* chapter 3), and hence their clinical significance may be unclear. Furthermore, if a liquid rather than ‘paste’ contrast is used, the consistency may not approximate that of native stool (Bharucha, 2006b).

The balloon expulsion test provides an overall assessment of rectal evacuation (Diamant et al., 1999). While it does not identify the cause of impaired evacuation (Bharucha, 2006b), it has been previously reported to be highly specific for dyssynergic defecation (DD) when this diagnosis was based on a combination of ARM and EP (and Rome II criteria) (Minguez et al., 2004). Although the routine use of EP has not been recommended in several ‘medical position’ statements and guidelines (Whitehead and Bharucha, 2010, Bharucha et al., 2013a), a recent consensus report from the Association of Italian Gastroenterologists and Endoscopists recommended dynamic imaging of defecation as the benchmark against which to test newer modalities (Bove et al., 2012); EP has also been recommended as the investigation of choice to exclude the diagnosis of DD when clinical features suggest dyssynergia, but ARM and BE test are equivocal (Wald et al., 2014).

Several guidelines advocate the use of ARM in conjunction with BE as the primary diagnostic tests in patients with suspected defaecatory problems (Whitehead and Bharucha, 2010, Rao and Meduri, 2011, Bharucha et al., 2013a). The BE test is cheap, simple and can

be performed even in the outpatient setting. In contrast, ARM requires more specialized equipment and is more expensive. Moreover, ARM is *de facto* not a test of evacuation but rather a test for functional abnormalities that may impair evacuation. Systematic reviews of studies in constipated patients have concluded that ARM has a relatively high yield for diagnosing dyssynergic defecation (DD) (Rao et al., 2005), a subtype of 'functional defecation disorder'. However, most included studies were uncontrolled and used the anticipated normal pattern (i.e. increased rectal pressure coordinated with anal relaxation) as the criterion to diagnose DD. In contrast, studies of healthy volunteers using both traditional (Sun and Read, 1989, Voderholzer et al., 1997a, Rao et al., 1999, Rao et al., 2006) and newer (high-resolution) (Noelting et al., 2012) methods have demonstrated that recto-anal in-coordination is not uncommon (table 5.1).

**Table 5.1:** Prevalence of dyssynergic defaecation in healthy volunteers (HV) and patients with constipation (FC) based on manometric criteria.

Study	HV/FC	Prevalence of dyssynergic defecation (%)	
		HV	FC
(Barnes and Lennard-Jones, 1988)	15/31	20	97
(Kerrigan et al., 1989)	29/16	12	73
(Wald et al., 1990b)	12/36	8	31
(Roberts et al., 1992)	20/71	5	24
(Merkel et al., 1993)	17/18	12	50
(Voderholzer et al., 1997a)	18/102	22	41
(Rao et al., 1998d)	25/35	20	51
(Ratuapli et al., 2013b)	62/295	82	92

\* Different criteria were used for diagnosis: paradoxical sphincter contraction or failed anal relaxation (Voderholzer et al., 1997a, Kerrigan et al., 1989, Merkel et al., 1993, Wald et al., 1990b, Barnes and Lennard-Jones, 1988), inability to raise intrarectal pressure (Roberts et al., 1992), negative rectoanal gradient (Ratuapli et al., 2013b, Rao et al., 1998d), during simulated evacuation. In one study (Roberts et al., 1992) the diagnosis was based on the combination of electromyographic recruitment >50%, evidence of an adequate intrarectal pressure on straining (>50 cmH<sub>2</sub>O) and defective evacuation (either quantitatively or in terms of prolonged straining).

It is important to clarify the diagnostic utility of anorectal tests because evacuatory disorders are managed with biofeedback therapy rather than laxatives. While the methods to evaluate anorectal functions have been compared (Halverson and Orkin, 1998, Bordeianou et al.,

2011, Videlock et al., 2013), no study has prospectively and systematically compared all contemporaneous tests (both 'direct' and 'indirect') based on strict inclusion criteria and guidelines (Rome III) for patients with functional constipation. Therefore, the main aims of this study were, in a prospective series of patients with functional constipation:

1. to compare the diagnostic yield (proportions of patients with an abnormal test result or test-derived Rome III diagnosis) and agreement between 'direct' tests of evacuation: balloon expulsion [standardised and individualized volumes] and proctography
2. to compare the diagnostic yield and agreement between ARM and 'direct' tests of evacuation.

## **5.2 MATERIAL AND METHODS**

### **5.2.1 PATIENTS**

One hundred consecutive adult patients (>18 years old) referred to a specialist tertiary centre (Barts Health NHS Trust) for investigation of their symptoms of chronic constipation were studied prospectively. All satisfied Rome III criteria (Bharucha et al., 2006) for functional constipation. The number of 100 was selected for pragmatic reasons.

#### **5.2.1.1 Inclusion criteria**

1. Patients should satisfy the Rome III criteria for functional constipation (Table 5.2).

#### **5.2.1.2 Exclusion criteria**

1. Patients below the age of 18 years.
2. Patients with active anal fissure or lacking a native rectum.
3. Patients with limited mobility precluding independent transfer from the couch to the commode for testing.
4. History of previous anorectal surgery (other than haemorrhoidectomy).
5. Patients unable to communicate in English.

**Table 5.2:** ROME III criteria for diagnosis of functional constipation(Bharucha et al., 2006)

Criteria fulfilled for the last 3 months with symptom onset at least 6months prior to diagnosis

1. Must include two or more of the following:
  - a. Straining during at least 25% of defecations
  - b. Lumpy or hard stools in at least 25% of defecations
  - c. Sensation of incomplete evacuation for at least 25% of defecations
  - d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
  - e. Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome (as per ROME III)

### 5.2.2 STUDY DESIGN

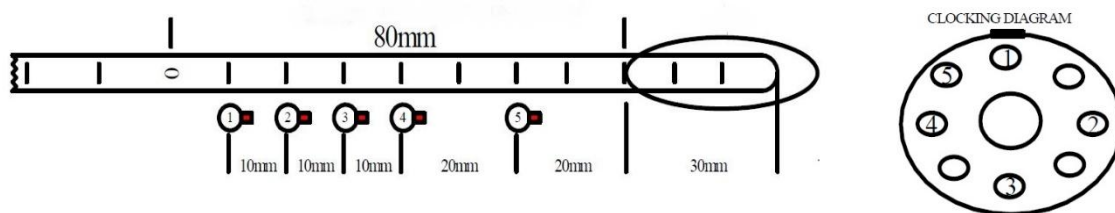
The study was designed as a prospective clinical service evaluation study. The R&D Department at Barts NHS Trust were contacted to discuss the need for ethical approval prior to the study. It was advised that since the study has been designed as a service evaluation study, does not include any change to routine clinical practice, and since all investigation results were communicated to the referring clinician, that no formal ethical approval will be needed.

After a structured interview, (based on the departmental questionnaire, *cf.* appendix) all patients underwent water perfused ARM with assessment of rectal sensation, BE tests (to both 'fixed' and 'individualised' volumes), and evacuation proctography in that order. Colonic transit was also evaluated (in patients where it was indicated according to our departmental protocol) using a radio-opaque marker technique: an x-ray of the abdomen was obtained at 100 hours after ingestion of 50 markers (Gladman et al., 2003b, Zarate et al., 2008a). All tests were performed on the same day.

### 5.2.3a DIRECT TESTS OF EVACUATION

#### 5.2.3a.1 Balloon expulsion tests ( $BE_{50}$ and $BE_{DDV}$ )

Balloon expulsion test was performed using a water-perfused catheter (4.9 mm outer diameter: Ardmore Healthcare, Buckinghamshire, UK) incorporating 5 side holes (for ARM: see below) and a central lumen for inflating an integrated non-latex balloon (4 cm length; maximum inflation volume of 400 ml) (Figure 5.1). The balloon was lubricated with KY jelly and introduced into the rectum with the patient in the lateral position. It was then inflated with 50 mls of warm water and the patient was transferred to a commode. They were then asked to evacuate the balloon as quickly as possible, in relative privacy, and say "out" as soon as the balloon was expelled. The time required to expel the balloon was recorded. The patient was then returned to the couch and the test was performed again, using an individualised volume of water (until patients reported a sustained desire to defecate - i.e.  $BE_{DDV}$ ) (Minguez et al., 2004). Although there is no general consensus regarding how much time should be allowed for the balloon expulsion test (*cf.* chapter 2), a cut-off of 60 seconds in men and 90 seconds in women was used in this study, based on the results of a large study on healthy volunteers designed to answer this specific question (Dedeli et al., 2007).



**Figure 5.1:** Configuration of anorectal manometry catheter.

#### 5.2.3a.2 Evacuation proctography (EP)

The rectum was filled with a substitute of stool (i.e. a mixture of barium, oats and water in a ratio of 1:2:1) until patients reported a sustained desire to defecate (median volume used 200 mls [range 100 mls - 450 mls]). Thereafter, fluoroscopic images were acquired while

patients were asked to evacuate in relative privacy as quickly as possible while seated on a radio-lucent commode. They were given a maximum of 2½ minutes to evacuate. The completeness and time required for evacuation and the presence of structural or functional abnormalities were defined relative to normal values with the same technique in 46 healthy volunteers (*cf.* chapter 3). Criteria for abnormal findings were: impaired evacuation (expulsion of <35% of neostool and / or evacuation lasting >134 secs) (*cf.* chapter 3, table 3.3); poor pelvic floor relaxation (defined as poor anal sphincter relaxation [maximal lower anal canal width <0.5 cm] and/or a persistent puborectalis impression (Jorge et al., 1993b); or structural abnormality (rectocele >4 cm in depth and/or recto-anal intussusception occluding the rectal lumen) (*cf.* chapter 3), which clearly impeded expulsion of neostool. There is no consensus on what constitutes proctographic evidence of dyssynergia - inadequate anal canal opening, inadequate puborectalis impression and failure to open the anorectal angle on straining have all been used in isolation or in combination. Anorectal angle change has been proven unreliable in isolation for diagnosis of dyssynergia (Halligan et al., 1995a), and hence was not used in this study.

## **5.2.3b INDIRECT TESTS OF EVACUATION**

### **5.2.3b.1 Anorectal manometry (ARM)**

Anorectal manometry was performed using the same water-perfused catheter as described above in the BE test. When positioned with the "0" mark (Figure 5.1) at the anal verge, recording ports were located at 1, 2, 3, 4 and 6 cm from the verge with the balloon located between 8 and 12 cm from the verge. The recording ports located at 1, 2, 3 and 4 cm were arrayed at 90° to each other. The catheter was connected to a pneumohydraulic water perfusion pump, linked to a manometry system for data display and analysis (Solar GI; Medical Measurement Systems, Enschede, The Netherlands). Before starting the investigation, the system was zeroed and calibrated appropriately. With the patient in the left lateral position with knees and hips flexed, the lubricated catheter was then introduced into the anorectum to the described position. It was taped securely to the patient's buttock to prevent movement. After a 5 minute run-in period, the anal canal resting pressure was measured (Rao et al., 2002), the subject was then instructed to bear down, as if trying to defecate (Rao et al., 2002). This 'push' manoeuvre was performed three times at 30 second intervals (Rao et al., 2002) and a single representative trace selected as previously described (Rao et al., 2002). An abnormal test was defined as: impaired anal relaxation (<20% reduction [or an increase] from resting anal pressure) (Bharucha et al., 2006) or an insufficient increase in rectal pressure (maximal increase in intrarectal pressure of <45 mm Hg (Bharucha et al., 2006)).

Rectal sensory testing was performed by previously described methods (Gladman et al., 2003b, Zarate et al., 2008a).

## **5.2.4 ANALYSIS**

**5.2.4.1 Diagnostic yield:** The proportions of patients with abnormal results using BE tests, proctography, and ARM were determined. Further, proportions of patients meeting criteria for the constipation-relevant Rome III-defined subtypes of functional anorectal disorders



(functional defecation disorder [FDD], impaired propulsion [IP] and dyssynergic defecation [DD]) were also determined. In line with the Rome III criteria (Table 5.3), FDD was defined (during attempts to defecate) by two or more of the following criteria: (a) evidence of impaired evacuation (on either BE or EP); (b) inappropriate contraction of the pelvic floor muscles (on either ARM or EP), or less than 20% relaxation of basal resting sphincter pressure (on ARM); (c) inadequate propulsive force. Inadequate propulsion was defined as inadequate increase in rectal pressure on ARM (peak rectal pressure <45 mm Hg) with or without inappropriate contraction of the anal sphincter during attempted defecation. Rome III criteria advises a surrogate measure for IP when using proctography: poor evacuation associated with pelvic floor excursion <3 cm (Halligan et al., 1995b, Bharucha et al., 2006). This was used as proctographic criteria for diagnosis of impaired propulsion. DD was defined as inappropriate contraction of the pelvic floor (on either ARM or EP), or less than 20% relaxation of basal resting sphincter pressure with adequate propulsive force during attempted defecation. Finally, recognised significant structural abnormalities (*cf.* chapter 3) were recorded (EP only). These diagnostic criteria used in this study are detailed in table 5.4.

**5.2.4.2 Test of agreement:** Agreement among tests for the diagnosis FDD and DD were assessed by the kappa-statistic with 95% CI, where the value is negative (<0) when the agreement is less than that expected by chance; 0 when the amount of agreement is what would be expected to be observed by chance, and 1 when there is perfect agreement. For intermediate values, the following published interpretations were used (Landis and Koch, 1977):

- Below 0                      No agreement
- 0        –        0.2      Slight
- 0.21   –        0.4      Fair
- 0.41   –        0.6      Moderate
- 0.61   –        0.8      Substantial
- 0.81   –        1        Almost perfect agreement

**Table 5.3:** ROME III criteria for the diagnosis of subtypes of constipation

1. Functional Defaecation Disorders (FDD) \*

1. The patient must satisfy diagnostic criteria for functional constipation (as in table 5.2)
2. During repeated attempts to defecate must have at least two of the following:
  - a. Evidence of impaired evacuation, based on balloon expulsion test or imaging
  - b. Inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) or less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
  - c. Inadequate propulsive forces assessed by manometry or imaging

\* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

1 a. Dyssynergic Defaecation (DD)

Inappropriate contraction of the pelvic floor or less than 20% relaxation of basal resting sphincter pressure with adequate propulsive forces during attempted defecation

1 b. Inadequate Defaecatory Propulsion (IP)

Inadequate propulsive forces with or without inappropriate contraction or less than 20% relaxation of the anal sphincter during attempted defecation

**Table 5.4** Diagnostic criteria for this study (based on the Rome III criteria)

Firstly, an individual patient was considered to have evacuatory disorder if any of the 4 test results were abnormal (i.e. ARM, BE<sub>50</sub>, BE<sub>DDV</sub> or EP, either singly or in combination).

**Functional defaecation disorder (FDD)**

1. Using ARM: BOTH impaired anal relaxation (<20% sphincter relaxation) and inadequate propulsive force (intra-rectal pressure <45 mm Hg) (Bharucha et al., 2006)
2. Using EP: any 2 of:
  - a. abnormal expulsion amount (<35%) OR abnormal expulsion time (>134 secs) (cf. chapter 3)
  - b. inadequate sphincter relaxation - i.e. maximal anal canal width <.5 cm (cf. chapter 3) /persistent puborectalis impression (Jorge et al., 1993b)
  - c. abnormal expulsion amount OR time AND impaired pelvic floor movement (<3 cm) (Halligan et al., 1995b, Bharucha et al., 2006)
3. Using ARM +/- BE<sub>50</sub>: any 2 of:
  - a. impaired balloon evacuation (failed BE<sub>50</sub>)
  - b. impaired anal relaxation on ARM
  - c. inadequate propulsive force on ARM
4. Using ARM +/- EP: any one of:
  - a. FDD on ARM (as per criteria above)
  - b. FDD on EP (as per criteria above)
  - c. abnormal expulsion amount OR time (EP) AND impaired anal relaxation (ARM) OR insufficient rectal pressure increase on ARM
  - d. inadequate sphincter relaxation (EP) AND inadequate propulsive force (ARM)
  - e. impaired anal relaxation (ARM) AND abnormal expulsion amount OR time (EP) AND impaired pelvic floor movement (EP)
5. Using EP +/- BE<sub>50</sub>: any one of:
  - a. FDD on EP (as per criteria above)
  - b. impaired balloon expulsion (BE<sub>50</sub>) AND inadequate sphincter relaxation (EP)
  - c. impaired balloon expulsion (BE<sub>50</sub>) AND abnormal expulsion OR abnormal time (EP) AND impaired pelvic floor movement (EP)
6. Using ARM +/- BE +/- EP: (using the criteria above)  
FDD on: ARM, or EP, or ARM +/- BE, or ARM +/- EP, or EP +/- BE

**Impaired Propulsion (IP)**

1. Using ARM: On bearing down, maximal intrarectal pressure <45 mm Hg (Bharucha et al., 2006)
2. Using EP: Abnormal expulsion amount OR time AND pelvic floor descent <3 cm (Halligan et al., 1995b, Bharucha et al., 2006).

**Dyssynergic Defaecation (DD)**

1. Using ARM: Impaired anal relaxation AND *adequate* increase in intra-rectal pressure (i.e. ≥45 mmHg) (Bharucha et al., 2006)
2. Using EP: Impaired sphincter relaxation AND no proctographic evidence of IP (according to the criteria above) (Bharucha et al., 2006)

**Structural abnormalities**

- On EP: Significant structural abnormality (cf. chapter 3)

## **5.3 RESULTS**

### **5.3.1 PATIENT COHORT**

Of the 100 patients, 86 were women (Table 5.5). Median age was 52 years (range 23 - 81). Eighty percent or more of the patients reported each of the following symptoms during 25% or more defecations: a sense of incomplete evacuation, excessive straining, and a sense of anorectal obstruction. Other symptoms (i.e. passage of hard stool, <3 defecations per week and use of manual manoeuvres to aid evacuation) were less frequently reported. The prevalence of these symptoms was not significantly different between men and women.

Forty-one percent of patients (45% females; 14% males;  $p=0.029$ ) had a history of previous pelvic or anorectal surgery, and 40% (43% females; 21% males;  $p=0.129$ ) had a previous history of abdominal surgery (these included cholecystectomies, umbilical and incisional hernia repair, surgery for perforated peptic ulcer disease, appendicectomies and one patient with small bowel resection and anastomosis). Among women, median parity was 2 (range 0 - 5).

Colonic transit was evaluated in 81 patients (72 F). In the remainder, this test was not clinically indicated according to our departmental protocol. Overall, 33 patients (41%; 31 F) had delayed colonic transit. Rectal sensation was reduced in 17% of patients (16% females; 21% males) and normal in the remainder.

**Table 5.5:** Demographic features, symptoms and associated physiological findings

	Male	Female	Overall	<i>p</i> value
N	14	86	100	
Median age	56 (30 – 80)	51 (23 – 81)	52 (23 – 81)	0.255
Straining *	12 (86%)	74 (86%)	86 (86%)	0.98
Hard stool *	11 (79%)	52 (60%)	63 (63%)	0.073
Sense of incomplete evacuation*	11 (79%)	86 (100%)	97 (97%)	NA
Sense of anorectal obstruction*	11 (79%)	69 (80%)	80 (80%)	0.892
Need to use manual manoeuvres*	4 (29%)	49 (57%)	53 (53%)	<b>0.050</b>
<3 defecations / week	5 (36%)	35 (41%)	40 (40%)	0.73
Vaginal deliveries - median (range)	-	2 (0-5)		
Pelvic or anorectal surgery ‡	2 (14%)	39 (45%)	41 (41%)	<b>0.03</b>
Abdominal surgery	3 (21%)	37 (43%)	40 (40%)	0.129
Meets Rome III criteria for chronic constipation	14 (100%)	86 (100%)	100 (100%)	NA
Delayed colonic transit	2 (n=9)† (22%)	31 (n=72)† (43%)	33 (n=81)† (41%)	0.237
Rectal hyposensitivity	3 (21%)	14 (16%)	17 (17%)	0.641
Low anal resting pressure	3 (21%)	17 (20%)	20 (20%)	0.891
Low anal squeeze pressure	1 (7%)	27 (31%)	28 (28%)	0.631

\* on >25% of defecations

† 19 patients did not have a transit study

‡ Pelvic surgeries included hysterectomy (n=32), uterine prolapse repair (n=6), ovarian cystectomy/oophorectomy (n=5), sterilisation (n=3), fibroid removal (n=2), bladder prolapse repair (n=2), TVT (n=2), surgery for ectopic pregnancy (n=1), laparoscopic hernia repair (n=1) and TURP (n=1). NA = not applicable.

### 5.3.2 DIAGNOSTIC YIELD OF INVESTIGATIONS

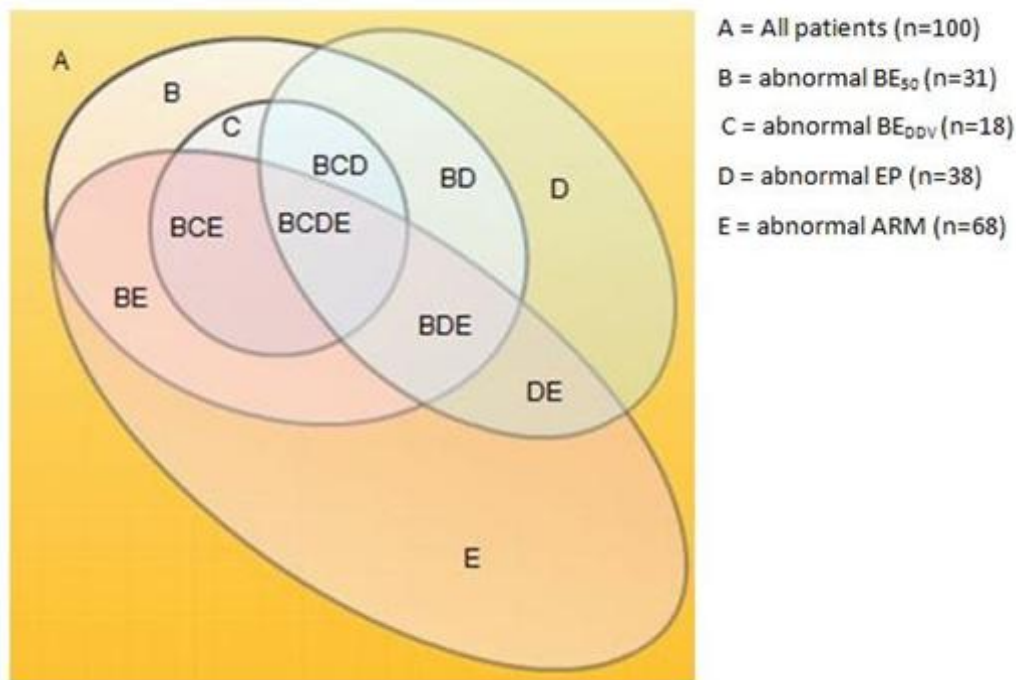
#### 5.3.2.1 Direct tests of evacuation: rectal balloon expulsion test and evacuation proctography

The prevalence of impaired evacuation on anorectal tests was as follows: BE<sub>50</sub> (31%), BE<sub>DDV</sub> (18%), and EP (38%). (Table 5.6; Figure 5.2a). Of the 38 patients with an abnormal EP, 30 had structural ('mechanical') abnormalities only, and 8 had functional abnormalities only. No patient with a significant structural abnormality had a functional abnormality. Of the 8 patients with functional abnormality, 5 met the criteria for FDD, 4 met the criteria for impaired propulsion and 4 had radiological evidence of DD. All 4 patients with impaired propulsion also satisfied the radiological criteria for FDD. 1 out of the 4 patients with dyssynergia also satisfied the criteria for FDD, the other 3 patients had poor anal sphincter relaxation, but normal evacuation parameters (hence did not satisfy the criteria for FDD). An additional 38 patients had 'borderline' structural abnormalities of uncertain clinical significance (e.g. non-obstructive intussuscepta and rectocoeles <4 cm in size) which were not deemed abnormal. Twenty four patients had a completely normal proctogram.

**Table 5.6:**Yield of investigations for evacuatory dysfunction and its subtypes

Tests	Overall Yield	Functional defecation disorder	Impaired propulsion	Dyssynergic defaecation
<i>Direct tests of evacuation</i>				
BE <sub>50</sub>	31	NA	NA	NA
BE <sub>DDV</sub>	18	NA	NA	NA
EP <sup>1</sup>	38	5	4	4
BE <sub>50</sub> ± EP	51	6	NA	NA
<i>Indirect test of evacuation</i>				
ARM	68	16	48	20
<i>Combinations of direct and indirect tests of evacuation</i>				
ARM ± BE <sub>50</sub>	80	27	X	X
ARM ± EP	80	20	X	X
ARM±BE <sub>50</sub> ±EP	86	29	X	X

<sup>1</sup> 29 of 38 patients had structural abnormalities only



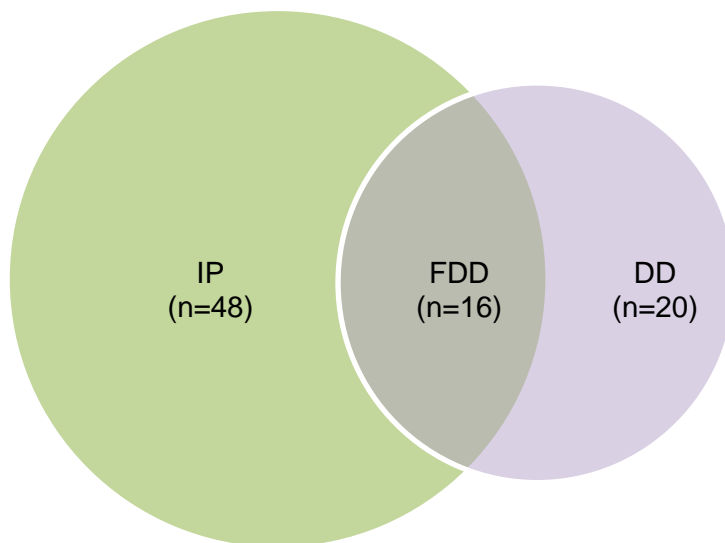
**Figure 5.2a:** Venn diagram showing overall yield of tests. The area encompassed by the outer square represents all 100 patients. The area within this square but outside zones B, C, D, and E represents 16 patients in whom all tests were normal. All patients with abnormal BE<sub>DDV</sub> also had an abnormal BE<sub>50</sub>. BCDE = all tests abnormal (n= 7), BDE (n=10), DE (n= 26), BD (n=18), BCD (n=13), BCE (n= 10), BE (n=19).

### 5.3.2.2 Indirect tests of evacuation: anorectal manometry

Of 68 patients (68%) with an abnormal manometry, 32 had isolated impaired rectal propulsion (IP), and 20 had poor anal relaxation with adequate increase in rectal pressure (DD) [Figure 5.2b, Table 5.6]. A further 16 patients had impaired rectal propulsion and poor anal relaxation. These 16 patients satisfied the Rome III criteria for diagnosis FDD and IP, but not DD. Thus, 20 patients had dyssynergic defecation and 48 had impaired rectal propulsion (16 of whom also met the criteria for diagnosis of functional defecation disorder).

Using combinations of tests (as per Rome III criteria), a FDD was diagnosed in 16% of patients with ARM alone, 20% with ARM and EP, and 27% with ARM and BE<sub>50</sub> test. When the results of *all* tests were combined, a diagnosis of FDD was found in 29% (compared to only 6%, based on 'direct' tests alone). For dyssynergia, the yield of ARM was 20%

(compared to only 4% using proctography). Similarly the yield for impaired propulsion was 48% and 4% using ARM or proctography respectively.



**Figure 5.2b:** Venn diagram with manometric yield for diagnosis of functional defaecation disorder (FDD), impaired [rectal] propulsion (IP) and dyssynergic defaecation (DD) in the 68 patients with abnormal ARM.

### 5.3.3 AGREEMENT BETWEEN TESTS

There was substantial agreement between the results of the 2 balloon expulsion tests ( $\kappa = 0.66$ ). By comparison, agreement between EP and the BE tests was only fair, i.e.  $\kappa$  was 0.27 versus  $BE_{50}$ , and 0.29 versus  $BE_{DDV}$ . Agreement between ARM and EP was slight ( $\kappa = 0.01$ ), and there was no overall agreement between ARM and either of the BE tests ( $\kappa = -0.07$  in both cases). Poor level of agreements between ARM and EP were again observed for diagnosis of dyssynergia and impaired propulsion [ $\kappa = 0.02$  (95% CI = -0.13 - 0.16) and 0.04 (95% CI = -0.04 - 0.13) respectively]. Agreement between tests for diagnosis of evacuatory dysfunction and FDD are shown in Tables 5.7 and 5.8 respectively. Overall, the agreement between test results ranged from slight to fair.



**Table 5.7** Agreement between investigations for the diagnosis of evacuatory dysfunction

	<i>Kappa</i> statistics (with 95% confidence intervals)		
	BE <sub>50</sub>	BE <sub>DDV</sub>	EP
<i>Direct tests of evacuation</i>			
BE <sub>50</sub>	xx	0.66 (0.49 - 0.82)	0.27 (0.08 - 0.47)
BE <sub>DDV</sub>	0.66 (0.49 - 0.82)	xx	0.29 (0.11 - 0.47)
<i>Indirect test of evacuation</i>			
ARM	-0.07 (-0.23 - 0.08)	-0.07 (-0.20 - 0.05)	0.01 (-0.16 - 0.17)

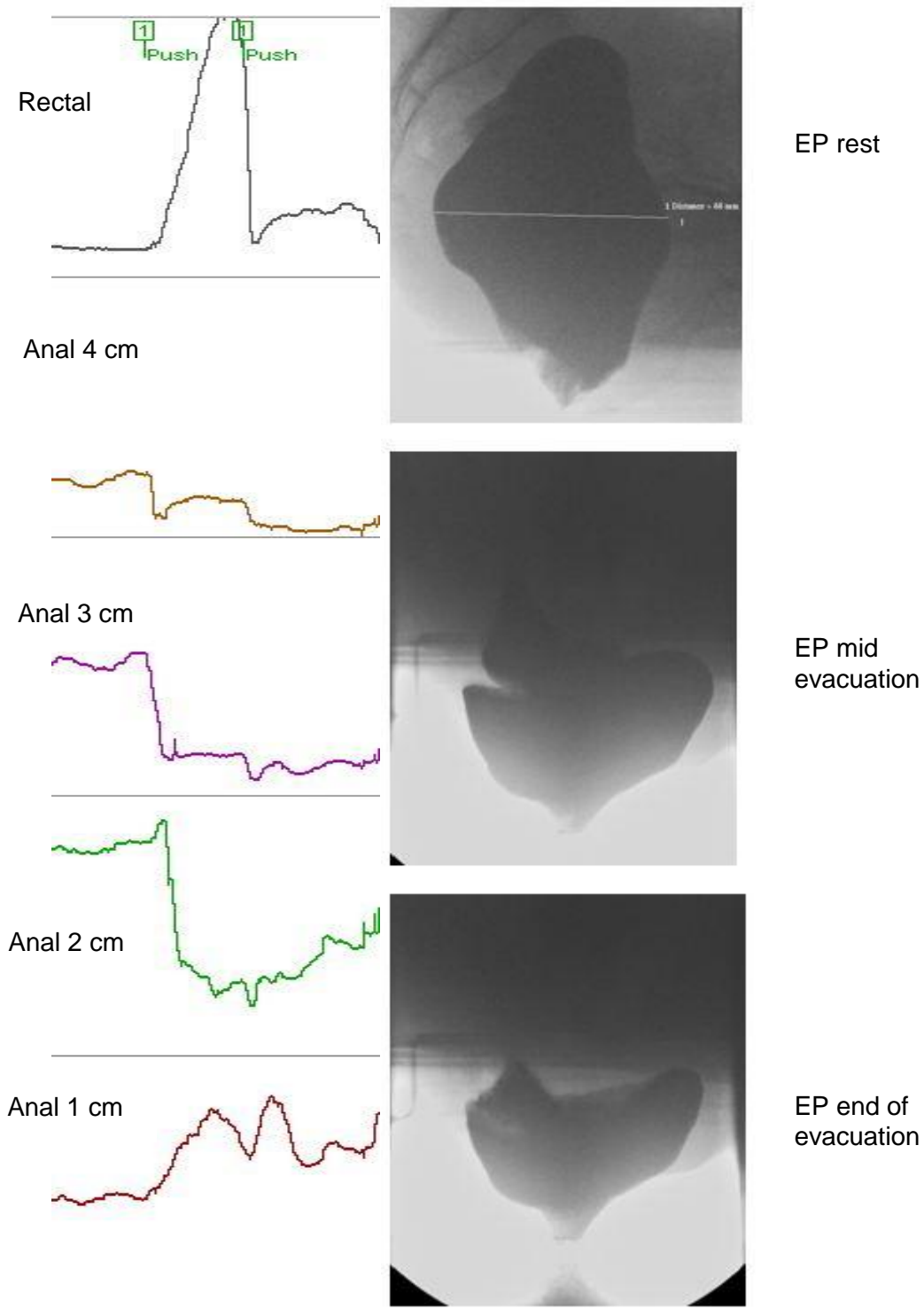
#### 5.4 DISCUSSION

In patients with chronic constipation unresponsive to laxatives, many recommend ARM and BE as initial tests for identifying defecatory disorders (Lembo and Camilleri, 2003, Bharucha et al., 2006, Whitehead and Bharucha, 2010, Bassotti and Villanacci, 2011, Ratuapli et al., 2012, Bharucha et al., 2013b), to be followed by EP if the results of these tests are discrepant or differ from the clinical impression (Bharucha et al., 2006, Whitehead and Bharucha, 2010, Bassotti and Villanacci, 2011, Bharucha et al., 2013b).

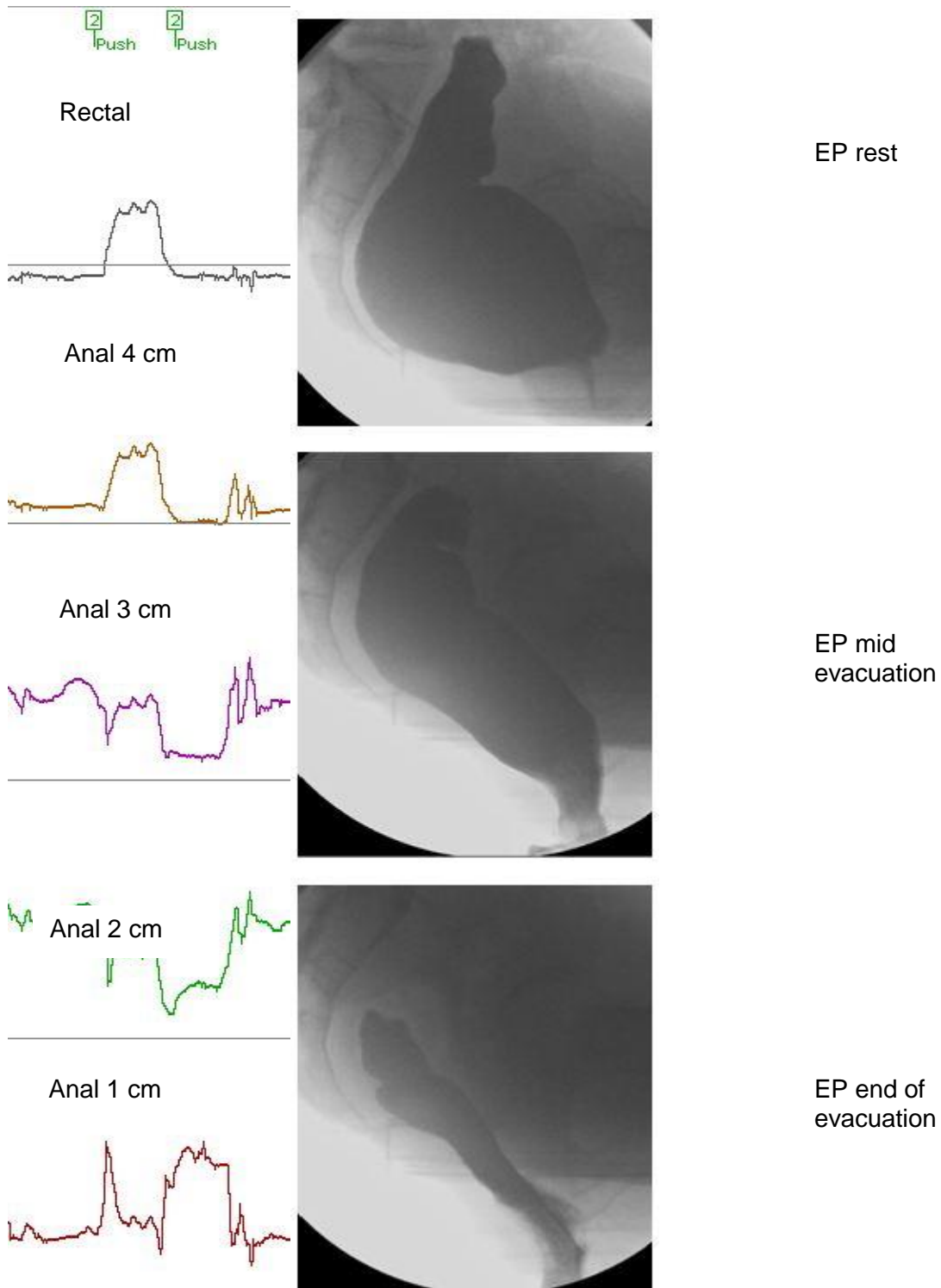
In this consecutive series of 100 patients with functional constipation, all 4 anorectal tests (i.e. ARM, BE test(s) and EP) were performed in all patients. The BE<sub>50</sub> test, EP and ARM documented features of abnormal evacuation in 31%, 38%, and 68% of patients respectively. Agreement between the results of 'direct' tests of evacuation was fair (i.e. between EP vs. BE) or substantial (i.e. between BE<sub>50</sub> vs. BE<sub>DDV</sub>). In contrast, agreement between ARM, which provides an indirect assessment of evacuation, and direct tests was only slight (i.e. versus EP) or non-existent (i.e. versus BE). When a combination of these tests was used for the diagnosis of Rome III-defined functional anorectal disorders, the agreements between various tests were only slight or fair. These findings confirm that diagnosis is strongly influenced by the type of diagnostic test utilized for investigation. Figures 5.3 - 5.8 highlight the heterogeneity of results seen with these investigations.

**Table 5.8** Agreement between investigations for the diagnosis of a functional defecation disorder

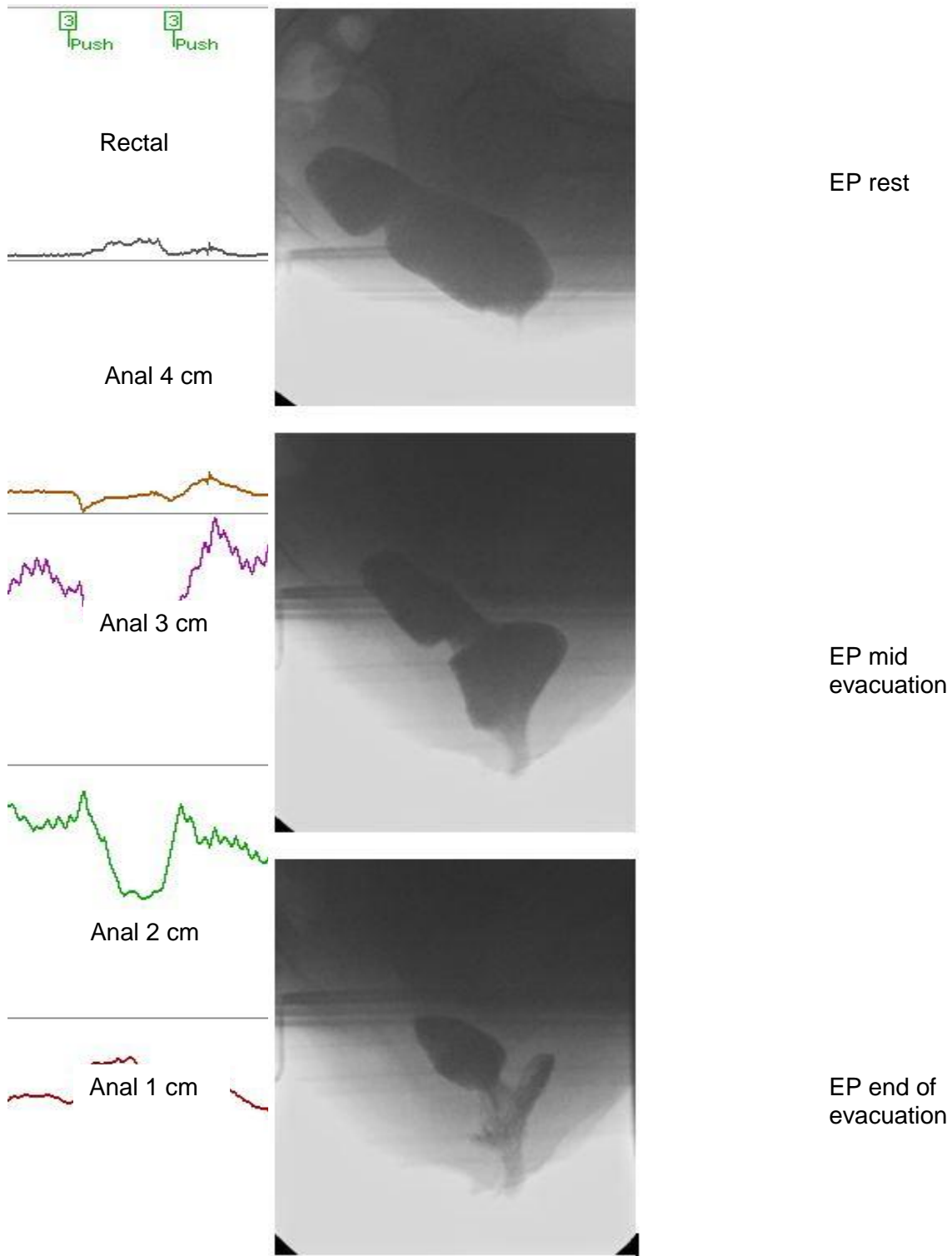
	<i>Kappa statistics (with 95% confidence intervals)</i>				
	EP	BE <sub>50</sub> ± EP	ARM ± BE <sub>50</sub>	ARM ± EP	ARM±BE <sub>50</sub> ± EP
<i>Direct tests of evacuation</i>					
EP	xx	0.9 (0.72 - 1)	0.18 (0 - 0.36)	0.35 (0.12 - 0.58)	0.23 (0.06 - 0.40)
BE <sub>50</sub> ± EP	0.9 (0.72 - 1)	xx	0.23 (0.04 - 0.41)	0.4 (0.18 - 0.64)	0.27 (0.09 - 0.45)
<i>Indirect test of evacuation</i>					
ARM	0.23 (-0.02 - 0.48)	0.3 (0.04 - 0.56)	0.68 (0.51 - 0.85)	0.86 (0.74 - 0.99)	0.64 (0.46 - 0.81)
<i>Combinations of direct and indirect tests of evacuation</i>					
ARM ± BE <sub>50</sub>	0.18 (0 - 0.36)	0.23 (0.04 - 0.41)	xx	0.7 (0.53 - 0.86)	0.95 (0.88 - 1)
ARM ± EP	0.35 (0.12 - 0.58)	0.4 (0.18 - 0.64)	0.7 (0.53 - 0.86)	xx	0.76 (0.61 - 0.90)
ARM±BE <sub>50</sub> ±EP	0.23 (0.06 - 0.40)	0.27 (0.09 - 0.45)	0.95 (0.88 - 1)	0.76 (0.61 - 0.90)	Xx



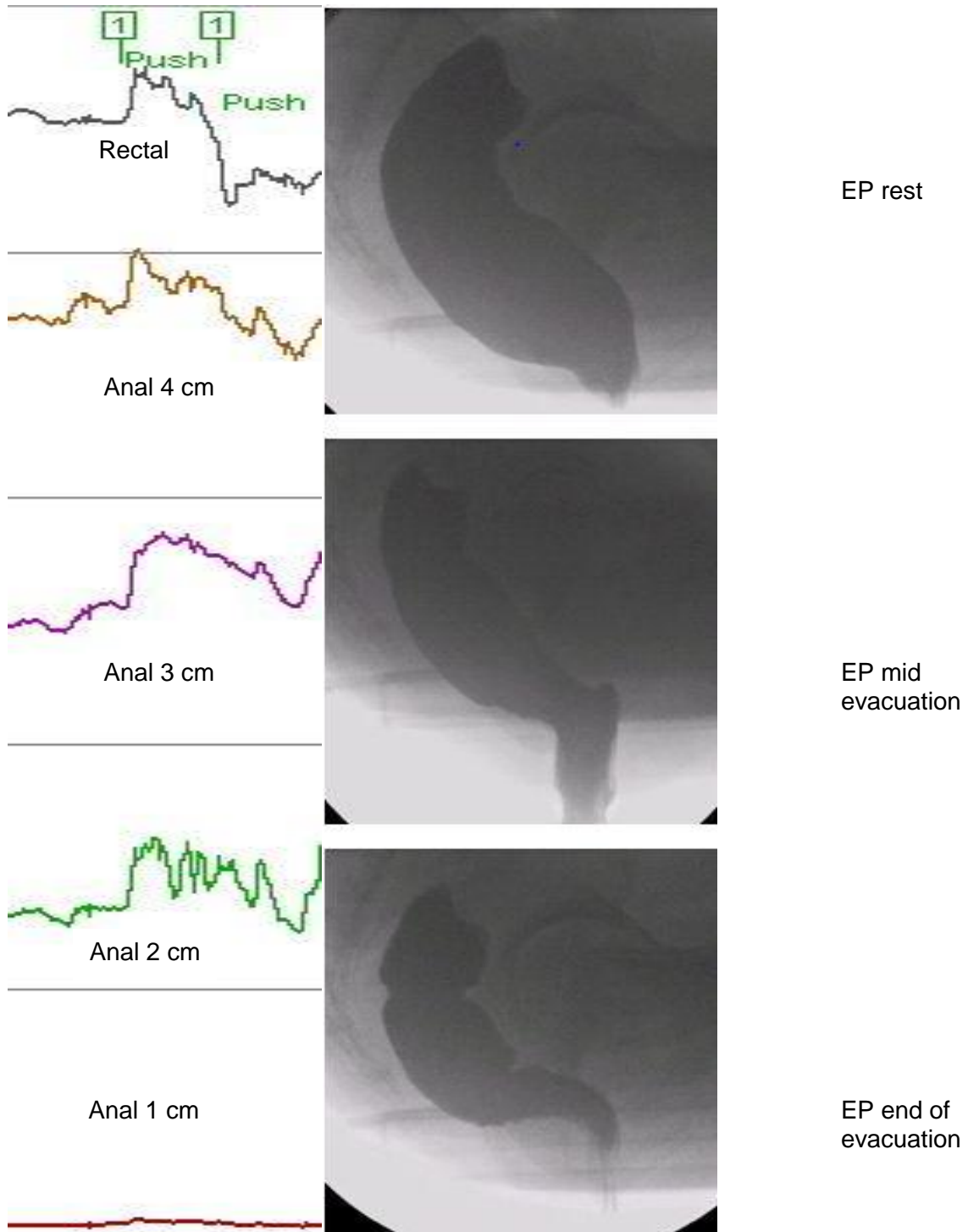
**Figure 5.3:** Shows normal manometry tracing on straining, but abnormal proctography (large rectal diameter, intussusception and a large rectocele).  $BE_{50}$  and  $BE_{DV}$  were both abnormal.



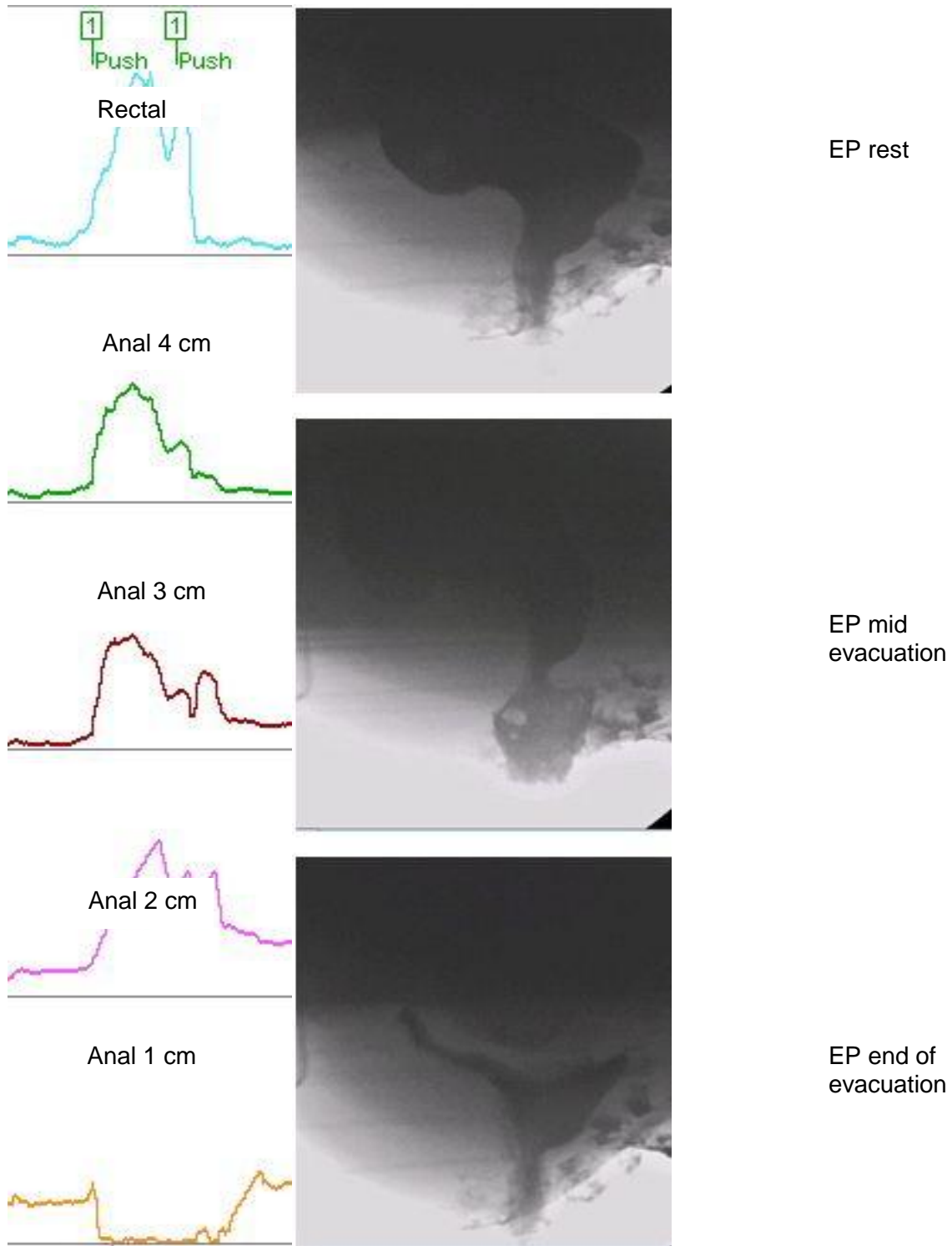
**Figure 5.4:** Shows impaired propulsion on straining in manometry (maximum rectal pressure = 24 mmHg). Proctography shows a large rectum with prolonged evacuation (>134 secs). Both balloon expulsion tests were normal  $BE_{50} = 15$  secs and  $BE_{DDV} = 25$  secs.



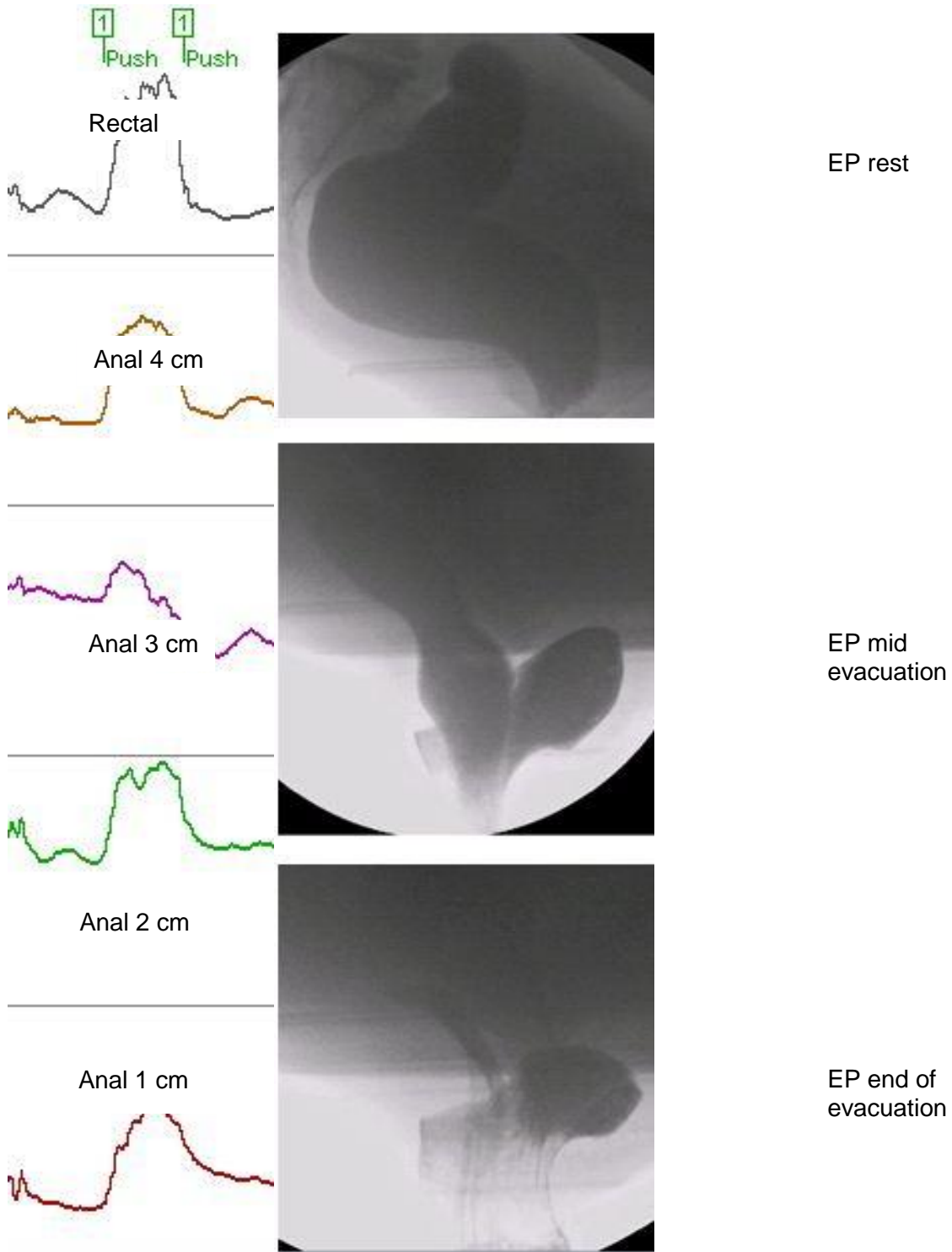
**Figure 5.5:** Shows impaired rectal propulsion on straining during manometry (intra-rectal pressure = 7 mmHg). Proctography shows an obstructing recto-anal intussusception with a small rectocoele. Both balloon expulsion tests were normal  $BE_{50} = 24$  secs and  $BE_{DDV} = 28$  secs



**Figure 5.6:** Shows a dyssynergic pattern during manometry and proctography. Both balloon expulsion tests were normal.  $BE_{50}=40$  secs;  $BE_{DDV}=34$  secs



**Figure 5.7:** Shows dyssynergic pattern on manometry and proctography (which also shows a small rectocele). Both balloon expulsion tests were normal ( $BE_{50} = 5$  secs;  $BE_{DDV} = 10$  secs)



**Figure 5.8:** Shows a dyssynergic pattern in manometry. Proctography shows a large rectocele with an external prolapse at the end of evacuation. BE<sub>50</sub> was abnormal, but BE<sub>DDV</sub> was normal (17 secs).



A systematic review of studies that compared diagnostic tests in constipated patients observed features of an evacuation disorder in a median of 51% (range 20-75%) patients with ARM, 53% (range 23-67%) with the BE test, but only 27% (range 13-52%) with EP (Rao et al., 2005). Similar results were also seen in our systematic review (*cf.* chapter 2). However, few studies (table 5.9) have evaluated the agreement between these tests (from which kappa values can be calculated) and none compared all 3 modalities within the confines of Rome III criteria. In one study, only 33 of 58 patients (57%) unable to expel a rectal balloon had dyssynergia on proctography (Bordeianou et al., 2011). Conversely, only 33 of 63 patients (52%) with dyssynergia on proctography had an abnormal balloon expulsion test (Bordeianou et al., 2011). Based on these data, a calculated kappa statistic suggests there is only slight agreement between these two tests ( $k = 0.11$  and percentage agreement = 55%), which is lower than the “fair” agreement in the current study. Two other studies from the same centre reported agreement between ARM and balloon expulsion (Rao et al., 1998c, Rao et al., 2004a). In one of these studies, ARM and the BE test were abnormal in 18 and 20 of 35 patients respectively; 16 patients (89%) with an abnormal ARM also failed to expel a balloon (Rao et al., 1998c). From these data, the calculated kappa statistic ( $k = 0.66$  and percentage agreement = 83%) demonstrates substantial agreement. However, this study predated the Rome III criteria for diagnosis of impaired propulsion, and although intra-rectal pressure was measured, the test was not considered to be abnormal when inadequate intra-rectal pressure was the only finding. In the second study, 70 of 100 patients had an abnormal ARM and 43 patients had an abnormal BE test; all patients with a normal ARM had a normal BE test (Rao et al., 2004a). A kappa calculation from these data shows moderate agreement between the tests ( $k = 0.49$  and percentage agreement = 73%). This study also predated Rome III classification, but a secondary analysis of the abnormal manometry studies, and reclassification according to Rome III criteria can be performed from the data presented. Of the 70 patients with an abnormal ARM, 24 had impaired propulsion and 46 had dyssynergic defaecation. Among the 24 patients with impaired propulsion, 14 (58%) had an abnormal balloon test, and among 46 dyssynergic patients, 29 (63%) had an

abnormal balloon test. A more recent study (Chiarioni et al., 2014) reported high levels of agreement between the BE test and manometry for the diagnosis of DD, particularly when expulsion times of up to 2 minutes were considered normal. Again, however, this study only used inadequate anal relaxation as a criteria for diagnosing DD on ARM, and did not take into account inadequate rectal propulsion; in fact, most of the discordance between the BE test and ARM in this study was due to impaired propulsion (Chiarioni et al., 2014).

**Table 5.9** Agreement between investigations for diagnosing dyssynergia (Kappa values and % agreements have been calculated from the data presented in these studies).

Study	Investigations	Kappa value	% agreement
(Bordeianou et al., 2011)	BE vs. EP	0.11	55%
(Rao et al., 1998c)	BE vs. ARM	0.66	83%
(Rao et al., 2004a)	BE vs. ARM	0.49	73%

Two studies performing proctography in patients with prior abnormal ARM yielded an abnormal proctographic test in approximately 37% (Wald et al., 1990a, Rao et al., 2004a). Others have performed ARM in patients with prior abnormal proctograms with a higher yield of approximately 60% (range: 43 – 67%) (Vidlock et al., 2013). Since none of these studies performed both tests in all patients, agreement between tests cannot be assessed.

There are several strengths in the current study. One hundred patients were studied representing a reasonable sample. Symptoms and anorectal functions were evaluated with validated and standardized techniques and interpreted by established criteria in all patients. However, the investigator could not be blinded to the results of preceding test(s) and the tests were not performed in a randomized order. Hence, an order effect or performance bias cannot be excluded. Nevertheless, it can be argued that performing EP as the last test is justified, since patients often do not empty their rectum completely, and residual barium may conceivably influence the outcome of subsequent tests.

#### **5.4.1 Clinical implications**

In patients with functional constipation, correctly identifying a functional anorectal disorder and its subtypes (FDD and DD) is important because these subgroups are best managed by pelvic floor retraining with biofeedback therapy rather than laxatives (Chiarioni et al., 2006, Heymen et al., 2007, Rao et al., 2007). However, biofeedback therapy is not widely available; hence accurate diagnosis is essential. Similarly, accurate diagnosis of clinically-relevant obstructive anatomical phenomena can guide appropriate surgical corrective intervention (Nyam et al., 1997, Gouvas et al., 2014, Van Geluwe et al., 2014).

Prior recommendations suggest that an abnormal ARM and BE tests or an abnormal ARM alone, suffice to diagnose FDD and its subtypes (Bharucha et al., 2006, Longstreth et al., 2006, Rao and Meduri, 2011). This study however suggests that ARM has a disproportionately high yield of identifying FDD and its subtypes, and agrees poorly with other tests. Due to poor agreement between tests, FDD and its subtypes should not be diagnosed based on the results of any single investigation, but should be done based on a combination of tests. Nevertheless ARM can identify the precise functional deficit, i.e. low rectal pressure, high anal pressure, or both (Bharucha et al., 2005). While proctography has been criticized for lack of standardization and inter-observer reproducibility, these limitations are operator-dependent and can be minimized (51). However, the substantive lack of agreement between all investigations suggests that currently available tests or current classification systems (or both) have deficiencies. With the Rome IV process now underway, it is hoped that these issues will be revisited.

In conclusion, there is considerable disagreement between the results of various tests used to diagnose FDD, DD and IP in constipated patients. Perhaps a diagnosis of FDD and its subtypes should be based on abnormal findings on 2 or more of the following tests, i.e. abnormal ARM, BE, EP.

*Personal communication [C Knowles: Rome functional anorectal disorders committee]:  
Rome IV has revisited the diagnostic criteria (Dec 2014) and 2 abnormal tests will be  
required in the future guidance.*

**Statement of contribution for chapter 6:** I have written the following chapter myself.

# 6

## *Conclusion*

Defecation is a complex physiological process that requires coordination between the colon, rectum, anal canal and the pelvic floor musculature and which is heavily influenced by central, spinal, peripheral and enteric neural activities. It is also influenced by several other factors like the posture assumed during defecation, diet, age and gender (*cf.* chapter 1a). Physiology of defecation can be divided into 4 temporally distinct phases: the basal phase (characterised mostly by colonic motor activity), the pre-expulsive phase (characterised by a series of events that ultimately result in a desire to defecate), the expulsive phase (during which evacuation occurs) and the termination phase (during which the changes that occurred in the evacuatory phase are reversed to bring the anorectal unit back into its normal state i.e. the basal phase) (*cf.* chapter 1a). There is a significant amount of functional compensation between the different organs involved in evacuation whereby a disorder in an organ can be masked, to a certain extent, by compensation in the function of another (Azpiroz et al., 2002). Intuitively, symptoms of constipation can develop when the degree of disorder in any of the organ exceeds the capability of the anorectal unit to compensate for it.

In epidemiological studies the prevalence of constipation varies between 2% to 35% (Johanson et al., 1989, Frexinos et al., 1998, Stewart et al., 1999). Chronic constipation is a significant economic burden for healthcare systems. A recent systematic review found that in the United States the estimated annual cost per patient year varies between US\$1,912 - \$7,522 depending on whether patients were treated in the community or as inpatients (Nellesen et al., 2013). Aetiopathogenesis of constipation depends on the organ involved, and many patients have two or more pathologies simultaneously (Ragg et al., 2011). Common causes of chronic idiopathic constipation include colonic hypomotility (Scott and Gladman, 2008), rectal sensory disturbance (hyposensation) (Gladman et al., 2009), rectal or

colonic structural abnormalities (large rectoceles, obstructing intussusceptions) (Mellgren et al., 1994, D'Hoore and Penninckx, 2003, Faccioli et al., 2010) and dyssynergic defecation (Rao et al., 2004c). A plethora of histochemical abnormalities, some of debateable significance, have also been described in the enteric nervous system and the neuroendocrine system of constipated patients (El-Salhy, 2003).

There is no universally agreed definition of constipation but several diagnostic criteria have been proposed (ACG, 2005, Bharucha et al., 2006). The Rome III criteria (Bharucha et al., 2006) is probably one of the most widely used diagnostic criteria for chronic constipation. Based on these criteria, functional constipation is defined on symptomatic criteria alone, but subtypes of functional constipation are diagnosed based on a combination of symptoms and specialist investigations of anorectal function. Diagnosis of the subtypes of constipation and hence subsequent treatment heavily depend on these investigations.

The aim of this project was to further evaluate the investigations most commonly used for diagnosis of the subtypes of chronic constipation as set out in the Rome III criteria viz. functional defecation disorders, dyssynergic defecation and impaired rectal propulsion. The studies performed as a part of this project included:

1. A systematic review of anorectal manometry (ARM), balloon expulsion test (BE) and evacuation proctography (EP) for constipation
2. Appraisal of the normal variability of evacuation proctography
3. A retrospective review of Rome III symptoms as predictors of proctographic findings in 500 constipated patients, and
4. A prospective comparison of yield and agreements between anorectal manometry, two balloon expulsion tests and evacuation proctography in 100 constipated patients.

A systematic review of all studies where ARM, BE or EP were performed in constipated patients between 1975 and 2014 showed significant differences in study methodology and data interpretation, which precluded a meta-analysis. The rate of dyssynergic defecation was significantly higher with ARM (range 22% -100%) than with EP (range 5.5% - 52%). The rate of abnormal BE, which has been recommended as a screening test for dyssynergia (Minguez et al., 2004), varied between 17% - 79%. Among the common tests of evacuation, EP is the only investigation that provides information regarding structural abnormalities. The systematic review showed that structural abnormalities were relatively common and were present in approximately 33% - 87% of all constipated patients. Rectocoeles and intussusceptions were the commonest structural abnormality.

Structural abnormalities seen during proctography are often present, albeit to a lesser degree, in healthy individuals (Goei et al., 1989, Freimanis et al., 1991b, Ikenberry et al., 1996), which can confound the interpretation of abnormal findings. I assessed the proctographic findings in 46 healthy adults (28 females) to ascertain the range of normal variability of so called 'structural abnormalities' (*cf.* chapter 3). Based on our findings I determined: (1) expulsion of <35% neostool in >134 seconds can be considered impaired evacuation; (2) failure to open the anorectal angle during defecation is very uncommon in health; (3) a rectal diameter >8.2 cm in men and >6.9 cm in women is indicative of megarectum; (4) rectocoeles >4.0 cm in antero-posterior depth should be considered abnormal; smaller rectocoeles, irrespective of the degree of 'trapping' are almost omnipresent in females; (5) the presence of a rectal intussusception impinging upon and occluding the anal canal, or involving an isolated anterior rectal wall prolapse only, is an abnormal finding (*cf.* chapter 3).

The retrospective study of 500 constipated patients, all of whom fulfilled Rome III criteria (Bharucha et al., 2006) for functional constipation, assessed correlation between common symptoms of constipation and proctographic findings. A sense of incomplete evacuation and



straining during evacuation were the commonest symptoms and were reported by approximately 94% and 91% of patients respectively. Among symptoms used in Rome III criteria, infrequent bowel movement was the least frequent symptom, reported by approximately 38% patients. None of the symptoms had an acceptable predictive capacity for a particular proctographic abnormality to be of clinical value. Functional defecation disorder was significantly more common in males while significant structural abnormalities were more common in females. Interestingly, such structural abnormalities were approximately 3 times as common as functional abnormalities. The commonest 'significant' proctographic abnormalities were rectocoeles (>4.0 cm) (23.8%), obstructing intussuscepta (17%) and dyssynergic defecation (14%). There was very significant overlap between abnormalities i.e. many patients had more than 1 co-existent abnormality.

The Rome III criteria use symptoms to diagnose functional constipation, but use investigations to diagnose subtypes of functional constipation. Although specific diagnostic criteria are provided in Rome III, the selection of investigative modality is left to the clinician or researcher. This is important particularly because there is variation in preference for investigation based on speciality and geographical location - a recent meta-analysis for dyssynergia found that most anorectal manometry was requested by gastroenterologists, particularly in the US, whereas most evacuation proctograms were requested from the surgical departments, particularly in Europe (Vidlock et al., 2013). It would however seem desirable that management should remain uniform irrespective of which investigation is employed i.e. the diagnosis should be the same. I prospectively studied 100 constipated patients, all meeting Rome III criteria and performed ARM, BE and EP in all patients. I followed the Rome III criteria strictly for diagnosis of functional defecation disorders, dyssynergia and impaired rectal propulsion, and assessed the yield of the investigation and agreement between them. I found that manometry was the most frequently abnormal test (68%) followed by EP (38%). There was very poor agreement between the investigations even when the Rome III criterion was followed strictly.

In summary, I found that there was significant variation in diagnostic algorithms, test methodology, and data interpretation which was further compounded by a range of findings that are often present in asymptomatic individuals. Large well designed studies aimed at standardising the common investigations are urgently required for the sake of methodological uniformity. There is also a complete lack of an accepted gold standard investigation. Further study needs to be undertaken to identify a gold standard investigation but this will only be achieved once all other investigations are fully standardised and a consensus is reached regarding what should be considered normal or abnormal. A revision of the diagnostic criteria is also needed - with the Rome III criteria the final diagnosis is heavily influenced by the choice of investigations.

# Appendix

## APPENDIX 1 Questionnaire used during interview (cf. chapters 3, 4 and 5)

### SECTION 1

1. Do you suffer with constipation?  Never  Yes

If Yes:

How long have you suffered with it?

- Less than 12 months
- 12 months to 4 years
- 5 to 9 years
- 10 to 19 years
- 20 years or more (or all of your life)

**How much does constipation bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

2. How often do you open your bowels?

- more than 5 times each day
- approx. 3-5 times each day
- 1-2 times every 1-2 days
- about 2 times each week
- about once each week
- about once every 10 days
- less than once every 14 days

**How much does this bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

- 3a. What is the usual consistency of your stools?

- Watery, no solid pieces
- Mushy, fluffy pieces with ragged edges
- Soft blobs, with clear edges (passed easily)
- Sausage-like, smooth surface (soft)
- Sausage-like, but with cracks on the surface
- Lumpy (may be sausage-shaped)
- Hard lumps, like nuts / pellets (hard to pass)
- Variable

**3b. IF your stools are hard and / or “pellet-like”, how often does this occur?**

- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does the hardness of your stools bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**4. On average, how long does it take to empty your bowels?**

- less than 5 minutes
- 5 to 9 minutes
- 10 to 19 minutes
- 20 to 29 minutes
- more than 30 minutes

**How much does this bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**5. Do you take laxative medication by mouth (not enemas)?**

No  Yes

If Yes, how often is it effective?

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**6. Do you require any of the following assistance to pass motions? (You may tick more than one box)**

- I use enemas / suppositories
- I put my fingers in my vagina
- I put my fingers in my back passage
- Other, please describe \_\_\_\_\_

**How often do you require such assistance to pass motions?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does this bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**7. How often do you need to strain when emptying your bowels?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does straining bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**8. How often when you try, are you unable to pass ANY motions?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- I always use my fingers to empty my bowels

**How much does this bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**9. How often do you feel that you have not completely emptied your bowels following a bowel movement?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does this feeling bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**10. How often do you sense a 'blockage' that prevents you, or makes it difficult for you to open your bowels easily?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does this sensation bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**11. How often is passing motions painful?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**Where do you feel this pain?**

- Abdomen/tummy
- Back passage
- Vagina
- Other, please describe \_\_\_\_\_

**How much does this pain on passing motions bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**12. Do you suffer with abdominal/tummy pain?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does abdominal pain bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**13. How often do you suffer with abdominal bloating that leads to nausea or vomiting?**

- Never
- Rarely (less than a quarter of the time)
- Occasionally (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**How much does the bloating bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**14. Do you pass blood from your back passage?**

- No  Yes

**15. Do you pass slime/mucus from your back passage?**

- No  Yes

**16. Do you associate the need to empty your bowels with any of the following?  
(you may tick more than one box if applicable)**

- A feeling/pressure in my back passage/rectum
- Cramping/pain in my abdomen/tummy
- Abdominal/tummy bloating
- None of the above, I go because I believe I should/out of routine
- Other, please describe\_\_\_\_\_

**17. Do you remember having any problems with your bowels, or going to the toilet  
as a child?                       No                       Yes**

If Yes, give details below

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**SECTION 2**

**1. How often are you incontinent to solid/formed stool?**

- Never ->**GO TO QUESTION 2**
- Less than once a month
- Less than once a week but more than once a month
- Less than once a day but more than once a week
- Once per day or more

**How long have you suffered with it?**

- Less than 12 months
- 1 to 4 years
- 5 to 9 years
- 10 to 19 years
- 20 years or more (or all of your life)

How much do you lose?

- smear (pea-size)
- equivalent to half an egg cup full
- whole motion

**Do you leak (you may tick more than one box):**

- without being aware of it at first?
- when you have great urgency and cannot get to the toilet in time to open your bowels?
- when you cough, sneeze or run?
- following a bowel movement?

**How much does this incontinence bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely



2. How often are you incontinent to liquid/loose stool/slime?

- Never ->**GO TO QUESTION 3**
- Less than once a month
- Less than once a week but more than once a month
- Less than once a day but more than once a week
- Once per day or more

**How long have you suffered with it?**

- Less than 12 months
- 1 to 4 years
- 5 to 9 years
- 10 to 19 years
- 20 years or more (or all of your life)

How much do you lose?

- smear (pea-size)
- equivalent to half an egg cup full
- whole motion

**Do you leak liquid/loose stool/slime (you may tick more than one box):**

- without being aware of it at first?
- when you have great urgency and cannot get to the toilet in time to open your bowels?
- when you cough, sneeze or run?
- following a bowel movement?

**How much does this incontinence bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**3. How often are you incontinent to wind?**

- Never ->**GO TO QUESTION 4**
- Less than once a month
- Less than once a week but more than once a month
- Less than once a day but more than once a week
- Once per day or more

**How long have you suffered with it?**

- Less than 12 months
- 1 to 4 years
- 5 to 9 years
- 10 to 19 years
- 20 years or more (or all of your life)

**How much does this incontinence bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**4. How often does your incontinence prevent you from doing everyday things (e.g. leaving the house, dressing, shopping, cleaning etc)?**

- Not Applicable - I do not suffer with incontinence
- Never
- Less than once a month
- Less than once a week but more than once a month
- Less than once a day but more than once a week
- Once per day or more

**5. Do you wear pads or anal plugs because of your incontinence?**

- Not Applicable - I do not suffer with incontinence
- No
- Yes

**How much does having to use these bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**6. Do you take Imodium, codeine or any other constipating medications on a daily basis?  No  Yes**

**How much does having to use these bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

7. **Can you “hold on” for 15 minutes when you feel the need to open your bowels?**  
 No  Yes

If NOT, how long can you “hold on” for \_\_\_\_\_

**How much does not being able to hold on bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

8. **Are you ever incontinent of faeces because you mistake it for wind?**  
 No  Yes

**How much does this bother you?**

Not at all 0---1---2---3---4---5---6---7---8---9---10 severely

**SECTION 3**

1. **Do you usually have a feeling of ‘bulging’ or something coming down (a ‘lump’) from the back passage?**     No     Yes

**If NO go to Section 4**

**How much does this bother you?**

Not at all    0---1---2---3---4---5---6---7---8---9---10    severely

2. **Can you see it?**     No     Yes

3. **When does it happen?**

- unpredictable
- when I strain excessively
- following a bowel motion
- during exercise
- continuously

4. **To make the ‘bulge’ / ‘lump’ go back, what do you have to do?**

- Nothing, it goes back by itself
- Push it back with my finger
- I can’t push it back myself
- Other, please describe \_\_\_\_\_

**How much does this bother you?**

Not at all    0---1---2---3---4---5---6---7---8---9---10    severely

5. **Does mucus or blood ever come from the ‘bulge’ / ‘lump’?**  
 No     Yes

**SECTION 4**

**1. Do you suffer with any of the following?**

- |                                    |                             |                              |
|------------------------------------|-----------------------------|------------------------------|
| Diabetes                           | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| Irritable Bowel Syndrome (IBS)     | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| Crohns / Ulcerative Colitis        | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| Lower back pain/ injury            | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| Neurological conditions e.g. M.S.  | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| Depression, anxiety, panic attacks | <input type="checkbox"/> No | <input type="checkbox"/> Yes |
| or other problems with your nerves | <input type="checkbox"/> No | <input type="checkbox"/> Yes |

**If Yes to any of the above please give details below**

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**2. Do you suffer with any other medical conditions?**

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**3. Have you ever had an operation on your back passage e.g. piles, fistula, tears (fissures) etc?**  No  Yes

If Yes, give details below

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**4. Have you ever had an operation on your bowel?**

No  Yes

If Yes, give details below

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**5. Please give details of any other operations that you have had (including removal of tonsils/appendix etc.) Women**

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**6. What medications (including laxatives) do you take regularly?**

Drug name	Duration of use	Dose/amount	Times per day	Regular or when needed

**7. Do any medical conditions run in the family?**

No  Yes

If Yes, give details below

\_\_\_\_\_

\_\_\_\_\_

**TO BE COMPLETED BY WOMEN ONLY**

**1. Have you ever had a hysterectomy or other operation on your womb or vagina?**

No  Yes

If Yes, give details below

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**2. Childbirth History**

Number of Deliveries: \_\_\_\_\_

For each delivery please **tick** appropriate box:

Delivery Number	Year	Normal Vaginal Delivery	Vaginal Delivery with Tear/Episiotomy	Suction	Forceps	Caesarean Section
1						
2						
3						
4						
5						
6						
7						
8						

**ADDITIONAL QUESTIONS**

**SECTION A**

**1. During the last 3 months have you suffered with regular abdominal / tummy pain or discomfort?**

(Please do NOT count cramps or pain with menstrual periods)

- Never → **GO TO SECTION B**  
 Yes → **Please answer all other questions in this section**

**2a. On average, how many days in each month do you suffer with it?**

- Rarely: 1 or 2 days  
 Sometimes: 3 to 10 days  
 Usually: more than 10 days, but not every day  
 Always: every day

**2b. Does this pain / discomfort *improve* after opening your bowels?**

- No  Yes

**2c. Is the *start* of the pain / discomfort usually associated with a change in the number of times that you open your bowels (less or more visits to the lavatory than usual)?**

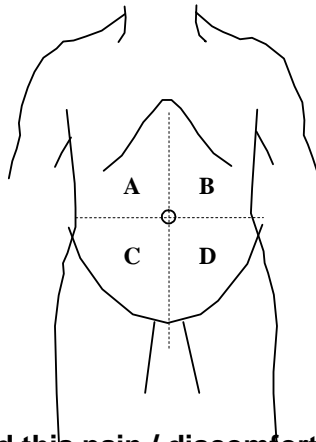
- No  Yes

**2d. Is the *start* of the pain / discomfort usually associated with a change in the consistency / appearance of your stools / motions compared to how they normally are?**

- No  Yes

3. **Where in your tummy / abdomen is the pain / discomfort?**

Please shade the area (A – D) of this drawing where you usually feel it?  
(You may shade more than one area)



4. **When in your life did this pain / discomfort first begin?**  
(as close as you can remember)

- Less than 6 months ago
- More than 6 months ago, but less than 12 months ago
- 12 months to 4 years ago
- 5 to 9 years ago
- 10 to 19 years ago
- 20 years ago or more (or all of your life)

5. **How *bad* is the pain / discomfort usually?**

- MILD: can be ignored if you don't think about it
- MODERATE: cannot be ignored, but does not affect your lifestyle
- SEVERE: affects your lifestyle
- VERY SEVERE: markedly affects your lifestyle

**How much does this pain / discomfort bother you?**








*not at all* 0---1---2---3---4---5---6---7---8---9---10 *severely*



**SECTION B**

By comparing your stool consistency to the chart below:

**PLEASE ANSWER EACH QUESTION a – c**

<p><i>Type 1</i></p> 	<p>Separate hard lumps, like nuts (hard to pass)</p>
<p><i>Type 2</i></p> 	<p>Sausage-shaped but lumpy</p>
<p><i>Type 3</i></p> 	<p>Like a sausage but with cracks on its surface</p>
<p><i>Type 4</i></p> 	<p>Like a sausage or snake, smooth and soft</p>
<p><i>Type 5</i></p> 	<p>Soft blobs with clear-cut edges (passed easily)</p>
<p><i>Type 6</i></p> 	<p>Fluffy pieces with ragged edges, a mushy stool</p>
<p><i>Type 7</i></p> 	<p>Watery, no solid pieces ENTIRELY LIQUID</p>

**a. How often are your stools types 1 &2**

- Never
- Rarely (less than a quarter of the time)
- Sometimes (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**b. How often are your stools types 3, 4 & 5**

- Never
- Rarely (less than a quarter of the time)
- Sometimes (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**c. How often are your stools types 6 &7**

- Never
- Rarely (less than a quarter of the time)
- Sometimes (a quarter to half of the time)
- Usually (more than half of the time)
- Always

**SECTION C**

1. **Can you now (or could you ever) place your hands flat on the floor without bending your knees?**

No  Yes



2. **Can you now (or could you ever) bend your thumb to touch your forearm?**

No  Yes



3. **As a child, did you amuse your friends by contorting your body into strange shapes OR could you do the splits?**

No  Yes

4. **As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?**

No  Yes

5. **Do you consider yourself double-jointed?**

No  Yes

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