RECTAL HYPOSENSITIVITY: CLINICAL AND PHYSIOLOGICAL IMPACT ON PATIENTS WITH CHRONIC CONSTIPATION

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ABSTRACT

Intact rectal sensation is integral to normal anorectal function. Rectal hyposensitivity (RH) implies diminished rectal sensory perception and is currently diagnosed using standard anorectal physiology tests. There is currently a lack of understanding regarding the nature and severity of symptoms, and pathophysiological mechasnisms by which RH leads to symptoms of constipation. Symptom severity and physiological abnormalities (potential pathophysiological mechanisms) were studied in patients with RH referred to a tertiary centre for evaluation of their symptom of intractable constipation. A pilot study using a novel technique to study recto-anal and recto-rectal reflexes in health and in patients with RH is also presented.

RH was not associated with more severe symptoms as assessed using a standard constipation severity questionnaire. RH is more commonly associated with rectal evacuatory dysfunction (functional type). RH is also associated with a specific pattern of transit delay, where there is more hold up of the isotope in the left colon and this is independent of rectal evacuatory dysfunction. Afferent dysfunction in the majority of patients with rectal hyposensitivity relates purely to visceral pathways. However, a combined viscero-somatic pelvic sensory neuropathy is present in a proportion of patients. Similarly, a combined sensori-motor dysfunction was also seen in a subgroup of patients. Patients with RH have abnormal sampling and rectal contractile response to distension and this may play an important role in the pathophysiology of symptoms.

The level of interruption of afferent pathway is likely to be heterogenous in patients with RH and constipation. Patients with RH display distinct physiological abnormalities that may be important to identify to tailor management. Whether, this leads to improved clinical outcomes needs to be further evaluated.

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To my family

STATEMENT OF ORIGINALITY

The author wishes to certify that all the work presented in this thesis is original in concept, design and execution. Some of the applied techniques have been described previously, or are in use in clinical practice. All the experiments, the acquisition and analysis of resulting data, and the subsequent production of this manuscript were performed by the author, unless clearly stated otherwise. Some of the standard anorectal physiologyl tests, the results of which are presented in Chapters 3, 4 & 5, were performed by members of staff within the Gastrointestinal Physiology Unit, and were not repeated by the author.

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2. Evaluation of somatic nerve function in patients with rectal hyposensitivity. **SP Vasudevan**, MA Gladman, S Ponsford, M Swash, NS Williams, SM Scott, P J Lunniss. *Association of Coloproctology of Great Britain and Ireland, Glasgow, UK, July 2007* (**awarded best SARS paper**).

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6. Anal sensation in patients with rectal hyposensitivity. **SP Vasudevan**, J Murphy, MA Gladman, SM Scott, P J Lunniss, NS Williams. *Association of Coloproctology of Great Britain and Ireland, Gateshead, UK, July 2006.*

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CONTENTS

Page No.

Title 1

Abstract 2

Acknowledgements 3

Statement of originality 5

Publications 6

Contents 9

Figures 22

Tables 25

Abbreviations 26

CHAPTER 1 BACKGROUND, LITERATURE REVIEW AND AIMS

1.1. INTRODUCTION 28

1.2. DEFINITION 28

1.3. NOMENCLATURE 29

1.4. DIAGNOSIS OF RECTAL HYPOSENSITIVITY 30

1.4.1. Balloon distenson 30

1.4.2. Electromechanical barostat 30

1.4.3. Electrical stimulation 31

1.4.4. Thermal stimulation 32

1.5. EPIDEMIOLOGY 32

1.6. PATHOPHYSIOLOGY 33
1.6.1. Rectal innervation 33
1.6.2. Pathophysiology of RH 35
1.6.2.1. Primary RH 37
1.6.2.2. Secondary RH 39

1.7. AETIOLOGY 39
1.7.1. Congenital 41
1.7.2. Acquired 41
1.7.2.1. Central disruption 41
1.7.2.2. Peripheral disruption 42
1.7.2.3. Neuropathies 43
1.7.2.4. Neurodegenerative / demyelinating diseases 43
1.7.2.5. Psychosocial disorders 44
1.7.2.6. Abnormal biomechanical / anatomical properties 44

1.8. CLINICAL ASSOCIATIONS 45
1.8.1. Constipation 45
1.8.2. Irritable bowel syndrome 47
1.8.3. Faecal incontinence 47

1.9. EXTRA-RECTAL INVOLVEMENT 48
1.9.1. Anal canal 48
1.9.1.1. Anal sensation 48
1.9.1.2. Recto-anal / recto-rectal reflexes 48
1.9.2. Colon 49
1.9.3. Proximal GI tract 50

1.9.4. Urinary bladder 50

1.10. TREATMENT 51

1.10.1. Bowel retraining / Biofeedback 51

1.10.2. Neuromodulation 52

1.10.2.1 Sacral nerve stimulation 53

1.10.2.2 Electrical stimulation 53

1.10.2.3 Magnetic stimulation 54

1.10.3 Surgery 54

1.11. Clinical / Research implications 55

1.12. AIMS 56

1.12.1. Specific aims 57

CHAPTER 2 MATERIALS AND METHODS

2.1. INTRODUCTION 58

2.2. RESEARCH ETHICS COMMITTEE APPROVAL 58

2.3. DIAGNOSIS OF RECTAL HYPOSENSITIVITY 59

2.3.1. Definition of rectal hyposensitivity 59

2.3.2. Assessment of rectal sensory function 59

2.3.3. Normal ranges for rectal sensation 61

2.3.4. Diagnostic criteria for rectal hyposensitivity 62

2.3.5. Critical appraisal of diagnostic criteria 62

2.4. PATIENTS 63
2.4.1. Recruitment 63
2.4.2. Patient selection (RH) 64
2.4.2.1. Inclusion criteria 64
2.4.2.2. Exclusion criteria 65
2.4.2.3. Study populations 66
2.4.3. Control groups 67

2.5. DATA COLLECTION 68
2.5.1. Methods of data collection 68
2.5.2. Storage of data 69
2.5.3. Clinical data 69

2.6. GASTROINTESTINAL PHYSIOLOGY INVESTIGATIONS 71
2.6.1. Anal manometry 72
2.6.2. Endoanal ultrasound 74
2.6.3. Pudendal nerve terminal motor latencies 75
2.6.4. Colonic transit study 77
2.6.5. Evacuation proctography 78
2.6.6. Classification of patients with anorectal dysfunction 82

2.7. DATA ANALYSIS 82
2.7.1. Statistical software 82
2.7.2. Statistical analysis 83
2.7.2.1. Comparing grouped numerical data 83
2.7.2.2. Contingency tables 83
2.7.2.3. Correlation and regression 84

2.8. LITERATURE REVIEW AND REFERENCING 84

CHAPTER 3 IMPACT OF RECTAL HYPOSENSITIVITY ON SYMPTOM SEVERITY AND OTHER COLORECTAL PHYSIOLOGICAL MEASURES IN PATIENTS WITH CONSTIPATION

3.1. INTRODUCTION 85

3.2. PATIENTS AND METHODS 87
- 3.2.1. Patients 87
- 3.2.2. Methods 88
  - 3.2.2.1. History and constipation severity scoring 88
  - 3.2.2.2. Anorectal physiology studies 88
  - 3.2.2.3. Data and statistical analysis 88

3.3. RESULTS 89
- 3.3.1. Rectal sensation 89
- 3.3.2. Primary presenting symptoms / onset 89
- 3.3.3. Severity based on rectal sensation (total score) 90
- 3.3.4. Effect of RH on individual symptom score 91
- 3.3.5. Influence of concommittent faecal incontinence 92
- 3.3.6. Impact of delayed gut transit on severity 92
- 3.3.7. Protographic findings 93

3.4. DISCUSSION 94

3.5. CONCLUSIONS 97

CHAPTER 4 **RECTAL HYPOSENSITIVITY IN SLOW TRANSIT CONSTIPATION: IMPACT ON RECTAL EVACUATION AND PATTERN OF TRANSIT DELAY**

4.1. INTRODUCTION 98

4.2. PATIENTS & METHODS 99

4.2.1. Patients 99

4.2.2. Methods 99

4.2.2.1. Rectal sensation and subgroups 100

4.2.2.2. Anorectal physiological investigation 100

4.2.2.3. Evacuation proctography / definition of rectal evacuatory dysfunction 100

4.2.2.4. Colonic scintigraphy 101

4.2.2.5. Data and statistical analysis 103

4.3. RESULTS 104

4.3.1. Subjects and classification 104

4.3.2. Evacuatory function 104

4.3.3. Scintigraphy 105

4.3.3.1. Global transit 105

4.3.3.2. Regional transit 108

4.4. DISCUSSION 111

4.5. CONCLUSIONS 115

CHAPTER 5 **RECTAL HYPOSENSITIVITY: EVALUATION OF ANAL SENSATION IN FEMALE PATIENTS WITH INTRACTABLE CONSTIPATION**

5.1. INTRODUCTION 116

5.2. PATIENTS & METHODS 117

5.2.1. Subjects 117

5.2.1.1. Patients 117

5.2.1.2. Controls 119

5.2.2. Methods 119

5.2.2.1. Anorectal physiological investigation 119

5.2.2.2. Anal electrosensitivity 119

5.2.2.3. Definition of rectal and anal hyposensitivity 120

5.2.2.4. Data and statistical analysis 121

5.3. RESULTS 121

5.3.1. Clinical findings 121

5.3.1.1. Demography and symptoms based on rectal sensory function 121

5.3.2. Physiological data 122

5.3.2.1. Rectal sensation 122

5.3.2.2. Anal sphincter function 123

5.3.2.3. Pudendal nerve motor latencies 123

5.3.2.4. Anal sensation 124

5.4. DISCUSSION 128

5.5. CONCLUSION 133

CHAPTER 6 **EVALUATION OF GENERAL AND PELVIC SOMATIC NERVE FUNCTION IN PATIENTS WITH RECTAL HYPOSENSITIVITY AND CONSTIPATION**

6.1. INTRODUCTION 134

6.2. SUBJECTS & METHODS 135
- 6.2.1. Subjects 135
  - 6.2.1.1. Patients 135
  - 6.2.1.2. Volunteers 136
- 6.2.2. Methods 136
  - 6.2.2.1. Anorectal physiology 136
  - 6.2.2.2. Rectal sensation (balloon distension) 137
  - 6.2.2.3. Rectal electrosensory thresholds 137
  - 6.2.2.4. Rectal compliance 138
  - 6.2.2.5. Neurophysiology study protocol 138
    - 6.2.2.5.1. Somatic function tests 138
  - 6.2.2.6. Data and statistical analysis 141

6.3. RESULTS 142
- 6.3.1. Rectal sensation 142
  - 6.3.1.1. Balloon distension 142
  - 6.3.1.2. Rectal electrosensory thresholds 142
- 6.3.2. Rectal compliance 143
- 6.3.3. Thermal thresholds 143
  - 6.3.3.1. Perineum (S3 dermatome bilateral) 143
  - 6.3.3.2. Lower limb (L5 dermatome) 146
  - 6.3.3.3. Upper limb (C6 dermatome) 147
- 6.3.4. Tactile thresholds 148

6.3.4.1. Perineum (S3 dermatome bilateral) 148
6.3.4.2. Lower limb (L5 dermatome) 149
6.3.4.3. Upper limb (C6 dermatome) 149
6.3.5. Nerve conduction studies 150
6.3.5.1. Peroneal nerve conduction velocity 150
6.3.5.2. Sural nerve conduction velocity 150
6.3.5.3. Pudendal nerve terminal motor latencies 151

6.4. DISCUSSION 152

6.5. CONCLUSIONS 155

CHAPTER 7 ASSESSMENT OF RECTAL CONTRACTILE RESPONSE IN PATIENTS WITH RECTAL HYPOSENSITIVITY

7.1. INTRODUCTION 156

7.2. PATIENTS & METHODS 157
7.2.1. Subjects 157
7.2.1.1. Patients 157
7.2.1.2. Controls 159
7.2.2. Methods 159
7.2.2.1. Anorectal physiology 159
7.2.2.2. Rectal sensory thresholds 159
7.2.2.3. Electromechanical barostat protocol 159
7.2.2.4. Rectal compliance 162
7.2.2.5. Parameters of the rectal contractile response 162
7.2.2.6. Data and statistical analysis 164

7.3. RESULTS 165
7.3.1. Rectal sensation 165
7.3.1.1. Balloon distension 165
7.3.1.2. Barostat: pressure thrsholds 165
7.3.2. Rectal compliance 166
7.3.3. Parameters of the rectal contractile response 167
7.3.3.1. Parameterts of the RCR at MDP + 4mmHg 168
7.3.3.2. Parameters of the RCR at MDT + 8mmHg 170

7.4. DISCUSSION 171

7.5. CONCLUSIONS 175

CHAPTER 8 **RECTO-ANAL REFLEXES IN HEALTH AND IN PATIENTS WITH RECTAL HYPOSENSITIVITY – A PILOT STUDY USING A NOVEL TECHNIQUE**

8.1. INTRODUCTION 176

8.2. SUBJECTS & METHODS 178
8.2.1. Subjects 178
8.2.1.1. Healthy controls 178
8.2.1.2. Patients with RH 178
8.2.2. Methods 178
8.2.2.1. Study visit and perception of urge to defaecate 178
8.2.2.2. Combined barostat- manometry technique: technical details 179

8.2.2.3. Test protocol 181
8.2.2.3.1. Anal function 181
8.2.2.3.2. Spontaneous anorectal activitiy and relation to conscious perception 182
8.2.2.3.3. Rectal compliance, rectal contractile response and sensation 183
8.2.2.4. Data and statistical analysis 184

8.3. RESULTS 184
8.3.1. Perception of the urge to defaecate 184
8.3.2. Anal function 185
8.3.3. Spontaneous anorectal activity and relation to conscious perception 185
8.3.3.1. Healthy volunteers 185
8.3.3.1.1. Spontaneous anal relaxation 185
8.3.3.1.2. Relationship to conscious perception 186
8.3.3.1.3. Associated rectal contraction 188
8.3.3.1.4. Associated EAS (external anal sphincter) contraction 188
8.3.3.2. Patient with RH 188
8.3.4. Rectal contractile response (RCR) to phasic distension 189
8.3.4.1. Healthy volunteers 189
8.3.4.2. Patients with RH 191
8.3.5. Rectal compliance 193

8.4. DISCUSSION 193

8.5. CONCLUSIONS 199

CHAPTER 9 SUMMARY AND CONCLUSIONS

9.1 IMPACT OF RECTAL HYPOSENSITIVITY ON SYMPTOM SEVERITY AND OTHER COLORECTAL PHYSIOLOGICAL MEASURES IN PATIENTS WITH CONSTIPATION 200

9.1.1 Summary 200

9.1.2 Conclusions 201

9.2 RECTAL HYPOSENSITIVITY IN SLOW TRANSIT CONSTIPATION: IMPACT ON RECTAL EVACUATION AND PATTERN OF TRANSIT DELAY 201

9.2.1 Summary 201

9.2.2 Conclusions 202

9.3 RECTAL HYPOSENSITIVITY: EVALUATION OF ANAL SENSATION IN FEMALE PATIENTS WITH INTRACTABLE CONSTIPATION 203

9.3.1 Summary 203

9.3.2 Conclusions 203

9.4 EVALUATION OF GENERAL AND PELVIC SOMATIC NERVE FUNCTION IN PATIENTS WITH RECTAL HYPOSENSITIVITY AND CONSTIPATION 204

9.4.1 Summary 204

9.4.2 Conclusions 204

9.5 ASSESSMENT OF RECTAL CONTRACTILE RESPONSE IN PATIENTS WITH RECTAL HYPOSENSITIVITY 205

9.5.1 Summary 205

9.5.2 Conclusions 205

9.6 RECTO-ANAL REFLEXES IN HEALTH AND IN PATIENTS WITH RECTAL HYPOSENSITIVITY- A PILOT STUDY USING A NOVEL TECHNIQUE 206

9.6.1 Summary 206

9.6.2 Conclusions 207

9.7 CONCLUDING REMARKS 207

9.8 FUTURE WORK 208

APPENDICES 212

REFERENCES 222

FIGURES

Page No.

1.01	Sensory pathway from rectum to cerebral cortex	34
1.02	Impact of rectal size on threshold volumes	36
2.01	Devise used for assessing rectal sensory function	60
2.02	Anal manometry apparatus	73
2.03	Ultrasound machine with transrectal probe	75
2.04	St. Mark's pudendal nerve electrode	77
2.05	Method showing area marking pre and post evacuation	80
2.06	Assesment of anorectal angle and anal canal opening	80
2.07	Medium size rectocele (A) rectal intussception (B)	81
3.01	Total cleveland clinic constipation severity score (RH vs. NS)	91
3.02	Total cleveland clinic constipation severity score (normal vs. delayed transit)	93
4.01	Evacuatory function in subgroups	105
4.02	Time activity curves of isotope progression through the colon (RH vs.NS)	107
4.03	Time activity curves of isotope progression through the colon (RH vs.NS with or without evacuatory dysfunction)	107
4.04	Regional activity in the right colon	110
4.05	Regional activity in the left colon	110
4.06	Regional activity in the left colon incorporating presence or absence of evacuatory dysfunction	110
4.07	Percentage of radio-isotope evacuated	111

5.01	Anal electrostimulation electrode	120
5.02	Anal electrosensory thresholds in healthy volunteers (HV) and patients	124
5.03	Anal electrosensory thresholds in healthy volunteers and subgroups of patients based on rectal sensation	125
5.04	Scatter plot showing the relationship between PNTML and anal electrosensory thresholds	126
5.05	Scatter plot showing the relationship between anal squeeze pressure and anal electrosensory thresholds	127
5.06	Scatter plot showing the relationship between age and anal electrosensory thresholds	127
6.01	Dermatome map: posterior dermatomes	139
6.02	Rectal electrosensory thresholds in the subgroups	143
6.03	Perineal thermal thresholds- sum of difference [warmth + cold]	144
6.04	Perineal warmth threshold	145
6.05	Perineal cold threshold	146
6.06	Right foot (L5 dermatome) - sum of difference [warmth + cold]	147
6.07	Right hand (C6 dermatome) - sum of difference [warmth + cold]	148
6.08	Perineal touch sensation- target force in weight (grams)	149
6.09	Peroneal nerve conduction velocity (m/sec)	150
6.10	Sural nerve conduction velocity (m/sec)	151
6.11	Correlation between PNTMLs and perineal thermal thresholds	152
7.01	Barostat bag attached to rectal catheter	160
7.02	Electromechanical barostat system	161
7.03	Barostat volume trace showing the rectal contractile response (RCR)	163
7.04	RCR amplitude at different pressures in HV	164
7.05	Barostat pressure thresholds	166

7.06	Rectal compliance in the subgroups	167
7.07	Relationship of FSP (first sensation pressure) to RCR	168
7.08	Percentage drop in volume at MDP+4 mmHg in the subgroups	169
7.09	Area over the curve expressed as a percentage of the whole area	170
8.01	Custom made rectal barostat catheter design	180
8.02	Solid state anal manometry catheter	180
8.03	MMS solar series	181
8.04	G&J Distender II series barostat machine	182
8.05	Recto-anal events during prolonged barostat distension to MDP+2 mmHg in healthy volunteers showing anal relaxation	186
8.06	Recto-anal events at MDP+2 mmHg in HV showing rectal contraction, associated anal relaxation and EAS contraction	187
8.07	Recto-anal events at MDP+2 mmHg in patient with RH showing complete absence of spontaneous sampling	189
8.08	Recto-anal events at phasic distension in HV showing RCR onset	190
8.09	Recto-anal events at phasic distension in HV showing RCR dissapearing at higher pressures	191
8.10	Recto-anal events at phasic distension in patient with RH showing diminished amplitude of RCR	192
8.11	Symptom genesis in patients with RH and constipation	198

TABLES

Page No.

1.01	Potential aetiological factors of RH and mechanisms	40
2.01	Normal ranges for rectal sensory thresholds	61
2.02	Clinical data for all subjects	70
3.01	Patient demographics	86
3.02	Primary presenting symptoms	89
3.03	Individual symptom score	91
5.01	Demography and symptomatology of patients	118
5.02	Demography and symptoms based on rectal sensory function	122
7.01	Demography and symptomatology	158

LIST OF ABBREVIATIONS

AOC	Area over curve
AUC	Area under curve
CCCS	Cleveland clinic constipation score
DDV	Desire to defaecate volume
DDP	Desire to defaecate pressure
EAS	External anal sphincter
ED	Evacuatory dysfunction
EMG	Electromyography
EP	Evacuation proctography
FSV	First sensation volume
FI	Faecal incontinence
fMRI	Functional magnetic resonance imaging
FSP	First sensation pressure
GCI	Geometric centre of isotope mass
HV	Healthy volunteer
IAS	Internal anal sphincter
IBS	Irritable bowel syndrome
IGLE	Intraganglionic laminar ending
IQR	Interquarantine range
MAP	Motor action potential

MDP	Minimal distending pressure
MS	Multiple sclerosis
MTP	Maximal tolerated pressure
MTV	Maximum tolerated volume
NE	Normal evacuation
NS	Normosensate
NT	Normal transit
OP	Operating pressure
PET	Positron emission tomography
PNTML	Pudendal nerve terminal motor latency
QST	Quantitative sensory testing
RACR	Recto-anal contractile reflex
RAIR	Recto-anal inhibitory reflex
RCR	Rectal contractile response
RED	Rectal evacuatory dysfunction
RH	Rectal hyposensitivity
ROI	Region of interest
SMR	Sensorimotor reflex
SNS	Sacral nerve stimulation
STC	Slow transit constipation
VAS	Visual analogue scale
WA	Whole area

1 BACKGROUND, LITERATURE REVIEW AND AIMS

1.1 INTRODUCTION

Functional lower gastrointestinal disorders are common and affect individuals of all ages, races and gender. They have an enormous negative impact on the quality of life of the individual concerned (Halder et al. 2004), and also are a big burden economically to health care providers (Nyrop et al. 2007). Intact rectal sensation is crucial to the normal process of defaecation and maintanence of continence (Palit et al. 2012). Abnormal visceral sensitivity is now widely recognised as an important factor in the development of functional bowel disorders.

There are numerous studies in the literature relating to heightened rectal sensation (rectal hypersensitivity) (Azpiroz et al. 2007). By contrast, rectal hyposensitivity (RH) has been relatively neglected by researchers and clinicians. Nevertheless, there is now growing acceptance of the importance of rectal hyposensitivity in association with functional hindgut disorders both in the adult and paediatric population (Gladman et al. 2006;Scott et al. 2011b).

1.2 DEFINITION

Rectal hyposensitivity (RH) literally means diminished rectal sensory perception. In clinical practice, it is diagnosed by the finding of diminished perception of rectal sensation to balloon distension (Whitehead et al. 1987;Keighley et al. 1989;Diamant et al. 1999;Lowry et al. 2001;Rao et al. 2002). However, other modalities of testing rectal sensation have been used in the research setting (Speakman et al. 1993b;Whitehead et al. 1997;Chan et al. 2003). RH was first objectively demonstrated in patients with neurogenic hindgut dysfunction (White et al. 1940) and subsequently in anorectal dysfunction (Goligher et al. 1951). The term rectal hyposensitivity was adopted several years later (Devadhar 1967).

1.3 NOMENCLATURE

Apart from rectal hyposensitivity, several terms have been used in the literature to describe diminished perception of rectal distension. Rectal sensory function has been described directly with adjectives (e.g., blunted/ impaired/ deficient/ reduced/ diminished rectal sensation) in some studies (Wald et al. 1984;Shouler et al. 1986;Hancke et al. 1987;Varma et al. 1988b;De et al. 1989;Smith et al. 1990;Harraf et al. 1998;Gosselink et al. 2001a;Crowell 2004). Other studies describe sensory thresholds obtained during testing (e.g., increased rectal sensitivity thresholds (Molnar et al. 1983) or delayed rectal sensation (Buser et al. 1986)). The above descriptions are confusing and in contemporary literature, the term *rectal hyposensitivity* is used, and which will used in this thesis.

1.4 DIAGNOSIS OF RECTAL HYPOSENSITIVITY

Rectal hyposensitivity is diagnosed when sensory thresholds to rectal distension are elevated beyond the normal range (Shouler et al. 1986;Azpiroz et al. 2002;Gladman et al. 2003a;Rao 2004a).

1.4.1 BALLOON DISTENSION

In clinical practice, this is performed by inflating a latex balloon in the rectum with a handheld syringe, at a constant rate (1 ml / sec). Three threshold volumes are volunteered; first sensation (FSV), desire to defaecate (DDV) and maximum tolerated volume (MTV). There is no consenus in literature about which of these threshold volumes has to be elevated above normal for a diagnosis of RH. However, most units consider elevation of one or more thresholds for a diagnosis of RH (Scott et al. 2008). Despite being reproducible, and quick and easy to perform, balloon distension has the limitation that it cannot be used to study intrinsic rectal wall properties.

1.4.2 ELECTROMECHANICAL BAROSTAT

More accurate measurement of rectal sensory thresholds along with assesment of rectal wall properties can be obtained with a computer-controlled electromechanical barostat. This technique is currently the gold standard for assessing rectal sensory function (Whitehead et al. 1997). In a barostat study, the rectum is distended with an

infinitely compliant balloon using a computer-generated distension protocol, which is pressure or volume controlled. The two main meaurement techniques are sensory thresholds and stimulus intensity measurements. In sensory threshold measurements, subjects are asked to indicate when first sensation, urge threshold and maximum tolerable pressures / volumes are reached in response to a distension protocol (Cremonini et al. 2005;Scott et al. 2008). For the stimulus intensity technique, the subject rates the intensity of stimulus on a visual analogue scale to a random distension paradigm (Whitehead et al. 1997;Steens et al. 2002;Gladman et al. 2005a). RH is diagnosed when thresholds are higher, or stimulus intensity is below the normal range (Scott et al. 2008). However, barostat studies are time consuming, cumbersome and not readily available. Nevertheless, they are currently used both in the clinical and research settings.

1.4.3 ELECTRICAL STIMULATION

Electrical stimulation of the rectum has also been used to assess visceral afferent function (Loening-Baucke et al. 1991;Loening-Baucke et al. 1992;Speakman et al. 1993b;Arebi et al. 2011;Burgell et al. 2012b). This is less physiological as it bypasses the mucosal receptors and directly stimulates the nerves. However, it is a very reproducible technique and can also be used to produce cortical evoked potentials (Hobday et al. 2002;Burgell et al. 2012b) which provide an objective measure of the afferent nerve pathway.

1.4.4 THERMAL STIMULATION

Thermal stimulation of the rectum has been found to be a reproducible technique for studying rectal sensory function (Chan et al. 2003;Brock et al. 2008). This relies on intact rectal receptors. However, the stimulus itself is noxius and not physiological, and is currently used only for research purposes (Chan et al. 2003).

1.5 EPIDEMIOLOGY

The true prevalence of RH in the community is not known. RH has been reported in 18-68% of patients with constipation (infrequent / obstructed defaecation) (Shouler et al. 1986;Meunier 1986;De et al. 1989;Kamm et al. 1990;Karlbom et al. 2004;Bharucha et al. 2005) and in 18% of patients with faecal incontinence (Sun et al. 1990b;Sun et al. 1992). The prevalance of RH was reported to be 16% in the largest series published to date in patients with hindgut dysfunction (n=1351) who were referred to a tertiary centre for anorectal physiological studies (Gladman et al. 2003a). Of these patients, 23% had constipation alone, 10% had incontinence alone, and 27% had both constipation and faecal incontinence (Gladman et al. 2003a). RH is found equally in male and female patients. It is also found in paediatric (Di et al. 2004) and elderly patients (Read et al. 1985;Read et al. 1986a;Varma et al. 1988a).

1.6 PATHOPHYSIOLOGY

1.6.1 RECTAL INNERVATION

The hindgut is innervated by four major types of neurons namely enteric, sympathetic, parasympathetic and extrinsic spinal sensory (Brookes et al. 2009). The enteric nervous system controls most aspects of colorectal motility. It is also involved in local reflex activity by a complex interplay with extrinsic sensory and interneurons. The visceral afferents innervating the rectum are both chemo and mechanosensitive. They are usually formed of unmyelinated type C fibres (Knowles et al. 2009a). However, Aδ fibres have also been identified. Visceral afferents end as bare nerve fibres in the myenteric plexus of the rectal wall (Berthoud et al. 2004). Although a true rectal mechanoceptor has not yet been identified in humans, studies of guinea pig rectum have identified intra-gangionic laminar ending (IGLE)(Lynn et al. 2003). These are thought to be low threshold mechanoreceptors that are seen in the myenteric ganglia. They are activated both by gut distension and focal mechanical probing. They may also respond to chemical stimuli.

Afferent signals from the rectum reach conscious perception through a three-order neuronal chain (Brookes et al. 2009;Sharma et al. 2009) (Figure 1.01). This results in both sensory discrimination as well as affective emotional perception. The first order neurons are the spinal afferents that pass from the rectal wall into the lateral ligaments (Speakman et al. 1991) through the pelvic plexus and the pelvic splanchnic nerves

(nervi erigentes) (Devroede et al. 1974;Speakman et al. 1991) to reach the sacral segments of the spinal cord. The vast majority of these fibres are thought to reach the S3 and 4 nerve roots. This has been extrapolated from the fact that division of the lateral ligaments and nervi erigentes results in loss of rectal sensory function. Similarly, low spinal anaesthetic (S1 level) (Harris et al. 2006), sacral nerve sacrifice (Gunterberg et al. 1976) and posterior rhizotomy of S2-4 nerve roots (Sun et al. 1995) have been found to result in loss of rectal sensation. The greatest impact appears to be secondary to disruption of the S3/4 nerve roots (Todd, Jr. et al. 2002).

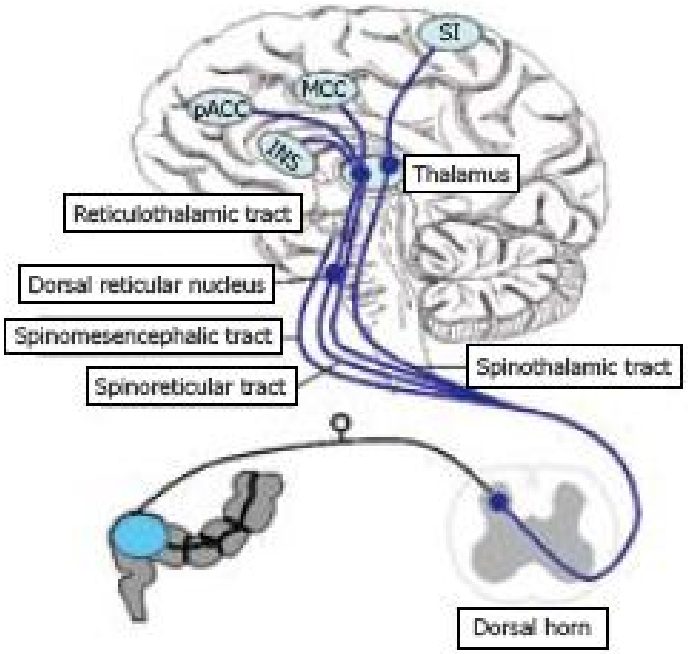


Figure 1.01: Sensory pathway from the rectum to the higher cortical centers (reproduced with permission: Sharma A, Lelic D, Brock C, Paine P, Aziz Q. New technologies to investigate the brain gut axis. World J Gastroenterol 2009; 15:182-191). pACC, perigenual anterior cingulate cortex; MCC, mid cingulate cortex; INS, insular; SI, somatosensory cortex.

The second order neurons project from the spinal cord to the thalamus and third order from the thalamus to the cerebral cortex. Recent studies using Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) studies have shown that there may be three possible pathways from the spinal cord to the cerebral cortex. The first pathway involves projection of second order neurons from the lamina I of the spinal cord to the thalamo-cortical relay nucleus in the posterolateral thalamus (VMpo)(Craig 2003). From here, third order neurons project into the dorsal posterior insular cortex. This region is regarded as the primary interoceptive cortex responsible for encoding painful and non-painful sensation. In the second pathway, signals are transmitted from the spinal cord to the ventral part (MDvc) of the medial dorsal nucleus of the thalamus. Third order neurons then relay to the dorsal anterior cingulate cortex. This area is thought to mediate the affective, autonomic and motivational response to the stimulus. Nociceptive stimuli from the pelvis can also reach the cerebral cortex directly through the dorsal column pathway (Willis et al. 1999).

1.6.2 PATHOPHYSIOLOGY OF RH

The exact pathophysiological mechanisms of RH are yet to be fully understood (Gladman et al. 2006). No animal model exists for the study of rectal hyposensitivity. The diagnosis of RH, based on elevated sensory thresholds to balloon distension, has been thought to reflect impaired afferent nerve function. However, recent studies

using complimental modalities i.e, barostat, electrical and thermal sensation and rectal fluoroscopy during distension, have highlighted the fact that elevated thresholds to balloon distension do not always imply a defect in the afferent pathway (Gladman MA et al. 2005;Gladman et al. 2005a;Gladman et al. 2007). This is particularly true in the presence of an enlarged rectum i.e megarectum, or abnormal rectal biomechanics resulting in increased compliance (Madoff et al. 1990;Lagier et al. 1999;Camilleri 2002). Here, increased volumes may reflect inadequate stimulation, due to a larger, more compliant rectum (though there may be coexistent afferent nerve dysfunction) (Figure 1.02).

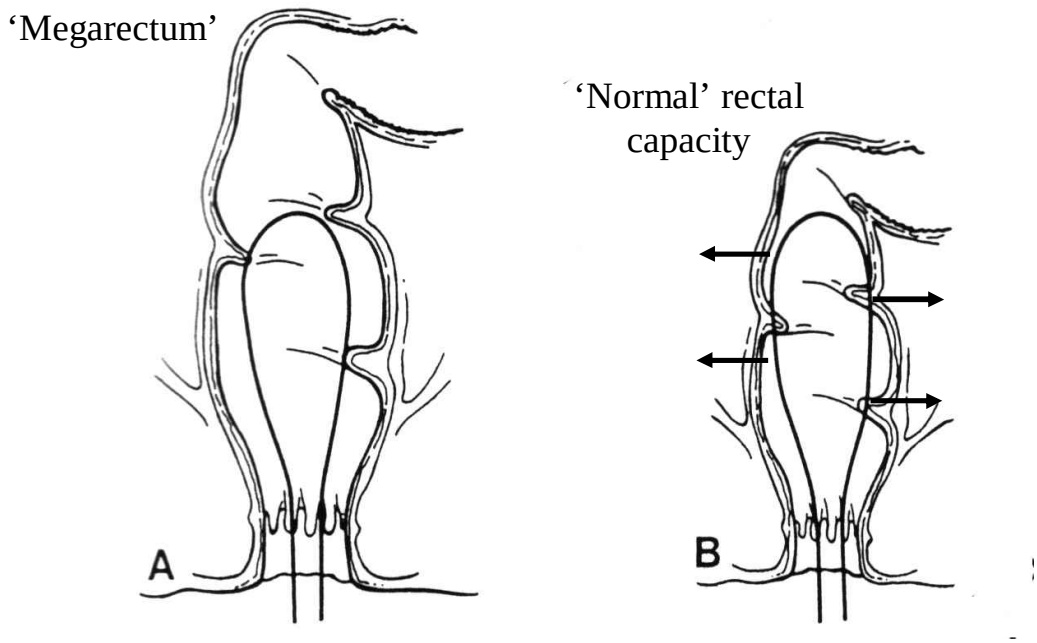


Figure 1.02: Impact of rectal size on rectal sensory threshold volumes. Larger volumes are required to elicit sensations during balloon distension in patients with megarectum (A), compared to those with 'normal' rectal capacity (B) *(modified from: Madoff et al. Int J Colorectal Dis 1990; 5: 37-40 © 1990 Springer Velag, with*

permission from Springer SBM)

RH due to dysfunction in the afferent pathway has been referred to as primary RH. RH due to abnormal rectal wall properties has been termed secondary RH (Burgell et al. 2012c). This distinction is fundamentally important, and could allow tailoring of both current and future therapeutic modalities. In the largest series to date subclassifying patients with RH, one third of patients had primary RH and a quarter had combination of primary and secondary RH. (Gladman et al. 2005a). Visceral sensory function is also known to be influenced by personality profile, autonomic nervous system function and psychological phenotype (Sarkar et al. 2000;Hobson et al. 2006;Paine et al. 2009;Coen et al. 2011).

1.6.2.1 Primary RH

Primary RH is thought to be due to direct disruption or dysfunction of the rectal afferent sensory pathway. Biomechanical properties of the rectum i.e, capacity and compliance, are normal. The exact cause of primary RH and the level of disruption of the afferent pathway are currently unknown. Intuitively, abnormalities of afferent nerve conduction can be as a result of dysfunction / disruption at any level of the brain-gut axis (Speakman et al. 1993b;Wingate et al. 2002;Azpiroz et al. 2002) (see section 1.6.1) namely:

- at receptor level: impaired transduction and transformation of stimuli;
- impaired afferent nerve transmission: this can be peripheral or central; or
- defective cortical processing

Where there is documented disruption of afferent pathway (eg, damage during pelvic surgery, spinal cord injury etc) a clear cause-effect relationship is evident. However, in a substantial proportion of patients the cause-effect relationship is less apparent. The role of sub-clinical neuronal dysfunction is also unclear. Direct damage to pelvic nerves during childbirth, as a result of chronic straining, and secondary to pelvic surgery have also been implicated as a potential cause of primary RH (Snooks et al. 1986;Lubowski et al. 1988b;Gladman et al. 2003b). Studies on recto-anal reflexes have shown that they are intact in patient with RH, but with a raised stimulation threshold (Remes-Troche et al. 2010); this may indicate that the level of disruption is higher than the reflex arc (i.e lower sacral segments). In a recent study using cortical evoked potentials, and an inverse modeling technique of cortical dipoles in patients with RH, a temporal delay in transmission was found in patients with RH compared to volunteers (Burgell et al. 2012b). However, there was no difference in cortical processing. Abnormal cortical processing has been found in patients with IBS and visceral hypersensitivity (Mertz et al. 2000), but not been adequately studied in hyposensitivity thus far. Similarly, the importance of activation of descending inhibitory pain pathways also needs to be evaluated further. This may be important in the genesis of RH in patients with severe physical and sexual abuse (Drossman 2011;Imhoff et al. 2012). The use of advanced diagnostic techniques such as spinal monitoring and brain imaging studies using PET and fMRI will help to delineate this further. It is very likely that the level of afferent dysfunction differs between individual patients based on the aetiology. In the future, diagnosing the exact level of involvement of the afferent pathway will be important in formulating therapeutic strategies, tailored to the individual patient.

1.6.2.2 Secondary RH

When rectal sensory thresholds are raised purely due to the presence of abnormal rectal wall properties (i.e increased capacity (mega-rectum) and/ or hyper-compliance) it is referred to as secondary RH (Burgell et al. 2012c). Under these circumstances, higher levels of stimulation are required to provoke sensation. In the largest study to date, 47% of patients with RH and hindgut dysfunction had secondary RH (Gladman MA et al. 2005). Rectal wall properties were normal in the remaining 53%, indicating true afferent dysfunction i.e, primary RH.

1.7 AETIOLOGY

The exact cause of RH is currently unknown. It has been found with increased frequency in certain groups of patients, and is associated with certain diseases or interventions (Table 1.01). However, a direct cause-effect relationship has not been established in many.

Table 1.01: Potential aetiological factors for RH and mechanisms

CONGENITAL FACTORS		
Afferent pathway defect	***Central***	Neural tube defects
	Peripheral	Sacral agenesis
Rectal abnormalities	***Megarectum***	Hirschprung's disease
		Anorectal malformations
ACQUIRED FACTORS		
Afferent pathway defect	***Central***	Cauda equina syndrome
		Conus medullaris lesions
		Supraconal lesions
	Demyelination / degeneration	Multiple sclerosis
		Tabes dorsalis
		Subacute combined degeneration of the cord
		Parkinson's disease
	Neuropathies	Diabetes mellitus
	Psychosocial	Behavioural disorders
	Peripheral	Pelvic surgery
		Resection of pelvic nerves
		Resection of sacral nerves
Rectal abnormalities	***Megarectum***	Idiopathic
		Psychiatric
		Central nervous system
		Neuronal degeneration
		Obstructive

Endocrine

1.7.1 CONGENITAL

RH has been reported in patients with congenital abnormalities that involve parts of the rectal afferent sensory pathway. It has been noted in sacral agenesis (Morera et al. 2003). It has also been found in children born with neural tube defects e.g. spina bifida and meningomyelocele (Wald 1981;Loening-Baucke et al. 1988;Agnarsson et al. 1993;Verity et al. 2003). Developmental abnormalities of the hindgut (agenesis, atresia and stenosis) can lead to secondary distension of the proximal bowel resulting in a megacolon (Hrabovszky et al. 2002). Similarly, failure of relaxation of an aganglionic segment of distal rectum can lead to proximal distension and megacolon and megarectum (Ehrenpreis 1967).

1.7.2 ACQUIRED

Disruption of the rectal afferent pathway both centrally and peripherally can result in RH (Table 1.01, individual causes are discussed below). As described previously, abnormal biomechanical properties of the rectum can also result in RH.

1.7.2.1 Central disruption

Central nervous system lesions at brainstem level or lesions of the spinal cord at any level, namely high, low or mixed have been associated with the finding of RH (White et al. 1940;Weber et al. 1985;Sun et al. 1990a;MacDonagh et al. 1992;Greving et al.

1998;Krogh et al. 2001;Awad et al. 2012). In the larger study by Gladman et al; 18% of patients had a history of spinal trauma (i.e surgery or back injury with confirmed disc pathology) (Sun et al. 1990a;Gladman et al. 2003b). The finding of RH and absence of conscious contraction of the external anal sphincter has been postulated as a marker for occult spinal cord injury (in up to 10%) (Sun et al. 1990a). Similarly, in another study, about a third of patients with constipation were found to have incidental spinal dysraphism (Varma et al. 1988b).

1.7.2.2 Peripheral disruption

It is thought that afferent sensory fibres from the rectum pass through the pelvic plexus along with the nervi erigentes to reach the dorsal horn of segments S2-4 of spinal cord (described in detail in section 1.6.1)(Knowles et al. 2001;Kaiser et al. 2002). Hence disruption to the pelvic and or sacral nerves can result in RH (White et al. 1940;Devroede et al. 1974;Gunterberg et al. 1976;Nakahara et al. 1986;Sun et al. 1995;Nakai et al. 2000). This can occur during pelvic surgery, especially those that involve mobilisation of the rectum and division of the lateral ligaments (Speakman et al. 1991). Damage to pelvic nerves can also occur during hysterectomy. This is especially true in radical hysterectomy. One study confirmed nerve damage during hysterectomy by demonstrating the presence of sensory and autonomic nerves in the resected specimens (Butler-Manuel et al. 2000). In a study of 261 patients with RH, 38% had history of previous pelvic surgery (Gladman et al. 2003b).

1.7.2.3 Neuropathies

Peripheral neuropathy, especially as a complication of diabetes mellitus, has been implicated as one of the causes for RH (Whitehead et al. 1987;Krogh et al. 2001). In symptomatic patients, this has been commonly seen in those with faecal incontinence. The importance of RH in the etiology has been confirmed by the fact that symptom improvement has been achieved by improving rectal sensitivity using biofeedback therapy (Wald et al. 1984;Caruana et al. 1991). RH has also been reported in diabetics with no gastrointestinal symptoms (Cozzolino et al. 1991). Here RH was present regardless of the degree of autonomic neuropathy or duration of disease. This suggests early involvement of the rectal afferent sensory pathway in diabetics (Cozzolino et al. 1991).

1.7.2.4 Neurodegenerative disorders / demyelinating diseases

Rectal sensory function is impaired in patients with multiple sclerosis (MS) when compared with asymptomatic controls (Caruana et al. 1991;Nordenbo et al. 1996). It is of greater severity in patients with faecal incontinence and MS. RH has also been found in patients with tabes dorsalis, characterised by demyelination of the interspinous portions of the sensory nerves in the dorsal roots (White et al. 1940), although this condition is now rare due to the low incidence of syphilis. Similarly, patients with subacute combined degeneration of the cord secondary to vitamin B12 defeciency may also develop RH (White et al. 1940). Furthermore, higher rectal

sensory thresholds have been reported in patients with Parkinson's disease (Stocchi et al. 1997;Sakakibara et al. 2011)

1.7.2.5 Psychosocial disorders

Psychosocial factors, through their effect on supra-spinal mechanisms, are thought to be important in the genesis of RH (Baldi et al. 1982). One area of particular interest is whether RH can be acquired through abnormal toileting behaviour (Lunniss et al. 2009). This has been described in adult patients with a long standing history of constipation (Scott et al. 2011b). It is also relevant in the paediatric population where functional faecal retention has been well described (Bongers et al. 2010). This is thought to be due to habitual supression of the desire to defaecate leading to increased rectal capacity / compliance, neuropathic degenaration, and ultimately to sensori-motor dysfunction and symptoms of hindgut dysfunction (Devadhar 1967;Harraf et al. 1998;Wingate et al. 2002;Di et al. 2004).

Physical and sexual abuse have also been implicated in the development of altered visceral sensation (Drossman 2011). This is likely to be secondary to altered cortical processing of afferent information i.e attenuation of central arousal systems or activation of descending pain inhibitory pathways in response to painful or undesirable rectal stimuli (Ringel et al. 2004).

1.7.2.6 Abnormal biomechanical / anatomical properties

The presence of an abnormally dilated and capacious rectum is referred to as megarectum. Megarectum is described as idiopathic when there is an absence of a known organic cause. It can also occur as a consequence of other conditions (listed above), where the presence of an insensate rectum long term will eventually result in a capacious, dysfunctional organ through progressive dilatation.

1.8 CLINICAL ASSOCIATIONS

Rectal sensation is crucial for the normal processes of defaecation and maintenance of continence. Therefore, impaired rectal sensation will affect both these processes. The strongest clinical associations with RH are constipation, constipation- predominant IBS and faecal incontinence (Gladman et al. 2006).

1.8.1 CONSTIPATION

In the largest published series to date on patients with RH and hindgut dysfunction, 48% presented with constipation alone, and 27% presented with coexistent constipation and faecal incontinence (Gladman et al. 2003b). The same study also showed that RH was the only physiological abnormality demonstrable in about half of these patients, and that about a third of those patients with RH and constipation had a 'functional' rectal evacuatory disorder (e.g. pelvic floor dyssynergia).

The pathophysiology of chronic constipation is considered an overlap between rectal evacuatory dysfunction and colonic dysmotility (Locke, III et al. 2000). However, the mechanism by which RH contributes to constipation is currently unclear. However,

several mechanisms have been postulated.

Firstly, impaired rectal sensation either due to afferent nerve dysfunction or abnormal rectal wall properties leads to faceal retention due to lack of awareness of stool or the urge to defaecate. Secondly, rectal evacuatory dysfunction can occur due to inadequate increase in rectal pressure or inadequate relaxation of the anal canal (Whitehead et al. 1999). An inadequate increase in rectal pressure during evacuation may occur due to attenuated rectal wall contractions in response to distension (signifying a combined sensorimotor dysfunction) (Read et al. 1986b;Schouten et al. 1998), or abnormal dispersal of evacuatory forces, especially in patients with megarectum (Locke, III et al. 2000;Wald 2001). Inadequate reduction in anal canal pressure occurs most commonly as a result of lack of pelvic floor relaxation during evacuation (Chan et al. 2001;Gladman et al. 2003b). This has been proven on proctography in a third of individuals with RH and constipation (Gladman et al. 2003b). This highlights the importance of intact sensation in recto-anal and pelvic floor coordination.

A third of patients with RH have delayed gastrointestinal / colonic transit (Gladman et al. 2003b). In these patients, the transit delay may reflect a primary colonic dysmotility, or be secondary to outlet dysfunction due to viscero-visceral reflex inhibition of proximal gut function (Maurer et al. 1995b;Camilleri et al. 1998a;Law et al. 2002). The exact site of hold up of colonic transit is yet to be fully studied.

Whether RH manifests as specific (discriminative) symptoms in patients with constipation is also currently unknown. Similarly, whether patients with RH have

more severe symptoms compared to other causes of constipation is not known.

1.8.2 IRRITABLE BOWEL SYNDROME

RH has been reported in patients with irritable bowel syndrome (IBS). This is particularly the case in patients with constipation-predominant IBS (C-IBS) (Prior et al. 1990;Harraf et al. 1998;Steens et al. 2002;Lea et al. 2003;Corazziari 2004). However, given the controversy concerning the criteria with which patients with functional bowel disorders are labelled, there is marked overlap between patients with functional constipation and those with C-IBS, and indeed they are almost certainly part of the same spectrum. The discriminating symptom is a primary complaint of abdominal pain relieved by defaecation, which suggests a diagnosis of IBS, though patients with functional constipation also suffer with abdominal pain (Preston et al. 1986;Knowles et al. 2000b).

1.8.3 FAECAL INCONTINENCE

Although RH is more often associated with constipation, it was recorded in 20% of patients presenting with faecal incontinence (Gladman et al. 2003b). One sixth of male patients with faecal incontience have RH (Burgell et al. 2012a). When associated with constipation, faecal incontinence could be secondary to faecal impaction, or impaired evacuation leading to overflow and faecal seepage (Scott et al. 2011a). In the absence of faecal impaction, RH may contribute to faecal incontinence through impaired conscious or subconscious contraction of the anal sphincters (Wald

et al. 1984;Sun et al. 1990b). Patients with RH have shown to have reflex relaxation of the internal anal sphincter at much lower volumes that required for conscious awareness of rectal sensation (Hancke et al. 1987;Sun et al. 1990b;Sun et al. 1992).

1.9 EXTRA-RECTAL INVOLVEMENT

1.9.1 ANAL CANAL

1.9.1.1 Anal sensation

Anal sensation has been found to be altered in patients with faecal impaction and faecal incontinence. However, in patients with constipation and RH, whether anal sensation is diminished has not been studied. This may provide important information as to the possible pathophysiological mechanisms of RH in these patients. The sensory information from the rectum is relayed by the recto-spinal afferents which travel through the autonomic nerves, whereas the anal canal is supplied by the pudendal nerve which is purely somatic (Chan et al. 2005b).

1.9.1.2 Recto-anal and recto-rectal reflexes

Distension of the rectum evokes several reflex motor resposes that are controlled by both the extrinsic and intrinsic innervation of the anorectum (Rogers 1992;Gladman et al. 2005a). Rapid distension of the rectum evokes rectal contraction (the rectal contractile response). This reflex is not well studied, but is thought to be related to

the perception of rectal distension (Sun et al. 1990d). Whether the rectal contractile response to distension is altered in patients with RH is currently unknown.

Rectal distension also induces reflex relaxation of the internal anal sphincter in health (recto-anal inhibitory reflex [RAIR]). This reflex has been found to be impaired in patients with constipation, faecal incontinence, diabetic neuropathy, and after radical hysterectomy (Kelly et al. 1998;Deen et al. 1998;Xu et al. 2008). Rectal distension also causes a brief contraction of the external anal sphincter (recto-anal contractile response [RACR])(Kumar et al. 1990;Rogers 1992;Bharucha 2006). Both reflexes are thought to occur independent of rectal sensory perception. More recently, Rao et al have described the sensori-motor response (SMR) in health (De et al. 2007). This is a consistent and reproducible anal contraction temporarily related to the onset of desire to defaecate on balloon distension. Unlike the RAIR and RACR, the SMR is associated with rectal perception. The same group found that in patients with constipation and RH, all the above reflexes were found to be intact, though greater distension volumes were required than in healthy controls. They also noted that in 43% of patients with RH, the SMR was associated with absent rectal sensation (Remes-Troche et al. 2010).

1.9.2 COLON

It has previously been shown that up to 13% of patients with constipation and RH have delayed colonic transit demonstrated on a radio-opaque marker study (Gladman et al. 2003b). The exact pattern of colonic delay in RH is currently unknown. As RH is associated with outlet dysfunction, intuitively a left sided delay would be expected.

However, if RH was part of a more generalised neuropathic disorder proximal colonic activity may also be affected. Patients with chronic constipation, even with normal transit, have been shown to have reduced fasting and post-prandial colonic tone, reflecting motor dysfunction (Ravi et al. 2010).

Colonic sensation has been studied in healthy subjects using a barostat but there is a paucity of studies in constipation and in patients with rectal hyposensitivity (Odunsi et al. 2010;Iturrino et al. 2012)

1.9.3 PROXIMAL GI TRACT

The impact of RH on the remainder of the gastro-intestinal tract is not known, and also whether the impairment of sensation extends beyond the rectum to more proximal regions. In patients with slow transit constipation, 43% have been found to have concomittent motor involvement of the upper GI tract (Zarate et al. 2009). Similarly, patients with Barrett's oesophagus have been shown to have diminished oesophageal sensitivity (Krarup et al. 2011). A pan-enteric visceral sensory impairement is thus feasible in patients with rectal hyposensitivity though not studied to date.

1.9.4 URINARY BLADDER

Afferent sensory fibres from the urinary bladder also travel in the pelvic nerves to sacral segments S2-4, in common with the rectospinal afferents (Wester et al.

1998;Shea et al. 2000;De et al. 2003). Patients with constipation have been shown to have reduced bladder sensation and increased capacity (Bannister et al. 1988;Kerrigan et al. 1989;MacDonald et al. 1991). In a pilot study of bladder sensation in patients with RH and constipation, Gladman *et al* found that the vast majority of such patients had impaired or absent bladder sensation (Gladman MA et al. 2004). This may indeed be a reflection of a pan-pelvic sensory neuropathy.

1.10 TREATMENT

1.10.1 BOWEL RETRAINING / BIOFEEDBACK

Bowel retraining, especially incorporating sensory training, has been used successfully both for management of constipation and rectal evacuatory dysfunction (Gladman et al. 2006;Rao 2011). Clinical improvement has been shown in patients with constipation and RH following bowel retraining, particularly incorporating biofeedback. However, patient numbers have been small and follow up limited to the short term (Rao et al. 1997). Improving sensory perception has been one of the principal aims of these treatment modalities. Sensory retraining involves inflating a balloon in the rectum until urge threshold is reached. With repeated sessions of treatment, lower sensory thresholds can be established (Peticca et al. 2002). However, although normalisation of sensory thresholds is perhaps central to treatment success, randomised controlled trials are lacking.

In patients with faecal incontinence, sensory re-training and biofeedback have also been shown to be beneficial (Wald et al. 1984;Buser et al. 1986;Chiarioni et al. 2002).

Some studies have shown that normalisation of sensory thresholds may be allied to a reduction in episodes of faecal incontinence. Benefit is sustained for 12-30 months following completion of therapy (Wald et al. 1984;Miner et al. 1990;Ozturk et al. 2004). One randomised, crossover study evaluated active sensory retraining and biofeedback alone; the only significant change in anorectal function was improvement in rectal sensory perception in those receiving active sensory retraining. This was not seen in the sham retraining group. All 'responders' (50% had no further incontinence episodes and >75% reduction in the remainder) had improved sensation following the treatment (Miner et al. 1990).

Nevertheless, there is still a paucity of quality data regarding the benefit of bowel retraining and sensory biofeedback. As bowel retraining incorporates several components, the efficacy of each of the individual components needs further evaluation.

1.10.2 NEUROMODULATION

Neuromodulation involves stimulation of the extrinsic neural control of the pelvic floor. Most studies have focussed on end organ outcomes. Several methods and techniques of neuromodulation exist currently. However, there is very little understanding of their mechanism of action. Neuromodulation seems to benefit patients with constipation, rectal evacuatory dysfunction and faecal incontinence alike. This likely highlights the possibility that they have common pathoaetiologies.

1.10.2.1 Sacral nerve stimulation

Sacral nerve stimulation (SNS) involves placing a temporary electrode alongside a sacral nerve root (usually S3). This is attached to an external stimulator. After a trial period, if the subject has benefitted, a permanent electrode is implanted. SNS has been found to be effective in patients with faecal incontinence (Jarrett et al. 2004;Hetzer et al. 2006;Mowatt et al. 2007) and also recently reported to be an effective treatment for constipation in up to two-thirds of patients studied (Kamm et al. 2010;Thomas et al. 2013). One such study showed reduction in urge and maximum tolerated thresholds with SNS (Kamm et al. 2010).With regard to rectal hyposensitivity *per se* and constipation, only one randomised double-blind trial has been performed, albeit with small numbers, and found normalisation of sensory thresholds with treatment and lead to increased bowel frequency and improved constipation severity scores (Knowles et al. 2012). However, the true lasting benefit of SNS needs to be confirmed with larger prospective studies with longer follow up (Thomas et al. 2013).

1.10.2.2 Electrical stimulation

Electrical stimulation techniques with an anal plug have been successfully used in the treatment of constipation. Rectal sensory thresholds also significantly improved in the electrical stimulation group compared to the group receiving only biofeedback therapy in a randomised trial setting (Chang et al. 2003a;Chang et al. 2004). Transabdominal electrical stimulation has also been used in treating children with

slow transit constipation successfully (symptomatic improvement was noted in two thirds of patients, with benefit lasting for up to two years in one third) (Ismail et al. 2009;Leong et al. 2011). Dorsal genital nerve stimulation has also been studied in patients with spinal cord injury, with a reduction in rectal diameter and compliance on stimulation (Worsoe et al. 2012). However, rectal sensory function was not investigated in the latter study.

1.10.2.3 Magnetic stimulation

Magnetic stimulation of the sacral dermatomes has been successfully used in the management of patients with constipation in a variety of settings i.e. idiopathic slow transit (Lee et al. 2006), constipation in the elderly (Wang et al. 2012), constipation associated with spinal cord injury (Tsai et al. 2009) and Parkinsonism (Chiu et al. 2009). Such studies have shown improvement in symtoms including bowel frequency and laxative use. Similarly improvements in objective measures on physiology studies such as colonic transit time and rectal sensory thresholds have been reported (Lee et al. 2006;Wang et al. 2012). However, the long term efficacy of this modality has not been studied; the longest follow up was 3 months (Tsai et al. 2009).

1.10.3 SURGERY

Surgical treatment is considered the last resort in patients whose constipation is refractory to other modalities of treatment. Several surgical options are available with variable success (Gladman et al. 2008). Most of these involve resection of part or all

of the colon and rectum. Success rates depend on the indication and type of procedure. However, surgery is usually irreversible and associated with a high morbidity (Knowles et al. 2009b). A novel approach, vertical reduction rectoplasty (Williams et al. 2000) to surgically reduce rectal size and also improve biomechanical properties has shown promise in patients with RH and megarectum. This procedure involves excision of part of the rectum, thereby reducing rectal capacity and compliance. This leads to better perception of rectal fullness and improves symptoms. Results have been shown to be maintained in the medium term (Gladman et al. 2005b) .

1.11 CLINICAL / RESEARCH IMPLICATIONS

It is currently unclear whether RH itself leads to hindgut dysfunction, or is a consequence of the same i.e. is there a true cause- effect relationship, or is it purely an epiphenomenon? The underlying causes of RH remain to be fully established. It is almost certain that both the aetiology and pathophysiology of RH are multifactorial, with the latter likely to involve biomechanical, neuroanatomical and behavioural factors. The level and extent of any disruption in the afferent nerve pathway needs to be fully established. Whether a defect in the afferent pathway is an isolated phenomenon, or is part of a generalised somatic / autonomic neuropathy needs to be investigated. Previously, it has been shown that patients with constipation, in whom colonic transit is delayed, have concurrent sytemic small fibre sensory and autonomic dysfunction (Altomare et al. 1992;Knowles et al. 1999). However, no studies have systematically investigated the above in patients with constipation and RH. The

pathogenesis of abnormal biomechanical properties also needs to be studied further.

Although the relationship between RH and rectal evacuatory dysfunction (RED) has been well established (Gladman et al. 2003b), the true clinical impact of RH is currently unclear.. Similarly, a strong link between RH and 'altered call to stool' has also been anecdotally reported (Harraf et al. 1998;Gosselink et al. 2001a), but not formally investigated. Furthermore, RH has been found to have an effect on other colorectal physiological functions, especially colonic transit (Gladman et al. 2003b). However, whether RH leads to specific patterns of colonic transit delay needs further evaluation. Ultimately, although RH has been found in patients with hindgut dysfunction, it is unknown if the presence of RH leads to specific symptoms or an increased severity of these symptoms. In addition, whether patients with RH and hindgut dysfunction represent a distinct clinical phenotype needs further evaluation. Finally, whether correction of RH is the mechanism responsible for symptomatic improvement in patients, treated with various modalities, for hindgut dysfunction (Rao et al. 1997;Chiarioni et al. 2002;Chang et al. 2003a;Lee et al. 2006;Knowles et al. 2012) needs to be confirmed with further large scale studies.

1.12 AIMS

The primary aim of the studies performed within this thesis is to evaluate the impact of RH on both clinical symptoms and physiology in patients who were referred to a tertiary centre for management of chronic and refractory constipation.

1.12.1 SPECIFIC AIMS

- To determine how RH impacts symptom profile and on severity in patients with chronic constipation.

- To determine whether the presence of RH results in specific patterns of colonic transit delay or type(s) of rectal evacuatory dysfunction in patients with chronic constipation.

- To determine the level of involvement of the afferent pathway in patients with RH and constipation by studying general somatic, anal and perineal sensation.

- To study if rectal motor function is affected in patients with RH and chronic constipation.

- To evaluate a novel technique for simultaneously studying recto-anal reflexes and rectal sensation in health and in patients with chronic constipation and RH.

2 MATERIALS AND METHODS

2.1 INTRODUCTION

This chapter covers the selection and recruitment of patients and volunteers for participation in the clinical studies performed within this thesis. The methodology used for studying rectal sensory function is also discussed. In addition, the criteria used for a diagnosis of RH and its limitations are discussed. Details of complimentary tests of anorectal function are also included. Clinical and physiological data collected for patients are presented in each individual chapter. The methodology pertaining to the preparation of this thesis is also presented. Due to the diverse nature of studies performed, specific methodologies pertaining to each study and their background will be discussed seperately with each chapter.

2.2 RESEARCH ETHICS COMMITTEE APPROVAL

The use of patient and control groups for the clinical studies included within this thesis was approved by the East London and the City Research Ethics Committee (ELCREC). The following ethics committee approvals cover the studies undertaken

ELCREC: **P/97/338**

ELCREC: **P/02/073**

ELCREC: **P/02/184**

ELCREC: **P/03/039**

ELCREC: **07/Q0604/36**

2.3 DIAGNOSIS OF RECTAL HYPOSENSITIVITY

2.3.1 DEFINITION OF RECTAL HYPOSENSITIVITY

For all studies, RH was defined as diminished or absent perception of rectal distension, diagnosed during anorectal physiological studies on the basis of having elevated thresholds to simple volumetric balloon distension (Azpiroz et al. 2002).

2.3.2 ASSESSMENT OF RECTAL SENSORY FUNCTION

This was performed as part of standard anorectal physiological investigations, by inflating a latex balloon positioned in the rectum with air using a hand-held syringe (Diamant et al. 1999). The threshold volumes for first constant sensation (FSV), desire to defaecate (DDV) and maximum toleration (MTV) were elicited (Farthing et al. 1978;Diamant et al. 1999;Rao et al. 2002).

Prior to anorectal physiological assessment, all patients had investigation to exclude organic rectal disease. As rectal sensitivity can be influenced by physiologial, environmental and pharmacological factors, the balloon distension protocol was

standardised. For all subjects, the physiology studies were performed in the same clinical laboratory under the same conditions to reduce the impact of environmental factors. All medications that could impact on gastrointestinal function were stopped 24 hours prior to assessment. No bowel preparation was used. All subjects were provided with standardised information for reporting rectal sensations prior to commencement of the studies. The examiner performed the tests but did not interact with the subjects after initial explanation. No auditory or visual cues were provided. All studies were performed with the subject in the left lateral position. A 6 × 4 cm latex balloon was secured to a 16G Foley catheter (Figure 2.01), and inserted into the rectum. The balloon was positioned with the balloon 'neck' lying 10 cm from the anal verge to ensure that the balloon was positioned in the mid / upper rectum and that distension did not impinge on the sensitive anal canal, thereby evoking anal sensation.

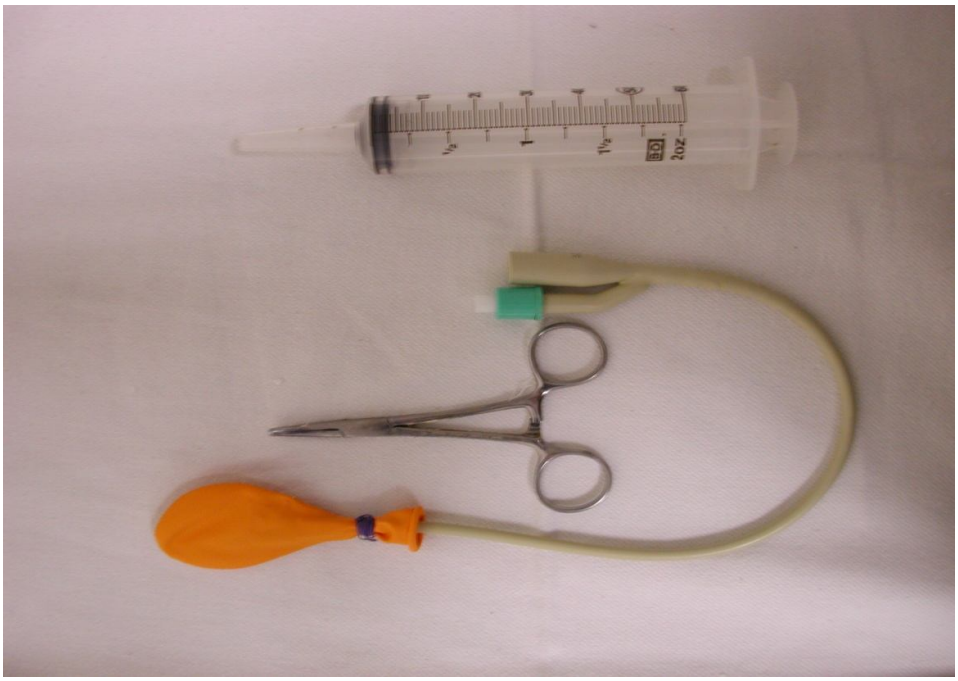


Figure 2.01: Device used for assessing rectal sensory function during anorectal physiology studies. A latex balloon was secured to a 16G Foley catheter and inflated

with air using a 60 ml hand-held bladder syringe.

Once the position of the balloon was confirmed, continuous 'ramp' distension was performed with air, at the rate of 1 ml/sec using a 60 ml bladder syringe. Threshold volumes for FCS, DDV and MTV were determined. As mentioned distension was performed using air. We acknowledge that different consistencies are perceived differently, i.e air, liquid and solid, but for the purpose of this thesis, and diagnosing RH, balloon distension with air was used.

2.3.3 NORMAL RANGES FOR RECTAL SENSATION

Normal ranges for rectal sensation were established within our unit by studying 91 healthy volunteers (50 female, median age 39 years, range 18-63 years) (Vasudevan et al. 2007a). All volunteers underwent comprehensive anorectal phsiological investigation, including testing of rectal sensory function as described previously (section 2.3.2). Values above the upper limit of normal (mean + 2 sd; log transformed data, Table 2.01) were considered to reflect diminished rectal sensory perception.

Table 2.01: Upper limits of the normal range for rectal sensory threshold volumes in males and females

Rectal sensation	*Threshold Volume (ml)*	
	Men	*Women*
First constant sensation	**150**	**110**
Desire to defaecate	**190**	**200**
Maximum toleration	**325**	**290**

2.3.4 DIAGNOSTIC CRITERIA FOR RECTAL HYPOSENSITIVITY

For the purposes of the studies performed as part of this thesis, RH was diagnosed when two or more of the three rectal sensory threshold volumes were elevated beyond the normal range (Table 2.01).

2.3.5 CRITICAL APPRAISAL OF DIAGNOSTIC CRITERIA

Volumetric distension using a simple latex balloon is widely employed for studying rectal sensory function in everyday clinical practice (see section 1.4.1). Volumetric distension is assumed to mimic the physiological process of rectal filling. Although multiple factors are known to affect rectal sensitivity, standardised protocols and methodology were employed to study patients and controls. However, certain factors such as menstrual cycle and psychological status could not be controlled. As simple balloon distension was used for diagnosing RH, it was historically not possible to control for rectal wall properties (i.e capacity and compliance). Henceforth subjects were included *irrespective* of the underlying mechanism of RH, on the basis that they *all* had '*impaired perception of rectal distension'* i.e. (RH).

There is considerable variation in the published medical literature on normal reference ranges for rectal sensation, dependent upon the methodology employed. Therefore, it is important for individual units to establish their own normal ranges (Felt-Bersma et al. 1991). The data provided for our unit, from 91 healthy volunteers (Table 2.01)

(Vasudevan et al. 2007a) serves as a robust reference range to allow for discrimination between normal and abnormal (i.e. hypo-) sensation. We have previously shown from our institution that balloon distension is reproducible by studying 31 healthy volunteers a median of four weeks apart (Chan et al. 2003)

Using elevated *two or more* sensory thresholds to define RH is a conservative approach, as there is no consensus in literature as to how many thresholds have to be elevated for a diagnosis of RH. Other studies have used variable definitions (Hancke et al. 1987;Lubowski et al. 1988a;De et al. 1989;Sun et al. 1990b;Remes-Troche et al. 2010). If at least 2 of the thresholds were above the normal range, then the criteria would be unlikely to include borderline / false positive results.

2.4 PATIENTS

2.4.1 RECRUITMENT

Patients recruited for the studies performed in this thesis were from those referred to the Gastrointestinal Physiology Unit (GIPU) at The Royal London Hospital for assessment of their symptoms of hindgut dysfunction. Healthy volunteers for normal control data were recruited through advertisement. All patients and healthy volunteers invited to participate in these studies were provided with written and verbal information according to Research Ethics Committee guidelines. No paediatric patients were recruited. All women of child bearing age had to have a negative pregnancy (urine β HCG) test prior to inclusion.

2.4.2 PATIENT SELECTION (RH)

2.4.2.1 Inclusion criteria

1) Rectal hyposensitivity (see section 2.3.4)

2) Initial: Fulfilment of diagnostic criteria for functional bowel disorders, defined as a variable combination of gastrointestinal symptoms that cannot be explained by mechanical or biochemical abnormalities.

3) Restricted to: fulfilment of criteria for functional constipation, irrespective of the presence or absence of concomittent faecal incontinence. Functional constipation was defined according to the Rome III criteria : symptoms for at least the last 3 months, with symptom onset at least 6 months prior to diagnosis:

    - > 2 of the following, affecting more than 25% of defaecations:
        i. Straining;
        ii. lumpy or hard stools;
        iii. sensation of incomplete evacuation;
        iv. sensation of anorectal obstruction/ blockage;
        v. manual manoeuvers to facilitate defaecation;
        vi. fewer than 3 defaecations per week;
    - loose stools rarely present apart from the use of laxatives;

- there are insufficient criteria for IBS;

4) Proof of fulfilment of the above, regardless of the underlying mechanism of RH (i.e primary or secondary, see chapter 1, section 1.6.2). However, division on the basis of underlying mechanism was employed in chapters 6, 7 and 8.

2.4.2.2 Exclusion criteria

The following categories of patients were excluded from the studies:

1) absence of objective proof of RH on physiological testing, despite symptoms suggestive of so i.e constipation and loss of desire to defaecate;
2) failure to fulfil diagnostic criteria set out in 3 (eg. RH on testing but no constipation and isolated faecal incontinence);
3) patients with abdominal pain and objective evidence of RH, but who fulfil the Rome III criteria for the 'irritable bowel syndrome' IBS on acccount of the pain being relieved by defaecation, and onset being associated with a change in form and frequency of stool. Constipated patients with RH and abdominal pain who did not fulfil the criteria for IBS were included;
4) age $\leq$ 16 years;
5) positive urine pregnancy test;
6) inability to provide informed consent (no such patient was referred);
7) evidence of Hirschprung disease on histology (no such patient referred);
8) evidence of other organic causes for constipation (no such patient referred)

2.4.2.3 Study populations

Chapter 3 The study population comprised 110 patients referred for anorectal physiological assesment between 2006 and 2008, of whom 55 had RH.

Chapter 4 The study comprised 120 patients referred for anorectal physiology studies between 2004 and 2007, of which 34 had RH.

Chapter 5 The population comprised 158 female patients referred between 2004 and 2006 of which there were 45 patients with RH.

Chapter 6 The study population comprised 18 patients (10 RH) and 19 healthy volunteers. Patients were referred for physiology studies between 2006 and 2008.

Chapter 7 The study population comprised 31 patients with constipation, of which 21 had RH. They were investigated between 2005 and 2006. Ten healthy controls were also studied.

Chapter 8 The study population comprised 4 patients with RH and 11 healthy volunteers investigated in 2008.

2.4.3 CONTROL GROUPS

The index study group in this thesis were patients with RH. However, appropriate control groups were also recruited for comparison:

1) **Patients with constipation and *normal* rectal sensation (NS).**

   These patients were recruited as the positive control group. Rationale for recruitment was to determine if differences observed were due to RH, and not to having symptoms of constipation.

2) **Asymptomatic healthy volunteers** (Appendix D)

   Normal ranges for all the parameters studied were obtained in healthy volunteers. Volunteers were screened comprehensively using validated gastrointestinal symptom questionnaires and were confirmed to be free of symptoms and signs of gastrointestinal disease. None had previous gastrointestinal illness, and were not on any medications. All volunteers were recruited after the protocol was explained to them, and they provided written informed consent.

2.5 DATA COLLECTION

2.5.1 METHODS OF DATA COLLECTION

Information regarding clinical details and anorectal physiology investigations were obtained from reviewing patient records (hospital notes, computerised health records and anorectal physiology reports) for all patients. Data were collected both retrospectively and prospectively.

1) Retrospectively Patients before February 2005.
2) Prospectively Patients presenting during the thesis study period between February 2005 to March 2008.

All prospectively evaluated patients had a formal clinical interview with the author. Validated questionnaires (Agachan et al. 1996;Vaizey et al. 1999, Appendix A and B) were used to acquire details about the nature and severity of symptoms of constipation and faecal incontinence. The Cleveland clinic score was used to assess constipation and its severity (Agachan et al. 1996). This comprised eight questions relating to bowel function. The total score ranges from 0 (normal) to 30 (severe constipation). A score of 8 or more is used to define constipation, and a score over 15 is considered significant constipation. It has 96% accuracy in predicting those with proven physiological abnormalities from those with normal physiology (Agachan et al. 1996). For quantifying faecal incontinence, the 'Modified Wexner Score' was used (Vaizey et al. 1999). This system has a score from 0 (fully continent) to 24 (severe incontinence), and whose scores have been shown to improve (i.e. decrease) with

therapeutic intervention (Vaizey et al. 1999).

2.5.2 STORAGE OF DATA

All data were stored on password protected computers in the GI Physiology Unit. Individual spreadsheets (Microsoft ® Excel 2000; Microsoft Corporation, Santa Rosa, CA, USA) for data recording were also password protected.

2.5.3 CLINICAL DATA

A detailed clinical history including presenting complaints, precipitating factors, past surgical / medical / obstetric history and family history was obtained from each individual as listed in Table 2.02. Prior to referral for anorectal physiology studies, all patients had undergone routine clinical examination in the outpatient setting. The examination included general and abdominal examination, digital rectal examination, proctoscopy and rigid sigmoidoscopy. Details of these examinations are not included. Furthermore, patients undewent blood tests (serum calcium, thyroid function tests and random blood sugar levels) to rule out metabolic and endocrine causes of their symptoms, and also underwent flexible endoscopies / barium enema where indicated.

Table 2.02: Clinical data obtained for all subjects

Essential details	***Name / D.O.B / Sex / Occupation / Hospital N^o***	
Presenting	***Constipation***	
complaints	***Faecal incontinence***	
	Other gastrointestinal symptoms	
Duration	***Age of onset / Duration (years)***	
Precipitating	***Pelvic or anorectal surgery /***	
factors	***Neurological disease / Spinal trauma***	
	Diabetes Mellitus /	
	Others / None	
Other systems	***Urological symptoms***	
	Neurological symptoms	Central nervous system
		Peripheral nervous system
		Autonomic nervous system
Past history	**Medical**	Neurological / endocrine
	Surgical	Abdominal / perineal / spinal
	Obstetric	Type of delivery / assistance
	Gynecological	Hysterectomy / Pelvic surgery
Family history	***Functional bowel disorders / others***	
Treatment	***Medications***	Laxatives
		Suppositories / enemata
	Behavioural therapy	Biofeedback
	Surgery	Abdominal / anorectal
Drug history		

2.6 GASTROINTESTINAL PHYSIOLOGY INVESTIGATIONS

Anorectal physiology studies are performed to objectively assess anorectal function. These investigations involve several complimentary tests of sensory and motor function of the anorectum and the colon, with the aim to identify underlying pathophysiological mechanisms (Diamant et al. 1999;Azpiroz et al. 2002). This section describes the other tests that are routinely performed in patients presenting to the GIPU. Rectal sensory assessment has been described in detail previously (section 2.3.2). All patients studied prospectively as part of this thesis had comprehensive anorectal physiological studies. The following tests were performed:

1) **Rectal sensory function**	First constant sensation
	Defaecatory desire volume
	Maximum tolerated volume
2) **Anal manometry**	Anal canal resting and squeeze pressures
	Rectoanal inhibitory reflex
3) **Endoanal ultrasound**	Evaluation of anal sphincter structure
4) **Pudendal nerve studies**	Measurement of terminal motor latencies
5) **Radio-opaque marker study**	Evaluation of colonic transit
6) **Evacuation proctography**	Anatomical and functional assessment of the pelvic floor and anorectum during simulated defaecation

2.6.1 ANAL MANOMETRY

Anal manometry involves measurement of pressures in the anal canal to evaluate anal sphincter strength. Several types of probes have been used satisfactorily to achieve this. They can be open- tipped or side opening water perfused catheters, air / water filled balloons or direct online solid-state transducers. Normal anal canal pressures vary according to age, sex and technique used (Diamant et al. 1999). Pressures are higher in men and younger individuals (Jameson et al. 1994). Low- rate perfusion manometry using catheters 5mm in diameter provide reliable measurements and are used commonly in clinical practice (Azpiroz et al. 2002).

There are three main parts to the perfusion manometry system: (a) the intraluminal water-perfused catheter; (b) pressure transducers; (c) the amplification / recording / display system (Figure 2.02). All patients included in this thesis had standard water perfused anal manometry using a single channel side hole catheter linked to an Arndorfer-type pneumohydraulic water perfused system (Arndorfer Medical Specialities, Greendale, USA). Anal canal pressures were measured from the distal rectum down to the anal verge using a station pull-through technique (Read et al. 1979). This technique avoids stimulation of the anal sphincters which may resuly in involuntary (and unwanted) contraction (Rao et al. 2002).

The aims of anal manometry were to identify ; functional anal canal length, and to record maximum resting anal pressure (tonic activity of the internal anal sphincter) (Engel et al. 1995) and voluntary squeeze anal pressure (external anal sphincter

function) (Engel et al. 1995). Distension of the rectum produces temporary relaxation of the anal canal thereby reducing resting anal pressures. This recto-anal inhibitory reflex is an intrinsic reflex mediated by the myenteric plexus. The presence or absence of this reflex was studied in all subjects by rapidly inflating a rectal balloon and simultaneously measuring anal pressure in the high pressure zone (Farthing et al. 1978).

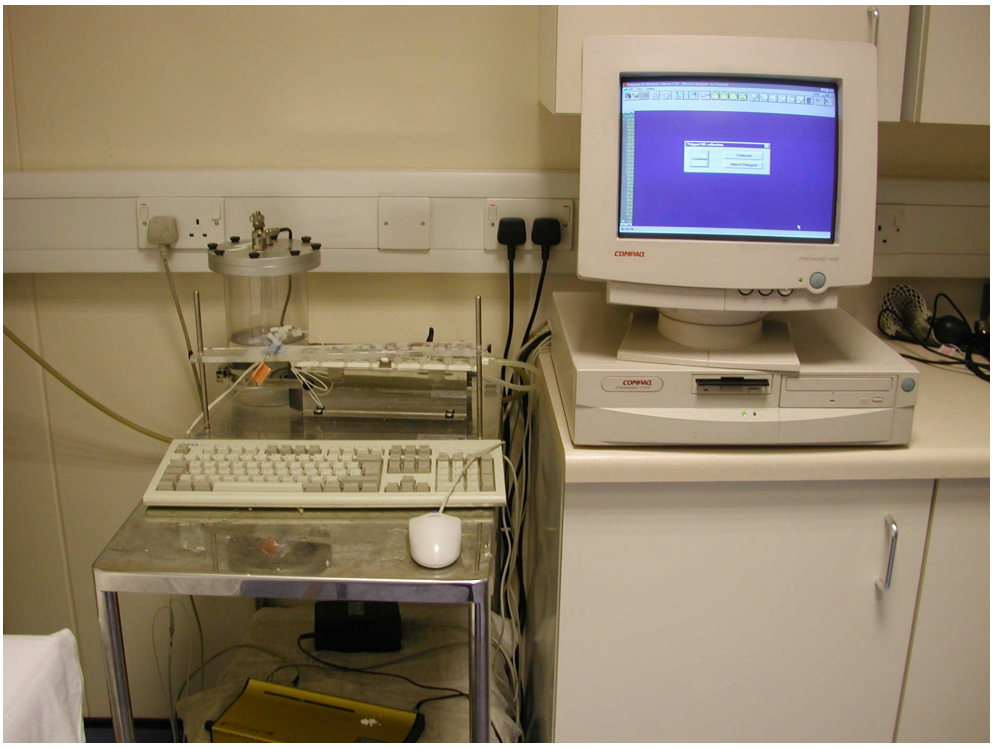


Figure 2.02: Anal manometry measurement apparatus.

Normal ranges for resting and squeeze pressure were taken from the literature from studies employing similar methodology: resting pressure (50-150 cmH_2O), squeeze increment (50-200 cmH_2O) (Jameson et al. 1994). These normal ranges are comparable to other studies in literature using similar techniques (Read et al. 1979). Based on these control values, patients were classified as either having normal or

abnormal sphincter pressures (resting, squeeze, or both). During the course of this thesis 91 healthy volunteers were studied in our unit and the results were comparable: lower limit of normal resting pressure (32 cmH_2O) and squeeze increment (35 cmH_2O).

2.6.2 ENDOANAL ULTRASOUND

Endoanal ultrasound is now the standard for determination of anal sphincter integrity. Several studies have shown that structural damage to the sphincters, rather than pudendal neuropathy, is the cause for faecal incontinence in the majority (Burnett et al. 1991;Law et al. 1991;Deen et al. 1993;Nielsen et al. 1993).

Endo-anal ultrasound was performed using a mechanically rotating endoprobe, using a 10 MHz transducer (transrectal probe, type 1850 and ultasound machine [model 184610]; B-K Medical, Berkshire, United Kingdom) (Figure 2.03a). The plastic cone surrounding the transducer is filled with water (Figure 2.03b), and is protected with a condom and covered with lubricant jelly to ensure good contact.

The probe was inserted into the rectum and gradually withdrawn through the anal canal, recording images from the upper, mid and lower anal canal. Images are obtained at right angles to the lumen as a 360^0 axial view.

Sensitivity of endoanal ultrasound for identification of anatomical defects approaches 100% if performed by an experienced practitioner (Sultan et al. 1993;Sultan et al.

1994). Both stuctural damage to the external and internal sphincters, and / or degenerative changes to the muscle can be identified using this technique (Vaizey et al. 1997).

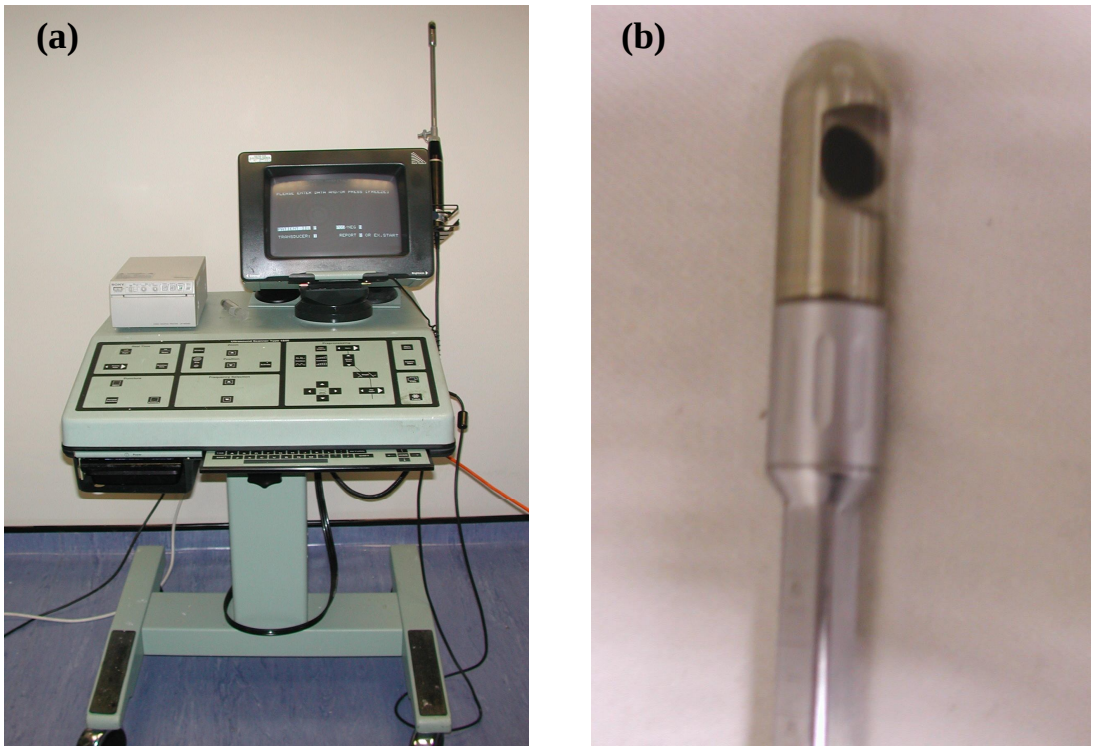


Figure 2.03: a) Ultrasound machine (model 184610) with **b)** 10 MHz transrectal mechanically rotating endoprobe, with plastic cone filled with distilled water.

2.6.3 PUDENDAL NERVE MOTOR LATENCIES

Branches of the pudendal nerve supply the pelvic floor, external anal sphincter and the perineum. Therefore it plays an important role in maintenance of normal pelvic floor function and continence. Pudendal neuropathy plays an important role in the aetiology of neurogenic faecal incontinence and other functional disorders of the hindgut (Hill et al. 2002). Pudendal nerve function is determined by measuring the

terminal motor latency (PNTML). This is the time required to evoke an external anal sphincter contraction from stimulation of the nerve at the level of the ischial tuberosity. Pudendal neuropathy is characterised by prolonged latencies and has been demonstrated in patients with faecal incontinence (Kiff et al. 1984).

All patients in this thesis had PNTML testing. This was done using a disposable glove-mounted stimulating and recording electrode (St. Mark's pudendal electrode, Dantec Electronic Ltd, Bristol, UK [Figure 2.04]) connected to an electromyographic recorder. The index finger with mounted electrode was inserted into the rectum and the ischial tuberosity palpated. The overlying nerve was then stimulated with square wave stimuli of 0.1 ms duration and 50 V applied at 1 s intervals. Normal values were taken from the literature using similar methodology. Latencies were defined to be prolonged if greater than 2.3 ms in patients less than 50 years of age, or greater than 2.5 ms if over 50 years (Jameson et al. 1994).

PNTML should, however, be interpreted with a certain degree of caution. Although abnormal (prolonged) latencies have been shown with idiopathic faceal incontinence, some studies have shown that patients with delayed latencies have normal squeeze pressures. This might be due to methodological limitations i.e. PNTML measures conduction in the fastest conducting fibres, and therefore can still be normal as long as some fibres remain intact (Cheong et al. 1995). Moreover, the technique is also operator dependent and difficult to perform in certain patient groups due to, for example, abnormal body habitus, fibrosis or discomfort.

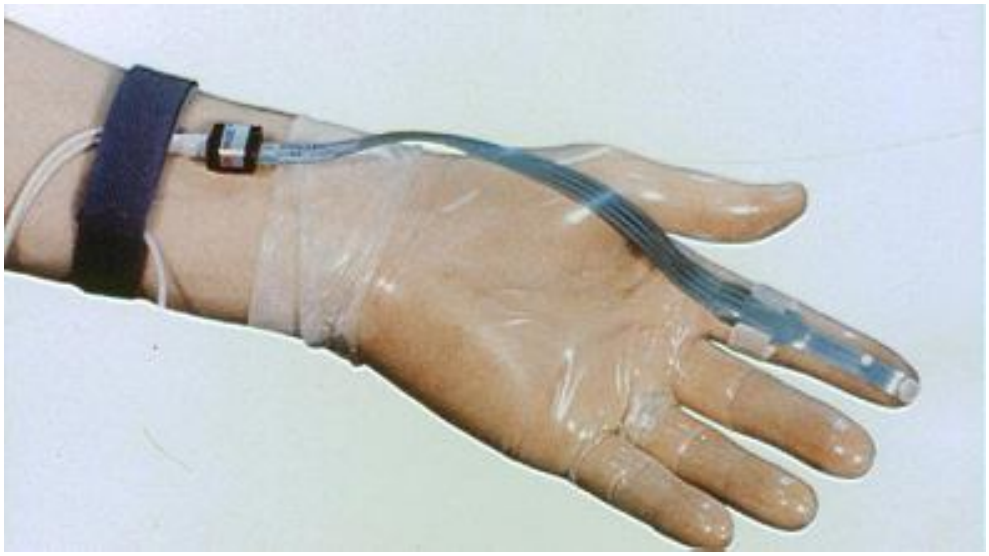


Figure 2.04: The St. Mark's pudendal nerve electrode (stimulating and recording electrodes mounted on a fixed array).

2.6.4 COLONIC TRANSIT STUDY

Constipation can result from the slow rate of progression of luminal contents in the colon (MacDonald et al. 1993). Colonic transit studies help to distinguish those with normal transit from those with delayed transit constipation (slow transit constipation: STC) (Diamant et al. 1999). Several methods have been used to study colonic transit including radiological, chemical, particulate, calorimetric and isotopic. The most common method used in everyday clinical practice is a simple radio-opaque marker study (Hinton et al. 1969). In this, the subject ingests non-absorbable pellets that are of similar density to food residue and do not have any effect on gastro-intestinal

motility. Plain abdominal films are obtained 3-5 days later (Hinton et al. 1969;Arhan et al. 1981;Metcalf et al. 1987). Although the most accurate method of measuring segmental colonic transit is radionuclide scintigraphy (Krevsky et al. 1986;Scott et al. 2001), this is limited to specialist centres and is time consuming for both patient and practitioner.

All patients (studied as part of this thesis) who presented with infrequency of defaecation had a colonic transit study. All medications that affect colonic transit (laxatives, opioids etc) were stopped 24 hours prior to the start of the study, and patients remained on a normal diet during the study period. Subjects ingested a gelatine capsule containing 50 radio-opaque markers, cut from a length of 2.5 mm (external) diameter radio-opaque vinyl tubing (SIMS Portex Ltd., Hythe, UK). A single plain abdominal radiograph was performed at 96 hours after administration of the capsule. Slow transit was defined as >20% of 50 administered markers remaining at 96 hours (Hinton et al. 1969;Bassotti et al. 1994;Scott et al. 2001).

2.6.5 EVACUATION PROCTOGRAPHY

Constipation can also occur secondary to rectal evacuatory dysfunction (Martelli et al. 1978). During evacuation proctography (EP), the rectum is imaged with a contrast medium and the process, rate and completion of rectal evacuation is recorded under fluoroscopy (Diamant et al. 1999). Anatomical abnormalities of the rectum (e.g prolapse, intussusception and rectocoele) can be identified using this technique. As with all tests of function / morphology there are drawbacks to the technique, e.g. 1)

the test may be considered non-physiological, as the test environment may inhibit normal evacuation; 2) incidental protographic “abnormalities” such as small rectocoeles or intussuscepta are seen in asymptomatic individuals (Shorvon et al. 1989).

All patients studied in this thesis had EP performed under controlled conditions. Artificial stool (barium sulphate mixed with porridge oats and water) was instilled into the rectum until maximum toleration was reached. The neostool was of uniform consistency for each subject, and was injected into the rectum using a 150 ml syringe via a proctoscope. The subject was then quickly transferred to a radiolucent commode and lateral fluoroscopy was performed during defaecation using an image intensifier (Siemens Plc., Bracknell, UK). Rectal evacuation was measured in terms of the speed (time taken for evacuation) and effectiveness (percentage of neostool evacuated). Both parameters were assessed from the initiation of evacuation to end-evacuation (the point at which the patient no longer felt the desire to defaecate). Percentage evacuated was calculated from the difference between initial resting and post-evacuatory images (Figure 2.05), a modification of a technique which correlates well with measured weights of evacuated contrast (Karlbom et al. 1999). Visual evidence of adequate recto-anal evacuatory manoeuvres (opening of the ano rectal angle ; relaxation of the anal canal, Figure 2.06) and propulsive forces through pelvic floor descent were also assessed (Halligan et al. 1995). Any gross mechanical abnormality observed to impede evacuation was noted, i.e. full thickness rectal intussusception; medium to large ‘trapping’ rectocoele (Figure 2.07)

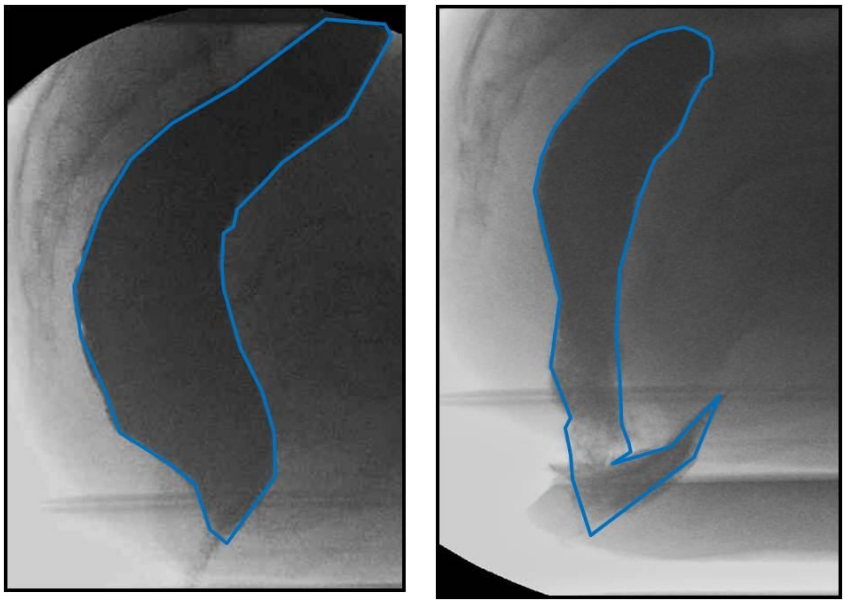


Figure 2.05: Method showing area marking on proctogram pre and post evacuation

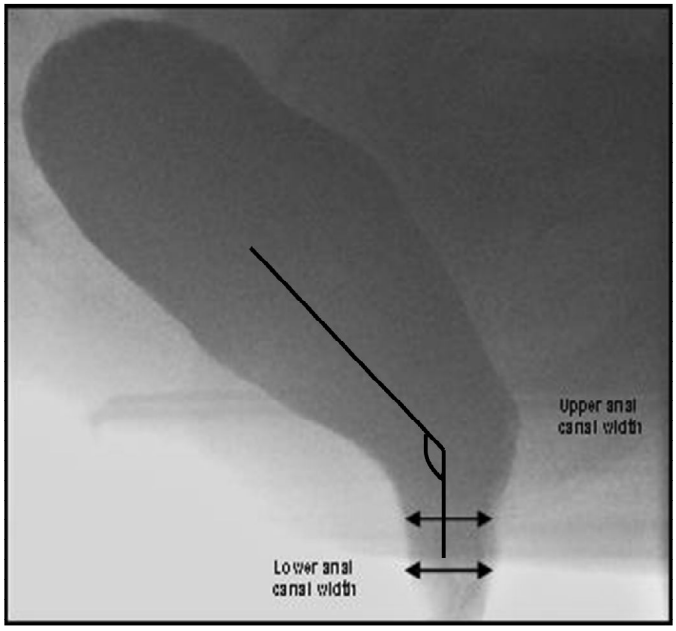


Figure 2.06 : Assesment of anorectal angle and anal canal opening

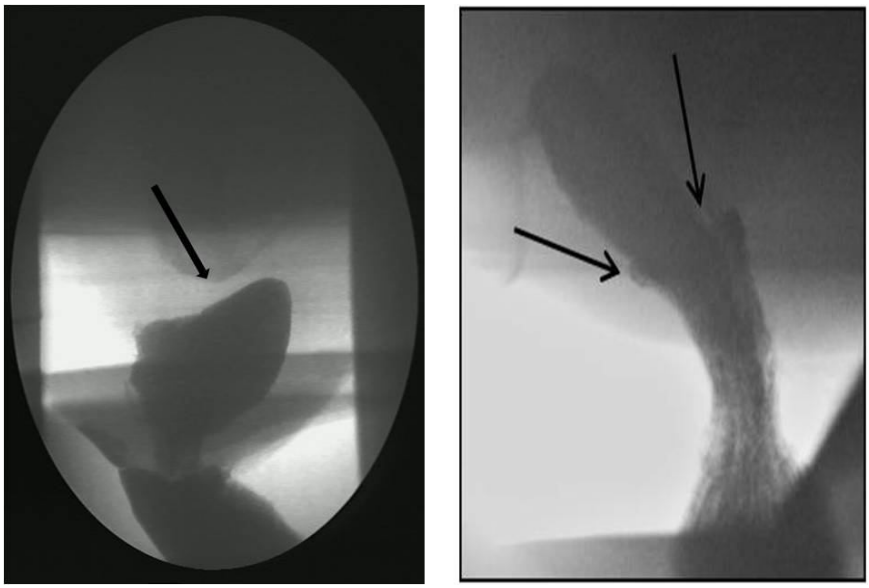


Figure 2.07: A; Medium sized rectocele (single arrow)

B: Rectal intussusception (two arrows)

The diagnosis of rectal evacuatory disorder was based on criteria proposed for functional defaecation disorders (Bharucha et al. 2006b), extended to embrace those with impaired evacuation secondary to a gross mechanical abnormality (since the proposed criteria only cover functional aspects) as described in section 2.6.5. Impaired evacuation, one of the criteria proposed for functional defaecatory disorders by Bharucha et al (Bharucha et al. 2006b), was defined as that protracted beyond 173 sec and / or the percentage of neo-stool expelled less than 55% (upper and lower limits of normal, respectively, derived from 49 healthy volunteers, (Scott et al. 2001;Dvorkin et al. 2005), and that a) at least 1 more of the diagnostic criteria proposed by Bharucha *et al* were met (i.e impaired evacuation, inappropriate contraction of pelvic floor muscles and inadequate propulsive forces; or b) a gross 'mechanical' obstructive feature was identified (i.e. rectocoele or intussusception).

Thus, an ED was subclassified into 'functional' (ED-F) or mechanical (ED-M), respectively. Where both a functional and mechanical features of impaired evacuation were present, subjects were subclassified into the group with the major obstructive component.

2.6.6 CLASSIFICATION OF PATIENTS WITH ANORECTAL DYSFUNCTION

On the basis of the physiological studies described, patients with constipation were classified as having 1) slow colonic transit, 2) rectal evacuatory dysfunction (mechanical, functional or both), 3) both or 4) neither. Those patients who had concomitant faecal incontinence were classified as having 1) isolated sphincter defects (external, intenal or both), 2) isolated neurogenic (secondary to pudendal neuropathy), 3) both (sphincter defect and pudendal neuropathy) or 4) neither, on the basis of endoanal ultrasound and pudendal nerve conduction studies.

2.7 DATA ANALYSIS

2.7.1 STATISTICAL SOFTWARE

Data was entered on to a spreadsheet (Microsoft ® Excel 2000; Microsoft Corporation, Santa Rosa, CA, USA). Statistical analysis was performed using commercially available statistical software packages (Prism 3.0®, GraphPad Software, Inc., San Diego, California, USA and SPSS 13.0, SPSS Inc. Chicago, Illinos, USA).

2.7.2 STATISTICAL ANALYSIS

Specific statistical analyses pertaining to individual chapters are described therein. Data were tested for deviation from normality using the Kolmogorov-Smirnov test with a *p* value calculated from Dallal and Wilkinson's approximation to Lilliefor's method. For normally distributed data, parametric statistical tests were employed and if the data were not normally distributed, non-parametric tests were used. A *P* value of <0.05 was considered to be statistically significant.

2.7.2.1 Comparing grouped numerical data

For comparison of 2 independent populations of parametric or non-parametric data, the Student's t-test and Mann-Whitney test were used, respectively. Similarly, if the data were paired, a paired t-test or Wilcoxin signed rank test were used, respectively. When studying 3 or more groups, an ANOVA (analysis of variance) was performed (along with the Bonferroni method for multiple comparisons between individual groups) for parametric data, or a Kruskal- Wallis test (with Dunn's multiple comparison post test), for non-parametric data.

2.7.2.2 Contingency table analysis

Contingency tables were analysed using the chi-square test (if greater than a 2×2 table). A Yates' continuity corrected chi-square test was used when 80% of the cells had expected frequencies of ≥ 5. The Fishers' exact test was used for 2×2 contingency tables. A two tailed *P* value was calculated in all cases.

2.7.2.3 Correlation and regression

Linear correlation or regression was used to compare the covariation between two variables. Whilst using linear regression analysis, 95% confidence intervals (CI), goodness of fit (r^2), and residuals were calculated. An F test was used to derive the *P* value to see if the slope was significantly different from zero.

2.8 LITERATURE REVIEW AND REFERENCING

References used in this thesis were obtained by performing internet searches of literature using Medline (Pubmed, National Centre for Biotechnology Information [www.ncbi.nlm.nih.gov]), EMBase, Cocharane library and Science Citation Index from the start of time frame through to April 2013. All references in this thesis have been prepared in accordance with the "Uniform requirements for manuscripts submitted to medical journals" developed by the international Committee of Medical Journal Editors (N Engl J Med 1991; 324: 424-428), based on formats for bibliographical references set out by the Vancouver Group. Commercially available software (Reference Manager 11, California, USA) was used for referencing in this thesis.

3 IMPACT OF RECTAL HYPOSENSITIVITY ON SYMPTOM SEVERITY AND OTHER COLORECTAL PHYSIOLOGICAL MEASURES IN PATIENTS WITH CONSTIPATION

3.1 INTRODUCTION

Functional constipation, which incorporates those with rectal evacuatory dysfunction, is a debilitating condition to patients and has a major impact on their quality of life (Thompson 2000;Halder et al. 2004;Nyrop et al. 2007;Liem et al. 2009). Symptom severity varies widely among patients, with several scoring systems available (Agachan et al. 1996;Frank et al. 1999;Knowles et al. 2000a;Chan et al. 2005a;Varma et al. 2008). The most widely utilised scoring system, proposed by Agachan *et al* (The Cleveland Clinic Constipation Score, CCCS) compared a constipation score with objective findings on physiology testing, that included a colonic transit study, anal manometry, cinedefecography and electromyography, and the authors concluded that the score correlated well with results of physiological testing, thereby allowing uniformity in assesment of severity of constipation (Agachan et al. 1996). The CCCS incorporates eight symptoms: frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per evacuatory attempt, assistance for evacuation, unsuccessful attempts in the last 24 hours, and duration of constipation. The total severity score ranges on a numerical scale between 0 and 30, with 30 representing the most severe symptoms.

Rectal hyposensitivity (RH) is found in a quarter of patients with constipation, with or without faecal incontinence (Gladman et al. 2003a). Whether blunted sensation is a cause or consequence of constipation is currently unknown. However, blunted sensation has been found to be the only demonstrable abnormality in a proportion of patients on function testing (Gladman et al. 2003b), and hence should be considered a potential pathophysiological factor. Several mechanisms by which RH can lead to symptoms of constipation have been postulated. These have been discussed in detail in Chapter 1 (section 1.8.1).

Whether rectal hyposensitivity is associated with a more severe symptom profile or influences other measures of colorectal function are currently unknown. In the largest study to date, the incidence of slow transit constipation, as diagnosed by radio-opaque marker study, was found to be similar between those with normal and blunted rectal sensation (Gladman et al. 2003a). However, the same study also showed that the prevalence of rectal evacuatory dysfunction was significantly higher in patients with RH, and that a major proportion of these did not have any demonstrable anatomical abnormality on proctography i.e. they were diagnosed with 'outlet dysfunction'. Nevertheless, no direct study thus far has investigated the severity of symptoms in patients with rectal hyposensitivity. Accordingly, the aim of this study was to compare symptom severity in patients with constipation with or without rectal hyposensitivity using the validated Cleveland Clinic questionnaire.

3.2 PATIENTS AND METHODS

3.2.1 PATIENTS

Fifty five consecutive patients with intractable constipation, who presented to our unit for anorectal physiology studies, and who were diagnosed as having RH were recruited. Rectal hyposensitivity was defined as having two or more sensory thresholds elevated above the normal range(s) (section 2.3.5). Fifty five age and sex matched patients with constipation and *normal* rectal sensation to balloon distension (NS) were recruited during the same time period as controls (Table 3.01 for patient demographics).

Table 3.01: Patient demographics

	NS	RH	*P* value
Age	49 (20-81 years)	49 (22-78 years)	NS
Gender	8:47 (Male, Female)	8:47 (Male, Female)	NS
Parity (F)	2 (0-7)	2 (0-7)	NS

(NS : Normosensate, RH: Rectal hyposensitivity. Values represent median and range.)

3.2.2 METHODS

3.2.2.1 History and constipation severity scoring questionnaire

A detailed history with regard to bowel symptoms was elicited by the investigator from each patient. Each subject also filled in the Cleveland Clinic constipation severity scoring questionnaire (Agachan et al. 1996) (Appendix A) at home prior to their appointment for diagnostic testing. Questions posed in the CCCS that involved quantification of symptoms were answered by the patients with the following descriptors (never = 0% of time, rarely = 25% of time, sometimes = 50% of time, usually = 75% of time and always = 100% of time).

3.2.2.2 Anorectal physiology studies

All subjects underwent a test of rectal sensory function to balloon distension, as previously described in Chapter 2 (section 2.3.2). Subjects also underwent anal manometry, endoanal ultrasound, evacuation proctography and a radio-opaque marker study to measure colonic transit, also as previously described in Chapter 2 (section 2.6).

3.2.2.3 Data and statistical analysis

Total CCCS were compared between the RH and NS subgroups. Similarly, scores for individual symptoms were compared between the two groups. Anorectal

physiological test results, notably the influence of colonit transit and proctographic abnormalities on symptom severity was also evaluted.

The Chi-square test was used to study differences in proportions, and logistic regression analysis was used to evaluate the influence of rectal sensation and other variables both on total and individual severity scores. Logistic regression was also used to evaluate the influence of RH on proctographic abnormalities. A *P* value of <0.05 was considered to show statistical significance.

3.3 RESULTS

3.3.1 RECTAL SENSATION

All three sensory threholds to balloon distension were significantly higher in the RH subgroup when compared to normosensate controls with constipation (FCS - NS: median 40 mls [range 15 -120]; RH: 140 [20 - 160] / DDV - NS: median 100 [50 - 210]; RH: 300 [150 - 360] / MTV - NS: median 180 [100 - 390]; RH: 360 [260 - 570], *P*<0.001 for all).

3.3.2 PRIMARY PRESENTING SYMPTOMS / ONSET

Presenting symptoms obtained from history were similar between the normosensate and the RH subgroups (Table 3.02). Duration of symptoms and onset of symptoms in childhood were also similar between the two subgroups.

Table 3.02 Primary presenting symptoms

	Normosensate (NS)	Rectal Hyposensitivity (RH)	*P* value
Duration (years)	19 (0.5-68)	21 (0.5-69)	0.480
Constipation	55 (100%)	55 (100%)	NS
Constipation / FI	15 (27%)	17 (31%)	0.675
Defaecation frequency < 3/week	28 (51%)	33 (60%)	0.337
RED	55 (100%)	55 (100%)	NS
Childhood onset	19 (35%)	22 (40%)	0.554

Symptoms derived from history taking (RED - rectal evacuatory dysfunction)
FI: faecal incontinence

3.3.3 SEVERITY BASED ON RECTAL SENATION (TOTAL SCORE)

The total constipation score was similar between the NS and the RH subgroups (median 17, range [2-25] vs. 19 [3-30], respectively; odds ratio=1.05, *P*=0.152, Figure 3.01)

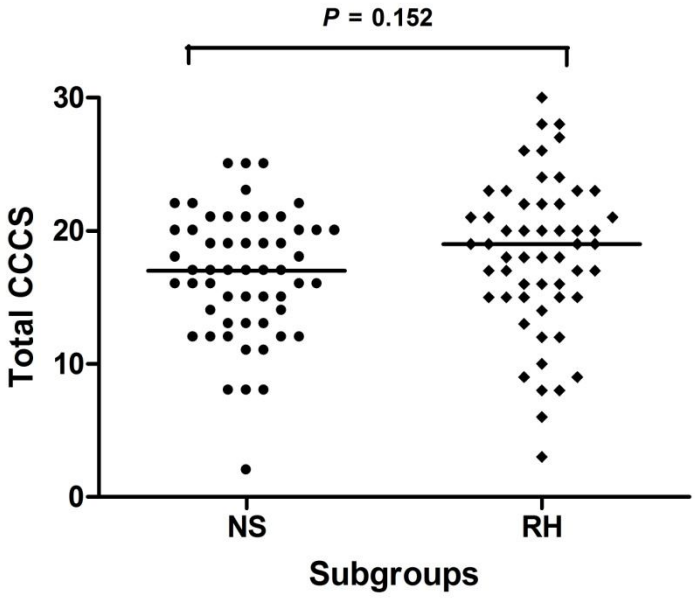


Figure 3.01: Total Cleveland Clinic constipation severity score (CCCS)

(NS- normosensate and RH- rectal hyposensitivity)

3.3.4 EFFECT OF RH ON INDIVIDUAL SYMPTOM SCORE

Individual scores for any of the eight questions on the CCCS questionnaire were similar between the NS and RH subgroups (Table 3.03).

Table 3.03 Individual symptom score

Symptoms	NS	RH	*P* value
Duration of constipation (years)	2 (0-4)	3 (0-4)	0.247
Frequency of BO	1 (0-4)	1 (0-4)	0.081
Time to defaecate	2 (0-4)	2 (0-4)	0.671
Assistance to defaecate	2 (0-2)	2 (0-2)	0.510
Unsuccessful attempts	2 (0-4)	3 (0-4)	0.935
Sense of incomplete evacuation	3 (0-4)	4 (0-4)	0.223
Pain on defaecation	3 (0-4)	3 (0-4)	0.889
Abdominal pain	2 (0-4)	3 (0-4)	0.185

(NS- normosensate and RH- rectal hyposensitivity)

Values represent median and range.

3.3.5 INFLUENCE OF CONCOMMITTENT FAECAL INCONTINENCE

There was no difference in severity between the NS and RH subgroup patients, regardless of the presence or absence of faecal incontinence (*P=NS).*

3.3.6 IMPACT OF DELAYED GUT TRANSIT ON SEVERITY

The presence of delayed gastrointestinal / colonic transit resulted in a significantly higher symptom severity score [normal transit; median 17, range (2-26) vs. slow

transit; 20, range (8-30), respectively; *P*=0.002*;* Fig 3.02).

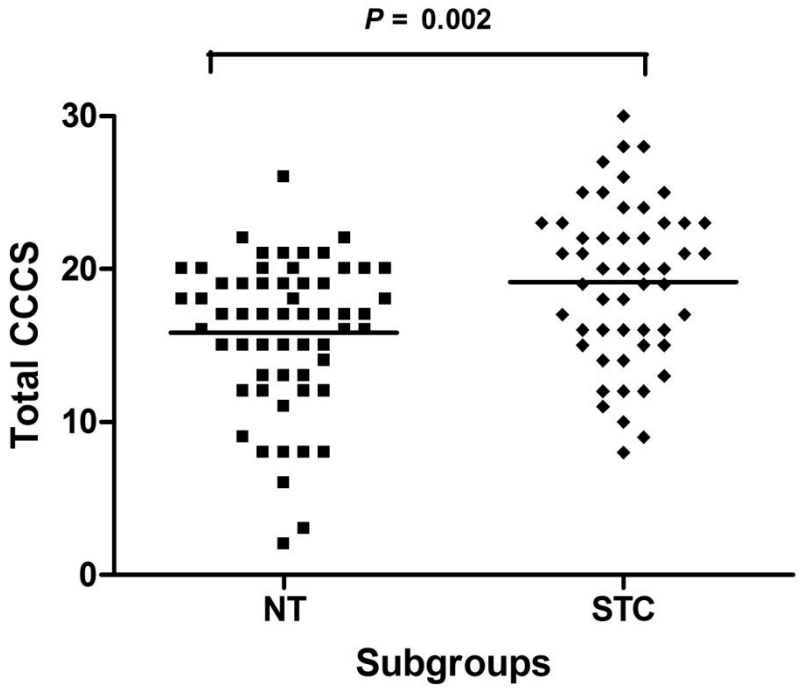


Figure 3.02 : Total Cleveland Clinic constipation severity score
(NT- normal transit and STC- slow transit constipation)

There were equal number of patients with delayed transit in the NS and RH subgroups (26 in each group).

3.3.7 PROCTOGRAPHIC FINDINGS

On evacuation proctography, 18/55 (33%) with NS compared to 29/55 (53%) with RH had a 'functional' outlet obstruction [odds ratio 2.29, *P*=0.03]. The incidence of mechanical causes of outlet obstruction (i.e rectocoele, intussusception) was similar in

both groups (22/55 (40%) NS and 20/55 (36%) RH, P=0.695). A significant proportion of patients with RH had rapid loss of the urge to defaecate soon after instillation of contrast into rectum [7/55 (13%) NS vs 24/55 (44%) RH, odds ratio 5.3, *P*=0.001].

3.4 DISCUSSION

This study has show that in a cohort of patients with constipation evaluated using a validated scoring system, the presence of rectal hyposensitivity did not result in greater severity of symptoms. In addition, the presence of concomitant faecal incontinence did not significantly affect the severity of symptoms. Furthermore, assessment of individual symptoms on the CCCS questionnaire showed similar severity in patients with constipation regardless of the presence or absence of RH. Nevertheless, a significantly greater proportion of patients with RH had evidence of a functional outlet obstruction when compared to the NS group. Moreover, almost half of the patients with RH had rapid loss of the sense of rectal fullness on proctography after instillation of barium neostool, requiring further neostool instillation to trigger the urge to defaecate and eventual defaecation. Overall, irrespective of sensory status, the presence of delayed GI / colonic slow transit, as diagnosed by the radio-opaque marker study, was consistently associated with more severe symptoms. The cohorts of patients studied were closely matched with regards to age, parity and associated symptoms.

The Cleveland Clinic constipation scoring system has been used for more than a

decade to study severity of constipation. The questionnaire covers the two main aspects of constipation: bowel infrequency and rectal evacuatory dysfunction. The finding that slow transit constipation leads to more severe symptoms in this study may be explained by the fact that the questionnaire gives disproportionate weight for the symptom of infrequency (i.e. those with infrequency will have a higher total score; if all other symptom severities are similar). Whether RH will eventually lead to slow transit constipation can only be proved by longitudinal studies.

As shown in this study, functional outlet obstruction is common in patients with RH. Since the completion of this study the obstructed defaecation syndrome (ODS) score has been devised and is now used commonly in clinical practice to evaluate symptoms of evacuatory dysfunction (Altomare et al. 2008). Comparing symptom severity in between the two groups using the above scoring sytem may be more relevant and will also help in identifying specific symptoms that commonly occur in patients with RH and rectal evacuatory dysfunction.

It is known that patients with functional bowel disorders have a limited symptom repertoire (Whitehead et al. 1999). The CCCS is itself limited to only seven cardinal symptoms plus another on symptom duration. Several other symptoms commonly volunteered by patients with constipation (e.g. sense of bloating, hard stools, excessive straining on defaecation, etc) are not included. In patients with RH and constipation, there have been several reports highlighting that these patients have a loss of urge or call to stool (Houghton 1999;Karlbom et al. 2004) compatable with the proctographic findings of this study. This particular symptom on its own can be very

distressing to patients. Similarly the quality of sensation of the desire to defaecate (i.e whether there is a sensation of 'pressure' in the anorectum or the urge to defaecate is purely felt as an abdominal / suprapubic pain, as seen anecdotally in patients with RH) are also important to study. Furthermore, faecal urgency has been reported in patients with RH and constipation, likely due to lack of rectal awareness of filling and no prior 'warning' until the stool reaches the sensitive anal canal. The severity of these symptoms, which may be specific to patients with RH may help in identifying if patients with RH do indeed have a more severe symptom profile. Further studies, in larger patient numbers, and with more detailed questionnaires, incorporating a much broader spectrum of symptoms of functional constipation, including those specific to those of blunted rectal sensation are necessary. In this study rectal biomechanical properties i.e capacity / compliance were not seperately assessed. It may be possible that those with primary RH (i.e due to true afferent dysfunction) may have a different symptom profile / more severe symptoms than those with secondary RH (altered rectal wall properties). Again, this warrants study.

The incidence of slow transit constipation in this study was similar between the normosensate and the RH subgroups as described previously (Gladman et al. 2003b). On proctography, the incidence of 'mechanical' rectal evacuatory dysfunction was also similar between the NS and RH groups, again consistent with previous reports (Gladman et al. 2003a). However, as shown in this and other studies, patients with RH had a higher incidence of 'functional' outlet obstruction (Gladman et al. 2003a). This is further supported by a recent study of rectal evacuation using high resolution manometry and balloon expulsion, which showed that patients with constipation and

RED, in the presence of RH, had prolonged balloon expulsion times despite the presence of low anal pressures (Ratuapli et al. 2012). This is a very important finding, and reinforces the fact that intact rectal sensation is crucial for normal defaecation and that impaired rectal sensation may lead to rectal evacuatory dysfunction. Similarly, loss of urge on proctography has been described in patients with RH previously (Chan et al. 2001). This in itself explain the higher incidence of functional outlet dysfunction in these patients. The exact mechanism is unknown, but it may be due to exaggerated rectal adaptation secondary to altered biomechanical properties (i.e hypercompliant/ megarectum) which are important in the pathophysiology of impaired rectal sensation.

3.5 CONCLUSIONS

In patients with constipation, rectal hyposensitivity is not associated with increased severity of symptoms as assessed by a standard questionnaire. Further studies with more detailed questionnaires are necessary to evaluate this further.

4 RECTAL HYPOSENSITIVITY IN SLOW TRANSIT CONSTIPATION: IMPACT ON RECTAL EVACUATION AND PATTERN OF TRANSIT DELAY

4.1 INTRODUCTION

The contribution of RH to the pathophysiology of constipation is incompletely understood. Currently, patients are classified according to the result of investigations that determine the speed of colonic transit and their evacuatory function. In patients classified as having slow transit constipation (STC) alone, a primary colonic dysmotility has been postulated (Read et al. 1986b;Bassotti et al. 1994;Gladman et al. 2005a), although dysmotility may also affect other parts of the GI tract (Zarate et al. 2009). In those with both STC and co-existent rectal evacuatory dysfunction, it is possible that the colonic motor disturbance occurs through reflex inhibition of proximal transit by the outlet obstruction (Maurer et al. 1995b), or that a primary colonic dysmotility results, through chronic straining, in a secondary disturbance of rectal evacuatory ability (Camilleri et al. 1998b;Law et al. 2002). Although RH has been documented in over half of patients with functional hindgut symptoms undergoing proctography in whom no mechanical cause to the dysfunction was found (Gladman et al. 2003a), it is currently unclear if the presence of rectal hyposensitivity *per se* can lead to impaired rectal evacuation or a particular pattern of colonic transit delay in patients with STC. Assessment of the contribution of RH to a transit delay may be important, as this could provide directed management aimed at correcting the sensory abnormality.

The aim of this study was to compare patterns of rectal evacuation and colonic transit in patients with slow transit constipation and associated rectal evacuatory dysfunction, with and without RH.

4.2 PATIENTS & METHODS

4.2.1 PATIENTS

The initial study population comprised 143 consecutive patients (136 females, average age 39, range 18-73) referred to a tertiary centre for further specialist investigations (Appendix E). All had a positive diagnosis of functional constipation based on Rome II diagnostic criteria (Thompson et al. 1999) and a confirmed delay in colonic transit demonstrated by radio-opaque marker study (more than 20 per cent of 50 markers administered remaining at 96 h on a plain abdominal radiograph(Hinton et al. 1969). In order to ascertain the influence of sensory function on rectal evacuation and global and regional colonic transit patients underwent 1) anorectal physiology investigation, including proctography and sensory evaluation; and 2) a colonic ^{111}In-[DTPA] scintigraphy study.

Completion of the scintigraphy study was the main limiting factor for inclusion in the study and depended on patients' geographical proximity and non competing work commitments (the scintigraphy study requires 9 visits over 5 days).

4.2.2 METHODS

4.2.2.1 Rectal sensation and subgroups

Rectal sensation was measured by inflating a latex balloon in the rectum and threshold volumes were determined as previously described (see section 2.3.2). RH was defined as 2 or more sensory thresholds raised beyond normal as shown previously from our unit data on healthy volunteers (see section 2.3.3). Patients with normal rectal sensation to balloon distension were defined as normosensate. Comparisons of different physiology parameters were performed between these two groups of patients (RH and NS).

4.2.2.2 Anorectal physiological investigation

All patients underwent standard anorectal physiological investigation, a radio-opaque marker study to determine GI / colonic transit and evacuation proctography as previously described (see section 2.6).

4.2.2.3 Evacuation proctography and definition of rectal evacuatory dysfunction

Evacuation proctography was performed by a standard technique with no prior bowel preparation as previously described (section 2.6.5). The persence of rectal evacuatory dysfunction and / or anatomical / functional abnormalities on evacuation proctography was noted (section 2.6.5). On this basis, subjects were classified into those with normal (NE), or impaired evacuation (evacuatory disorder; ED) if at least 2 criteria of the 3 proposed by Bharucha et al (Bharucha et al. 2006b) for a diagnosis of an

impaired evacuation were present (section 2.6.5). If impaired evacuation was present and this was due to a gross mechanical abnormality, the subject was also classified as having an ED, but sub classified as being due to a mechanical rather than functional obstruction. When both functional and mechanical obstructive components were present, subjects were subclassified into the group in which the major obstructive component had most impact (section 2.6.5). No attempt was made to grade the degree of mechanical abnormalities (i.e Oxford grading for intussusception).

4.2.2.4 Colonic scintigraphy

3.7 MBq ^{111}In-radiolabelled diethylene triamine penta-acetic acid (Amersham International, Amersham, UK), equivalent to an effective whole-body dose of 1.1 mSv in normal individuals, was ingested orally in a small quantity of water on the afternoon of day 1 (time zero). Anterior (supine) and posterior (prone) abdominal scans were obtained using a large field-of-view gamma camera and medium energy collimator (Scintiview^{TM}; Siemens, Bracknell, UK) twice a day for the following 4 days, at 18, 24, 42, 48, 66, 72, 90 and 96 hours. Any bowel movement that occurred following ingestion of the radioisotope, and before the first scan, was collected and the activity therin counted. Laxative medication and opiate analgesics were stopped 24 hours before the start of the study and avoided until its completion. Subjects remained on their normal diet during the study period.

Six regions of interest (ROI) were drawn around computer-generated images of the anterior and posterior abdominal scans for each subject: (1) caecum and ascending colon, (2) hepatic flexure, (3) transverse colon, (4) splenic flexure, (5) descending

colon, (6) sigmoid colon and rectum (Roberts et al. 1993b). Excreted faeces was considered a seventh ROI. The percentage activity (of total ingested activity) in each ROI was calculated at each time point by customized computer software (Micas V, Nucmed^{TM} software; Bartech Technologies Ltd, Farnborough, UK), which corrected scans for decay, and averaged corresponding anterior and posterior scans to correct for tissue attenuation (geometric mean). Geometric centre of isotope mass (GCI) for each time point was determined: GCI=$\sum^{1}$ fraction of activity in ROI_n x n where n = ROI number. A GCI close to 7 indicates that the majority of radio-isotope has been excreted, whilst a low GCI indicates that most activity is in the proximal colon. Patients with normal colonic transit, defined as GCI > 6.3 at 72 h , were excluded from further analysis (Roberts et al. 1993b).

Variables Analyzed

1. Global:

a) transit delay was classified as generalised (GCI <3.6 at 48h), or left-sided (GCI ≥3.6 at 48 h), based on previously published criteria (Roberts et al. 1993a;Maurer et al. 1995a);

b) progression of the isotope along the whole colon over the study period was analysed using time-activity curves (Krevsky et al. 1986;Roberts et al. 1993b). These show the GCI (see formula previously defined) plotted as a function of time.

c) severity of transit delay was determined by:

i. gradient of GCI progression (ROIs / time). This was calculated by linearising the time-activity curves using a best fit approach (Excel 2003; Microsoft

Corporation; Redmond, Washington); the gradient was calculated and expressed in ROIs per 100 h (Scott et al. 2001).

ii. estimated complete evacuation time, in hours, was calculated using $y=mx+c$, where y=7 (GCI in faeces), m is the gradient, x the estimated evacuation time and c the intercept (Scott et al. 2001);

iii. percentage of radio-isotope remaining in the whole colon at 96 h;

2. Regional:

a) transit along the right colon was defined as the summation of percentage activity in ROIs 1 and 2 (caecum, ascending colon and hepatic flexure), and was plotted as a function of time.

b) transit along the left colon, which was defined as the summation of percentage activity in ROIs 4-6 (splenic flexure, descending colon and recto-sigmoid region), was also plotted as a function of time.

4.2.2.5 Data and statistical analysis

The Chi-squared test was used to assess the effect of grouping variable (RH or NS) on various proctographic parameters and on the categorical classification of colonic transit (left-sided or generalised). A repeated measures ANOVA was used to analyse the effect of two factors on the progression of isotope over multiple time points: namely, 1) presence or absence of RH; and 2) results of proctography. These analyses were performed for each individual factor alone, as well as for both factors combined, in order to adjust for the influence of the outcome of proctography on the progression of the isotope in the NS and RH groups and *vice versa*. Non-parametric comparisons

(Mann-Whitney U-test) between the RH and NS groups were performed on the gradient of GCI progression, the estimated complete evacuation time, and the percentage activities in the whole colon at various time points. Tests were performed using a commercially available statistical package (SPSS 13.0, SPSS Inc. Chicago, Il). A value of $P < 0.05$ was taken to indicate statistical significance.

4.3 RESULTS

4.3.1 SUBJECTS AND CLASIFICATION

Colonic scintigraphy revealed 23 patients (16%) to have overall normal colonic transit, and these subjects were thus excluded from subsequent analysis. Of the remaining 120 patients, 34 (5 males; median age 46, range 30-67 years; mean duration of symptoms 258 months) had rectal hyposensitivity (FCS mean±SE: 151±15 ml; DDV: 314±16 ml; MTV: 382±19; n.b. in the majority of patients, balloon inflation was terminated at 360 ml) and 86 (2 males; average age 40, range 18-72 years; duration of symptoms 220 months) had normal rectal sensation (FCS: 56±4 ml; DDV: 127±5 ml; MTV 191±6 ml) to balloon distension. As expected, these differences were statistically significant between the two groups under study ($P < 0.001$).

4.3.2 EVACUATORY FUNCTION

On the basis of evacuation proctography, 79 patients had NE, and 41 had an ED. When subdivided on the basis of rectal sensory function, of the 34 patients with RH, 13 (38%)

were classified as having NE and 21(62%) had an ED. Of the 86 patients with NS, 66 (77%) had NE, and 20 (23%) had ED (P<0.0001), Figure 4.01. Time for evacuation was significantly longer in the RH subgroup, compared to the NS subgroup (177±20 sec vs 115±9 sec; *P* = 0.002). Similarly, percentage of neo-stool excreted was lower for the RH compared to the NS group (54±6% vs 74±3%; *P* = 0.003). Widening of the anorectal angle and relaxation (opening) of the anal canal could not be determined in one subject in the NS and in another subject in the RH group. Failure of anorectal angle opening was noted in 15/33 patients with RH vs 4/85 patients with NS (*P* = 0.0001). Failure of anal canal opening was noted in 13/33 patients with RH and in 8/85 patients with NS (*P* = 0.0008). Mechanical abnormalities precluding effective rectal evacuation were found in similar proportions: in 9/34 (26%) patients with RH and in 33/86 (38%) patients with NS (*P* = 0.29).

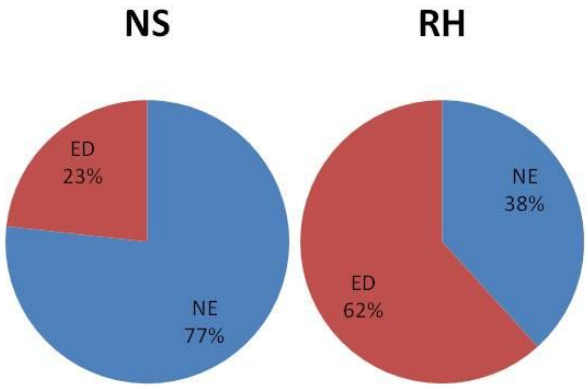


Figure 4.01: Evacuatory function in subgroups (ED- evacuatory dysfunction and NE- normal evacuation

4.3.3 SCINTIGRAPHY

4.3.3.1 Global transit

a) The distribution of the two traditionally recognised patterns of transit delay (i.e. generalized or left-sided) was similar in the two groups of patients studied (RH: 20 left-sided delay and 14 generalized delay *vs.* NS: 36 left-sided delay and 50 generalized delay; $P = 0.09$).

b) There was a significant difference between the NS and RH groups in the overall progression of isotope throughout the colon as defined by time-activity curves with isotope progression faster in the RH group as a whole (P=0.02, Figure 4.02). Conversely, overall progression of isotope was similar between the subgroups of patients (NE and ED) as classified on proctography (P=0.15). Repeat analysis, incorporating both factors (rectal sensation and rectal evacuation), in order to adjust for the possible confounding influence on each other and progression of the isotope, showed that isotope progression over time was similar between both the NS and RH subgroups (P=0.07) and the NE and ED subgroups (P=0.33). This shows that the faster progression of isotope in the whole colon was influenced by evacuatory function and not rectal sensation.

Comparison of progression of the radioisotope marker between patients with RH or NS with or without co-existent evacuatory dysfunction showed that rectal sensation was the determinant factor for the speed of transit and the group of subjects with normal rectal sensation and no evacuatory disorder (NS and NE) demonstrated the slowest progression of the isotope (Figure 4.03) although Bonferroni post-Hoc test for multiple comparisons did not show any statistical difference in the overall progression of isotope throughout the colon as defined by time-activity curves between any group of patients ($P>0.05$).

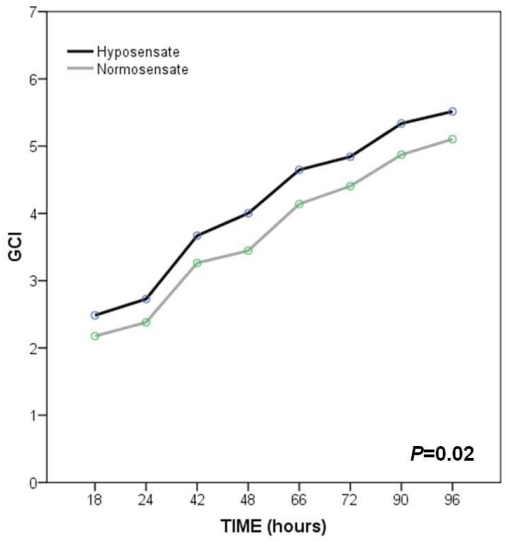


Figure 4.02: Time activity curves of isotope progression through the colon. There is faster overall progression in the RH than the NS group (*P*=0.02).

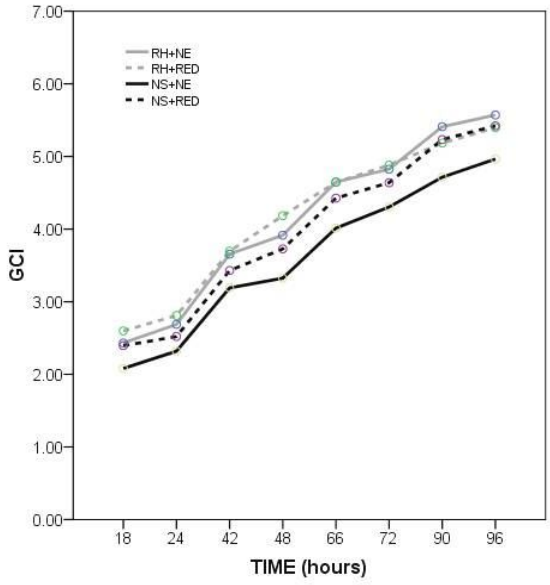


Figure 4.03: Time activity curves between patients with RH and NS, with or without evacuatory dysfunction. These indicate that rectal sensation has a greater impact on the speed of transit than rectal evacuation. Patients with NS and NE showed the slower progression of the radio-isotope over time although Bonferroni post-Hoc test for multiple comparisons of progression of isotope over time did not show any statistical difference between patient groups (P>0.05).

c) The estimated time for complete evacuation was similar between both groups (RH: mean time 162±13 h; NS: 175±9 h, *P* = 0.49). In addition, the gradient of the time-activity curve was also similar (RH: 3.6±2.5 ROI/100h; NS: 3.5±1.6 ROI/100h, *P* =0.88). Finally, there was no difference in the percentage of radio-isotope retained within the whole colon at 96 h (RH: 75±4%; NS: 77±8%, *P*=0.87).

4.3.3.2 Regional transit

a) Overall, activity in the right colon over time was not significantly different between the RH and NS groups (Figure 4.04; *P* = 0.08). However, ingested isotope moved significantly faster through the right colon (ROIs 1&2) in patients in the RH group compared to those in the NS group at both 18 h (RH median activity present 42±17%[IQR] vs NS 73±36%; *P* = 0.02) and at 24 h (RH median 42±43% vs NS median 66±36%; *P* = 0.01).

No differences were found in the overall activity in the right colon over time between the 2 subgroups of patients (NE and ED) classified by the results of proctography (*P*=0.06). Furthermore, ingested isotope moved similarly between both groups at both 18 h (NE median 73±46% [IQR] vs ED 67±42%; *P* = 0.26) and at 24 h (NE 63±41% vs ED 59±37%; *P* = 0.32). Repeated measures analysis incorporating sensation and proctographic variables (as described above) showed overall activity in the right colon to be similar between the NS and RH groups (*P*=0.12) and between the 2 proctography groups (*P*=0.22).

Percentage of overall activity in the left colon (ROIs 4-6) over time was significantly higher in the RH than NS group (P = 0.006, Figure 4.05). This difference is attributable to both more rapid radio-isotope arrival at the left colon and perhaps also more prolonged retention within the left colon in the RH group particularly towards the end of the scintigraphic study period: RH median activity present 84±11% [IQR] vs NS 61±51 at 72 h (P = 0.02) and RH 91±38% vs NS 62±50% (P = 0.049) at 90 h. Differences between these groups did not achieve significance at 96 h (RH 90±55% vs NS 52±58%; P = 0.11).

No differences were found in the overall activity in the left colon over time between the 2 subgroups groups of patients classified on the results of proctography (P=0.34). Furthermore, percentage of activity present at 72, 90 and 96 h was not significantly different between the two subgroups: NE 69±50% vs ED median 63±59% at 72h (P = 0.81), NE 67±46% vs ED 63±64% at 90 h (P = 0.39) and NE 65±54% vs ED 54±76% at 96h (P = 0.30). However, repeated measures analysis incorporating sensation and proctographic variables (as described above) revealed overall activity in the left colon over time to be persistently different between the NS and RH groups (P=0.02) (Figure 4.06), but not between the 2 different proctography groups (P=0.61).

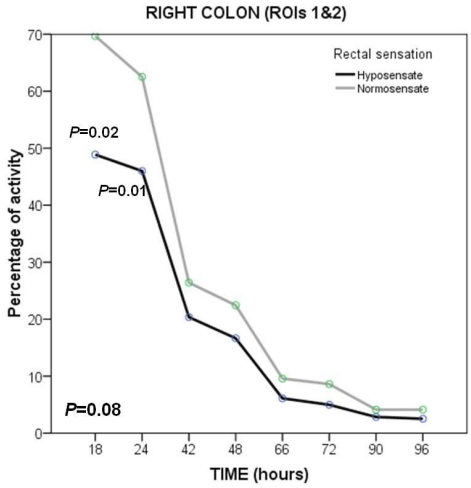


Figure 4.04: Regional activity in the right colon. Percentage of the isotope in the right colon is similar between the RH than NS group (*P*=0.08).

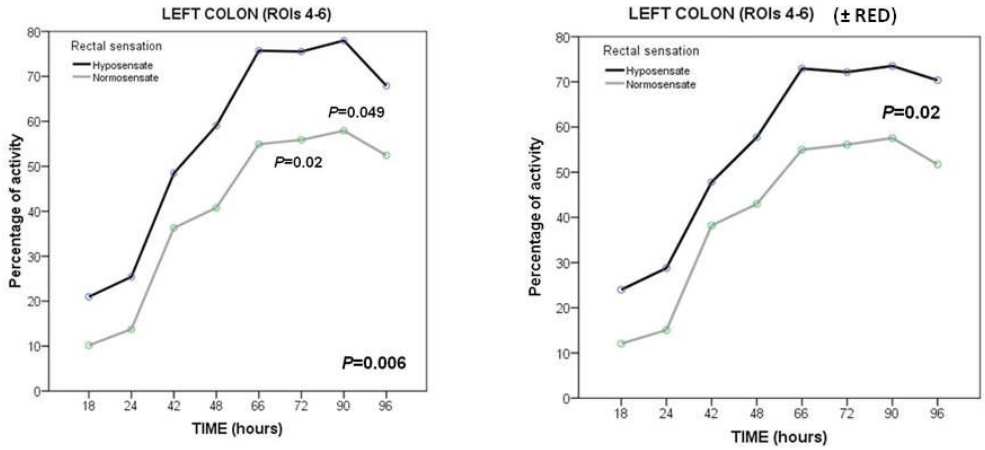


Figure 4.05: Regional activity in the left colon. The percentage of isotope in the left colon is significantly higher in the RH than NS group (P = 0.006).

Figure 4.06: Analysis repeated incorporating type of rectal evacuation (normal or evacuatory disorder) to correct for confounding factors; percentage of retention of isotope in the left colon remains different between both groups (*P*=0.02). (RED: rectal evacuatory dysfunction).

The reduced percentage of activity in the left colon in the NS subgroup was due to delayed proximal transit and not due to previous rectal evacuation. Rectal evacuation of radio-isotope was similar (*P*=NS) between the NS and Rh groups at all time points (Figure 4.07)

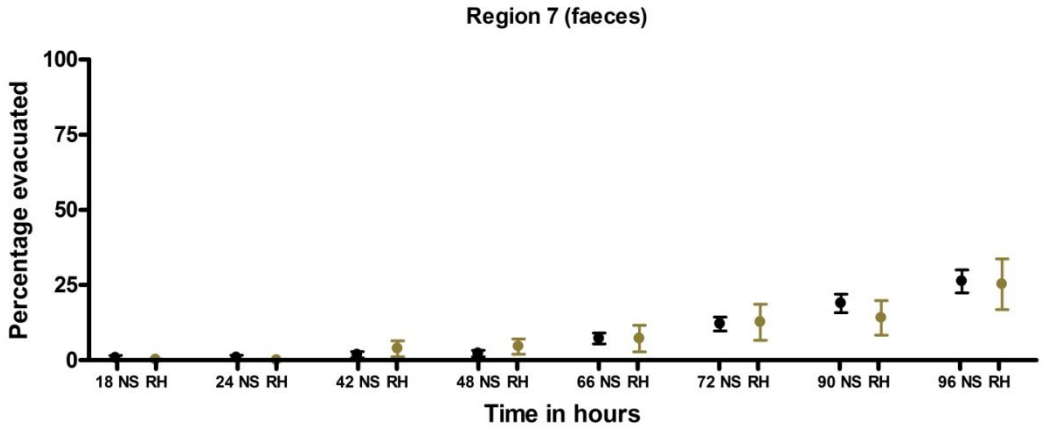


Figure 4.07: Percentage of radio-isotope evacuated at different time points between NS and RH groups

4.4 DISCUSSION

This study shows that, in this cohort of consecutive patients with STC, rectal hyposensitivity is present in more than 50% of patients with slow transit constipation and a co-existent evacuatory disorder. In these patients, rectal hyposensitivity is found more frequently in those with a functional rather than mechanical cause (Gosselink et al. 2001a;Gladman et al. 2003a). In addition, RH in patients with STC is associated with a specific pattern of colonic transit delay, characterised by a tendency to more rapid movement along the large bowel and a faster filling and hold up in the left colon over time. Although such a pattern has been shown to be associated with impaired rectal evacuation (Lundin et al. 2004), we have demonstrated that the main factor

responsible for this pattern of delay is impaired rectal sensory function, rather than abnormal evacuation. These findings support the concept that sensory impairment appears to be important in the pathophysiology of constipation in certain patients (Meunier 1986;Gladman et al. 2003a;Gladman et al. 2006). Furthermore, the approach of using validated criteria (Bharucha et al. 2006a) for the definition of a rectal evacuatory disorder, and the comparison of different parameters relevant to effective rectal evacuation between the two groups under study (RH and NS) is novel and scientifically more rigorous than that used in previous reports.

The nature of the relationship between RH and ED is unclear: cause or consequence; true phenomenon or epiphenomenon? On one hand, RH could lead to the development of a ED, as: 1) the sensation of rectal filling and the call to stool are integral to the process of normal, rather than forced evacuation, and lack of proper sense of urge can cause poor coordination of the evacuatory effort (Chan et al. 2001), 2) in those cases of RH associated with highly compliant, flaccid rectums (Gladman et al. 2005a) abnormally large faecal volumes might be necessary to elicit the sense of urge, compromising effective evacuation, and 3) in a flaccid rectum, the contraction forces necessary for faecal expulsion might be inadequate, leading to ineffective emptying (Read et al. 1986b;Schouten et al. 1998). In this study, individualised volumes of barium neostool instilled at proctography necessary to reach the subject's consciousness were used, rather than a fixed volume (Chan et al. 2001;Rao et al. 2006) in order to standardise the stimulus conditions for rectal emptying. Conversely, ED could theoretically (through faecal retention) lead to 1) progressive changes in the viscoelastic properties of the rectal wall, increasing the thresholds for rectal

perception (this has long been proposed as a cause for constipation in the paediatric population (Voskuijl et al. 2006), and 2) impairment of peripheral afferent nerve signalling, due to long term alterations in mechanical receptor function, secondary to persistent stimulation. Whichever the mechanism, the critical role of intact sensory function for effective emptying is supported by normalisation of evacuation following restoration of rectal sensation (Chang et al. 2003b).

Previous reports suggest that in patients with RH and a co-existent colonic transit delay, the major site of hold up is the left colon and/or rectum (Verduron et al. 1988). However, formal assessment of global and regional transit using colonic scintigraphy, the accepted gold-standard technique for assessment of colonic transit (Camilleri 2010), has thus far been lacking. Furthermore, it is currently unknown if this pattern of delay is due to the RH *per se* or due to a coexistent ED, frequently associated with RH. The present study demonstrated a faster transit for the RH compared to NS group but not between patients with NE or ED. However, the statistical difference between RH and NS was lost when the influence of evacuatory function (NE or ED) was controlled for. This suggests that right sided transit is in fact normal and not increased in patients with RH. A type II error could also give a similar finding. However, rectal sensation did have an impact on transit along the left colon, in that filling of left side was significantly greater in patients with RH and this was independent of rectal evacuatory function. We have previously reported that patterns of transit delay do not distinguish patients with STC alone compared to STC and coexistent ED as determined proctographically (Zarate et al. 2008); it may be concluded therefore that rectal hyposensitivity itself impacts on regional colonic transit. There is support in the

literature to suggest that retention of faecal material can lead to delayed colonic transit through; decrease in frequency of proximal colonic propagating sequences (Dinning et al. 2004), and that colonic transit may normalize after biofeedback treatment of an ED (Emmanuel et al. 2001). This mechanism is mediated through the activation of spinal inhibitory recto-colonic reflexes (Hughes et al. 1999b). It could be hypothesised that impaired rectal afferent pathways in patients with RH could be associated with inadequate activation of these entero-enteric reflexes, with attenuated delay of colonic transit in the right colon. It is also reasonable to postulate that reflex inhibition of colonic motor activity in the distal, but not whole colon, or an associated disorder of distal colonic motility in patients with RH could also explain these findings, areas of research that could be investigated using pancolonic manometric catheters.

In terms of study limitations, patients were not subclassified on the basis of a barostat study into those with or without rectal biomechanical abnormalities. It is currently unknown if both impaired rectal evacuation and the pattern of delayed colonic transit demonstrated in this study are different between the two pathophysiological subgroups of RH (true RH and hypercompliance/ increased capacity). The results of this study are also limited to patients with diagnosed STC. The impact of RH on regional progression of colonic contents in patients with constipation but otherwise normal transit is unknown. This information is particularly relevant in those patients with RH who have no other physiological abnormality identified (approximately 20% of patients with RH) and in those with an ED but normal transit time (approximately 45%) (Gladman et al. 2003b). Assessment of colonic transit is usually performed by

radio-opaque marker studies that do not provide accurate information on regional transit. It is unlikely that subtle alterations in patterns of transit of colonic contents would be identified through a radio-opaque marker study.

In summary, in patients with STC, the incidence of a functional evacuatory disorder is significantly greater in those with co-existent rectal hyposensitivity compared to those with normal rectal sensation. Furthermore, indices of colonic transit delay are altered in the RH group. Such findings strengthen the concept that blunted perception to rectal filling is contributory to the pathoaetiology of constipation and should be considered alongside evacuatory dysfunction and colonic dysmotility as the third principal pathophysiological mechanism of this condition. Assessment of rectal sensation in patients with chronic intractable constipation should be mandatory.

4.5 CONCLUSIONS

This study has revealed that rectal hyposensitivity is more commonly associated with rectal evacuatory dysfunction (functional type) in patients with slow transit constipation. Rectal hyposensitvity is also associated with a specific pattern of transit delay, where there is more hold up of the isotope in the left colon. These findings strengthen the concept that blunted perception to rectal filling is contributory to the pathoaetiology of constipation.

5 RECTAL HYPOSENSITIVITY: EVALUATION OF ANAL SENSATION IN FEMALE PATIENTS WITH INTRACTABLE CONSTIPATION

5.1 INTRODUCTION

Diminished sensation (hyposensitivity) has been demonstrated in both the rectum and anal canal in a variety of anorectal disorders, notably chronic constipation (Felt-Bersma et al. 1997;Gladman et al. 2003a), and faecal incontinence (Lubowski et al. 1988a;Rogers et al. 1988b;Gladman et al. 2003a). In patients with rectal hyposensitivity (RH), the precise pathophysiological mechanisms leading to symptom development are currently unclear; however, in constipation, sensorimotor dysfunction (Read et al. 1986b;Schouten et al. 1998;Gladman et al. 2005a), perhaps leading to chronic distension and impaction may play a role. RH may also contribute to the pathophysiolgy of constipation by other mechanisms, e.g. reflex (viscero-visceral) inhibition of proximal gut function (Kellow et al. 1987;Law et al. 2002) and also a secondary colonic dysmotility (recto-colonic inhibitory reflexes)(Hughes et al. 1999a;Dinning et al. 2005).

The aetiopathogenic mechanisms underlying anorectal hyposensitivity are similarly unclear. In RH, it has been suggested that disruption of the rectal afferent pathway (e.g. following pelvic or spinal surgery) leads to diminished perception of rectal distension in certain patients (Gladman et al. 2006). Furthermore, Bannister et al have demonstrated reduced bladder sensation in patients with constipation (Bannister et al. 1988); this finding was replicated in 12/17 (70%) patients with RH in a pilot study

(Gladman MA et al. 2004), which raises the possibility of a pan-pelvic neuropathic process, consistent with their common innervation. By contrast, although the rectum and anal canal are anatomically adjacent, they are innervated by different sensory pathways. The sensory information from the rectum is conveyed via the rectospinal (visceral) afferents (Grundy et al. 2006) that ascend predominantly via parasympathetic pathways to reach the dorsal horn of the spinal cord, whereas the sensory pathway from the anal canal is via the pudendal nerves (somatic), although there may be a degree of overlap in the transition zone. Both these pathways are derived from the sacral plexus (roots S2, 3 and 4), and hence are closely related anatomically at this level. Thus, if the afferent pathway is disrupted proximal to the sacral roots, one would intuitively expect impaired anal as well as rectal sensation.

This aim of this study was to investigate anal sensation in constipated female patients with RH to determine whether there was evidence of a combined visceral and somatic sensory neuropathy.

5.2 PATIENTS & METHODS

5.2.1 SUBJECTS

5.2.1.1 Patients

The study cohort comprised consecutive patients referred for investigation of their primary symptom of chronic constipation [Rome II criteria (Thompson et al. 1999)]; those with a history of spinal injury, spinal surgery, perineal, bowel or anal surgery,

diabetes mellitus and multiple sclerosis were excluded. One hundred and fifty eight eligible female patients formed the study population (demographics, symptomatology, Table. 5.01), of whom 36 had concomitant faecal incontinence (36% of these had passive incontinence, 38% had urge incontinence and the remainder had a combination of the two). Men were excluded from this study as constipation is female predominant and also to limit heterogeneity.

Table 5.01: Demography and symptomatology of patients

Patients (n=158)	
Median age in years (range)	49 (19-80)
Parity, median (range)	2 (0-8)
Median duration of symptoms in months (range)	120 (6-936)
Symptoms (% of patients)	
Infrequency(<3 bowel openings/week)	53
Sense of incomplete evacuation	70
Unsuccessful evacuation	36
Straining to defaecate	39
Abdominal pain unrelated to defaecation	50
Incontinence	23
Precipitating factors present	30% (48/158)
Childbirth	22/48
Hysterectomy	9/48
Others (abdominal and bladder surgeries, eating disorders, laxative abuse, etc)	17/48

5.2.1.2 Controls

Data for rectal and anal sensation were compared with those obtained in 32 healthy female volunteers (median age: 43, range 18-60, *P*= 0.024 vs. patients).

5.2.2 METHODS

5.2.2.1 Anorectal physiological investigation

All patients underwent standard anorectal physiological investigation, and studies of colonic transit and defaecatory function using evacuation proctography when clinically indicated, as previously described (section 2.6). The results of colonic transit study and evacuation proctography are not seperately presented as they are not relevant to this study.

5.2.2.2 Anal electrosensitivity

Anal electrosensitivity was measured using a bipolar ring electrode (21L10, Dantec, Bristol, UK) mounted on a Foley catheter with centimetre markings; this was positioned such that the distal end of he electrode was 1 cm from the anal verge (Figure 5.01). The electrode was then connected to a constant current stimulator (Keypoint, Dantec, Bristol, UK), which delivered a constant electrical current to the mucosa, regardless of tissue impedance, and also indicated if there was lack of contact. A stimulus of 5 Hz frequency and 100 µsec pulse duration (Roe et al. 1986;Rogers et al. 1988b) was administered, starting at 0 mA and gradually increasing the stimulus intensity until the subject reported a sensation (usually of

tingling or pricking nature). This was repeated three times, and the lowest of the thresholds was taken as the sensory threshold. The position of the electrode was verified once again before removing the catheter. The electrode was then removed from the disposable catherer and immersed in CIDEX disinfectant overnight. Anal electrosensory thresholds measured by the above technique has been found to be repeatable (Rogers et al. 1989)

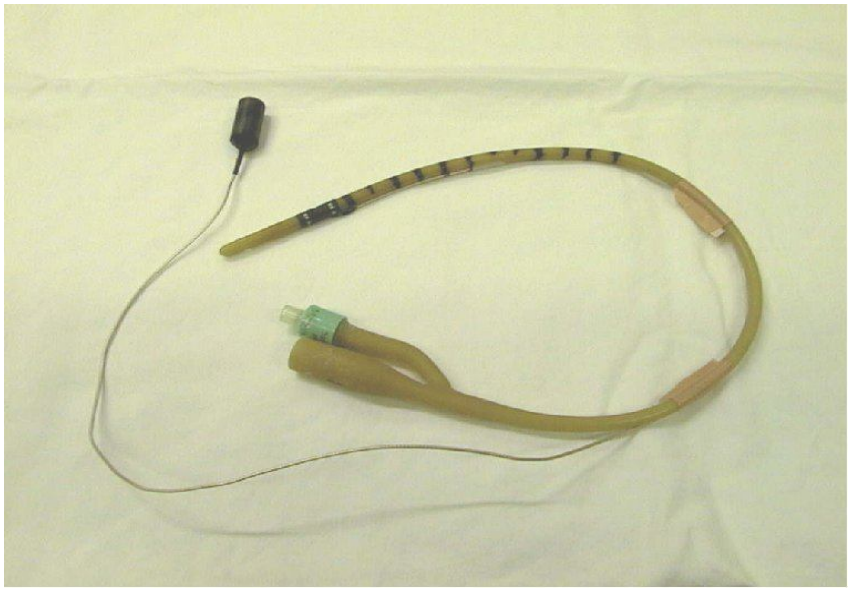


Figure 5.01: The stimulating electrode consisting of a bipolar urethral ring electrode mounted on a 14G Foley catheter.

5.2.2.3 Definition of rectal and anal hyposenitivity

RH was diagnosed on balloon distension as two or more sensory thresholds raised above normal limits as previously described (section 2.3.2 and 2.3.3). Patients were categorised into those with RH and those without (NS).

Based on study of the 32 healthy female control subjects, a value above 4.2 mA (upper limit of normal in healthy volunteers, mean + 2SD was 3.03 mA) for anal electrosensory threshold was considered abnormal.

5.2.2.4 Data and statistical analysis

For non-parametric data, comparison between groups was performed using Mann Whitney U test or Kruskal-Wallis test with Dunn's multiple comparison where appropriate. Contingency tables were analysed using the Chi-square test. Correlation between variables was assessed using the Spearman's test. A logistic regression analysis was performed using the standard maximum likelihood model to determine if anal sensation was influenced by co-variates (age, duration of symptoms and parity).

5.3 RESULTS

5.3.1 CLINICAL FINDINGS

5.3.1.1 Demography and symptoms based on rectal sensory function

Of the 158 patients, 45 had rectal hyposensitivity (RH) to balloon distension. The remaining 113 patients had normal rectal sensory thresholds and were classified as the normosensate subgroup (NS). The age distribution of patients was similar in both the subgroups (NS median age: 49, range 19-79; RH median age: 49, range 27-80, P=0.334). No differences were found between patients with NS and RH with regard to demographics and symptomatology (Table 5.02).

Table 5.02: Demography and symptoms based on rectal sensory function

PATIENTS (N=158)	**NS (N=113)**	**RH (N= 45)**	***P* VALUE**
Median age in years (range)	49 (19-79)	49 (27-80)	0.334
Parity, median(range)	2 (0-8)	2 (0-5)	0.862
Median duration in months (range)	120 (8-768)	96 (6-936)	0.507
Symptoms (% of patients)			
Infrequency(<3 bowel openings/week)	55	47	0.352
Sense of incomplete evacuation	74	60	0.075
Unsuccessful evacuation	37	33	0.651
Straining to defaecate	42	33	0.337
Abdominal pain (unrelated to defaecation)	48	53	0.529
Faecal Incontinence	23	22	0.915

NS- normal rectal sensation, RH- rectal hyposensitivity

5.3.2 PHYSIOLOGICAL DATA

5.3.2.1 Rectal sensation

All three sensory threholds to balloon distension were significantly higher in the RH subgroup when compared to normosensate controls (FCS - NS: median 40 mls [range 10 - 105] vs. RH: 110 [15 - 235] / DDV- NS: median 100 mls [range 15 - 200] vs.

RH: 225 [90 - 510] / MTV- NS: median 180 mls [range 90 - 270] vs. RH: 320 [200 - 515], (P<0.001)).

5.3.2.2 Anal sphincter function

Resting anal pressures were similar between healthy volunteers and patients as a whole (median: 73 cmH_2O [range 34-127] vs. 74 cmH_2O [20-153], respectively; *P*=0.780), but squeeze pressures were significantly higher in healthy volunteers (median: 69 cmH_2O [45-249] vs. 50 cmH_2O [10-204], respectively; *P*<0.0001). Patients with constipation and coexistent faecal incontinence had significantly lower resting pressures when compared to the constipation only subgroup (median: 58 cmH_2O [range 18-144] vs. 80 cmH_2O [34-137], respectively; *P*<0.05). Squeeze pressures were also lower in the concomittent incontinence group (median: 30 cmH_2O [range 7-137] vs. 51 cmH_2O [10-204], respectively; *P*<0.05).

5.3.2.3 Pudendal nerve latencies

Pudendal nerve terminal motor latencies (PNTML) were significantly prolonged on the right side in patients compared to healthy volunteers (median: 2.25 msec [1.6-4.5] vs. 2.20 msec [1.6-2.7], respectively; *P*= 0.047), but were similar on the left (median: 2.30 msec [1.7-4.8] vs. 2.30 msec [1.7-3.1] respectively; *P*= 0.477). PNTMLs were significantly higher in patients who had coexistent incontinence when compared to those who had constipation alone (median PNTML: 2.55 msec [1.8-4.8] vs. 2.45 msec [1.7-3.8], respectively; *P*= 0.021).

5.3.2.4 Anal sensation

Anal mucosal sensory thresholds to electrical stimulation were significantly higher in patients as a group than those of healthy volunteers (median: 2.4 mAmp [0.4-19.6] vs. 1.1 mAmp [0.1-4.2], respectively; *P*<0.0001; Figure 5.01).

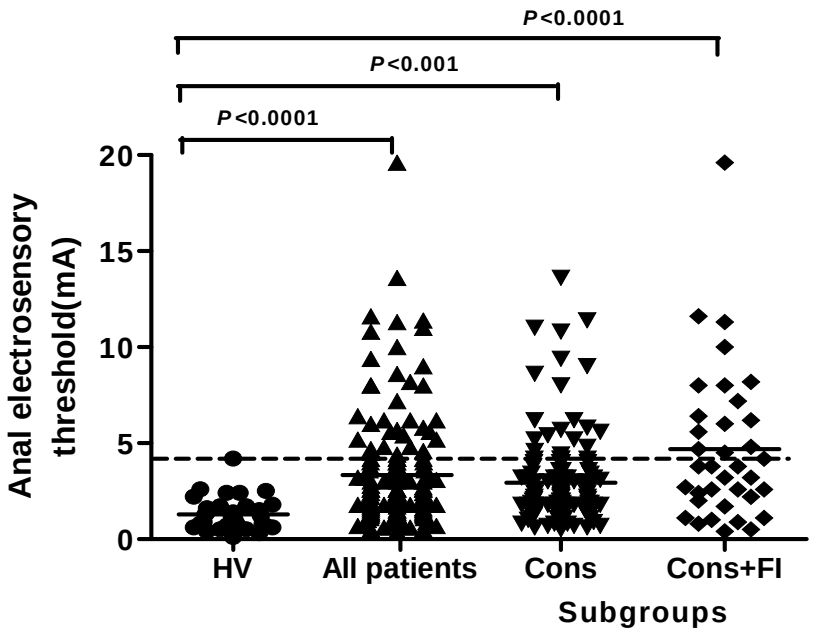


Figure 5.02: Anal electrosensory thresholds in healthy volunteers (HV) and patients. Cons- patients with constipation only; Cons + FI- patients with constipation and faecal incontinence.

Individually, 34 patients (22%) had evidence of anal hyposensation (i.e. an elevated anal sensory threshold). The proportion of patients with symptoms of both constipation and faecal incontinence who had anal hyposensitivity (15/36: 42%) was significantly greater (*P*=0.0008) than in patients with constipation alone (19/122: 16%). One patient had grossly abnormal anal electrosensory threshold. She had both

constipation and faecal incontinence. She had a 3rd degree tear during childbirth and had both external and internal sphincter defect on endoanal ultrasound.

Anal mucosal electrosensory thresholds were similar between the NS and RH sub-groups (Figure 5.02). There were 11 (24%) patients in the RH subgroup found to have anal hyposensation, and 23 (20%) in the NS subgroup (*P*=0.572). Equally, the presence of RH had no impact on the frequency of anal hyposensitivity in those with constipation alone (NS vs. RH, *P*=0.7618), or those with constipation and faecal incontinence (NS vs. RH, *P*=0.529). Anal sensory thresholds were abnormal in a similar proportion of patients who had protracted rectal emptying (21%) when compared with those with normal evacuation on proctography (22%, *P*=0.860).

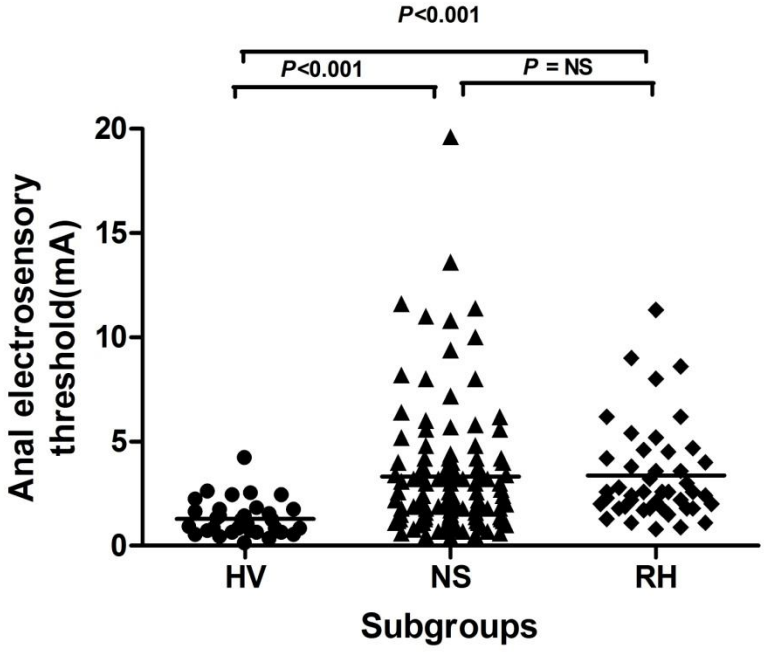


Figure 5.03: Anal electrosensory thresholds in healthy volunteers and subgroups of patients based on rectal sensation, NS (normosensate) and RH (rectal hyposensate).

There was no correlation between PNTML and anal sensation in patients (P=0.550; Figure 5.03). The incidence of pudendal neuropathy (unilateral or bilateral) was similar (*P*=0.391) in the patients who had normal (59/124: 48%), and those with elevated (19/34: 56%) anal electrosensory thresholds.

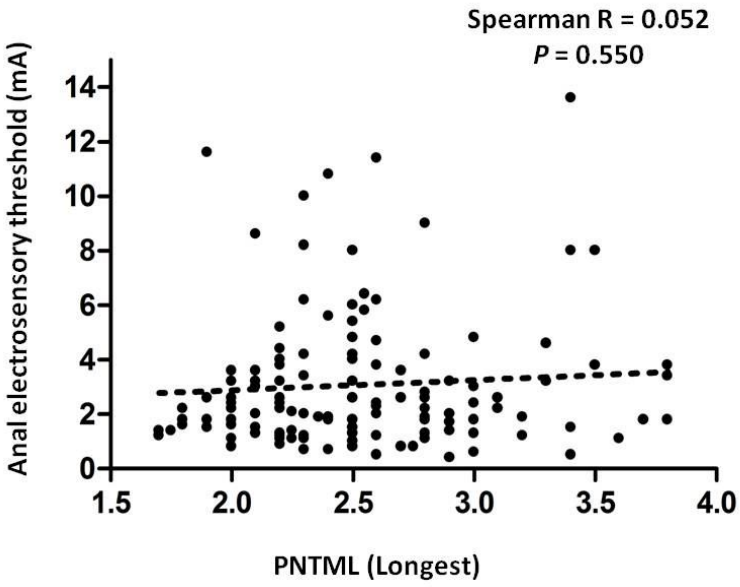


Figure 5.04: Scatter plot showing the relationship between PNTML (the longer of the two in each subject) and anal electrosensory thresholds.

However, there was a significant inverse correlation between anal electrosensory thresholds and squeeze pressures (r =-0.190, *P*=0.017, Figure 5.04) but not PNTML and squeeze pressures (r =-0.061, P=0.483).

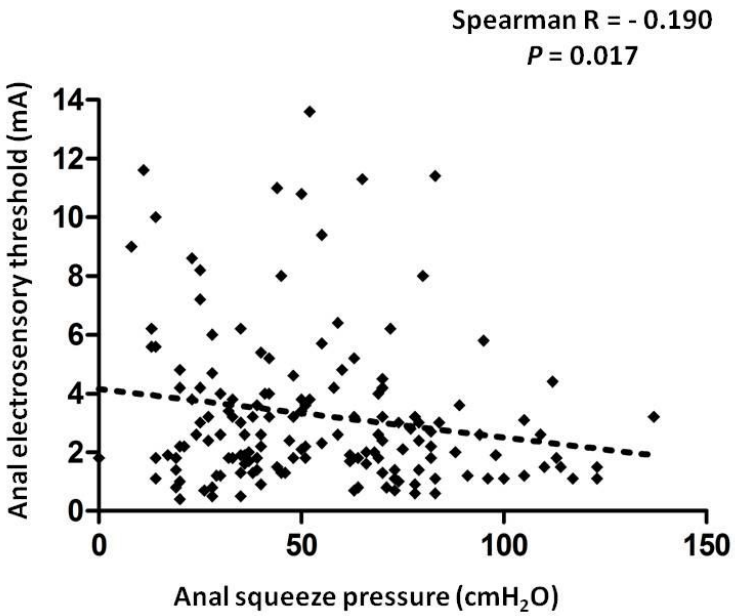


Figure 5.05: Scatter plot showing the relationship between anal squeeze pressure and anal electrosensory thresholds.

There was also a positive correlation between increasing age and anal sensory thresholds (r =0.215, *P*=0.007, Figure 5.05).

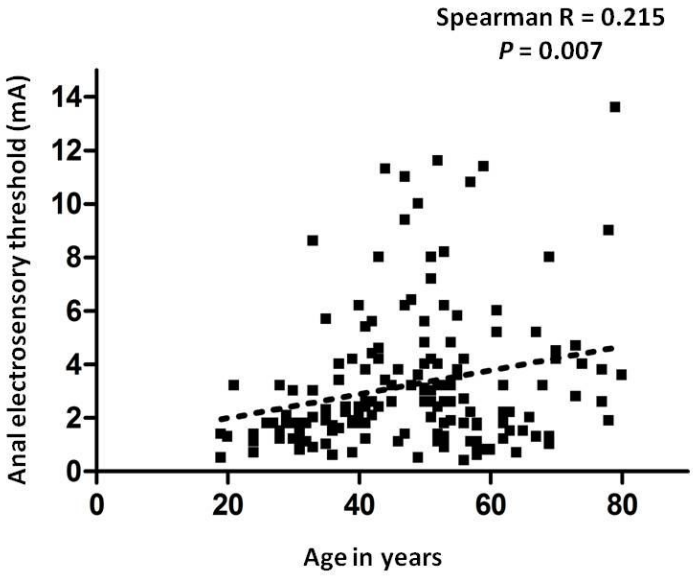


Figure 5.06: Scatter plot showing the relationship between age and anal electrosensory thresholds.

Irrespective of rectal sensory function, on logistic regression analysis there was a significant association between duration of symptoms (coefficient = 0.003, odds ratio = 1.003, *P*= 0.012), but not age (coefficient = 0.019, odds ratio = 1.019, *P*= 0.378) or parity (coefficient = 1.735, odds ratio = 5.671, *P*=0.120) with the finding of anal canal hyposensitivity [model R^2 = 0.14, *P*=0.02].

5.4 DISCUSSION

This study examined the relationship between rectal hyposensitivity and anal sensation in patients presenting with constipation as their main symptom. The major findings may be summarised as follows:

1. as a group, constipated patients had blunted anal sensation, irrespective of their rectal sensory status, with one fifth of individual patients having evidence of diminished anal sensitivity;
2. patients with constipation and faecal incontinence had a greater incidence of anal hyposensation when compared to those with constipation only, irrespective of rectal sensory status;
3. there was no correlation between abnormal anal sensation and pudendal nerve terminal motor latencies (PNTML);
4. there was a positive correlation between duration of symptoms and the finding of elevated anal sensory thresholds.

The finding that patients with symptoms of intractable constipation, sufficient to prompt physiological investigations, have, as a group, blunted distal anal canal sensation when compared to healthy volunteers, is consistent with previous studies (Solana et al. 1996;Felt-Bersma et al. 1997). Furthermore, this study also confirmed that blunted anal sensation correlated with increasing age (Jameson et al. 1994;Ryhammer et al. 1997), with a significant association with duration of symptoms. However, there appeared to be no association between the presence of RH and the presence of anal hyposensitivity.

Read and Abouzekry demonstrated impaired anal, perianal and rectal sensation in a proportion of patients with faecal impaction and incontinence, and proposed this, together with an obtuse anorectal angle, as a mechanism for their faecal incontinence (Read et al. 1986a). These findings were replicated by the same group in a cohort of elderly patients with faecal impaction alone(Read et al. 1985); they likened the results to those seen in patients with low spinal cord injuries. Impaired anal sensation has been noted in patients with faecal incontinence in other studies (Miller et al. 1988b;Barrett et al. 1989;Speakman et al. 1993a).

The pudendal nerve supplies sensory fibres to the anoderm of the distal anal canal and motor fibres to the external anal sphincter, and arises from the sacral roots S2, 3 and 4 We have shown previously that in healthy volunteers, anal sensory function, but not distal rectal sensitivity, could be blunted by distal pudendal nerve blockade, supportive of separate, distinct afferent innervation (Chan et al. 2005b). Evaluation of sensory pathways from the anal canal has been achieved using various techniques

including thermal stimulation (Rogers et al. 1988a), touch sensation and electrostimulation (Roe et al. 1986). Estimation of anal mucosal electrosensory thresholds is a reproducible method; traditionally, this involves assessment at three levels in the anal canal (1, 3 and 5 cm from the anal verge). We have used data at 1 cm only, as this represents that part of the anal canal preferentially innervated by the pudendal nerve, although it is feasible in a minority that pelvic floor descent and caudal displacement of the anoderm may result in this level being covered by upper anal/rectal type mucosa (as is probably the case with the 2 outliers in Figure 5.01). As resting pressures were similar between patients and healthy volunteers, it is unlikely that elevation of anal sensory thresholds in patients was as a result of inadequate electrode contact.

The lack of association between blunted rectal and anal sensation suggests that in the majority of patients with RH, there is an isolated visceral sensory neuropathy, and that different aetiopathogenic mechanisms are responsible for development of anal hyposensation (present in 20% of NS patients). This may occur due to chronic straining, childbirth etc, which may not be reflected by abnormal PNTML measurement. Nevertheless, it is still possible that in a proportion of those RH patients with anal hyposensation (24%), neuronal disruption proximal to or including the sacral roots resulting in a combined pelvic and pudendal neuropathy may exist. Alternatively, separate coexisting pudendal and rectospinal afferent dysfunction may be present. Previously, we have shown that in patients with RH, 13% had a history of spinal injury or surgery (Gladman et al. 2003b). Conceptually, this group may represent those most likely to have a combined visceral-somatic neuropathy from a

unifying aetiological basis. However, such patients were excluded from the present study in order to avoid bias. This may have contributed to the apparent lack of association between rectal and anal sensory dysfunction.

Rectal sensation is usually, as in this study, assessed by determination of thresholds to simple volumetric distension of an intrarectal balloon. Such methodology however, may not always reflect afferent nerve dysfunction if the rectum is dilated (megarectum), or over compliant, in which case elevated rectal sensory thresholds may reflect inadequate stimulation (Gladman et al. 2006). No patient in this study had megarectum, but compliance was not assessed, and it is possible that up to one-third of these patients had an intact afferent pathway, despite elevated thresholds (Gladman MA et al. 2005).

The presenting types of faecal incontinence were no different between those with normal, and those with abnormal anal or rectal sensation. Different mechanisms may, however, underlie loss of bowel contents in these patients. In those with abnormal anal sensation and normal rectal sensory function, sphincteric dysfunction (internal, external anal sphincters) is presumably predominant. In those with both anal and rectal hyposensitivity, incontinence may be linked to the absence of conscious external sphincter contraction during sampling (Sun et al. 1990b), and in other instances when the faecal stream reaches the anal canal, such as raised intra-abdominal pressure during coughing etc. The possibility of a prolonged rectoanal inhibitory reflex secondary to faecal impaction as a contributing cause has been questioned by the fact that disimpaction does not alter anal resting pressures (Read et

al. 1986a). Patients who have intact anal canal sensation but blunted rectal sensation may complain of extreme faecal urgency (Gladman et al. 2006), where presumably the sense of impending defaecation, as conveyed by the rectum, is absent, and urge to defaecate is only recognised when the rectum is loaded and faeces are impinging upon the upper anal canal.

We did not demonstrate a relationship between pudendal nerve terminal motor latencies and raised anal sensory thresholds. Supporting evidence is contradictory; Felt-Bersma et al (Felt-Bersma et al. 1997) have also shown this previously, wheareas Speakman and Kamm (Speakman et al. 1993a) found increased anal sensory thresholds only in the presence of pudendal neuropathy in patients with faecal incontinence. However, there are numerous methodological limitations to the measurement of pudendal nerve latencies (Diamant et al. 1999). PNTML reflects the function of the fastest conducting motor fibres and thus normal latencies may be recorded in a damaged nerve, as long as some fast-conducting fibres remain. In addition, the test is operator dependent, and may be technically difficult to perform in some patients, notably those with a high body mass index or a long anal canal. Sphincter EMG's would be the preferred alternative to PNTML but was not done due to its invasive nature. Similarly, endoanal ultrasound if had been carried out would have helped in exploring the reasons for the unilaterally abnormal latencies in patients. Nevertheless, it is possible that the lack of association between PNTML and anal sensation in this study may reflect the presence of either an isolated sensory, or motor neuropathy.

The association between increasing age and elevated anal sensory thresholds is consistent with previous reports (Jameson et al. 1994), suggesting that future studies should be stratified for age, especially since the control group in this study was significantly younger than the patient group. The influence of duration of symptoms in constipated patients on anal sensory thresholds may relate to chronic straining and consequent damage to the afferent fibres of the pudendal nerve (Gee et al. 1995).

5.5 CONCLUSIONS

This study has shown that patients with chronic intractable constipation and rectal hyposensitivity, as diagnosed on simple balloon distension, do not have an increased incidence of anal hyposensitivity, when compared to constipated patients with normal rectal sensation. This suggests that afferent dysfunction in the majority of patients with rectal hyposensitivity relates purely to visceral pathways. Further studies are needed after subgrouping patients with rectal hyposensitivity based on rectal wall biomechanics, and using other markers of pudendal nerve sensory function (e.g. perianal skin sensation).

6 EVALUATION OF GENERAL AND PELVIC SOMATIC NERVE FUNCTION IN PATIENTS WITH RECTAL HYPOSENSITIVITY AND CONSTIPATION

6.1 INTRODUCTION

Impairment of rectal sensation (rectal hyposensitivity [RH]) is present in one-quarter of patients with constipation (Gladman et al. 2003a), and is increasingly being accepted as an important pathophysiological mechanism (Burgell et al. 2012c). In patients with 'primary' RH (see section 1.6.2), attempts to understand why and how rectal afferent nerve function becomes disrupted may be crucial to prognosis and successful management. However, the level of interruption of the rectal afferent pathway in patients with RH is currently unknown, and, as detailed in chapter 1 (section 1.6.2), could occur anywhere from the rectum to the brain. Nevertheless, there is some evidence to suggest that sensorimotor dysfunction of the rectum is associated with extrinsic parasympathetic nerve disruption at the level of the pelvic nerves (Knowles et al. 2001;Gosselink et al. 2001b). Preliminary results from assessment of bladder function in patients with RH support this hypothesis, given that bladder sensation is also impaired (Gladman MA et al. 2004). Nevertheless, although the premise of pelvic nerve injury is attractive, it is possible that impaired rectal sensory function simply reflects a more widespread underlying (and undiagnosed) neurological disorder. Indeed dysfunction of the autonomic nervous system has been

implicated as a cause for constipation in patients with diabetes and other neurological disorders (Johanson et al. 1992), and neuronal dysfunction has also been found in patients with slow transit constipation (Kerrigan et al. 1989;Camilleri et al. 1990;Altomare et al. 1992;Raethjen et al. 1997;Knowles et al. 1999). Furthermore, evaluation of patients with impaired bladder sensation has previously revealed the presence of undiagnosed neurological disease in up to 35% of subjects (Wyndaele 1993).

The primary aim of this study was to evaluate general and pelvic somatic nerve function (via testing of regional somatic pathways), to exclude the presence of 'generalised' small or large fibre neuropathy using standard neurophysiological techniques (Guy et al. 1985;Knowles et al. 1999), to test the hypothesis that rectal afferent pathway disruption does occur at the level of the pelvic nerves in patients with RH.

6.2 SUBJECTS & METHODS

6.2.1 *SUBJECTS*

6.2.1.1 Patients

Ten patients (7 female; median age: 47 years, range: 38-54 years) with intractable constipation, as defined by the Rome II diagnostic criteria (Thompson *et al.*, 1999), and rectal hyposensitivity were recruited. All 10 patients had raised rectal

electrosensory thresholds, and were considered to have a true afferent defect (i.e. 'primary' RH, section 1.6.2). All 10 patients also had a rectal barostat study, from which one male patient was also found to have increased rectal compliance. In addition, 8 consecutive patients (7 women; median age: 42 years, range: 32-62 years) with normal rectal sensory function (NS) on physiological assessment and intractable constipation according to Rome II criteria were studied for comparison. None of the 18 patients had any established or current evidence of neurological disease. This was confirmed by history taking and standard neurological examination. None of the patients were on any medications that could affect neurological function. Patents with systemic diseases that could lead to polneuropathy (e.g. diabetes) were also excluded.

6.2.1.2 Volunteers

Nineteen healthy volunteers (HV) (10 female; median age: 46 years, range: 32-55 years) with no evidence of gastrointestinal or neurological disorders were studied.

6.2.2 METHODS

6.2.2.1 Anorectal physiology

All patients underwent standard anorectal physiological investigation including studies of colonic transit and evacuation proctography as part of evaluation of their symptoms of constipation, as detailed in Chapter 2 (section 2.6). The results of these investigations are not seperately presented, as they are not relevant to this study.

6.2.2.2 Rectal sensation (Balloon distension)

Rectal sensation was measured by inflating a latex balloon, and RH was defined as two or more thresholds raised above the normal limits (sections 2.3.2 & 2.3.3).

6.2.2.3 Rectal electrosensory thresholds

A 1 cm long bipolar urethral ring electrode (Dantec Electronics Ltd., Bristol, UK), mounted on a 14G Foley catheter (chapter 5, Figure 5.01), was positioned within the mid rectum under direct vision during proctoscopic examination. The electrode was placed in contact with the rectal mucosa at 10 cm from the anal verge in the 12 o'clock position. The electrode was then connected to a constant current stimulator (Dantec Electronics Ltd.), which provided a constant current regardless of tissue impedance, and indicated if contact with the mucosa was lost. A stimulus of 500 μsec duration and 10 Hz frequency was then applied from 0 to a maximum of 60 mA at a rate of 1 mA/sec, controlled using an adjustable rheostat (Kamm et al. 1990). Subjects were warned about anal sensation related to the presence of the proctoscope and were asked to ignore this, and report the onset of any 'new' sensation (usually felt as "tingling", "pulsating", "burning", or discomfort within their rectum / pelvis / abdomen). This was recorded as the electrosensitivity threshold. The process was repeated three times, and the lowest of the readings accepted as the definitive electrosensitivity threshold. This tecnique has found to be well tolerated, accurately quantifiable and reproducible (Kamm et al. 1990). The electrode was then removed from the catherer (disposable) and immersed in CIDEX disinfectant overnight.

6.2.2.4 Rectal compliance

Rectal compliance ($\Delta V/\Delta P$), in $ml.mmHg^{-1}$, was derived from the slope of the steep portion of the pressure-volume curve (Whitehead et al. 1997) from a rectal barostat study (see section 7.2.2.3).

6.2.2.5 Neurophysiology study protocol

All tests were carried out in a quiet, temperature controlled room under the same test conditions for each subject.

6.2.2.5.1 Somatic function tests

Afferent Pathways:

1) Thermal thresholds	Warm	Small myelinated/unmyelinated (Aδ/C)
	Cool	Small myelinated sensory (Aδ)

Thresholds for warm and cool sensations were measured using a Marstock stimulator (Thermotest, Somedic Ab, Stockholm, Sweden) using a previously described technique that is reproducible (Guy et al. 1985;Knowles et al. 1999;Chong et al. 2004). Thermal thresholds assesed this way have been found to have high test reproducibility both at shorter and longer intervals (Heldestad et al. 2010). Ramp thermal stimuli was delivered with a standard rate of change of temperature of 1°C

per second, rising from a neutral temperature (25°C) up to the temperature when the subject is aware of the desired sensation (method of limits). Similarly thresholds for cold sensation were measured by reducing temperature at a standard rate of 1°C per second from neutral until the subject was aware of sensation. Subjects pressed a button immediately when they became aware of a given sensation, returning the stimulator to the neutral starting point. Each sensation was tested five times in succession, and the threshold taken as the average degree centigrade change from the neutral point calculated from the recording. The sum of the difference in temperature (from neutral [warmth + cold]) was also calculated (Chong et al. 2004). The S3 dermatome in the perineum was tested bilaterally. The instep of the right foot (L5 dermatome) and the C6 dermatome on the right hand (see Figure 6.01) were also tested to look for a generalised small fibre neuropathy.

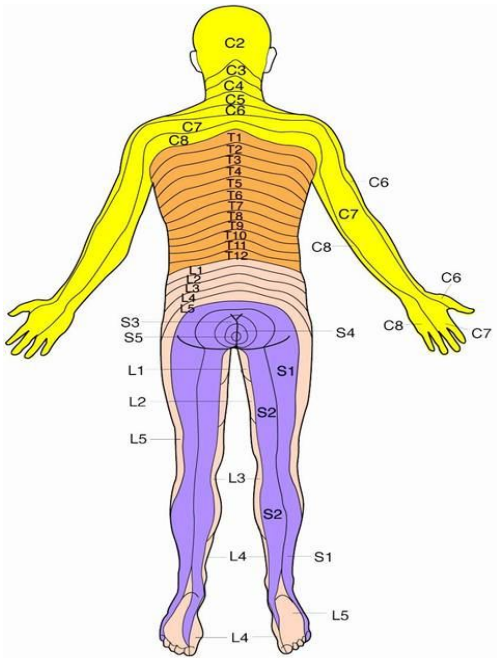


Figure 6.01: Dermatome map: posterior dermatomes

2) Tactile threshold (Large myelinated sensory [Aβ])

Semmes-Weinstein monofilaments ("Von Frey hairs"), numbered 1 to 20 (incremental stimuli), were used to produce a punctate stimulus in the dermatome under investigation (Semmes et al. 1960). The monofilament tip was placed over the dermatome under investigation and force applied until the shaft of the monofilament began to buckle. This meant that appying any more force did not lead to a greater stimulus intensity. An ascending method of limits was used by using progressively larger stimuli, applied with the patient's eyes closed until sensation was felt. The above method of determining tactile thresholds has been shows to be valid and reproducible (Valk et al. 1997). The S3 dermatome (perineum) was tested bilaterally. One dermatome over the instep of the right foot (L5 dermatome) and the C6 dermatome on the right hand were also tested to investigate for the presence of generalised somatic sensory neuropathy.

3) Sural nerve conduction (Large myelinated sensory [Aβ])

For recording the sural nerve sensory action potential the nerve was stimulated on the posterior surface of the lower leg 1-3 cm lateral to the midline. The recording electrode was placed behind the lateral malleolus of the foot. The sural nerve was stimulated and the sensory action potential (SAP) was recorded. The amplitude and delay were also recorded. The conduction velocity [m/sec] was then determined (Pugdahl et al. 2008). The above technique is routinely used in clinical practice.

Efferent Pathways:

1) Pudendal nerve terminal motor latency (PNTML)

PNTMLs were determined bilaterally by stimulating the pudendal nerve transrectally using a St Mark's electrode as described previously. Latencies were defined to be prolonged if greater than 2.3 ms in patients less than 50 years of age, or greater than 2.5 ms if over 50 years (Jameson et al. 1994) (see section 2.6.3).

2) Peroneal nerve conduction (Large motor [Aα])

The common peroneal nerve was stimulated with the stimulating electrode just below the head of the fibula. The recording electrode was placed over the ankle. Motor action potential (MAP) was then recorded from the EDB muscle (extensor digitorum brevis) while the nerve was stimulated below the fibular head (Ward et al. 2013). The amplitude and delay were also recorded and the conduction velocity [m/sec] was thus determined. The above technique has also been routinely used in clinical practice for evaluation of peripheral nerves.

6.2.2.6 Data and statistical analysis

Parameters of somatic nerve function were compared between the three study groups. Data were analysed using appropriate statistical tests as detailed in chapter 2 (section 2.7.2). A *P* value of < 0.05 was considered to show statistical significance.

6.3 RESULTS

6.3.1 RECTAL SENSATION

6.3.1.1 Balloon distension

All three sensory thresholds to balloon distension were significantly higher in the RH subgroup when compared to healthy volunteers and normosensate controls with constipation (FCS - HV: median 45 mls [range 10 - 110]; NS: 50 [40 -110]; RH: 175 [115 - 240] / DDV- HV: median 110 mls [range 60 - 180]; NS: 120 [80 - 180]; RH: 275 [240 - 360] / MTV- HV: median 180 mls [range 100 - 290]; NS: 200 [120 - 290]; RH: 355 [290 - 420], (P<0.01 for all thresholds)).

6.3.1.2 Rectal electrosensory thresholds

Patients with RH had significantly higher rectal electrosensory thresholds compared to healthy volunteers and normosensate controls (HV: median 12.4 mA [range 5.4 - 19.4]; NS: 14.8 [9.2 - 22.0]; RH: 35.6 [23.6-54.6], P<0.01 vs. NS; P<0.001 vs. HV, Figure 6.02).

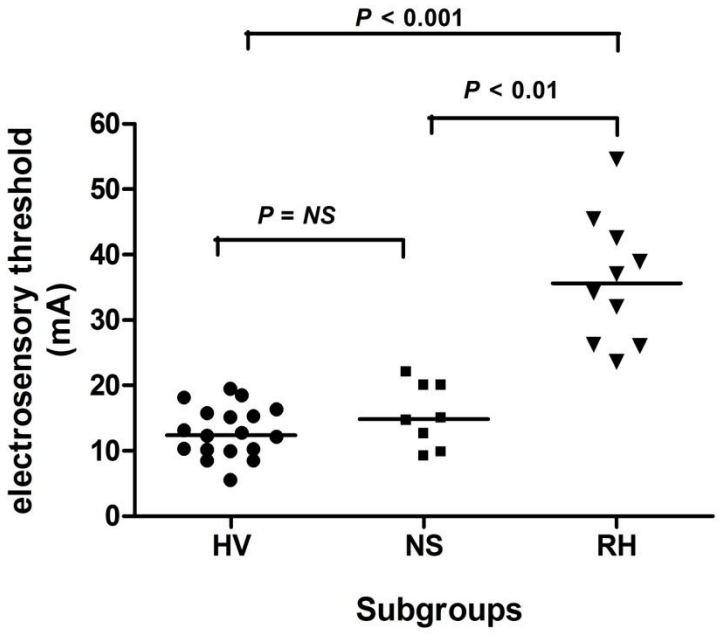


Figure 6.02: Rectal electrosensory thresholds (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

6.3.2 RECTAL COMPLIANCE

Rectal compliance was similar between the three subgroups of patients (HV: median 11.2 ml.mmHg^{-1} [range 7.4 - 17.8]; NS: 9.3 [7.3 - 19.3]; RH: 14.3 [7.8 - 23], *P*=0.176)

6.3.3 THERMAL THRESHOLDS

6.3.3.1 Perineum (S3 dermatome bilaterally)

As a group, thermal thresholds, expressed as sum of difference [warmth + cold], in the perineum were significantly higher in patients with RH compared to HV and NS (HV: median 7.9°C [range 2.8 - 18.6]; NS: 6.9°C [3.9 - 14.8]; RH: 11.8°C [4.8 - 29.5],

P<0.01 vs. NS; *P*<0.01 vs. HV, Figure 6.03).

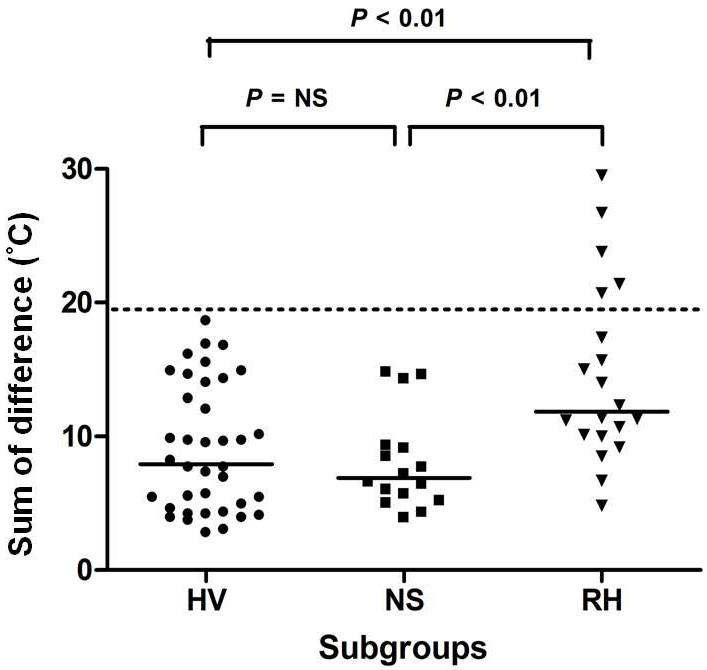


Figure 6.03: Perineal thermal thresholds: sum of difference [warmth + cold]. There are two values per subject reflecting each side (left / right). (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity; dotted line represents upper limit of normal in healthy volunteers)

Individually, 4/10 patients with RH had abnormal perineal thermal thresholds (expressed as sum of difference [warmth + cold]). One of these was bilateral and three were unilateral. The bilaterally abnormal threshold was in a male patient with normal rectal comlpliance and no history of neurological disease or previous surgery (these were exclusion criteria) for enrolment in the study. The three unilateral abnormal thresholds were in women who also had normal compliance and no history of neurological disease.

Warmth sensation (heat) thresholds in the perineum were also significantly higher in the RH subgroup when compared to HV and NS controls (HV: median 6.5°C [range 2.3 - 15.2]; NS: 5.5°C [3.4 - 14.8]; RH: 10.8°C [4.3 - 19.7], *P*<0.05 vs. NS; *P*<0.01 vs. HV, Figure 6.04). Similarly, cold sensation thresholds were significantly higher in the perineum in the RH subgroup (HV: median 1.4°C [range 0.1 - 3.9]; NS: 1.4°C [0.4 - 3.1]; RH: 2.6°C [0.5 - 9.8], *P*<0.05 vs. NS; *P*<0.05 vs. HV, Figure 6.05).

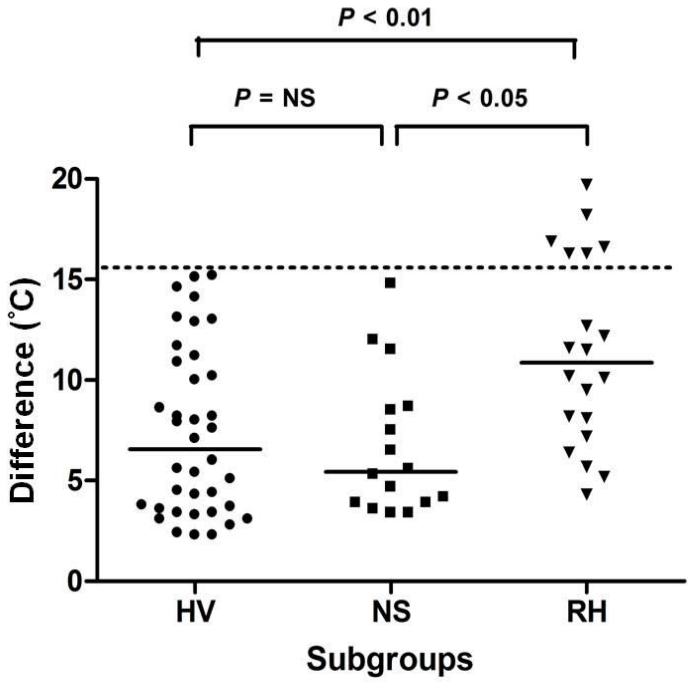


Figure 6.04: Perineal warmth thresholds. There are two values per subject reflecting each side (left / right). (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity; dotted line represents upper limit of normal in healthy volunteers)

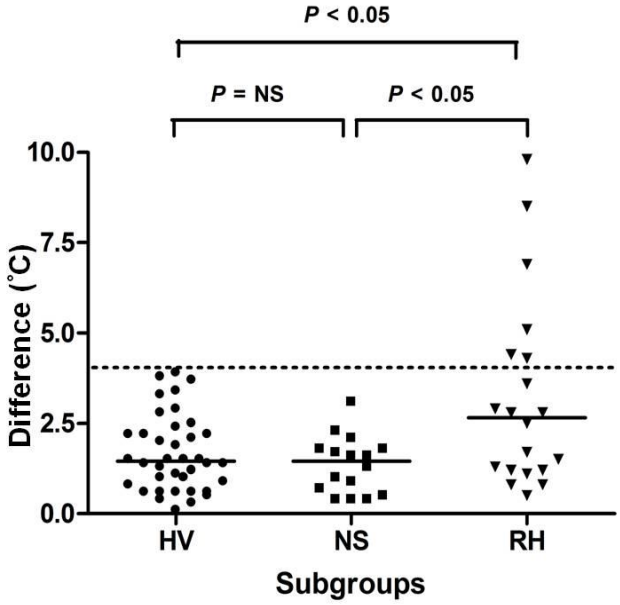


Figure 6.05: Perineal cold thresholds. There are two values per subject reflecting each side (left / right). (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity; dotted line represents upper limit of normal in healthy volunteers)

Individually there were 6 readings above the normal limit for perineal warmth sensation in the RH group. Of these, 2 were bilateral and 2 unilateral (i.e. 4 individual patients). Similarly there were 6 readings for abnormal cold sensation in the perineum in the RH group (2 bilateral / 2 unilateral). These corresponded to the same individuals and sides as the abnormal warmth thresholds.

6.3.3.2 Lower limb (L5 dermatome)

Thermal thresholds measured as sum of difference (warmth + cold) in the right lower limb were similar between the three subgroups (HV: median 5.3°C [range 2.4 - 10.2]; NS: 5.9 [3.1 – 11.3]; RH: 7.7 [2.6 – 13.6], *P* = 0.352, Figure 6.06).

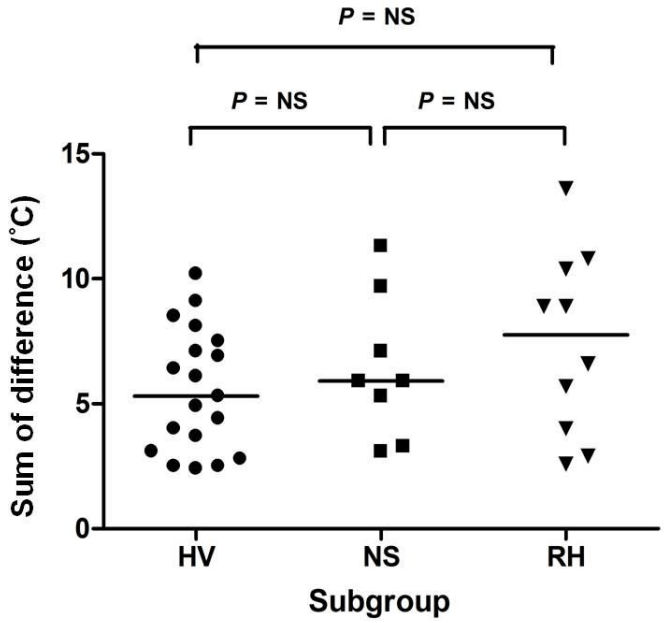


Figure 6.06: Right foot (L5 dermatome) - sum of difference [warmth + cold] (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

However, one patient in the RH group had raised thermal thresholds in the right foot. This individual had normal thermal and tactile thresholds in the perineum and the upper limb.

6.3.3.3 Upper limb (C6 dermatome)

Thermal thresholds measured as sum of difference (warmth + cold) in the right upper limb were also similar (HV: median 3.0˚C [range 1.5 - 9.6]; NS: 3.8 [2.1 - 6.2]; RH: 4.3 [2.2 - 10.3], *P* = 0.211, Figure 6.07).

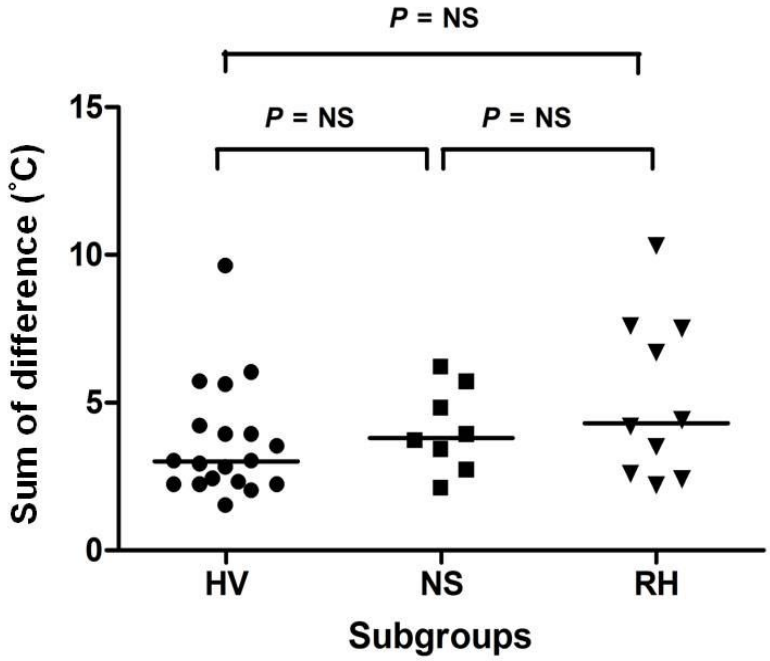


Figure 6.07: Right hand (C6 dermatome) - sum of difference [warmth + cold] (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

6.3.4 TACTILE THRESHOLDS

6.3.4.1 Perineum (S3 dermatome bilaterally)

As a group, patients with RH had significantly higher tactile thresholds in the perineum than patients in the other two groups (HV: median 0.07 g [range 0.02 - 0.4]; NS: 0.05 g [0.04 - 0.4]; RH: 0.28 g [0.04 - 0.6], $P < 0.05$ vs. NS; $P < 0.05$ vs. HV, Figure 6.08). Individually, two patients had values above the normal range. Both these individuals had an abnormal thermal threshold in the perineum on the corresponding side.

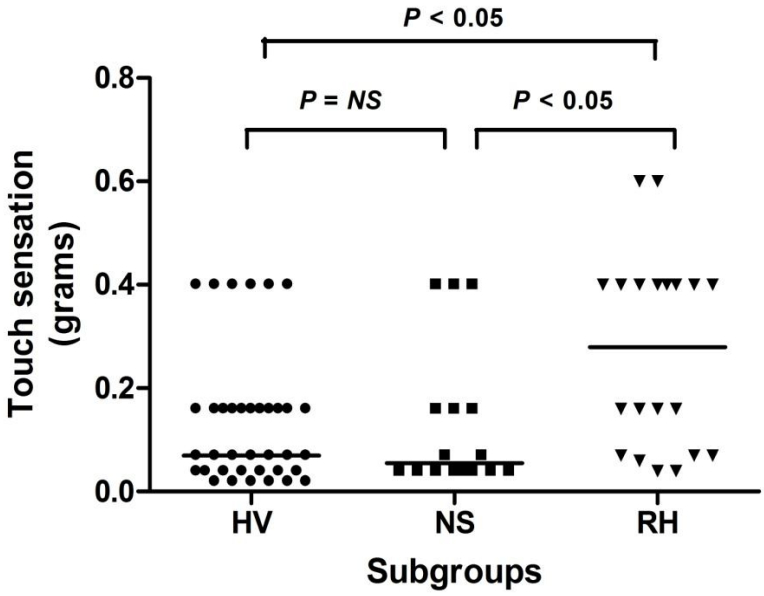


Figure 6.08: Perineal touch sensation to 'Von Frey' hairs: Target force in weight (grams). (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

6.3.4.2 Lower limb (L5 dermatome)

Tactile thresholds in the foot were similar between the three subgroups (HV: median 0.07 g [range 0.04 - 0.4]; NS: 0.16 g [0.08 - 0.4]; RH: 0.16 g [0.04 - 0.4], $P = 0.561$).

6.3.4.3 Upper limb (C6 dermatome)

Tactile thresholds in the hand were also similar between the three subgroups (HV: median 0.04 g [range 0.02 - 0.16]; NS: 0.04 g [0.02 - 0.16]; RH: 0.07 g [0.04 - 0.16], $P = 0.08$).

6.3.5 NERVE CONDUCTION STUDIES

6.3.5.1 Peroneal nerve conduction velocity

Peroneal nerve conduction velocities were similar between the three subgroups (HV: median 52 m/sec [range 41 – 57]; NS: 55 m/sec [47 – 63]; RH: 53 m/sec [43 – 58], *P*=0.192, Figure 6.09).

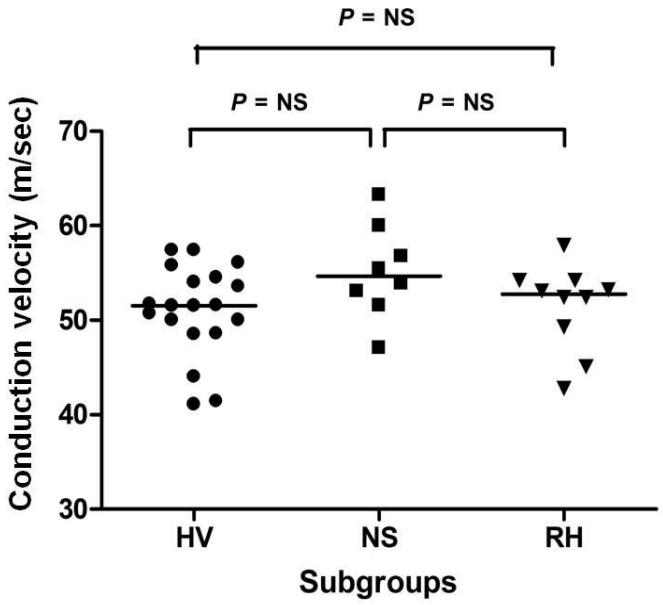


Figure 6.09: Peroneal nerve conduction velocity (m/sec) (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

6.3.5.2 Sural nerve conduction velocity

Sural nerve conduction velocities were also similar between the subgroups (HV: median 54 m/sec [range 40 - 70]; NS: 49 m/sec [46 - 53]; RH: 54 m/sec [46 - 67], *P*=0.188, Figure 6.10).

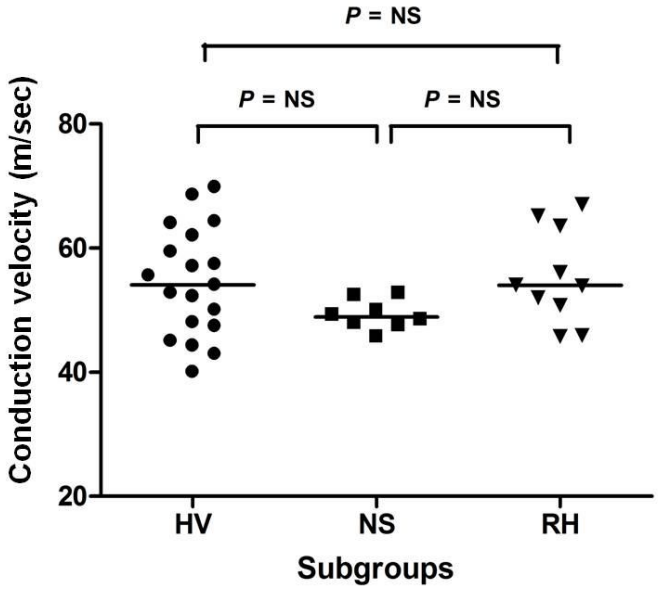


Figure 6.10: Sural nerve conduction velocity (m/sec) (HV- healthy volunteers, NS- normosensate and RH- rectal hyposensitivity)

6.3.5.3 Pudendal nerve terminal motor latencies (PNTML)

PNTMLs were similar between the three subgroups of patients (HV: median 2.2 ms [range 1.9-2.5]; NS: 2.4 ms [1.8-3.3]; RH 2.2 ms [1.8-3.1], *P*=0.263). Although 6 had evidence of pudendal neuropathy (values prolonged above normal range: 4 NS (2 bilateral and 2 unilateral; 2 RH (both unilateral)], none of these patients had elevated thermal or touch thresholds on the corresponding side.

PNTMLs could not be determined in 4 patients with RH (3 bilateral and 1unilateral). Of these, two patients (one bilateral) had abnormal thermal thresholds on the corresponding side in the perineum.

There was an inverse correlation between PNTMLs and perineal thermal thresholds (spearman R = - 0.312, *P* = 0.012, Figure 6.11).

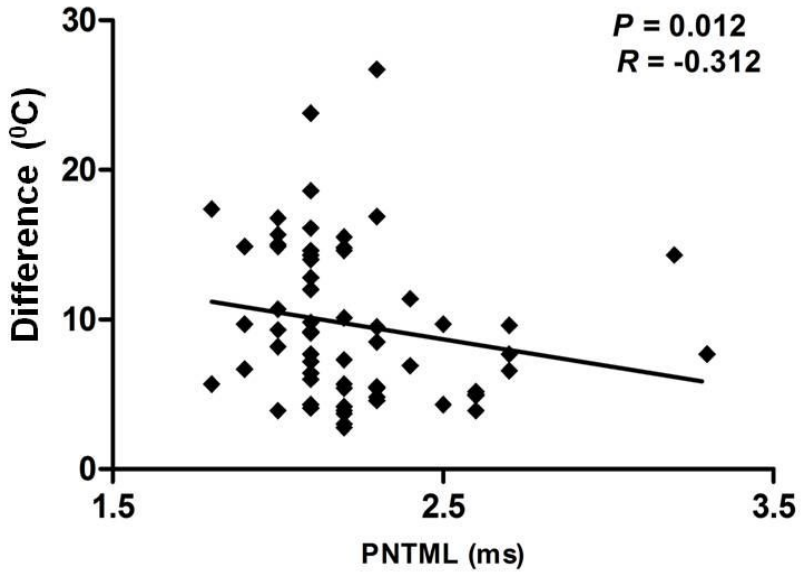


Figure 6.11: Correlation between PNTMLs and perineal thermal thresholds (sum of difference [Warmth + Cold] in healthy volunteers and patients

6.4 DISCUSSION

This study, performed in a homogenous group of patients with RH and constipation, and who were known to have raised rectal electrosensory thresholds (i.e. they represent patients believed to have 'primary' RH), has shown there is evidence of subclinical pelvic somatosensory neuropathy (small and large fibre) in 40%. This may reflect dysfunction in afferent conduction at the level of the pelvic nerve. All other tests of general somatic function were similar between the two groups of constipated

patients (impaired and normal rectal sensation). None of the patients in this study had a history or clinical evidence of neurological disorders or systemic illnesses such as diabetes that could lead to somatic or autonomic neuropathy. In the remaining majority of patients with RH and constipation, in whom there was no evidence of pelvic somatosensory neuropathy (60%), it is likely that the afferent defect is preferentially localised to the visceral afferents from the rectum.

There is a large body of literature on constipation and evacuatory dysfunction in patients with both partial and complete spinal cord injuries (Ebert 2012). RH is seen commonly in such patients (Awad et al. 2013). However, the incidence of undiagnosed or subclinical neuronal dysfunction in patients with RH and constipation is currently unknown. Varma *et al* found prolonged latencies of the pudendo-anal reflex in 15 patients with constipation, suggesting the possibility of a central neurological deficit (Varma et al. 1988b). These patients also had elevated rectal sensory thresholds. Another study using a validated sweat test concluded that a degree of autonomic denervation was commonly seen in patients with constipation (Altomare et al. 1992), although general autonomic function testing did not reveal any abnormalities in patients with slow transit constipation (STC) in another study (Knowles et al. 1999). Nevertheless, Knowles *et al* have shown that two-thirds of patients with slow transit constipation (STC) had evidence of somatic sensory neuropathy (Knowles et al. 1999), manifest as abnormal thermal thresholds in the lower limb, suggesting a generalised small-fibre neuropathy. In the absence of any overt neurological disease, quantitative sensory tests (QSTs) may be the only indicators of small fibre neuropathy (Knowles et al. 1999). QSTs are widely used in

clinical practice for the assesment of patients with peripheral neuropathy, and are reproducible and reliable psychophysical investigations for assesment of both large and small fibre sensory modalities (Chong et al. 2004). However, pelvic nerve function was not specifically investigated in this study.

In the current study, only two of the four constipated patients with RH who had abnormal thermal and tactile thresholds (signifying small / large fibre neuropathy) in the perineum had evidence of delayed gastrointestinal / colonic transit. Moreover, abnormalities to thermal / tactile stimuli were restricted to the perineum, as these patients did not have evidence of neuropathy in the upper or lower limbs. Similarly, there were no abnormalities in sensori-motor nerve conduction in these patients. This supports the hypothesis of an isolated pelvic somato-sensory neuropathy in this subgroup of patients with known impairment of rectal sensation.

The pudendal nerve is known to supply the anal canal and perianal skin. Accordingly, somato-sensory dysfunction in the perianal dermatomes can be related to pudendal neuropathy, secondary to injury, chronic straining, etc. However, as shown in this study, not all patients with abnormal perineal sensation had abnormal PNTMLs and *vice versa*. Furthermore, there was an inverse correlation between PNTMLs and perineal thermal threshold, which is surprising. Nevertheless, there are several drawbacks to PNTML testing (covered in section 2.6.3); indeed no correlation between PNTML and anal sensory threshold has been shown previously in patients with constipation (Vasudevan et al. 2007b).

6.5 *CONCLUSIONS*

An isolated pelvic visceral sensory neuropathy is commonly found in patients with rectal hyposensitivity. However, a combined viscero-somatic sensory neuropathy is present in a proportion of patients. Further tests of sacral somatic, autonomic and central function can be applied to validate these findings and elucidate the neuroanatomical level of afferent sensory neuropathy.

7 ASSESSMENT OF RECTAL CONTRACTILE RESPONSE IN PATIENTS WITH RECTAL HYPOSENSITIVITY

7.1 INTRODUCTION

Barostat studies of colorectal sensorimotor function have been widely performed in patients with functional bowel disorders, and have helped identify potential pathophysiological mechanisms for symptom causation (e.g. increased or reduced compliance, altered sensory function etc). During barostat distension studies (both rapid phasic (Akervall et al. 1989) and ramp inflation paradigms (Andrews et al. 2007), one phenomenon consistently observed in the early phase of distension is a transient reduction in volume and concomitant increase in pressure within the intra rectal bag. This is believed to be due to rectal contraction (termed the rectal contractile response: RCR); the significance of this event is incompletely understood, although it is believed to be a reflex related to perception of rectal sensation (Sun et al. 1990d).

Intact rectal sensory function is fundamental to normal defaecation and maintenance of continence (Rao et al. 2004;Rao 2004b). In patients with constipation, combined sensory and motor dysfunction (Read et al. 1986b;Schouten et al. 1998;Gladman et al. 2005a) of the rectum is thought to contribute to symptoms of evacuatory dysfunction and perhaps to secondary inhibition of proximal gut function through intrinsic entero-

enteric reflex mechanisms (Kellow et al. 1987;Law et al. 2002), as well as colonic dysmotility (Hughes et al. 1999a;Dinning et al. 2005). If perception of rectal distension (a sensory phenomenon) is indeed associated with the rectal contractile (motor) response, then it would be reasonable to speculate that the RCR may be attenuated in patients with constipation and rectal hyposensitivity. The aim of this study was thus to investigate if parameters of the rectal contractile response were altered in patients with RH and chronic constipation when compared to those with normal rectal sensation and chronic constipation, and also healthy controls.

7.2 PATIENTS & METHODS

7.2.1 SUBJECTS

7.2.1.1 Patients

The study cohort comprised twenty one consecutive patients with RH and chronic constipation [Rome II criteria (Thompson et al. 1999)]. Ten age and sex-matched patients with normal rectal sensation and constipation were also studied. (demographics, symptomatology, Table.7.01).

Table 7.01: Demography and symptomatology

	NS (N=10, 7F)	RH (N=21, 18F)	*P* VALUE
Age (years)	46 (24-63)	47 (25-71)	0.932
Duration of symptoms (months)	189 (11-744)	249 (12-828)	0.133
Symptoms (no of patients)			
Infrequency (<3BO/ week)	2	14	0.023
Incomplete evacuation	6	19	0.067
Unsuccessful evacuation	2	6	1.000
Straining to defaecate	6	16	0.417
Abdominal pain (unrelated to BO)	3	10	0.452
Concomittent faecal incontinence	5	6	0.423

Values for age and duration are presented as median (range)

(NS- normosensate & RH- rectal hyposensate)

No differences were found between patients with NS and RH with regard to demograpics and symptoms, except for a higher incidence of infrequency in the RH subgroup.

7.2.1.2 Controls

Ten healthy volunteers (7 female; median age 40, range 25-58) with no history of bowel symptoms comprised the control group.

7.2.2 METHODS

7.2.2.1 Anorectal physiology

All patients underwent standard anorectal physiological investigation and studies of colonic transit and evacuation proctography, as detailed previously (section 2.6).

7.2.2.2 Rectal sensory thresholds

Rectal sensation was measured by inflating a latex balloon, and RH was defined as two or more thresholds raised above the normal limits (section 2.3.2 & 2.3.3).

7.2.2.3 Electromechanical barostat protocol

A proctoscopic examination was performed to determine if the rectum was empty. If the rectum was loaded with stool, a gentle lukewarm tap water enema was administered till effluents were clear. A 1000 ml infinitely compliant polyethylene bag (Synectics Medical Ltd, Enfield, Middlesex, UK, Figure 7.01), secured to the distal end of a closed, double lumen PVC tube (Inflation channel diameter 1.8 mm,

Synectics Medical Ltd) was then inserted and positioned in the rectum with the aid of a rigid sigmoidoscope so that the centre of the bag was 10 cm from the anal verge in all subjects. The catheter was securely taped and subjects were placed in the prone position for the duration of the study. The catheter was then connected to an electronic barostat device (Synectics Medical Ltd, Figure 7.02) with a maximum flow rate of 38 ml/s.

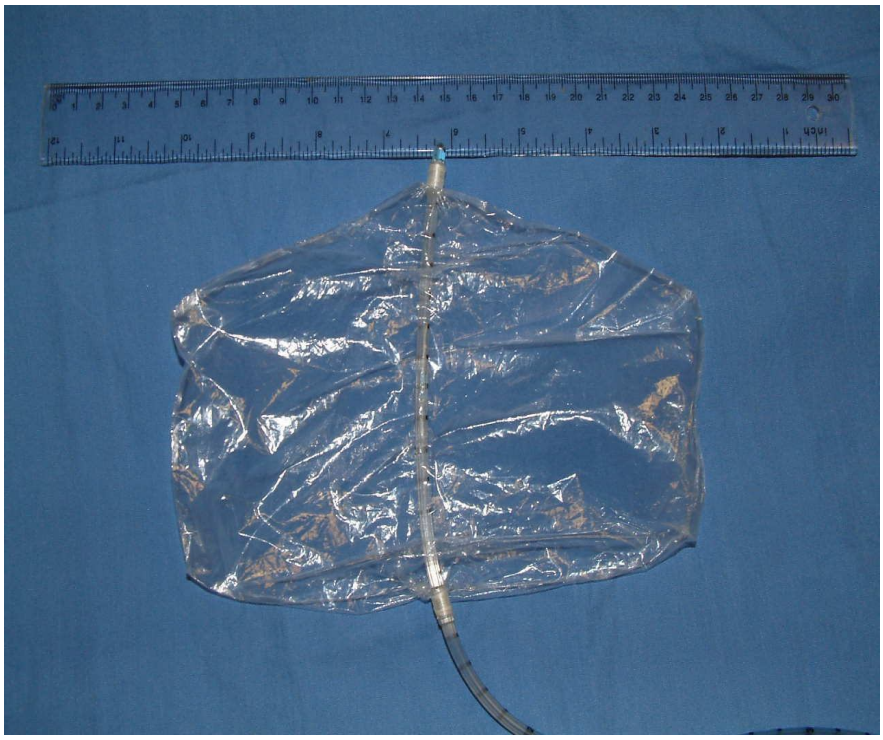


Figure 7.01: Barostat bag attached to rectal catheter

Figure 7.02: Electromechanical barostat system

The bag was first unfolded with 200 ml of air and then completely deflated. In order to familiarise subjects, enhance reproducibility and stabilise basal tone, a conditioning distension (Hammer et al. 1998) was performed by increasing bag pressure from 0 to maximum tolerated pressure or 36 mmHg (whichever came first) in 4 mmHg increments at 30 second intervals. The pressure at which respiratory excursions were clearly seen on the volume trace (minimum distensing pressure: MDP) (Bell et al. 1991) was then determined with a 1 mmHg stepwise ascending method of limits protocol, each distension lasting for 60 seconds. Sensory thresholds pressures for first sensation, defaecatory desire and maximum toleration were determined using a phasic distension protocol with increments of 2 mmHg from 0 mmHg till maximum

toleration was reached. Each distension lasted for 60 seconds with a 60 second rest period between distensions when pressure returned to 0 mmHg.

7.2.2.4 Rectal compliance

Rectal compliance ($\Delta V/\Delta P$), in $ml.mmHg^{-1}$, was derived from the slope of the steep portion of the pressure-volume curve (Whitehead et al. 1997).

7.2.2.5 Parameters of the rectal contractile response

Assessment of the rectal contractile response was performed at MDP+4 mmHg during the phasic distension protocol. The RCR was defined as the transient, first appreciable drop in the volume trace once the target pressure (MDP+4 mmHg) was reached (Figure 7.03). The following parameters of the RCR (reflecting the magnitude of contraction) were then analyzed using Polygram for Windows^{TM} V1.1 software (Synectics Medical Ltd).

Reduction in volume %: this was calculated as a ratio of the minimum volume during a contraction to the largest volume preceding the contraction once target pressure (MDP+4 mmHg) was reached. The ratio is expressed as a percentage. Values < 21% were considered abnormal (mean -2SD in healthy volunteers)

Area over the curve (AOC): This was calculated as the area above the contraction and is expressed as a percentage (AOC/AOC+AUC × 100) of the whole area (WA=

AUC+AOC, see inset Figure 7.03) for the duration of the contraction. Values < 9% were considered abnormal (mean -2SD in healthy volunteers).

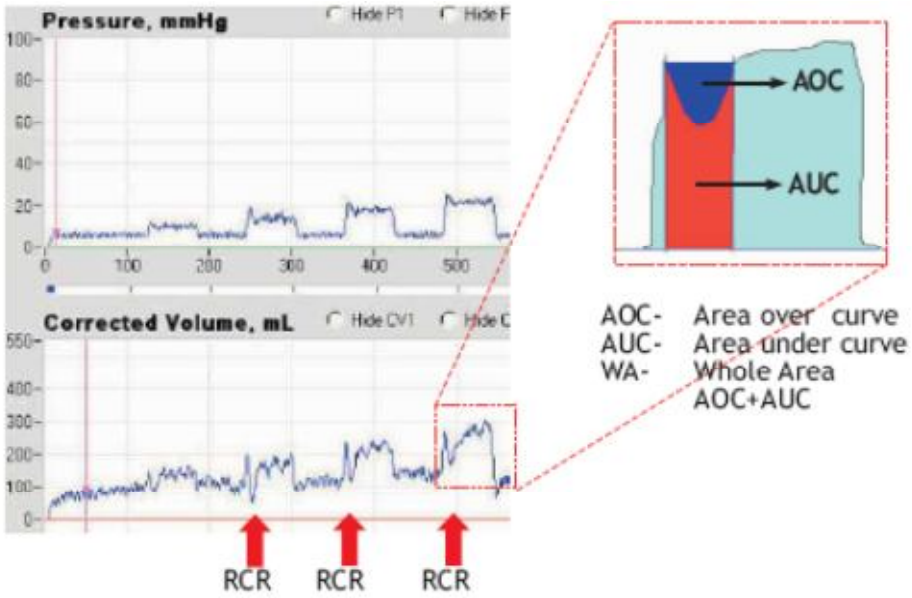


Figure 7.03: Barostat volume trace showing the RCR. (Inset) shows how AOC and reduction in volume were determined

The value of MDP + 4mmHg was selected because maximum RCR amplitude was demonstrated in healthy volunteers at this pressure (Figure 7.04). In addition the parameters of RCR at MDP + 8 mmHg were also studied to confirm consistency of results at other pressures.

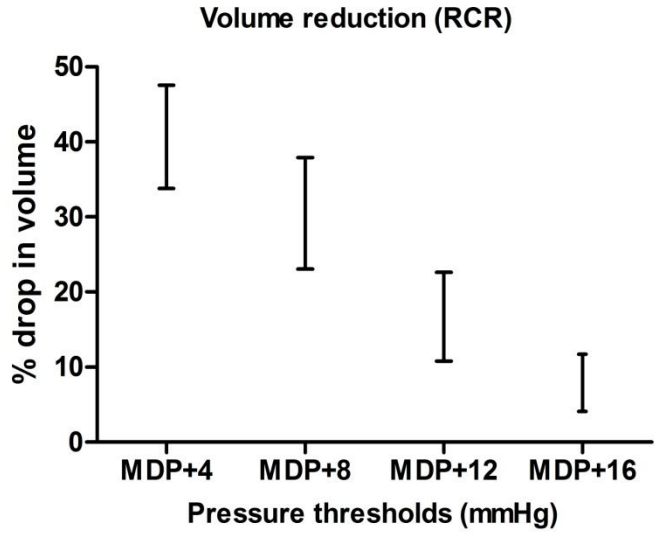


Figure 7.04: RCR amplitude in healthy volunteers at increasing pressures showing maximum amplitude at MDP + 4mmHg.

7.2.2.6 Data and statistical analysis

For non-parametric data, comparison between groups was performed using the unpaired t test, Mann-Whitney U test or Kruskal-Wallis test with Dunn's multiple comparison where appropriate. Contingency tables were analysed using the Fischer's exact test. All values are expressed as median and range unless otherwise stated. $P<0.05$ was considered to be statistically significant. Data were analysed using a commercially available statistical software package (Graphpad Prism 4, California, USA).

7.3 RESULTS

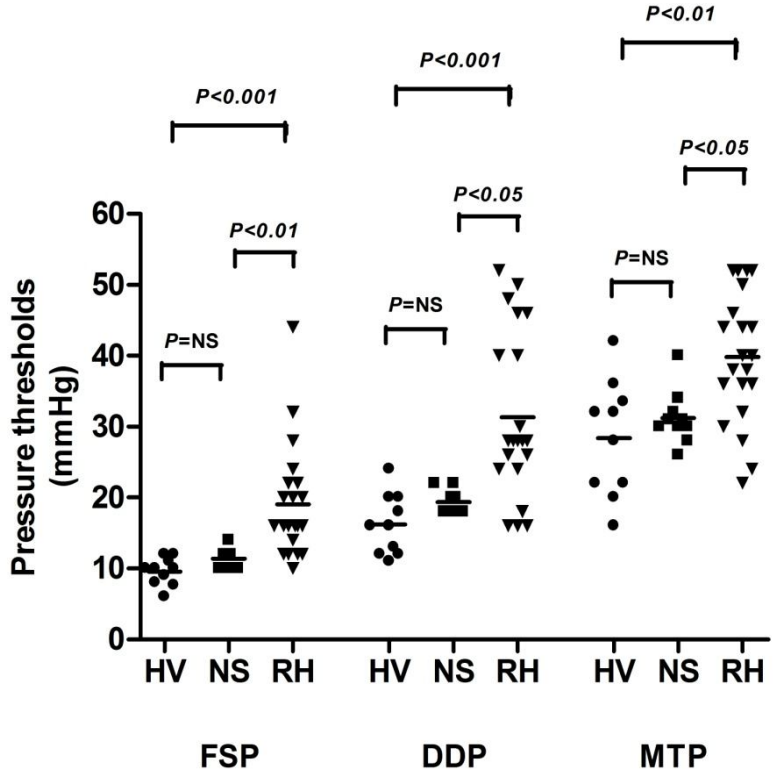
7.3.1 RECTAL SENSATION

7.3.1.1 Balloon distension

All three sensory threholds to balloon distension were significantly higher in the RH subgroup when compared to normosensate controls (FCS - NS: median 30 mls [range 10 - 105] vs. RH: 120 [20 - 360] / DDV- NS: median 105 mls [range 50 - 160] vs. RH: 300 [140 - 420] / MTV- NS: median 180 mls [range 60 - 360] vs. RH: 360 [210 - 420], $P = 0.003$ for FCS and $P<0.001$ for DDV and MTV).

7.3.1.2 Barostat: pressure thresholds

Patients with RH had significantly higher pressure thresholds (FSP, DDP and MTP) when compared to the NS subgroup and healthy volunteers (Figure 7.05).



4).

Figure 7.05: Barostat pressure thresholds (FSP-first sensation, DDP- desire to defaecate & MTP- maximum tolerated) in the 3 study groups (HV- Healthy controls, NS- normosensate & RH- rectal hyposensate)

7.3.2 RECTAL COMPLIANCE

Patients with RH as a group had significantly increased (*P*<0.001, Figure 7.06) rectal compliance when compared to the NS subgroup. Individually, 10/21 patients with RH had compliance above the normal limit for our unit (19.1 ml.mmHg^{-1} [Mean + 2SD]). None in the NS subgroup had increased rectal compliance.

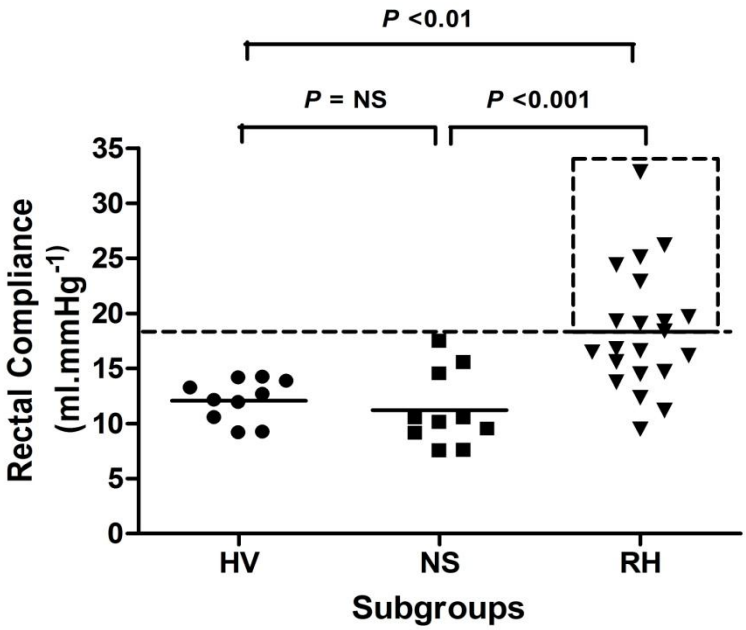


Figure 7.06: Rectal compliance in the 3 study groups (HV- healthy controls, NS- normosensate & RH- rectal hyposensate; dotted line indicates upper limit of normal [mean + 2SD]; values inside box are abnormal [hypercompliant])

7.3.3 PARAMETERS OF THE RECTAL CONTRACTILE RESPONSE

Threshold pressures for eliciting the RCR were similar to the FSP (first sensation pressure) in healthy volunteers and NS patients (HV: median 10 mmHg [6-14] vs. 10 mmHg [6-12]; NS: median: 11 mmHg [10-14] vs. 12 mmHg [10-14], respectively; *P*= NS for both). However, in patients with RH, the threshold for RCR was significantly below the FSP threshold (median: 10 mmHg [4-38] vs. 16 mmHg [10-44], respectively; *P*<0.001, see figure 7.07). Individually, in the RH group the RCR was elicited at subsensory threshold level in 18 patients, at FSP in 1 and higher than FSP in 2 individuals.

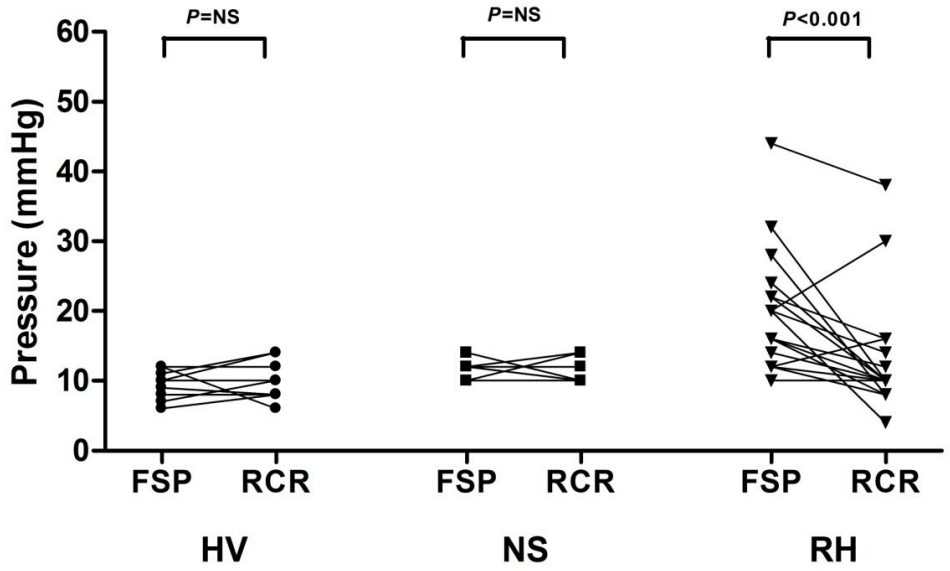


Figure 7.07: Relationship of FSP (first sensation pressure) to RCR (rectal contractile response) in the 3 study groups. (HV- healthy controls, NS- normosensate & RH- rectal hyposensate)

In all healthy volunteers, the RCR started at pressures significantly below the desire to defaecate pressure [DDP] (median: 10 mmHg [6-14] vs. 16 mmHg [11-24], respectively; *P*=0.003). Similarly, in patients with NS and RH, RCR started at lower pressures than DDP (NS: median 11 mmHg [10-14] vs. 19 mmHg [18-22]; *P*<0.001 and RH: median 10 mmHg [4-16] vs. 28 mmHg [16-52]; *P*<0.001). At higher pressure distensions the RCR diminished and finally disappeared.

7.3.3.1 Parameters of the RCR at MDP + 4 mmHg

Reduction in volume%: This was significantly lower in the RH subgroup when compared to the NS subgroup (median: 15% [0-55] vs. 30% [15-65], respectively;

P=0.049, Figure 7.08). Individually, 10/21 patients with RH had a magnitude of RCR below the lower limit of normal (*P* = 0.011). Indeed, the RCR was absent at MDP + 4 mmHg in 7 of these (5 with normal rectal compliance and 2 with hypercompliant rectum).

Area over the curve (AOC): was also significantly smaller in the RH subgroup when compared to the NS subgroup (median: 8% [0-34] vs. 16% [8-37], respectively; *P*=0.036, Figure 7.09). Individually 9/21 patients with RH were below the lower limit of normal (*P* = 0.030).

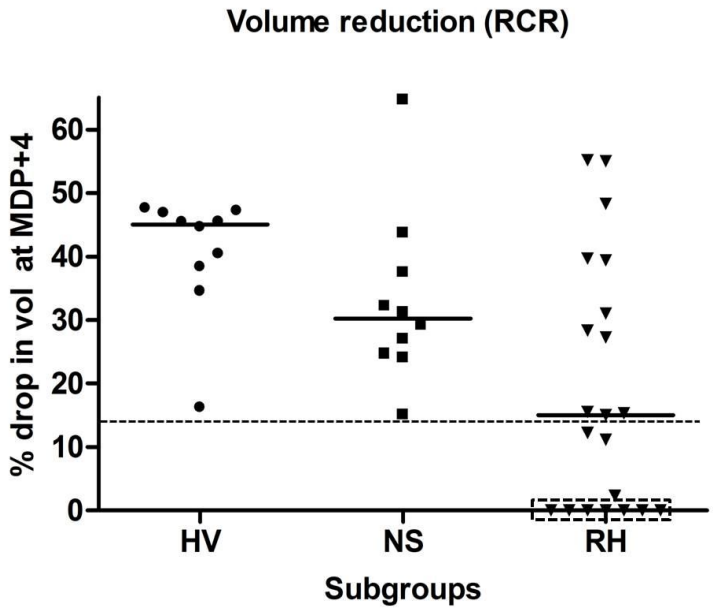


Figure 7.08: Percentage drop in volume of the RCR at MDP+4 mmHg in the 3 study groups (HV- healthy controls, NS- normosensate & RH- rectal hyposensate; dotted line indicates lower limit of normal in controls; values in box represent absent response at MDP + 4mmHg)

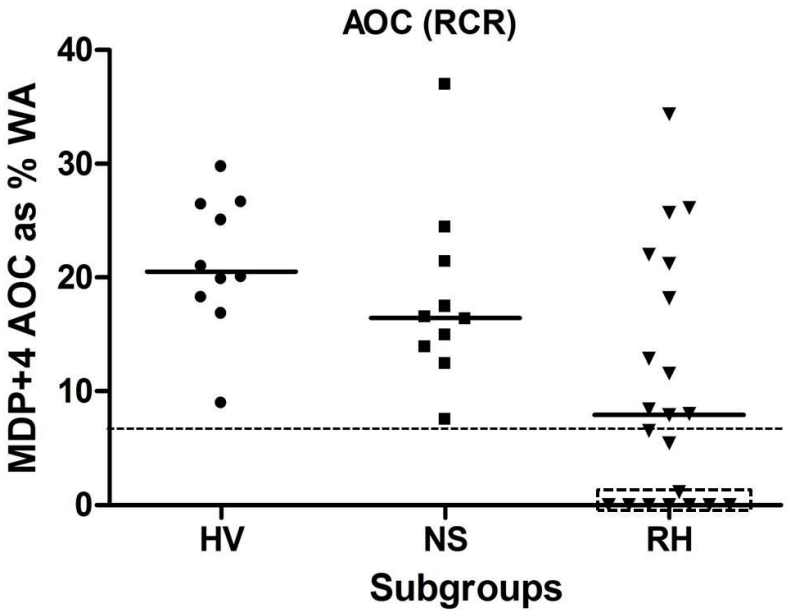


Figure 7.09: Area over the curve of the RCR expressed as a percentage of the whole area in the 3 study groups (HV- healthy controls, NS- normosensate & RH- rectal hyposensate dotted line indicates lower limit of normal in controls; values in box represent absent response at MDP + 4mmHg)

Rectal compliance and RCR: None of the normosensate atients had blunted RCR. 5/10 patients with increased compliance (hyper) and 5/11 patients with normal compliance had a blunted RCR (*P*=NS). Of the seven patients with an absent RCR, only 2 patients had a hypercompliant rectum. The remaining five had normal rectal compliance.

7.3.3.2 Parameters of the RCR at MDP + 8 mmHg

Parameters of the RCR at MDP+8 mmHg were consistent with those obtained at

MDP + 4mmHg with patients with RH having diminished amplitude when compared to those with NS and in HV (reduction in volume % HV: median: 29% [14-49], NS: median 28% [13-52], RH median: 15% [0-70] respectively; $P<0.05$ and AOC as % WA HV: median: 15% [9-29], NS: median 16% [8-36], RH median: 8% [0-37] respectively; $P<0.05$). Six individuals with RH had an absent response at this pressure. The above six patients also had absent response at MDP + 4mmHg.

7.4 DISCUSSION

This study has examined parameters of the rectal contractile response in healthy controls and in patients with constipation, sub-grouped into those with normal and blunted rectal sensation. The major finding was that constipated patients with rectal hyposensitivity, as a group, had a diminished response (reduced amplitude), and that in a third of patients with RH, the RCR was indeed absent. In healthy volunteers and normosensate patients with constipation the RCR was elicited at threshold pressures similar to the FSP. However, in patients with RH the threshold pressure for eliciting RCR was significantly below the FSP. In all subjects (patients and volunteers), the RCR occurred well below the desire to defaecate presure (DDP).

The rectum serves as a reservoir for stool and plays an important role in evacuation. Intact rectal sensori-motor function is crucial for normal defaecation to occur. Several reflex responses contribute to normal anorectal sensori-motor function including the RCR, recto-anal inhibitory and recto-anal excitatory reflexes. Rectal contraction in response to rectal distension has been observed previously (Read et al.

1986b;Akervall et al. 1989;Kwan et al. 2002;Andrews et al. 2007). This occurs either as a result of smooth muscle contraction in response to stretch of the muscle fibres or, more likely, a spinally mediated reflex phenomenon (Akervall et al. 1989). However, the true function of this reflex is currently unknown.

The finding of a blunted rectal contractile response in patients with RH indicates that motor dysfunction of the rectum coexists in a proportion. However, 10 of the 21 patients with RH also had increased rectal compliance; of these, 5 had a blunted RCR. In this subgroup, laxity of the rectal wall could have primarily contributed to the blunted response. Nevertheless, at MDP+4 mmHg pressure, there were 7 patients with a totally absent response, of whom only 2 had increased compliance. This indicates that intact rectal sensation plays a pivotal role in this reflex. We used the pressure threshold of MDP + 4 mmHg to ensure that the earliest onset rectal contractions were studied for their importance to rectal sensory perception. This was also the pressure at which the maximal amplitude of the RCR was present. The RCR also reduced in intensity and eventually dissapeared at higher distension pressures as the rectal wall was stretched and therefore MDP + 4 mmHg was chosen. The results were also consistent at MDP + 8 mmHg. As seen on the graphs depicting the amplitude of the RCR results for the normosensate group seem to lie midway between healthy volunteers and patients with RH suggesting that patients with NS are evolving in a continum and will develop RH. However from our own experience patients with RH are a distinct subgroup and only longitudinal studies will be able to exlore this adequately.

Whatever the cause, an abnormal RCR may contribute to the development of disordered rectal evacuation, which may contribute to symptomatology both in patients with constipation and those with overflow faecal seepage. Previously, in a study of 14 severely constipated women and 29 age matched controls, Read *et al* were able to elicit regular rectal contraction to distension in 71% of controls, compared to only 36% of the constipated patients (Read et al. 1986b). They hypothesised that regular rectal contraction to distension helps to squeeze rectal contents into the ampulla, thereby priming the area for defaecation. In another study in healthy volunteers using isobaric rectal distension, the RCR was not identified in only four of 36 subjects and only displaced a small volume in the remaining subjects (Akervall et al. 1989). However, urge to defaecate was experienced close to the threshold for maximal RCR in this study (Akervall et al. 1989). Hence RCR may be associated with conscious perception of the urge to defaecate. They also hypothesised that the limited magnitude of the RCR in the study may reflect an inhibition from spinal and supraspinal centres (perhaps reflecting social behavioural training [i.e. toilet training] or due to a subconscious reflex). This is supported by the observation that rectal contractions that completely empty the bowel have been observed in patients with high spinal cord injury (Denny Brown et al. 1935;Akervall et al. 1989) where these spinal / supraspinal inhibitory mechanisms can be affected. The reverse situation to that observed in this study is seen in patients with faecal incontinence and rectal hypersensitivity, who have been found to have increased frequency, amplitude and duration of the RCR when compared to those with normal rectal sensation (Sun et al. 1992). Such pathological ‘hyperreactivity’ may play a role in the pathophysiology of the symptoms of urgency that is classically observed in these patients.

In the current study, threshold pressures required to elicit the RCR were similar to the FSP in healthy volunteers and the NS subgroup. However, in those with RH, threshold volumes to elicit the RCR were significantly lower than the FSP. All healthy volunteers and patients with constipation with or without blunted rectal sensation had an appreciable RCR at pressures lower than their threshold for desire to defaecate (DDP). This suggests that the urge to defaecate sensation is not entirely dependant on rectal contraction. However, at sub-urge threshold, onset of RCR may contribute to sensation by transiently increasing rectal pressures to supra threshold levels before rectal accommodation begins. We have not measured sensory ratings during each distension in this study. Such information would have been very useful to study the relationship of the RCR to rectal sensation. Similarly, the intensity of sensation has been found to vary during different parts of a phasic distension protocol in healthy controls (Akervall et al. 1989;Kwan et al. 2002). Also studying the relationship of the RCR to recto-colonic and recto-anal reflexes will provide valuable information regarding hindgut coordination in this subgroup of patients. It is acknowledged that the group studied is small especially the healthy volunteers cohort. But they were well caharcterised with regards to their sensory status and is unlikely that this would have influenced the results.

7.5 CONCLUSIONS

In conclusion, the rectal contractile response to rapid phasic distension is diminished in patients with rectal hyposensitivity, irrespective of rectal compliance. This may reflect combined sensori-motor dysfunction in a subgroup. Further studies are necessary to assess the relationship between rectal sensation and the RCR.

8 RECTO-ANAL REFLEXES IN HEALTH AND IN PATIENTS WITH RECTAL HYPOSENSITIVITY - A PILOT STUDY USING A NOVEL TECHNIQUE

8.1 INTRODUCTION

Intact rectal sensation is central to normal defaecation and maintenance of continence. Entry of stool into the rectum initiates a series of events. Initially, the rectal wall will distend, leading to a change in its properties (i.e. stress, strain or tension). These events may or may not be consciously perceived depending on their magnitude. Entry of stool into the rectum also initiates recto-anal and recto-rectal reflexes that play an important role in hindgut function. These reflexes may contribute to spontaneous 'sampling' episodes (Duthie et al. 1963;Read et al. 1982;Sun et al. 1990c), involving distension-induced rectal contraction (rectal contractile response: RCR) (Akervall et al. 1989), internal anal sphincter relaxation in response to distension (recto-anal inhibitory reflex: RAIR)(Gowers 1877;Denny Brown et al. 1935) and external anal sphincter contraction (recto-anal contractile reflex: RACR) (Garry 1933;Goligher et al. 1951;Sun et al. 1990a;De et al. 2007;Remes-Troche et al. 2010), which are thought to allow rectal conents to come into contact with the sensitive upper anal canal, and allows discrimination between flatus and stool (and hence conscious control over voidance). Such coordinated events may, however, be altered in anorectal disorders. For example, the RCR has been found to be exaggerated in patients with irritable bowel syndrome who present with faecal incontinence (Corsetti et al. 2004).

Likewise, the RAIR has been found to be altered in patients with constipation (faster recovery in obstructed defaecation (Netinho et al. 2005)), occurs at smaller volumes in patients with faecal impaction (Read et al. 1986a) and also in those with faecal incontinence (less frequent spontaneous sampling) (Miller et al. 1988a), and with a greater amplitude of relaxation (Kaur et al. 2002)). Similarly, it has been suggested that the RACR may be impaired in patients with constipation and overflow, especially in the presence of blunted rectal sensation (Read et al. 1986a). Nevertheless, fundamental questions regarding the physiology and complex interplay of sensorimotor (recto-anal and recto-rectal) reflexes remain unanswered. The RCR, RAIR and RACR must be synchronised for normal defaecation to occur and continence to be maintained. Most studies investigating these hindgut reflexes have been limited by the fact that they have been studied in isolation. Very few studies have investigated reflex activity as an integrated entity either in health or in patients with hindgut dysfunction. This is principally due to technical difficulties in studying various parameters of anorectal activity in real time which involves integration of different modalities. When such studies have been performed, they have provided valuable information on pathophysiological mechanisms in patients (Sun et al. 1992;Remes-Troche et al. 2010). Furthermore, despite the link between anorectal reflexes and anorectal sensation, the relationship between such reflex activity and impairment of rectal sensation has not been systematically explored. Nevertheless, rectal hyposensitivity (RH) is known to be present in 16% of patients presenting with symptoms of hindgut dysfunction, and up to 30% in those with combined constipation and incontinence (Gladman et al. 2003b) and is becoming increasingly recognised as important in the pathophysiology of these conditions.

The principal aim of this pilot study was to devise a novel method by which to investigate recto-anal reflex activity in real time in healthy volunteers, and secondarily, to extend the study to patients with RH and constipation.

8.2 SUBJECTS AND METHODS

8.2.1 SUBJECTS

8.2.1.1 Healthy controls

Eleven healthy volunteers (8 female, median age 48 years [range 22-61]) with no history of bowel symptoms were studied.

8.2.1.2 Patients with RH

Four patients with RH and constipation (3 female, median age 48 years [range 29-54] were also studied. RH was defined as having two or more sensory thresholds to balloon distension elevated beyond the normal range (see section 2.3.5). All four also had elevated rectal electrosensory threholds but normal rectal compliance (i.e. 'primary' RH, see section 1.6.2.1).

8.2.2 METHODS

8.2.2.1 Study visit and perception of the urge to defaecate

All study subjects arrived after an overnight fast, and filled in a questionnaire about presence of any bowel symptoms. As part of this questionnaire, they were asked to mark on a topograph where they perceived their normal urge to defaecate (see Appendix C). A digital rectal examination was then performed, and if the rectum was not empty, a lukewarm tap water enema was administered until returns were clear. All tests were done with the subjects in the left lateral position in a temperature controlled room.

8.2.2.2 Combined barostat-manometry technique: technical details

A purpose-built barostat / rectosigmoid manometry catheter (Mui Scientific, Mississauga, Canada, Figure 8.01) was inserted into the rectum under rigid sigmoidoscopic guidance so that the centre of the barostat bag (max volume = 1000 ml) lay in the rectum, 10 cms from the anal verge. Five cm from the top end of the bag, a water-perfused manometry channel was incorporated into the catheter, (Figure 8.01). Another fine, purpose-built solid-state manometry catheter, incorporating three unidirectional pressure sensors (Unisensor AG, Attikon, Switzerland [Figure 8.02]) was then inserted into the anal canal. These sensors were placed 1, 2.25 and 3.5 cm from the anal verge; the sensors were oriented posteriorly, and confirmed to be in good contact with the anal canal and away from the barostat catheter. Once the catheters were in position, they were securely taped to the perianal skin to avoid any displacement. Two surface EMG electrodes were then carefully glued to the skin over the EAS on either side and connected to an amplifier. The manometry, barostat and EMG signals were all integrated into custom-designed proprietary software (Medical

Measurement Systems [verion 9.1], Enschede, The Netherlands), through a manometry system (Solar: MMS, Figure 8.03), so that all the channels were integrated on the output and were visible on screen in real time.

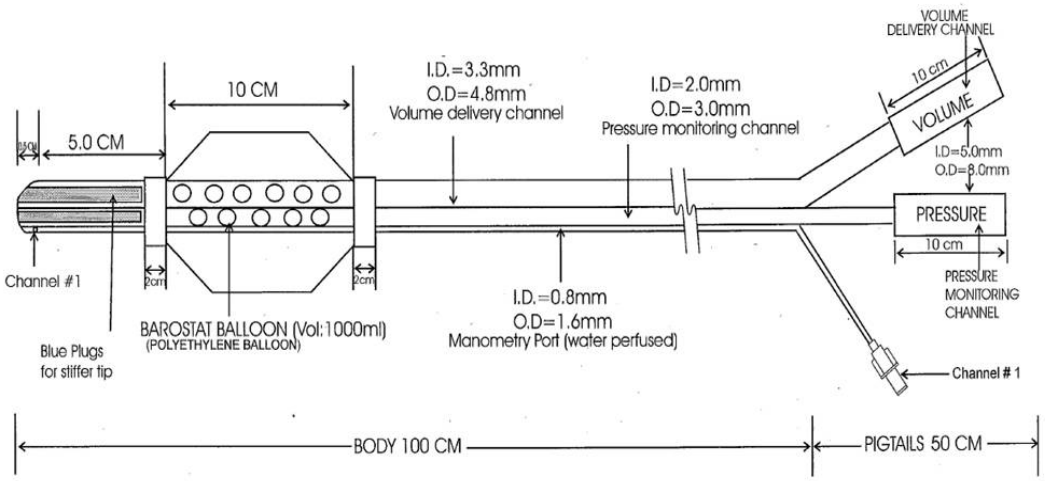


Figure 8.01: Custom made rectal barostat catheter design with water perfusion manometry channel at tip

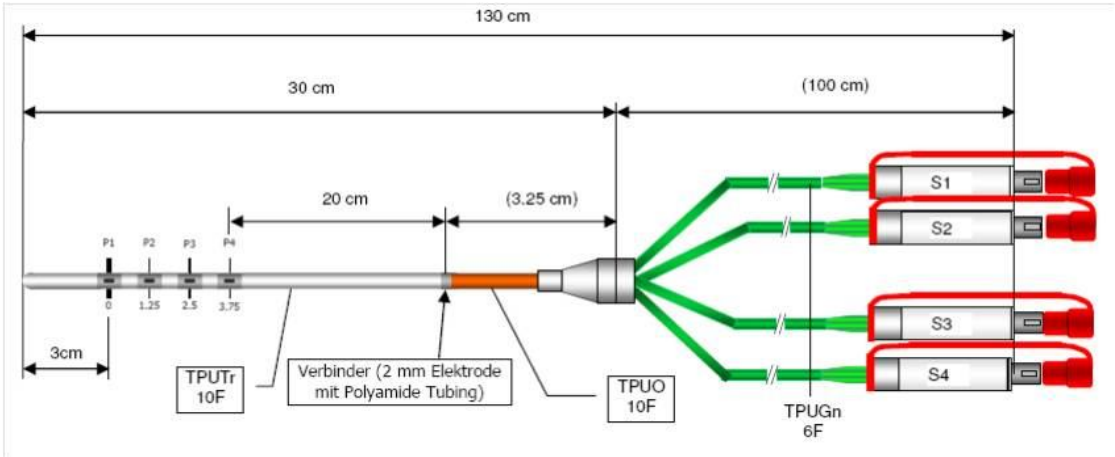


Figure 8.02: Solid-state anal manometry catheter design showing pressure transducers

Figure 8.03: MMS Solar Series

8.2.2.3 Test protocol

8.2.2.3.1 Anal function

After a 5 minute rest period to allow for familiarisation, the water-perfused manometric channel, with the recording port located in the recto-sigmoid, was connected to an Arndorfer-type pneumohydraulic water-perfusion system (Figure 8.03), and perfused at a rate of 0.2 ml/min. It was then calibrated. Recordings were also acquired from the solid-state anal manometry catheter. Data acquisition from both catheters was started simulatneously. The maximal resting anal pressure was determined from the transducer in the anal canal that had the highest pressure reading.

Anal squeeze pressures were determined by asking the subjects to contract their anal musculature three times for 5 seconds, with a rest period of 30 seconds between each 'squeeze', and averaging the values. Cough reflex contractions were not elicited.

8.2.2.3.2 Spontaneous anorectal activity and relation to conscious perception

The barostat catheter channels were connected to a single-staged rigid barostat system (G&J, Canada, Figure 8.04). The barostat bag was first unfolded, followed by a conditioning distension from 0 to 30 mmHg in 2 mm increment steps, each step lasting 30 seconds. The mimimal distending pressure was then determined by using an ascending method of limits phasic distension protocol from 0 mmHg, increasing by increments of 1 mmHg lasting 30 seconds, until respiratory variations were clearly seen on the volume trace.

Figure 8.04: G&J Distender II series barostat machine

Following another 5 minute rest period, the barostat bag was inflated to operating pressure (MDP+2 mmHg) and maintained at this pressure for 30 minutes to study spontaneous anorectal activity. Subjects were asked to press a keypad for the duration of any sensation they felt during this 30 minutes. They were also asked to describe the nature (i.e flatus, urge or discomfort) and intensity of the sensation on a visual analogue scale (with 0 being no sensation and 10 being unbearable, Appendix C). The manometry channels were active for the entire duration of the study. At the end of the 30 min period, the barostat bag was deflated. MDP+ 2mmHg distension pressure was chosen because at this pressure the balloon was in contact with the rectal wall but the pressure was low enough not to induce any distension induced ano-rectal events, particularly because this protocol was used to study spontaneous ano-rectal evants.

8.2.2.3.3 Rectal compliance, rectal contractile response and sensation

Following a further 10 minute rest period, the manometry channels were restarted and a (pseudo) random ascending method of limits phasic distension protocol was started, from 0 mmHg with increments of 2 mmHg, each distension lasting 1 minute with rest period of 1 minute between distensions. The randomisation was done in such a way that overall, distension pressures generally increased, but individual pressures were randomised (e.g. 6, 4, 10, 8, 12, 16, 14, 20, 18 mmHg etc), thereby making it difficult for the subjects to predict the intensity of the subsequent distension. For each distension, the subject was asked to press and hold the keypad for the duration of any sensation (if) perceived, and rate that sensation on a visual analogue scale (as described

earlier). At the end of this period, the barostat bag was deflated and the catheter was removed.

8.2.2.4 Data and statistical analysis

For group data, a paired t-test or Mann Whitney U test was used, where appropriate. Contingency tables were analysed using Fisher's exact or Chi Squared tests. Data were analysed using a commercially available statistical software package (GraphPad Prism 4, California, USA). A *P* value of < 0.05 was considered to show statistical significance.

8.3 RESULTS

8.3.1 PERCEPTION OF THE URGE TO DEFAECATE

From the symptom questionnaire, all healthy volunteers indicated that they perceived the urge to defaecate (as defined on the topograph) in the rectum / anal canal. Conversely, all four patients with RH and constipation attributed lower abdominal pain to the need to defaecate ($P<0.0007$).

8.3.2 ANAL FUNCTION

All healthy volunteers (HV) and patients with RH had good anal resting and squeeze pressures (resting pressure HV: median 57 mmHg [range 40-90] vs RH: median 67 mmHg [range 55-82]; *P*=0.40; squeeze pressures HV: median 164 mmHg [range 98-242] vs RH: median 115 mmHg [range 76-150]; *P*=0.04).

8.3.3 SPONTANEOUS ANORECTAL ACTIVITY AND RELATION TO CONSCIOUS PERCEPTION

8.3.3.1 Healthy volunteers

8.3.3.1.1 Spontaneous anal relaxation

Spontaneous relaxation of the anal canal (Figure 8.05) to constant distension at MDP + 2 mmHg (taken to reflect 'sampling') was seen in all healthy volunteers (median 5 episodes [range 2-19]. In all, there were 70 episodes of spontaneous anal relaxation among the 11 volunteers during the 30 min baseline period, with amplitude (drop in anal pressure) of the relaxations varying between 34-100% in the channel with maximal drop in anal pressure (median 63%). However, at no point did rectal pressure exceed the overall anal pressure in any of the volunteers as the anal pressures were still above the rectal pressure as recorded in at least one of the three anal transducers.

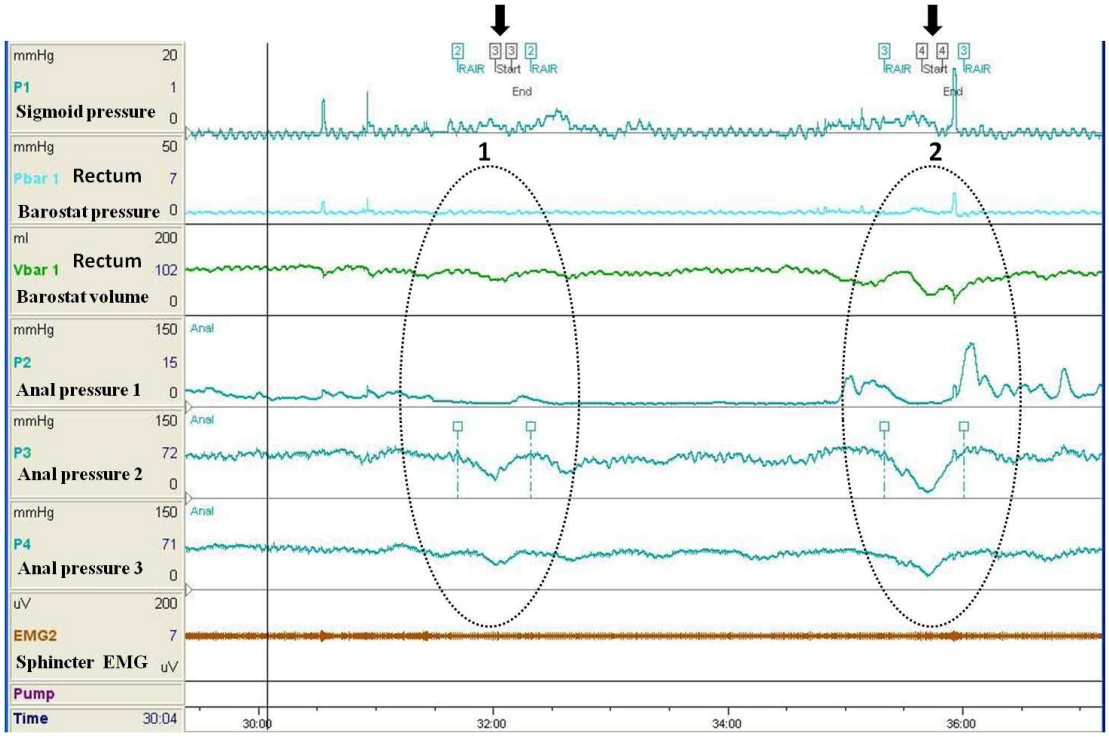


Figure 8.05: Recto-anal events during prolonged barostat distension to MDP+2 mmHg. In this example, operating pressure was 7 mmHg in a HV. Anal relaxation either with (event no 2: see volume reduction in barostat trace [Vbar 1], coincident with recto-sigmoid contraction [sigmoid and rectal pressure channels]) or without (event no 1) associated rectal contraction are noted. These events, taken to represent 'sampling' episodes, were both consciously perceived as awareness of flatus (see sensation marker on top of screen indicated by block arrows).

8.3.3.1.2 Relationship to conscious perception

All but one volunteer (2 episodes of anal relaxation) perceived the majority of the sampling episodes as a transient sense of awareness of flatus. Overall, 42 of the 70

episodes were consciously perceived (Figure 8.06). Those episodes perceived had a higher magnitude, although this did not achieve statistical significance (amplitude of perceived [N=42] median 69% [range 34-100] vs not perceived [N=28] median 61% [range 38-100]; *P*=0.07).

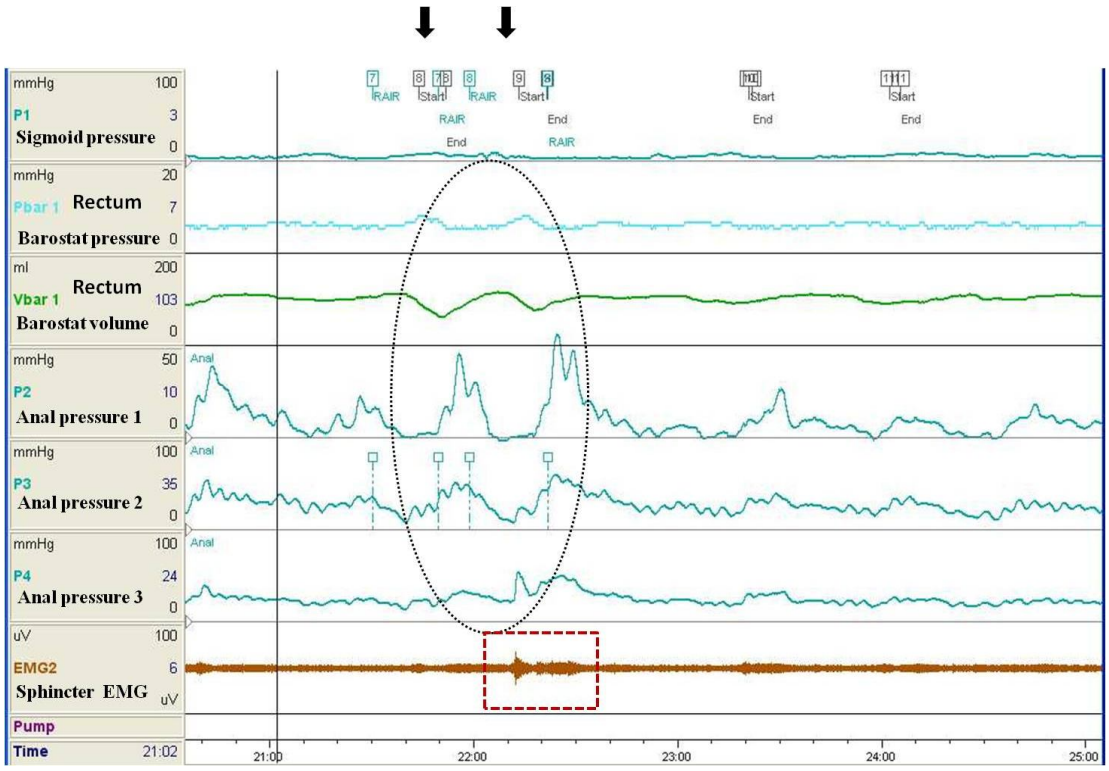


Figure 8.06: Recto-anal events during prolonged barostat distension to MDP+2 mmHg. In this example in a HV, with operating pressure at 7 mmHg; rectal contractions (Vbar channel), associated with anal relaxation (P2/3 channel), were followed by an EAS contraction (EMG and P4 channel). This episode reached conscious perception as awareness of flatus (see sensation marker on top indicated by block arrows).

8.3.3.1.3 Associated rectal contraction

Forty one of the 42 consciously perceived episodes of anal relaxation were accompanied by contraction of the rectum (seen as significant reduction on the barostat volume trace, Figures 8.05 & 8.06), as opposed to only 21 of 28 episodes that were not consciously perceived [P=0.006].

8.3.3.1.4 Associated EAS (external anal sphincter) contraction

Twenty nine of the 42 consciously perceived episodes of anal relaxation were associated with EAS contraction (Figure 8.06). Of the 28 episodes of anal relaxations that were not consciously perceived, only 1 episode was associated with EAS contraction (P<0.0001).

8.3.3.2 Patients with RH

None of the four patients with RH had any episodes of spontaneous anal relaxation at MDP+2 mmHg (Figure 8.07). Similarly there was no spontaneous rectal contraction or EAS contraction during the 30 min distension period.

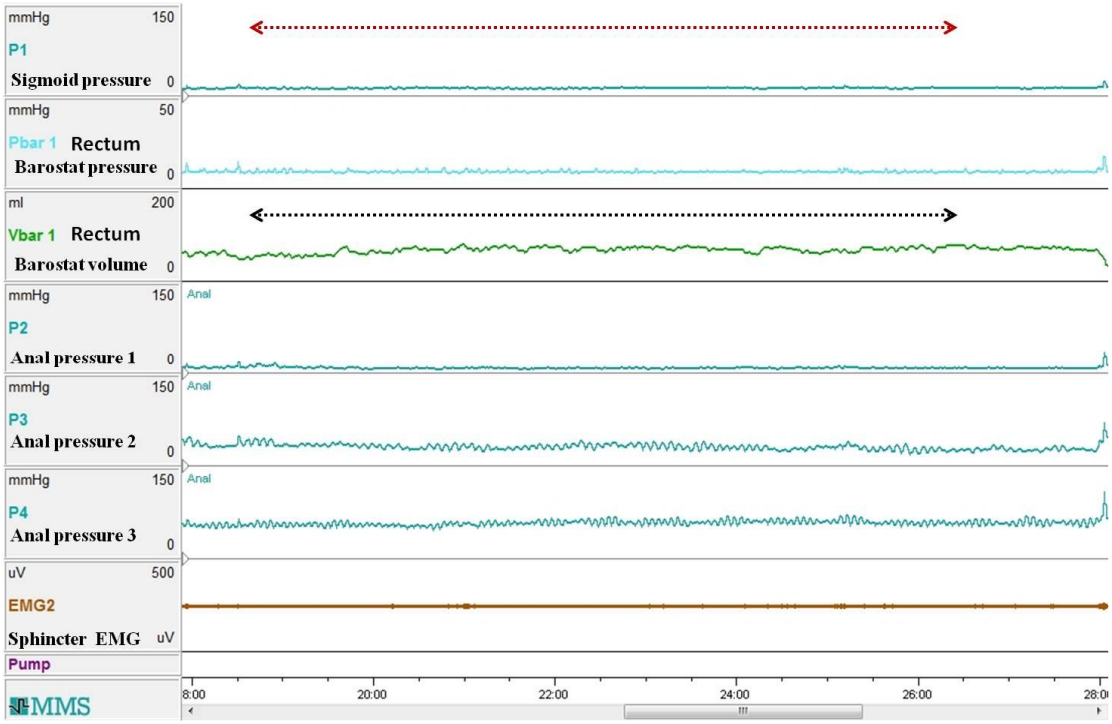


Figure 8.07: Recto-anal events during prolonged barostat distension to MDP+2 mmHg in a patient with RH. In this 10 minute example, with operating pressure at 10 mmHg there is a complete absence of spontaneous anal relaxation (P2/3 channel), spontaneous rectal contaction (see black horizontal arrow on Vbar trace), or EAS contraction (EMG and P4 channel). There were also no consciously perceived events (see red horizontal arrow on the top).

8.3.4 RECTAL CONTRACTILE RESPONSE (RCR) TO PHASIC DISTENSION

8.3.4.1 Healthy volunteers

An RCR to phasic distension was seen in all healthy volunteers. In all subjects, the onset of RCR was consistently below the first sensation pressure (Figure 8.08). The

onset of RCR was not coincident with transient sensations (flatus, urge or discomfort) in any subject. The RCR dissapeared at higher pressures in all volunteers (Figure 8.09).

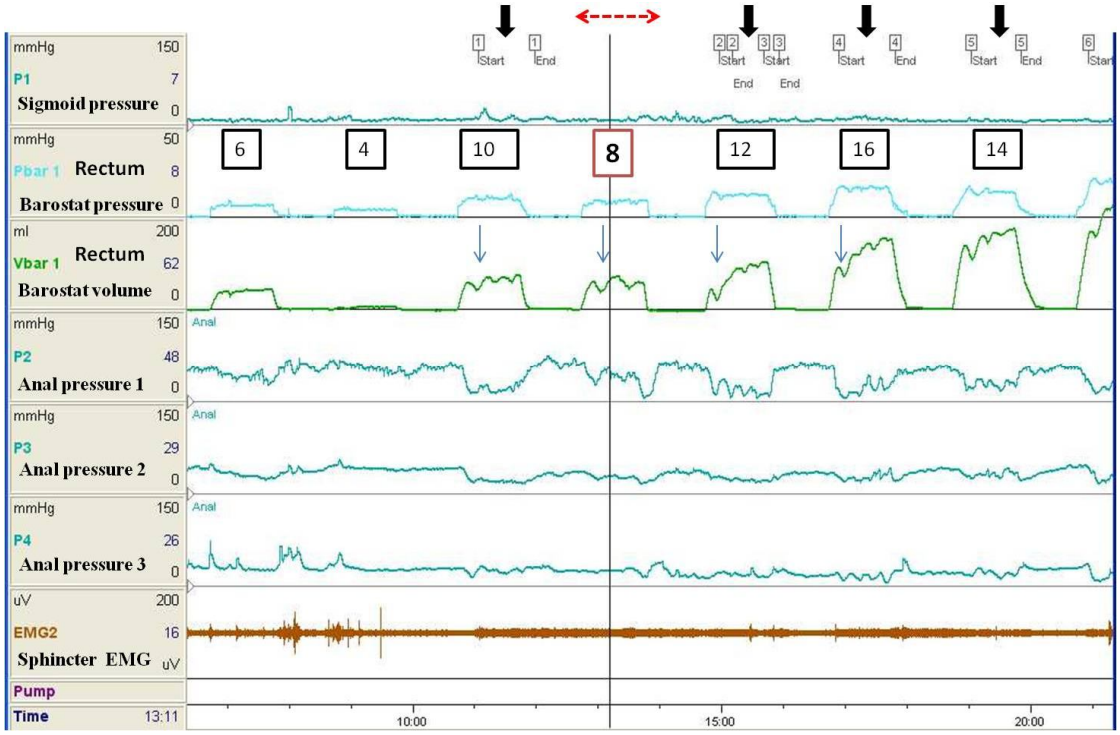


Figure 8.08: Recto-anal events during (pseudo) random phasic distensions in HV. This example shows RCR onset at 8 mmHg (seen as volume reduction in Vbar [see thin arrow]). This was not associated with conscious perception (see horizontal red arrow on top) as opposed to the 10 mmHg distension that was perceived (see block arrow on top of the figure), as were all other subsequent distensions (12-16 mmHg). Individual distension pressures are also shown in the Pbar trace.

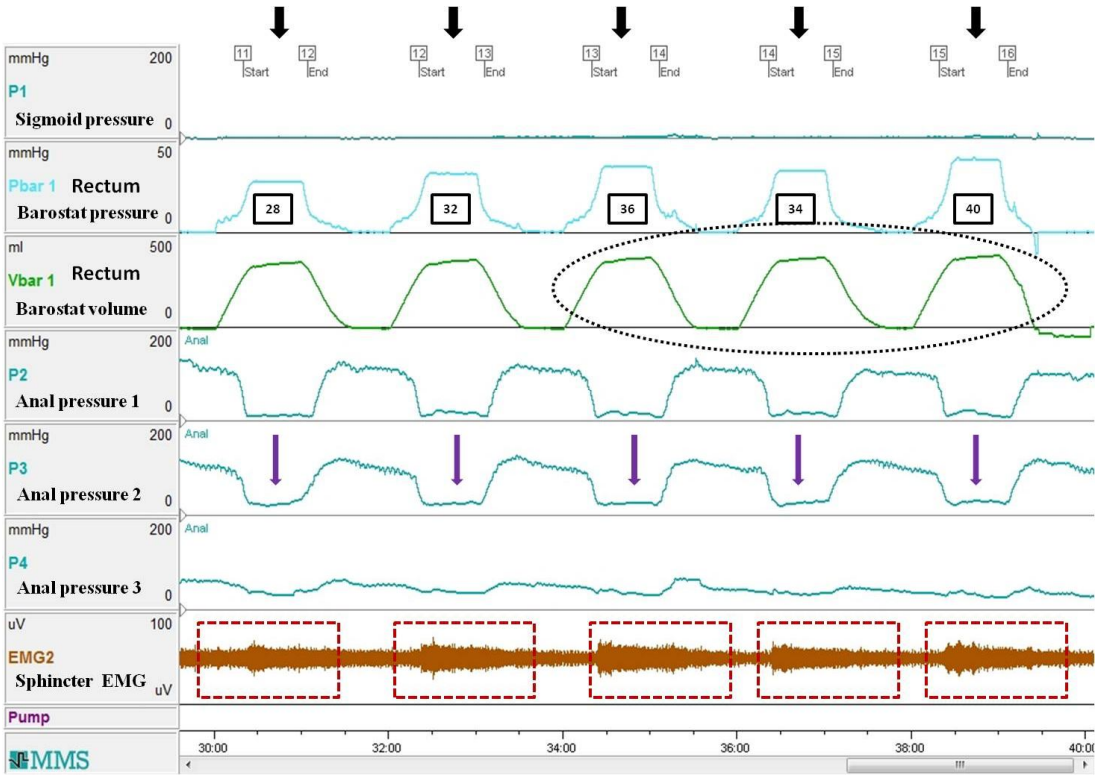


Figure 8.09: Recto-anal events during (pseudo) random phasic distensions. In this example in a HV, RCRs are absent at high pressures (see 'flat' trace on Vbar channel enclosed by ellipse). Also seen is coincident IAS relaxation (RAIR- in anal pressure channels 1-3) and EAS contraction (see areas enclosed by rectangles on EMG trace) to distension. All of the above distensions were consciously perceived (indicated by black arrows near sensation markers). Individual distension pressures are also shown in the Pbar trace.

8.3.4.2 Patients with RH

All four patients with RH had an RCR to phasic distension. However, they appeared to be of much smaller amplitude (Figure 8.10, small numbers- hence no comparisons are

made in this study). This reflex has been studied in detail in chapter 7. As seen in healthy volunteers, the onset of RCR was well below the first sensation pressure and was not associated with transient sensations (flatus, urge or discomfort). As seen in HV, the RCR disappeared at higher pressures in all four patients.

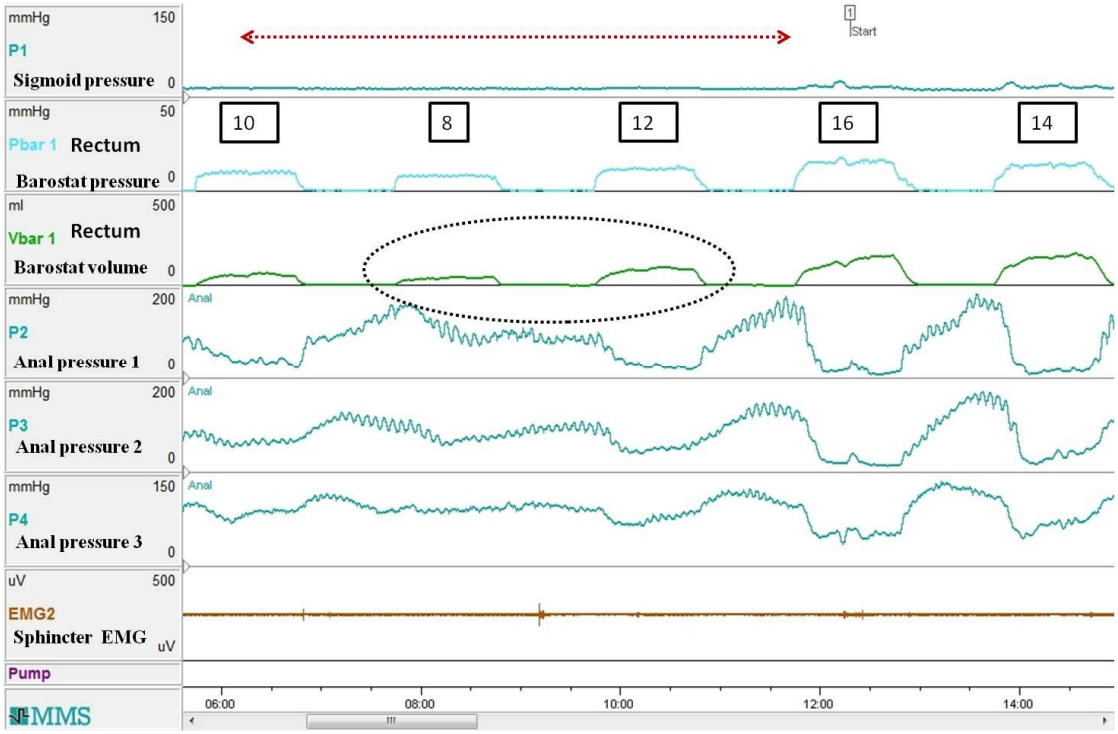


Figure 8.10: Diminished amplitude of RCR in patients with RH. Individual distension pressures are shown in Pbar trace. In this example, none of these distensions were perceived consciously (see absence of sensory markers over distension on top of screen indicated by red horizontal arrow).

8.3.5 RECTAL COMPLIANCE

Rectal compliance ($\Delta V/\Delta P$) in $ml.mmHg^{-1}$, was derived from the slope of the steep portion of the pressure-volume curve on the phasic distension protocol (Whitehead et al. 1997). Rectal compliance was similar between the two study groups (HV: mean: 12.6 $ml.mmHg^{-1}$ [range 7.5 - 15.6] vs RH: median 11.9 $ml.mmHg^{-1}$ [range 10.2- 14.5]; *P*=0.56).

8.4 DISCUSSION

This study has revealed the following findings:

- This new integrated technique to study recto-anal sensorimotor events / reflexes is feasible and has allowed us to study this in real time and has thus eliminated some of the drawbacks of previous techniques.

- Healthy volunteers perceive the sensation of desire to defaecate in their rectum / anal canal as opposed to a small cohort of patients who all perceived the call to stool as an abdominal sensation.

- Spontaneous anal relaxation is seen in healthy volunteers, and the vast majority of these (presumed) sampling episodes were coincident with transient sensation of awareness of flatus. Events accompanied by rectal contraction were more likely to result in sensory awareness. By contrast, patients with RH did not have any spontaneous episodes of anal relaxation at low pressures.

- RCR to phasic distension was seen in all healthy volunteers at threshold pressures below FCP. RCR was also seen in patients with RH below FCP, but with smaller amplitude. Both in HV and RH, RCR to phasic distension was not accompanied by transient sensations at onset and disappeared at higher distension pressures.

The mechanisms by which RH may contribute to constipation are currently unclear, although it has been suggested that rectal outlet dysfunction and colonic dysmotility may occur as a consequence. One postulated mechanism of outlet dysfunction is that it may occur due to an inadequate increase in rectal pressure due to abnormal rectal contractility in response to rectal distension (Read et al. 1986b;Schouten et al. 1998), or due to inadequate relaxation of the anal canal and the pelvic floor (Whitehead et al. 1999). Colonic dysmotility can occur primarily or secondarily as a result of reflex viscero-visceral inhibition of proximal gut function secondary to outlet dysfunction (Dinning et al. 2005).

Distension of the rectum initiates a fall in anal canal pressure secondary to relaxation of the internal sphincter (RAIR) with subsequent recovery. This RAIR is thought to allow 'sampling' of rectal contents by the sensitive epithelial lining of the anal canal e.g. to discriminate stool from flatus (Miller et al. 1988c). Previous studies suggest that sampling of rectal contents may occur intermittently in the absence of rectal distension or change in rectal pressure, although such studies were performed with what can now be considered obsolete technology (Miller et al. 1988a). In this study, we have found

that spontaneous anal relaxation occurs an average of 10 times per hour in healthy volunteers, and the majority of these were consciously perceived as transient sensation of awareness to pass flatus, especially those that were accompanied by rectal contraction. This may also be an accomodation reflex. It is important to remember, however, that these investigations were performed under test conditions with the subjects concentrating on sensory awareness from the anorectum. Nevertheless, the absence of spontaneous anal relaxation and rectal contraction in the four patients with RH and constipation is of potential pathophysiological significance, though the small number of subjects studied is obviously acknowledged. It may be argued that the base pressure of MDP+ 2 mmHg was low and hence the absense of spontaneous ano-rectal activity in patients with RH. However, this in itself is a very important finding in patients with RH as these are subconscious events and may contribute to pathophysiology. Mechanistically, an absence of 'sampling' may result in build-up of stool in the rectum, with lack of awareness perhaps leading to impaction/ overflow. Intact rectal sensation may thus also be crucial for normal sampling, despite the RAIR being mediated by the enteric nervous system.

Rapid distension of the rectum initiates a rectal contractile response (RCR) (Akervall et al. 1989), and also a brief contraction of the external anal sphincter (RACR). The true function of the rectal contractile response (RCR) remains unclear, though it has been found to correspond to the urge to defaecate in healthy volunteers (Akervall et al. 1989;Sun et al. 1990d), indicating a sensori-motor phenomenon which is thought to be a spinally mediated reflex (Lium 1939). As shown in chapter 7, the RCR to phasic distension was seen to be present before the onset of first sensation in all

healthy volunteers, and disappeared at high pressures. In patients with RH there was a diminished response, again as shown in the previous chapter. This again may signify concomitant motor involvement of the rectum, or that sensation may play a role in the afferent limb of the reflex.

There is now a good body of evidence for combined sensorimotor dysfunction in patients with both slow transit constipation and those with evacuatory dysfunction (Rao et al. 2010;Scott et al. 2011b;Singh et al. 2013), and also in faecal incontinence (Andrews et al. 2007). Furthermore, it has been studied in patients with other functional gastrointestinal disorders such as functional dyspepsia (Van et al. 2008). In patients with rectal hyposensitivity, evidence for the existence of combined sensorimotor dysfunction is limited. One study showed higher volume thresholds to elicit RAIR and the rectal sensorimotor response (Remes-Troche et al. 2010), although use of isovolumetric distension can lead to methodological flaws especially if the rectum has elevated compliance or capacity. In the current study, all four patients with RH had normal compliance and elevated rectal electrosensory thresholds (i.e. primary RH). Hence, they represent a fairly homogenous cohort (despite small numbers), implying that differences seen between RH and HV were independent of rectal biomechanical properties.

Another factor that might influence the outcome of this study is the anal sphincter function. Resting pressures were similar between HV and patients with RH, and hence estimations of magnitude of anal sphincter relaxations are comparable between the two groups. Conversely squeeze pressures in RH as a group were lower than HV. Despite this the mean squeeze pressure in the RH group was 115 mmHg, which

would be regarded as good EAS function. Also, the magnitude of EAS contraction apart from squeeze pressure has not been separately measured during any part of this study.

The finding that patients with RH do not perceive a desire to defaecate as a recto-anal/ pelvic sensation is in itself very interesting. This may imply that patients with RH rely on colonic / abdominal sensation as the trigger for defaecation. We did not study the site of perceived sensation (on the topograph) to individual distension for fear of overburdening the subjects. Such information would have been useful to see differences between HV and RH (i.e do patients with RH perceive sensations to distension different to those with normal rectal sensation).

The combination of lack of sensation of the urge to defaecate, absence of spontaneous anal relaxation (leading to lack of sampling) and diminished rectal contraction could lead to faecal retention and RED. This may also lead to abberations in recto-colic and other entero-enteric reflexes that are involved in normal gut function, thereby, leading to a delay in colonic transit and constipation (Figure 8.11). This provides a plausible explanation for symtom genesis in patients with RH and constipation.

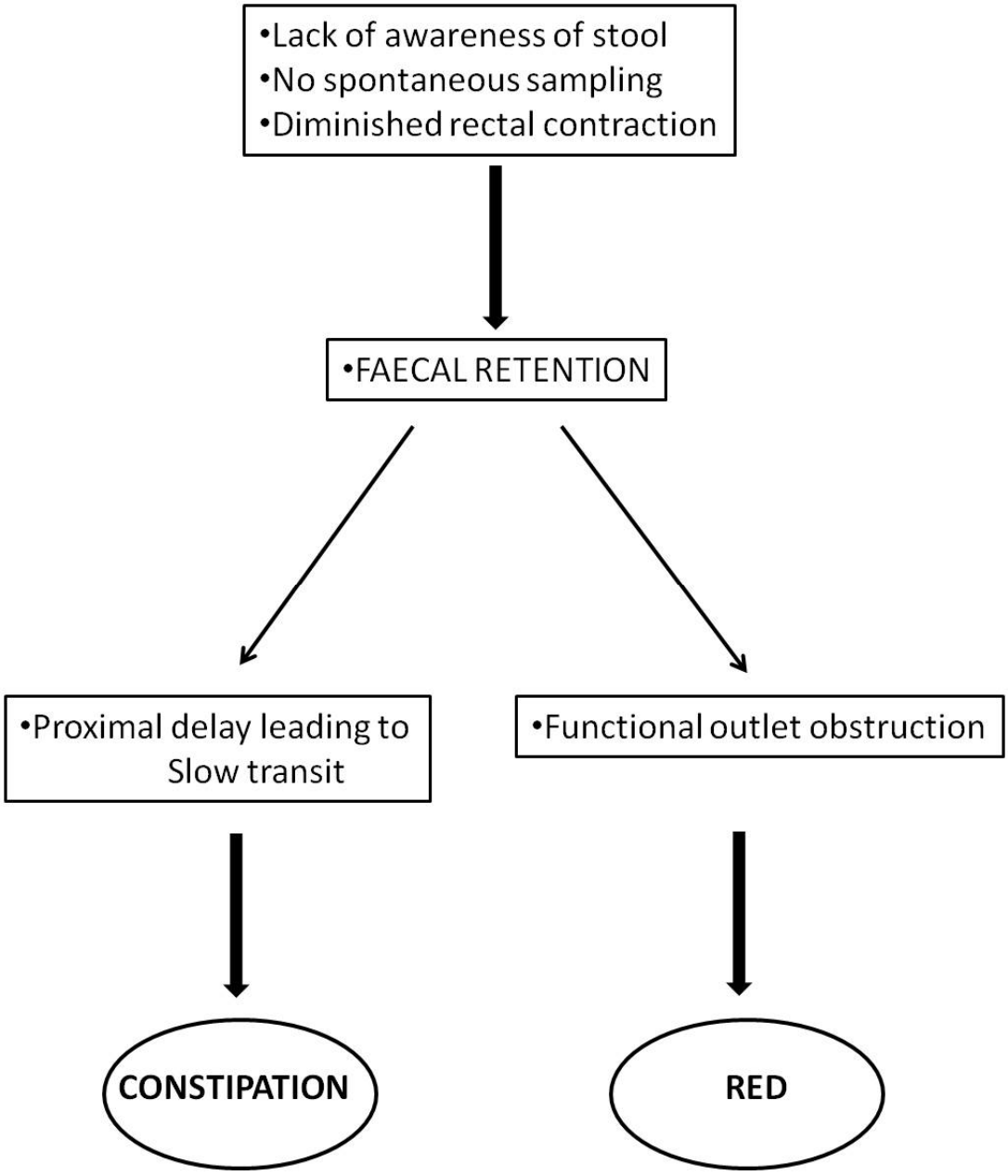


Figure 8.11: Symptom genesis in patients with RH and constipation
(RED: rectal evacuatory dysfunction)

8.5 CONCLUSIONS

The majority of spontaneous episodes of anal relaxation in healthy volunteers were associated with rectal contractions and were consciously perceived. RCR occurs at threshold pressures below conscious perception in health and is unlikely to be the initiator of sensory awareness to distension. Patients with RH have abnormal 'sampling' and RCR. This may indicate combined sensori-motor dysfunction in this group. Further studies including more patients are required following this pilot.

9 SUMMARY & CONCLUSIONS

9.1 IMPACT OF RECTAL HYPOSENSITIVITY ON SYMPTOM SEVERITY AND OTHER COLORECTAL PHYSIOLOGICAL MEASURES IN PATIENTS WITH CONSTIPATION

9.1.1 SUMMARY

This study evaluated the severity of symptoms of constipation in 55 patients with rectal hyposensitivity (RH) compared to 55 age and sex matched controls with normal rectal sensation (NS) using a commonly used constipation scoring system (The Clinic Constipation Score). The results showed that the presence of rectal hyposensitivity was not associated with greater symptom severity, either by total score, or within individual symptoms. Furthermore, the presence of concomitant faecal incontinence did not significantly affect the severity of symptoms. Nevertheless, on proctography, a significantly greater proportion of patients with RH had evidence of a 'functional' outlet obstruction when compared to the NS group (P=0.03). Moreover, almost half of the patients with RH had rapid loss of the sense of rectal fullness on proctography after instillation of barium neostool, requiring further neostool instillation to trigger the urge to defaecate and eventual defaecation (P=0.001). Overall, irrespective of sensory status,

the presence of delayed GI / colonic slow transit, as diagnosed by a radio-opaque marker study, was consistently associated with more severe symptoms (*P*=0.002).

9.1.2 CONCLUSIONS

1. On the basis of a commonly used scoring tool, incorporating 8 questions, rectal hyposensitivity does not appear to be associated with more severe symptoms compared to constipated patients with normal rectal sensation.
2. Patients with rectal hyposensitivity have a higher incidence of functional outlet obstruction and rapid loss of urge on proctography.
3. The presence of delayed gut transit was associated with more severe symptoms of constipation.

9.2 RECTAL HYPOSENSITIVITY IN SLOW TRANSIT CONSTIPATION: IMPACT ON RECTAL EVACUATION AND PATTERN OF TRANSIT DELAY

9.2.1 SUMMARY

One hundred and twenty patients with slow transit constipation (34 RH) had global and regional colonic transit evaluated by scintigraphy and rectal evacuation by proctography. A significantly higher proportion of patients with RH had rectal evacuatory dysfunction (functional type) than those with NS. There was a significant

difference between the NS and RH groups in the overall progression of isotope throughout the colon as defined by time-activity curves with isotope progression faster in the RH group (P=0.02). Upon evaluating regional transit, ingested isotope moved significantly faster through the right colon in patients in the RH group compared to those in the NS group at both 18 h (P = 0.02) and at 24 h (P = 0.01) but overall right colon activity was similar once corrected for evacuatory dysfunction.. Percentage of overall activity in the left colon over time was significantly higher in the RH than NS group (P = 0.006). Statistical analysis incorporating sensation and proctographic variables revealed overall activity in the left colon over time to be persistently different between the NS and RH groups (P=0.02), but not between the 2 different proctography groups i.e normal evacuation vs. rectal evacuatory dysfunction (P=0.61).

9.2.2 CONCLUSIONS

1. Rectal hyposensitivity is more commonly associated with rectal evacuatory dysfunction (functional type) in patients with slow transit constipation.

2. Rectal hyposensitvity is also associated with a specific pattern of transit delay, wherein there is hold up of the isotope in the left colon, and that this is independent of rectal evacuatory dysfunction.

9.3 RECTAL HYPOSENSITIVITY: EVALUATION OF ANAL SENSATION IN FEMALE PATIENTS WITH INTRACTABLE CONSTIPATION

9.3.1 SUMMARY

One hundred and fifty eight female patients (45 RH) with chronic constipation underwent physiological investigation including rectal sensation to volumetric balloon distension, and distal anal mucosal sensation to electrostimulation. Data were also obtained from 32 healthy female volunteers. Anal mucosal electrosensory thresholds were significantly higher in constipated patients compared to volunteers ($P<0.0001$), but there was no difference in the incidence of blunted anal sensation between those with normal rectal sensation and RH ($P=0.572$). Irrespective of rectal sensory function, there was a strong association between symptom duration ($P=0.012$) and anal hyposensitivity.

9.3.2 CONCLUSIONS

1. Patients with chronic intractable constipation and rectal hyposensitivity, as diagnosed on simple balloon distension, do not have an increased incidence of anal hyposensitivity, when compared to constipated patients with normal rectal sensation.
2. This suggests that sensory dysfunction in the majority of patients with rectal hyposensitivity relates purely to visceral afferent pathways.

9.4 EVALUATION OF GENERAL AND PELVIC SOMATIC NERVE FUNCTION IN PATIENTS WITH RECTAL HYPOSENSITIVITY AND CONSTIPATION

9.4.1 SUMMARY

Ten patients with intractable constipation and 'primary' rectal hyposensitivity, 8 matched controls with intractable constipation and normal rectal sensation, and 19 healthy volunteers had their general and pelvic somatic nerve function assessed using standard neurophysiological techniques. Results showed evidence of subclinical pelvic somatosensory neuropathy (small and large fibre) in 40% of patients with RH studied. This may reflect dysfunction in afferent conduction at the level of the pelvic nerve.

9.4.2 CONCLUSIONS

1. An isolated pelvic visceral sensory neuropathy is commonly found in patients with rectal hyposensitivity.

2. However, a combined viscero-somatic pelvic sensory neuropathy is present in a proportion of patients.

9.5 ASSESMENT OF RECTAL CONTRACTILE RESPOINSE IN PATIENTS WITH RECTAL HYPOSENSITIVITY

9.5.1 SUMMARY

The study cohort comprised 21 consecutive patients with rectal hyposensitivity and chronic constipation, 10 age and sex-matched patients with normal rectal sensation and constipation, and 10 healthy volunteers. All subjects underwent a rectal barostat study and the amplitude of the rectal contractile response was compared between the different groups. The major finding was that constipated patients with rectal hyposensitivity, as a group, had a diminished response (reduced amplitude), and that in a third of patients with RH, the RCR was indeed absent. In healthy volunteers and normosensate patients with constipation the RCR was elicited at threshold pressures similar to the first sensation pressure (FSP). However, in patients with RH the threshold pressure for eliciting RCR was significantly below the FSP. In all subjects (patients and volunteers), when, present the RCR occurred well below the desire to defaecate presure (DDP).

9.5.2 CONCLUSIONS

1. The rectal contractile response to rapid phasic distension is diminished in patients with rectal hyposensitivity and this is regardless of wall compliance.

2. These findings suggest combined sensori-motor dysfunction in a subgroup of patients with rectal hyposensitivity.

9.6 RECTO-ANAL REFLEXES IN HEALTH AND IN PATIENTS WITH RECTAL HYPOSENSITIVITY - A PILOT STUDY USING A NOVEL TECHNIQUE

9.6.1 SUMMARY

This pilot study investigated recto-anal events in health and in patients with rectal hyposensitivity. A novel technique was used, combining rectal barostat and solid state anal manometry on an integrated platform enabling the study of recto-anal events in real time. Eleven healthy volunters and 4 patients with RH were studied. Healthy volunteers perceived the sensation of the desire to defaecate in their rectum/ anal canal, as opposed to patients with RH who reported a more diffuse abdominal sensation. Spontaneous anal canal relaxations were seen in all healthy volunteers, and the vast majority of these were associated with transient sensation of awareness of flatus. Anal relaxation, accompanied by rectal contraction, was more likely to be associated with sensory awareness. Patients with RH did not have any spontaneous anal relaxations at operating pressure. The rectal contractile response (RCR) to rapid phasic distension was seen in all healthy volunteers at threshold pressures below first sensation threshold. Both in healthy volunteers and patients with rectal hyposensitivity, the RCR to phasic distension was not temporally associated with transient sensations at the onset, and the RCR disappeared at higher distension pressures.

9.6.2 CONCLUSIONS

1. The majority of spontaneous episodes of anal relaxation in healthy volunteers were associated with rectal contractions and were consciously perceived.

2. The rectal contractile response occurs at threshold pressures below conscious perception in health and is unlikely to be the initiator of sensory awareness to distension.

3. Patients with rectal hyposensitivity have abnormal spontaneous anal relaxations (thought to reflect 'sampling') and rectal contractile response to distension. This may indicate combined sensori-motor dysfunction in this group leading to a functional outlet dysfunction which could responsd to biofeedback therapy. Further studies including more patients are required following this pilot.

9.7 CONCLUDING REMARKS

The studies performed in this thesis have shown that

- Patients with RH have a specific pattern of transit delay (left sided).

- RH is frequently associated with rectal evacuatory dysfunction (functional type).

- RH likely reflects an isolated visceral sensory dysfunction in the majority. However, it is associated with a pelvic somatic sensory dysfunction in a subgroup.
- Rectal motor dyfunction and attenuated recto-anal reflexes may play an important role in the pathoaetiology of RH.

The above findings shed light on the pathophysiological mechanisms by which RH can lead to symptoms, and may help direct management. For example, those with STC and RH are likely to have a left-sided delay, and hence interventions can be aimed at effective emptying of rectum and left colon (e.g. suppositories, enemas and rectal irrigation). Whether a left sided segmental colectomy will improve symptoms will also need to be studied further. In those in whom RH likely reflects an isolated visceral neuropathy, neuromodulation may be more effective. In patients who have an associated pelvic somatic neuropathy neuromodulation may be less effective (as yet unproven).

9.8 FUTURE WORK

The results of the studies in this thesis have highlighted some important physiological abnormalities in patients with RH. However, several fundamental questions regarding rectal sensation in health and in those with RH remain unanswered.

Future studies can be classified as follows

Clinical impact and pathophysiology

- To determine the true clinical impact of RH using questionnaires incorporating symptoms of rectal evacuatory dysfunction i.e the ODS score. This will also help determine if patients with RH can be identified from symptoms alone.
- To assess psychosocial functioning and Quality of life (QoL) in patients with RH using standardised psychometric and QoL tests.
- Longitudinal studies following normosensate patients with constipation to study if they will eventually develop RH. Similarly longitudinal studies in patients with RH to see if their sensory thresholds worsen with time.

Basic physiology

Associated sensory abnormality

- To evaluate whether RH is an isolated phenomenon or if sensitivity in the rest of colon is also affected.
- To determine whether RH is a manifestation of a pan-enteric sensory dysfunction by studying sensation in the upper GI tract (oesophagus, stomach and duodenum).
- To investigate whether RH is a pan-pelvic sensory neuropathy by studying urinary bladder and sexual function.

Associated motor dysfunction

- To determine whether there is associated motor dysfunction in the rest of the colon in patients with RH using prolonged manometry and a colonic barostat study.
- Recto-anal coordination- by studying the recto-anal reflexes in a large group of patients with RH, including those with RH and faecal incontinence, using an integrated tecnique (barostat/ solid state manometry) akin to that used in the pilot study in chapter 8.

Level of interruption of afferent pathway

- To determine the level of interruption of afferent conduction using spinal monitoring.
- To evaluate whether there is abnormal/ delay in cortical processsing of afferent rectal sensory stimuli using functional MRI or cortical evoked potentials.

Receptor level

- What is the trigger for rectal sensation in humans (receptor level) in health, and is this affected in RH?

Treatment

- To study the effect of sensory retraining / biofeedback in patients with RH and hindgut dysfunction classified on the basis of physiology (level of interruption of

afferent conduction and associated anomalies) thereby helping to identify which subgroup will benefit.

- To study the effect of neuromodulation (e.g. SNS, PTNS, magnetic and percutaneus stimulation) in patients with RH (subgrouped based on presumed level of interruption of afferent pathway) to identify subgroups that would derive most benefit.

The ultimate aims are to subgroup patients according to symptoms and pathophysiologies, and thereby tailor management.

Appendix A: Cleveland Clinic Constipation severity score

Frequency of bowel movements

0 1-2 times per 1-2 days
1 2 times per week
2 Once per week
3 Less than once per week
4 Less than once per month

Time: minutes in lavatory per attempt

0 Less than 5
1 5-10
2 10-20
3 20-30
4 More than 30

Difficulty: painful evacuatory effort

0 Never
1 Rarely
2 Sometimes
3 Usually
4 Always

Assistance: type of assistance

0 Without assistance
1 Stimulant laxatives
2 Digital assistance or enema

Completeness: feeling incomplete evacuation

0 Never
1 Rarely
2 Sometimes
3 Usually
4 Always

Failure: Unsuccessful attempts /24 hours

0 Never
1 1-3
2 3-6
3 6-9
4 More than 9

Pain: abdominal pain

0 Never
1 Rarely
2 Sometimes
3 Usually
4 Always

History: duration of constipation (years)

0 0
1 1-5
2 5-10
3 10-20
4 More than 20

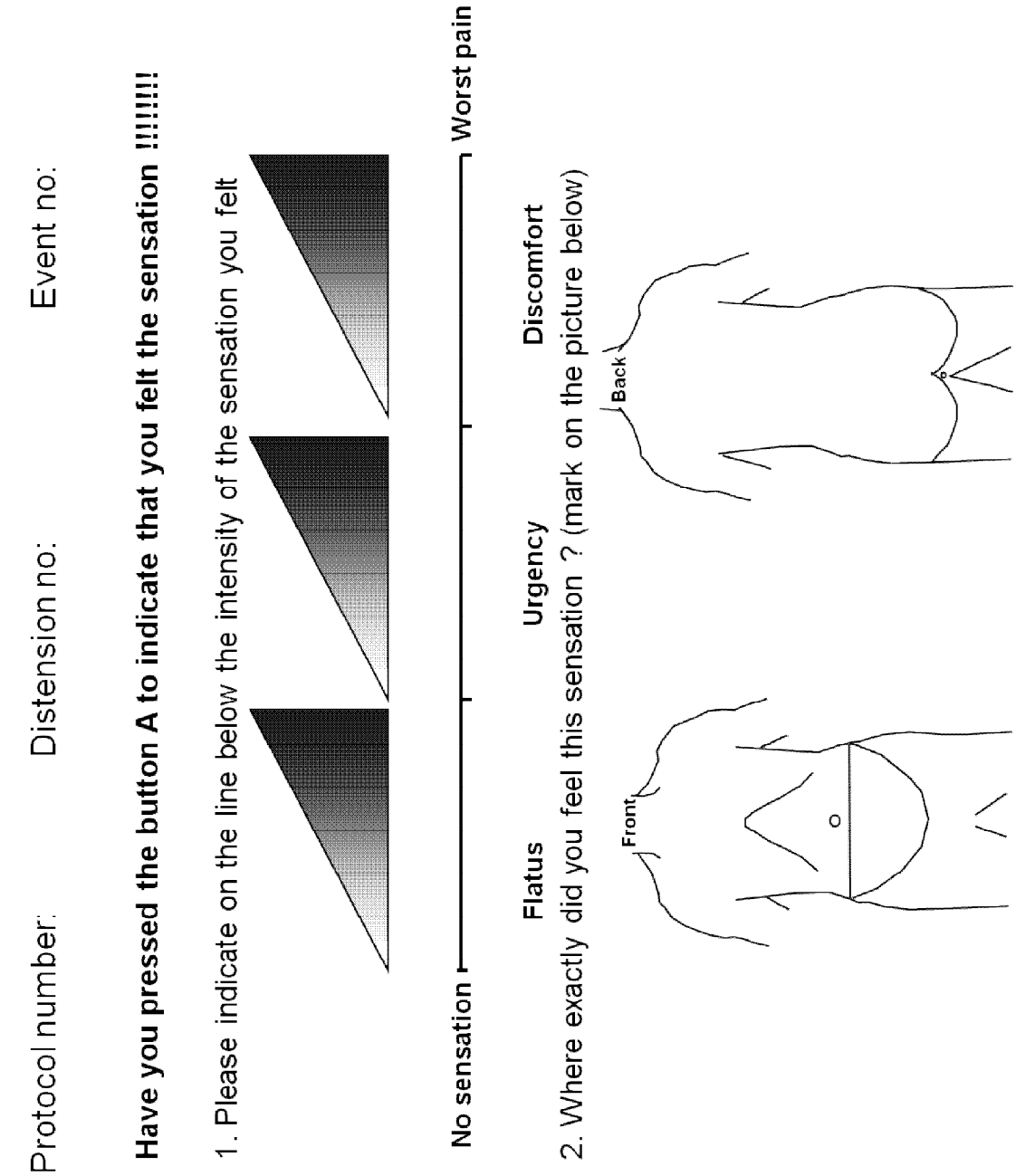
Appendix B: Vaizey modification of St Mark's faecal incontinence score

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4

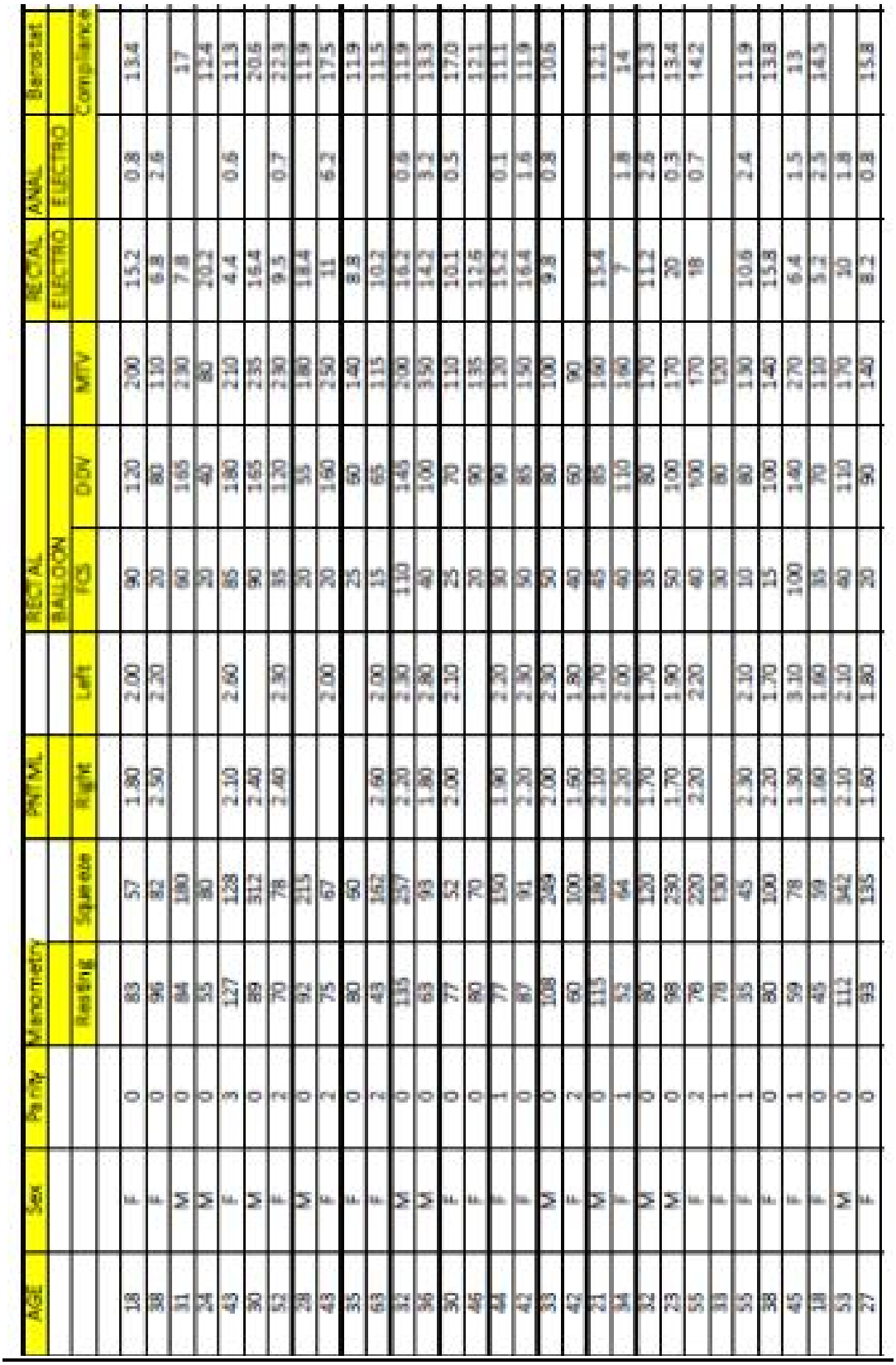
	No	Yes
Need to wear a pad or plug	0	2
Taking constipating medicines	0	2
Lack of ability to defer defecation for 15 minutes	0	4

Never, no episodes in the past four weeks; rarely, 1 episode in the past four weeks; sometimes, ≥1 episode in the past four weeks but <1 a week; weekly, 1 or more episodes a week but <1 a day; daily, 1 or more episodes a day.
Add one score from each row: minimum score = 0 = perfect continence; maximum score = 24 = totally incontinent.

Appendix C: visual analogue scale and quality of rectal sensation data entry form



Appendix D: Healthy volunteers data

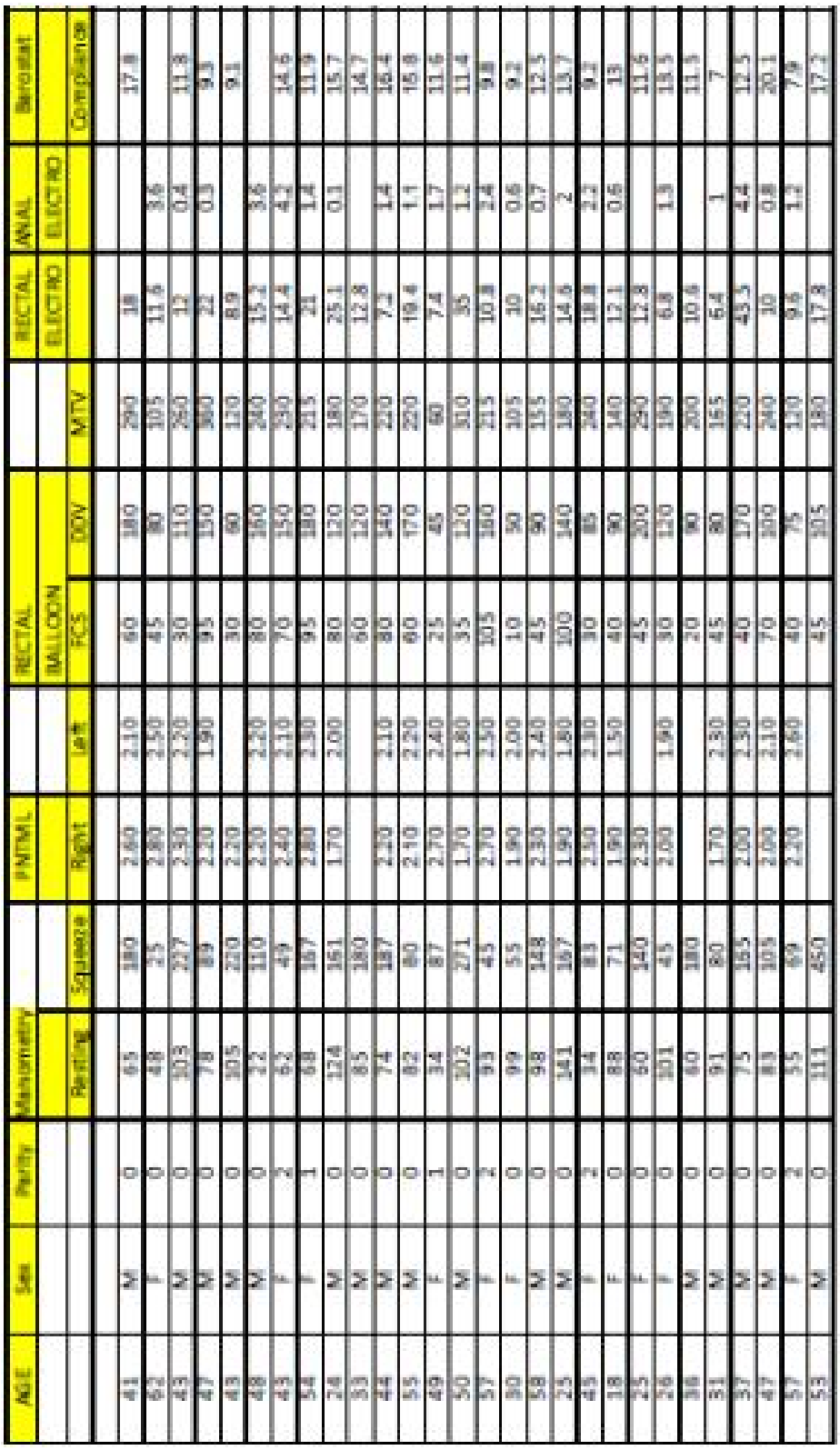


AGE	Sex	Parity	Manometry		PAIRVAL		RECTAL BALLOON			RECTAL ELECTRO	ANAL ELECTRO	Barostat
			Resting	Squeeze	Right	Left	FOS	DSV	MRV			Compliance
18	F	0	83	57	1.80	2.00	90	120	200	15.2	0.8	134
38	F	0	96	82	2.50	2.20	20	80	110	6.8	2.6	
31	M	0	84	180			60	165	230	7.8		17
24	M	0	55	80			20	40	80	20.7		124
43	F	3	127	128	2.10	2.60	85	180	210	4.4	0.6	113
30	M	0	89	312	2.40		90	165	235	15.4		205
52	F	2	70	78	2.40	2.30	35	120	230	9.5	0.7	213
28	M	0	92	215			20	55	180	184		119
43	F	2	75	67		2.00	20	160	250	11	6.2	175
35	F	0	80	60			25	60	140	8.8		119
63	F	2	43	152	2.60	2.00	15	65	115	10.2		115
32	M	0	115	257	2.20	2.30	110	145	200	16.7	0.6	119
56	M	0	63	93	1.80	2.80	40	100	350	14.2	3.2	133
30	F	0	77	52	2.00	2.10	25	70	110	10.1	0.5	170
46	F	0	80	70			20	90	135	17.6		121
44	F	1	77	150	1.90	2.20	90	90	120	15.2	0.1	111
42	F	0	87	91	2.30	2.30	50	85	150	16.4	1.6	119
33	M	0	108	259	2.00	2.30	50	80	100	9.8	0.8	105
42	F	2	80	100	1.60	1.80	40	60	90			
21	M	0	115	180	2.10	1.70	45	85	180	15.4		111
34	F	1	52	64	2.30	2.00	40	110	180	7	1.8	114
32	M	0	80	120	1.70	1.70	35	80	170	11.2	2.6	123
23	M	0	98	230	1.70	1.80	50	100	170	20	0.3	134
55	F	2	78	220	2.20	2.20	40	100	170	18	0.7	142
33	F	1	78	150			30	80	150			
55	F	1	35	45	2.30	2.10	10	80	130	10.6	2.4	119
38	F	0	80	100	2.20	1.70	15	100	140	15.8		138
45	F	1	59	78	1.90	3.10	100	140	270	6.4	1.5	13
18	F	0	45	99	1.60	1.80	35	70	110	5.1	2.5	145
53	M	0	112	342	2.10	2.10	40	110	170	10	1.8	
27	F	0	93	135	1.60	1.80	20	90	140	8.2	0.8	158

Appendix D: Healthy volunteers data (contd)

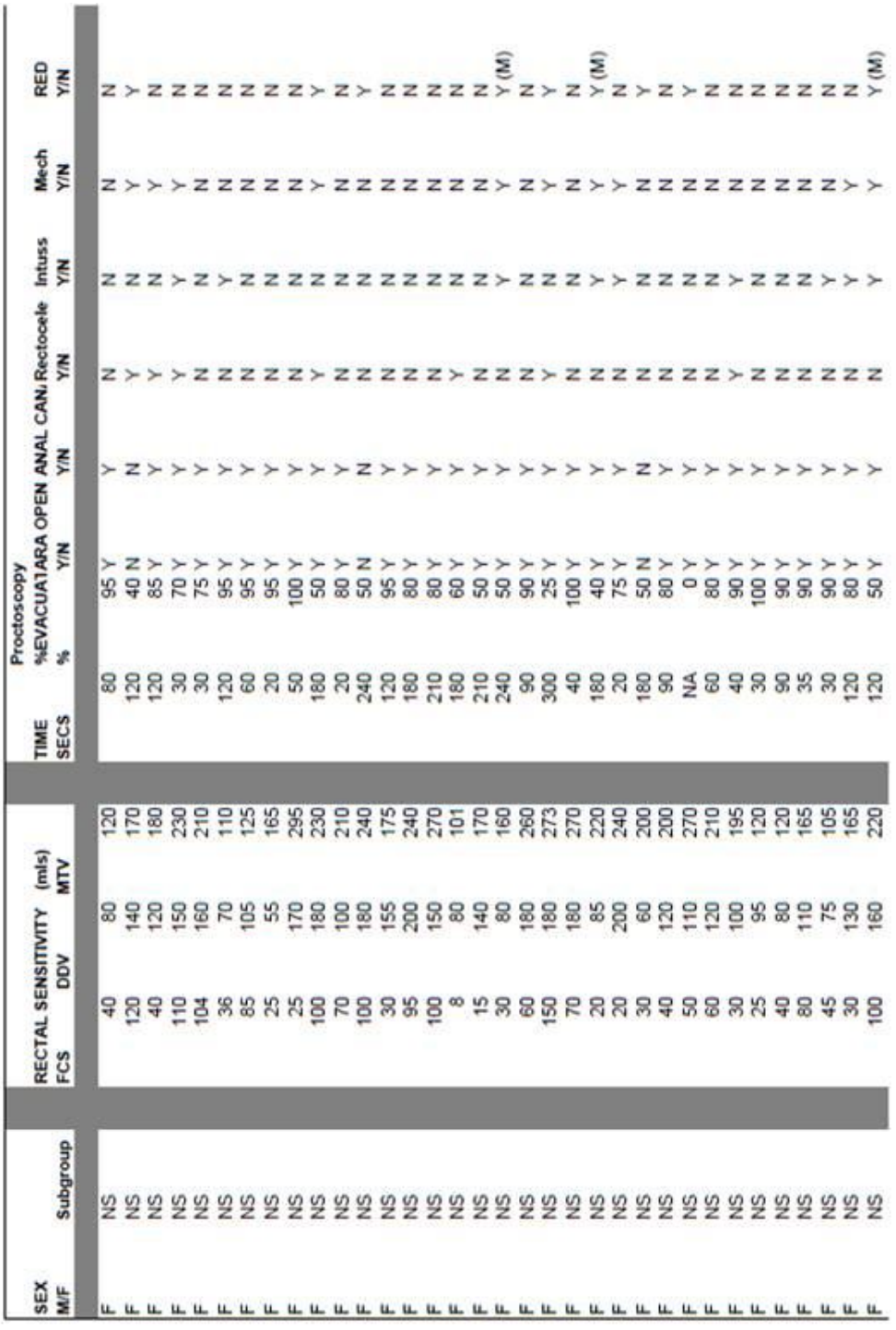
AGE	Sex	Parity	Manometry		PNTML		RECTAL			RECTAL	ANAL	Barostat
							BALLOON			ELECTRO	ELECTRO	
			Resting	Squeeze	Right	Left	FCS	DDV	MTV			Compliance
25	F	0	100	150			40	80	150	12.9		15.5
58	M	0	62	104	2.40	2.50	80	120	155	2.6	1.8	8.7
51	F	1	85	200	2.30	2.40	15	40	90	11.8	0.7	12.4
34	F	0	100	70			30	60	110	10.2		13.3
36	M	0	105	299	2.30	2.30	100	140	160	11.4		
53	F	2	94	56	2.10	3.00	30	100	150	8	0.4	13.1
38	M	0	89	110		2.10	85	150	270	8.6		
43	F	1	73	247	2.20	2.50	20	70	105	11.2	1	10.9
50	M	0	100	64	2.30	2.00	30	90	140	18.2	1.3	11.4
23	M	0	67	115	1.80	2.00	30	70	150	10.6	1.4	12.8
50	F	1	110	190	2.20	2.50	85	120	160	5.4	2.6	8.9
32	M	0	115	170			25	50	90	12.2		10.5
24	M	0	108	70	2.10	1.80	100	190	250	22.5	2.6	16.2
50	F	2	72	135	2.10	2.70	25	80	215	15.6	1.7	11.5
60	F	3	81	107	2.30	2.70	10	25	75	12	0.5	6.5
22	M	0	52	195	2.00	1.80	20	140	270	7.6	0.5	16.4
34	F	0	78	65	2.00	1.90	60	90	150	18.4	1.2	16.8
26	F	0	98	208			10	60	140	18.2		16.2
25	F	0	54	54	1.80	2.00	20	80	100	6.5	1.2	12.3
42	M	0	72	238	2.40	1.75	90	145	220	15.2		
42	M	0	107	143	2.30	2.20	90	140	180	6.8	1.2	
41	F	3	50	53	2.70	2.60	75	200	255	14.6	0.9	7.7
27	M	0	85	200	1.80	1.70	50	100	190			18.5
44	M	0	40	90			10	95	125	15		7.4
24	M	0	67	105	1.90	1.80	30	100	230	15	2.1	14.3
58	F	2	50	120			30	75	130	11		14.1
27	F	0	80	100	1.70	2.30	40	90	120	18.5		15.9
52	F	4	85	107	2.20	2.70	45	100	220		0.8	11.9
49	F	2	75	48		2.30	30	70	140	5.2	1.4	12.7
42	F	0	52	145	2.60	2.30	20	60	150	11.2	0.3	8.5
52	F	3	68	47	1.80	1.90	25	60	115	12	0.8	7.6
22	F	0	100	100	1.90	1.80	25	75	135	13.5		10.5

Appendix D: Healthy volunteers data (contd)



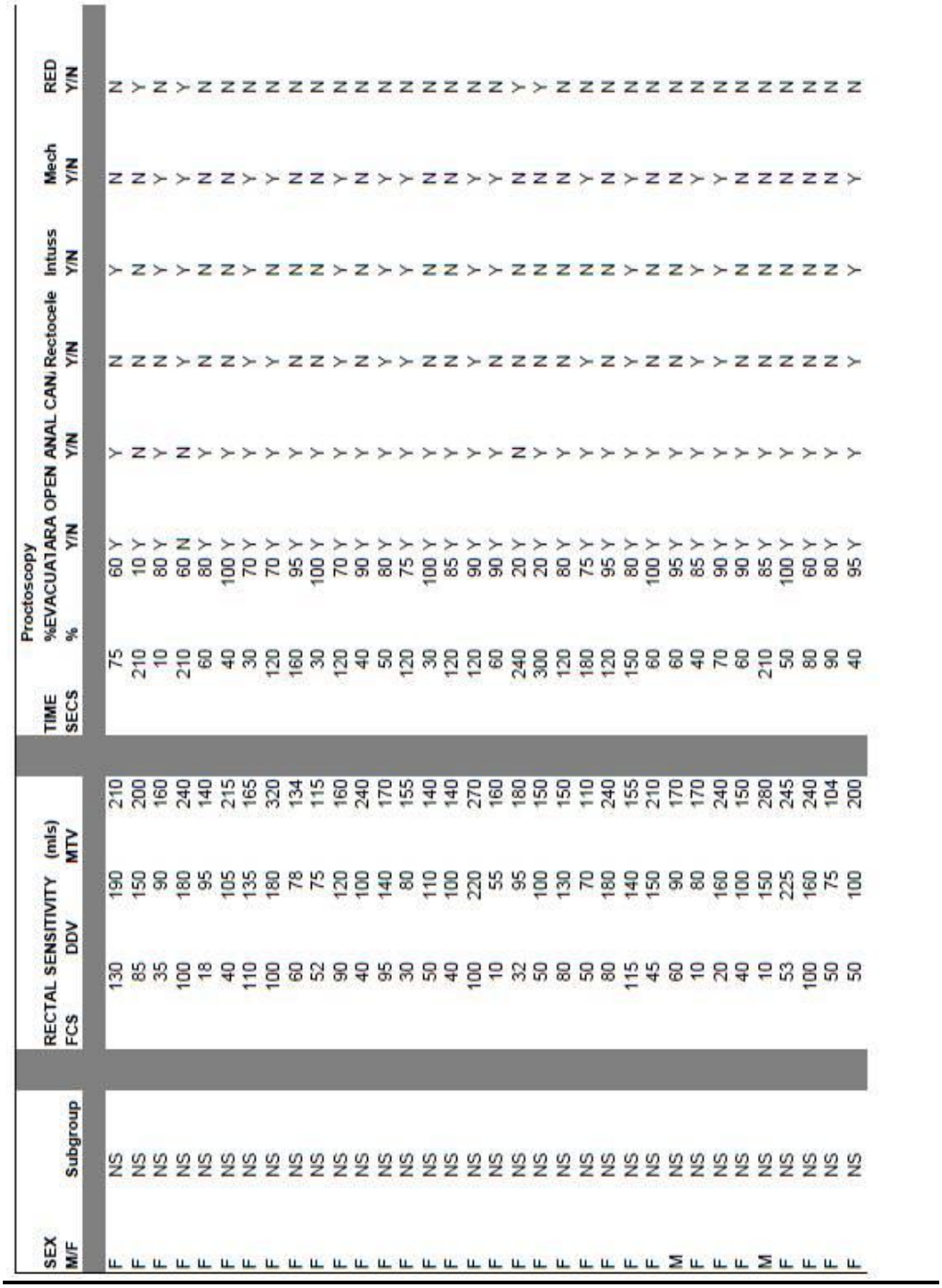
AGE	Sex	Parity	Manometry		PNTM/L		RECTAL			RECTAL		ANAL	Bergonzini
			Resting	Squeeze	Right	Left	BALLOON	FCS	DDV	MTV	ELECTRO	ELECTRO	Compliance
41	M	0	65	180	240	210	60	60	180	290	18		17.8
62	F	0	48	25	280	250	80	45	80	105	11.6	3.6	
43	M	0	103	227	230	220	110	30	110	260	12	0.4	11.8
47	M	0	78	89	220	190	150	95	150	360	22	0.8	9.5
43	M	0	105	220	220		60	30	60	170	8.9		9.1
48	M	0	112	110	220	220	180	80	180	240	15.7	3.6	
45	F	2	62	49	240	210	150	70	150	230	14.4	4.2	14.6
54	F	1	68	187	280	230	180	95	180	215	21	1.4	11.9
24	M	0	124	161	170	200	120	80	120	180	25.1	0.1	15.7
33	M	0	85	180			120	60	120	170	12.8		14.7
44	M	0	74	187	220	210	140	80	140	220	7.2	1.4	16.4
55	M	0	82	80	210	230	170	60	170	220	19.4	1.1	15.8
49	F	1	34	87	270	240	45	25	45	60	7.4	1.7	11.6
50	M	0	202	271	170	180	120	35	120	310	35	1.2	11.4
57	F	2	93	45	270	250	180	105	180	215	10.8	2.4	9.8
30	F	0	69	55	190	200	90	10	90	105	10	0.6	9.2
58	M	0	98	148	230	240	90	45	90	155	16.2	0.7	12.5
25	M	0	141	197	190	180	140	100	140	180	14.6	2	13.7
45	F	2	84	83	250	280	180	80	180	260	18.8	2.2	9.2
18	F	0	88	71	190	150	90	40	90	140	12.1	0.5	13
25	F	0	90	240	230		200	45	200	250	12.8		11.6
26	F	0	101	45	200	190	120	30	120	190	6.8	1.3	13.5
36	M	0	80	180		230	80	20	80	200	10.6		11.5
31	M	0	91	80	170		80	45	80	165	6.4	1	7
37	M	0	75	165	200	230	170	40	170	220	45.5	4.4	12.5
47	M	0	83	105	200	210	100	70	100	240	10	0.8	20.1
57	F	2	55	69	230	260	80	40	75	170	8.6	1.3	7.9
53	M	0	111	450			105	45	105	180	17.3		17.2

Appendix E : NS Data Chapter 4



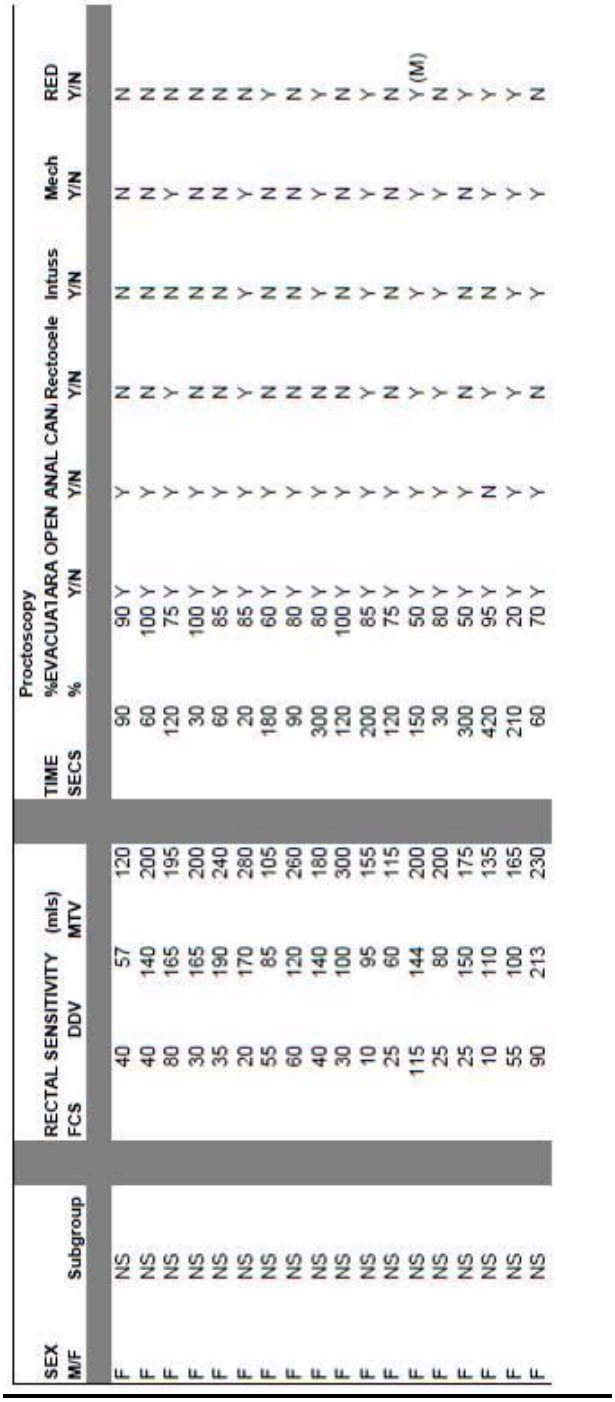
SEX M/F	Subgroup	RECTAL SENSITIVITY (mls) FCS	DDV	MTV	Proctoscopy TIME SECS	%EVACUA	1ARA OPEN Y/N	ANAL CAN. Y/N	Rectocele Y/N	Intuss Y/N	Mech Y/N	RED Y/N
F	NS	40	80	120	80	95	Y	Y	N	N	N	N
F	NS	120	140	170	120	40	N	N	Y	N	Y	Y
F	NS	40	120	180	120	85	Y	Y	Y	N	Y	N
F	NS	110	150	230	30	70	Y	Y	Y	Y	Y	N
F	NS	104	160	210	30	75	Y	Y	N	N	N	N
F	NS	36	70	110	120	95	Y	Y	N	Y	N	N
F	NS	85	105	125	60	95	Y	Y	N	N	N	N
F	NS	25	55	165	20	95	Y	Y	N	N	N	N
F	NS	25	170	295	50	100	Y	Y	N	N	N	N
F	NS	100	180	230	180	50	Y	Y	Y	N	Y	Y
F	NS	70	100	210	20	80	Y	Y	N	N	N	N
F	NS	100	180	240	240	50	N	N	N	N	N	Y
F	NS	30	155	175	120	95	Y	Y	N	N	N	N
F	NS	95	200	240	180	80	Y	Y	N	N	N	N
F	NS	100	150	270	210	80	Y	Y	N	N	N	N
F	NS	8	80	101	180	60	Y	Y	Y	N	N	N
F	NS	15	140	170	210	50	Y	Y	N	N	N	N
F	NS	30	80	160	240	50	Y	Y	N	Y	Y	Y (M)
F	NS	60	180	260	90	90	Y	Y	N	N	N	N
F	NS	150	180	273	300	25	Y	Y	Y	N	Y	Y
F	NS	70	180	270	40	100	Y	Y	N	N	N	N
F	NS	20	85	220	180	40	Y	Y	N	Y	Y	Y (M)
F	NS	20	200	240	20	75	Y	Y	N	Y	Y	N
F	NS	30	60	200	180	50	N	N	N	N	N	Y
F	NS	40	120	200	90	80	Y	Y	N	N	N	N
F	NS	50	110	270	NA	0	Y	Y	N	N	N	Y
F	NS	60	120	210	60	80	Y	Y	N	N	N	N
F	NS	30	100	195	40	90	Y	Y	Y	Y	N	N
F	NS	25	95	120	30	100	Y	Y	N	N	N	N
F	NS	40	80	120	90	90	Y	Y	N	N	N	N
F	NS	80	110	165	35	90	Y	Y	N	N	N	N
F	NS	45	75	105	30	90	Y	Y	N	Y	N	N
F	NS	30	130	165	120	80	Y	Y	N	Y	Y	N
F	NS	100	160	220	120	50	Y	Y	N	Y	Y	Y (M)

Appendix E : NS Data Chapter 4 (contd)



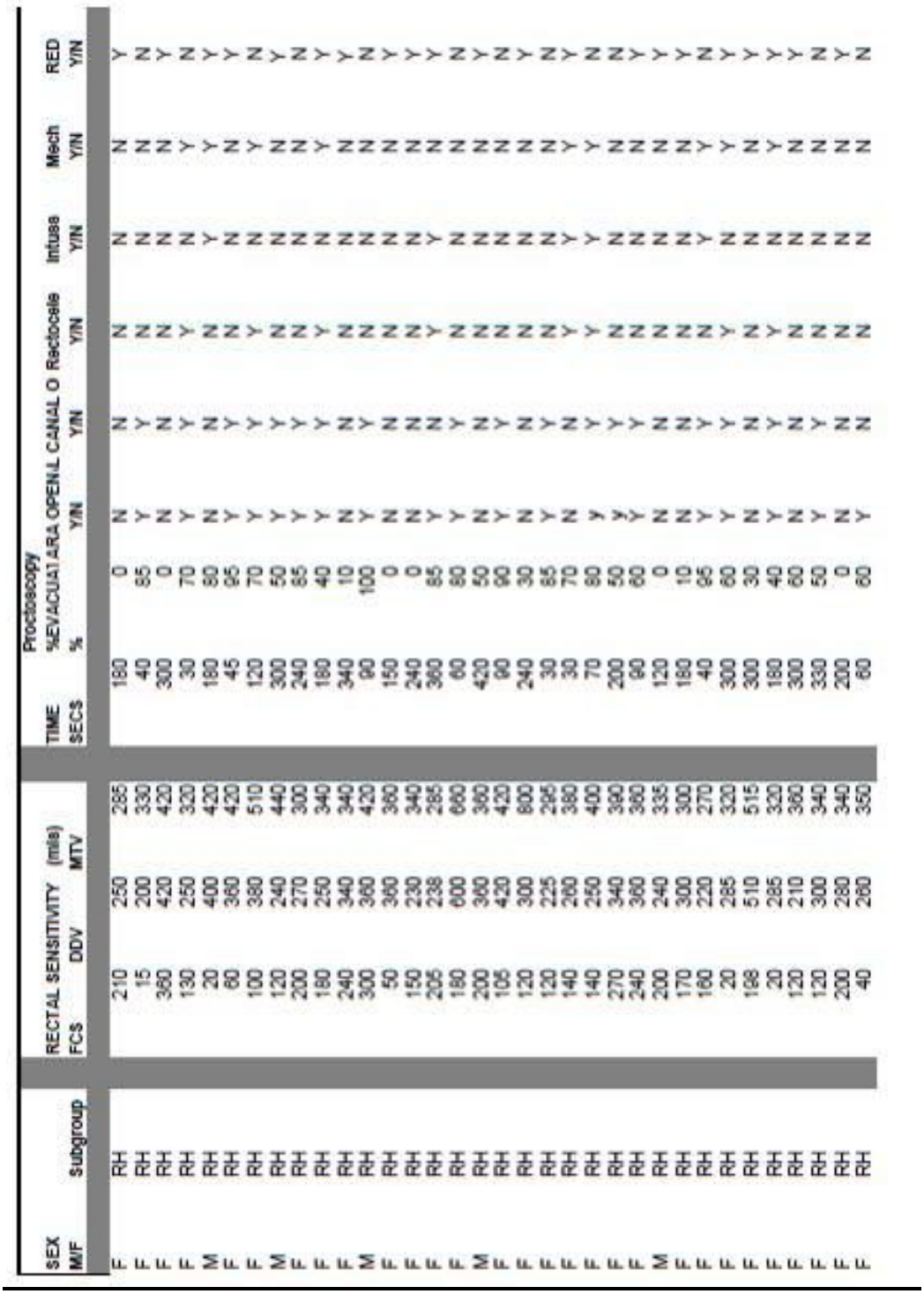
SEX			RECTAL SENSITIVITY (mls)			Proctoscopy							
M/F	Subgroup		FCS	DDV	MTV	TIME SECS	%EVACUA %	1ARA OPEN Y/N	ANAL CAN Y/N	Rectocele Y/N	Intuss Y/N	Mech Y/N	RED Y/N
F	NS		130	190	210	75	60 Y	Y	N	Y	N	N	
F	NS		85	150	200	210	10 Y	N	N	N	N	N	Y
F	NS		35	90	160	10	80 Y	Y	N	Y	Y	Y	N
F	NS		100	180	240	210	60 N	N	Y	Y	Y	Y	Y
F	NS		18	95	140	60	80 Y	Y	N	N	N	N	N
F	NS		40	105	215	40	100 Y	Y	N	Y	N	N	N
F	NS		110	135	165	30	70 Y	Y	Y	Y	Y	Y	N
F	NS		100	180	320	120	70 Y	Y	Y	Y	N	Y	N
F	NS		60	78	134	160	95 Y	Y	N	N	N	N	N
F	NS		52	75	115	30	100 Y	Y	N	Y	N	N	N
F	NS		90	120	160	120	70 Y	Y	Y	Y	Y	Y	N
F	NS		40	100	240	40	90 Y	Y	N	N	N	N	N
F	NS		95	140	170	50	80 Y	Y	Y	Y	Y	Y	N
F	NS		30	80	155	120	75 Y	Y	Y	Y	Y	Y	N
F	NS		50	110	140	30	100 Y	Y	N	N	N	N	N
F	NS		40	100	140	120	85 Y	Y	N	N	N	N	N
F	NS		100	220	270	120	90 Y	Y	Y	Y	Y	Y	N
F	NS		10	55	160	60	90 Y	Y	N	N	Y	Y	N
F	NS		32	95	180	240	20 Y	N	N	N	N	N	Y
F	NS		50	100	150	300	20 Y	Y	N	N	N	N	Y
F	NS		80	130	150	120	80 Y	Y	N	N	N	N	N
F	NS		50	70	110	180	75 Y	Y	Y	Y	N	Y	N
F	NS		80	180	240	120	95 Y	Y	N	N	N	N	N
F	NS		115	140	155	150	80 Y	Y	Y	Y	Y	Y	N
F	NS		45	150	210	60	100 Y	Y	N	N	N	N	N
M	NS		60	90	170	60	95 Y	Y	N	N	N	N	N
F	NS		10	80	170	40	85 Y	Y	Y	Y	Y	Y	N
F	NS		20	160	240	70	90 Y	Y	Y	Y	Y	Y	N
F	NS		40	100	150	60	90 Y	Y	N	N	N	N	N
M	NS		10	150	280	210	85 Y	Y	N	N	N	N	N
F	NS		53	225	245	50	100 Y	Y	N	N	N	N	N
F	NS		100	160	240	80	60 Y	Y	N	N	N	N	N
F	NS		50	75	104	90	80 Y	Y	N	N	N	N	N
F	NS		50	100	200	40	95 Y	Y	Y	Y	Y	Y	N

Appendix E: NS Data Chapter 4 (contd)



SEX M/F	Subgroup	RECTAL SENSITIVITY (mls) FCS	DDV	MTV	Proctoscopy TIME SECS	%EVACUA	TARA Y/N	OPEN ANAL Y/N	CANA Y/N	Rectocele Y/N	Intuss Y/N	Mech Y/N	RED Y/N
F	NS		40	57		90	90 Y	Y		N	N	N	N
F	NS		40	140	120	60	100 Y	Y		N	N	N	N
F	NS		80	165	200	120	75 Y	Y		Y	N	Y	N
F	NS		30	165	195	30	100 Y	Y		N	N	N	N
F	NS		35	190	200	60	85 Y	Y		N	N	N	N
F	NS		20	170	240	20	85 Y	Y		Y	Y	Y	N
F	NS		55	85	280	180	60 Y	Y		N	N	N	Y
F	NS		60	120	105	90	80 Y	Y		N	N	N	N
F	NS		40	140	260	300	80 Y	Y		N	Y	Y	Y
F	NS		30	100	180	120	100 Y	Y		N	N	N	N
F	NS		10	95	300	200	85 Y	Y		Y	Y	Y	Y
F	NS		25	60	155	120	75 Y	Y		N	N	N	N
F	NS		115	144	115	150	50 Y	Y		Y	Y	Y	Y (M)
F	NS		25	80	200	30	80 Y	Y		Y	Y	Y	N
F	NS		25	150	175	300	50 Y	Y		N	N	N	Y
F	NS		10	110	135	420	95 Y	N		Y	N	Y	Y
F	NS		55	100	165	210	20 Y	Y		Y	Y	Y	Y
F	NS		90	213	230	60	70 Y	Y		N	Y	Y	N

Appendix E: RH Data Chapter 4 (contd)



SEX M/F	Subgroup	RECTAL SENSITIVITY (mils) FCS	DDV	MTV	Proctoscopy TIME SECS	%EV/ACUATARA %	OPEN L CANAL O Y/N	Rectocele Y/N	Infuse Y/N	Mech Y/N	RED Y/N
F	RH	210	250	285	180	0	N	N	N	N	Y
F	RH	15	200	330	40	85	Y	N	N	N	N
F	RH	360	420	420	300	0	N	N	N	N	Y
F	RH	130	250	320	30	70	Y	Y	N	Y	N
M	RH	20	400	420	180	80	N	N	Y	Y	Y
F	RH	60	360	420	45	95	Y	N	N	N	Y
F	RH	100	380	510	120	70	Y	Y	N	Y	N
M	RH	120	240	440	300	50	Y	N	N	N	Y
F	RH	200	270	300	240	85	Y	N	N	N	N
F	RH	180	250	340	180	40	Y	Y	N	Y	Y
F	RH	240	340	340	340	10	N	N	N	N	Y
M	RH	300	360	420	90	100	Y	N	N	N	Y
F	RH	50	360	360	150	0	N	N	N	N	Y
F	RH	150	230	340	240	0	N	N	N	N	Y
F	RH	205	238	285	360	85	Y	Y	Y	N	Y
F	RH	180	600	660	60	80	Y	N	N	N	N
M	RH	200	360	360	420	50	N	N	N	N	Y
F	RH	105	420	420	90	90	Y	N	N	N	N
F	RH	120	300	800	240	30	N	N	N	N	Y
F	RH	120	225	285	30	85	Y	N	N	N	N
F	RH	140	260	380	30	70	N	Y	Y	Y	N
F	RH	140	250	400	70	80	Y	N	N	N	N
F	RH	270	340	390	200	50	Y	N	N	N	Y
F	RH	240	360	360	90	60	Y	N	N	N	Y
M	RH	200	240	335	120	0	N	N	N	N	Y
F	RH	170	300	300	180	10	N	N	N	N	Y
F	RH	160	220	270	40	85	Y	N	Y	Y	Y
F	RH	20	285	320	300	60	Y	N	N	N	N
F	RH	198	510	515	300	30	N	N	N	N	Y
F	RH	20	285	320	180	40	Y	Y	N	Y	Y
F	RH	120	210	360	300	60	N	N	N	N	Y
F	RH	120	300	340	330	50	Y	N	N	N	N
F	RH	200	280	340	200	0	N	N	N	N	Y
F	RH	40	260	350	60	60	N	N	N	N	N

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