Opening and closing function of the anal canal assessed by Acoustic Reflectometry

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Abbreviations

AAR	Anal acoustic reflectometry
AGA	American gastroenterology association
ANS	Autonomic nervous system
AR	Acoustic reflectometry
ARA	Anorectal angle
ARM	Anorectal physiology measurement
AVFS	Anal verge to function sphincter
BET	Balloon expulsion Test
bPNB	Bilateral pudendal nerve block
Ce	Closing elastance
CLM	Conjoined longitudinal muscle
CNS	Central nervous system
Cp	Closing pressure
CSA	Cross sectional area
CT	Computer tomography
DRE	Digital rectal examination
DSP	Digital signal processor
DVE	Digital vaginal examination
DVF	Denonvilliers fascia
EAS	External anal sphincter
EAUSS	Endoanal ultrasound scan
EMG	Electromyography
FI	Faecal incontinence
FIQL	Faecal incontinence quality of life score
FISI	Faecal incontinence severity index
FRI	Fatigue rate index
GA	General anaesthetic
GIQLI	Gastrointestinal quality of life index
HAD	Hospital anxiety and depression Scale
HPZ	High pressure zone
HRAM	High resolution anorectal manometry
Hy	Hysteresis

IAS	Internal anal sphincter
IBS	Irritable bowel syndrome
ICC	Interstitial cells of Cajal
ICS	International continence society
MDT	Multidisciplinary team
MEP	Motor evoked potential
MHQ	Manchester health questionnaire
MRI	Magnetic resonance imaging
MRP	Maximum resting pressure
MSP	Maximum squeeze pressure
MU	Motor unit
MUP	Motor unit potential
NICE	National institute of clinical excellence
NMB	Neuromuscular block
ODS	Obstructive defecation syndrome
Oe	Opening elastance
Op	Opening pressure
PCO	Patient centred outcomes
PNE	Peripheral nerve evaluation
PNTML	Pudendal nerve terminal motor latencies
PTNS	Posterior tibial nerve stimulation
PSNS	Parasympathetic nervous system
QOL	Quality of life
RAIR	Recto-anal inhibitory reflex
RBL	Rubber band ligation
RCT	Randomised control trial
REC	Regional Ethics Committee
rIGLE's	Rectal intraganglionic laminar endings
SF-36	Medical Outcomes Survey Short-Form
SM	Smooth muscle
SNS	Sacral nerve stimulation
SOE	Squeeze opening elastance
SOP	Squeeze opening pressure
SPSS	Statistical package for the social sciences

SyNS	Sympathetic nervous system
SqOe	Squeeze opening elastance
SqOp	Squeeze opening pressure
SUI	Stress urinary incontinence
TTNS	Transcutaneous tibial nerve stimulation
UI	Urinary incontinence
UPR	Urethral pressure reflectometry
WPAM	Water perfused anal manometry

Abstract

Anal acoustic reflectometry (AAR) is a technique that is currently under investigation for the assessment of faecal incontinence. It uses reflected sounds waves to measure cross sectional area at different pressures leading to a profile of the anal canal, and in particular the high pressure zone of the anal sphincters. The cross sectional area from the high pressure zone is then plotted on a graph to give seven characteristic parameters. AAR has been shown to be reproducible and reliable, able to distinguish between continence and incontinence, correlate with the severity of incontinence and able to discriminate between the three patterns of incontinence (urge, passive and mixed). Opening pressure has been shown to be an independent predictor of success with peripheral nerve evaluation, the trial period before sacral nerve stimulation. This thesis aimed to validate AAR against manometry and explore its physiological and clinical potential.

A retrospective analysis of 265 patients who had undergone AAR was undertaken in order to develop a surrogate marker for anal canal length. The surrogate marker did find the expected difference between men and women but this was not clinically significant. Furthermore, the surrogate marker was unable to differentiate between incontinence and continence. A technical limitation (Gibbs phenomenon) of AAR was subsequently shown to explain this unexpected result.

Prior manometry could possibly interfere with the interpretation of AAR, and therefore a prospective randomised cohort study of 30 patients was conducted to assess two orders of data collection. Reassuringly it does not matter which one of these investigations is undertaken first.

In order to test the hypothesis that the greater the challenge to the anal sphincter, the greater the response, the effect of two rates of anal canal stretch was investigated in a prospective randomised cohort study of 50 patients with faecal incontinence. No difference was found between normal or fast rates of AAR. This study has validated a faster method of AAR that can be used alongside manometry in any order.

A pudendal nerve block was used to investigate whether AAR assesses primarily internal or external sphincter function in a prospective cohort study of 15 patients using both AAR and manometry. Bilateral pudendal nerve block reduced the function of the external anal sphincter but had no effect on the internal sphincter using both techniques. This study suggests that AAR at rest is predominately an investigation of the internal anal sphincter.

A prospective study of 30 patients with faecal incontinence was carried out to establish if AAR can predict the outcome from posterior tibial nerve stimulation. Posterior tibial nerve stimulation improved rectal sensation, manometry squeeze pressures, quality of life, severity of incontinence and was more effective for patients with urge incontinence. A variety of demographic, clinical and physiological measures were unable to predict the success of posterior tibial nerve stimulation.

The results presented in this thesis suggest that the full clinical potential of AAR has yet to be realised and it will be necessary to compare it with high resolution anal manometry in the future. Progress in this field would be greatly facilitated by establishing the normal values for this technique and the development of a robust AAR assessment of the external anal sphincter.

Declaration

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Dedication

I would like to dedicate this work to Emma my beautiful wife and our perfect children Darcey and Joseph born during my time in research.

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Publications and Presentations

Published Papers

Anal acoustic reflectometry – review of a new investigation of the pelvic floor. J E Nicholson, B Hornung, P Mitchell, N Klarskov, G Lose, K J Telford, E S Kiff (Submitted to Colorectal Disease).

Abstracts

Anal acoustic reflectometry is a test of the internal anal sphincter? J Nicholson, J Pearson, A Worthington, W DeMellow, K Telford, E Kiff. University Hospital of South Manchester. Digestive Disease Foundation, Excel London, June 2015.

Response of the anal canal to stretch and Anal Acoustic Reflectometry. J Nicholson, J Pearson, A Sharma, K Telford, E Kiff. University Hospital of South Manchester. Digestive Disease Foundation, Excel London, June 2015.

Is posterior tibial nerve stimulation an effective treatment for faecal incontinence? J Nicholson, J Pearson, C Molyneux, A Sharma, K Telford, E Kiff. University Hospital of South Manchester. Digestive Disease Foundation, Excel London, June 2015.

Response of the anal canal to stretch and Anal Acoustic Reflectometry. J Nicholson, A Sharma, K Telford, E Kiff. University Hospital of South Manchester. American Society of Colon & Rectal Surgeons, Boston, USA, June 2015.

Anal acoustic reflectometry is a test of the internal anal sphincter? J Nicholson, A Worthington, W DeMellow, K Telford, E Kiff. University Hospital of South Manchester. American Society of Colon & Rectal Surgeons, Boston, USA, June 2015.

Methodological validation of a minimally invasive pelvic floor investigation – Anal Acoustic Reflectometry. Nicholson J, Kiff E, Sharma A, Telford K. University Hospital South Manchester. Tripartite Colorectal Meeting, Birmingham, July 2014.

Oral Presentations

Nicholson J, Kiff E, Sharma A, Telford K. Methodological validation of a minimally invasive pelvic floor investigation – Anal Acoustic Reflectometry. Tripartite Colorectal Meeting, Birmingham, July 2014.

J Nicholson, J Pearson, C Molyneux, A Sharma, K Telford, E Kiff. Is posterior tibial nerve stimulation an effective treatment for faecal incontinence? The Pelvic Floor Society Winter Scientific Meeting, Bristol, January 2015.

J Nicholson, J Pearson, C Molyneux, A Sharma, K Telford, E Kiff. Is posterior tibial nerve stimulation an effective treatment for faecal incontinence? Manchester Medical Society Section of Surgery trainees' prize meeting, March 2015.

Section 1 Literature Review

Introduction

This thesis further explores a new method of investigating the function of the anal canal - anal acoustic reflectometry (AAR). AAR is an anorectal physiology measurement (ARM). My review of the literature will concentrate on ARM's, but also discuss the anatomy & physiology of muscle and the anal sphincters. Following this I will cover the background and literature surrounding pressure reflectometry and AAR.

Chapter 1 Anatomy & Physiology

Anatomy

The Pelvis

The pelvis is part of the trunk, below and posterior to the abdomen. It is the transition between trunk and lower limbs and it is enclosed by walls of bony, ligamentous and muscular portions. The bony pelvis is the basin shaped ring of bones that protects the distal parts of the intestinal and urinary tracts and internal genital organs. It is comprised of hip bones (ileum, ischium and pubis), sacrum and coccyx. The hip bones are joined anteriorly at the pubic symphysis forming a pelvic girdle that is firmly attached to the sacrum for support of the lower limbs [1].

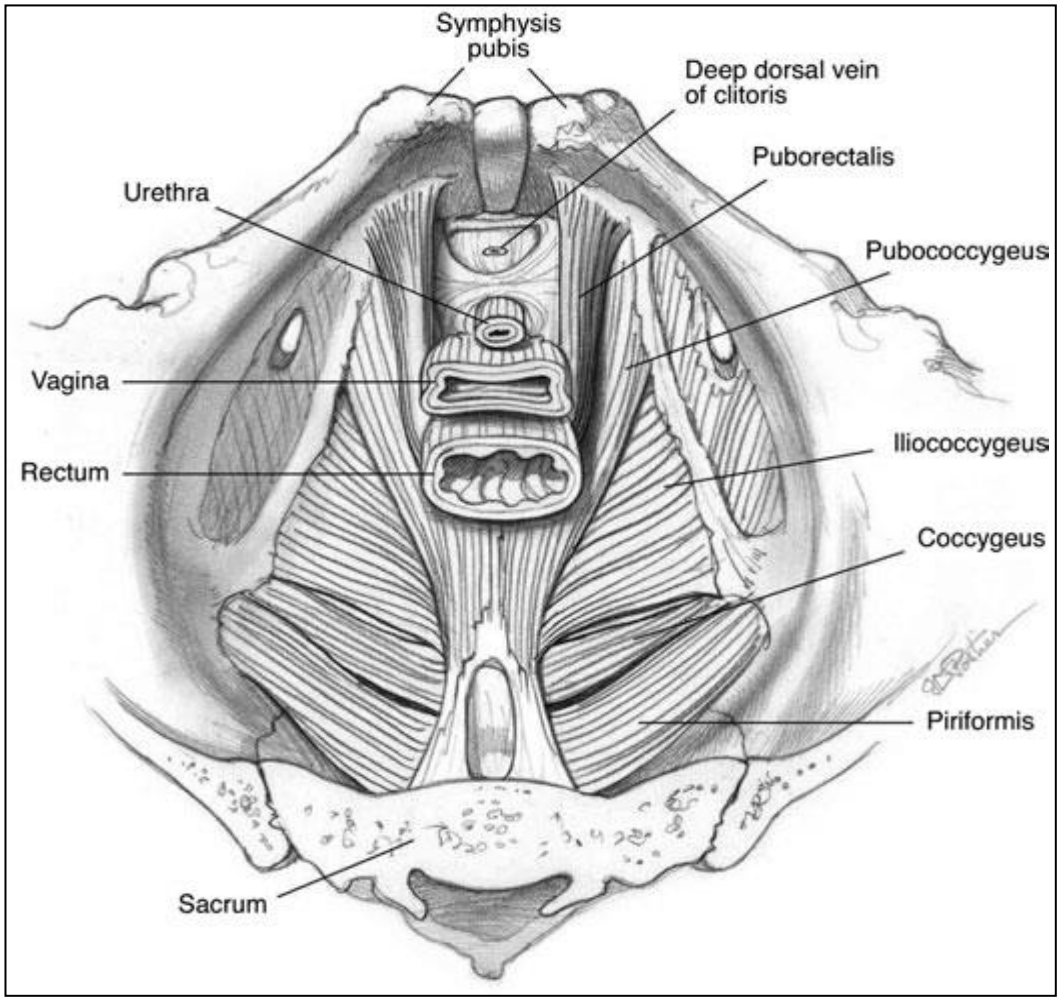
The Pelvic Floor

The pelvic floor is a dome shaped muscular sheet that predominately contains striated muscle and has midline defects enclosing the bladder, uterus and rectum. The

traditional segregation of the pelvic floor into anterior, middle and posterior compartments has lost favour in recent years and there is an increasing enthusiasm for viewing the pelvic floor from a global perspective [2]. The midline defects are closed by connective tissue anterior to the urethra, anterior to the rectum – the perineal body, and posterior to the rectum – the postanal plate.

The levator ani or pelvic diaphragm is subdivided into four muscles; pubo-coccygeus, ileo-coccygeus, coccygeus, and puborectalis. These muscles are attached peripherally to the pubic body, the ischial spine, and to the arcus tendinus, a condensation of the obturator fascia in between these areas (Figure 1). The pelvic diaphragm divides the pelvis into the main pelvic cavity above and the perineum below.

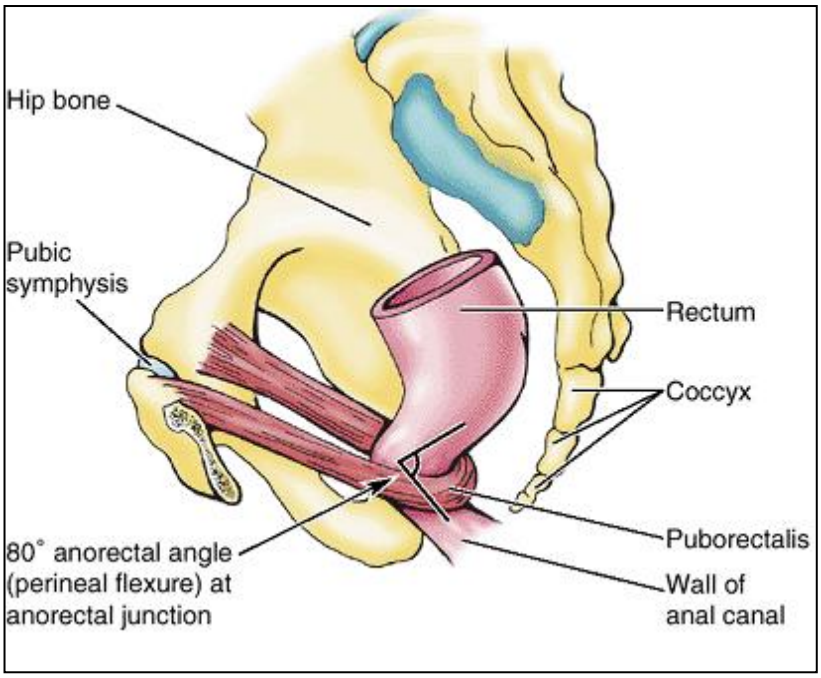
Figure 1 Pelvic view of the levator ani.



Pelvic view of the levator ani. Demonstrating its four main components: puborectalis, pubococcygeus, iliococcygeus, and coccygeus. Dyck and Thomas [3].

The puborectalis muscle forms a powerful sling around the anorectal junction angulating it anteriorly and creating the anorectal angle (ARA) which aids continence [4]. The ARA is a feature clearly demonstrated on lateral radiographic films of the pelvic floor, where a sharp 80° angulation is seen between the anal canal and the rectum (Figure 2). Puborectalis is an integral part of both the levator ani and the external anal sphincter complexes [5]. It, together with the superior borders of the internal and external sphincters, forms the anorectal ring, which delineates the anal canal from the rectum.

Figure 2 Puborectalis Muscle.



Puborectalis Muscle. The left hip bone has been removed to demonstrate the U shaped course of the puborectalis muscle around the anorectal junction, the tone of which is responsible for anorectal angle. Moore et al., [1].

The pelvic floor muscles have two major functions: they provide support or act as a floor for the abdominal viscera including the rectum; and they provide a constrictor or complex continence mechanism to the urethral, anal, and vaginal orifices (in females) [6].

Rectum & Anal Canal

Rectum

The rectum is 15-20cm long [2]. It begins anterior to the third sacral vertebra at the recto-sigmoid junction and follows the sacral curvature for its entire length. It ends antero-inferior to the tip of the coccyx by turning posteroinferiorly and becoming the anal canal.

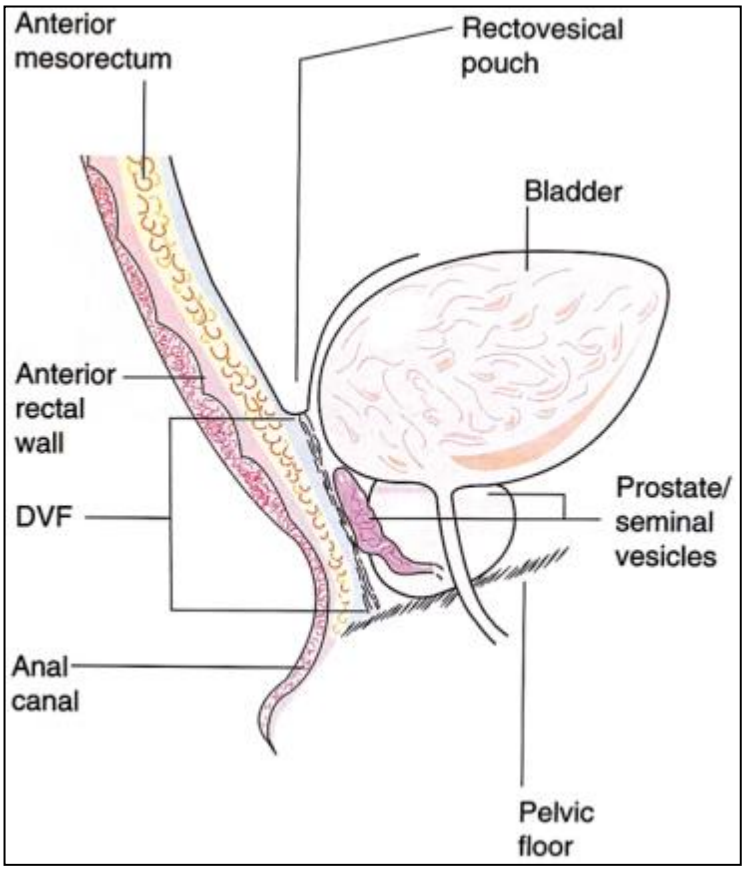
Anatomically the transition from sigmoid colon to rectum occurs with the cessation of the surgical mesocolon, with loss of the taeniae coli and appendices epiploicae. Modern series in the English literature arbitrarily define the rectum as composed of three parts: the low rectum (up to 6cm from the anal verge) the mid rectum (from 7-11cm) and the upper rectum (from 12 to 15cm) [7].

Three sharp flexures (superior, intermediate, and inferior) are apparent when the rectum is viewed anteriorly. The flexures are formed in relation to three internal infoldings (the circular valves of Houston [7]): two on the left and one on the right side. The folds overlie thickened parts of the circular muscle layer of the rectal wall. The dilated terminal part of the rectum, lying directly superior to and supported by the pelvic diaphragm (levator ani) and anococcygeal ligament, is the ampulla of the rectum. The ampulla receives and holds an accumulating faecal mass until it is expelled during defecation [1]. The rectum initially contracts upon filling, which is then followed by a fall in the intraluminal pressure back to the predistention level, a phenomenon referred to as the accommodation response [8]. The ability of the rectum to act as a reservoir to store stool depends upon the compliance of the rectal walls and the overall capacity of the rectum.

Peritoneum covers the anterior and lateral surfaces of the superior third of the rectum, only the anterior surface of the middle third, and no surface of the inferior third because it is subperitoneal. The posterior wall of the rectum is covered with a thick layer of pelvic fascia. Laterally, the lower portion of the rectum is supported on each side by reflections of endopelvic fascia known as the lateral ligaments of the rectum. The anterior extra-peritoneal surface of the rectum is separated from the

anterior structures by the Denonvilliers pelvic fascia (DVF, Figure 3). An important plane for the colorectal surgeon when preserving the pelvic nerves, although its precise surgical anatomy is still controversial [9].

Figure 3 Lateral view of Denonvilliers Fascia



Lateral view of Denonvilliers Fascia (DVF) and its relations. Lindsey et al., [9].

Anal Canal

The anal canal approximately 4cm long (varies from 2-5cm in length [7]) is the terminal part of the large intestine. It begins at the superior aspect of the pelvic diaphragm where the rectal ampulla narrows at the level of the puborectalis. The canal ends at the anus. There is significant difference between the sexes in the length of the anal canal. In men the average surgical length was 4.4 cm (range 3.2–5.3 cm) compared with the average length of 4.0 cm (range 3.0–5.0 cm) in women [10].

The proximal canal is lined by simple columnar epithelium, changing to stratified squamous epithelium lower in the canal via an intermediate transition zone just above the dentate line [11]. Several longitudinal mucosal folds, the columns of Morgagni, arise in the proximal anal canal and end at the dentate line, where they surround the anal sinuses, into which open the anal glands. The mucosa proximal to the dentate line lacks somatic innervation, but the mucosa below is richly supplied with cutaneous sensory nerve endings.

The anal lining is thick and folded to form anal cushions which are highly vascular and interdigitate to plug the anus at rest [12, 13]. The blood-filled vascular tissue of the anal mucosa also plays an important role in producing a more perfect closure of the anus. An in-vitro study showed that even during maximal involuntary contraction, the internal sphincter ring was unable to close the anal orifice completely and a gap of approximately 7 mm was left open. This gap was filled by the anal cushions [14], which may exert pressures of up to 9 mm Hg and thereby may contribute 10% to 20% of resting anal pressure [15].

The anal canal is surrounded by the anal sphincter complex, comprising the internal and external sphincters.

Figure 4 Diagram of the Anal Canal

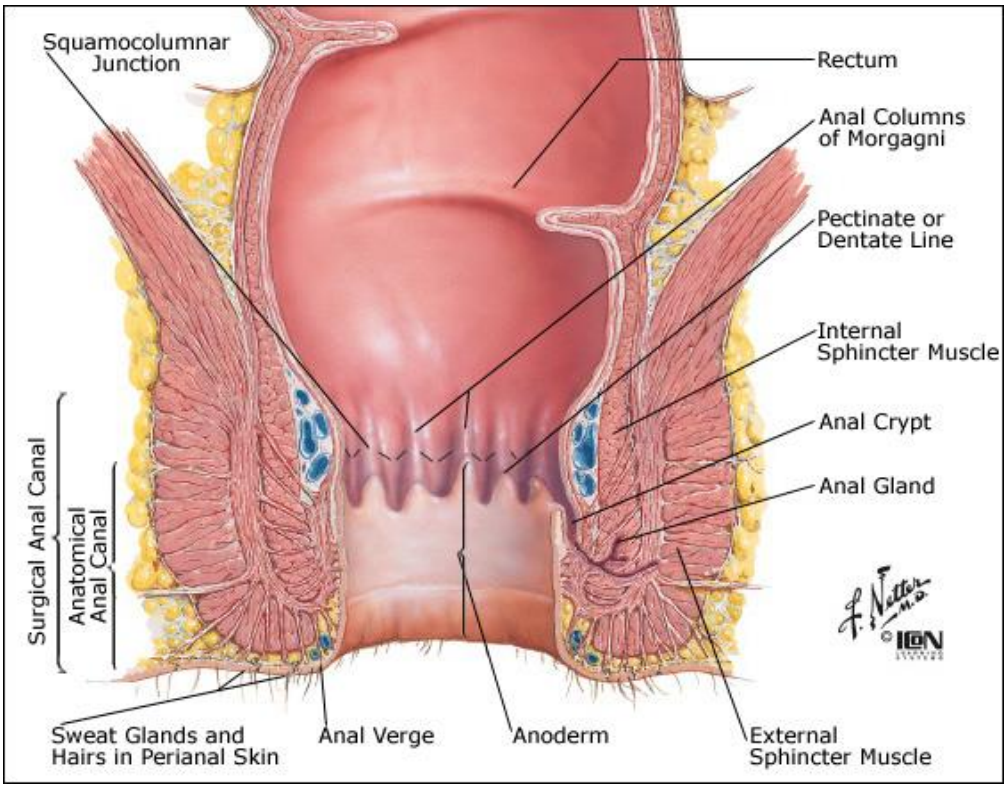


Diagram of the Anal Canal. Netter [16].

Anal Sphincters

The anal sphincters (internal anal sphincter and external anal sphincter) comprise of two cylindrical sleeves of muscle encompassing the anal canal and are critical in maintaining continence.

Internal Anal Sphincter

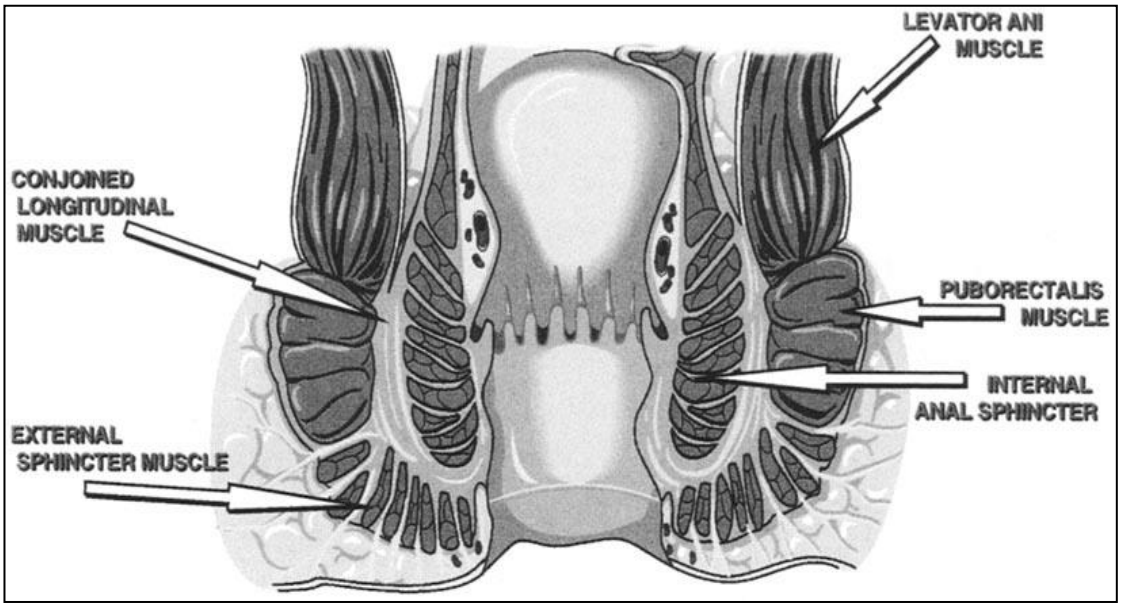
The internal anal sphincter (IAS) is the thickened extension of the circular SM layer surrounding the colon and rectum. It is therefore an involuntary muscle that remains tonically contracted at rest to help maintain continence.

The IAS is not merely a thickened extension of SM, in dog studies the IAS contains discrete muscle bundles separated by large septa not found in the rectal circular

muscle layer. Also in the rectum the interstitial cells of Cajal (ICC) are organised in dense networks along the submucosal and myenteric borders. In the IAS the ICC are located along the periphery of the muscle bundles within the circular layer [2] in comparison to being found along the submucosa in the rectum. Recently ICC have been suggested to play a significant role in the excitatory and inhibiter neurotransmission in the gastrointestinal tract [17]. However the role of the ICC in the SM sphincter tone and its inhibitory neurotransmission is controversial [18].

Anatomically the IAS does not occupy the whole anal canal [19], it extends from the anorectal ring to approximately 1.5cm below the dentate line, lying medial and just proximal to the caudal extension of the external anal sphincter (EAS, Figure 4). The intersphincteric groove is palpable at this level and is an important surgical landmark [20].

Figure 5 The Internal and External anal sphincter.



Diagrammatic representation of the anal canal showing the distribution of the internal anal sphincter (IAS) and the external anal sphincter (EAS). Sangwan et al., [20].

Running in-between the anal sphincters is the conjoined longitudinal muscle (CLM, Figure 5), a complex structure with both SM and striated muscle bundles and fibroelastic tissue that invests the sphincter complex and fixes it in place [21]. The exact anatomy is controversial but it runs down the intersphincteric plane with extensions that pierce and divide the subcutaneous EAS to attach to the perianal skin. It is thought that the extensions of the CLM, by dividing the subcutaneous EAS, may have a role in the containment of sepsis. The CLM contracts to shorten and widen the anal canal during defecation, everting the anal orifice [22].

In recent years endoanal ultrasound scanning (EAUSS) has increased our understanding of the anatomy of the anal sphincters and also been a significant advancement in the diagnosis and management of conditions such as sphincter trauma and faecal incontinence (FI) as well as in the staging of ano-rectal cancer. EAUSS has shown no difference in the IAS between males and females whereas the EAS is thicker in men especially anteriorly. The EAS becomes thinner with age in both sexes, whereas the IAS appears thicker [23].

External Anal Sphincter

The EAS is a cylindrical ring of striated muscle under voluntary control surrounding the outermost part of the anal canal; it is continuous above with fibres of puborectalis. The EAS is a powerful muscle and due to the fact it is under voluntary control in its normal state is often referred to as the emergency break muscle preventing socially embarrassing accidents [24]. The exact anatomy of the EAS has been debated since the first description by Santorini in 1715 [25]. Santorini described the EAS as having three separate muscular parts; the subcutaneous, the superficial

and the deep components. Since then many authors have agreed with this configuration [26-29]. However Goligher in 1955 [19], Oh and Kark in 1972 [30] and Ayoub in 1979 [31] contested this view presenting alternative structures. Oh and Kark presented a two part structure after a detailed anatomical study of dissection and histological examination (Figure 6). They published schematic drawings comparing the different proposed structures at the time to their new 2 part structure which consisted of; a deep compartment comprising the puborectalis and deep EAS plus the superficial compartment comprising the superficial and subcutaneous EAS. Other authors have supported this theory using different techniques from dissection to histology and more recently magnetic resonance imaging [32-34].

Figure 6 Historical views of the composition of the external anal sphincter.

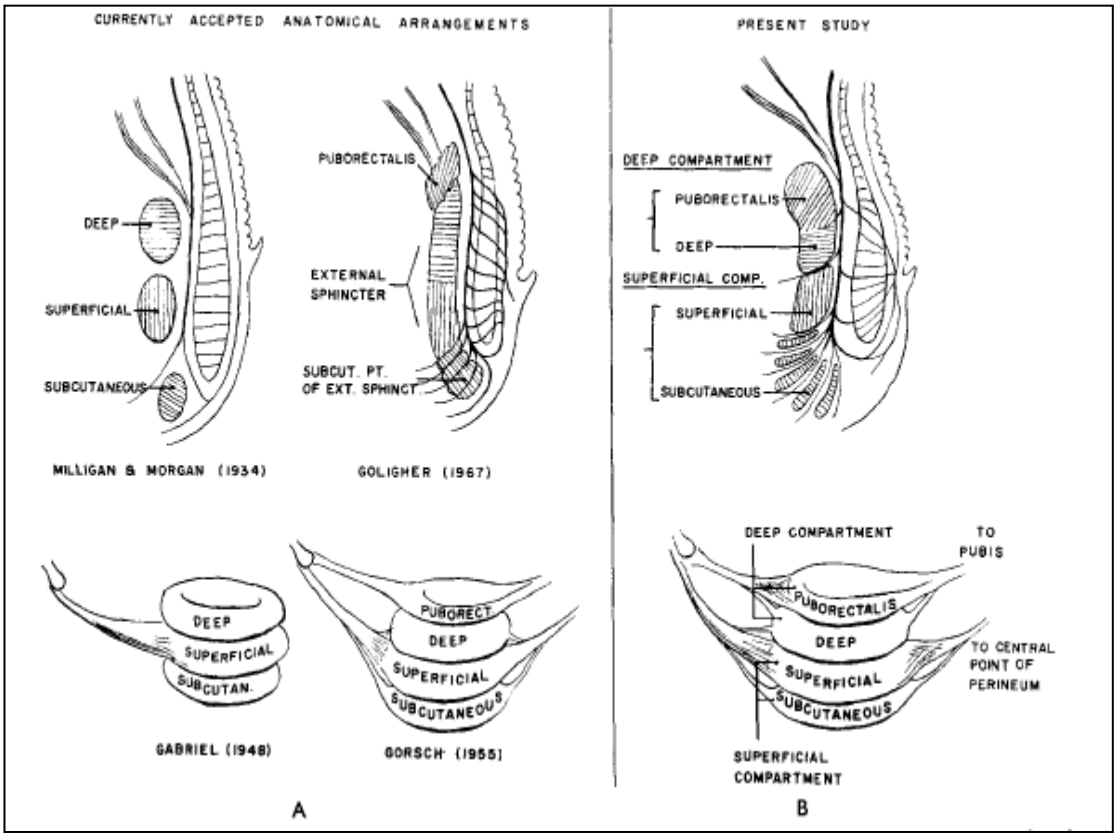
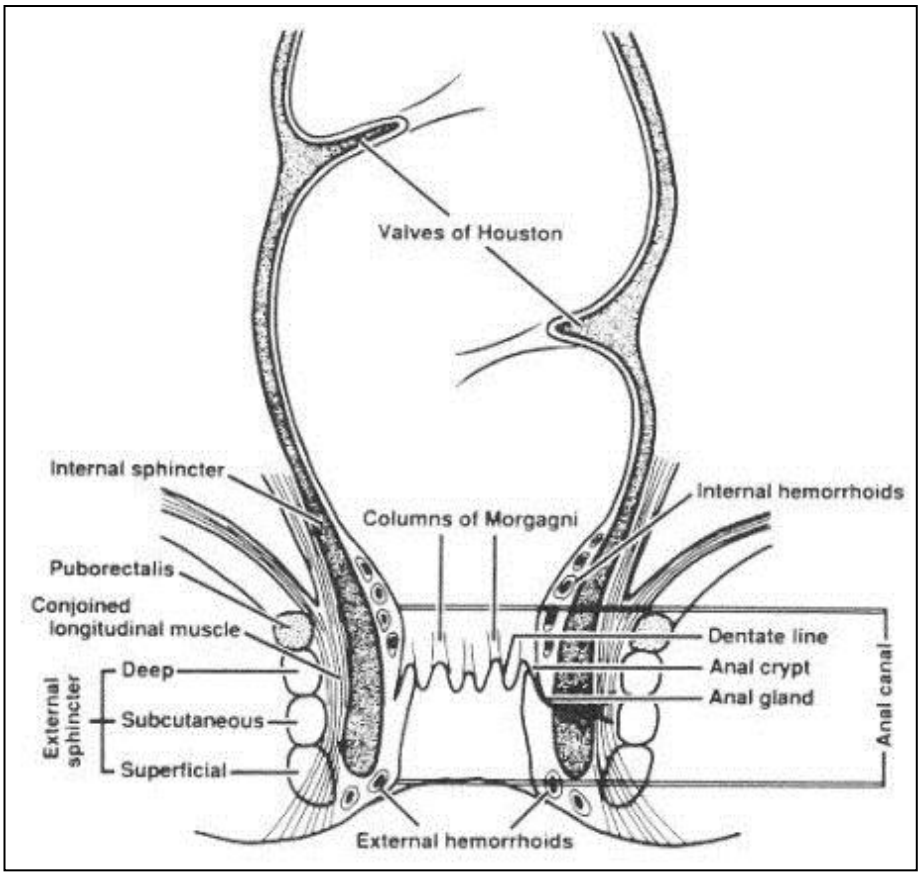


Diagram of the external anal sphincter (EAS) comparing the different historical views of its composition. A – Shows coronal sections of the arrangement of the EAS in the view of Milligan & Morgan (trilaminar, 1934) and of Goligher (bilaminar, 1967). Gabriel's (1948) view of the posterior attachment of the superficial sphincter which differs from Gorsch's (1955) finding that all the components attach posteriorly. B – Shows the bilaminar finding of Oh & Kark that the EAS could be divided into the deep compartment (puborectalis & deep sphincter) and the superficial compartment (superficial and subcutaneous sphincter) plus their views on the pattern of anteroposterior attachment. Oh & Kark [30].

With the emergence of endoanal ultrasound scanning (EAUSS) in the last 20 years the anal sphincters has been further defined. Despite the controversy surrounding the exact anatomy, with EAUSS it is now generally thought that the EAS has 3 segments; deep, superficial and subcutaneous (Figure 7). The deep part merges with puborectalis dorsa-laterally, the superficial ends at the caudal extent of the IAS and the subcutaneous part curves inward towards the anal margin [21].

Figure 7 3 part structure to the external anal sphincter.



The anal canal showing the 3 part structure to the external anal sphincter. Gordon et al., [35].

In 1994 Sultan and colleagues performed EAUSS on 114 healthy volunteers and found the EAS was shorter anteriorly in females, an important fact to be aware of during EAUSS to prevent false positive findings of sphincter deficiency. They also found the EAS was thicker bilaterally in males compared to females which related to the greater weight of the males. They found no relationship between the manometric resting or squeeze pressures in the anal canal, and the EAS or IAS thickness [36]. These findings were then confirmed on a 3D EAUSS study by Williams in 2000 [37] and again by endoanal magnetic resonance imaging (MRI) studies [38]. On 3D studies no significant difference in length between the sexes was found for puborectalis or the IAS, but there was a significant difference in the length of the

EAS in all planes; confirming that the EAS is generally shorter, particularly anteriorly, in women [38].

The sphincters are affected by age. The IAS in neonates is very thin (<1mm), measuring 1-2mm in young adults, 2-3mm in middle age and 3-4mm in the elderly [21]. However the EAS thins significantly in older nulliparous women, but the longitudinal layer, subepithelium or puborectalis was unchanged on EAUSS [39].

I will discuss the physiology of the anal sphincters plus EAUSS in subsequent sections.

Blood supply to the anal canal

Branches of the superior rectal artery (a branch of the inferior mesenteric artery) supply the upper end of the anal canal. The middle rectal and median sacral arteries supply a small part of the muscular wall whilst the lower end of the anal canal receives a blood supply from the inferior rectal artery, a branch of the internal pudendal artery.

Nerve Supply to the Pelvic floor

The anorectum and pelvic floor are supplied by the sympathetic, parasympathetic (autonomic nervous system) and somatic fibres (somatic nervous system) [40].

Autonomic nervous system

The anal sphincter and motility of the bowel including colonic relaxation and propulsion during defecation are partly under the control of the autonomic nervous system (ANS). The ANS also referred to as the involuntary or unconscious nervous system is classically divided into 2 subsystems: the parasympathetic nervous system (PSNS) and the sympathetic nervous system (SyNS). Although many exceptions exist the SyNS is thought of as a 'quick response mobilising system' and the PSNS as a 'more slowly activated dampening system.'

The SyNS preganglionic fibres originate from the lowest thoracic ganglion in the paravertebral sympathetic chain (Figure 8) and join branches from the aortic plexus to form the superior hypogastric plexus. The superior hypogastric plexus divides into right and left hypogastric nerves and unite with parasympathetic fibres to form the inferior hypogastric plexus. These parasympathetic fibres are derived from the pelvic splanchnic nerves.

The nerve supply to the rectum and anal canal is derived from the superior, middle and inferior rectal plexus;

- The superior rectal plexus is a division of the inferior mesenteric plexus which in turn is derived chiefly from the aortic plexus. The inferior mesenteric plexus surrounds the inferior mesenteric artery and is distributed to all parts supplied by the artery.
- The middle rectal plexus supplies the middle part of the rectum and is a branch of the inferior hypogastric plexus. The middle rectal plexus was

previously referred to by anatomists as Copeland's Web after it was identified by Charles Copeland in the early 1900's.

- The inferior rectal nerve is a branch of the pudendal nerve which arises from the 2nd to 4th sacral nerve roots. I will discuss the pudendal nerve in more detail under the somatic nervous system.

Sacral PSNS pathways to the colon have excitatory and inhibitory components [41]. Excitatory pathways play an important role in colonic propulsive activity, especially during defecation. Inhibitory pathways allow colonic volume to adapt to its contents, and also mediate descending inhibition that initiates colonic relaxation ahead of a faecal bolus [2].

The rectum and upper half of the anal canal are only sensitive to stretch. The involuntary IAS is supplied by sympathetic fibres from the inferior hypogastric plexus and by the PSNS fibres from the pelvic splanchnic nerves. At rest the SyNS supply has a tonic, excitatory effect on the IAS tone [42, 43]. Parasympathetic innervation does not appear to affect the IAS tone [44].

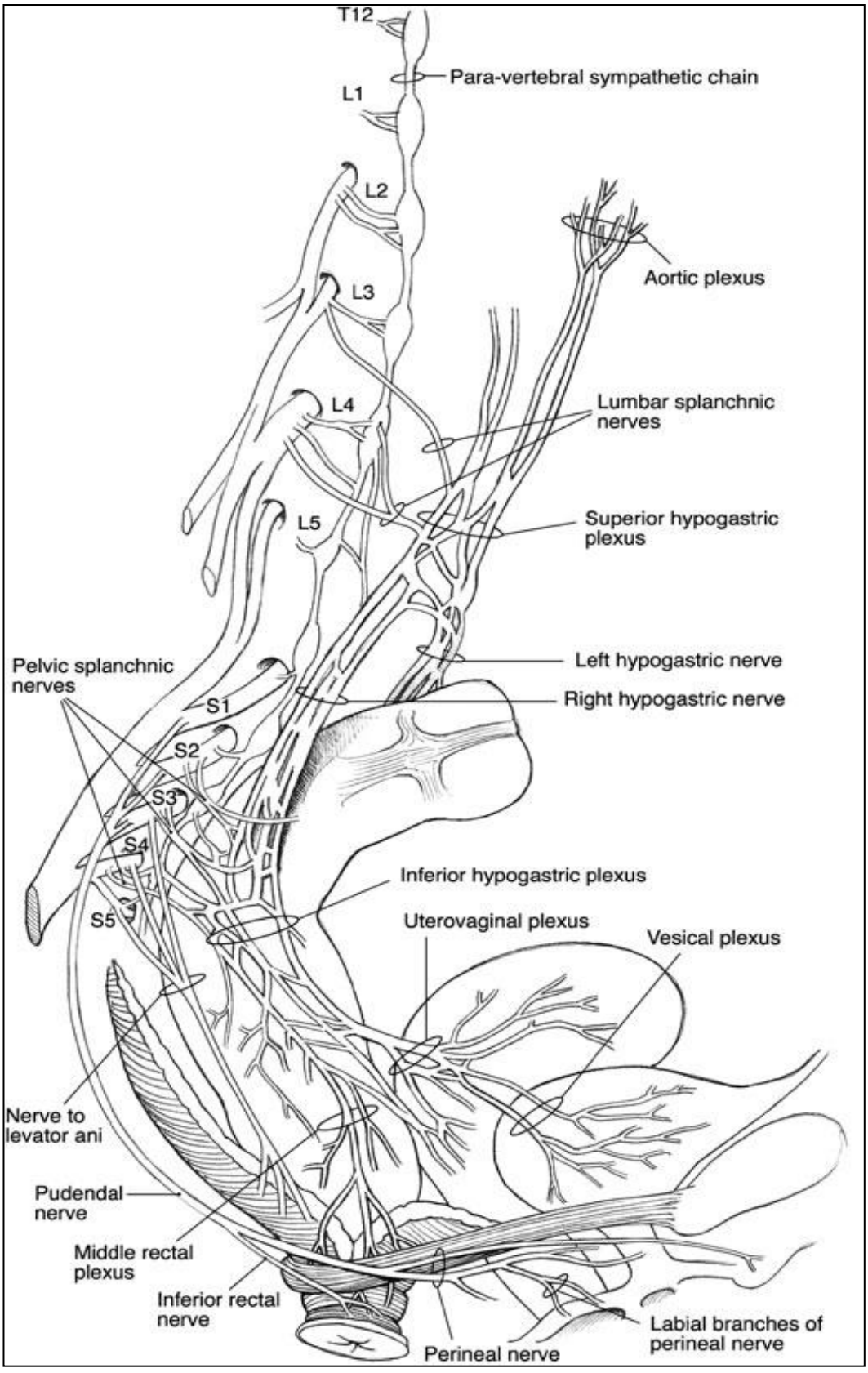
Somatic Nervous System

The somatic nervous system or voluntary nervous system is associated with the voluntary control of body movements via skeletal muscles. It comprises afferent fibres (sensory) and efferent fibres (motor). The pelvic floor muscles are innervated by branches from the sacral nerve roots of S2-S4 via the sacral plexus [45].

The pudendal nerve is a mixed somatic nerve (motor and sensory) that arises from the 2nd to 4th sacral nerve roots. It travels with the internal pudendal artery leaving the pelvis through the greater sciatic foramen between the piriformis and coccygeus muscles. It then hooks around the sacrospinous ligament and enters the perineum through the lesser sciatic foramen. It then runs in Alcock's canal (also known as the pudendal canal) along with the pudendal artery and vein and via its branches supplies the muscles and skin of the perineum and the EAS [46]. The inferior rectal nerve is the first branch of the pudendal nerve and supplies the motor innervation to the EAS and the afferent sensory innervation to the mucous membrane of the lower half of the anal canal. The EAS has dual innervation from both left and right pudendal nerves. The pudendal nerve then splits to form the dorsal nerve of the penis (or clitoris) and the perineal nerve [1, 45].

According to Bharucha the nerve supply to the puborectalis muscle has been subject to controversy [2]. Early dissection work suggested that the puborectalis was innervated from below the pelvic floor [47] by the pudendal nerve and its branches; hence the puborectalis was regarded as being derived from the EAS and not the levator-ani. However work by Percy et al., with electrical stimulation from above the pelvic floor found EMG activity in puborectalis but not EAS, implying the origin of puborectalis may be from the levator-ani [48].

Figure 8 Nerve supply to the anorectum



Sympathetic, parasympathetic and pudendal nerve supply to the anorectum. Dyck and Thomas [3].

In the 1960's Duthie and Gairns [49] described the free and specialised nerve endings that provide the rich sensory innervation of the anorectum. This rich sensory innervation is now thought to be important for example in the sampling reflex and a patient's ability to differentiate between gas, liquid and solid stool. The following is a summary of the distribution of sensory nerve ending [50];

- Perianal skin - Intraepithelial free or non-specialized nerve endings, no organized or specialized nerve endings.
- Anal Canal proper
    - Anal margin – Organised nerve endings similar to Krause end-bulbs (thermosensitive).
    - Anal Canal – Richly innervated with various organized endings such as touch sensitive (Meissner corpuscles), thermosensitive (Krause end-bulbs), pressure sensitive (Golgi-Mazzoni) and friction sensitive (genital corpuscles) nerve endings.
    - Region of crypts and valves – Similar to the anal canal above but in different proportions, more friction sensitive and less pressure sensitive ending.
- Rectal mucosa – No free or organised nerve endings. The rectum is insensitive to pain, temperature and touch and has no specialized receptors. It is sensitive to distension more so than the colon. In contrast to colonic distension which generally evokes ill-defined discomfort and eventually pain, rectal distension is perceived as a more localized sensation of rectal fullness, interpreted by the patient as a desire to pass wind or motion

The Central Nervous System

The central nervous system (CNS) exhibits strong descending control from the cerebral cortex [51] over the voluntary sphincter muscles of the anorectum. Although faecal incontinence is more frequently related to peripheral nerve damage one must not overlook the role the CNS plays and the fact that patients with stroke or frontal lobe damage may also have symptoms of FI [52-54]. In 1997 Nakayama et al., found that in patients with larger strokes and when the cerebral cortex was involved, were more likely to have faecal incontinence [53]. Patients with multiple sclerosis are also frequently found to have problems with FI and constipation which may represent a central or peripheral process [55]. In 1999 cortical mapping with transcranial magnetic stimulation suggested that rectal and anal responses are bilaterally represented on the superior-medial motor cortex (Brodmann area 4) [56].

Physiology

Motility of the Colon and Rectum

Approximately 90% of the whole gut transit time is accounted for by colonic transit [57]. The large intestine stores undigested remnants prior to defecation. The colon is inactive for a large proportion of the time but when contraction occurs it can either be segmental or peristaltic in nature [58]. The slow segmental contractions (3-4 per minute) mix the luminal contents and improve absorption. Propulsive activity or mass movements occur infrequently (2-3 per day) and drive the colonic contents towards the rectum.

Accommodation Response

The rectum initially contracts upon filling, which is then followed by a fall in the intraluminal pressure back to the pre-distension level, known as the accommodation response [8].

Anal Reflexes

Recto-anal Inhibitory Reflex

The rectum is normally empty but its distension (sensed by mechanoreceptors) caused by a mass movement from the colon induces relaxation of the SM of the IAS and the urge to defecate. In paraplegics this and the contraction of the rectum will lead to automatic defecation, but normally reflex contraction of the EAS allows retention of the rectal contents until socially acceptable. The inhibition of IAS by rectal distension is called the recto-anal inhibitory reflex (RAIR) and is coupled with a transient contraction of the EAS (inflation reflex).

The RAIR was first described by Gowers in 1877 [59] and later confirmed by Denny-Brown and Robertson in 1935 [60]. Gowers studied 3 patients with FI due paraplegia or nerve roots damage affecting the sacral nerves, and noticed voluntary contraction of the EAS to be absent. However the IAS was held in a state of permanent contraction which was inhibited when air was injected into the rectum resulting in IAS relaxation. Subsequent authors have confirmed this and added that the effectiveness of the reflex increases as the air filled balloon moved distally

towards the rectum [61, 62] and that the degree of relaxation was proportional to the degree of rectal distension [42, 61].

The RAIR was found to be present in normal subjects and in patients with proximal spinal lesions and was therefore initially thought to be a spinal reflex. Later it became apparent that the reflex was reliant on an intact intramural neural plexus. Lubowski et al., found that the RAIR was still present after bilateral hypogastric nerve blockade and after complete isolation of the rectum from its extrinsic nerve supply but absent when the rectum was inflated proximal to a circumferential myotomy of the rectum [63]. They therefore concluded that the neural pathway of the RAIR reflex was entirely in the wall of the anus and rectum.

The RAIR is absent in Hirschsprung's disease in which intramural ganglia are absent over a length of rectum and colon [64]. The RAIR has also found to be abolished after surgery to remove the rectum but recovers post operatively after approximately 1 year [65, 66]. The reflex is thought to recover by regeneration of the intrinsic intramural nerve fibres across an anastomosis.

Brain centres can however, via descending pathways to somatic nerves to the EAS, keep the EAS closed thus allowing the delay of defecation and maintaining anal pressure despite the IAS relaxing. The prolonged distension of the rectum initiates a reverse peristalsis, driving the rectal contents back into the sigmoid colon. The urge to defecate then subsides until the next mass movement [67].

Anorectal Sampling

The sampling response consists of transient relaxation of the upper part of the internal anal sphincter as part of the RAIR, which allows the rectal contents to come into contact with the highly sensitive area in the anal canal to assess the nature of the content. This sampling allows discrimination between solids, liquids and gas [68, 69]. Using a sophisticated digital recording technique, Miller et al., were able to measure mid-IAS and rectal pressure in ambulant subjects over a 3-h period [70]. They have confirmed that the IAS pressure falls to equal to or less than the rectal pressure approximately seven times hourly, showing that anorectal sampling occurs as a normal physiologic process. The mechanism by which the anal canal is able to discriminate between different stool consistency remains unclear [50].

The Closing Reflex

As the stool passes through the anal canal it stretches the EAS creating a traction force upon it. After the last bolus of stool is passed, the "closing reflex" of the external sphincter is stimulated by the release of traction [71]. The EAS temporarily contracts, puborectalis contracts restoring the anorectal angle and the IAS tone recovers. In this way anal continence is maintained after the act of defecation [72].

The Cough Reflex

A transient increase in abdominal pressure is seen during a cough and is associated with a reflex contraction of the EAS. This reflex contraction prevents FI and is seen in paraplegics [73]. In 2006 Deffieux and colleagues found that during coughing,

EAS electromyogram activity increases before external intercostal muscle activity. The contraction of the EAS preceding the activation of muscles involved in coughing indicated that the response is not a result of a simple spinal reflex, but more likely the result of a more intricate reflex involving complex integrative centres [74].

Classical Anal reflex

The classical anal reflex is manifested by a contraction of the anus in response to pricking the anal mucosa or the perianal skin. The original description of the reflex was given by Rossolimo (1891) [75], who reported the constant appearance of the reflex in normal subjects and has been replicated by Pedersen et al., [76], who also demonstrated that this reflex is present in spinal shock. The reflex is known to be unaffected by spinal cord transection in man [77] but absent in cauda equina lesions [78]. It is thought to be a polysynaptic reflex response [79].

Physiology of the Anal Sphincters

The tonic contraction of the anal sphincters at rest results in an anal canal pressure that exceeds rectal pressure therefore maintaining a closed anal canal to rectal contents [80].

Internal Anal Sphincter Tone

The IAS has an intrinsic sinusoidal slow wave activity with a frequency of 20-40 cycles per minute and is primarily responsible for the resting tone of the anus [81]. The other contributors to anal resting tone include the EAS, the anal mucosal folds

and puborectalis [2]. A number of authors have tried to estimate the contribution of the different factors above on resting tone. In 1975 Frenckner and Euler found the IAS to contribute about 85% of the resting anal pressure which is measured at between 50 to 120mmHg in health [82]. Later, in 1992, Penninckz et al., estimated that anal resting tone was generated by nerve-induced activity in the IAS (45% of anal resting tone), myogenic tone in the IAS 10%, the EAS 35% and the haemorrhoidal plexus 15% [44]. Weakness or disruption of the IAS results in passive leakage of faecal contents and incontinence of flatus [83].

External Anal Sphincter Tone

The striated and fatigable EAS muscle receives its nerve supply from the pudendal nerve. The EAS is composed of both tonically contracting slow twitch fibres (type 1 fatigue-resistant) and phasically contracting fast twitch fibres. The EAS is primarily responsible for the voluntary contraction (emergency break muscle) of the sphincter with pressures of between 50 to 200mmHg being generated. Obstetric trauma to the EAS is associated with a significantly reduced maximum squeeze pressure (MSP) [84].

The only other striated muscles that display resting activity are the puborectalis, external urethral sphincter, cricopharyngeus and the laryngeal abductors.

Puborectalis Muscle and the Anorectal angle

The pelvic diaphragm is composed of a number of muscles all of which can be considered as acting in concert. The pelvic floor relaxes during defecation with an

increase in intra-abdominal pressure during the Valsalva manoeuvre and tensing of the muscles of the anterior abdominal wall. A failure of this process causes functional disorders such as anismus [85].

The striated puborectalis muscle slings round the upper anal canal (see figure 2) and is tonically active, maintaining the resting ARA. The ARA describes the acute angle between the rectum and the upper anal canal and led Sir Alan Parks to propose the flap-valve theory of incontinence [4]. However subsequent radiological studies have disproved this theory and shown no difference in ARA between incontinent patients and controls [86, 87]. Puborectalis contraction during a sudden rise in abdominal pressure reduces the ARA preserving continence and can maintain continence even in the absence of functioning anal sphincters [88, 89].

Anal & Rectal Sensation

As described earlier the distribution of sensory nerve endings of the anal canal and rectal mucosa have been established by Duthie and Gairns [49]. The anal canal is richly innervated with multiple nerve trunks containing both myelinated and non-myelinated fibres from various organized endings, including Meissner corpuscles (touch sensitive), Krause end-bulbs (thermosensitive), Golgi-Mazzoni bodies (pressure-sensitive), and genital corpuscles (friction –sensitive). The anal canal was also found to be exquisitely sensitive to pain and temperature, more so than the surrounding skin or rectum. The rectum however is insensitive to pain, temperature and touch. It is sensitive to distension more so than the colon, resulting in the subjective feeling of rectal fullness and an urge to defecate in contrast to colonic distension that produces pain and colic [50]. In addition to their histological studies

on the distribution of nerve endings Duthie and Gairns also investigated the precise levels of sensation in the anal canal. They found that the anal canal was sensitive to touch 0.25-0.75cm above the anal valves and sensitive to pain and temperature 0.5cm proximal to that. This distribution also correlated with the density of nerve endings. In summary the anal canal is sensitive to pain, temperature, touch, pressure and friction; the rectum is only sensitive to distension.

The type and location of rectal receptors is under investigation [72]. The rectum has functionally unique rectal intraganglionic laminar endings (rIGLE's). rIGLE's are flattened vagal nerve endings within the myenteric ganglia [90]. In vitro studies have shown that rIGLE's are more sensitive than colonic counterparts, acting as slowly adapting mechanoreceptors responding to tension and rapid distension [91, 92].

Rectal hypersensitivity is defined as a reduced sensory threshold to volumetric distension [93]. Immunohistochemical studies have also identified mucosal afferents that are both mechano and chemosensitive and which may be increased in number in rectal hypersensitivity [91]. Rectal hypersensitivity is associated with bowel frequency and urgency [93] and postulated as a cause of FI in patients with proctitis and functional bowel disorders [94, 95]. Rectal hypersensitivity is also associated with the feeling of incomplete evacuation in patients with functional bowel disorders such as irritable bowel syndrome [96].

Rectal Compliance

The normal rectum is capable of accommodating increases in volume with only minor alterations of pressure. Rectal compliance is the volume response to a pressure

distension of the rectum and is measured using a barostat. Commonly this consists of a polyurethane catheter balloon in the rectum attached to a barostat and a sensory level is measured (first constant sensation, defaecatory desire and maximum toleration [97]) with changes in balloon volume [72].

Unfortunately a lack of standardised protocols and the contribution of abnormal rectal sensation make interpretation difficult. Rectal compliance can be altered due to abnormalities of sensation or contractility or a combination of both. A number of studies have shown low maximum tolerated volumes with normal sensation and compliance or hypersensitivity and reduced compliance [98, 99]. Thus rectal compliance is a measure of the combined sensorimotor function and has an important role in normal defecation.

The Anal Stretch Receptor

There is little published on the anal stretch receptor, but to understand stretch of the pelvic floor and in specific the anal sphincter complex one also needs to understand muscle spindles. Muscles spindles are sensory receptors within the belly of striated muscle that primarily detect changes in the length of that muscle. They convey length information to the CNS via sensory neurons. This information can be processed by the brain to determine the position of body parts. The response of muscle spindles to changes in length also plays an important role in regulating the contraction of muscles, by activating motor-neurons via the stretch reflex to resist muscle stretch. Muscle spindles have both sensory and motor components. The sensory component has primary and secondary nerve fibres that spiral around and terminate on the central portions of the intrafusal muscle fibres, providing the

sensory component of the structure via stretch sensitive ion-channels of the axons [100].

The Stretch Reflex

The stretch reflex is muscle contraction in response to stretching within the muscle which provides automatic regulation of skeletal muscle length. When a muscle is stretched primary sensory fibres of the spindle respond to both changes in muscle length and velocity and transmit this activity to the spinal cord. The reflex evoked activity in the alpha motor-neurons is then transmitted via their efferent axons to the extrafusal fibres of the muscle, which generate force and resist stretch [100].

Muscle spindle stretch receptors have been demonstrated in the levator ani, puborectalis and EAS muscles since the 1960's [101-103]. Histological studies have shown a predominance of type 1 fibres (slow twitch fibres, red in colour and fatigue resistant) in the puborectalis and EAS [104, 105] allowing the constant tonic activity via a monosynaptic spinal reflex drive. This tonic activity is not present in patients with tabes dorsalis (syphilitic myelopathy) because the condition selectively destroys afferent sensory fibres and interrupts the spinal reflex arc at the level of the dorsal root entry zone [106]. However voluntary EAS activation is still possible with tabes dorsalis.

Tonic activity is mediated by the stretch receptor in the muscles as discussed above [78]. Lane and Parks saw that EAS activity continued even after complete excision of the rectum, supporting the concept that these receptors are located in the levator ani [65]. Furthermore attenuated EAS responses to rectal distension and anal

sphincter responses to abdominal pressure can still be found in patients with complete spinal lesions above the level of the conus medullaris reinforcing the notion that the EAS response is a spinal reflex triggered by tension or stretch in the pelvic floor [107].

Puborectalis and the EAS contain muscle spindle stretch receptors [103]. The constant tonic activity of these muscles may represent a spinal reflex response to the weight of the abdominal contents, which is termed the postural reflex of the pelvic floor [71]. This continuous activity and the sudden contraction activity caused by distention, therefore, may be induced by the same receptors.

Maintenance of Continence

The maintenance of faecal continence is a complex multifactorial process involving;

- Stool volume and consistency
- Bowel motility
- Neurological function (central and peripheral)
- Pelvic floor musculature
- Puborectalis and the anorectal angle
- Internal and external anal sphincter complex
- Anal mucosa and cushions
- Rectal compliance and sensation
- Comorbidities (e.g. stoke, dementia, colitis and operations such as anterior resection)

A problem with any single factor above can result in faecal incontinence; however it may not become apparent until later in life when it is commonly multifactorial.

Stool Consistency

In healthy adults approximately 100-150mls of stool of variable consistency enters the rectum each day [108]. The mechanisms that ensure continence are best suited to formed stool, as the rapid arrival of liquid stool into the rectum may lead to urgency and incontinence. In 1997 Lewis and Heaton presented a clinically useful scale to assess the form of stool [109]. The 7 point Bristol Stool form scale was validated and correlated with whole gut transit time and has also been useful in the research setting [110, 111].

Normal Defecation

The frequency of normal adult defecation is difficult to quantify but in broad terms lies between once a week to three times a day [112, 113]. Most people have irregular bowels although the most common habit is once daily and most defecation occurs in the early morning (earlier in men than women) [112].

Defecation commences with rectal sensory awareness of mechanical distension due to its contents which is relayed to the cerebral cortex as the perception of the need to evacuate the rectum [114]. When the subject is in a socially appropriate setting to defecate they adopt a sitting or squatting position. The squatting position is optimal straightening the rectal angle and allowing a more effective propulsion of its contents

[115]. The straightening effect is further increased by straining resulting in lessening the resistance at the anorectal junction and increasing the ease of defecation. The rectal distension triggers the RAIR and thus relaxation of the IAS and puborectalis opening the ARA and allowing exposure of the rectal contents to the upper anal canal. This sampling of rectal contents by the sensitive upper anal canal allows the subject to discriminate between flatus, liquid and stool. Following the RAIR the anal cushions flatten due to the action of the longitudinal muscle aiding a further reduction in anal canal pressure. The subject then performs a Valsalva manoeuvre, the anterior abdominal wall contracts, all in an attempt to funnel pressure down to the pelvis. The pelvic floor relaxes and giant spontaneous recto-sigmoid contractions push stool through the relaxed anal canal until the rectum is empty [72]. This seems to be reflex mediated at the spinal cord level since even spinally injured patients can void a complete stool from the rectum, once initiated [116]. As stool passes through the anal canal it stretches the EAS creating traction force upon it. After the last bolus of stool is passed the closing reflex of the EAS is stimulated by the release of traction [71]. This together with passive distension of the anal cushions serves to close the anal canal [117].

Chapter 2 Faecal Incontinence

Definition

Faecal incontinence (FI) can be defined as either the involuntary passage or the inability to control the discharge of faecal matter through the anus [118]. The International Continence Society (ICS) collaboration modified this to define anal

incontinence as the involuntary loss of flatus, liquid or stool that is a social or hygiene problem. The definition of FI is similar with the exclusion of flatus incontinence [119].

Clinically there are 3 subtypes;

1. Passive incontinence – the involuntary discharge of stool or gas without awareness,
2. Urge incontinence – the discharge of faecal matter in spite of active attempts to retain bowel contents,
3. Faecal seepage – the leakage of stool following otherwise normal evacuation.

There may be an overlap between the 3 subtypes and large variation in severity. FI can contribute to medical morbidity such as urinary tract infections and decubitus ulcers and can burden patients with substantial financial expenses [120]. The socioeconomic impact is significant and accounts for an estimated $8 billion to $11 billion in elderly care annually in the US [121]. However its main effect is on quality of life (QOL) [122]. Patients often reorganise their lives around the constant need to be in close proximity to a toilet. Unable to enjoy the freedom that most take for granted, such as going shopping and sexual intercourse. Incontinent patients have been reported to be less likely to marry and hold a normal job [121]. The subsequent impact on an individual's life is enormous and can lead to social isolation [123] and an increased risk of psychiatric disorders, particularly anxiety and depression [124, 125]. Unfortunately there remain a number of barriers to treatment; including the unwillingness of patients to present to health care professionals often because of embarrassment and the ignorance of healthcare professionals plus the lack of robust pathways to specialist units and care [126].

Epidemiology of Faecal Incontinence

Although FI affects people of all ages, its prevalence is disproportionally higher in women, in the elderly, and in nursing home residents. The true prevalence is unknown owing to the lack of standard definitions, differences in data collection, under-reporting by patients and variations in the populations sampled. Prevalence depends on the definition of FI which varies between studies. Many population based and cross-sectional studies of FI in both community dwelling and institutionalized individuals have been done and conclude that prevalence varies depending on gender, age, health status, and place of residence [127]. In 2004 Nelson reviewed the epidemiology of FI comparing 34 population based surveys of the prevalence of FI involving countries from all over the world. He concluded that the prevalence varies from 1.5% in children to more than 50% in nursing home residents [127]. According to the guidelines in 2004 from the American Journal of Gastroenterology the prevalence of FI ranges between 1% and 7.4% in otherwise healthy people and up to 25% in those who are institutionalized [118]. In the United States FI is the second leading cause for placement in nursing homes [128]. A recent Spanish study in 2010 by Pares et al., found the prevalence of FI to be 10.8% in patients presenting to their general practitioner [129]. However the most recent UK based study by Perry et al., in 2002 saw 1.4% prevalence in over 40 year olds but excluding nursing home resident making comparison difficult. An older postal questionnaire study by Thomas et al., in the UK compared the reported prevalence (to health and social services) to the questionnaire prevalence and found that patients were not seeking help, young men more so than women. They also reported prevalence's of FI of 4.2% for men aged 15-64 and 10.9% >64 years old and 1.7% for women aged 15-64 and 13.3% for women >64 years old [130]. FI is often seen in association with urinary incontinence

and a higher incidence of mixed FI and urinary incontinence has also been reported in nursing home residents [131-133].

Aetiology

FI is caused by one or more of the mechanisms that maintain continence being disrupted to an extent that the other mechanisms are unable to compensate. Hence the cause of FI is often multifactorial. A prospective study found that 80% of patients with FI had more than 1 pathogenic abnormality [134]. The causes of FI are listed in Table 1.

Table 1 Causes of Faecal Incontinence

Trauma	**Neurological**
Obstetric	Spinal Cord Trauma
Iatrogenic	**Spina bifida**
Anal Stretch	Meningocele/myelomeningocele
Haemorrhoidectomy	
Sphincterotomy	Urogynaecological
Fistula Surgery	**Pelvic Organ Prolapse**
Colectomy, Pouch procedures	
Radical Prostatectomy	**Cognitive**
	Dementia, Stroke, Learning
Radiation Damage	
Anal, Prostate, Cervical Cancer	Degenerative
Direct effect on IAS	**IAS degeneration**
Radiation Proctitis	
	Medical
Congenital	Inflammatory Bowel Disease
Imperforate Anus	Diarrhoea predominant IBS
Anal Agenesis	Coeliac Disease
Hirschsprung's Disease	Diabetes Mellitus
	Multiple Sclerosis
Colorectal	Psychiatric Illness/behavourial
Rectal Prolapse	Debility/poor mobility
Prolapsing haemorrhoids	
Tumour	Gastrointestinal Stimulants
	Drugs – any that cause diarrhoea
	Foods (caffeine, Alcohol,

Causes of Faecal Incontinence, adapted from Chatoor et al., [135]. The commonest causes are in bold type. IAS – internal anal sphincter, IBS – irritable bowel syndrome.

Congenital malformations can cause FI such as rectal agenesis but a greater proportion of cases are acquired. Sphincter complex disruption from obstetric trauma of vaginal childbirth is the most common sphincter injury causing FI.

Vaginal delivery affects the entire pelvic floor. There is evidence of damage to the innervation [136], pelvic organ support [137], anal sphincter complex [84] and pelvic floor musculature. Given that the fetal head with an area of 70-100cm^2 must pass through the levator hiatus which measures 6-36cm^2 in nulliparous women it is not surprising [138]. In prospective studies, nearly 35% of primiparous women showed evidence of sphincter disruption following vaginal delivery [84, 139, 140]. Anal incontinence occurs in 6-9% of new mothers [141, 142] whereas new FI has been found to have a prevalence of 0.7-4% post-partum [143, 144]. Risk of developing FI increases with higher number of deliveries [145] and there is evidence of symptomatic improvement at 6 months post-partum [84]. Other important risk factors include forceps delivery, prolonged second stage of labour, large birth weight and occipito-posterior presentation [83, 146]. Perineal tears, even when carefully repaired can be associated with FI and patients may either present immediately or several years following delivery [140]. Traction injury to the pudendal nerve commonly accompanies obstetric sphincter laceration and contributes to FI [147]. Pudendal neuropathy is thought to be caused by descent of the pelvic floor which stretches the nerve as it exits Alcock's canal denervating its target muscles. This may be the same pathophysiologal process seen in FI due to rectal prolapse [148], chronic straining [149, 150] and pelvic floor descent [150].

Other anatomical defects can be caused by anorectal surgery and trauma from impalement or pelvic fractures; they account for much of the FI seen in men. The following anorectal operations have been shown to cause FI:

1. Lateral internal sphincterotomy [151, 152],
2. Fistulotomy [152]
3. Haemorrhoidectomy [153]
4. Anal Dilation (Lord's Stretch) [154]
5. Sphincter sparing colorectal resections (because of the loss of the rectum and stretching of the sphincter complex during surgery) [155, 156].

Faecal impaction can cause overflow incontinence particularly in older people and those living in institutions. Many patients with dementia are also incontinent because of a lack of interest in or awareness of bowel function. Abnormal gastrointestinal function such as in inflammatory bowel disease can also cause FI, often due to excessive stool volume and frequency which can overwhelm the pelvic floor.

Scoring Systems

In an aim to quantify the severity and impact of FI on QOL many scoring systems and questionnaire have been developed (see Table 2 for a brief summary of some commonly used tools). As discussed earlier the main effects of FI (allowing for the socioeconomic and medical impact), are on QOL. Qualifying the success or failure of an intervention therefore requires data on whether a patient's QOL has improved or not. Gathering such robust data is difficult, reflected by the plethora of tools available.

Table 2 Scoring Systems used in Faecal Incontinence

Measurement of Severity in FI	Measurement of QOL in FI
Pescatori Score [157]	Rockwood (Faecal Incontinence Quality of life score or FIQL Score) [158]
Jorge-Wexner Score [159]	Manchester Health Questionnaire (MHQ) [160]
Rockwood (Faecal Incontinence Severity Index or FISI) [161]	Gastrointestinal Quality of life Index (GIQLI) [162]
Vaizey Severity Score [163]	

A Selection of common Scoring Systems used in Faecal Incontinence

Tools that assess the impact of FI are separated into those that measure severity and those that measure QOL because the two do not necessarily correlate.

The symptom of severity is scored by assessing frequency and type of incontinence, the extent of lifestyle change and the use of pads and anti-diarrhoeal medication such as the Vaizey incontinence score (Table 3) [163]. In 2004 Madoff and colleagues [126] discussed the problems that needed to be resolved before an ideal severity scoring system could be developed. The issues are similar to those faced when trying to study prevalence;

- The definition of incontinence must be standardised,
- The optimum method of data collection must be decided (diary v patient recall),

    - One would logically conclude that the prospective daily bowel diary to be a more stringent method in comparison to patient recall. However the diary method is limited by the confounding factor that the most severely affected patient can appear continent by refusing to venture from a nearby toilet, a situation seen frequently in our clinical practice.
- Need for data beyond type and frequency must be assessed,
- The assignment of numerical values to the combinations of type and frequency must be validated.

The Vaizey Score was found to have the best correlation with clinical impression and clinician assessment after definitive surgical treatment. It was also the score with the highest degree of change and highest level of significance. It is the severity score used in this thesis (Table 3) [163].

Table 3 Vaizey Severity Score

	Never	Rarely	Sometimes	Weekly	Daily
	No episodes in a 4 week period	1 episode in a 4 week period	1 or more episodes in a 4 weeks period but less than once a week	1 or more episodes per week but less than once a day	1 or more episodes per day
Do you ever leak solid stools?	***0***	***1***	***2***	***3***	***4***
Do you ever leak liquid stools but can hold onto solid stools?	***0***	***1***	***2***	***3***	***4***
Do you ever only leak gas but hold onto solid and liquid stools?	***0***	***1***	***2***	***3***	***4***
How often does your bowel leakage problem affect your lifestyle?	***0***	***1***	***2***	***3***	***4***
			No	**Yes**	
Do you need to wear a pad or plug?			***0***	***2***	
Do you need to take constipating medicines to make your stools firmer and more controllable?			***0***	***2***	
If you had the urge to open your bowels would you have had an accident if you could not reach a toilet within 15 minutes?			***0***	***4***	

The Vaizey Severity Score adapted from Vaizey et al., [163]. Add one score from each row; 0= perfect continence, maximum score 24=totally incontinent.

QOL scales are divided into 3 categories [164]:

1. Generic scales that permit the measurement of gross change and compare the experience of the target population to other populations. Such as the medical Outcomes Survey Short-Form (SF-36) [165].
2. Specialized scales are most useful in trying to isolate effects of specific variables. Such as the Hospital Anxiety and Depression Scale (HAD) [166].
3. Condition specific QOL scales measure the relationship between specific medical conditions or treatments and QOL (see Table 2, second column).

The first validated QOL tool developed specifically for FI was by Rockwood et al., in 2000 named the Faecal Incontinence Quality of life Score (FIQL) [158]. The tool was found to be reliable over time and able to discriminate between patient with FI and other gastrointestinal disturbances. Another commonly used and validated tool is the Manchester health Questionnaire (MHQ) [160].

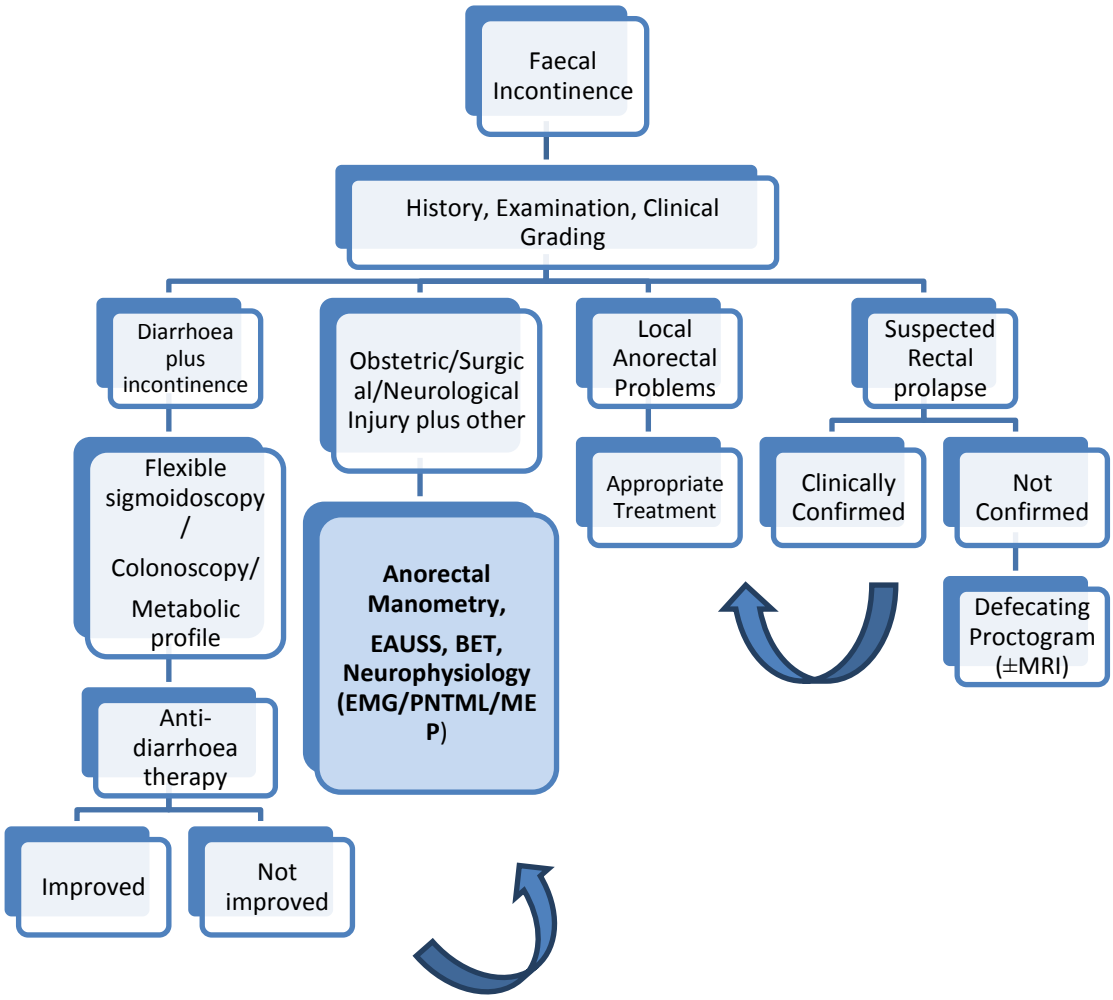
Finally descriptive measures are used but no summary scores are calculated making them difficult to use in research studies. The approach may be useful in population based research for example to determine the incidence or prevalence of FI (e.g. Mayo Clinic Faecal Incontinence Questionnaire [167]). A long and detailed review of all the different types of measurement in FI was published in 2003 by Baxter et al., who concluded that precious resources should not be invested in new measures unless a clear need is established, however QOL tools are an essential component in assessing new interventions [168].

Chapter 3 Anorectal Investigations

Investigations

Imaging and anorectal physiology are useful as diagnostic tools to analyse the magnitude of anatomic and physiologically defects. Often in the face of a normal physical examination tests such as EAUSS or a defecating proctogram are able to diagnose a sphincter defect or rectal prolapse that would otherwise remain occult. In one prospective study, history alone could detect an underlying cause in only 9 of 80 patients (11%) with FI whereas physiological tests revealed an abnormality in 44 patients (55%) [169]. Below is a suggested algorithm for the investigation of FI (Figure 9).

Figure 9 Algorithm for the investigation of Faecal Incontinence



Basic algorithm for the investigation of Faecal Incontinence. EAUSS – Endoanal Ultrasound Scan, BET – Balloon Expulsion Test, EMG – Electromyography, PNTML – Pudendal Nerve Terminal Motor latencies, MEP – Motor Evoked Potential. Adapted from Attaluri and Rao [170].

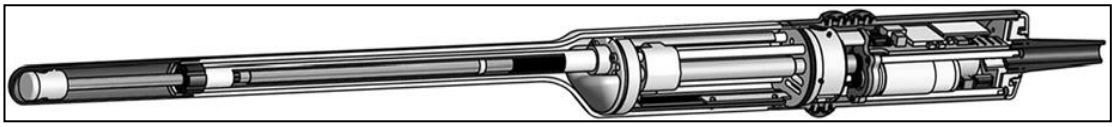
Imaging

There are many opinions on the diagnostic approach to the pelvic floor. The following assumes exclusion of serious pathology, such as cancer, by a combination of endoscopy (colonoscopy) and/or computer tomography (CT scan).

Endo-anal Ultrasound Scan

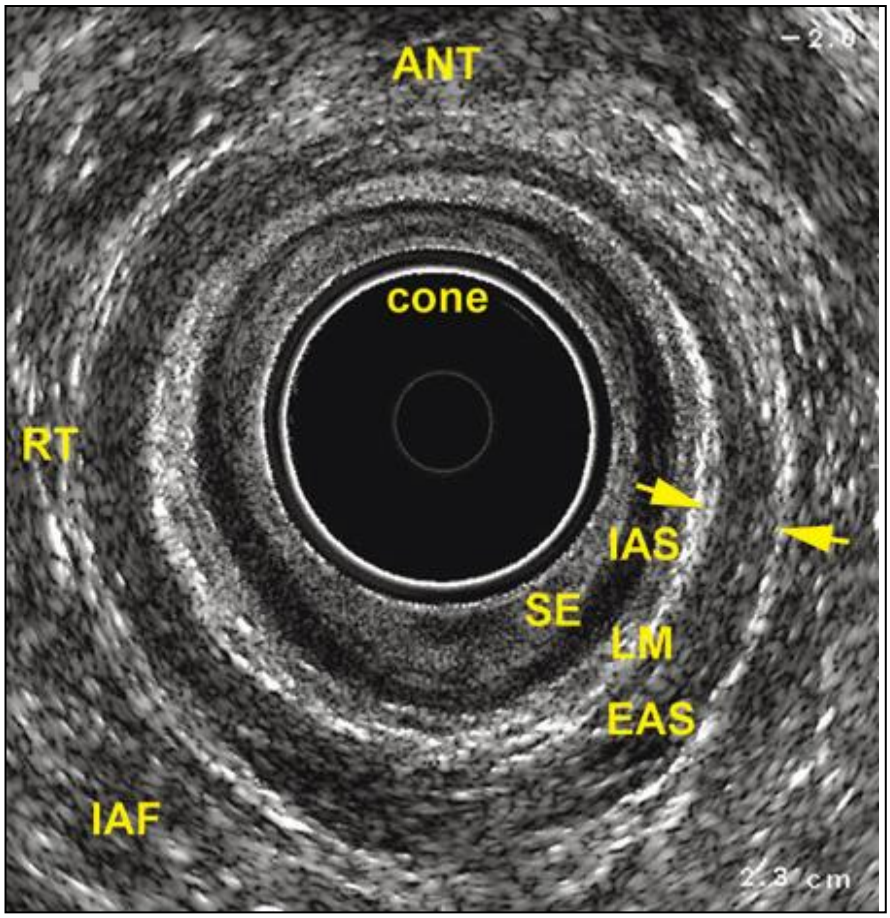
Since it was first described in 1989 [171] EAUSS has become a simple, rapid, cheap and widely available technique. EAUSS is now regarded as the gold standard for assessing anal sphincter pathology in the investigation of anal incontinence [172]. It permits accurate delineation of anal sphincter anatomy. Providing an assessment of the thickness and structural integrity of the EAS & IAS, it can also detect scarring and loss of muscle tissue [173]. 2D EAUSS is performed by using a 7-12mHz rotating transducer probe (Figure 10) with a focal length of 1-4cm [174, 175], providing a 360° axial view of the anal canal (see Figure 11 for normal 2D EAUSS anatomy). The patients are usually scanned in the left lateral position and the probe is inserted approximately 6cm into the anal canal. Figure 12 shows the 4 levels used during scanning to assess the cross sectional images of the puborectalis, longitudinal muscle, EAS, IAS and anal epithelium.

Figure 10 Endoanal Ultrasound Probe



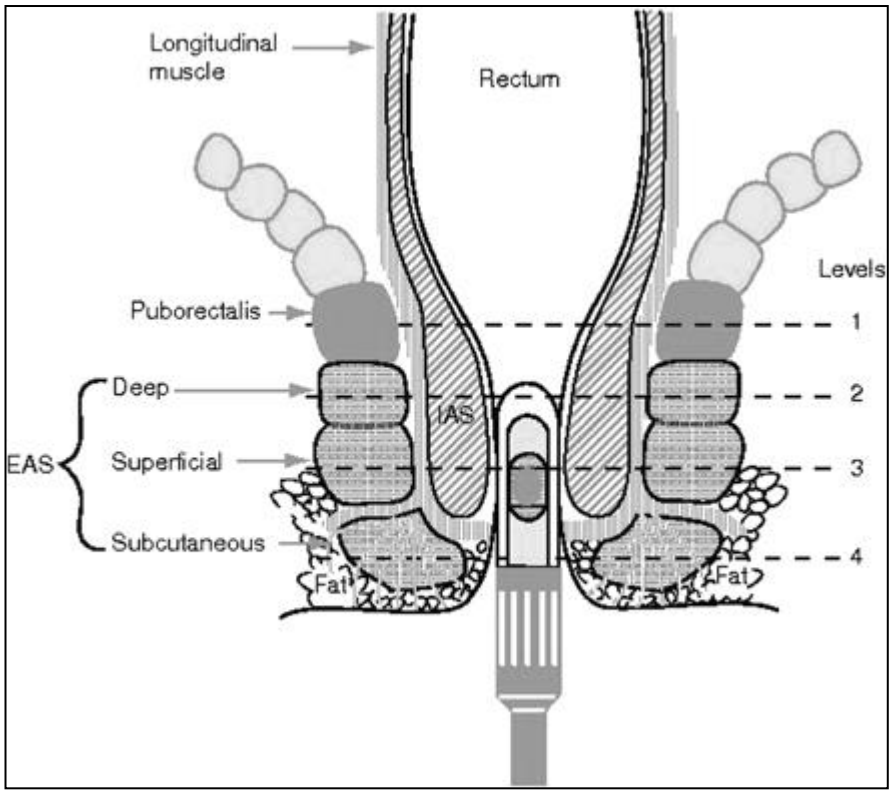
Example of a cut away 3D transducer probe from BK Medical 2050. Bartram 2008 [21].

Figure 11 Normal EAUSS orientation and anatomy



2D EAUSS showing normal orientation and anatomy. ANT - anterior, RT – right, IAF – ischioanal fossa, EAS – external anal sphincter, LM – longitudinal layer, IAS – internal anal sphincter, SE – subepithelial tissues, cone – 2 bright interface reflections are seen from the cone of the probe, Arrows – interface bright reflection seen between fascial planes (longitudinal layer/external sphincter and external sphincter/ischioanal fossa. The puborectalis is not shown at this level. Bartram 2008 [21].

Figure 12 EAUSS Schematic representation



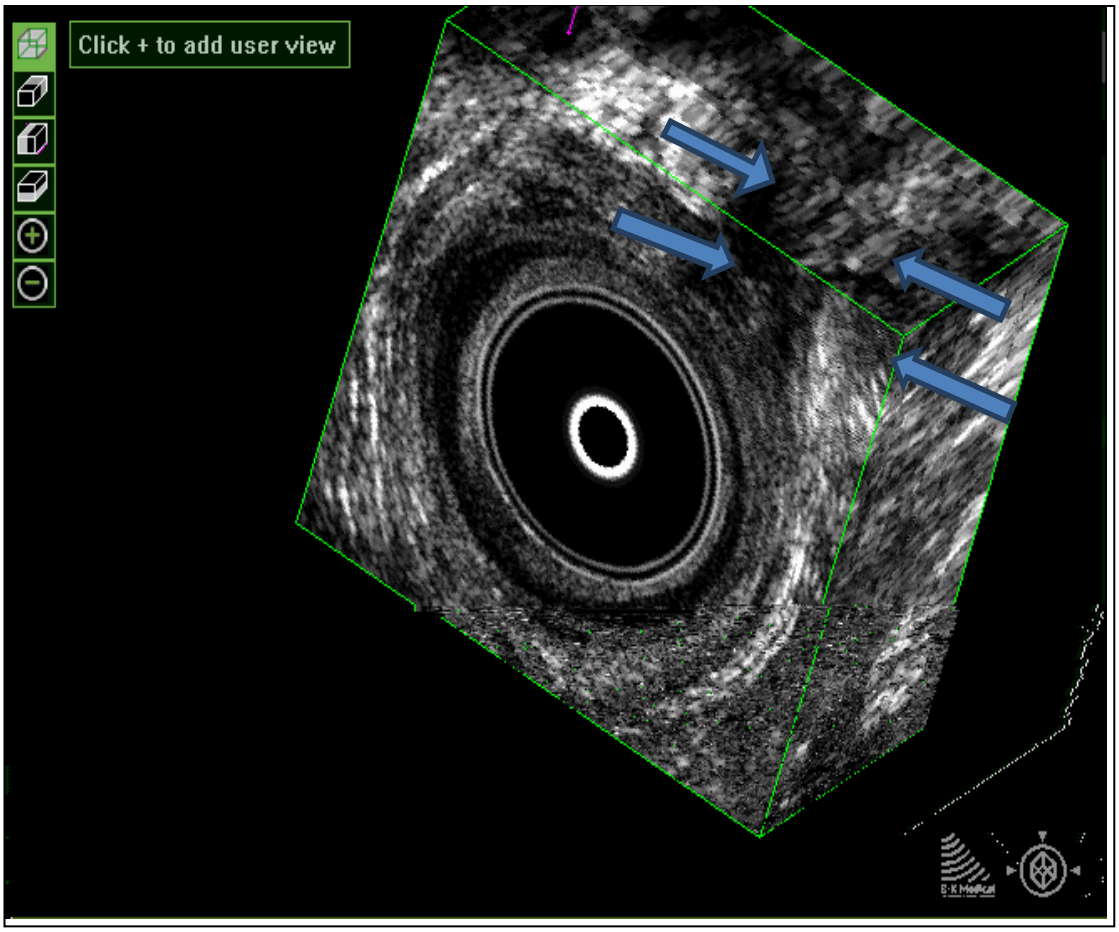
Schematic representation of the 4 levels of 2D EAUSS assessment with probe in situ. Level 1 Puborectalis, Level 2 Deep (proximal) EAS, Level 3 Superficial (mid) EAS, Level 4 Subcutaneous (distal) EAS note at this level the IAS is not seen. Abdool et al., [172].

EAUSS has sensitivity and specificity of almost 100% in identifying IAS and EAS defects [176] and has excellent intra-observer and inter-observer reliability [177]. Sphincter abnormalities are shown on EAUSS in up to 90% of women whose sole risk factor for FI is obstetric trauma, hence it is essential for complete assessment in FI parous women [126].

EAUSS has a central role in deciding suitability for surgery and with the recent advent of 3D EAUSS it has the potential it improve diagnostic capabilities further. It is thought that 3D EAUSS which was first described in 1999 [178] can show the radial and linear extent of injuries to the sphincter complex better and visualise the supporting structures such as the puborectalis, transverse perineii and puboanalis

clearer [179, 180]. As opposed to 2D static EAUSS, 3D EAUSS imaging allows volume measurement which may be displayed as multiplanner images (coronal, sagittal and axial) or tomographic which allows better visualisation of defects (Figure 13). Imaging has now evolved to 4D EAUSS which includes a time vector giving a dynamic assessment of the sphincter complex during manoeuvres such as valsalva; thus giving a real time view of pathology such as intussusception, normally requiring a proctogram to diagnose.

Figure 13 3D EAUSS cube



3D EAUSS cube demonstrating the planes (coronal, sagittal and axial) available for assessment and the circumference, width and length of an anal sphincter defect (blue arrows). Abdool et al., [172].

Magnetic resonance Imaging

There are many different MRI techniques that aim to delineate the pelvic and sphincter complex anatomy and function better, such as; endo-anal coil MRI, dynamic pelvic MRI and MRI colpocystography. The use of an endo-anal coil enhances the resolution and allows precise identification of sphincter muscle structural abnormality [181]. Endoanal MRI has also been shown in a small study to be superior in imaging the EAS [182]. A major contribution of anal MRI has been the recognition of EAS atrophy and how this can adversely affect surgical sphincter repair regardless of pudendal neuropathy [183, 184]. The advantages of MRI include lower dependency on the operator, a wider field of view and the ability to undertake dynamic studies. A study in 2000 by Malouf et al., showed that EAUSS & MRI have similar accuracy in diagnosing defects of the EAS but EAUSS is more accurate when diagnosing IAS injuries [185]. Comparative studies that assess cost, availability, technical know-how, clinical utility, and how MRI may influence treatment decisions are, however warranted [118].

Defecating Proctogram

Defecating proctogram, dynamic pelvicography, proctography, defaecography and evacuation proctography all mean the same thing! A defecating proctogram examines rectal emptying of a soft barium paste under fluoroscopy. Approximately 150mls of contrast material is placed into the rectum and the subject is asked to squeeze, cough and expel the contrast. It is of value in patients with constipation or ODS in whom the following problems are suspected; inappropriate contraction of the

puborectalis muscle, enterocele and anterior rectocele [97]. It is also used to assess parameters such as the ARA, pelvic floor descent and anal canal length.

Defecating proctograms have limited value in most incontinent patients. Its role in FI is to help diagnose occult rectal prolapse (or mucosal intussusception) or a poorly emptying rectocele which will usually result in seepage in comparison to true FI [126]. In one study defecating proctograms revealed abnormalities in 77% of subjects but there was no relationship between symptoms and abnormalities [173, 186]. Although it can detect a number of abnormalities these can also be seen with otherwise asymptomatic individuals and their presence correlates poorly with impaired rectal evacuation [187-189]. It also has the disadvantages of radiation exposure, embarrassment, inter-observer bias and inconsistent methodology [190]. Hence the AGA did not recommend defecating proctograms as an investigation of value in patients with FI [97].

Anorectal Physiology

Anorectal physiology continues to be the gold standard for defining sphincter function [135]. Table 4 shows an evidence based summary of the anorectal physiology tests available.

Anal Manometry

Manometry uses a microballoon, a water-perfused catheter, or a solid state transducer to measure the pressure within the rectum and anal canal. Anal manometry allows assessment of;

1. Resting pressure or tone
    a. Many terms have been used to refer to the same measurement e.g. Maximum basal pressure [191], resting anal canal pressure [192] and maximum sphincter pressure [193]. In this study I will use maximum resting pressure (MRP).
    b. MRP is defined as the highest resting pressure recorded above rectal pressure [194].
    c. Primarily a reflection of IAS function.
2. Voluntary squeeze pressure
    a. More commonly referred to as maximum squeeze pressure (MSP).
    b. MSP is defined as the pressure increment above resting pressure after voluntary squeeze contraction and is a calculated value that is the difference between maximum voluntary pressure and MRP at the same level of the anal canal [194].
    c. A reflection of EAS function.
3. Anal canal length
    a. Functional length or high pressure zone (see below).
4. Sphincter Muscle Fatigue (not commonly performed)
    a. The fatigability of the EAS is important in the ability to defer defecation. Manometry has been used to quantify EAS fatigue through a Fatigue Rate Index (FRI). It has been shown that the FRI is significantly shorter in incontinent patients compared with controls [195, 196].
5. Anorectal Reflexes
    a. Rectoanal inhibitory reflex (RAIR)

i. The RAIR is demonstrated by a drop in resting anal pressure in response to rectal distension by inflation of a rectal balloon.

b. Cough Reflex

i. Not commonly performed.

6. Anorectal Sensory testing (see below)

a. Rectal Sensation

i. Detects rectal hypersensitivity.

b. Rectal Compliance

Measurements are either taken with a simultaneous channel technique that records the pressure at sites along the catheter inside the anus simultaneously (stationary technique) or by using a station pull through technique. A rapid pull through technique also exists but can give falsely high sphincter pressures [97, 192]. In the station pull through technique (used in this thesis) measurements are taken along the length of the anal canal from proximal to distal at centimetre intervals [197]. At each centimetre interval a basal resting pressure is recorded and a voluntary squeeze pressure is recorded.

Normal values of both resting and squeeze pressures vary among patients; they are lower in women than men and in older patients of both sexes [192]. Due to this variation in pressures, the variation in methods of performing manometry, no agreed method of interpretation of results and no consistency in units of pressure used there are no defined normal ranges. Despite a general relationship that exists between sphincter pressure and continence, pressures vary substantially in continence and incontinence [198]. Furthermore, successful treatment of incontinence does not necessarily correct manometric abnormalities [126]. Therefore interpreting

manometry results and what is within the ‘normal range’ should be used with caution and in conjunction with a full clinical assessment and other anorectal investigations. Manometry has been found to be useful in assessing objective improvement following drug therapy [199], biofeedback therapy [200] and surgery [201].

Anal manometry is still the most widely used investigation in the assessment of the anal sphincters but has significant limitations. There seems to be considerable overlap between the values of anal manometry in continent and incontinent subjects [191, 202]. There is also inconsistency between the severity of incontinence and anal manometry. Some authors have shown a linear correlation with severity (a large study of 351 women noted a weak but positive correlation with MRP and FI severity index, but no correlation with MSP) and manometric variables [203], whereas others have shown no relationship including a recent study by Hornung et al., from this unit [204, 205].

Manometry and Anal Canal length

The length of the anal canal can be defined on manometry as the region where the resting pressures are at least 5mmHg higher than rectal pressure [97, 206]. Manometry can also be used to measure the functional anal canal or high pressure zone (HPZ). The HPZ can be defined as the length of the anal canal with resting pressures at least 30% higher than rectal pressure [194]. The HPZ has been found to be longer in continent individuals compared to patients with FI [207] and longer in men compared to women [208].

Anorectal Sensory Testing

Rectal balloon distension can be used to assess the sensory responses and the compliance of the rectal wall. By distending a balloon in the rectum with incremental volumes, it is possible to study the thresholds for first perception, a first desire to defecate or urgent need to defecate [193, 209]. A higher threshold for sensory perception suggests impaired rectal sensation [210]. Hypersensitivity (or a lower threshold for sensory perception) can be seen with inflammatory disorders, after irradiation, and with irritable bowel syndrome and can be associated with to urge incontinence [211].

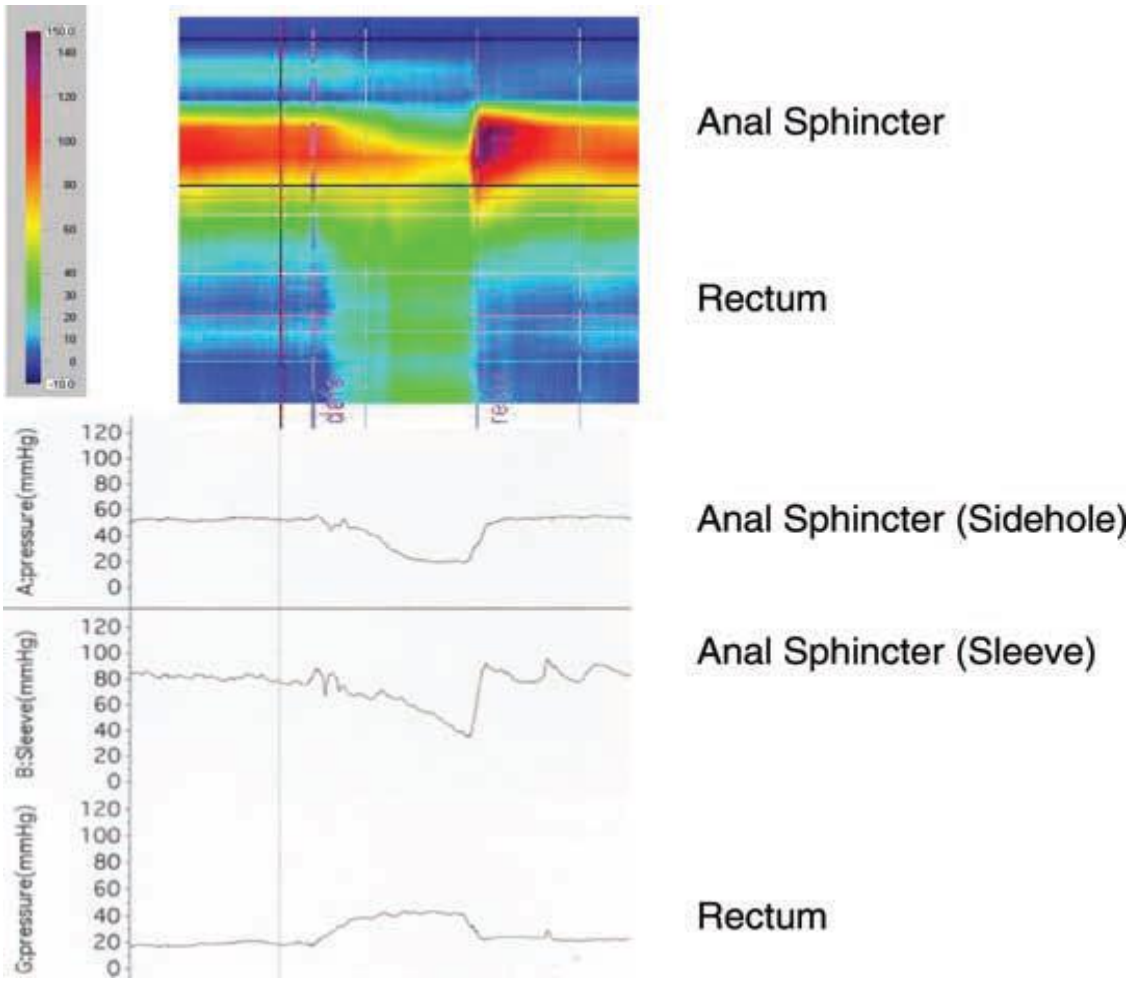
Rectal compliance can be calculated by assessing the changes in rectal pressure during balloon distension. Rectal compliance is reduced in patients with colitis [212] and in patients with low spinal cord lesions and in diabetics with incontinence [213, 214]. In contrast compliance is increased in high spinal cord lesions [215].

High Resolution Anorectal Manometry

High resolution manometry (HRM) is new in the assessment of the anorectum. It has primarily been used in the oesophagus where it has shown greater physiologic resolving power than standard manometry [216-218]. High resolution anorectal manometry (HRAM) provides greater physiologic resolution and minimizes movement artefact. It uses for example a 12 channel solid state catheter (Sierra Scientific Instruments, Los Angeles, CA), although other manufacterers exist. The 12 sensors are placed at 1cm intervals and each sensor sector has 12 radially dispersed sensing elements that are 2.5mm in length. Sector pressures (12 elements) are

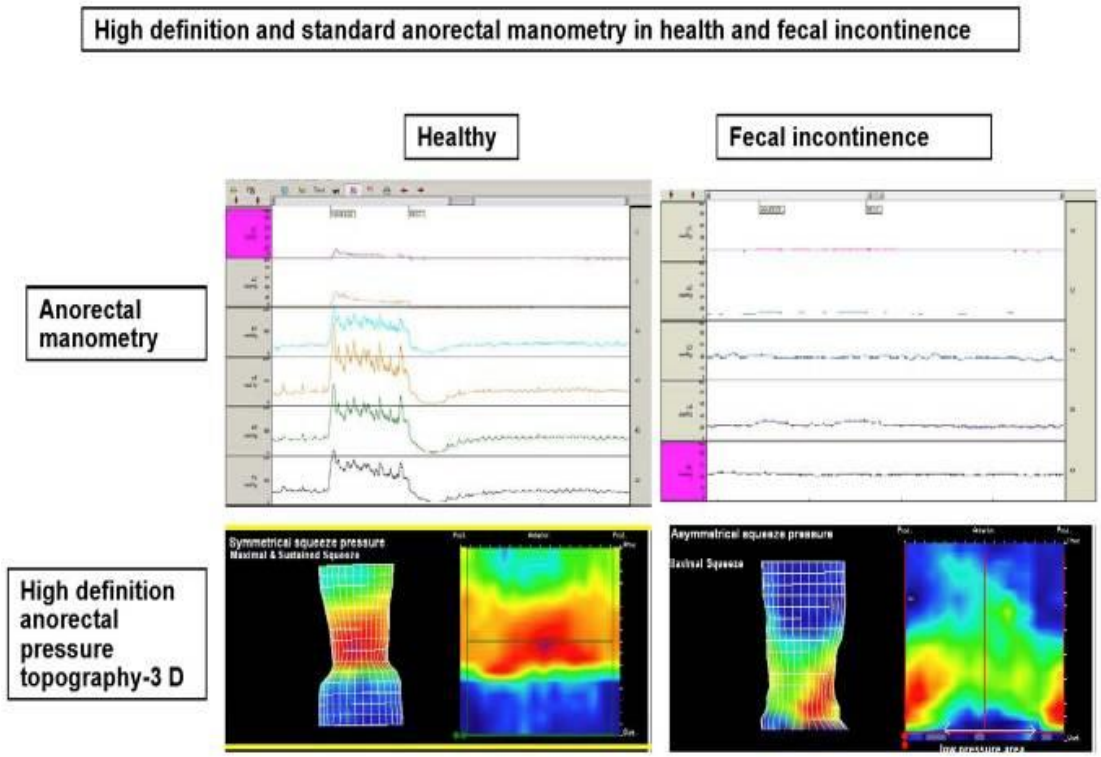
averaged within each of the 12 sensors making it circumferentially sensitive. The development of algorithms has given 3D topographical plots of intraluminal pressure events relative to time and location (Figure 14 & Figure 15). They can give a continuous dynamic representation of pressure changes displayed as a colour contour plot with the pressure magnitude indicated by colour intensity. The cooler colours represent lower pressure (blue) and warmer colours represent higher pressure (red). The first published study in 2007 by Jones et al., has demonstrated that HRAM highly correlated with water perfused manometry measurements and provided greater anatomic detail [219]. Further studies continue to be published in validating HRAM and generating normative data [220-222]. HRAM has the ability to standardise patient assessment allowing results to be transferable between institutions. A recent HRAM study by Ratuapli et al., has identified 3 phenotypes (high anal, low rectal and hybrid) that can discriminate among patients with normal and abnormal balloon expulsion time [223].

Figure 14 2D High Resolution Anorectal manometry versus Manometry



Comparison of 2D High Resolution Anorectal manometry (top panel) with a standard water perfused manometry sleeve system (bottom panel) during pseudodefecation. Showing appropriate increases in rectal pressure and decreases in anal sphincter pressures. Jones et al., [219].

Figure 15 3D High definition anorectal manometry versus manometry



Example of high definition anorectal manometry (HRAM) 3D topography in comparison to conventional anorectal manometry during rest and voluntary squeeze. Left – showing a normal increase in pressure during voluntary squeeze in a continent patient. Right – showing weak squeeze pressures in an incontinent patient. Rao [190].

Balloon Expulsion Test

The balloon expulsion test (BET) can identify patients with impaired evacuation and is often done in conjunction with manometry. Patients are asked to expel a balloon containing 50mls of warm water or an artificial silicon stool from the rectum [224]. The test is considered positive in the view of Dedeli et al., (i.e. the patient failed to expel the balloon) if not completed <30secs for men <40 years old, <60secs for men >40 years old and <60secs for women regardless of age [225]. Almost all normal subjects can successfully do this in the required time [193]. The BET has been seen to be useful in the diagnosis of dyssynergia in patients with faecal seepage and in the

elderly with FI due to impaction. Dyssynergia describes a condition where there is lack of coordination between the abdominal, pelvic floor and anal sphincter muscles during defecation [118]. The BET has 80– 90% specificity and 97% negative predictive value for identifying dyssynergia. Although it has a sensitivity of only 50%, it is a simple and useful screening procedure to identify patients who do not have dyssynergia [226].

Dyssynergia is similar to anismus which is defined as inappropriate contraction of the pelvic floor during attempted evacuation. However anismus is thought to be due to the paradoxical contraction of the puborectalis sling during defecation. A study in 1997 by Schouten from the Netherlands saw extremely poor agreement between the 3 tests (BET, EMG and defecating proctogram) used to diagnose anismus in patients with obstructive defecation syndrome (ODS), FI, constipation and controls [227]. They found that paradoxical contraction of puborectalis was not exclusively seen in patients with constipation or ODS and concluded by doubting the clinical significance of anismus.

Neurophysiology

It has been known for over fifty years that neurological injury can lead to dysfunction of the continence mechanism [71]. Electromyography and pudendal nerve terminal motor latency measurement can assess the neurophysiology of the pelvic floor, along with a new test called motor evoked potentials.

Electromyography

Electromyography (EMG) is seldom used in current clinical practice and has been superseded by the emergence of EAUSS [135]. EMG was performed for three reasons [97]:

1. To identify areas of sphincter injury by mapping the sphincter,
2. To determine whether the muscle contracts or relaxes,
3. To identify denervation-reinnervation potential indicative of nerve injury.

EMG can be performed using a needle electrode or surface electrode. Needle electrodes may be concentric (samples about 50 motor units) or single fibre (samples up to seven motor units). The number of motor units recruited during EMG squeeze assessment correlates with anal canal squeeze pressures [228]. Mapping of a sphincter injury with EMG agrees well with EAUSS [229] and longer motor action potentials in FI are thought to reflect neurogenic damage to the pudendal nerve [230, 231]. However EMG is not recommended by the American Gastroenterological Association (AGA) for evaluation in FI [97]. EMG findings have not been validated against histological evidence of damage. The severity of EMG changes has not been correlated with the magnitude of incontinence [232, 233]. EAUSS has been found to be more sensitive for sphincter injury when compared to surgical or histological data [176]. Plus EAUSS is less painful and therefore better tolerated by patients and able to map the entire length of the anal canal [229, 230]. EMG is still used in research and clinically in the evaluation of imperforate anus and in biofeedback training.

Concentric Needle EAS EMG

A motor unit (MU) is defined as one motor neuron and all of the muscle fibres it innervates. When a MU fires the impulse called an action potential (mV) is carried down the motor neuron to the neuromuscular junction or motor end plate. After the impulse has crossed the junction action potentials are elicited in all of the innervated muscle fibres of that particular motor unit. The sum of all of the action potentials is called the motor unit potential (MUP). The myoelectric activity of the muscle recorded is displayed on an oscilloscope at rest and with voluntary squeeze (Figure 17) [234].

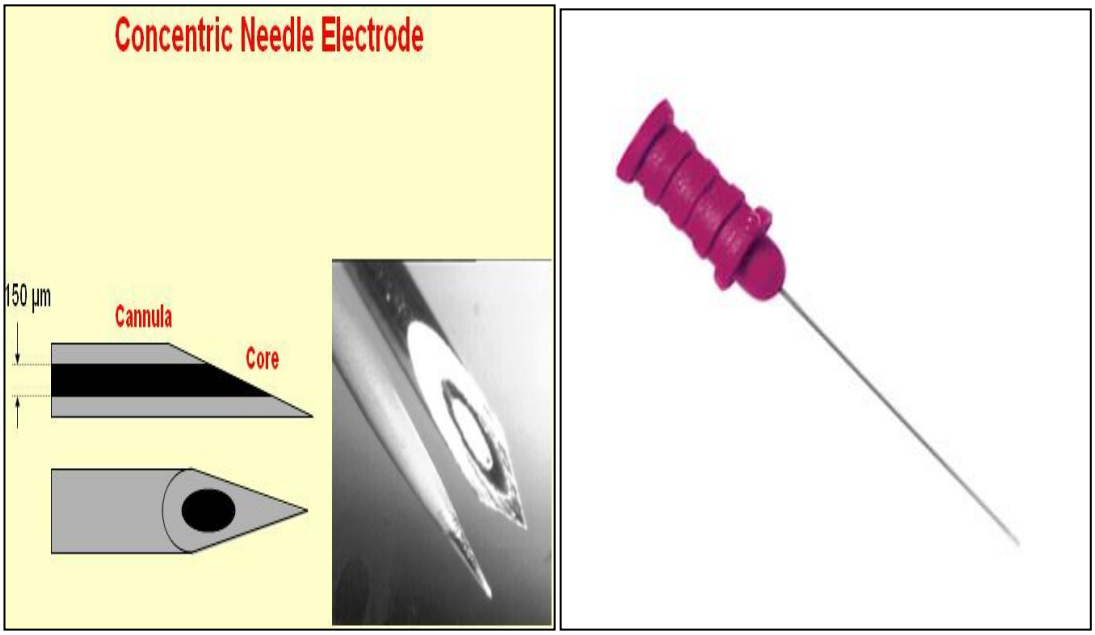
In this study I will be using concentric needle EMG in the EAS. This technique has been standardized by a group of Neurophysiologists from Slovenia in 1999 [235]. The patient will be in the lithotomy position due to the concurrent pudendal nerve block procedure and a ground electrode placed on the left thigh. A standard concentric needle EMG electrode (Figure 16) is inserted into the subcutaneous EAS with a shallow insertion (approx. 2-5mm under the mucosa), 10mm lateral to the anal orifice without anaesthesia. Due to how thin the subcutaneous EAS muscle is Podnar et al., [235] have advised a sharp angle of insertion relative to the mucosal surface for sampling motor unit potentials (MUP).

The superficial and deeper part of the EAS can be measured by needle insertion at the anal orifice at an angle nearly perpendicular to the mucosal surface slanted at about 30 degrees to the anal canal axis. Muscle will be found at a depth of 15-25mm. Bilateral examination of the anterior and posterior parts of the EAS muscle (i.e. 12, 3, 6 and 9 O'clock) provides adequate sampling. It is not possible to distinguish the

superficial and deep parts of the EAS muscle as advancing the needle electrode does not disclose any consistent 'silent' areas between them [235].

Sphincter muscles are distinguished from most other skeletal muscles by a proportion of continuously active [106] low threshold MU [235]. Podnar et al., 2002 have described a technique to quantify the continuous activity of the EAS during relaxation [236]. Using this technique where up to 6 MUP's are sampled by the computers algorithm (multi-MUP analysis [237, 238]) system at four sites in each part of the EAS (described above) giving quadruplets with scores of 0-6. The sum of these scores can then be used to calculate a percentage reduction in activity after nerve block. They found significant effects of gender (larger MUP counts in men) and EAS muscle part (larger MUP counts in the subcutaneous part) on MUP counts. The effect of the number of deliveries (decrease in MUP count with parity) was borderline significant [236].

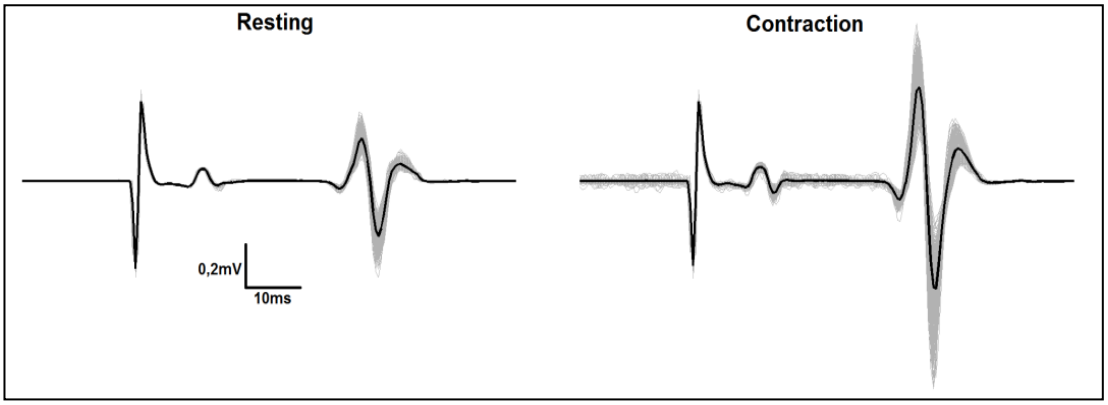
Figure 16 Concentric EMG needle



Left:Cross section of a concentric needle showing its conducting core and

surrounding cannula. Right: An example of an Ambu Neuroline Concentric EMG needle used in this study.

Figure 17 Electromyography trace



Example of a normal EAS EMG trace at rest and during contraction [234].

Pudendal Nerve Terminal Motor Latency Testing

Pudendal nerve terminal motor latency (PNTML) testing uses a disposable glove mounted intra-anal electrode (St Marks electrode, Dantec-Medtronic, Minneapolis MN) [239] to measure conduction time from stimulation of the nerve at the ischial spine to contraction of the EAS. It therefore measures the integrity between the terminal portion of the pudendal nerve and the anal sphincter. The latency measured reflects the function of the fastest conducting nerve fibres. An injury to the pudendal nerve leads to denervation of the anal sphincter muscles and muscle weakness, hence a prolonged PNTML suggests pudendal neuropathy and help distinguish muscle injury from nerve injury. Prolonged PNTML are associated with traction injury to the nerve as well as with primary neuropathies (e.g. diabetes) [126] and commonly associated with traumatic childbirth (prolonged second stage of labour or forceps delivery) [240, 241]. As PNTML measures only the fastest conducting fibres in the

pudendal nerve even in a damaged nerve the test may still be normal as long as some fast-conducting fibres remain [97].

The AGA did not recommend PNTML for the evaluation of FI because it poorly correlated with clinical symptoms and histological findings, it did not discriminate muscle weakness caused by nerve injury or muscle injury, it had poor sensitivity and specificity, it was operator dependant and did not predict surgical outcome [118]. However 2 reviews reported that patients with pudendal neuropathy generally have poor surgical outcome when compared to those without neuropathy [186, 242]. Hence although not recommended by the AGA, some experts suggest that PNTML may facilitate selection of patients prior to sphincter repair [186].

Motor Evoked Potentials

Motor evoked potentials (MEPs) are a novel way of assessing the entire spino-anorectal pathway. It involves using magnets placed over the lumbar and sacral regions which induced a MEP that is recorded via a probe with electrodes in the rectum and anus. Studies have shown that trans-lumbar MEP and trans-sacral MEP of the rectum and anus provide better delineation of the peripheral neuromuscular injury in subjects with faecal incontinence and those with spinal cord injury and is superior to PNTML [190, 243-245].

The author is aware that new anorectal physiology tests are currently under investigation including the Endoflip system (Crospon Ltd, Galway, UK), however they are not within the scope of this thesis [246].

Table 4 Evidence-based summary for tests in faecal incontinence.

Test	Clinical Utility		Evidence	Recommendation (Grade)	Comments
	Strengths	**Weaknesses**			
Physiologic Tests					
Anorectal Manometry	Quantifies sphincter pressures, rectal sensation & compliance & recto-anal reflexes	Lack of standardization	Good	B2	Widely used. Facilitates diagnosis of incontinence and dyssynergic defecation
Needle EMG	Quantifies Spike potentials and reinnervation pattern indicating neuropathy/myopathy	Invasive, painful, not widely available	Fair	B3	Only used in research labs
Surface EMG	Displays EMG activity and can provide information on normal or weak muscle tone	Inaccurate, Artifacts	Fair	B3	Largely used for Biofeedback
Pudendal Nerve Terminal Motor Latency	Measures latency of terminal portion of pudendal nerve, simple	Minimally invasive, low sensitivity, interobserver differences	Fair	B3	Conflicting recommendations
Translumbar & Transsacral Motor Evoked Potentials	Quantifies spino-anal and spino-rectal nerve conduction Minimally invasive,	Lack of Training & Controlled studies, Availability	Fair	B3	Promising Noninvasive objective test,

Evidence-based summary of the commonly performed physiologic diagnostic tests in faecal incontinence. Rao [190] and Remes-Troche et al., [247]. Recommendation Grades; Grade A1 - Excellent evidence in favour of the test based on high specificity, sensitivity, accuracy and positive predictive values. Grade B2 - Good evidence in favour of the test with some evidence on specificity, sensitivity, accuracy, and predictive values. Grade B3 - Fair evidence in favour of the test with some evidence on specificity, sensitivity, accuracy, and predictive values. Grade C - Poor evidence in favour of the test with some evidence on specificity, sensitivity, accuracy, and predictive values.

Chapter 4 Acoustic Reflectometry

What is Acoustic Reflectometry?

Acoustic Reflectometry is a technique that uses sound waves to measure cross sectional area of a cavity. Acoustic Reflectometry is not to be confused with the similar urethral pressure reflectometry (UPR) or anal acoustic reflectometry (AAR) both of which will be discussed in detail in chapters to come.

History of Acoustic Reflectometry

Acoustic Reflectometry (AR) originates from seismology; the scientific study of earthquakes and the propagation of elastic waves through the earth. Reflection seismology (or seismic reflection) is a method of exploration geophysics that uses the principles of seismology to estimate the properties of the earth's subsurface from reflected seismic waves. The method requires a controlled seismic source of energy, such as dynamite. The reflected waves are measured at the earth's surface and can map out the different rock layers and composition of the earth's crust. The technique was developed for analysis and stratification of the earth's crust and used in the sixties in the search for oil [248].

In 1969 Ware and Aki developed a complex mathematical algorithm to understand the reflected pressure waves and subsequently produced an estimate of cross sectional area (CSA) [249]. Using this algorithm Sondhi & Gopinath in 1971 [250] described how AR could theoretically be used to determine vocal tract shape (an open non-collapsible biological tube in comparison to the collapsible anal canal).

This technique had the advantage that no prior knowledge regarding the area or length of the vocal tract was required. Jackson et al., used this theoretical technique in 1977 to measure airway geometry of excised dogs' lungs and proved it to be rapid, reproducible and non-invasive [251]. 10 years later Fredberg et al., were the first to use AR in humans and since then several human trials have demonstrated successful use in measurements of airways with a loud speaker as the sound wave source of energy [252]. Subsequently it was adapted for the use in the nasal cavity by Hilberg et al., [253].

Today because acoustic reflectometry is easy to perform, non-invasive and requires little patient co-operation is has been used clinically in diagnosing allergy, in infant rhinometry assessment, diagnosis of otitis media, endotracheal tube placement and sleep apnoea. All of these clinical uses have been in non-collapsible biological tubes until Klarskov and Lose (part of Danish research group of Urogynaecologists based in Herlev hospital just outside Copenhagen) adapted the technique for use in the urethra. They did this by adding a pressure pump and polyurethane bag allowing a collapsible tube to be investigated through its acoustic impulse response during inflation and deflation [254].

How Reflectometry works

A digital signal processor (DSP) produces wide band sound waves (100Hz - 16 kHz) which are transmitted into a polyurethane bag. A microphone (FG-3329, Knowles Electronics) measures the reflected sound waves from the bag within the tube under investigation. The reflected sound waves or acoustic impulse response depends upon the reflection coefficients which in turn depend on the impedance to sound of the

cavity walls. Acoustic impedance indicates how much sound pressure is generated by the vibration of molecules of a particular acoustic medium at a given frequency. In an acoustic plane wave field, changes in the acoustic impedances are caused by variations in the cross sectional area. Throughout acoustic reflectometry, all waves are assumed to be plane waves. In closed cavities this is a reasonable assumption. Applying the Ware Aki algorithm to the acoustic impulse response results in a calculation of the cross sectional area of the tube. The equipment described and optimised by Djupesland and Lyholm [255] and used by Klarskov measured approximately 20 cross sectional area profiles per second which was sufficient to determine more than 99% of the pressure changes during a cough. During Klarskov's original experiments they only used 10 cross sectional area measurements per second. Instead, they paired the cross sectional area profiles in order to reduce noise and increase accuracy of the examination.

Urethral Pressure Reflectometry (UPR)

Following adaption of the technique Klarskov and colleagues began to validate and improve the method for use in the urethra. They were particularly interested in investigating stress urinary incontinence (SUI) in women.

To put it in simple terms a patient becomes incontinent when the bladder pressure exceeds the urethral pressure. This assumption led many researchers to develop methods of measuring pressure in the urethra and the bladder. Most of these used a catheter base technique and most of which had significant methodological problems. The problems varied from large overlapping values between continent and SUI [256-

258], no association with severity [259-261], issues with the catheter changing the mechanical properties of the urethra [262], problems with test retest variation [258, 263] to a lack of standardisation [263].

The simple equation with a bladder pressure higher than the urethral pressure leading to incontinence is only true when urethral pressure is defined as, 'the fluid pressure needed to just open a closed (collapsed) urethra [264, 265].' However conventional methods all require the introduction of a probe into the urethra and hence opening of the lumen. This led Klarskov along with Steen Rasmussen (inventor of the reflectometry technique) and a group of engineers from a Danish company called Oticon to develop a catheter free method for simultaneous measurement of pressure and CSA in the female urethra based on AR. Therefore eliminating the artefacts and drawbacks of the previous techniques which all required a catheter in the urethral lumen during the examination.

Unfortunately the method that was developed required a catheter to create a closed space for the following reasons;

- To be able to create a pressure above the urethral pressure inside the PVC bag and thereby open the urethra,
- To enclose the reflectometry energy and thereby avoid dissemination of energy in order to optimise the result of the CSA measurement.

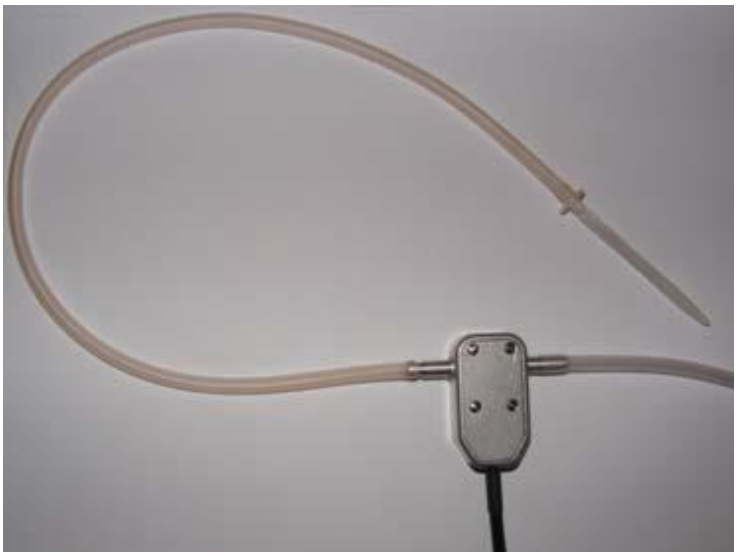
However the catheter used is a highly flexible polyurethane bag with a wall thickness of 0.025mm and diameter of 5mm, therefore minimising the distortion of the urethra. The highly flexible bag only occupies 0.4mm^2 and is therefore regarded as a catheter free technique. Also during reflectometry CSA measurements are taken every

millimetre along the entire length of the bag at the same time allowing a more accurate assessment of the high pressure zone [266]. The high-pressure zone (HPZ) of the urethra is defined as 'the position in the urethra where the CSA was smallest at a given pressure (Figure 19).' The same definition holds true in the anal canal where the HPZ is 'the point of minimal cross-sectional area and reflects the most functional part of the sphincter complex.'

Urethral Pressure Reflectometry Method (Stepwise technique)

The empty, thin, distensible polyurethane bag (Figure 18) is placed in the urethra and connected to a pump and an acoustic microphone transducer via a PVC tube. The polyurethane bag is inflated by pumping air into it in a stepwise manner. The cross sectional area within the bag, and thus the urethra, can then be measured every mm with acoustic reflectometry. The minimal measureable cross sectional area is 0.4 mm^2 and maximum cross sectional area is approximately 16 mm^2. Pressure within the bag can be applied and measured from 0 to 200 cmH_2O. In a similar stepwise manner the bag deflates to a pressure of zero.

Figure 18 AAR Polyurethane catheter

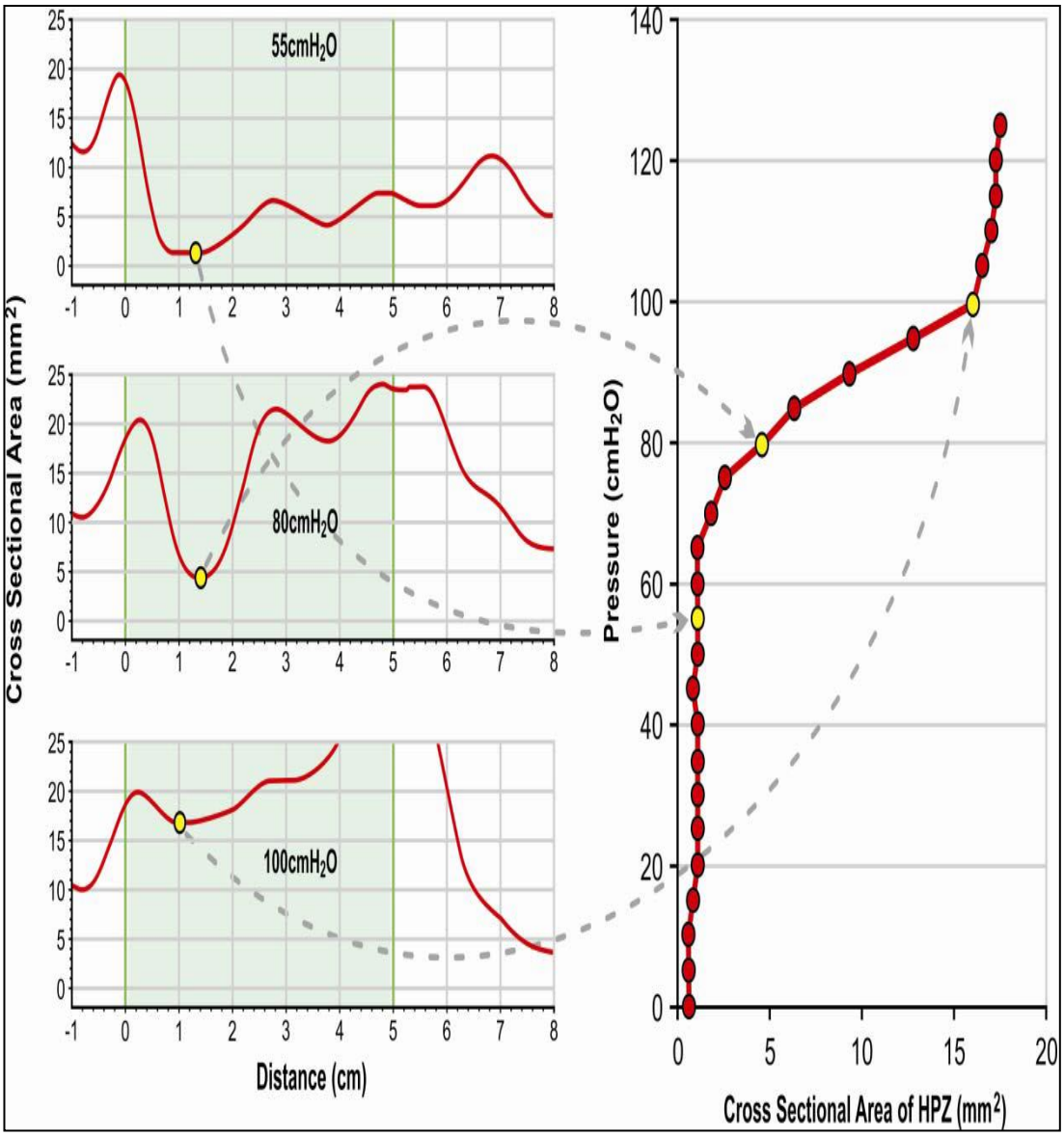


Polyurethane catheter bag attached via PVC tubing to a silver microphone transducer. Mitchell et al.,[267].

The patient is placed in the lithotomy position, and the bladder is emptied with a catheter (10F). The polyurethane bag is placed in the urethra using a Ch. 5 baby feeding tube as guide wire, and the PVC tube is anchored to the urethral meatus using a Duroderm® plaster. To ensure correct placement of the bag, it was inflated and deflated.

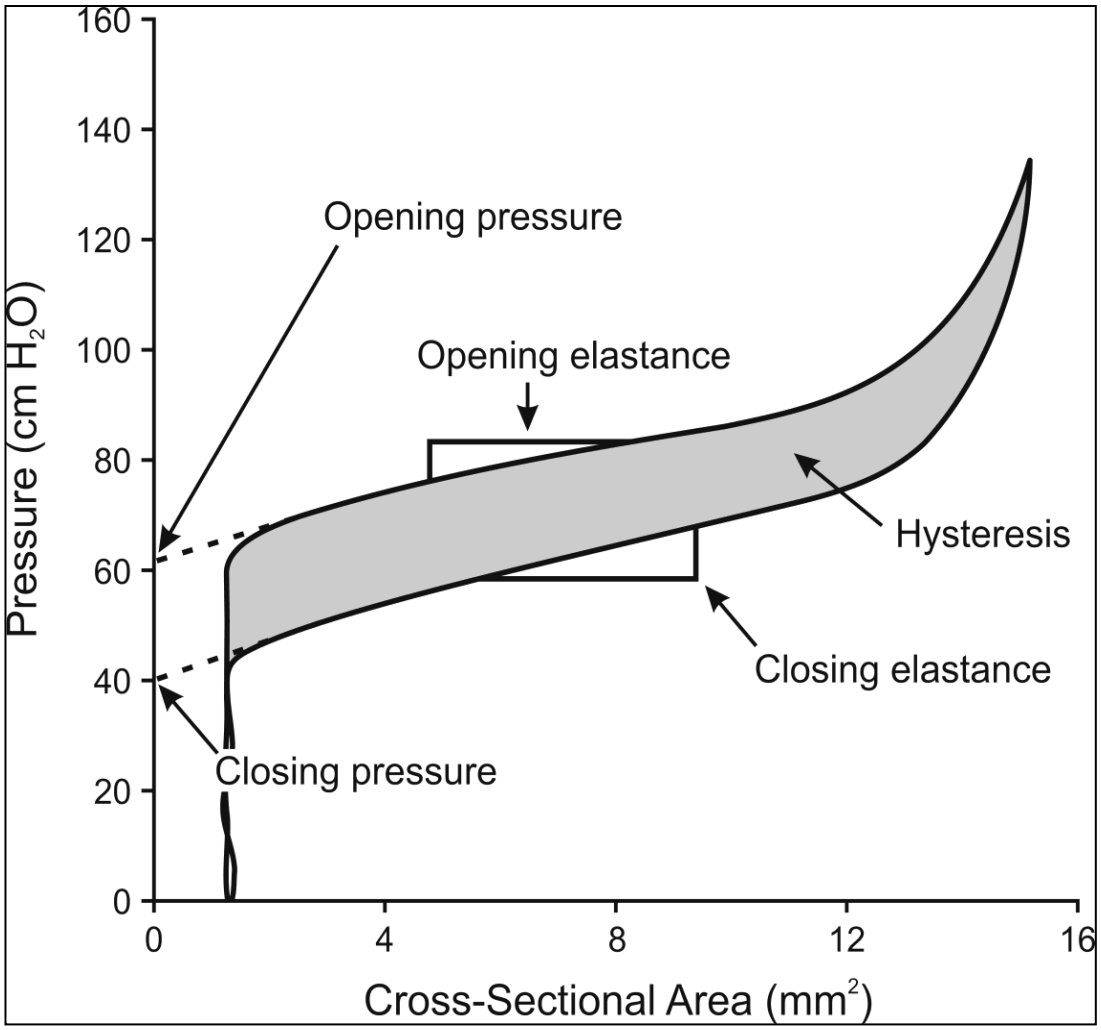
Measurements are conducted while resting and squeezing. All measurements are conducted twice and the average of each parameter is calculated. It is important to note that the pressure must be increased in steps as the cross sectional area cannot be measured while changing the pressure because the noise from the pump interferes with the reflectometry microphone measurement. CSA measurements from the HPZ of the urethra at each pressure level are then plotted on a graph (Figure 19). Analysis of this graph gives characteristic parameters (Figure 20).

Figure 19 Cross-sectional area vs. distance into the urethra



Graphs of cross-sectional area vs. distance into the urethra (left) are plotted initially for each pressure step. Values taken from the HPZ (yellow dots) are then plotted on a graph of pressure vs. cross-sectional area to produce a characteristic graph showing AAR parameters (Figure 20 below). Mitchell et al., [267].

Figure 20 UPR Opening and Closing graph



Pressure vs. area graph showing opening and closing traces and characteristic UPR parameters [267].

The opening and closing traces seen in Figure 20 enables the clinician to record five physiological parameters which describe the dynamics of the urethra. The opening pressure and closing pressure values reflect the pressure at which the urethra just starts to open/close. The opening elastance is calculated as the gradient of the opening trace and represents the resistance of the urethra to open, while the closing elastance is the gradient of the closing trace, and is an expression of the ability of the urethra to close against a pressure. Finally the hysteresis is represented by the difference between the areas below the inflating and deflating curves, and is an

expression of the amount of energy dissipated while inflating and deflating the bag and urethra [266]. These parameters are described below with reference to the anal canal and under the condition of squeeze.

Findings with Urethral Pressure Reflectometry

Klarskov et al., [254] found that during their in vitro studies that the cross sectional area behind a constriction was unreliable and therefore only the HPZ was evaluated in vivo.

Also it is important to note that the end of the plastic bag is very steep and therefore the measurements of the CSA from the last 1 cm of the plastic bag is not reliable. The error is due to a phenomenon known as ringing or the Gibbs phenomenon. Ringing is due to a spectral limitation of the signal [268]. The phenomenon was seen in vitro where halving of the cross sectional area within a shorter distance than 4 mm gave relatively large errors of the cross sectional area measurements around the halving. It was expected that ringing would only have a limited error during *in vivo* measurements in the urethra (or anal canal); due to the lack of rigid structures in the human body in comparison to in vitro experiments on acrylic models. However a rigid stricture might prove difficult to demonstrate correctly in vivo.

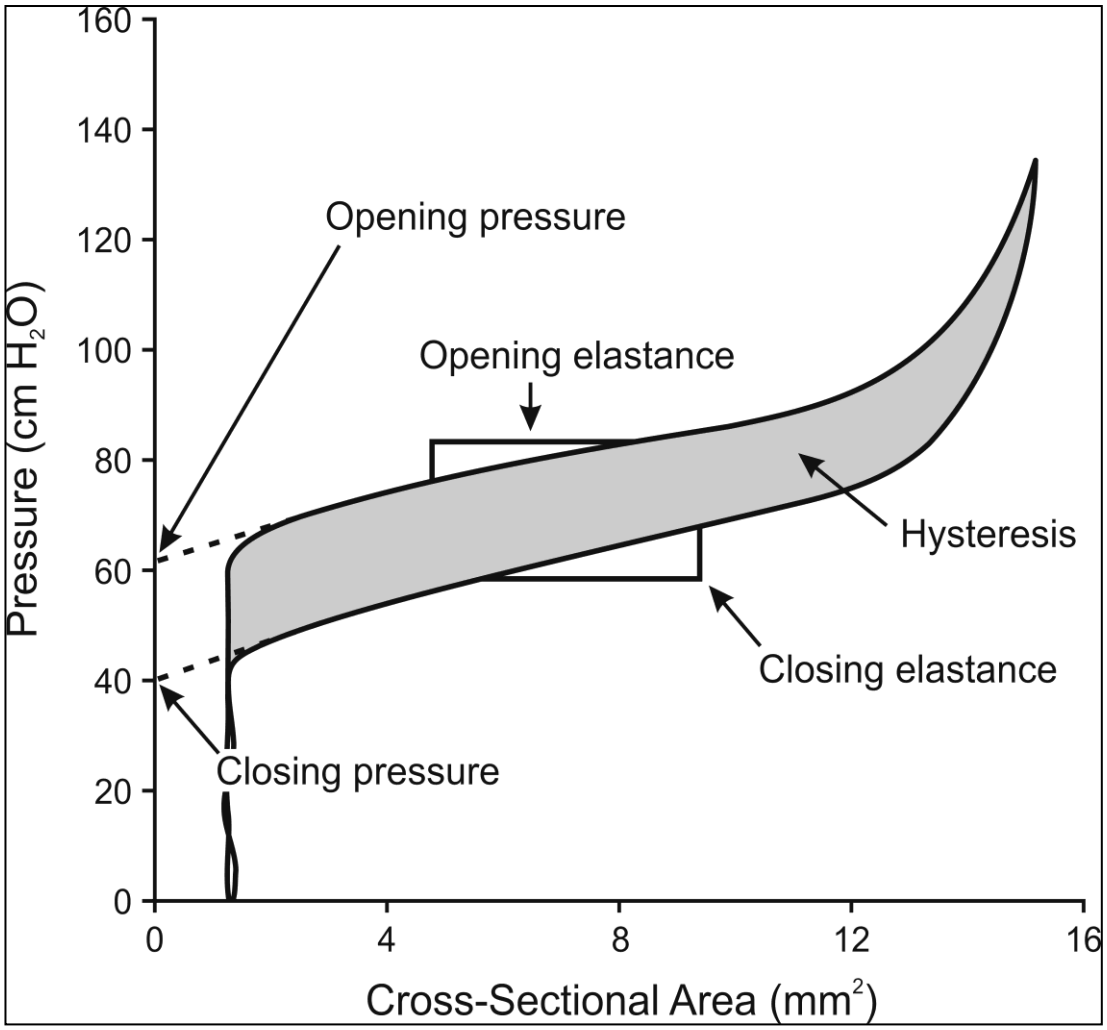
In vitro testing [254] of this technique has confirmed it is accurate and reliable [269] in measuring cross sectional area from 1cm–5cm within the cavity and at pressures from 10-200cmH_2O. The absolute error in measurement of the models did not exceed 1.2mm^2 (at pressures from 30-200cmH_20).

Klarskov and Lose went on to question the clinical significance of this new technique and compared it to standard urethral pressure profilometry in women. They found it to be equally accurate but reflectometry was more reproducible [269]. In a study published a year later they proved UPR was reliable and able to discriminate between continence and incontinence with more accuracy [270].

Anal Acoustic Reflectometry (AAR)

For 4 years pressure reflectometry has been used in the anal canal in the research setting. The stepwise method proposed by Klarskov and colleagues in 2008 [266] has been adapted by Mitchell et al., and published in 2010 [267] for use in the anal canal. The technique is called anal acoustic reflectometry (AAR). Performed in the left lateral position it measures 5 physiological parameters seen above in UPR;

Figure 21 AAR Opening and Closing graph



Pressure vs. area graph showing opening and closing traces and characteristic AAR parameters [267].

AAR Parameters

Opening Pressure (Op)

The pressure at which the anal canal just starts to open during assessment at rest, measured in cmH_2O. Functionally it represents the ability of the anal canal to remain closed against an increasing pressure. It is therefore a measurement of the closing forces from all the tissues and structures in and around the anal canal that contribute towards continence [271].

Closing Pressure (Cp)

The pressure at which the anal canal just starts to close during assessment at rest after an episode of dilation, measured in cm H_2O.

Opening Elastance (Oe)

Gradient of the opening curve during bag inflation represents the resistance of the anal canal to dilate after just starting to open during assessment at rest, measured in cm H_2O/mm^2.

The elastance is defined as the resistance of an object to deformation by an external force [272] and is the inverse of compliance. The opening elastance expresses the resistance against dilation, thus the lower the elastance the more the anal canal will open when the anal canal exceeds the opening pressure. Conversely a strong anal canal sphincter complex will have a high opening elastance.

Closing Elastance (Ce)

The gradient of the closing slope during bag deflation represents the ability of the anal canal to close down against a reducing pressure during assessment at rest, measured in cm H_2O/mm^2.

Hysteresis (Hy)

This represents the amount of energy dissipated during inflation and deflation of the bag and anal canal. It is the difference between the areas below the

inflation and deflation curves, given as a percentage in relation to the inflation curve. It is expressed as a percentage (Hysteresis % = (Opening Pressure at $10mm^2$ - Closing Pressure at $10mm^2$) divided by opening pressure at $10mm^2$ x 100).

Each type of fiber in the body has its own well defined hysteresis and the hysteresis may reveal different fiber compositions in different groups of patients. A high value of hysteresis could be an indication of fibrosis or scar tissue as collagen fibers have a greater hysteresis than elastin fibers [266].

These variables are calculated at rest and when the subject performs a squeeze at each pressure step, AAR can also be used to assess voluntary contraction of the anal sphincters. Two parameters are measured during voluntary contraction: squeeze opening pressure (SOP cmH_20) and squeeze opening elastance (SOE cmH_20):

Squeeze Opening Pressure (SOP)

The pressure at which the anal canal opens during an assessment of voluntary contraction, measured in cmH_2O. An expression of the maximal closure forces generated by the anal continence mechanism. AAR equipment can produced a maximum pressure of $200cmH_2O$, thus the maximum recordable SOP is also $200cmH_2O$.

Squeeze Opening Elastance (SOE)

Gradient of the opening slope during an assessment of voluntary contraction, measured in cm H_2O/mm^2. A further index of EAS function

AAR offers a number of advantages over manometry as discussed in the papers by Mitchell and colleagues [267, 271, 273];

1. The rigid manometry catheter distorts the anal canal in comparison to the completely collapsible and flexible AAR catheter which occupies an area of only 0.4mm^2 and is therefore considered a catheter free technique.
2. This also means that the anal canal is essentially closed the beginning of the test allowing assessment of the opening and closing function.
3. AAR offers a dynamic assessment of the opening and closing of the anal canal as the bag inflates and deflates. A process that occurs in normal defecation and not replicated in other tests such as manometry.
4. The catheter occupies the whole length of the anal canal allowing simultaneous assessment of cross sectional area and pressure over the complete length of the canal every millimetre. Hence an accurate measurement of the HPZ the most functional part of the sphincter complex.

Attempts at measuring simultaneous anal cross-sectional area and pressure during distension of the anal canal have previously been reported [274, 275]. These reports however were limited as they used the field gradient principle to measure cross-sectional area. The field gradient principle was first described by Harris et al., in 1971 [276] but meant that measurement was only possible at one particular point on the balloon and in Rasmussen's work the data presented with regard to the accuracy of this technique in measuring tubes of known cross-sectional area were very unclear [274]. The main disadvantage of this technique however is the inability to measure cross-sectional area simultaneously along the entire length of the anal canal. Cross-

sectional area measurements are made at one particular part of the anal canal and in Rasmussen's work this occurred at "the middle of the anal canal" [274]. There is no accurate way to check that the position of the probe is correct and recording the HPZ where the most active part of the anal sphincter complex resides. The advantage of AAR is that cross-sectional area measurements are taken simultaneously along the entire length of the anal canal at each pressure step. This ensures that data is recorded from the HPZ with more meaningful results.

Mitchell et al., reported the results of a comparative study in 2011 demonstrating that the new parameters of AAR have a reproducibility comparable to the parameters with manometry. All of the parameters had an acceptable mean difference in both studies of test-retest and interrater reliability. The repeatability coeffients were lower in AAR parameters compared with manometry equivalents during the study of test-retest reliability, although overall, neither AAR nor manometry had a superior reproducibility when compared with each other [271].

Following this work Mitchell assessed 81 continent patients with AAR and found that age negatively correlated with values for opening pressure and opening and closing elastance in males and with values for opening and closing pressure in females. No significant difference was found between the sexes in the resting AAR parameters; however males had a significantly greater squeeze opening pressure compared to females [277].

An age and sex matched study involving 100 subjects (50 faecally incontinent and 50 continent women) was performed by Mitchell and colleagues and published in 2012 to assess whether the measured parameters were clinically sensitive [273]. They

found that Opening pressure (Op) was significantly reduced in faecally incontinent women; a similar finding was seen in the urethra of women with stress urinary incontinence (SUI) when compared to healthy controls [270]. Mitchell et al also compared Op with MRP and found Op to have a superior diagnostic accuracy after analysing ROC curves when discriminating between continent and incontinent subjects. The Cp was significantly reduced in the faecally incontinent group, not a surprising result as it represents the pressure at which tonic contractions of the IAS and EAS are able to occlude the canal lumen again. This is a function that is poor in patients with faecal incontinence due to weak anal sphincter musculature. Hysteresis was significantly greater in faecally incontinent women. Interestingly this finding was not mirrored in the urethra of women with SUI [270]. Histological studies of the EAS and IAS composition in both continent and FI subjects have found a reduction in the number of muscle fibers and an increase in fat, fibrous, and collagen deposition in the muscles of incontinent subjects [104, 278]. Because of these compositional changes such incontinent subjects may have a more inefficient functioning of their anal canal musculature, resulting in a greater dissipation of energy and higher hysteresis. This has lead the authors to hypothesise that the parameter of hysteresis may provide an assessment of the composition of the anal sphincter muscles, however concluding that further AAR and histological correlation work would need to be performed. When discussing SqOp and SqOe the authors advised a degree of caution. Both SqOp and SqOe represent a measurement of the voluntary function of the EAS. Hence an effort dependant measurement, however it does appear that SqOp is a clinically valid parameter with measurements being significantly reduced in the FI subjects. The authors continued to explain that measurements made when the subject is asked to squeeze will not only reflect the function of the EAS, but also the degree of connective tissue and volume of the IAS

that will need to be compressed to transmit a pressure on the measuring device. When SqOp was compared with MSP in its ability to discriminate between continent and incontinent individuals, neither parameter was found to be superior.

Work into AAR continued, and Hornung et al., found that unlike anal manometry AAR measurements correlated with severity of incontinence. Reporting that as the Vaizey incontinence severity score increased AAR parameters significantly decreased (Op/Oe/Cp/SqOp) [204]. The authors also reported that AAR could discriminate between patterns of FI (urge, passive and mixed FI) unlike manometry. In the work by Hornung and colleagues manometry and AAR were unable to distinguish between women with and without anal sphincter defects. The only AAR variable that showed a significant difference between women with a sphincter defect and those without was hysteresis. This was possibly explained by a defect in the sphincter muscle leading to fibrosis and the deposition of collagen, which is known to have a higher hysteresis than muscle [273]. Hornung et al., concluded AAR to be more sensitive than manometry in assessing disease severity and more effective than anal manometry in detecting differences in anal sphincter function between symptomatic subgroups [204].

Neuromodulation is a treatment of FI whether in the form of sacral nerve stimulation (SNS) or posterior tibial nerve stimulation (PTNS) [279-282]. Percutaneous nerve evaluation (PNE) is a trial period to identify patients who are likely to have a successful result from the insertion of a permanent sacral nerve stimulator. A clinical study of 52 patients undergoing PNE, found that the AAR variable of Op was an independent predictor of success with PNE [283]. An Op of greater than 18.4cmH_2O

predicted success with a sensitivity of 0.81 and a specificity of 0.6. This was the first study to demonstrate a pre-operative measure of predictive value in the selection of patients for this expensive and invasive treatment option. Patients with a successful PNE had a higher Op, reflecting a greater ability of the anal canal to remain closed against an increasing pressure. The authors suggested that the patients with a higher Op are likely to respond successfully to SNS because their anal sphincter complex and surrounding connective tissues are functionally more robust. Although there appears to be good correlation between PNE and SNS stimulation outcomes [284] approximately 10% of patients who benefit from PNE do not have a good response after SNS implantation [285-287]. Hence, current work aims to follow this cohort to see if the prediction holds true for those patients implanted with a SNS. This will determine whether AAR can be successfully used to predict which patients will benefit in the long term from SNS. Clinical studies are also continuing into the application of AAR in the prediction of success from PTNS.

In as yet unpublished work Hornung [288] and colleagues recruited 25 continent men to a study to determine the relative contribution of the EAS and IAS to AAR parameters. The subjects were measured with AAR and manometry pre operatively, under general anaesthetic (GA) without neuromuscular block (NMB) and under GA with NMB. The NMB was achieved with Atracurium (Hameln Pharmaceuticals, UK) a competitive neuromuscular blocking agent that would completely paralyse the voluntary striated muscle of the EAS but not the SM of the IAS. The results were surprising. After GA a significant drop in Op, Cp and MRP was seen. After administration of the NMB agent a significant increase in Op was demonstrated. In a control group of 10 continent men under GA who did not receive a NMB agent but underwent sequential measurements with AAR and manometry these changes were

not replicated, suggesting that the differences were due to the NMB agent. The EAS after NMB is completely paralysed therefore the Op is predominately a measure of IAS function. Hence a marked increase in IAS function was observed when the EAS was paralysed. The mechanism by which the NMB caused modulation in the function of the IAS is unknown. A possible explanation for this finding could be that a spinal or enteric reflex mechanism exists that serves to increase IAS tone. Once the EAS is paralysed this reflex is triggered to increase IAS tone, thereby compensating for the reduction in resting pressure, with the resultant effect of increasing Op. Evidence already suggests that the resting EAS tone may be reliant on a spinal reflex arc and independent of higher cerebral control from studies of patients with tabes dorsalis and complete spinal cord transection above the 3rd lumbar segment [77, 106]. The authors concluded that the unexpected increase in Op following NMB requires further clarification, but suggest the presence of complex neuropharmacological and reflex mechanisms involved in maintaining resting and anal sphincter tone and anal continence.

AAR has also been used to study a distinct clinical sub-group of male patients with faecal leakage, who typically complain of leakage in the hours following defecation without symptoms of FI throughout the rest of the day. Sentovich et al., [289] defined faecal leakage as, 'the loss of stool, resulting in minor staining of underclothes.' Ano-rectal physiology studies are frequently normal in this group and most have structurally normal sphincters on EAUSS [290, 291]. In contradiction to these findings Sentovich et al., [289] found leakers to have significantly lower anal resting and squeeze pressures than the continent males, but higher pressures than incontinent males. The anal sphincter length was also found to be significantly longer in leakers compared with normal and incontinent men, a finding also observed by

Parellada et al., [292]. Sentovich proposed that in leakers the longer anal sphincter that generated an intermediate pressure allowed stool to become trapped in the anal canal only to leak thereafter. Despite disagreement within the literature and no consistent pathophysiological abnormality all agree that male faecal leakage appears to be a distinct clinical entity.

Hornung and colleagues in unpublished work [288] prospectively studied 15 age matched male patients with faecal leakage and compared them to 15 continent men using AAR and manometry. They found that male leakers had a significantly reduced Op and Cp ($p=0.003$ and $p=0.001$ respectively) compared to continent men. No difference was found with anal manometry. AAR appears to be sensitive enough to discriminate male leakers from continent men in contrast to anal manometry. The authors suggested a new hypothesis in contrast to the theories proposed by Sentovich and Parellada that in male leakers the ability of the anal canal to return to its closed form after defecation is impaired as shown by the reduced Cp. This together with the impaired resistance to dilatation resulting in lower Op results in leakage of stool.

We recognise that to date all AAR studies and data have come from one group. This is due to a lack of hardware. Only 3 AAR machines exist, 1 in Manchester, UK and 2 in Copenhagen, Denmark (for use in the urethra).Currently a new manufactuer has taken over the patents and is developing the hardware. Until this process has produced new hardware other units are unable to study AAR and contribute to the body of evidence.

This thesis aims to validate AAR against manometry and explore its physiological and clinical potential.

Section 2 Materials and Methods

Chapter 5 Methods

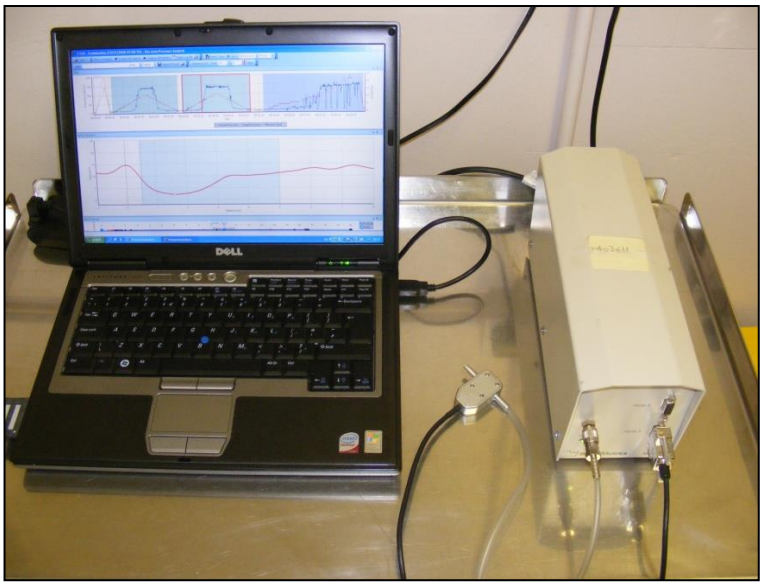
Method of performing AAR

Equipment

- Collapsible polyurethane bag (Oticon A/S, Copenhagen, Denmark)
- Acoustic reflectometry digital signal processor (wide band sounds 100Hz-16kHz) transmitter (ED-1932, Knowles Electronics Inc., Itasca, Il, USA)
- Rigid walled polyvinyl chloride (PVC) tubing 45cm long (inner/outer diameter 3.7/5.3mm ±0.3mm)
- Microphone (FG-3329, Knowles Electronics Inc., Itasca, Il, USA)
- Transducer (SX30DN, Sensym sensor system)

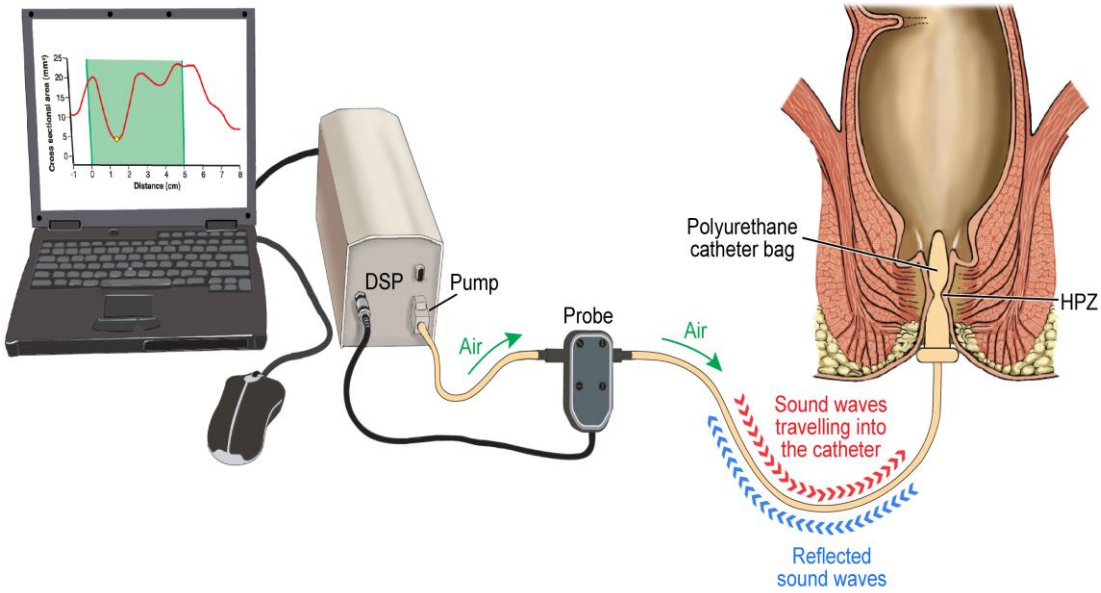
An example of the AAR system setup (Figure 22) and a schematic representation (Figure 23) can be seen below.

Figure 22 AAR equipment



Portable AAR equipment set up showing computer, digital signal transmitter (DSP) and pump and silver microphone transducer or probe [267].

Figure 23 Schematic representation of AAR setup



AAR setup – schematic representation. The probe contains a loudspeaker and a microphone to amplify the signal from the DSP and record the reflected sound waves. The graph shows distance into the anal canal in cm on the x axis v cross sectional area in mm^2 on the y axis, the green shaded area represents the zone of the anal canal under investigation. The yellow dot on the graph represents the HPZ of the sphincter complex. DSP digital signal processor, HPZ high pressure zone.

Performing Anal Acoustic Reflectometry

1. Patients are placed in the left lateral position (on their side). No bowel preparation is required.
2. A thin polyurethane bag (6cm in length, 0.025mm thick when collapsed and 5mm max diameter when inflated) is positioned within the anal canal with the aid of a narrow low friction introducer. A small amount of air is placed through the introducer, allowing its removal and ensuring the reflectometry bag remains in the correct position. The PVC tubing is attached to the sensor, and the pressure pump is activated to a level above 100cmH_2O in order to ensure that the system is recording correctly. Measurement then commences with the pressure pump slowly inflating the polyurethane bag from 0–120cmH_2O, before slowly deflating until it returns to its collapsed form. The pressure increases/decreases in a 5cmH_2O stepwise manner and at each pressure level, lasting three seconds, cross sectional area profiles of the anal canal are recorded. This resting assessment is repeated three times, before a voluntary contraction assessment when the patient squeezes at each pressure step. In assessments of voluntary contraction the bag inflates from 0 to 200 cmH_2O in intervals of 10cmH_2O. Participants perform one squeeze during each interval with a ten second rest. During resting assessments graphs of cross sectional area vs. pressure are plotted for the high pressure zone (HPZ). Five parameters at rest are therefore measured (opening and closing pressure, opening and closing elastance and hysteresis). Similarly, from the squeeze assessment a graph of area vs. pressure is plotted for the HPZ, allowing calculation of the squeeze opening pressure and squeeze opening elastance.

The other parameters are not measured during voluntary contraction as their assessment only occurs during inflation of the polyurethane bag.

3. The time to complete the test is 20 minutes.
4. The acoustic reflectometry balloons are sterilised in a Sterilox endoscopy sterilisation system after use. Previous work by Mitchell [277] has confirmed that, with repeated use and sterilisation, the acoustic reflectometry balloons remain accurate for up to a maximum of ten cycles. The balloons are therefore discarded after being used on ten occasions.

AAR learning curve

A period of handover from previous investigator to current investigator ensured the required level of expertise to perform AAR. Following this period a randomly selected group of patients from Hornung (2012) [288] were selected and re-analysed with the new investigator blinded to the results. Comparison to the prior analysis by Hornung (2012) showed minimal variation, thereby confirming accurate use of AAR for future studies.

Method of performing Manometry

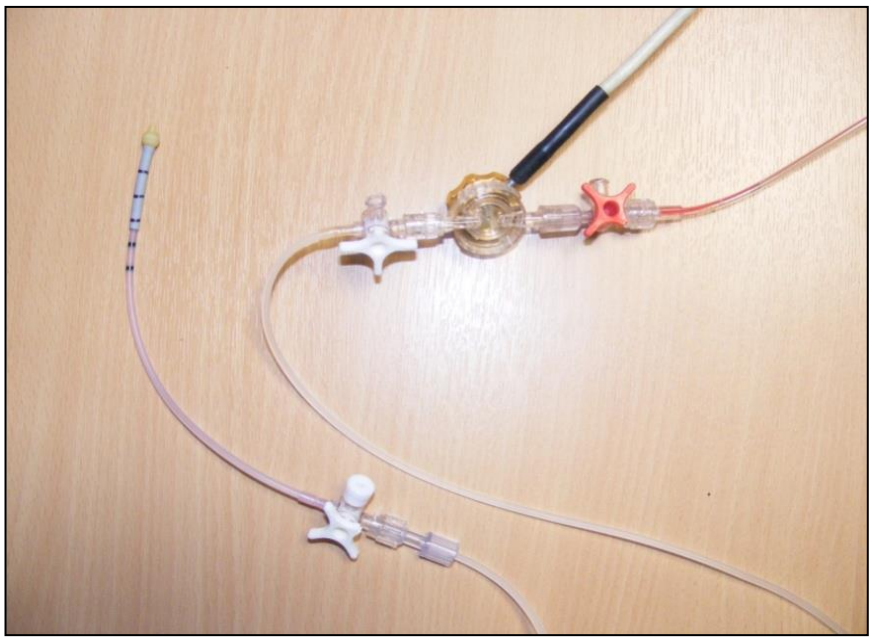
Equipment

- Balloons (Precision Dippings Marketing Ltd, UK)
- 'A-Line' tubing (Protect-A-Line, Vygon Ltd, UK)
- Heat shrink wrap
- Three-way luer lock tap (BD ConnectaTM, Sweden)
- Pressure transducer (SensoNOR840)
- DasyLab computer Software (DASYLab 'Data Acquisition System Laboratory' Version10.0, Adept Scientific UK).

Anal manometry was performed using a portable, closed water-filled system. The manometry balloons are disposable and were made by gluing a microballoon (Precision Dippings Marketing Ltd, UK) to the end of a 15cm length of 'A-Line' tubing (Protect-A-Line, Vygon Ltd, UK). A small piece of heat shrink wrap then covered the end of the tubing leaving just the microballoon visible. The manometry catheter was then marked with 1 cm graduated markings from the base of the balloon for a distance of 5 cm. The proximal end of the 'A-Line' tubing was then connected to a three-way luer lock tap (BD ConnectaTM, Sweden). The manometry catheter was then flushed through with water ensuring that all air bubbles were removed. The catheter was then connected to the manometry system incorporating the pressure transducer (SensoNOR840), ensuring that the entire circuit was water-filled and free of air bubbles. The transducer sent the signal through an amplifier to the computer. Analysis was performed using DasyLab computer Software (DASYLab 'Data Acquisition System Laboratory' Version10.0, Adept Scientific UK).

An example of the water filled manometry setup can be seen below (Figure 24).

Figure 24 Manometry catheter



Water perfused manometry catheter connected to a pressure transducer

Performing Manometry

1. The patient is positioned in the left lateral position and the equipment is zeroed with the micro-balloon held level with the anus. The micro-balloon (5mm thick) is inserted past the 5 cm marking and then withdrawn so that the 5 cm marking is level with the anal verge. The pressure is then recorded with the patient at rest first and while voluntarily contracting their EAS. Patients are given a standard instruction, to 'squeeze their bottom muscles as if trying to prevent opening their bowels'. This recording of both rest and squeeze pressure is then repeated at four, three, two and one centimetre levels into the anal canal ('station pullthrough' technique). From analysis of these five

interval readings, the patient's overall maximal resting pressure and maximal squeeze pressure are documented.

2. Calibration of the portable water filled system is performed at the bedside by raising the balloon to a known height, which should be equal to the pressure measured in cm H_2O.
3. Approximate time for the participant to complete the test will be 5 minutes.

Method of performing Electromyography (EMG)

Equipment

- Medtronic 4 channel portable EMG system (Medtronic A/S Denmark)
- Keypoint software portable suit XP edition (Medtronic A/S Denmark)
- Neuroline concentric needles 50x0.45mm (2”x26G) single use (Ambu A/S Denmark)
- Neuroline concentric cable (Ambu A/S Denmark)
- Neuroline ground single patient surface electrode (Ambu A/S Denmark)

An example of the EMG system used can be seen below (Figure 25).

Figure 25 Electromyography system.

Medtronic 4 channel portable EMG system.

Performing Electromyography

EMG method and analysis were independently verified by a consultant neurophysiologist.

1. The patient is in the lithotomy position (required to perform the nerve blocks).
2. The left thigh is electronically grounded using a disposable earthing pad.
3. A single concentric EMG needle is inserted into the EAS before the nerve block in the following positions;

a. Subcutaneous EAS at 12, 3, 6 and 9 o'clock, identified by standardized topography [235] 1cm from the anal orifice using a sharp angle of needle entry.
b. Superficial and deep EAS at 12, 3, 6 and 9 o'clock, at anal orifice. Advancing the needle to a depth of 1.5-2.5cm at a 30 degree angle to the anal canal axis.

4. The patient is then asked to squeeze their sphincter muscles and characteristic activity is observed confirming correct needle placement.
5. Once the needle position is confirmed the patient is asked to relax and measurement is delayed by 60 seconds to allow the trace to return to resting activating following the voluntary squeeze effort.
6. The patients are not asked to empty their bladder prior to measurement. This is because although a full bladder has been shown to influence the level of continuous activity [293], each patient in our study acts as their own control and data will be compare to themselves pre and post block with the same bladder volume.
7. Pre nerve block continuous activity during rest is recorded by multi MUP analysis present on the electromyography system [236].
8. Steps 4-7 are repeated for each insertion site detailed in step 3.
9. Patients then undergo bilateral pudendal nerve blocks as part of normal NHS practice by a Consultant Anaesthetist (see method below).
10. 5 minutes post nerve block activity is recorded again by repeating steps 3-8. Therefore resulting in EMG measurements from 4 quadrants of the subcutaneous and deep/superficial EAS pre and post block.
11. Percentage reduction or absence of EMG activity is then calculated after the nerve block.

Method of Performing a Pudendal Nerve Block

Transvaginal Bilateral Pudendal Nerve Block

Equipment

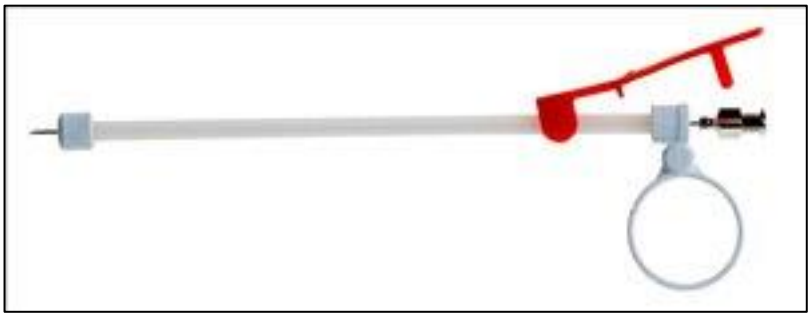
- R57040 Rocket Pudendal Block Needle (Rocket medical, Washington UK) (Figure 26)
- Mix the local anaesthetic and steroid solution into a total volume of 8mls;
    - Local anaesthetic – 6mls Lidocaine Hydrochloride 1% (Amdipharm Mercury Company Limited, London UK)
    - Corticosteroid – 80mg Triamcinolone acetonide (40mg/ml Kenalog, E.R. Squibb & Sons Limited, Middlesex UK).
- Nerve stimulator (Multistim Sensor, Pujunk Medical tech, Newcastle Upon Tyne UK)
- Sterile gloves

Transvaginal method

1. The patient is awake in the lithotomy position in theatre with monitoring in place (blood pressure cuff and oxygen saturation probe).
2. Administer analgesia and sedation; IV fentanyl (25mcg-50mcg) and IV midazolam (1-2mg), based on age, weight and perceived anxiety.
3. Aseptic technique using 0.2% aqueous chlorhexidine gluconate to clean the perineum.
4. A vaginal examination is performed, palpating the ischial spine with the index finger to locate Alcock's canal (containing the pudendal nerve & pudendal artery).

5. Confirm the point of maximal tenderness, the place where the patients' symptoms may be replicated by palpation.
6. To perform a left sided block, palpate the ischial spine with the index finger of the left hand, hold the syringe (Figure 26) in the right hand and guide the needle between the index and middle finger of the left hand toward the ischial spine.
7. Advance the needle through the vaginal mucosa at the point of maximal tenderness until it touches the sacrospinous ligament 1cm medial and posterior to the ischial spine.
8. Advance the needle further through the sacrospinous ligament for a distance of 1cm until a loss of resistance is detected. The needle tip now lies in the area of the pudendal nerve.
9. Aspirate the needle to ensure that the injection is not intravascular.
10. Inject 4mls (half) of the corticosteroid and local anaesthetic solution using the Rocket needle (used to limit the depth of penetration).
11. Repeat the method on the contralateral side to complete a bilateral block.

Figure 26 Pudendal nerve block needle



Rocket pudendal nerve block needle (Rocket medical,Washington UK).

Transgluteal Bilateral Pudendal Nerve Block

Equipment

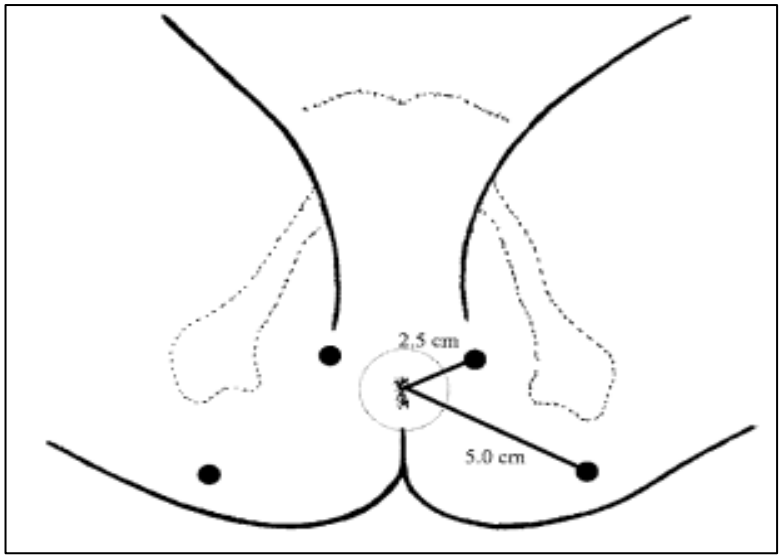
- 8mls Lidocaine Hydrochloride 1% (Amdipharm Mercury Company Limited, London UK) for local anaesthetic of the skin.
- Mix the local anaesthetic and steroid solution into a total volume of 22mls;
    - Local anaesthetic – 20mls Lidocaine Hydrochloride 0.5% (Amdipharm Mercury Company Limited, London UK)
    - Corticosteroid – 80mg Triamcinolone acetonide (40mg/ml Kenalog, E.R. Squibb & Sons Limited, Middlesex UK).
- 22 gauge 10cm and 5cm stimulating needle.
- Nerve stimulator (Multistim Sensor, Pujunk Medical tech, Newcastle Upon Tyne UK)
- Sterile gloves

Transgluteal Method

1. The patient is awake in the lithotomy position in theatre with monitoring in place (blood pressure cuff and oxygen saturation probe).
2. Administer analgesia and sedation; IV fentanyl (25mcg-50mcg) and IV midazolam (1-2mg), based on age, weight and perceived anxiety.
3. Aseptic technique using 0.2% aqueous chlorhexidine gluconate to clean the perineum.
4. Four separate injections sites are used as indicated in Figure 27.

5. Infiltrate each injection site with 2ml of 1% lignocaine to numb the area prior to nerve block.
6. At the posterior injection points in the 4 and 8 o'clock positions insert the stimulator needle and advance 7-10cm perpendicularly stimulating with a current of 2.5-5mA and 1Hz. In these positions the branches of the pudendal nerve; inferior rectal nerve and perineal branches will be visualized as ipsilateral contractions of the posterior parts of the anal sphincter.
7. Optimise the needle tip position by preserving muscle contraction while reducing the stimulating current to 0.5-0.6mA and then inject approximately 5.5mls of the local anaesthetic and steroid mix.
8. Repeat above method in the 2 and 10 o'clock positions but only advancing the needle to a depth of 4-5cm. The visual responses to nerve stimulation in these positions consist of contraction of the anterior parts of the ipsilateral anal sphincter and contraction of the transversalis perineum superficial muscle.

Figure 27 Landmarks for a transgluteal pudendal nerve block



Landmarks for the injection points of a transgluteal pudendal nerve block [294].

Method of performing Posterior Tibial Nerve Stimulation

Equipment

1. Urgent PC Neuromodulation System (Uroplasty Ltd., Manchester, UK).
    - 34 gauge needle electrode
    - Surface electrode
    - Lead wire
    - Hand held pulse generator powered by a 9V battery (adjustable current setting ranging from 0-9mA in preset 0.5mA increments, fixed pulse width of 200microseconds and fixed frequency of 20Hz).
    - Ethanol skin wipe

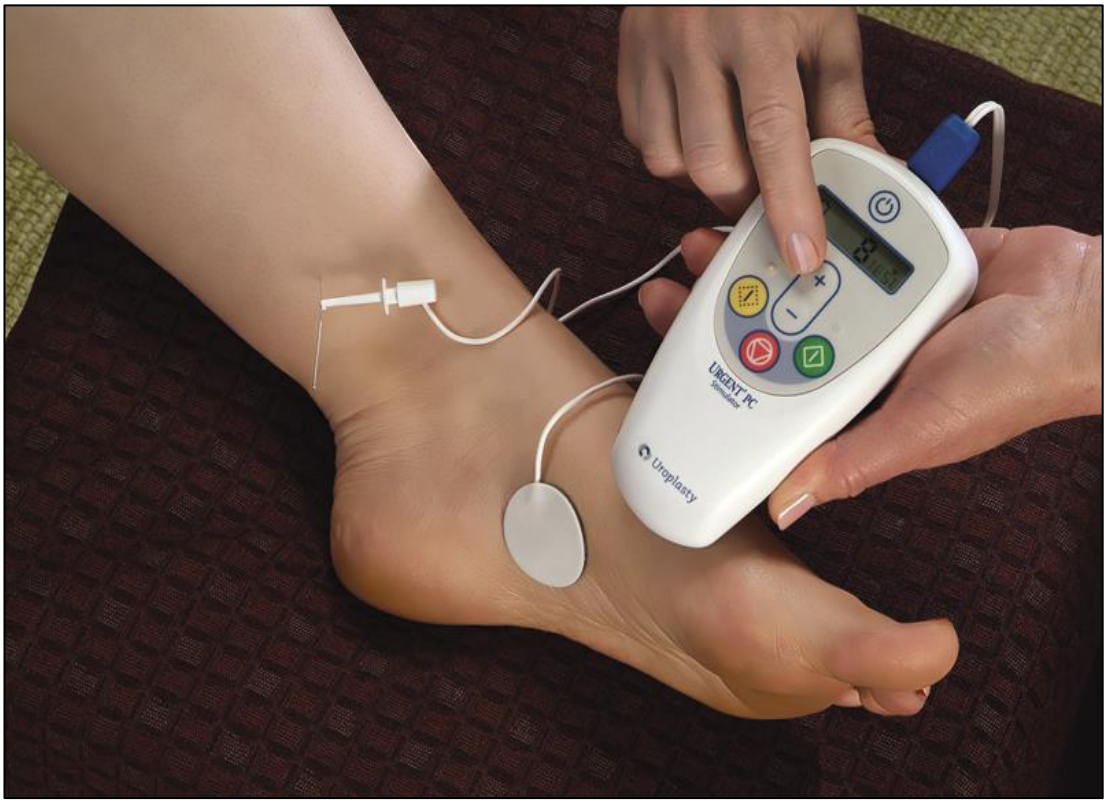
Performing Posterior Tibial Nerve Stimulation

The protocol for posterior tibial nerve stimulation (PTNS) has been described [295-297]. The following method has been based on these studies, manufacturer recommendation and NICE guidance (IPG395 May 2011).

1. The patient is in the sitting position in an outpatients department.
2. The right ankle is used unless contraindicated in which case the left ankle can be used.
3. Insert the needle electrode 5cm caphalad (approximately 3 finger breaths) to the medial malleolus and 2cm posterior (approximately 1 finger breath) to the tibia at a 60 degree angle to the skin and advance in a rotating motion approximately 2cm.

4. The surface electrode is attached to the medial aspect of the ipsilateral foot over the calcaneus.
5. Both electrodes are attached to the reusable stimulator that provides visual and auditory feedback.
6. Correct needle placement is confirmed by slowly increasing through the current increments until sensory and or motor responses are evident;
    - Motor: great toe flexion or extension of the entire foot.
    - Sensory: tingling sensation in the ball of the foot or toes.
7. After correct positioning (Figure 28) the stimulation is carried out for 30mins at the current that generated the optimal response. If correct placement is not elicited the needle is repositioned.

Figure 28 PTNS needle placement



Needle in place at the left ankle attached to the portable stimulator unit. Urgent ® PC neuromodulation system (Uroplasty Ltd., Manchester, UK).

Process

All patients received an invitation letter, patient information sheet and consent form prior to enrolment in one of the studies. All patients completed a Vaizey FI severity score questionnaire and a data collection proforma plus visual analogue scale of their experience (Appendix B).

The information recorded in the proforma was as follow;

- Demographics
    - Study ID, date of test, reason for test, DOB, age, sex, weight.
- Continence
    - Faecal incontinence, Urinary incontinence, normal continence.
- Type of Incontinence
    - Urge, passive, leakage, difficulty in defecation, difficulty in wiping.
- Gynaecology
    - Parity, No. of vaginal deliveries, No. of C-Sections, use of forceps, use of ventouse, obstetric injuries, previous gynaecology surgery.
- Previous surgery & bowel type & neuromodulation
    - Last bowel movement, Bristol stool chart, previous anorectal surgery, abdominal surgery, previous rubber band ligation.
- Previous anorectal physiology investigation results
    - Date, anal canal length, MRP, MSP, Rectal sensation (onset, call urgency), PNTML, EAUS, RAIR, BET.
- AAR results
    - AAR bag No., Op, Oe, Cp, Ce, Hy, SqOp, SqOe.
- Manometry results

- MRP, MSP.

Data above was recorded in an excel database and interrogated using SPSS Statistics version 20 software (IBM, Chicago, IL). Statistical advice was sought from Mrs Julie Morris (Head of Medical Statistics, UHSM).

Ethical approval

Ethical approval has been sought and granted from the Greater Manchester West Regional Ethics Committee (REC) for all studies as follows (appendix A);

- Anal Acoustic Reflectometry and Manometry. The order of data collection – **REC Reference Number 13/NW/0469, awarded 8th August 2013.**
- The effect of different filling rates in the anal canal on anal acoustic reflectometry parameter – **REC Reference Number 13/NW/0470, awarded 8th August 2013.**
- Investigation with anal acoustic reflectometry of the isolated internal anal sphincter using a regional nerve block – **REC Reference Number 13/NW/0237, awarded 21st May 2013.**

Section 3 Results

Chapter 6 AAR as a surrogate marker for anal canal length

Introduction

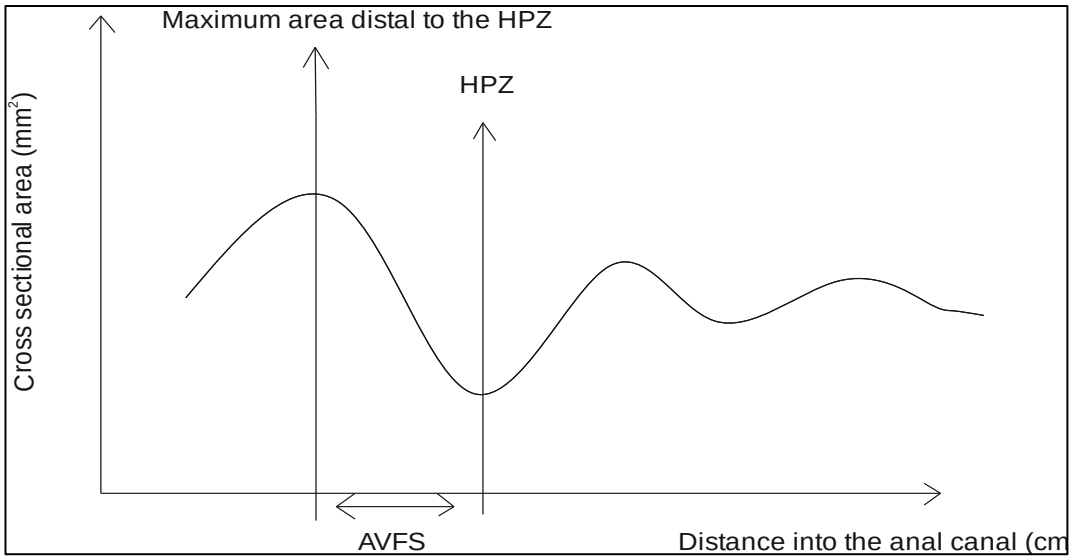
We know that there are differences in anal canal length between men and women [10]. It is also known that patients with FI have a shorter HPZ in comparison to continent patients [207]. The aim of this study was to determine whether AAR can measure the length of the anal canal by testing the following hypothesis;

- Incontinent patients have a shorter distance from the anal verge to the high pressure zone in comparison to asymptomatic patients using AAR.

Methods

Retrospective analysis of 265 patients recruited over a 4 year period from the pelvic floor service. All patients underwent AAR as per the method described above. All raw data and graphs were re-analysed. The distance from the maximum area distal to the HPZ to the HPZ was recorded as a surrogate marker of anal canal length (Figure 29). The distance was labelled AVFS (anal verge to functional sphincter complex). The data was then analysed using SPSS (Version 20 IBM Chicago IL).

Figure 29 Surrogate marker of anal canal length graph.



Schematic graph of Cross sectional area (mm^2) v Distance into the anal canal (cm) showing the distance from the maximum area distal to the HPZ to the HPZ representing a surrogate marker of anal canal length (AVFS).

Results

265 patients were re-analysed with a mean age of 58 and a range of 24-85 years old. 62 patients were excluded due to missing data or an unclear graph therefore rendering analysis inaccurate. The remaining 203 patients comprised 63 men and 140 women. 113 FI and 90 continent individuals with an overall mean AVFS length of 13.15mm (range 7-45). Different subsets of AVFS were then statistically analysed using a 2 factor ANOVA comparison of means. The subsets were men and women, FI and continent, and the 4 subsets of FI women (n=97), continent women (n=43), FI men (n=16) and continent men (n=47).

Table 5 Surrogate anal canal length descriptive statistics

Variable	(n=203)
Median age (range)	60 (24-85)
Sex (%) Male Female	 63 (31) 140 (69)
Continence (%) Continent Feacal incontinence	 90 (44) 113 (56)
Overall mean AVFS (range) Male Female Continent Faecal Incontinence	13.15 (7-45) 14.67 12.46 14.13 12.36

AVFS length (mm)

Table 6 Sex, continence and mean AVFS

Mean AVFS	Continent	Faecally Incontinent	Total
Male	14.96 (n=47)	13.81 (n=16)	14.67 (n=63)
Female	13.23 (n=43)	12.12 (n=97)	12.46 (n=140)
Total	14.13 (n=90)	12.36 (n=113)	13.15 (n=203)

Descriptive statistics showing mean AVFS length in mm within 4 subgroups of FI.

Table 7 Effect of sex and continence on AVFS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	263.024[a]	3	87.675	5.371	.001
Intercept	24966.807	1	24966.807	1529.423	.000
sex	99.310	1	99.310	6.084	.014
continence	43.289	1	43.289	2.652	.105
sex * continence	.011	1	.011	.001	.979
Error	3248.542	199	16.324		
Total	38603.000	203			
Corrected Total	3511.567	202			

a. R Squared = .075 (Adjusted R Squared = .061)

Two Factor ANOVA analysis of Sex and Continence on the dependent variable of AVFS length (mm). Analysis of the effect of sex allowing for continence on AVFS and effect of continence allowing for sex on AVFS. The only significant result is the difference seen between male and female sex on AVFS length (p=0.014 shown in red).

The only statistically significant difference in AVFS length is between male and female sex (male n=63 mean 14.7mm, female n=140 mean 12.5mm p=0.014). When comparing AVFS in 4 groups of male incontinent, male continent, female incontinent and female continent no significance was found (p=0.105 & p=0.979). This may be partially explained by the low number of male incontinent patients (n=20, 7.5%) in our study in comparison to female incontinent patients (n=135, 50.9%).

Discussion

Anal canal length is most commonly measuring during ano-rectal physiology measurements specifically manometry [97]. Standard pull through manometry is an operator dependant technique with questionable accuracy [126, 191, 192, 204, 205]. With the introduction of high resolution manometry accuracy may improve. The aim of this study was to use AAR to establish a useful surrogate marker (AVFS) for anal canal length that showed correlation with the subgroups of FI men, continent men, FI women and continent women.

It has been known for some time that the anal canal of men is longer than that of women as is the anal canal of the continent in comparison to that of the incontinent [10, 207]. One might therefore expect to observe a difference within the subgroups under investigation.

In this study sex was the only statistically significant difference in AVFS length. The mean difference observed of 2.21mm in AVFS between men and women although statistically significant is small.

A possible explanation for the lack of significance for AVFS length between male continent and incontinent patients could be the low numbers of men with incontinence (n=16) in this study. Hence under-representing men who may have a shorter AVFS distance. This is a methodological limitation due to the relatively low number of men with incontinence in comparison to women.

The term AVFS was developed to represent the anal verge to functional sphincter complex or HPZ length in mm. However I was unable to confirm that the point of maximal area distal to the HPZ was the same point as the anal verge. Therefore AVFS has been used as a label for distance and not the acronym (AVFS - anal verge to functional sphincter).

This study does not support the current literature which states that incontinent patients have a shorter anal canal than continent patients. However, care must be taken in the analysis of this data. The surrogate marker of anal canal length (AVFS) only measures the lower part of the anal canal from the HPZ distally to the anal verge. It is possible that this distance remains unchanged in incontinence and it is the upper or proximal part of the anal canal that is responsible for the difference in length observed in the literature.

Exploring the reasons for the small observed difference between AVFS in men and women led to a discovery in the literature of a phenomenon called ringing or Gibbs phenomenon [298]. Ringing describes the effect of reflected sound waves at the end of a tapering tube such as a blind ended catheter. Halving the cross sectional area within a distance shorter than 4mm gives a relatively large error around the halving. Ringing is due to a spectral limitation of the signal. The limitation means that the more the abrupt the changes are, the larger the error becomes. The end of the catheter is very steep and therefore the measurements of the cross sectional area from the last 1cm and the first 1cm are not reliable [254]. This phenomenon explains our unexpected results.

Conclusion

In conclusion this study has found that AAR cannot be used to measure the length of the anal canal nor can this current method be used as a surrogate marker of anal canal length due to a phenomenon called ringing.

Chapter 7 AAR and Manometry the order of data collection

Introduction

The current gold standard test of anal sphincter function is manometry. However anal manometry has limitations. It does not correlate with severity [204, 205, 299], it cannot distinguish between faecal incontinence and continence [198], nor can it distinguish between subgroups of incontinence (passive, urge or mixed) [204]. Furthermore despite a paper in 2002 [300] detailing the minimum standards for anorectal manometry there is still no agreed methodology, units of measurement and a lack of normative data.

AAR and manometry may have a complementary role and can be performed sequentially. AAR is considered a catheter free technique that does not distort and open the anal canal. It thus allows investigation of the opening and closing function of the anal canal. For AAR to become a clinically useful technique and be used alongside other tests of the ano-rectum we must establish whether AAR is influenced by prior manometry examination.

Aims

This study has been designed to answer a methodological question following criticism before previous publication. Did performing manometry before AAR affect the results and would changing the order to AAR before manometry result in a

different outcome? Our aim was to add further validation to our method by testing the following hypothesis:

- Prior manometry investigation does not alter the opening pressure of the anal canal using AAR?

Methods

Patients

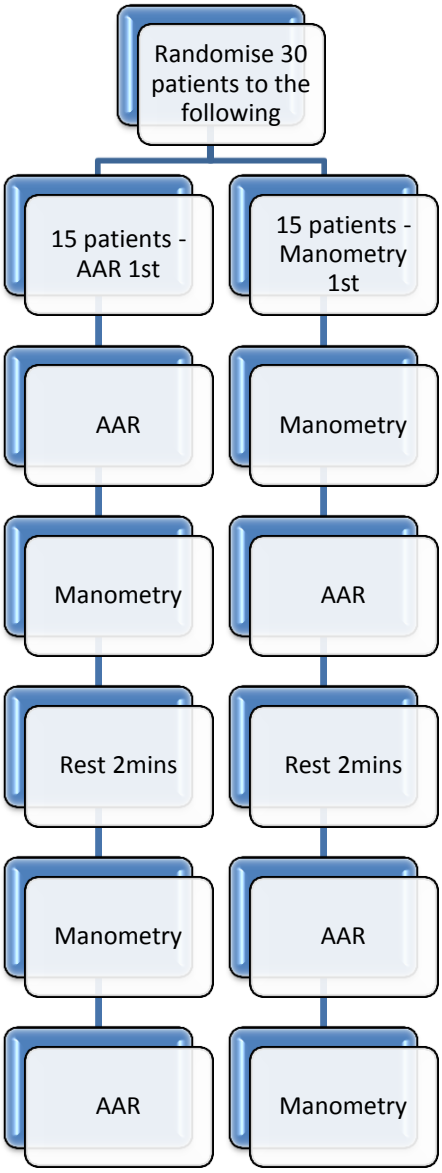
Male or female patients >18 years old and able to consent were prospectively recruited from a pelvic floor clinic. They could be faecally continent or incontinent. They received an invitation letter, patient information sheet and consent form and were given >24 hours to consider their inclusion in the study. Patients excluded were minors under 18 years old or unable to consent. Recruited patients were randomised to the order of data collection. Randomization was conducted using a computer generated random sequence assigned to manometry first and AAR second or vice versa by an independent person. This sequence was then placed individually into 30 sealed envelopes and opened immediately prior to each measurement. Demographic and clinical data were recorded as detailed in Chapter 7.

Protocol

Patients underwent manometry or AAR as per randomisation in the left lateral position (see Materials and Methods Chapter 6) followed by a 2 minutes rest before

manometry and AAR were repeated in the opposite order, see overview of process below (Figure 30).

Figure 30 Overview of Process - Order of data collection



Statistical Analysis

A sample size calculation was performed using previous data. This suggested that with 30 patients the study would have an 80% power at a conventional significance level of 0.05 to detect differences in resting OP between 1st and 2nd order AAR of greater than 7.4cmH_2O using a standard deviation of 14cmH_20. Normal continuous data were compared using the paired t-test and continuous data not normally distributed with the Wilcoxon Signed Rank test. All data were recorded in an excel database and interrogated using SPSS Statistics version 20 software (IBM, Chicago, IL).

Results

30 patients were recruited and randomised over a 4 month period in 2013; demographic data can be seen in Table 8 below. The median age was 63 (range 30-84), 23 of the patients were female (77%) and 16 had urge incontinence (53%). Their mean parity was 2.6 of which 21 of 22 were vaginal deliveries (1 by C-section). 65% of women had traumatic childbirth. 61% of traumatic childbirth was caused by vaginal tears of varying degrees and episiotomies. In comparison, forceps and ventouse deliveries accounted for 43% and 9% respectively. The group as a whole had a high rate of previous surgery (91%) whether anorectal, abdominal or gynaecological.

Table 8 Order Study Demographics

Variable	Patients Undergoing Investigation (n=30)
Median age (range)	63 (30-84)
Sex	
Male	7 (23)
Female	23 (77)
Type of incontinence	
Continent	9 (30)
Urge	16 (53)
Passive	4 (13)
ODS	1 (3)
Mean Bristol Stool chart (range)	4 (1-6)
Median Vaizey Score (range)	15.5 (0-24)
Mean parity (range)	2.6 (0-4)
Mean vaginal delivery (range)	2.5 (0-4)
Median C-section (range)	0 (0-1)
Traumatic childbirth	15 (65)
Forceps	10 (43)
Ventouse	2 (9)
Tears	14 (61)
Previous gynaecological surgery	12(52)
Hysterectomy	6
Prolapse repair	2
Oophorectomy	1
Repair of perineum	1
Sterilization	1
Uterine ablation	1
RBL of haemorrhoids	6 (20)
Previous Anorectal Surgery*	12 (40)
Haemorrhoidectomy	2
PTQ	4
Delormes	2
SNS	4
PTNS	1
Sphincter repair	2
Rectocele repair	3
I&D of perianal abscess & seton	1
Previous abdominal surgery	18 (60)
Colectomy	6
Anterior resection	2
Rectopexy	4
Cholecystectomy	2
Appendicetomy	2
Adhesiolysis	1
Nissens Fundoplication	1

Demographics for the order of data collection study (values in parenthesis are percentages unless otherwise stated).

*Urge=inability to defer defecation, passive=faecal soiling without awareness, ODS=obstructive defecation syndrome, Bristol stool chart ranges from 1 to 7 (1=hard stool and 7=liquid stool), Vaizey=faecal incontinence severity score which ranges from 0 to 24 (24 being the most severe incontinence), RBL=rubber band ligation of haemorrhoids, PTQ=anal silicone implant to bulk the anal canal and treat passive FI, SNS=sacral nerve stimulation, PTNS=posterior tibial nerve stimulation, I&D=incision and drainage.*Patients who underwent previous anorectal surgery often had more than 1 procedure accounting for a greater number of procedures than patients.*

The variables measured by AAR and manometry can be seen in Table 9 below. No statistically significant difference was found between all variables regardless of which test was performed first.

Two continent men were able to completely occlude the lumen of the AAR catheter during a voluntary squeeze effort up to the maximum pressure of 200cmH_2O therefore completing the test. SOP & SOE cannot be calculated in this circumstance hence they were removed from statistical analysis.

Table 9 Effect of order on AAR and Manometry variables.

Variable	AAR performed 1st (n=30)	AAR performed 2nd (n=30)	P value
AAR			
Opening Pressure (cmH_2O)	34 (2-86)	36 (3-89)	0.47
Opening Elastance (cmH_2O/mm^2)	0.98 (0.31-3.07)	1.02 (0.42-1.07)	0.72
Closing Pressure (cmH_2O)	24 (1-77)	24 (2-78)	0.80
Closing Elastance (cmH_2O/mm^2)	0.90 (0.13-2.61)	0.94 (0.22-1.65)	0.57
Hysteresis %	25 (0-62)	22 (1-67)	0.25
Squeeze Opening Pressure (cmH_2O)	75 (4-179)	75 (3-181)	0.26*
Squeeze Opening Elastance (cmH_2O/mm^2)	1.29 (0.15-3.46)	1.22 (0.63-2.57)	0.78*
Anal Manometry			
MRP (cmH_2O)	54 (15-146)	54 (0-142)	0.16
MSP (cmH_2O)	94 (30-357)	99 (37-265)	0.44

*Comparison of the order of data collection on AAR and Manometry variables. Values shown are medians (range). Comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. *Paired samples t-Test. Significance level <0.05.*

Figure 31Figure 39 below show Bland Altman plots for the agreement of AAR and manometry variables and the order of data collection. The graphs shows the mean bias line and 2 lines showing the upper and lower 95% limits of agreement. 95% of data falls with the 95% limits of agreement representing good agreement.

Figure 31 Agreement for AAR variable Opening pressure depending on order.

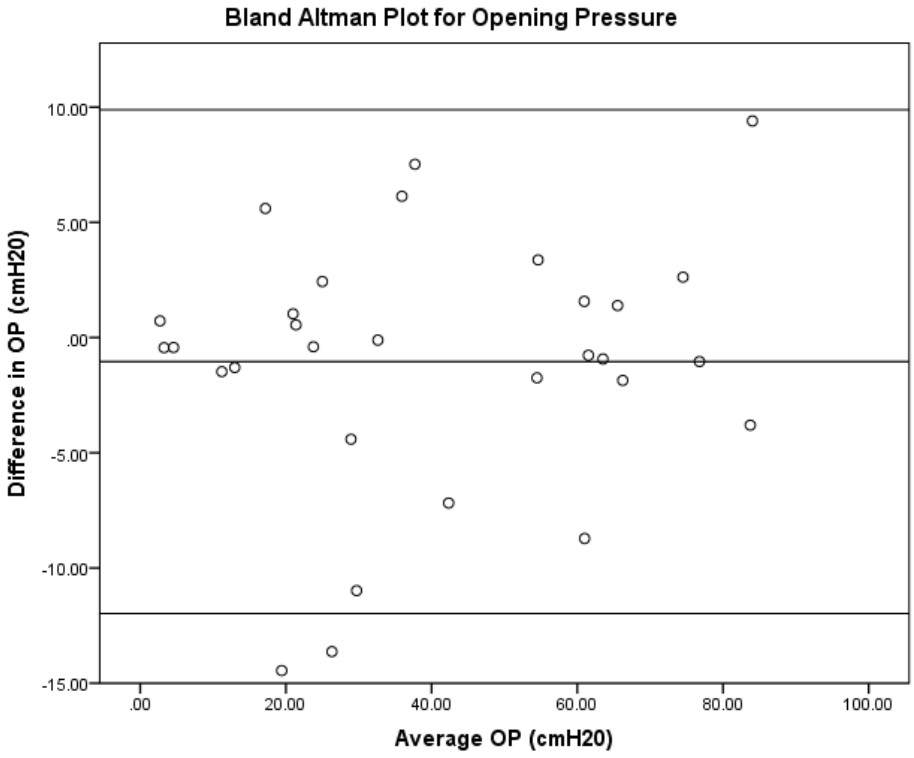


Figure 32 Agreement for AAR variable Opening elastance depending on order

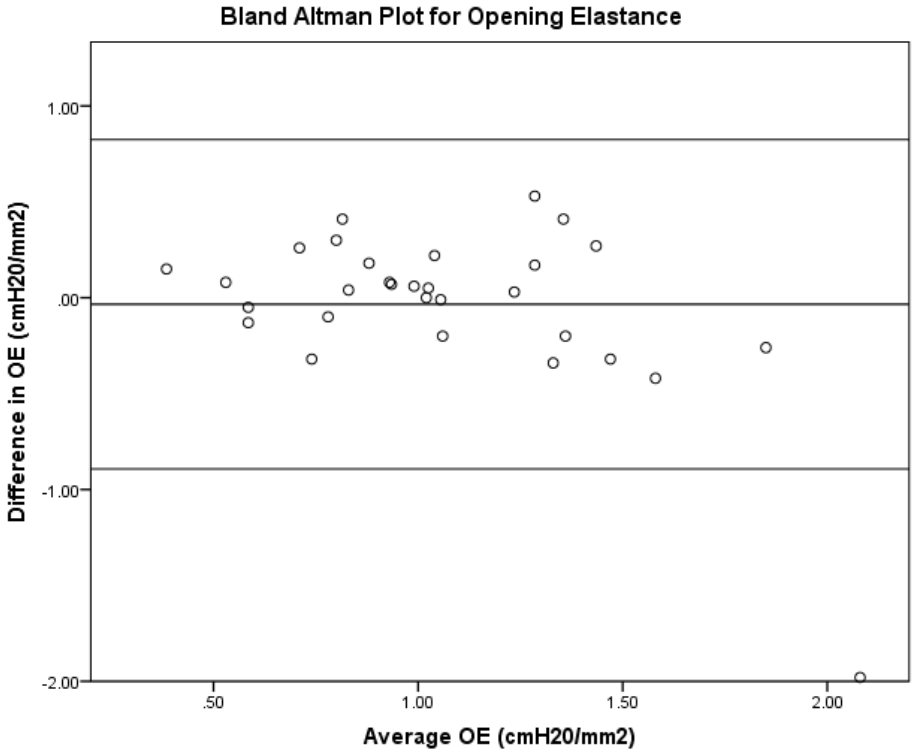


Figure 33 Agreement for AAR variable Closing pressure depending on order

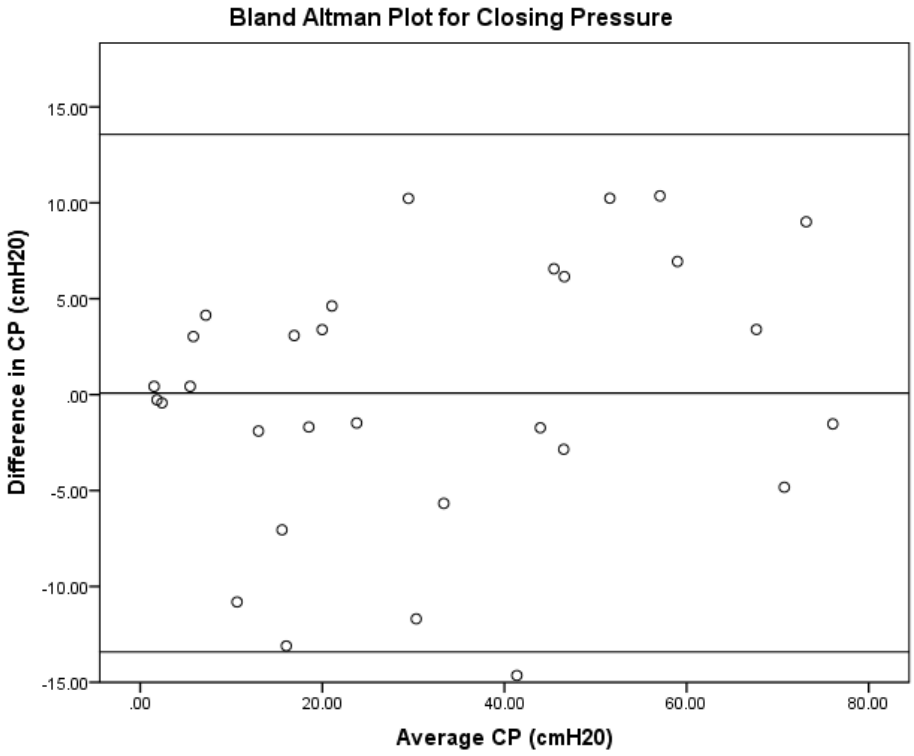


Figure 34 Agreement for AAR variable Closing elastance depending on order

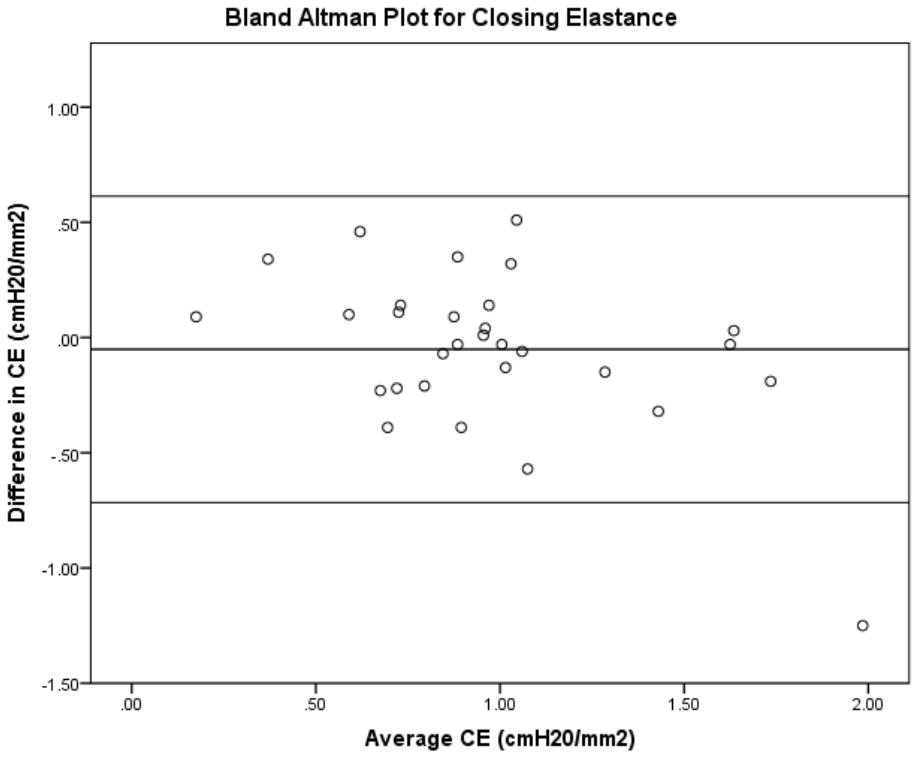


Figure 35 Agreement for AAR variable hysteresis depending on order

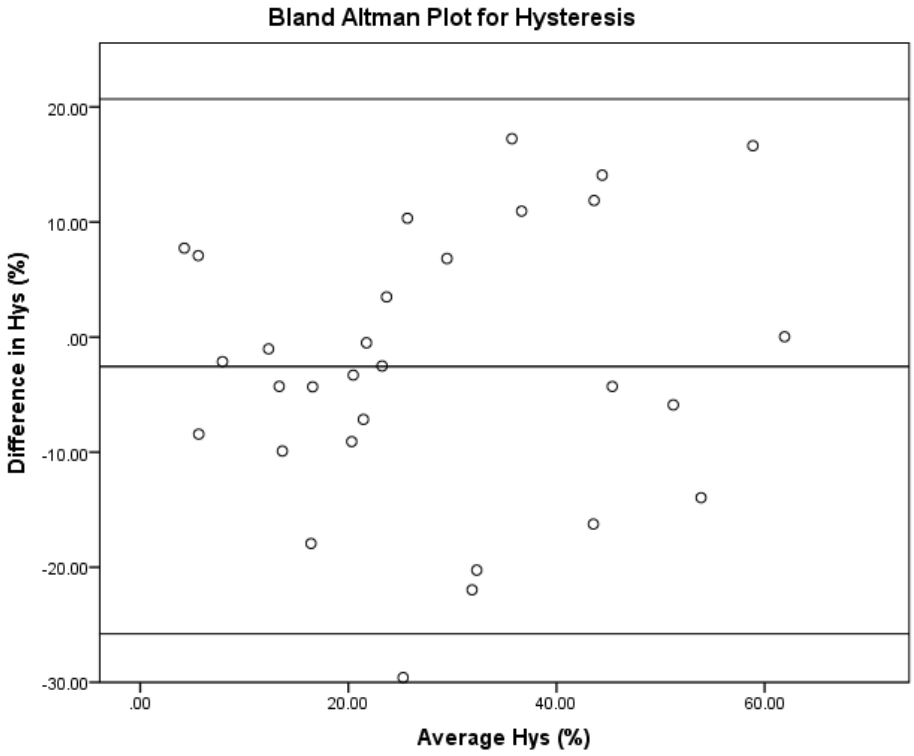


Figure 36 Agreement for AAR variable squeeze opening pressure depending on order

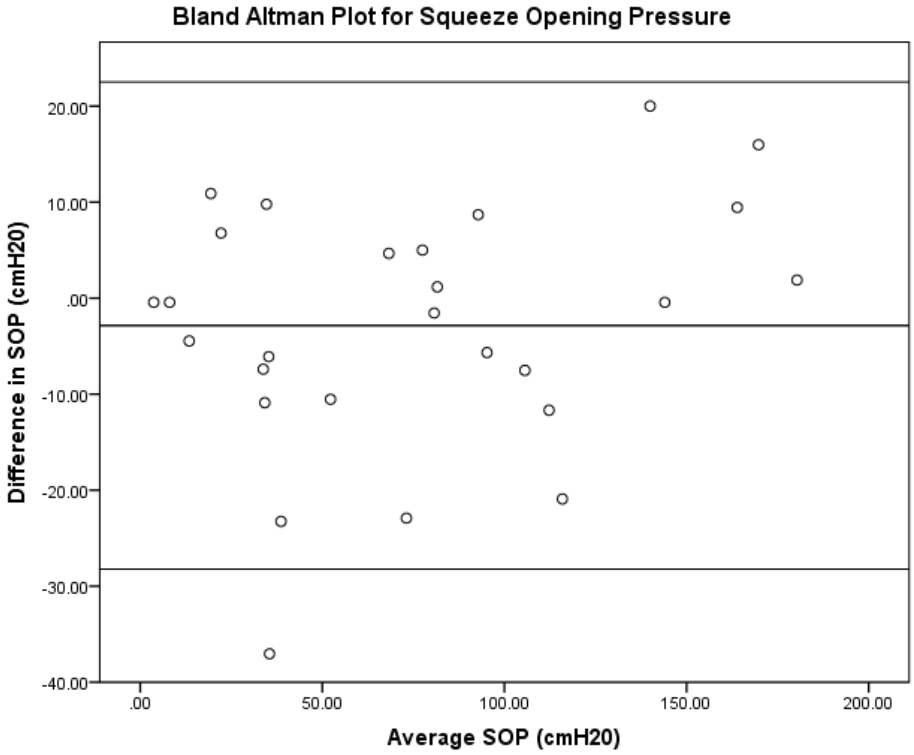


Figure 37 Agreement for AAR variable squeeze opening elastance depending on order

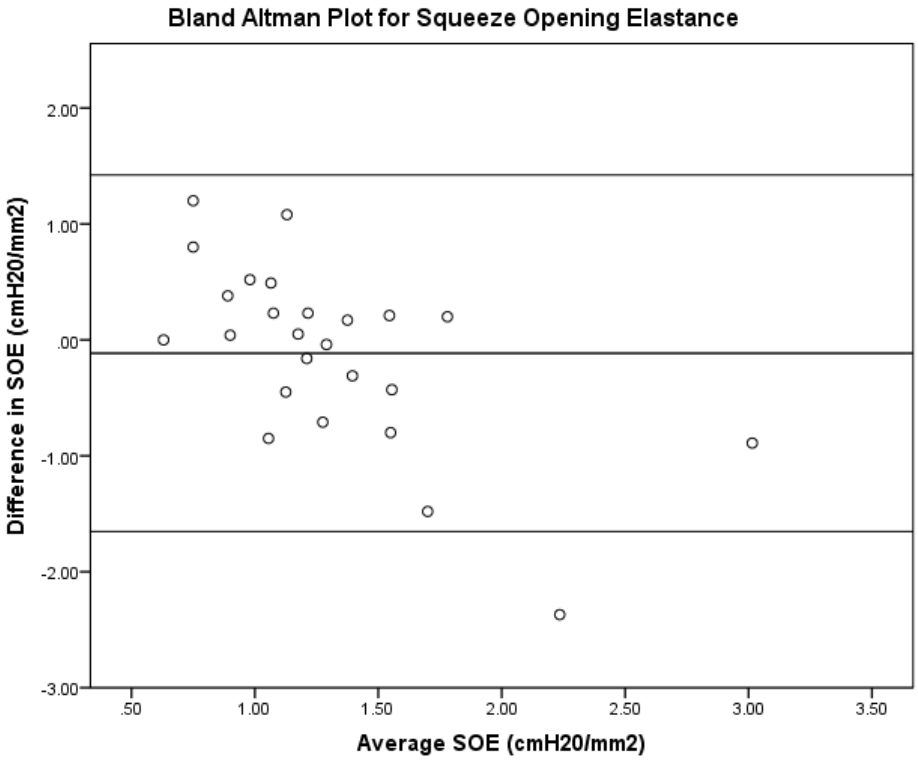


Figure 38 Agreement for manometry variable maximum resting pressure depending on order

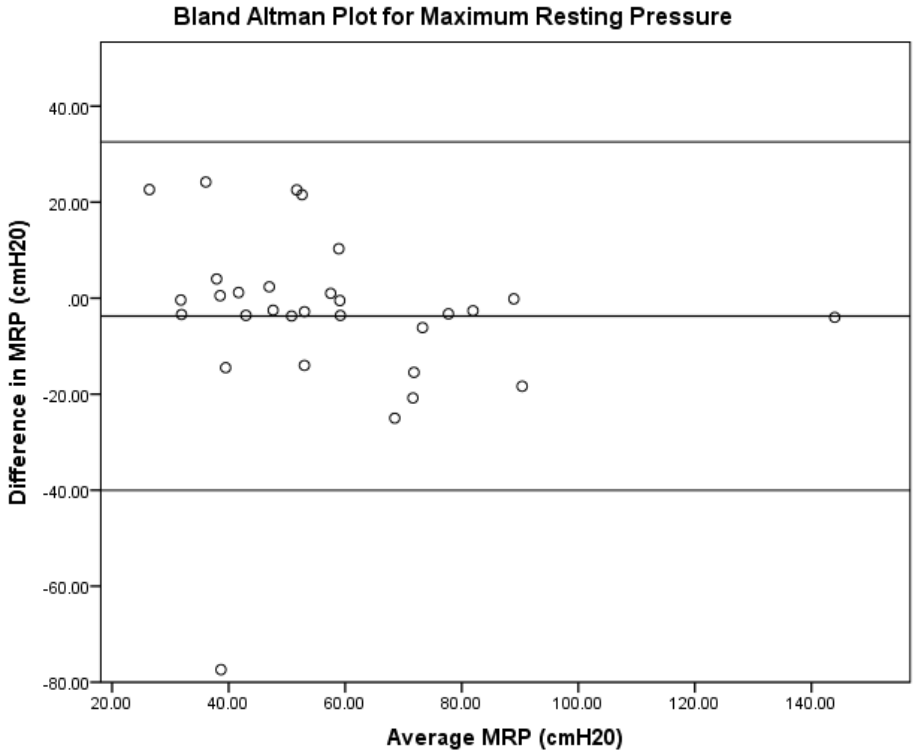
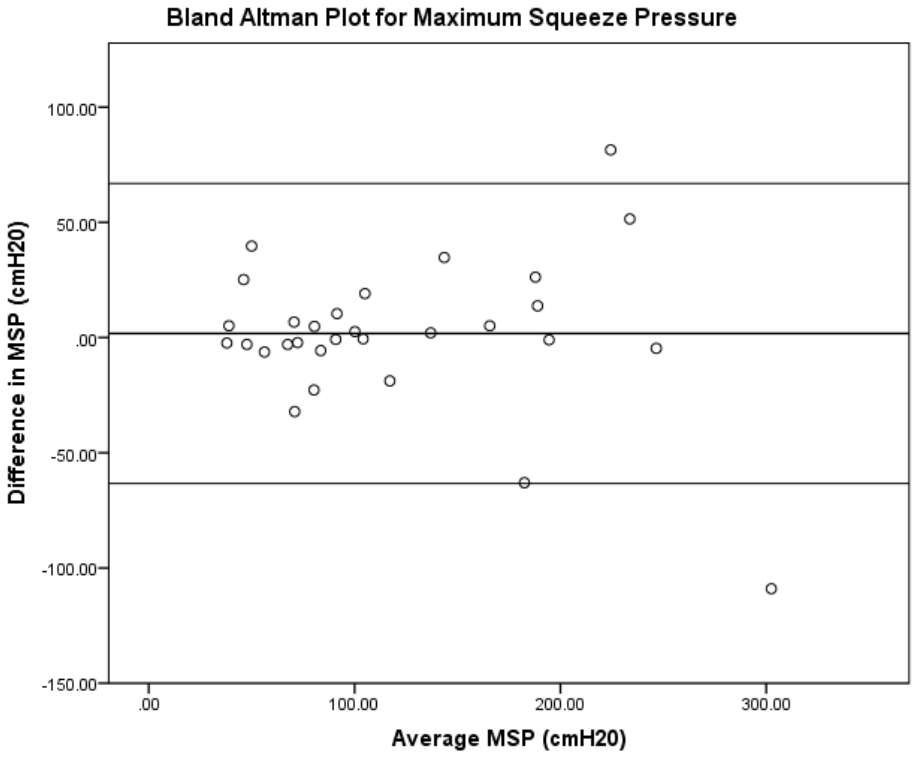


Figure 39 Agreement for manometry variable maximum squeeze pressure depending on order



Discussion

This study was designed in response to a criticism that our methodology was not robust. The criticism stated that the results of AAR variables may be influenced by prior manometry investigation. AAR is intended to be used alongside other tests of the ano-rectum thus it is critical that results are not influenced by a concomitant test.

The current study examines 2 orders of data collection with manometry and AAR being performed twice on each recruited patient. It was not necessary to establish equally matched groups because each patient acted as their own control and were compared to themselves on repeated samples.

The two orders of data collection were separated by a 2min rest period. This duration was chosen for two reasons. Firstly for practical reasons, it is necessary to show that this new test can be implemented alongside other investigations without onerous time delays. However it takes at least 2mins to re-calibrate the AAR machine before use. Secondly the 2min rest period was chosen to preserve uniformity with previous AAR methodology and therefore allow direct comparison of results. For example, Mitchell et al., [271] used a 2min rest period when studying the repeatability and reproducibility of AAR and for this study to offer further validation of the method used by Mitchell et al., the rest period must be uniform.

Vaginal delivery and higher parity is strongly linked with pelvic floor dysfunction [301]. It is thus unsurprising that the women recruited to this study from the pelvic floor clinic had, with one exception, had a vaginal delivery and that as a group they had a higher parity rate of 2.6 in comparison to women born in 1968 (a similar age matched group) of 1.92 [302]. Traumatic childbirth was seen in 65% of women in our study which is low in comparison to the 85% of women that will suffer some form of perineal trauma and up to 69% who will require sutures in the UK [303]. It was expected that in view of the process of recruitment from a tertiary colorectal and pelvic floor clinic that rates of traumatic childbirth would be high in this cohort, therefore this was an unexpected finding. The likely explanation is that data was retrospectively collected and therefore reliant on memory in comparison to Kettle et al., who quoted prospective trials of any level of perineal trauma. A high previous surgery rate (anorectal, abdominal and gynaecological) of 91% can also be explained by the process of recruitment from a colorectal and pelvic floor surgical clinic, a predetermined cohort of patients. This predetermined group are likely by the nature of being in a surgical clinic to have had previous operations, complications of

operations or be due to have operations in the future. It is therefore expected that this group of patients would have a high rate of surgery.

The variables of AAR and manometry were not influenced by the order of performing the tests (Table 9 and Figures 31-39). Hence prior examination with manometry does not affect the results of AAR. This study is important for 3 reasons; firstly AAR can now be confidently used alongside other tests of the ano-rectum, secondly it adds further validation to AAR methodology, and lastly it vindicates previous research and results.

This study adds further validation to AAR methodology. AAR has been used to investigate the anal canal for 4 years producing a considerable body of data. Over this period the method has been unchanged. However it brings previous data into disrepute if the order of data collection influences the results, questioning the accuracy of 4 years' worth of data. This study gives confidence in the data set and reassurance going forward that our method is robust. For future data collection it can be recommended that a minimum of 2mins is allowed between manometry and AAR.

Due to the fact that all patients were recruited by a single investigator from a single institution and clinic the possibility of selection bias must be considered. However because each patient acted as their own control a truly randomized and representative population is not required. Another form of selection bias was avoided by randomising patients to the order they received the investigations. This avoided the possibility of the investigator or patient being able to choose the order they received the investigations.

During analysis of each individuals raw data the HPZ must first be identified to permit subsequent interrogation of the pressure v CSA graph which gives us the characteristic AAR variables. Interpretation of where the HPZ sits is a potential third source of bias. This bias is prevented by using the computer to select the minimum CSA along the length of the anal canal during the course of inflation and deflation of the catheter which represents the HPZ by definition. Providing the 2 points selected by the investigator that represent the length of the anal canal are picked appropriately and do not include the rigid PVC tubing proximally and the second dip in CSA which often represents the effect of the puborectalis muscle distally, this is a reliable method to reduce potential bias.

This study is limited by its comparison to a water perfused station pull-through manometry (WPAM) technique. Since this study was performed in 2013 high resolution anal manometry (HRAM) has become widespread and more commonly performed at our institution. HRAM (Medical Measurement Systems, Netherlands) uses a significantly larger catheter balloon than WPAM. The HRAM balloon is inserted through the anal canal into the rectum enabling a demonstration of a RAIR and testing of rectal sensitivity. This raises the question whether a further study comparing AAR to HRAM should be planned? Such a study should include not only a comparison of the order of data collection but also a comparison of HRAM, WPAM and AAR. Although previous studies have shown good correlation between HRAM and WPAM a number of studies have consistently found that resting and squeeze pressures have been significantly higher when using HRAM [219, 304, 305]. These include a large study from France of 201 patients that found pressure values with 3D HRAM correlated with those from WPAM but were systematically higher [304]. Despite the higher values found using HRAM the authors did not conclude

that this meant a more sensitive test but that this was likely to be due to the technical characteristics of the probe. They hypothesized that 3D HRAM may provide more accurate and useful physiological values [304]. AAR has been shown to correlate with severity [204], be able to distinguish between FI and continence [273] and distinguish between subgroups of FI [204] unlike WPAM, but studies have not been completed comparing AAR to HRAM.

Conclusion

Prior manometry examination does not affect the results of AAR variables thus adding further methodological validation and vindicating previous data. This study has shown that AAR and manometry can be performed in any order with reliable results.

Chapter 8 The effect of different filling rates of the anal canal on AAR parameters

Introduction

In contrast to rectal distention, little is known about the effect of stretch on the anal canal. This study investigated the change in AAR parameters during different rates of stretch of the anal canal. Conducted mainly at rest, we predominantly assessed the smooth muscle (SM) of the IAS.

With the exception of the upper one third of the oesophagus and the EAS, the muscular layers of the bowel wall are made up of SM cells. The properties of skeletal and cardiac muscle are well-defined but less is known about visceral SM and often its behaviour is explained on the basis of the properties of the other two. In 1971 Gordon and Siegman listed the reasons why visceral SM was difficult to study [306];

- SM is arranged in two independently contracting layers,
- SM has nonparallel arrangements,
- SM contracts spontaneously leading to difficulty in interpreting the effects of stimulation and masks the passive tension reference point,
- SM exhibits a phenomenon called the stress-relaxation response,
    - SM briefly responds to stretch but then adapts to its new length, retaining its ability to contract. This enables organs such as the stomach and bladder to temporarily store contents.
- SM has the ability to contract in response to stretch.

The main body of work investigating the response to distension or stretch of the large bowel and sphincters was performed by Garry on 30 cats in 1933 [307-309]. Using two distended tandom balloons Garry found that stimulation of the rectum caused contraction of the rectum and relaxation of the anal canal [308]. This response, the RAIR, was first shown by Gowers in 1877 [310]. Garry also found that stimulation of the anal canal caused dilatation of the anal canal, mainly the IAS, and that stimulation of the anal canal caused contraction of the large bowel. Bishop et al., studied the electromyographic activity of the exposed EAS in decerebrate cats [309]. They found that the EAS shows tonic activity which persists even after transection of the spinal cord in the lower thoracic region, but simple distension of the anal canal reduced the tonic activity. Activity ceased when the pudendal nerves were cut, during spinal anaesthesia of the lumbo-sacral region and during general anaesthetic. Distension of the colon also caused inhibition of the tonic activity of the EAS. This response was destroyed by section of the pelvic nerves or by anaesthesia of the mucous membrane of the colon, suggesting that the reflex must have receptors that lie not far from the colonic mucosa, with afferents in the pelvic nerves. The work by Garry and colleagues highlights the complex nervous control of continence.

What is known about gastrointestinal SM? Gastrointestinal SM obeys the sliding filament theory of muscle contraction and the length-tension curve which describes the optimum length for tension development [306, 311]. It is difficult to study due to its inherent qualities listed above. Gastrointestinal SM's are autonomous, generating spontaneous electrical activity that does not depend upon input from nerves and are driven by intrinsic pacemaker activity (such as the interstitial cells of Cajal that are electrically coupled to SM cells). However in order to contract and produce meaningful movement the SM cells create a syncytium with multiple levels of

regulatory cells, motor neurons, hormones, paracrine substances and inflammatory mediators that are superimposed upon myogenic activity to generate normal and abnormal contraction. Sheets of SM such as those found in the bowel therefore exhibit slow synchronized contraction in peristaltic unison. This unison reflects their electrical coupling with gap junctions allowing action potentials to be transmitted from cell to cell [312]. It should be noted that SM tissues are not homogenous and that there are differences in electrical and mechanical properties in different regions of the gastrointestinal tract such as the sphincters. Most of the work on gastrointestinal SM comes from animal models making extrapolation to the human anal sphincter tenuous [313].

Although this study is mainly concerned with the response to stretch at rest, the IAS does not operate independently. The striated EAS has been calculated to contribute 30% to resting pressure in one study [314] and contains stretch receptors within its muscles spindles. Stretch receptors can also be found in the levator ani and puborectalis [65, 103], other pelvic floor muscles that may contribute to continence.

The standard stepwise rate of inflation (5cm$H_2$0/3secs) used in prior studies has been adapted from work in the urethra. The rationale behind this rate is not described in the literature. Deciding upon a rate of inflation is a balance, between obtaining sufficient data (the equipment only measures when the pump is inactive) and the length of the test, within the aims of the study in question. The stepwise rate of 5cm$H_2$0/3secs has been used in our unit for 5 years. A faster rate of 5cm$H_2$0/1secs has been chosen to enable adequate data to be collected whilst being sufficiently different to the accepted standard rate to expose a difference.

Aims

The aim of this study was to investigate the response of the anal canal to different filling rates, by testing the following hypothesis;

- The opening pressure of the anal canal will be greater at a higher filling rate of 5cmH_2O/1secs.

Method

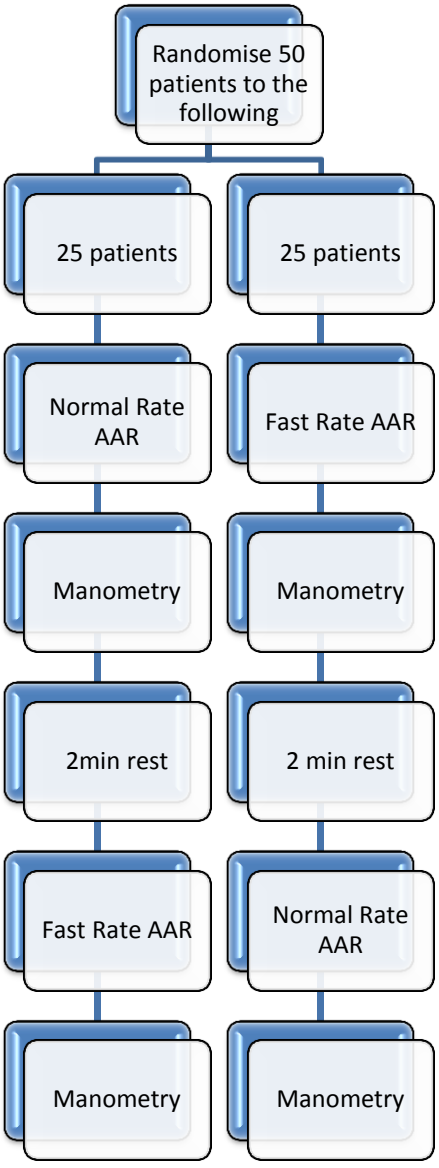
Patients

Patients attending a healthy bowel clinic were approached by a person independent to the study. Patients who agreed to participate were phoned and sent an invitation letter and patient information sheet by the principal investigator. Male or female patients over 18 years old and able to consent were then prospectively recruited and measured. Patients excluded were minors under 18 years old or those unable to give consent. Recruited patients were randomised to the rate of AAR (see overview of process below). Randomization was conducted using a computer generated random sequence and assigned to fast rate AAR (5cmH_2O/1secs) then normal rate AAR (5cm$H_2$0/3secs) or vice versa by an independent person. This sequence was then placed individually into 50 sealed envelopes and opened prior to each measurement. Demographic and clinical data were recorded as detailed in Chapter 7.

Protocol

Patients underwent AAR and manometry as per randomization in the left lateral position (see Material and Methods Chapter 6) followed by a 2 min rest then the opposite rate of AAR and manometry (see overview below Figure 40).

Figure 40 Overview of Process – Rate of filling



Statistical Analysis

A sample size calculation was performed using previous data, suggesting that with 50 patients the study would have an 80% power at a conventional significance level of 0.05 to detect differences in resting OP between fast and normal rate AAR of greater than 5.6 cmH_2O using a standard deviation of 14cmH_20. Normal continuous data were compared using the paired t-test and continuous data not normaly distributed with the Wilcoxon Signed Rank test. All data were recorded in an excel database and interrogated using SPSS Statistics version 20 software (IBM, Chicago, IL).

Results

50 patients were recruited and randomised over a 10 month period in 2014; demographic data can be seen in Table 10 below. The median age was 62 years, 40 (80%) of the patients were female and 26 (52%) had mixed faecal incontinence. The average stool type was 4 on the Bristol stool chart (1 = hard pellet stool and 7 = watery diarrhoea). The median Vaizey incontinence severity score was 16 on a scale of 0-24 (24 = most severe incontinence). Their mean parity was 2, 83 of 88 (94%) births were by vaginal delivery. 35 (88%) women experienced traumatic childbirth from all causes, most of those were tears. Many women experienced more than one form of trauma, whether that was forceps instrumentation followed by a tear or a ventouse assisted delivery plus an episiotomy. 26 (65%) women had had previous gynaecological surgery, 21 of those operations were a hysterectomy. 19 (38%) patients recruited had previous abdominal surgery, one of those patients had 7 laparotomies for adhesional obstruction.

Table 10 Demographics for the rate of filling study

Variable	Patients Undergoing Investigation (n=50)
Median age (range)	62 (30-78)
Sex	
Male	10 (20)
Female	40 (80)
Type of incontinence	
Mixed	26 (52)
Urge	16 (32)
Passive	8 (16)
Mean Bristol Stool chart (range)	4 (1-6)
Median Vaizey Score (range)	15.6 (2-24)
Mean parity (range)	2.2 (0-5)
Mean vaginal delivery (range)	2.1 (0-4)
Median C-section (range)	0 (0-2)
Traumatic childbirth	35 (88)
Forceps	21
Ventouse	5
Tears	34
Previous gynaecological surgery	26 (65)
Hysterectomy	21
Sterilisation	1
Repair of perineal Body	1
Diagnostic Laparoscopy	1
Fentons procedure	1
Dilation & Curettage	1
RBL of haemorrhoids	17 (34)
Previous Anorectal Surgery*	27 (54)
SNS	10
Sphincter repair	8
Haemorrhoidectomy	4
PTQ	2
Anal Stretch	2
I&D of perianal abscess & seton	2
Delormes	1
Transanal Resection of Rectal Ulcer	1
Previous abdominal surgery	19 (38)
Adhesiolysis	12
Appendicetomy	5
Anterior resection	2
Cholecystectomy	2
Diagnostic Laparoscopy	2
Spinal Tumour	2
Bowel Resection as a Child	1

Demographics for the rate of filling study (values in parenthesis are percentages unless otherwise stated). Urge=inability to defer defecation, passive=faecal soiling

*without awareness, mixed=combination of both urge and passive incontinence symptoms. Bristol stool chart ranges from 1 to 7 (1=hard stool and 7=liquid stool), Vaizey=faecal incontinence severity score which ranges from 0 to 24 (24 being the most severe incontinence), RBL=rubber band ligation of haemorrhoids, PTQ=anal silicone implant to bulk the anal canal and treat passive FI, SNS=sacral nerve stimulation, I&D=incision and drainage.*Patients who underwent previous anorectal surgery often had more than 1 procedure accounting for a greater number of procedures than patients.*

There was no statistical difference when comparing fast and normal rates of AAR for all 7 variables (Table 11). SOP was approaching significance (p=0.06), however a difference of 2cmH_2O or 4cmH_2O when comparing medians and means respectively is not clinically relevant. Manometry variables of MRP and MSP did not show a significant difference when performed after AAR at 2 different rates (Table 11). Therefore manometry is not influenced by prior examination with either fast or normal rate AAR.

Table 11 Comparison of the rate of AAR on manometry and AAR variables.

Variable	Normal Rate AAR (n=50)	Fast Rate AAR (n=50)	P value
AAR			
Opening Pressure (cmH_2O)	31 (6-89)	36 (3-87)	0.08
Opening Elastance (cmH_2O/mm^2)	0.93 (0.42-1.90)	0.99 (0.34-1.66)	0.87
Closing Pressure (cmH_2O)	24 (1-77)	29 (2-72)	0.44
Closing Elastance (cmH_2O/mm^2)	0.90 (0.46-1.58)	0.95 (0.31-1.85)	0.67
Hysteresis %	19 (0-86)	19 (0-56)	0.73*
Squeeze Opening Pressure (cmH_2O)	57 (10-170)	55 (1-181)	0.06
Squeeze Opening Elastance (cmH_2O/mm^2)	1.06 (0.17-2.00)	1.03 (0.09-2.17)	0.82
Variable	**Manometry after Normal Rate AAR (n=50)**	**Manometry after Fast Rate AAR (n=50)**	**P value**
Anal Manometry			
MRP (cmH_2O)	31 (5-110)	38 (7-108)	0.34*
MSP (cmH_2O)	57 (17-190)	60 (13-186)	0.73*

*Comparison of the rate of AAR on manometry and AAR variables. Values shown are medians (range). Comparisons made using paired samples t-test unless otherwise stated. *Wilcoxon Signed Rank Test. Significance level <0.05.*

Figure 41Figure 49 below show Bland Altman plots for the agreement of AAR variables and the two different rates of filling. The graphs shows the mean bias line and 2 lines showing the upper and lower 95% limits of agreement. 95% of data falls with the 95% limits of agreement representing good agreement.

Figure 41 Agreement for AAR variable opening pressure depending on rate.

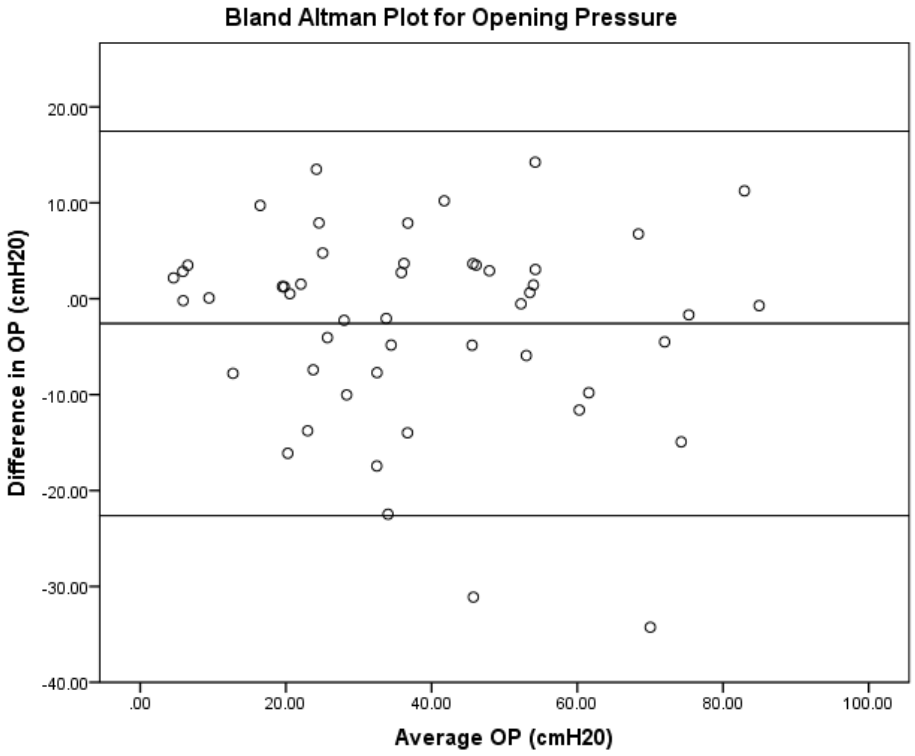


Figure 42 Agreement for AAR variable opening elastance depending on rate

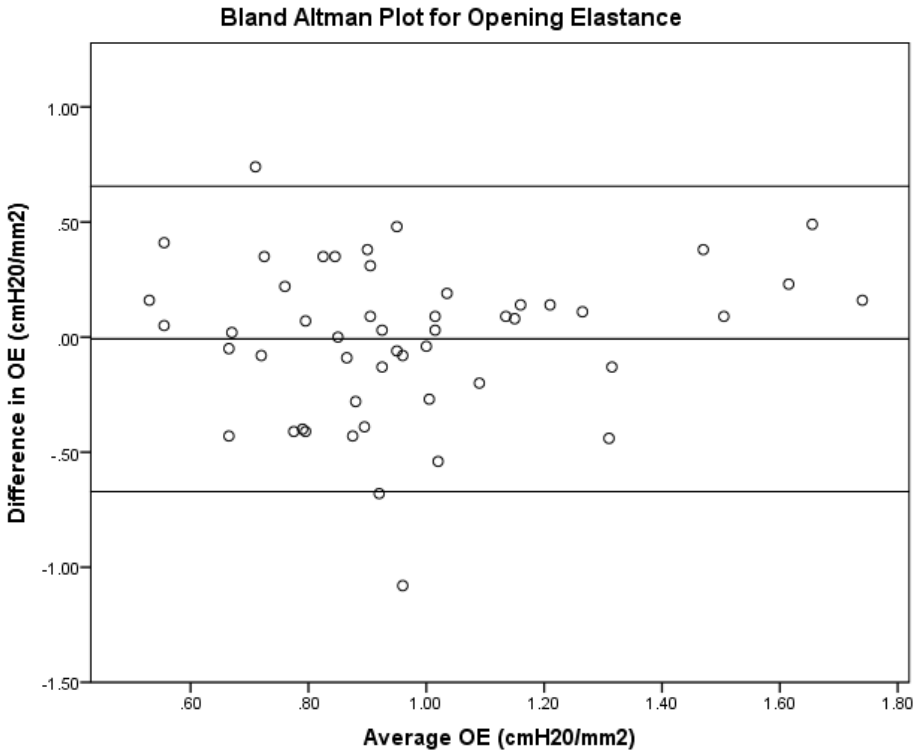


Figure 43 Agreement for AAR variable closing pressure depending on rate

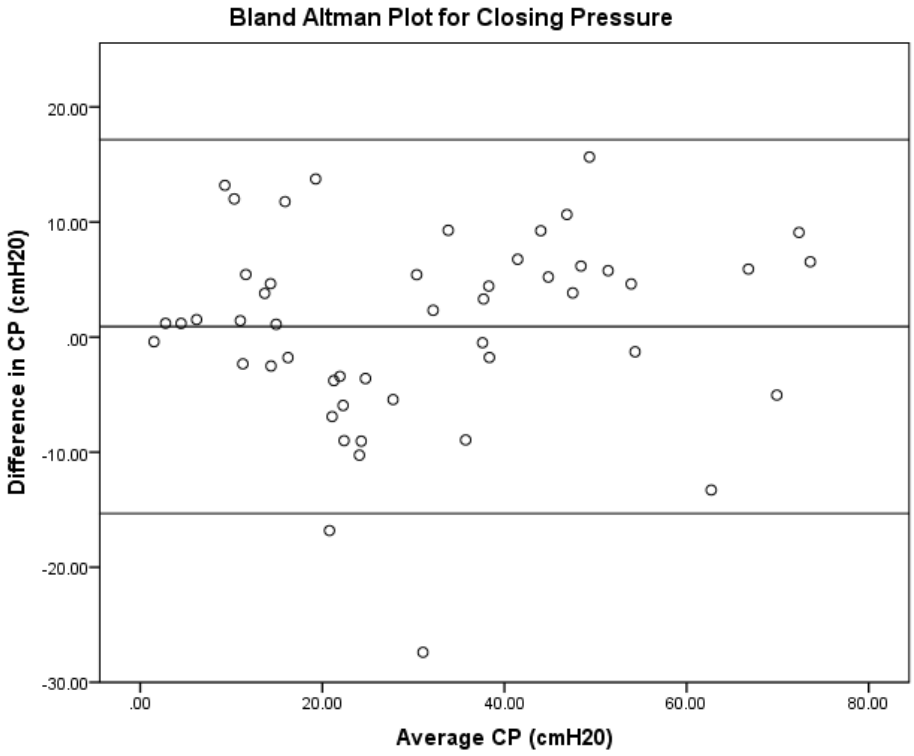


Figure 44 Agreement for AAR variable closing elastance depending on rate

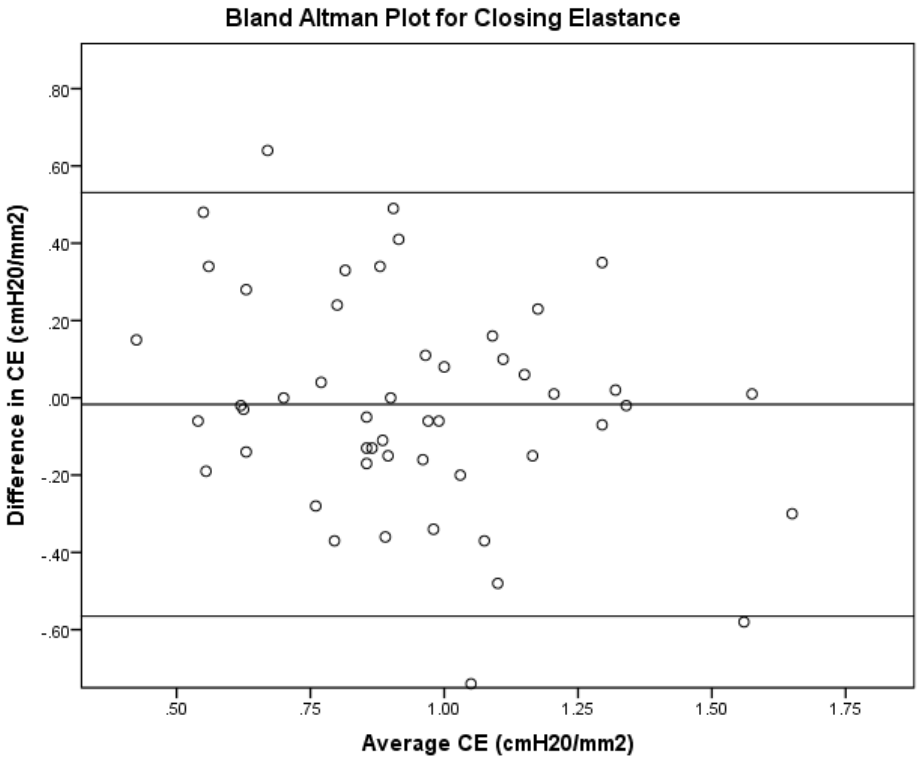


Figure 45 Agreement for AAR variable hysteresis depending on rate

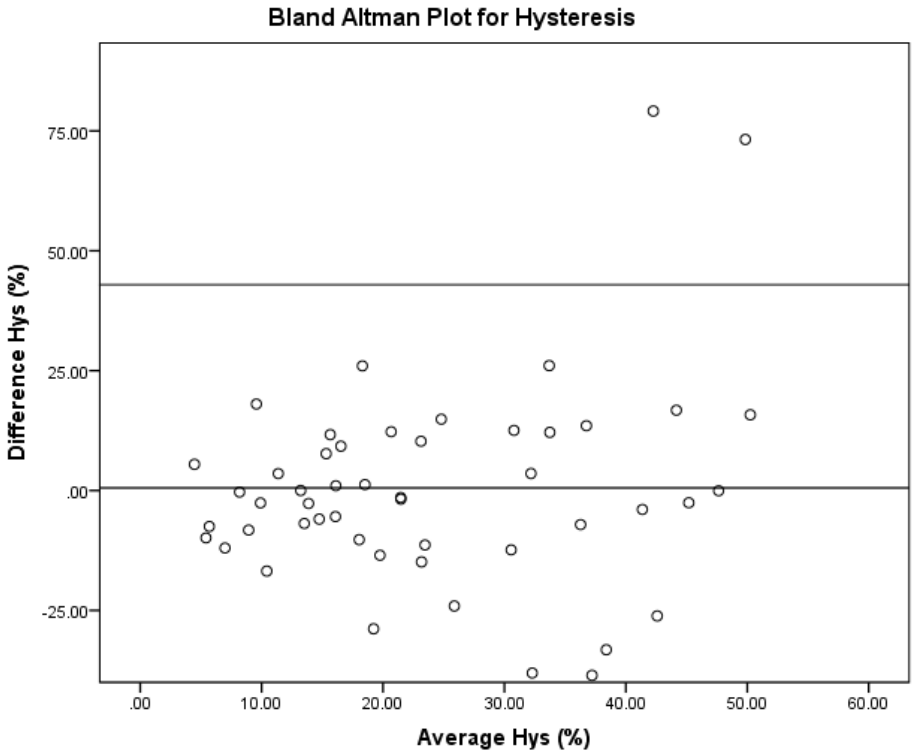


Figure 46 Agreement for AAR variable squeeze opening pressure depending on rate

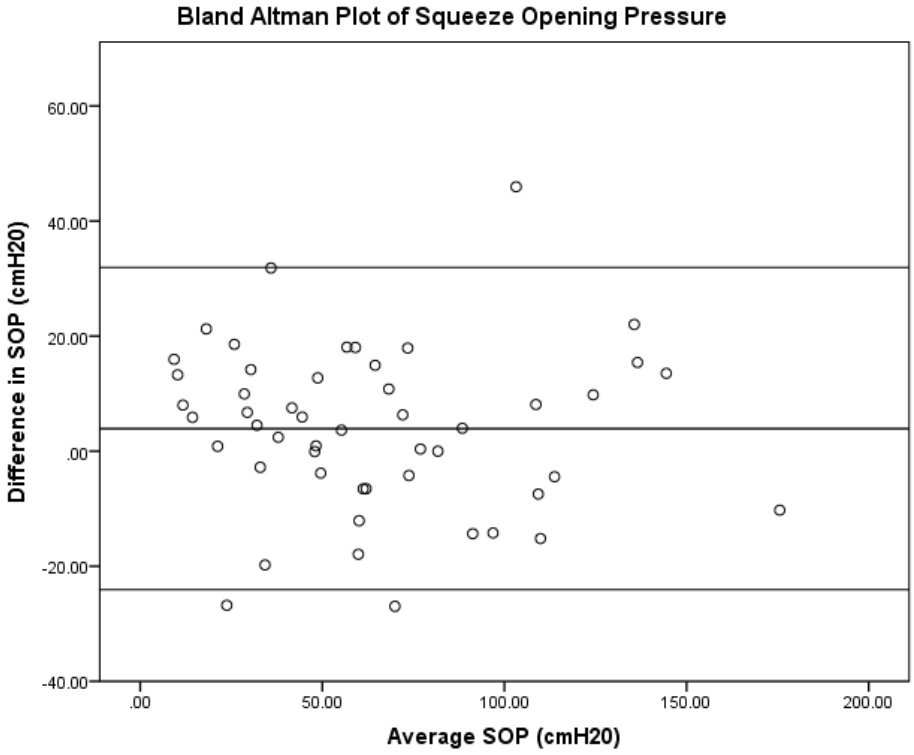


Figure 47 Agreement for AAR variable squeeze opening elastance depending on rate

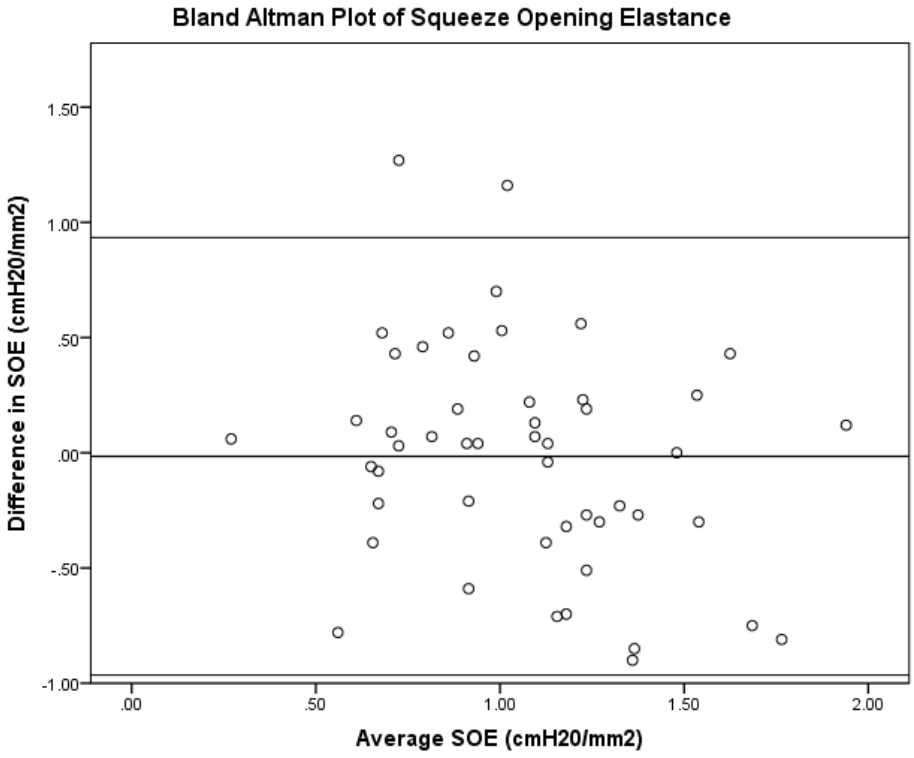


Figure 48 Agreement for manometry variable maximum resting pressure depending on AAR rate

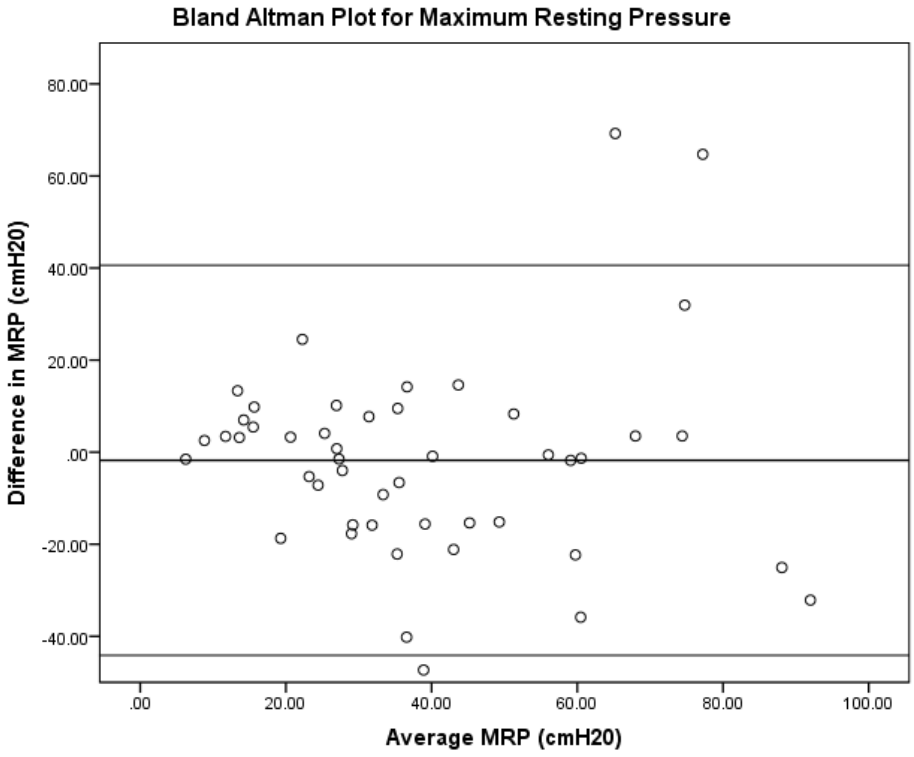
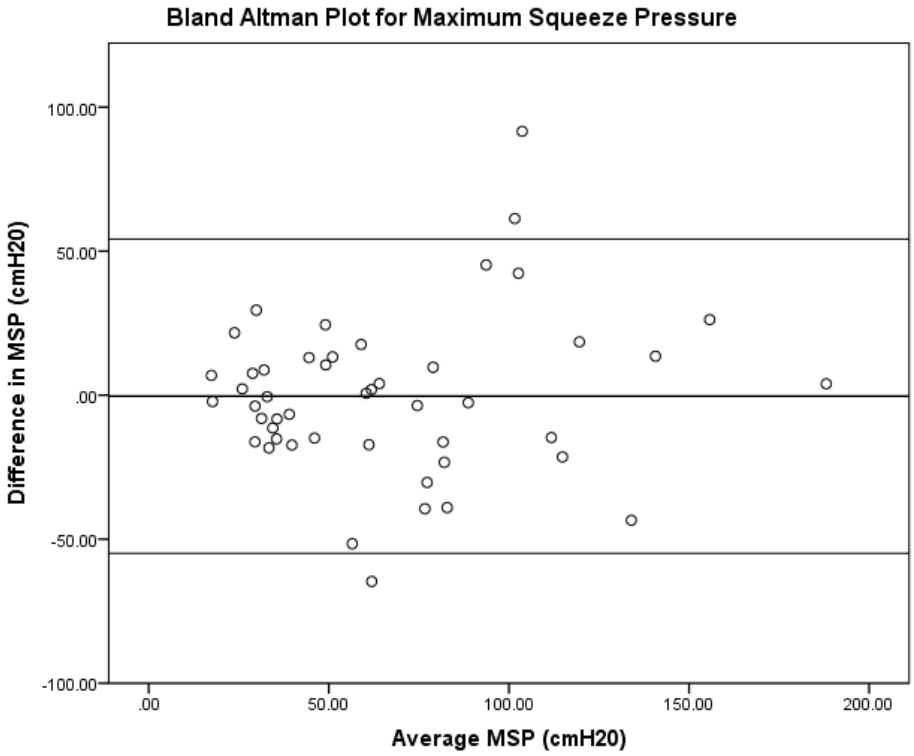


Figure 49 Agreement for manometry variable maximum squeeze pressure depending on AAR rate.



A subgroup analysis of 8 patients with passive FI did not show a significant difference between normal and fast rate of AAR, nor did it have a significant effect on subsequent manometry assessment (Table 12).

Table 12 Rate of AAR and passive incontinence.

Variable	Normal Rate AAR (n=8)	Fast Rate AAR (n=8)	P value
AAR			
Opening Pressure (cmH_2O)	62 (7-89)	70 (4-82)	0.78
Opening Elastance (cmH_2O/mm^2)	0.81 (0.58-1.06)	0.91 (0.35-1.26)	0.87
Closing Pressure (cmH_2O)	56 (3-77)	58 (2-72)	0.58
Closing Elastance (cmH_2O/mm^2)	0.87 (0.61-1.17)	1.00 (0.31-1.34)	0.40
Hysteresis %	17 (0-82)	12 (3-43)	0.89
Squeeze Opening Pressure (cmH_2O)	97 (22-170)*	91 (21-181)*	0.07^{∞}
Squeeze Opening Elastance (cmH_2O/mm^2)	0.96 (0.80-1.48)	1.45 (0.42-1.81)	0.50
Variable	**Manometry after Normal Rate AAR (n=8)**	**Manometry after Fast Rate AAR (n=8)**	**P value**
Anal Manometry			
MRP (cmH_2O)	36 (10-100)	42 (8-63)	0.67
MSP (cmH_2O)	64 (30-169)	68 (13-143)	0.48

*Comparison of the rate of AAR on manometry and AAR variables for patients with passive incontinence. Values shown are medians (range). Comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. *Means (range), $^{\infty}$Paired samples t-test. Significance level <0.05.*

A subgroup analysis of 16 patients with urge FI did not show a significant difference between normal and fast rate of AAR, nor did it have a significant effect on subsequent manometry assessment (Table 13).

Table 13 Rate of AAR and urge incontinence.

Variable	Normal Rate AAR (n=16)	Fast Rate AAR (n=16)	P value
AAR			
Opening Pressure (cmH_2O)	39 (6-85)*	40 (6-85)*	0.71$^{\infty}$
Opening Elastance (cmH_2O/mm^2)	1 (0.58-1.90)	1 (0.53-1.66)	0.70
Closing Pressure (cmH_2O)	33 (5-77)*	30 (4-70)*	0.15$^{\infty}$
Closing Elastance (cmH_2O/mm^2)	1.10 (0.62-1.58)	0.98 (0.49-1.85)	0.98
Hysteresis %	20 (8-86)	23 (8-55)	0.16
Squeeze Opening Pressure (cmH_2O)	65 (17-113)	64 (4-113)	0.87
Squeeze Opening Elastance (cmH_2O/mm^2)	1.08 (0.56-1.66)*	1.07 (0.44-2.06)*	0.94$^{\infty}$
Variable	**Manometry after Normal Rate AAR (n=16)**	**Manometry after Fast Rate AAR (n=16)**	**P value**
Anal Manometry			
MRP (cmH_2O)	34 (5-110)	42 (7-108)	0.15
MSP (cmH_2O)	64 (17-132)	74 (19-156)	0.12

*Comparison of the rate of AAR on manometry and AAR variables for patients with urge incontinence. Values shown are medians (range) unless otherwise stated. Comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. *Means (range), $^{\infty}$Paired samples t-test. Significance level <0.05.*

Discussion

This prospective randomised study of 50 patients with faecal incontinence assessed two different rates of stretch of the anal canal using AAR; the standard rate of stretch was 5cmH_20/3secs and the faster rate was 5cmH_20/1secs. The study was designed to recreate the clinical scenario of a faecal bolus arriving at the anal canal and assess its response to a more rapid passage.

No difference was found between normal or fast rates of AAR in all 5 variables at rest (Op, Oe, Cp, Ce and Hys). We must therefore reject our hypothesis that the pressure at which the anal canal opens will be greater at higher filling rates.

A possible explanation for these findings could be that the sphincters were already working at their maximum capacity at the normal rate of 5cmH_20/3secs. A further study at a slower filling rate would be required to explore such a possibility. Additional slower rates were not chosen for this study as it would have resulted in unacceptably long appointments. Was the rate of distension fast enough to expose a significant difference? This explanation is difficult to prove with the current method and equipment, as a faster rate between 5cmH_20/1secs and continuous, would risk the quality and quantity of data produced due to an insufficient plateau phase. It is during the plateau phase that measurement takes place. It seems however, that this explanation is less likely as the study was powered to detect a difference in Op of greater than 5.6cmH_20 at the conventional significance level of 0.05. If an increase of 2secs in the rate of inflation, i.e. inflating three times as fast does not show (5cmH_20/3secs to 5cmH_20/1secs) a statistical difference of more than 5.6cmH_20, then increasing the rate by less than 1sec is unlikely to produce a clinically or statistically significant difference. Another explanation could be that the IAS does not augment its response to challenge at all. It would require a study of continent patients over a range of rates (very fast to very slow) to examine this unlikely hypothesis. AAR has been shown to be more sensitive than manometry [204, 283]; it is therefore implausible that AAR as a test is too blunt an instrument to detect a change.

It is important to note that this study was concerned with a faster rate of inflation at rest and not concerned with voluntary squeeze variables (SOP & SOE). However this study can state that prior examination with either fast or normal rate AAR does not influence SOP & SOE (Table 11).

The resistance of the anal canal to opening (Oe) was not found to be different nor was the ability of the anal canal to close following a period of distention (Ce) with a faster rate of inflation. The pressure at which the anal canal closed (Cp) was also unchanged. Hence regardless of the rate of stretch, the anal canal resists opening, is able to close and closes at the same rates and pressures.

Previous manometry and EMG studies have shown IAS spontaneous slow wave activity and reflex activity in response to rhythmic rectal pressure waves [315, 316]. SM has also been shown in marine models (*Holothuria nigra*) since 1926 to contract in response to stretch [306, 317]. These properties make a base line reference point difficult to establish and opens up debate as to whether an observation of SM activity is the result of spontaneous activity or a response to stretch. Furthermore, changes in intra-abdominal pressure (under circumstances such as standing up, cough or a Valsalva manoeuvre) cause reflex changes in EAS sphincter pressure [318]. This raises the question of whether true resting pressure exists – indeed is there any activity at all without stretch? It seems that the anal sphincters are in a constant state of flux, responding to various stimuli to maintain the status quo of continence. In order to achieve true rest the following criteria must at least be met;

- An Empty bowel,
- Elimination of central and peripheral nervous input,

- Block muscle activity,
- Control for intra-abdominal pressure,
- Position the patient supine.

If the IAS has no activity at true rest, it is fundamentally different to the properties of SM described by Gordon and Siegman (Ch12 Introduction) [306]. It seems more likely that there is resting activity in the anal sphincters but that measuring devices that stretch it, such as manometry catheters and balloons, may significantly increase its activity.

Analysis of the reflected sound waves cannot occur at the same time as the pump is active because the noise it creates interferes with AAR measurement. The pump cannot be isolated from the patient (for example in a separate room) in its current setup as the sound wave production occurs in the same unit as the pump and is connected via 1 metre of tubing. Measurement begins immediately after each inflation step (when the pump switches to inactive) and continues until the pump becomes active again, taking 1200 cross sectional area measurements per second. Therefore it measures the cross sectional area after the stretch has taken place. This limitation creates a blind spot in data capture and the possibility of missing a transient rise in pressure in response to stretch. The time lag between stretch and measurement using the stepwise technique is as much as 3 seconds in comparison to the milliseconds it takes for muscle to respond. Thus it is entirely possible that muscle could respond before measurement occurs. Constant measurement, a topic of future studies would not only provide a more robust method but allow investigation

of the sphincters in response to cough or Valsalva manoeuvres that occur over a short period of time.

There are two possible explanations for the results of this study, firstly that rates of anal canal stretch had no effect on AAR values or secondly that AAR was unable to measure a true difference. The current methodology has found no effect of different rates of stretch on AAR values. However it is also possible that this methodology is unable to measure a true response. There are inherent properties of SM that make measurement difficult. SM also has the ability to contract spontaneously and can adapt to a new muscle length (stress-relaxation response). The ability of SM to contract spontaneously is alone unlikely to mask a true difference between fast and normal rates of stretch. Even if a proportion of the 50 patients measured with the fast rate AAR spontaneously contracted one would also expect a similar proportion to do the same in the normal rate group. Therefore when compared over 50 patients a true difference should still be observed. However the ability of SM to adapt to a new muscle length may be missed during a blind spot in data capture if the muscle adapts before measurement begins. This would mean that the method is unable to measure a transient true difference. Lastly although this study was conducted at rest and concerned primarily with the stretch response of the IAS, it must not be forgotten that a contribution may exist from the EAS. The EAS has been reported to contribute 15-40% of resting pressure and be responsible for a reflex muscle contraction via the EAS spindle stretch receptor. However as patients were designed to be their own control the more predictable striated EAS contribution was accounted for.

A significant difference was not found in manometry variables (MSP & MRP) after prior investigation with either normal or fast rate AAR. This finding adds a further

layer of validation to that described in Chapter 11 when assessing the order of data collection. It confirms that AAR and manometry can be performed in any order and at either rate with reliable results. This study has validated a faster method of AAR that can be used alongside manometry. Fast rate AAR (4mins 30secs to complete) at rest is 50% faster than normal rate AAR (9mins to complete). A quicker investigation may lead to greater patient satisfaction and more patients that can be seen within a unit of time, thus reducing costs.

It would be a logical progression to investigate a faster assessment of AAR with squeeze. Current investigation of urge FI, the most common pattern of FI is poor and does not correlate with symptom severity [205, 319]. One reason for this is that it requires patients who already have weakened sphincters to squeeze maximally over a period of time, resulting in fatigue and thus unreliable results. Inevitably any method of assessing voluntary contraction of the EAS relies on patient cooperation and effort, which can vary. Nonetheless some of these problems could be reduced with a faster method of assessment.

Conclusion

This study has found no difference between AAR variables at the normal rate of inflation and a fast rate of inflation, validating a faster method of performing AAR. The faster method of performing AAR does not influence subsequent manometry variables and vice versa, thus validating the use of manometry and the fast rate of AAR in any order.

Chapter 9 Investigation of the IAS with AAR using regional nerve blocks

Introduction

This study was designed to further establish what AAR measures. Is AAR an investigation that solely assesses the IAS, the EAS or does it measure both? If both, what are the relative contributions of IAS and EAS to resting pressure?

A number of authors have attempted to determine the relative contribution of the IAS to resting pressure by using manometry and isolating the IAS or the EAS for interrogation. They tried to achieve isolation in various ways – use of the RAIR, neuromuscular blockade (NMB) and general anaesthetic (GA), bilateral pudendal nerve block (bPNB) and electromyographic (EMG) extrapolation. Lestar et al., measured 21 patients in 1989 during maximal RAIR, under GA and again after abdominal perineal resection and found that the IAS contributed 50-60%, EAS 30% and the haemorrhoidal plexuses 15% to resting pressure [314]. However the method used by Lestar et al., was complex and isolation of the sphincters was assumed and not proven with EMG unlike other studies. 10 years earlier Schweiger measured 20 patients simultaneously with EAS EMG and anal manometry, he then extrapolated the part played by the IAS to be 75% of total resting pressure using correlating regression lines [320]. Schweiger tested his assumption that the isolated IAS pressure can be extrapolated via a regression curve, by comparing his results to MRP post EMG confirmed curarization. The same 10 patients were curarized until no EMG spikes were seen in the EAS, hence isolating the IAS for re-examination with manometry. The MRP was then compared with the extrapolated IAS pressure results

with a low mean error. This suggested a reliable method of extrapolation, that also complemented previous work by Duthie and Watts in 1965 [321]. Duthie and Watts used manometry to measure 10 male patients at rest, under GA and under GA with muscle relaxant. They found a significant reduction in mean resting pressure following GA but no difference was demonstrated in mean resting pressure with the addition of muscular paralysis. Frenckner and Euler measured 10 patients before and after the EAS had been paralysed by a bPNB and found that the IAS contributed 85% of the pressure in the anal canal at rest but only about 40% after sudden rectal distention [82]. They used EMG to assess the success of the bPNB, a method also used in the present study. No EMG activity at all was detected in half of the 10 subjects and only single motor units were detected in the others.

In summary, four manometry based studies have reported a 60-85% contribution of the IAS to resting pressure.

At present it is hypothesised that at rest the AAR variables of Op, Oe, Cp, Ce and Hys measure predominantly IAS function and during voluntary squeeze the variables of SOP and SOE measure predominantly EAS function.

Previous unpublished work with AAR by Hornung and colleagues [288] led to the design of this present study. They recruited 25 continent men to determine the relative contribution of the EAS and IAS to AAR parameters. The subjects were measured with AAR and manometry pre operatively, under GA without NMB and under GA with NMB. NMB completely paralyses the striated muscle of the EAS allowing analysis of the IAS in isolation. The results were surprising. After GA a significant drop in Op, Cp and MRP was observed, but after subsequent

administration of the NMB a significant increase in Op was demonstrated. In a control group of 10 continent men under GA who did not receive a NMB agent but underwent sequential measurements with AAR and manometry these changes were not replicated, suggesting that the differences were due to the NMB agent. The EAS after NMB is completely paralysed therefore the Op is predominately a measure of IAS function. Although in this study EAS paralysis was not confirmed with EMG, confirmation of complete NMB was performed by the anaesthetist using a facial nerve stimulator. Hence a marked increase in IAS function was observed when the EAS was paralysed. This phenomenon has not been seen with previous manometric studies [321]. The mechanism by which the NMB caused modulation in the function of the IAS is unknown. The authors concluded that the unexpected increase in Op following NMB requires further clarification, but suggested the presence of complex neuropharmacological and reflex mechanisms may be involved in maintaining resting and anal sphincter tone and anal continence.

The work by Hornung and colleagues provided the motivation to design this study to elucidate their findings. This study involves AAR and manometry assessment before and after bPNB with electromyography confirmation, thereby blocking the sole nerve supply to the EAS and isolating the IAS for interrogation. Thus it excludes the variable of a GA and uses EMG to confirm isolation of the IAS.

Aim

The aim of this study was to establish if AAR is a test of IAS function independent of EAS function, by testing the following hypothesis;

- Resting AAR variables will not be influenced by bPNB.
- Squeeze AAR variables will show a linear relationship with EMG activity.

Methods

Patients

All patients undergoing a bPNB for pudendal neuralgia received an invitation letter, patient information sheet and consent form in the post over 1 week before their appointment. Patients were encouraged to contact the principal investigator for more information if required and contact details were supplied. Patients were approached on the day of their nerve block by a nurse who was independent of the study. Adults >18 years old, able to consent and who were about to undergo a bPNB were included in the study. Patients with or without symptoms of incontinence were included. Minors <18 years old or others who were unable to consent were excluded from the study. Patients with coagulation defects (or on anticoagulation medication), a pacemaker, permanent or temporary sacral nerve stimulator or external wires were also excluded from the study. Patients who wished to take part in the research were then consented by the principal investigator. Demographic and clinical data were recorded as detailed in Chapter 7.

Recruitment

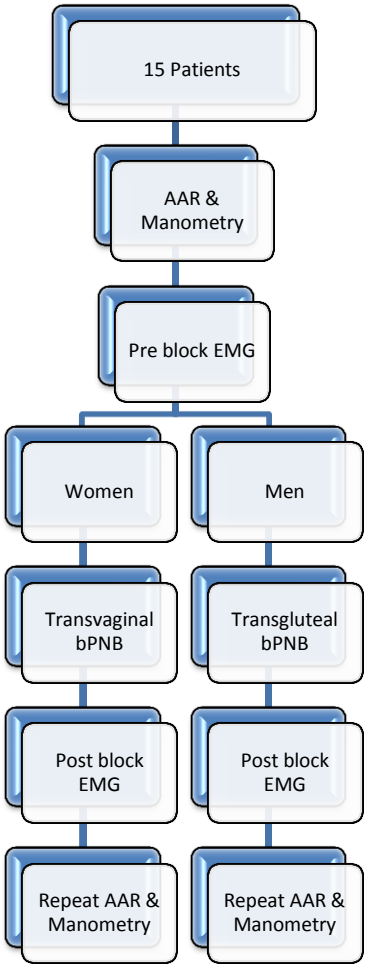
The study was powered to recruit 2 patients per month for 15 months to achieve a total of 30 patients. The monthly recruitment target was based on 2 local anaesthetic

nerve block lists per month with usually 3 patients per list receiving a bPNB. Target recruitment was 1 patient per list, allowing for 2 of 3 patients either being unsuitable or unwilling to take part in research. During the study dates nerve block procedures were reconfigured to concentrate all bPNB into one half day list per month. To allow sufficient time to consent and repeat AAR, manometry and EMG measurements only one patient could be recruited per half day list. Each patient recruited constituted an individual study that took 5 hours to complete before data was inputed. In total 90 patients were approached and 15 recruited. Service reconfiguration therefore halved recruitment to 15 patients in 15 months.

Protocol

Patients underwent manometry and AAR in the left lateral position followed by electromyography (EMG) in the lithotomy position once in theatre. Women underwent a transvaginal bPNB and men underwent a transgluteal bPNB (see Materials and Methods Chapter 6 for all techniques described here). After a 5 min rest EMG assessment was repeated to assess success of the nerve block. EMG method and analysis were independently verified by a consultant neurophysiologist. 30mins after the nerve block manometry and AAR were repeated (Figure 50).

Figure 50 Overview of Process – AAR and bPNB



Potential Risk and Harms

This study involves the insertion of a concentric EMG needle into the external anal sphincter. EMG is a widely used technique in current practice [322]. Patients may experience discomfort from insertion of the needle into the sensitive perianal area, however the procedure is well tolerated and complications are rare [323]. Complications of the needle can include bleeding, infection, nerve injury and other local trauma. There are no reported cases of bleeding complications with patients on antiplatelet medications; however patients who are anticoagulated (warfarin or coumarins) or have a coagulation defect were excluded from the study [323]. In addition, as with all electrical devices, there is a low risk of electrical injury.

Therefore patients with pacemakers, permanent or temporary sacral nerve stimulators or any external wires were also excluded.

Statistical Analysis

A post hoc sample size calculation was performed. This suggested that with 15 patients the study would have an 80% power at a conventional significance level of 0.05 to detect differences in resting OP before and after bPNB of greater than 11cmH_2O using a standard deviation of 14.9cmH_20. Normal continuous data were compared using the paired t-test and not normally distributed continuous data with the Wilcoxon Signed Rank test for paired variables or Mann-Whitney U test for independent variables. Pearson's correlation coefficient and scatter graphs were used to assess agreement of variables and EMG activity. Parametric correlation statistics were used to reflect the hypothesis that a linear relationship may exist between EMG activity and AAR variables and that data normality cannot be proven in a small data set. All data were recorded in an excel database and interrogated using SPSS Statistics version 20 software (IBM, Chicago, IL).

Results

15 patients were recruited over a 15 month period (August 2013 to October 2014); demographic data can be seen in Table 14 below. The median age was 59 (range 25-89), 10 (67%) patients were female and 12 (80%) were continent. The 15 patients recruited had a normal mean type 4 stool on the Bristol stool chart and the median Vaizey score was 0 reflecting the continence of the group.

Table 14 Demographics for the study of AAR before and after bPNB

Variable	Patients Undergoing Investigation (n=15)
Median age (range)	59 (25-89)
Sex	
Male	5 (33)
Female	10 (67)
Type of incontinence	
Continent	12 (80)
Mixed	2 (13)
Passive	1 (7)
Mean Bristol Stool chart (range)	4 (2-6)
Median Vaizey Score (range)	0 (0-19)
Mean parity (range)	1.3 (0-4)
Median vaginal delivery (range)	1 (0-4)
Median C-section (range)	0 (0-1)
Traumatic childbirth	5 (33)
Forceps	2 (13)
Ventouse	1 (7)
Tears	5 (33)
Previous gynaecological surgery	8 (80)
Hysterectomy	6
Sterilisation	1
Diagnostic Laparoscopy	1
RBL of haemorrhoids	2 (13)
Previous Anorectal Surgery*	2 (13)
Haemorrhoidectomy	1
PTNS	1
Previous abdominal surgery	8 (53)
Cholecystectomy	4
Appendicetomy	2
Inguinal hernia repair	1
Cystectomy & ileal conduit	1
Nissens	1
Gastrectomy (benign disease)	1

Demographics for the study of AAR before and after bPNB (values in parenthesis are percentages unless otherwise stated).

*Urge=inability to defer defecation, passive=faecal soiling without awareness, mixed=combination of both urge and passive incontinence symptoms. Bristol stool chart ranges from 1 to 7 (1=hard stool and 7=liquid stool), Vaizey=faecal incontinence severity score which ranges from 0 to 24 (24 being the most severe incontinence), RBL=rubber band ligation of haemorrhoids, PTNS=percutaneous tibial nerve stimulation.*Patients who underwent previous abdominal surgery often had more than 1 procedure accounting for a greater number of procedures than patients.*

9 patients had a transvaginal bPNB and 6 patients had a transgluteal bPNB. One female patient did not tolerate a transvaginal bPNB therefore underwent a transgluteal block. EMG results from 6 of 15 patients were removed from analysis for the following reasons; 2 due to the EMG learning curve of the principal investigator, 1 due to the absence of recordable motor unit potentials in all parts of the EAS, 2 EMG recordings were abandoned at the patients' request and 1 patient had a failed block which saw an increase in EMG activity (Table 15). The median reduction in EMG motor unit activity after both routes of bPNB was 45% (range -25-48%). A comparison of transvaginal and transgluteal bPNB's found no significant difference (p=0.79) between the 2 routes (Table 16).

Table 15 Reduction in EMG activity post bPNB

Patient No (n=15)	Sex	bPNB Route	Reduction in EMG Activity %
1	Female	Transvaginal	Discarded
2	Male	Transgluteal	Discarded
3	Female	Transvaginal	45
4	Female	Transvaginal	No MUP
5	Female	Transvaginal	48
6	Male	Transgluteal	37
7	Male	Transgluteal	26
8	Male	Transgluteal	46
9	Female	Transgluteal*	Not completed
10	Female	Transvaginal	Not completed
11	Female	Transvaginal	20
12	Male	Transgluteal	45
13	Female	Transvaginal	48
14	Female	Transvaginal	46
15	Female	Transvaginal	-25
Median (range)			45 (-25-48)

*Reduction in EMG activity post bPNB. Results from patients 1&2 were discarded due to a learning curve in performing EMG, no motor unit potentials (MUP) were found in patient 4, EMG was abandoned in patients 9 & 10 at the patients request. *Patient 9 did not tolerate a vaginal bPNB therefore underwent the transgluteal approach. All 5 patients without a reduction in EMG stated for the reasons above went on to have repeat AAR and manometry measurements.*

Table 16 bPNB by route

N=10	Transvaginal route	Transgluteal route	P Value
Reduction in EMG Activity %	46 (-25-48)	41 (26-46)	0.76

bPNB by route. Values shown are medians (ranges) and routes were compared using Mann-Whitney U test.

When analysing all patients (n=15) after bPNB no significant difference was found in AAR assessment at rest (Op, Oe, Cp, Ce and Hys). However SOP was significantly reduced (p=0.04) from 112cmH_2O to 105cmH_2O. Similar to AAR results at rest, MRP was not significantly different after block, but MSP and ISP were significantly reduced from 129cmH_2O to 96cmH_2O (p=0.02) and 63cmH_2O to 28cmH_2O (p=0.02) respectively (Table 17).

AAR equipment can produce a maximum pressure of 200cmH_2O, therefore during a voluntary squeeze assessment a patient may be able to occlude the lumen of the catheter up to this pressure but the machine is unable to produce a greater pressure. Hence the maximum recordable SOP is 200cmH_2O. Continent individuals, especially men can produce pressures in excess of 200cmH_2O when asked to squeeze. The SOP in 3 patient's pre block exceeded 200cmH_2O and in this circumstance the SOP is recorded as 200cmH_2O, an underestimate of the true value. 2 patients recorded pressures in excess of 200cmH_2O before and after bPNB, resulting in the inability to measure a change in SOP at all. Despite this the overall median SOP was found to be significantly reduced post bPNB (Table 17). Secondly, because SOE is calculated from the gradient of the SOP curve, when the pressure exceeds 200cmH_2O no squeeze opening curve is generated and subsequently the gradient or SOE could not

be calculated. Therefore SOE has not been recorded and analysed in 5 cases pre block and 2 cases post block.

Table 17 AAR and manometry variables pre & post bPNB

Variable	AAR pre bPNB (n=15)	AAR post bPNB (n=15)	P value
AAR			
Opening Pressure (cmH_2O)	68 (10-89)	47 (10-93)	0.09
Opening Elastance (cmH_2O/mm^2)	0.94 (0.46-2.43)	1.08 (0.28-2.15)	0.53
Closing Pressure (cmH_2O)	52 (4-77)	46 (6-92)	0.83
Closing Elastance (cmH_2O/mm^2)	1 (0.46-2.96)	1.01 (0.56-1.79)	0.55
Hysteresis %	19 (13-52)	13 (1-62)	0.31
Squeeze Opening Pressure (cmH_2O)	112 (45-200)	105 (25-200)	0.04
Squeeze Opening Elastance (cmH_2O/mm^2)	0.95 (0.67-1.35)	1.17 (0.33-2.46)	0.51
Variable	**Manometry pre bPNB (n=15)**	**Manometry post bPNB (n=15)**	**P value**
Anal Manometry			
MRP (cmH_2O)	75 (14-161)*	71 (14-146)*	0.47∞
MSP (cmH_2O)	129 (37-309)	96 (35-350)	0.02
ISP (cmH_2O)	63 (8-217)	28 (8-243)	0.02

*AAR and manometry variables pre & post bPNB. Values shown are medians (range). Comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. *Means (range), ∞Paired samples t-test. Significance level <0.05.*

9 patients had a successful bPNB, defined as any reduction in EMG activity. Subgroup analysis of this group only found a significant reduction post bPNB in the variables of SOE and MSP (Table 18). With a small data set (n=9) statistical significance is difficult to prove, however a relationship or trend can be observed in

other variables assessing the function of the EAS; such as SOP (129 to 110cmH_2O, p=0.13) and ISP (66 to 32cmH_2O, p=0.09).

Table 18 AAR and manometry variables pre & post successful bPNB.

Variable	AAR pre bPNB (n=9)	AAR post bPNB (n=9)	P value
AAR			
Opening Pressure (cmH_2O)	72 (24-86)	61 (23-93)	0.59
Opening Elastance (cmH_2O/mm^2)	1.02 (0.78-2)	1.08 (0.56-2.15)	0.14
Closing Pressure (cmH_2O)	53 (18-72)	52 (12-92)	0.67
Closing Elastance (cmH_2O/mm^2)	1.01 (0.77-1.51)	1.08 (0.56-1.58)	0.64
Hysteresis %	14 (13-25)	13 (1-56)	0.68
Squeeze Opening Pressure (cmH_2O)	129 (49-200)	110 (43-200)	0.13
Squeeze Opening Elastance (cmH_2O/mm^2)	1.01 (0.67-1.35)	1.36 (0.92-1.71)	0.05
Variable	**Manometry pre bPNB (n=9)**	**Manometry post bPNB (n=9)**	**P value**
Anal Manometry			
MRP (cmH_2O)	89 (14-108)	79 (32-107)	0.31
MSP (cmH_2O)	155 (69-309)	98 (64-350)	0.05
ISP (cmH_2O)	66 (20-217)	32 (17-243)	0.09

AAR and manometry variables pre & post bPNB for the 9 patients with a successful bPNB (a successful block was defined as a positive reduction in EMG activity). Values shown are medians (range). Comparisons made using Wilcoxon Signed Rank Test. Significance level <0.05.

Previous studies have shown a linear correlation between the electromyographic activity of a striated skeletal muscle (such as EAS) and its pressure increase [324]. Table 19 below shows a subgroup analysis of the 9 patients with a successful bPNB block in comparison to the percentage reduction in variables of AAR and

manometry. The variables chosen reflect the hypothesis' that; tests of the EAS (SOP, MSP and ISP) will show a linear relationship with EMG activity (i.e. SOP will reduce as EMG activity reduces) and tests of the IAS (Op and MRP) will not show a linear relationship with EMG activity (i.e. Op is a test of the IAS independent of EAS function).

Table 19 EMG activity compared to AAR and manometry variables

Patients with successful bPNB (n=9)	Reduction in EMG Activity (%)	Reduction in Op (%)	Reduction in SOP (%)	Reduction in MRP (%)	Reduction in MSP (%)	Reduction in ISP (%)
11	20	5	-8	1	6	18
7	26	-1	1	-214	6	55
6	37	-1	48*	9	66	84
3	45	38	46	27	52	82
12	45	-9	0*	15	33	65
8	46	1	0*	0	-13	-20
14	46	-21	-4	4	10	26
5	48	3	15	0	12	27
13	48	62	11	53	33	-22
Median (ranges)	**45 (20-48)**	**1 (-21-62)**	**1 (-8-46)**	**4 (-214-53)**	**12 (-13-66)**	**27 (-22-84)**

*Comparison of the reduction in EMG activity with the reduction in AAR and manometry variables. A successful block was defined as a positive reduction in EMG activity, numbers from the first column correlate with table 15. A negative value represents an increase in change. [α]Patient 6 exceeded a SOP of 200cmH_2O (the limit for AAR measurement) pre block, therefore 48% is an underestimate of the potential reduction in SOP. *****2 patients who exceeded 200cmH_2O pre and post block therefore resulting in a 0% change and thus excluded from analysis.*

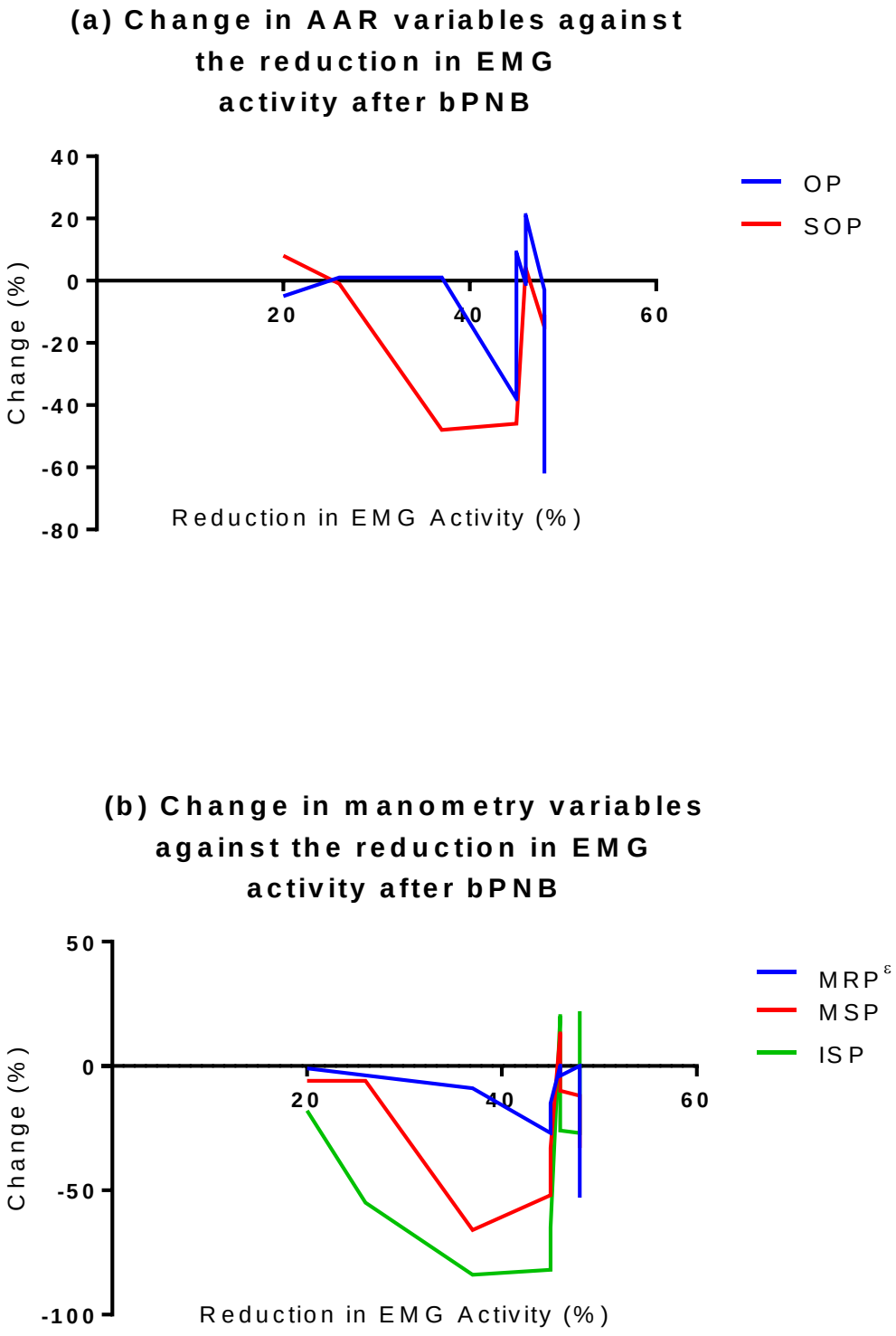
The variables of AAR (Op and SOP) and manometry (MRP, MSP and ISP) had no correlation with EMG activity (Table 20) that was not significant. Graphs 4a and 4b below show the absence of relationships. One MRP value (214% increase in MRP after bPNB) from patient 7 was found to be an anomaly and therefore removed from Figure 51b and subsequent scatter graph analysis.

Table 20 Correlation of AAR and Manometry variables with EMG activity

Variable	Pearson Correlation Coefficient	P value
AAR correlation with % reduction in EMG post bPNB		
Change in Opening Pressure (%)	0.215	0.58
Change in Squeeze Opening Pressure (%)	0.517	0.24
Anal Manometry correlation with % reduction in EMG post bPNB		
Change in MRP (%)	0.562	0.12
Change in MSP (%)	0.165	0.67
Change in ISP (%)	-0.185	0.64

Pearson correlation coefficients between reduction in EMG and change in AAR and Manometry variables (+1 is perfect positive correlation and -1 is perfect negative correlation, 0 is no association). Pearson 2-tailed significance level <0.05.

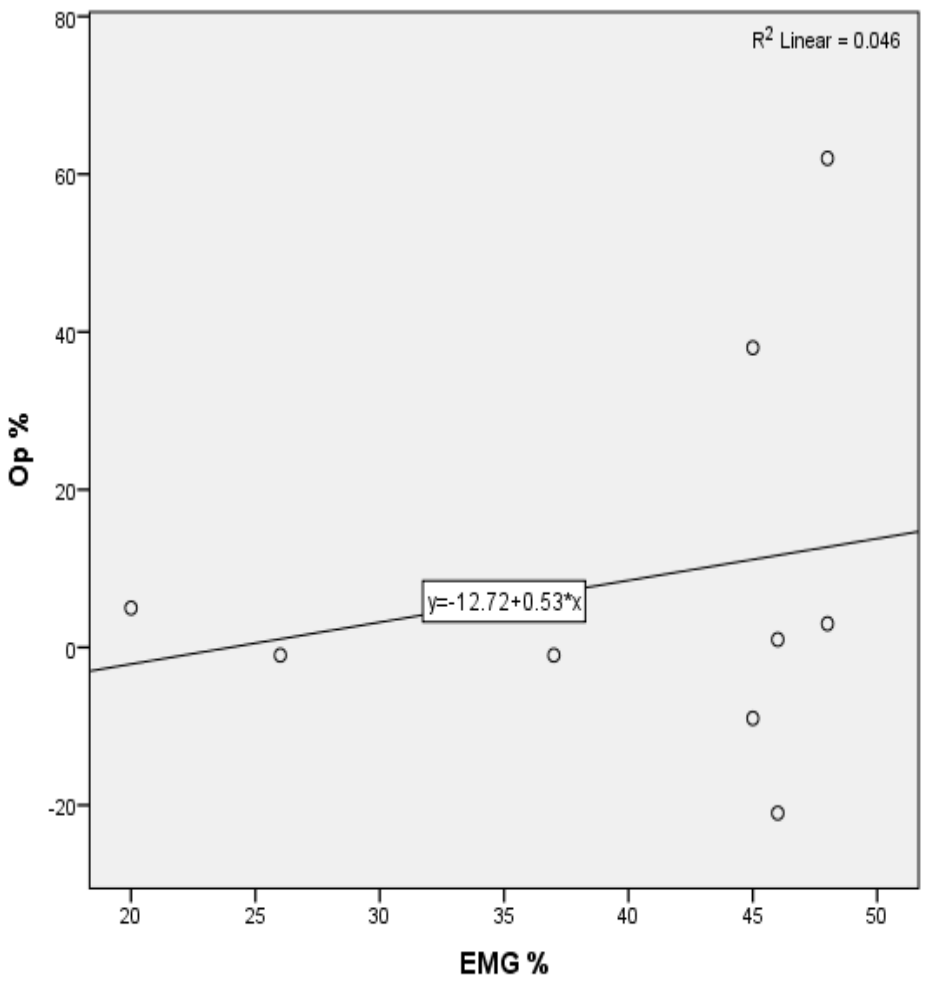
Figure 51 AAR and manometry variables against EMG activity after bPNB



(a) Change in AAR variables (Op and SOP) against reduction in EMG activity after bPNB. (b) Change in manometry variables (MRP, MSP and ISP) against reduction in EMG activity after bPNB. $^{\varepsilon}$*One patient was excluded from MRP analysis. No significant difference found between Op and SOP (p=0.74), MRP and MSP (p=0.14), MRP and ISP (p=0.12) and MSP and ISP (p=0.14) using the Wilcoxon Signed rank test.*

Similar to the Pearson correlation data, scatter graph analysis (Figure 52 for example) of EMG activity and the reduction in AAR and manometry variables (Op, SOP, MRP, MSP and ISP) found no agreement in all variables between data points and the line of best fit. With no linear relationship demonstrated it was not possible to extrapolate the data any further to estimate the effect on AAR parameters of a complete block of the EAS.

Figure 52 Reduction in Op against the reduction in EMG activity.



Scatter Graph showing the reduction in Op against the reduction in EMG activity. No correlation found between EMG activity and Op reduction (R^2=0.046, where 1 is perfect agreement between the data points and the line of best fit and 0 shows no agreement).

Discussion

The purpose of this study was to establish what happens to AAR parameters if the EAS is blocked. Successful isolation of the IAS should make it possible to measure the IAS alone and establish what AAR is measuring.

15 patients with pudendal neuralgia were recruited and underwent AAR and manometry before and after a bPNB. bPNB had no effect on AAR variables at rest, or in other words the function of the IAS (Op, Oe, Cp, Ce, Hys and MRP). However tests of the EAS (SOP, MSP and ISP) were all significantly reduced, as one would expect following a pudendal nerve block targeting the sole nerve supply to the EAS. One patient was found to have a 214% increase in MRP after bPNB, this value is likely to represent voluntary contraction at rest secondary to patient anxiety and pain as manometry was performed first after bPNB.

The success of the bPNB was assessed by EMG. EMG involved inserting a concentric needle into the EAS muscle and measuring MUP's before and after nerve block to establish a percentage reduction. The two routes of bPNB (transvaginal and transgluteal) were found to be equivalent in reduction of EMG activity. 9 of 15 patients had a successful bPNB (defined as any reduction in EMG activity) and these patients had a median reduction in motor unit activity of 45%. Previous work by Scudamore and Yates in the field of obstetric analgesia found a similar success rate of 50% for the transvaginal route but 25% for the transperineal route [325]. In contrast, Frenckner and Euler reported no EMG activity at all in half of 10 subjects and only single motor units in the other half [82]. In this study we found a maximum

reduction of activity of 48% in 2 patients. Despite a partial success in 50% of patients Frenckner and Euler assumed the remaining activity was due to the IAS alone stating that the IAS contributed 85% to resting pressure.

Interestingly, subgroup analysis of the 9 patients with a successful bPNB only found a significant reduction in SOE and MSP in contrast to analysis of all 15 patients where a significant reduction was seen in SOP, MSP and ISP. This is likely to reflect the small data set which is unable to deliver statistical significance. The relationship between variables is more important and a trend towards significance can also be seen in SOP and ISP. Again no change was observed in the function of the IAS but a reduction in the function of the EAS after successful bPNB. These results and the results of the analysis of all 15 patients suggest that AAR at rest is primarily an investigation of the IAS.

Unfortunately no correlation or agreement was found between the reduction in EMG activity and variables of AAR and manometry. This was perhaps expected for Op and MRP, as they are thought to be largely measures of the IAS, which if true, should not alter much when the EAS is blocked albeit to varying degrees. In view of previous studies one might expect a proportional linear relationship between the reduction in EMG activity and reduction in function of the EAS (SOP, MSP and ISP) [320]. However this was not observed. Without demonstrating a linear relationship it was not possible to extrapolate the data any further to estimate the effect on AAR parameters of a complete block of the EAS.

This study builds on previous unpublished work by Hornung and colleagues [288] who used a muscle relaxant to block the EAS for investigation with AAR. They

found a reduction in MRP and Op under GA. However with the addition of a NMB a significant increase in Op was observed. This was a surprising result and prevented Hornung and colleagues from estimating the contribution of the IAS to resting pressure by AAR. They concluded that complex neuropharmacological and reflex mechanisms may be responsible. In contrast, manometry studies by Frenckner and Euler showed a decrease in MRP after complete bPNB and Duthie and Watts did not find a significant change in MRP with the addition of a NMB agent [82, 321]. The current study was designed without the confounding factor of a GA and using EMG to confirm EAS paralysis, but did not witness a reflex increase in Op following partial block and is unable to elucidate the findings of Hornung and colleagues but lends support to their hypothesis that they observed a neuropharmacological effect rather than a local muscle effect.

This study is critical to understanding AAR but difficult to conduct for the following reasons;

- Difficulties in obtaining ethical approval especially when inserting needles into the anal sphincter in patients who already have pudendal neuralgia.
- The time taken for a neurophysiologist to teach the principle investigator to perform EMG of the EAS and analyse the results. All EMG analysis was checked by a consultant neurophysiologist.
- Service re-organisation resulted in a reduction in the number of bPNB lists resulting in target recruitment being halved. This led to a small data set and the statistical problems of proving normality and significance. However the numbers recruited were comparable with previous studies [82].

- Inherent difficulties in recruiting patients who have chronic pelvic and perianal pain conditions to have perianal needle EMG and 2 perianal catheter based tests. 6 patients were approached for every patient recruited over 15 months.

This study is limited by the nature of a partial bPNB which makes interpretation of results difficult. A complete block would allow one to conclude that the remaining function was mainly due to the IAS and any reduction in sphincter function was the part played by the EAS at rest. The pudendal nerve is the sole bilateral nerve supply to the EAS, however a one sided block may result in an intact contralateral supply and partially intact ipsilateral supply owing to the overlapping innervation, therefore preventing a successful block [326]. An alternative would be to perform the block under CT guidance (unavailable during the study dates) which may improve block success rates and provide anatomical evidence of correct infiltration; however EMG would still be required to assess success.

The local anaesthetic used was lidocaine hydrochloride which has a rapid onset of action and rapidly spreads through surrounding tissues, it has an approximate duration of action of 60-90mins. EMG was recorded 5mins after bPNB allowing sufficient time for its onset of action and the average time for the patients to repeat AAR and manometry was less than 60mins.

It is impossible to replicate the exact EMG needle placement within the EAS muscle before and after the block, causing an inconsistency in measurement. This error was minimised by using a clear anatomical protocol for needle placement and confirmation of placement within the muscle using EMG.

All patients in this study had pudendal neuropathy and a number will go on to be diagnosed with pudendal nerve entrapment syndrome. The effects of pudendal nerve pathology on continence and the EAS is inconsequential to this study as each patient acted as their own control, they were compared to themselves. Hence it was the difference that was important not the size of the value.

Lastly the assessment of SOP is limited for patients who record pressures exceeding 200cmH_2O, causing an underestimate in SOP disparity, or the inability to identify a change at all after bPNB. However, despite this limitation because the overall median SOP was found to be significantly reduced after bPNB it has not influence the interpretation of results.

Conclusion

In conclusion the bPNB's did not work rendering subsequent analysis difficult, bPNB should be performed under CT guidance. However this study has found a reduction in measurements of EAS function following a partial bPNB. No change was found after a 45% median reduction in EAS activity in AAR measurements at rest or MRP, suggesting that AAR at rest is predominately an investigation of IAS function. A linear relationship was not found between reduction in EMG activity and variables of AAR and manometry which also suggests that the EAS plays little part in the parameters of AAR at rest.

Chapter 10 Can AAR predict the response to Posterior tibial nerve stimulation?

Introduction

AAR was shown in one study to predict the outcome of percutaneous nerve evaluation (PNE), the trial period often used before sacral nerve stimulation (SNS) [283]. This study aimed to establish if AAR can predict the outcome from posterior tibial nerve stimulation (PTNS). The ability to predict response to PTNS would improve patient selection and have obvious economic advantages. This introduction will outline the current evidence for PTNS and studies that have attempted to find predictive factors in neuromodulation. There is an inevitable paucity of evidence for such a new treatment therefore some evidence from the more established treatment of SNS will also be discussed.

Mechanism of action

Neuromodulation of the pelvic floor is a relatively new treatment that uses electrical stimulation of a peripheral nerve. There are two types; SNS and PTNS. Despite the wide acceptance of SNS, the exact mechanisms of action of both are poorly understood [327]. It is thought that neuromodulation is based on the recruitment of residual anorectal neuromuscular function [279]. A systematic review of 53 articles by Carrington et al., in 2014 of the mechanisms of action of SNS concluded that due to the large body of evidence demonstrating effects located outside the anorectum it appears likely that the effect on anorectal function occurs at a pelvic afferent or central level [282]. A number of studies have investigated the central effect of SNS. Positron emission tomography has shown that PNE increases blood flow centrally and it seems that activity in some brain areas can be changed after chronic

stimulation [328]. Furthermore a reversible reduction in corticoanal excitability has been shown after PNE using transcranial magnetic stimulation, suggesting that SNS resulted in inhibition of the motor cortex to the EAS [329]. Carrington et al., continued to postulate a modus operandi that SNS is likely to modify ascending supraspinal control of defecation, inhibiting the activation of the spinobulbar pathways thereby reducing descending inhibition of sphincter function and rectal contractility via Onuf's nucleus [282].

Tibial nerve stimulation is a newer alternative to SNS. The tibial nerve contains afferent and efferent fibres originating from the fourth and fifth lumbar nerves and the first, second and third sacral nerves. Thus stimulation in this region may lead to changes in anorectal neuromuscular function similar to those observed with SNS owing to the shared sacral roots. First described in 1983 by McGuire and colleagues [330] for urinary incontinence the transcutaneous method was adjusted by Stoller [331] to use a percutaneous needle. In 2003, Shafik proposed using percutaneous PTNS for FI [332]. A detailed method for PTNS can be seen in Chapter 6. Following a large randomised control trial (RCT) of 145 patients transcutaneous tibial nerve stimulation (TTNS) was not found to be superior to sham stimulation, therefore attention turned to the percutaneous method.

The evidence for percutaneous posterior tibial nerve stimulation

A systematic review of tibial nerve stimulation found six cases series and one small RCT investigating PTNS [279]. The small pilot RCT of 30 patients compared PTNS (n=11) to TTNS (n=11) and to sham treatment (n=8) and found that PTNS had a greater reduction in the number of incontinence episodes and patients were able to

defer defecation for a longer interval than those undergoing TTNS or sham stimulation [333]. Three case series studies reported a 50% or greater reduction in the number of FI episodes immediately after treatment, in 63-82% of patients [295, 296, 333]. In one study that reported on this outcome after 1 year, 59% of patients still experienced treatment success [295]. The Cleveland clinic incontinence score which is a commonly used measure of severity improved in four studies (summary median reduction of 13 to 8) [295, 296, 333, 334] and five studies have reported improved changes in quality of life (QOL) especially in the parameters of depression, coping/behaviour, embarrassment and lifestyle [295, 332-335]. Two studies assessed anorectal manometry after treatment and both found an improvement in mean peak squeeze pressure, but not in resting pressure or rectal sensation [333, 334]. A more recent study from Lopez-Delgado et al., in 24 patients with FI found an increase in resting pressure (21.7 to 37.6mmHg, p=0.021) and maximum squeeze pressure (58.2 to 72.2mmHg, p=0.045) after PTNS [336]. Horrocks et al., concluded that as no adequate RCT of PTNS v sham has been conducted, conclusions cannot be drawn regarding the treatment, also commenting that such a study has nearly finished recruitment (The CONFIDeNT Trial ISRCTN 88559475).

A recent pilot RCT by Thin and colleagues investigated SNS versus PTNS in 40 patients [337]. They found that both treatments provided some short term benefits but due to the pilot design were unable to provide direct statistical comparison. However, for nearly all outcomes the within-group effect estimates were larger for SNS than PTNS. They found 61% for SNS and 47% for PTNS had a 50% or greater reduction in FI episodes per week at 6 months, in comparison to 63% (range 33-66) and 71% (63-82) respectively in published systematic reviews [279, 281]. Thin et al., concluded that a definitive RCT directly comparing SNS and PTNS would not be

feasible on the basis of the data from the pilot study; however SNS and PTNS could be made available to suitable patients based on their preference.

In a small non-randomised study of 20 patients over a 3 year period, SNS was found to be successful in 68% of patients refractory to PTNS based on incontinence episodes per week and the Cleveland clinic incontinence score [280].

PTNS has almost no reported adverse effects, avoids the risks of 2 operations required for SNS and can be performed in outpatients or even at home [338]. SNS is also much more expensive in terms of direct equipment costs (in the UK approximately £8000 versus £500 for PTNS) [337]. The cost of treating a patient for 1 year was £11 374 for SNS versus £1 740 for PTNS [339].

In summary, there is evidence to show PTNS to be successful in the short term based on bowel diaries and questionnaires. The most common definition of success seems to be a greater than 50% reduction in FI episodes per week. A number of studies have shown an increase in MSP following PTNS. A definitive trial of PTNS versus SNS seems unfeasible but the results of a definitive trial of PTNS versus sham is eagerly awaited.

Predictive factors for the success of posterior tibial nerve stimulation

To the author's knowledge there are no studies that assess prognostic factors for the success of PTNS for FI. In a study of 132 patients receiving PTNS for urological conditions poor mental health was found to be a negative predictive factor for

objective success, outcome was not found to be dependent on symptom severity [340].

Authors have attempted to identify predictive factors for the success of SNS & PNE. A French study of 200 consecutive patients receiving SNS found stool consistency (loose) and low stimulation intensity (1.7v2.4V, p=0.02) were related to a favourable outcome [341]. They go on to explain that loose stool consistency should be interpreted with caution because it was measured by a subjective non-validated score and advise further studies to use the Bristol stool chart. A 10 year cohort analysis of 81 patients found a low threshold to obtain a motor response during temporary lead insertion was associated with improved outcome and the need for a repeated PNE procedure was associated with subsequent failure during screening [342]. A number of other studies struggled to identify predictive factors, but did show that factors such as age, gender, body mass index, duration and severity of symptoms, QOL, causes of FI, manometry or endoanal ultrasound results did not affect clinical outcome [341-345]. The lack of predictive factors and disagreement in some studies (i.e. whether age [341, 346] and rectal sensation [342, 347] are predictive factors) emphasises the complexity of the mechanism of action in neuromodulation. A European consensus statement published in 2015 therefore states that 'any patient' with FI should be considered for SNS unless contraindicated [345].

Hornung et al., used AAR to investigate 52 patients undergoing PNE and found the parameter of Op to be an independent predictor of success (28 versus 17cmH_2O, P=0.008, success versus fail respectively). An Op greater than 18.4cmH_2O predicted successful PNE with a sensitivity of 0.81 and specificity of 0.60. Success was

defined as a greater than 70% reduction in the number of incontinence episodes per week and/or in the Vaizey incontinence score.

Aim

The aim of this study was to establish if AAR could predict the outcome of PTNS by testing the following hypothesis;

- The AAR parameter opening pressure can predict success from PTNS?

Secondary aims were to report on the success of PTNS and establish other predictive factors.

Methods

Patients

Patients referred for PTNS from a Pelvic floor clinic were approached by a specialist physiotherapist independent of the study. Patients who agreed to take part were phoned by the principal investigator and sent the following information pack in the post at least 2 weeks before their first appointment;

- Invitation letter (see appendix B for an example)
- Patient information sheet (see appendix B for an example)
- Consent form (see appendix B for an example)
- 2 week validated bowel diary

- 6 validated questionnaires, a combination of quality of life (QOL) scores and severity of symptoms scores;
    - Vaizey questionnaire, a faecal incontinence severity score,
    - Manchester Health Questionnaire (MHQ), a QOL tool specific for FI,
    - Gastrointestinal Quality of Life Index (GIQL), a QOL tool specific for gastrointestinal complaints incorporating FI but not specific for FI,
    - Patient Reported Outcome Form (PCO), a combination of 8 visual analogue scores on the issues shown to be the most important to patients (e.g. hygiene and odours, effect on social life, embarrassment etc…),
    - Short Form 36 (SF-36), a generic QOL tool,
    - Quality of Life Scale for Faecal Incontinence (FIQL), a FI specific QOL tool.

Patients were asked to bring the completed pack to the first appointment. Patients able to consent >18 years old with passive or urge FI having failed conservative measures were included in the study. Patients unable to consent, complete study paperwork (bowels diaries and questionnaires) or less than 18 years old were excluded from the study. Patients with the following conditions were also excluded from the study;

- Any condition that would preclude PTNS at the ankle (peripheral vascular disease, leg ulcers, diabetic neuropathy, painful peripheral neuropathy, cellulitis etc…),
- Bleeding disorder,
- Pacemaker or external wires,

- Previous PTNS.
- Unable to commit to travel to hospital every week for 12 weeks.

Patients were consented at their first appointment by the principal investigator. Demographic and clinical data were recorded as detailed in Chapter 7.

Following treatment patients were divided for analysis into subjective or objective success. Subjective success was defined as whether patients felt the treatment had worked or not (recorded as subjective success or failure). Objective success was defined in 3 ways;

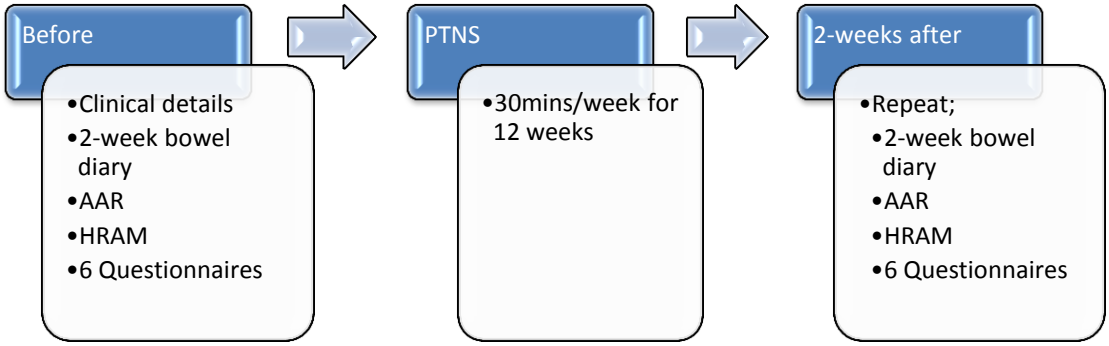
1. 50% threshold
    a. ≥50% improvement in 2 or more of 6 variables (total FI episodes, urgency episodes, urge FI episodes, passive FI episodes, Vaizey score, MHQ score) over 2 weeks.
2. 70% threshold
    a. ≥70% improvement in 2 or more of 6 variables (total FI episodes, urgency episodes, urge FI episodes, passive FI episodes, Vaizey score, MHQ score) over 2 weeks.
3. Percentage of patients who had at least a 50% reduction in total FI episodes per week.

Protocol

At their first appointment recruited patients underwent AAR and high resolution anal manometry (HRAM) followed by the first of a 12 week course of PTNS for 30mins

each week. Methodology for each investigation and treatment can be found in Chapter 6. Following the 12 week course of PTNS patients repeated the 2 week bowel diary, AAR, HRAM and questionnaires (Figure 53).

Figure 53 Overview of Process – AAR and PTNS



Statistical Analysis

A sample size calculation was performed using previous data. This suggested that with 30 patients the study would have an 80% power at a conventional significance level of 0.05 to detect differences in resting OP between 1st and 2nd order AAR of greater than 7.4cmH_2O using a standard deviation of 14cmH_20. Normal continuous data were compared using the independent samples t-test and the paired t-test. Continuous data not normally distributed were compared using the Mann-Whitney U test and Wilcoxon Signed Rank test. A Binomial test and Fisher's exact test were used to compare success and failure for within group and subgroup analysis. Data were recorded in an excel database and interrogated using SPSS Statistics version 20 software (IBM, Chicago, IL).

Results

30 patients with faecal incontinence were recruited over a 17 month period between November 2013 and March 2015; demographic data can be seen in Table 21 below.

The average time to complete the 12 session course of PTNS, from the date of the first session to the date of the last session was 14 weeks (mean 98 days and range 55-157 days). The most common reason for requiring extra time was patient holidays. One patient required significantly more time to complete the 12 sessions (22 weeks or 157 days) due to a broken ankle and was unable to attend hospital. He began his treatment again from session one once he was able to travel and included in the analysis. One patient was unable to complete the post PTNS bowel diaries due to psychiatric illness, she did however complete the other tests and her data excluding diaries have been included in analysis.

The median age was 63 with a range of 31-78 years. 24 (80%) patients were women and 50% had mixed FI. 21 of 24 (88%) women had had a traumatic childbirth, defined as any delivery that required forceps, ventouse assistance or resulted in a tear. 19 (90%) episodes of traumatic childbirth resulted in a tear, the degree of tear was recorded but has not been analysed as information from patients and the notes was unreliable. 20 previous anorectal surgical procedures had been performed on this group of 30 patients, included five PNE's, one SNS implant and five sphincter repairs (Table 21 & Appendix D Table 35).

Table 21 PTNS & AAR study demographics

Variable	Patients Undergoing Investigation (n=30)
Median age (range)	63 (31-78)
Sex	
Male	6 (20)
Female	24 (80)
Type of incontinence	
Mixed	15 (50)
Urge	11 (37)
Passive	4 (13)
Urinary Incontinence	15 (50)
Mean parity (range)	2 (0-4)
Median vaginal delivery (range)	2 (0-4)
Median C-section (range)	0 (0-1)
Traumatic childbirth	21 (88)
Tears	19 (90)
Previous gynaecological surgery*	14 (58)
Hysterectomy	10
Sterilisation	2
Colposuspension	1
Dilation & Curettage	1
Fentons procedure	1
RBL of haemorrhoids	4 (13)
Previous Anorectal Surgery*	15 (50)
SNS/PNE	6
Sphincter Repair	5
Haemorrhoidectomy	2
PTQ	2
I&D of perianal abscess	1
Delormes	1
Perineal Reconstruction	1
Anal Stretch	1
Transanal resection of rectal ulcer	1
Previous surgery*	7 (23)
Spinal Surgery	2
Diagnostic laparoscopy	2
Appendicetomy	1
Bowel resection	2
Transobturator tape	1

*Demographics for patients in PTNS & AAR study (values in parenthesis are percentages unless otherwise stated). Urge=inability to defer defecation, passive=faecal soiling without awareness, mixed=combination of both urge and passive incontinence symptoms. RBL=rubber band ligation of haemorrhoids, PTQ=anal silicone implant to bulk the anal canal and treat passive FI, SNS=sacral nerve stimulation, PNE=peripheral nerve evaluation, I&D=incision and drainage.*Patients who underwent previous surgery often had more than 1 procedure each accounting for a greater number of procedures than patients.*

AAR and manometry results

One AAR variable SOE was found to be significantly lower after PTNS (table 22). Rectal sensation (call to stool and urgency) had significantly improved. MSP and ISP had significantly increased, by median differences of 20mmHg and 10mmHg respectively after PTNS (Table 22).

Table 22 AAR & HRAM variables before and after PTNS

Variable	Pre PTNS median (range) (n=30)	Post PTNS median (range) (n=30)	P value
AAR			
Opening Pressure (cmH_2O)	38 (3-90) $^{\alpha}$	39 (1-85) $^{\alpha}$	0.67*
Opening Elastance (cmH_2O/mm^2)	0.89 (0.45-3.07)	0.86 (0.42-1.82)	0.63
Closing Pressure (cmH_2O)	31 (1-77) $^{\alpha}$	34 (0-77) $^{\alpha}$	0.29*
Closing Elastance (cmH_2O/mm^2)	0.92 (0.46-1.49) $^{\alpha}$	0.87 (0.34-1.58) $^{\alpha}$	0.42*
Hysteresis %	20 (0-48)	17 (1-82)	0.89
Squeeze Opening Pressure (cmH_2O)	66 (17-162) $^{\alpha}$	71 (9-170) $^{\alpha}$	0.15*
Squeeze Opening Elastance (cmH_2O/mm^2)	1.17 (0.56-3.42)	0.94 (0.17-1.81)	0.02
Variable	**Pre PTNS median (range) (n=30)**	**Post PTNS median (range) (n=30)**	**P value**
High Resolution Anal Manometry			
Rectal Sensation – onset (mls)	40 (16-100)	35 (10-53)	0.09
Rectal Sensation –call (mls)	80 (34-150)	54 (32-83)	<0.01
Rectal Sensation – Urgency (mls)	105 (48-240)	84 (41-158)	<0.01
MRP (mmHg)	32 (15-74)	48 (13-81)	0.10
MSP (mmHg)	58 (19-219)	78 (21-215)	<0.01
ISP (mmHg)	21 (1-165)	31 (2-154)	<0.01

*AAR & HRAM variables before and after PTNS. Values are medians (ranges) and comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. $^{\alpha}$Mean (range), *paired samples t-test and a significance level of <0.05.*

Bowel Diary Results

Episodes of urgency were significantly worse, deteriorating from a median of 3 to 8 over a 2 week period; however urge FI episodes improved from 3 (range 0-37) to 1 (range 0-22). Staining and pad use had also significantly improved (Table 23).

Table 23 2 week bowel diary before and after PTNS

2 week bowel diary (episodes in 2 weeks)	Pre PTNS median (range) (n=30)	Post PTNS median (range) (n=30)	P value
Total frequency	41 (12-88) [α]	42 (5-105) [α]	0.59*
Urgency episodes	3 (0-67)	8 (0-49)	0.02
Urge FI episodes	3 (0-37)	1 (0-22)	<0.01
Passive FI episodes	5 (0-43)	3 (0-28)	0.27
Staining episodes	8 (90-14)	4 (0-14)	0.01
Pad use (days)	7 (0-14)	0 (0-14)	0.02
Enema use (days)	0 (0-14)	0 (0-14)	0.18
Effects social life (days)	4 (0-14)	3 (0-14)	0.13
Bristol Stool Chart	4 (2-6)	4 (2-7)	0.24

*2 week bowel diary before and after PTNS. Bristol stool chart ranges from 1 to 7 (1=hard stool and 7=liquid stool). Values are medians (ranges) and comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. [α]Mean (range), *paired samples t-test with a significance level of <0.05.*

Questionnaire Results

All of the quality of life (QOL) or severity tools specific for FI (Vaizey, GQLI, FIQL–except lifestyle and MHQ) showed significant improvements after PTNS in comparison to the generic ones (SF-36 and PCO), which apart from one parameter (SF-36-physical functioning) hadn't improved (Table 24). The MHQ (QOL tool

specific for FI) showed improvement in 5 of 10 parameters and a significant improvement in the total MHQ score (p=0.02).

Table 24 Questionnaires before and after PTNS

Questionnaire	Pre PTNS median (range) (n=30)	Post PTNS median (range) (n=30)	P value
Vaizey (0-24) lower better	18 (6-23)	16 (4-24)	0.01
GQLI (0-144) higher better	95 (51-128)	100 (48-129)	0.05
PCO (0-80) lower better	69 (32-80)	70 (29-80)	0.13
SF-36 (0-100) higher better			
Physical Functioning	65 (5-100)	75 (0-100)	0.02
Role Limitation due to physical health	88 (0-100)	75 (0-100)	0.96
Role limitations due to emotional Problems	83 (0-100)	100 (0-100)	0.86
Energy/Fatigue	50 (0-85)$^{\alpha}$	52 (0-85 $^{\alpha}$	0.53*
Emotional well being	67 (20-100)$^{\alpha}$	70 (32-100)$^{\alpha}$	0.56*
Social Function	75 (0-100)	69 (0-100)	0.30
Bodily Pain	69 (0-100)$^{\alpha}$	66 (0-100)$^{\alpha}$	0.42*
General Health	50 (12-100)	55 (5-90)	0.89
FIQL (1-4) higher better			
Lifestyle	2.9 (1.5-4)	2.8 (1.8-4)	0.38
Coping behaviour	1.7 (0.4-3.4)$^{\alpha}$	2.1 (1-3.6)$^{\alpha}$	<0.01*
Depression	2.7 (1.1-4)	3 (0.9-4)	0.04
Embarrassment	2 (1-3.7)	2.3 (1-3.7)	0.03
MHQ (0-100) lower better			
General health	25 (0-75)	38 (0-100)	0.25
Impact	76 (25-100)$^{\alpha}$	68 (25-100)$^{\alpha}$	0.02*
Role	50 (0-100)	38 (0-100)	<0.01
Physical	58 (0-100)$^{\alpha}$	50 (0-100)$^{\alpha}$	0.08*
Social	47 (0-100)$^{\alpha}$	41 (0-92)$^{\alpha}$	0.09*
Personal	44 (0-100)	31 (0-100)	0.02
Emotions	58 (8-100)	50 (8-100)	0.18
Sleep	41 (0-100)$^{\alpha}$	38 (0-88)$^{\alpha}$	0.51*
Severity	73 (10-100)	53 (5-100)	<0.01
Total (0-900)	474 (107-783)$^{\alpha}$	424 (72-814)$^{\alpha}$	0.02*

*Questionnaires before and after PTNS. Vaizey - Incontinence Severity Score, GQLI - Gastrointestinal quality of life questionnaire, PCO – Patient centred outcomes form, SF-36 – The short form health survey, FIQL – Quality of life scale for faecal incontinence, MHQ - Manchester health Questionnaire. Values are medians (ranges) and comparisons made using Wilcoxon Signed Rank Test unless otherwise stated. $^{\alpha}$Mean (range), *paired samples t-test with a significance level of <0.05.*

Objective and Subjective Results

20 (67%) patients subjectively improved after PTNS, 18 (60%) patients objectively improved at the 50% threshold and 11 (37%) at the 70% threshold. 52% of patients had a 50% or greater reduction in total FI episodes (Table 25). None of these outcomes were significant. Data on the agreement between objective and subjective success can be seen in Appendix D (Table 31Table 32).

Table 25 Summary of the subjective and objective success of PTNS

Summary **Variable (n=30)**	**Success (%)**	**Fail (%)**
Subjective	20 (67)	10 (33)
Objective		
≥50% reduction ≥2 variables	18 (60)	12 (40)
≥70% reduction ≥2 variables	11 (37)	19 (63)
≥50% reduction in total FI episodes (n=29)	15 (52)	14 (48)

Summary of the subjective and objective success of PTNS. Subjective success defined as patient stated they derived benefit at the end of treatment. Objective success defined as ≥50% or ≥70% improvement in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ) and proportion of patients with a ≥50% reduction in total FI episodes per week.

The mean age of patients at the 70% threshold of success was not significantly different from those that failed (58 versus 60 respectively, p=0.679), this relationship was also seen using the 50% threshold and >50% reduction of FI episodes measures of success (57 versus 62, p=0.313 and 60 versus 57, p=0.59 respectively). Likewise sex was not found to be a significant factor on the outcome of success or failure after PTNS (50% threshold p=0.66, 70% threshold p=1 and >50% reduction in episodes of FI p=0.390).

Pre-PTNS variables of age, sex, AAR, HRAM, bowel diaries and six questionnaires were not significantly different between the groups of success and failure, using all definitions of success (Table 26Table 28, Appendix D Table 33 Table 34). Therefore further analysis could not be done to identify independent predictors of success for PTNS.

Table 26 AAR and HRAM variables with objective success 50 for PTNS.

Objective Success 50 Variable (n=30)	Success (n=18)	Fail (n=12)	P value
AAR (pre PTNS)			
Opening Pressure (cmH_2O)	32 (3-90)	31 (8-67)	0.88
Opening Elastance (cmH_2O/mm^2)	0.95 (0.45-3.07)	0.86 (0.58-1.90)	0.63
Closing Pressure (cmH_2O)	32 (1-77)$^{\alpha}$	30 (3-67)$^{\alpha}$	0.8*
Closing Elastance (cmH_2O/mm^2)	0.87 (0.46-1.49)	0.80 (0.56-1.47)	0.49
Hysteresis %	20 (7-48)	20 (0-45)	0.6
Squeeze Opening Pressure (cmH_2O)	75 (17-129)	43 (22-162)	0.66
Squeeze Opening Elastance (cmH_2O/mm^2)	1.16 (0.56-1.84)	1.32 (0.93-3.42)	0.11
Variable	**Success (n=18)**	**Fail (n=12)**	**P value**
High Resolution Anal Manometry (pre PTNS)			
Rectal Sensation – onset (mls)	34 (16-100)	47 (17-90)	0.11
Rectal Sensation –call (mls)	83 (40-150)	75 (34-150)	0.57
Rectal Sensation – Urgency (mls)	115 (50-240)	100 (48-220)	0.42
MRP (mmHg)	42 (15-74)	49 (16-71)	0.42
MSP (mmHg)	60 (27-135)	54 (19-219)	0.66
ISP (mmHg)	21 (3-93)	21 (0-165)	0.42

*AAR and HRAM variables with objective success 50 for PTNS. Objective success defined as >50% improvement in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ). Values are medians (ranges) and statistical comparisons made using Mann-Whitney U test unless otherwise stated. $^{\alpha}$Mean (range), *independent samples t-test and a significance level of <0.05.*

Table 27 AAR and HRAM variables with objective success 70 for PTNS

Objective Success 70 **Variable (n=30)**	**Success (n=11)**	**Fail (n=19)**	**P value**
AAR (pre PTNS)			
Opening Pressure (cmH_2O)	31 (3-70)	32 (8-90)	0.47
Opening Elastance (cmH_2O/mm^2)	1.02 (0.65-1.55)	0.85 (0.45-3.07)	0.19
Closing Pressure (cmH_2O)	31 (1-77)$^{\alpha}$	31 (3-74)$^{\alpha}$	0.97*
Closing Elastance (cmH_2O/mm^2)	0.92 (0.46-1.36)	0.80 (0.56-1.49)	0.47
Hysteresis %	16 (7-48)	21 (0-45)	0.67
Squeeze Opening Pressure (cmH_2O)	59 (17-129)$^{\alpha}$	69 (17-162)$^{\alpha}$	0.5*
Squeeze Opening Elastance (cmH_2O/mm^2)	1.19 (0.74-1.84)	1.15 (0.56-3.42)	0.67
Variable	**Success (n=11)**	**Fail (n=19)**	**P value**
High Resolution Anal Manometry (pre PTNS)			
Rectal Sensation – onset (mls)	35 (16-100)	40 (17-90)	0.47
Rectal Sensation –call (mls)	85 (42-150)	75 (34-150)	0.61
Rectal Sensation – Urgency (mls)	110 (66-180)	100 (48-240)	0.67
MRP (mmHg)	38 (20-74)	45 (14-71)	0.33
MSP (mmHg)	58 (27-135)	59 (14-219)	0.55
ISP (mmHg)	21 (6-64)	21 (0-165)	0.61

*AAR and HRAM variables with objective success 70 for PTNS. Objective success defined as >70% improvement in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ). Values are medians (ranges) and statistical comparisons made using Mann-Whitney U test unless otherwise stated. $^{\alpha}$Mean (range), *independent samples t-test and a significance level of <0.05.*

Table 28 AAR and HRAM variables with objective success for PTNS

≥50% reduction in total FI episodes Variable (n=29)	Success (n=15)	Fail (n=14)	P value
AAR (pre PTNS)			
Opening Pressure (cmH_2O)	33 (3-90)	31 (8-72)	0.95
Opening Elastance (cmH_2O/mm^2)	0.95 (0.59-3.07)	0.85 (0.45-1.90)	0.31
Closing Pressure (cmH_2O)	33 (1-77)	30 (3-67)	0.79*
Closing Elastance (cmH_2O/mm^2)	0.90 (0.46-1.49)	0.80 (0.56-1.47)	0.33
Hysteresis %	19 (7-48)	21 (0-45)	0.78
Squeeze Opening Pressure (cmH_2O)	57 (17-129)	63 (22-162)	0.78
Squeeze Opening Elastance (cmH_2O/mm^2)	1.19 (0.62-1.84)	1.15 (0.56-3.42)	0.51
Variable	**Success (n=15)**	**Fail (n=14)**	**P value**
High Resolution Anal Manometry (pre PTNS)			
Rectal Sensation – onset (mls)	32 (16-100)	43 (17-90)	0.11
Rectal Sensation –call (mls)	80 (40-150)	75 (34-130)	0.88
Rectal Sensation – Urgency (mls)	110 (50-180)	100 (48-240)	0.72
MRP (mmHg)	29 (14-72)	47 (15-65)	0.25
MSP (mmHg)	51 (20-212)	64 (14-219)	0.78
ISP (mmHg)	22 (1-183)	22 (3-129)	0.65

*AAR and HRAM variables with objective success for PTNS. Objective success defined as the proportion of patients with a ≥50% reduction in total FI episodes over 2 weeks. One patient was excluded from analysis who was unable to complete post the PTNS bowel diary. Values are medians (ranges) and statistical comparisons made using Mann-Whitney U test unless otherwise stated. [α]Mean (range), *independent samples t-test and a significance level of <0.05.*

Urge and Passive Results

Patients were divided into subgroups of urge FI and passive FI. Patients with mixed FI but symptoms of predominantly urge or passive FI were assigned to the corresponding group (for example a patient with mixed FI but predominant symptoms of urge FI was placed in the Urge FI group). 2 patients did not have a predominant symptom and were therefore excluded from subgroup analysis. PTNS was successful (at the 50% objective threshold) for 72% of patients with urge FI in comparison to 30% of patients with passive FI (p=0.049). Although patients with urge FI did better than passive FI using other measures of success (subjective, 70% objective threshold and ≥50% reduction in total FI episodes) these differences were not found to be significant (Table 29).

Table 29 Success of PTNS and the subgroups of urge and passive FI

FI Subgroup Analysis	Urge FI n=18 (%)	Passive FI n=10 (%)	P value
Subjective Success	13 (72)	5 (50)	0.41
Objective Success			
50% threshold	13 (72)	3 (30)	0.049
70% threshold	8 (44)	2 (20)	0.25
≥50% reduction in total FI episodes	11 (61)	2 (20)	0.10

Subjective and objective success of PTNS for the subgroups of urge and passive FI. Patients with mixed FI were included using there predominant symptoms and placing them in the corresponding group, 2 patients did not show predominant symptoms therefore excluded leaving 28 from 30. Values compared using a Fisher's Exact test with a significance level of <0.05.

Discussion

In this prospective observational cohort study of 30 patients, the aim was to establish if AAR could predict the response of PTNS. We did not find any variables of AAR that could predict response to PTNS. The secondary aim was to report on the success of PTNS and identify any other predictive factors for success. We found 67% (20) of patients had subjective success, 60% (18) objective success (50% threshold), 37% (11) objective success (70% threshold) and 52% (15 of 29) of patients had a ≥50% reduction in FI episodes per week, none of which proved significant.

Predictive factors for the success of posterior tibial nerve stimulation

This is the first study to investigate predictive factors for the success of PTNS for faecal incontinence. None of the seven variables of AAR were found to discriminate between success and failure following PTNS. The factors of age, sex, high resolution anal manometry, bowel diary variables and six questionnaires were not found to be predictive of success after PTNS. At the 70% objective threshold of success the FIQL domain of embarrassment was approaching significance (p=0.056), suggesting that patients with more embarrassment were more likely to fail. Apart from one study, the lack of a predictive factor has also been seen with SNS, despite a number of authors attempting to find such an important marker that would drive down cost and potential harm to patients [341]. A number of studies have reported improvements in anorectal physiological parameters however none of these have been able to predict success [333, 334, 336]. In the field of urology poor mental

health has been shown to predict poor outcome from PTNS and may need future investigation within the field of faecal incontinence [340].

Success and effect of percutaneous posterior tibial nerve stimulation

One variable of AAR (SOE) was found to be significantly lower following PTNS. SOE is the ability of the anal canal to resist opening after the squeeze opening pressure has been achieved. Lower SOE suggests that the anal canal opens with greater ease during the assessment of squeeze after PTNS.

Rectal Sensitivity, Manometry and PTNS

Following PTNS this study saw a significant increase in rectal sensitivity manifest in lower rectal sensation parameters of call to stool and urgency (80 to 54mls and 105 to 84mls respectively, $p < 0.01$). This finding has not been replicated in the two other studies to report on this parameter [333, 334]. However 37 studies have sought changes in rectal sensitivity after SNS, 14 of which cite significant heightened rectal sensitivity, in keeping with our results [282]. It must also be noted that 3 of the 37 studies reported reduced rectal sensitivity and two other studies found normalization of sensation, i.e. those with hyposensitivity showed a reduction in sensory thresholds and vice versa for those with hypersensitivity. The mechanism of action by which rectal sensation is modulated is a topic of much debate. In a review by Carrington et al., with regard to SNS it was concluded that the effect on anorectal function occurs at a pelvic afferent or central level [282]. It would seem logical that PTNS with its effect on shared nerve roots may work in a similar fashion.

In agreement with three other studies we found a significant increase in MSP and ISP after PTNS (58 to 78mmHg and 21 to 31mmHg respectively, p=<0.01) [333, 334, 336]. Again much work has been done in this area with SNS and 14 of 40 studies have reported significant increases in voluntary anal squeeze, the mechanism of action is unclear but is also thought to work on the afferent pathways [282, 335].

AAR has been shown to be a more sensitive test than manometry however AAR did not change significantly after PTNS where HRAM did [283]. HRAM showed a difference in the performance of squeeze as described above, but neither test observed a difference in resting pressure. The most likely explanation for this difference is that AAR largely measures IAS function at rest and is therefore less influenced by PTNS in comparison to HRAM which is better at measuring squeeze function. AAR assessment of squeeze is limited mainly by fatigue, as SOP is determined by the patient's ability to occlude the lumen of the AAR catheter in a stepwise progression of increasing pressure over a period of time. As the test progresses the pressure at which the patient has to occlude the lumen increases as to does their fatigue. HRAM MSP in comparison is calculated from the mean of two best efforts in our institution. This methodological difference may account for the fact that HRAM observed an increase following PTNS in squeeze function where AAR did not.

Bowel diaries and PTNS

Urge incontinence episodes significantly improved after treatment (median 3 to 1, p<0.01), an effect not observed in patients with passive FI. This finding was

replicated in a study of 100 patients by Hotouras et al., who found that PTNS was effective in treating patients with urge FI as well as mixed FI [348]. Staining and pad use also significantly improved, although multifactorial, likely in part due to a non-significant reduction in passive episodes. Interestingly however episodes of urgency (defined as an urgent call to stool without FI) increased after PTNS (median 3 to 8, p=0.02). A combination of improved rectal sensation and increased squeeze pressures leading to the ability to defer defecation for longer and better awareness of the need to pass stool may explain the increased episodes of urgency witnessed. Further subgroup analysis has shown that at the 50% threshold PTNS significantly improved the outcome for patients with urge FI in comparison to passive FI (13(72%) versus 3(30%), p=0.05 respectively). Within group effects were greater for urge FI than passive FI for all other measurements of success although these differences were not found to be significant. Our results suggest that PTNS is a treatment that may be more effective for patients with urge FI.

Questionnaires and PTNS

Improvements were seen in the Vaizey score a measure of severity of FI in keeping with findings using the Wexner Score (Cleveland Clinic Incontinence Score, also used to assess severity and similar to the Vaizey score) in other studies [295, 296, 334, 349]. All three bowel specific QoL scales (FIQL, MHQ and GQLI) showed significant improvements. Studies by de la Portilla et al., and Govaert et al., support the observations of improved FIQL (Rockwood score) domains of coping behaviour, depression and embarrassment in particular [295, 334]. However the generic tools SF-36 and PCO were not seen to improve, except the physical function domain of the

SF-36 (one of eight domains). In contrast Govaert et al., found that all domains of the SF-36 improved except vitality at 12 months. The total Manchester Health Questionnaire score significantly improved following treatment and was used in combination with the Vaizey score to form part of the assessment of objective success, therefore incorporating a measure of severity with a measure of QoL.

Objective and subjective success and PTNS

Objective success was measured in three ways; ≥50% (50% threshold) or ≥70% (70% threshold) reduction in 2 or more of 6 variables (total FI episodes, urgency episodes, urge FI episodes, passive FI episodes, Vaizey Score and total MHQ score) and the proportion of patients with a 50% or greater reduction in total FI episodes per week. Using these measures, success rates were 60, 37 and 52 per cent respectively, none of which were significant. At the 70% threshold Hornung at al., found a 62% success rate after PNE in comparison to 37% in this study after PTNS [283]. Three other studies found a 63 to 82 per cent reduction in the number of FI episodes immediately after PTNS treatment in comparison to 52% in our work [295, 296, 333]. A review of the short term success of SNS on an intention to treat basis found 63% of patients had ≥50% reduction in FI episodes per week [281]. An explanation for the lower success rates in comparison to all other studies of neuromodulation may lie with the pragmatism of this study. Previous work excluded patients with spinal surgery, neurological conditions such as multiple sclerosis, inflammatory bowel disease, recent surgery and previous neuromodulation. On this basis up to 11 patients may have been excluded from the current study [333]. Five patients underwent previous PNE (three failed) and one SNS (successful but removed due to trauma)

before PTNS. All three of the patients who had failed PNE went on to have subjective and objective success with PTNS at all levels.

Patients were asked in a binary fashion if PTNS had worked, 67% stated subjective success. Although open to criticism (such as investigator bias) this binary approach in comparison to a visual analogue scale has advantages, such as the selection of patients who might enter top up treatments when faced with equivocal information.

Limitations

The present study has a number of limitations. The authors accept that there is a lack of standardization in reporting outcome measures in FI. There are now so many different systems that it is rare to find two studies that have used the same score [350]. The authors also accept that patient reported tools such as bowel diaries have been shown to be unreliable in comparison to electronic monitoring [351]. The definitions of success used in this study have attempted to maintain a level of uniformity with the most widely published outcome measures whilst allowing comparison with local protocol and results. Most published work uses the St Marks Score (Vaizey Score) or Cleveland Clinic incontinence score (Wexner Score) and the proportion of patients with a reduction in FI episodes per week of 50 per cent or more [279]. The Vaizey and Wexner Scores differ by two questions in which the Vaizey score enquires about medication to slow the bowel down and the ability to delay a bowel motion, hence the Vaizey score was felt to be a more robust measurement and therefore chosen. The thresholds of 50% and 70% were chosen to

reflect the outcome measures used to select patients following PNE for SNS, thus allowing for a direct comparison of treatments.

The observational design of this study did not allow for a control group and therefore the study was not randomized. Without a control group or sham treatment arm the size of a placebo effect cannot be estimated. The placebo effect in this study may be significant due to a motivated cohort of patients undergoing 12 weeks of one to one treatment with a health care professional. A similar situation can be seen when using biofeedback to treat FI. In a Cochrane review by Norton in 2012, despite 60 uncontrolled trials reporting improved symptoms in all groups the results in favour of biofeedback from randomised controlled trials were weak [352]. However the main aim of the study was not to report on the success of PTNS but identify a predictive factor for success and the methodology reflects this. Patients were referred from a pelvic floor clinic by one of two Consultants raising the possibility of selection bias, however owing to a wide and pragmatic inclusion criteria (for example patients with previous surgery or previous PNE or SNS were not excluded) the cohort of patients was comparable with most specialist pelvic floor practice.

It is possible that with small patient numbers the study is prone to a type II error. The study was powered to identify a difference in AAR variables therefore firm conclusions cannot be drawn on other predictive factors. However we did not find any variables approaching significance that would benefit from a larger study.

To date PTNS enjoys favourable results however the results of the first large scale RCT of PTNS versus sham are awaited (The CONFIDeNT Trial ISRCTN

88559475). Treatment dilemmas still exist: What are the best endpoints for stimulation and is a motor response better than a sensory response? Is bilateral PTNS better than unilateral? Does home based PTNS work [338, 353]? What are the best parameters of treatment? Top up treatments, how many and for how long? What is the long term efficacy of PTNS [354]?

Although AAR has failed to identify a predictive factor for the success of PTNS, it found Op was an independent predictor of success in PNE [283]. Future work should concentrate on whether AAR can predict success from SNS.

Conclusion

In conclusion this study has found that PTNS improved rectal sensation, manometry squeeze pressures, quality of life and severity of incontinence and was more effective for patients with urge FI. Non-significant improvements were found in all measures of objective success. However, age, sex, AAR, high resolution anal manometry, bowel diaries and questionnaires were not found to be predictive factors for the success of percutaneous PTNS.

Section 4 Conclusions

Chapter 11 Overarching Conclusions

AAR is a research investigation used in the assessment of pelvic floor disorders and primarily faecal incontinence. It was developed primarily as a technique that would permit the investigation of the opening and closing functions of the anal canal, but without the distortion of the anal canal associated with other techniques such as manometry. Acoustic reflectometry originates from seismology and was developed in the sixties in the search for oil. In 2010 acoustic reflectometry was adapted for use in the anal canal and was termed anal acoustic reflectometry. AAR uses reflected sounds waves to measure cross sectional area at different pressures and thus profiles the anal canal and more specifically the high pressure zone of the anal sphincters. The cross sectional area measurements from the high pressure zone of the anal canal at each stepwise pressure level are then plotted on an opening and closing graph which gives five characteristic parameters while at rest and two parameters during a voluntary squeeze.

The current stepwise AAR technique has been investigated for over four years using a combination of physiological, clinical and methodological validation studies. AAR has been found to be reproducible and reliable, distinguish between continence and faecal incontinence, correlate with the severity of faecal incontinence and able to discriminate between patterns of faecal incontinence. Opening pressure has also been shown to be an independent predictor of success with peripheral nerve evaluation, the trial period before sacral nerve stimulation.

This thesis represents the next step in the evolution of a new investigation. The aim was to add further methodological validation, develop a new understanding of the physiology of the anal canal and test AAR in a clinical situation.

AAR and anal canal length

Patients with faecal incontinence and women have shorter anal canal lengths in comparison to continent individuals and men. In a retrospective analysis of 265 patients a surrogate marker (AVFS) was developed to determine whether AAR can be used to measure anal canal length. AVFS was only found to be significantly different between men and women. Men had a longer mean AVFS of 2.21mm, although statistically significant it is unlikely to be a clinically significant difference. This study does not support the current literature which states that incontinent patients have a shorter anal canal than continent patients. The search for an explanation led to the discovery of a phenomenon called ringing or Gibbs phenomenon. This phenomenon describes the effect of reflected sound waves at the end of a tapering tube such as a blind ended catheter. Ringing is due to a spectral limitation of the signal. The limitation means that the more the abrupt the changes are, the larger the error becomes. The end of the catheter is very steep and therefore the measurements of the cross sectional area from the last 1cm and the first 1cm are not reliable. This phenomenon explains our unexpected results.

In conclusion this study has found that AAR cannot be used to measure the length of the anal canal nor can this current method be used as a surrogate marker of anal canal length due to a phenomenon called ringing.

AAR and Manometry the order of data collection

AAR and manometry may have a complementary role and are performed sequentially. This prospective randomised cohort study of 30 patients assessed two orders of data collection, with the aim of establish if AAR was influenced by prior manometry examination. The variables of AAR and manometry were not influenced by the order of performing the tests. Hence prior examination with manometry does not affect the results of AAR. This study was important for 3 reasons; firstly AAR can be confidently used alongside other tests of the ano-rectum, secondly it adds further validation to AAR methodology, and lastly it vindicates previous research and results which had been questioned.

Filling rates of the anal canal and AAR

Two rates of anal canal stretch were investigated in a prospective randomised cohort study of 50 patients with faecal incontinence. Little is known about anal canal stretch and this study aimed to add to our physiological knowledge. No difference was found between normal or fast rates of AAR in all five variables of AAR at rest. Secondly, no difference was found in manometry variables after prior investigation with either normal or fast rate AAR. This study has validated a faster method of AAR that can be used alongside manometry in any order. Fast rate AAR at rest is fifty percent quicker than normal rate AAR. A quicker investigation may lead to greater patient satisfaction and more patients that can be seen within a unit of time.

Investigation of the IAS with AAR using regional nerve blocks

The purpose of this prospective cohort study of 15 patients with pudendal neuralgia was to establish what happens to AAR parameters if the external anal sphincter is blocked by a bilateral pudendal nerve block. Is AAR an investigation that assesses the internal anal sphincter, the external anal sphincter or does it measure both? The partial bilateral pudendal nerve block had no effect on AAR variables at rest, or in other words on the function of the internal anal sphincter. However tests of the external anal sphincter were significantly reduced as one might expect following a nerve block targeting the sole nerve supply to the external anal sphincter. This study suggests that AAR at rest is predominately an investigation of internal anal sphincter function. It has shown that the external anal sphincter contributes much less activity to the anal canal at rest than had previously been thought. This study also suggests that bPNB's should be performed under CT guidance.

Can AAR predict the response to Posterior tibial nerve stimulation?

AAR has been shown in one study to predict the outcome of percutaneous nerve evaluation, the trial period often used before sacral nerve stimulation. This aim of this prospective study of 30 patients with faecal incontinence was to establish if AAR can predict the outcome from percutaneous posterior tibial nerve stimulation. Posterior tibial nerve stimulation was found to improve rectal sensation, manometry squeeze pressures, quality of life, severity of incontinence and was more effective for patients with urge faecal incontinence. Non-significant improvements were found in all measures of objective success. However, neither age, sex, AAR, high resolution

anal manometry, bowel diaries nor six questionnaires were found to be predictive factors for the success of PTNS.

The information resulting from further evaluation of this novel method is leading us to a new understanding of the physiology of the anal canal and its response to stretch. It is profiling the anal canal under conditions of stress with a greater level of sensitivity and accuracy than before. Further studies into AAR are critical to establish how we use the new information it provides outside the research arena and should be assessed against high resolution anal manometry. Future studies should concentrate on a fast AAR technique that eliminates muscle fatigue. Whether AAR can predict response from sacral nerve stimulation and formally assess if AAR is better tolerated than high resolution anal manometry.

Appendix A

REC approval letters

NHS
Health Research Authority

National Research Ethics Service

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08 August 2013

Mr J Nicholson
c/o Miss Telford Secretary
Consultant Surgeon
Acute Block 2nd Floor
University Hospital South Manchester
Southmoor Road
Manchester
M23 9LT

Dear Mr Nicholson

Study title: **The effect of different filling rates in the anal canal on Anal Acoustic Reflectometry Parameters.**
REC reference: **13/NW/0470**
IRAS project ID: **129352**

Thank you for your email of 25 July 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 18 July 2013.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering Letter		25 July 2013
Participant Consent Form	5	25 July 2013
Participant Information Sheet	3	25 July 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering Letter	Filling study	05 June 2013
Covering Letter		25 July 2013

Investigator CV	Telford	
Letter of invitation to participant	2	26 March 2013
Other: CV: PhD Student	Nicholson	
Other: CV: Academic Supervisor	Kiff	
Other: CV: Academic Supervisor	Whorwell	16 December 2012
Other: GCP Certificate	Nicholson	15 October 2012
Other: GCP Certificate	Telford	17 April 2012
Other: Data Collection Proforma	2	17 April 2013
Other: Unfavourable Opinion letter	REC 13/NW/0127	04 March 2013
Other: Favourable Opinion letter	REC 13/NW/0237	21 May 2013
Participant Consent Form	5	25 July 2013
Participant Information Sheet	3	25 July 2013
Protocol	1	12 June 2013
Questionnaire: Vaizey		
REC application	3.5	30 May 2013
Summary/Synopsis	1	05 June 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/NW/0470 **Please quote this number on all correspondence**

Yours sincerely

A. Totenhofer

Dr Ashley Totenhofer
Committee Co-ordinator

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Copy to: Miss Karen Telford - University Hospital South Manchester

Mrs Sian Hanison - University Hospital South Manchester

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08 August 2013

Mr J Nicholson
c/o Miss Telford Secretary
Consultant Surgeon
Acute Block 2nd Floor
University Hospital South Manchester
Southmoor Road
Manchester
M23 9LT

Dear Mr Nicholson

Study title: **Anal Acoustic Reflectometry and manometry, the order of data collection.**
REC reference: **13/NW/0469**
IRAS project ID: **128558**

Thank you for your email of 27 July 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 18 July 2013.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering Letter		25 July 2013
Participant Information Sheet	3	25 July 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

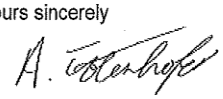
Document	*Version*	*Date*
Covering Letter		05 June 2013
Covering Letter		25 July 2013
Investigator CV	Telford	

Letter of invitation to participant	2	26 March 2013
Other: CV Academic Supervisor	Kiff	
Other: CV PhD Student	Nicholson	
Other: CV Academic Supervisor	Whorwell	16 December 2013
Other: GCP Certificate	Telford	17 April 2013
Other: GCP Certificate	Nicholson	15 October 2012
Other: Data Collection proforma	2	17 April 2013
Other: Unfavourable Opinion letter	REC Ref 13/NW/0127	04 March 2013
Other: Favourable Opinion letter	REC Ref 13/NW/0237	21 May 2013
Participant Consent Form	4	17 April 2013
Participant Information Sheet	3	25 July 2013
Protocol	1	12 June 2013
Questionnaire: Vaizey		
REC application	3.5	30 May 2013
Summary/Synopsis	1	05 June 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/NW/0469 **Please quote this number on all correspondence**

Yours sincerely



Dr Ashley Totenhofer
Committee Co-ordinator

E-mail: nrescommittee.northwest-gmwest@nhs.net

Copy to: Miss Karen Telford - University Hospital South Manchester

Mrs Sian Hanison - University Hospital South Manchester

Health Research Authority
National Research Ethics Service

NRES Committee North West - Greater Manchester West
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ
Tel: 0161 625 7817
Fax: 0161 625 7299
Email: nrescommittee.northwest-gmwest@nhs.net

Miss Karen Telford
Consultant Surgeon
University Hospital South Manchester
Southmoor Road
Manchester
M23 9LT

21 May 2013

Dear Miss Telford

Study title:	**Investigation with Anal Acoustic Reflectometry of the isolated internal anal sphincter using a regional nerve block.**
REC reference:	**13/NW/0237**
IRAS project ID:	**127496**

Thank you for your emails dated 07 May 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Ms Cynthia Carter, nrescommittee.northwest-gmwest@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore

apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter ✓		15 March 2013
GP/Consultant Information Sheets ✓	1	14 January 2013
Investigator CV ✓	Mr James Nicholson	15 March 2013
Investigator CV ✓	Mr E S Kiff	
Investigator CV ✓	Professor Peter Whorwell	16 December 2012
Letter of invitation to participant ✓	3	17 April 2013
Other: Unfavourable Opinon letter from NRES Committee Northwest - GM North ✓		04 March 2013
Other: GCP Certificate - Karen Telford ✓		17 April 2012
Other: GCP Certificate - James Nicholson ✓		15 October 2012
Other: Independent Review ✓	1	07 May 2013
Other: Data Collection Proforma ✓	2	17 April 2013
Participant Consent Form ✓	4	17 April 2013
Participant Information Sheet ✓	3	17 April 2013
Protocol ✓	2	19 October 2012
Protocol ✓	1 - EMG Specific	17 April 2013
Questionnaire: Study Vaizey ✓	2	17 April 2013
REC application ✓	3.4	07 March 2013
Response to Request for Further Information ✓	1	07 May 2013

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/NW/0237	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Dr Lorraine Lighton**
Chair

This letter has been signed electronically. If you require a wet ink version please request one from the Committee Co-ordinator by email and it will be sent in the post.

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Mrs Sian Hanison, R&D office for University Hospital South Manchester sian.hanison@manchester.ac.uk

Mr James Nicholson, MD Student james.nicholson@manchester.ac.uk

Professor Peter Whorwell, University Hospital South Manchester peter.whorwell@uhsm.nhs.uk

Mr E S Kiff, University Hospital South Manchester eskiff@doctors.org.uk

Appendix B

Example of Invitation letter

University Hospital of South Manchester NHS
NHS Foundation Trust

Pelvic Floor Unit Research
Study Title – Anal Acoustic Reflectometry and
Manometry the order of data collection.

c/o Miss Telford Secretary
Dept of General Surgery
2nd Floor Acute Block
Wythenshawe Hospital
University Hospital South Manchester
Southmoor Road
Manchester
M21 9LT
Tel 0161 291 6654
Fax 0161 291 6658

Dear Mr/Mrs

This is an invitation to take part in my clinical study, which is taking place at Wythenshawe Hospital. It involves a new test to examine the muscles of the back passage, which we hope will provide more information than is currently available to help treat patients with pelvic floor dysfunction.

Attached is a detailed Information sheet, which will explain the study and answer any questions or concerns that you have. You do not have to participate in the study if you don't want to. This will not affect your treatment in any way.

Please do not hesitate to contact me if you have any further questions.

Thank you for your time, I look forward to meeting you when you attend the hospital.

Yours Sincerely

Mr James Nicholson BSc(Hons) MBChB MRCS
Research Registrar to Miss Telford MD FRCS
Consultant Colorectal & Pelvic Floor Surgeon

Example of Patient information sheet

University Hospital of South Manchester NHS
NHS Foundation Trust

Study Title – Anal Acoustic Reflectometry (AAR) and Manometry the order of data collection.

Participant Information Sheet

You have been invited to take part in a study to help our understanding of how the anal sphincter (muscles of the back passage) work. Sometimes these sphincter muscles do not work correctly, which results in faecal incontinence (the involuntary passage of faeces, 'Soiling'). This is an embarrassing and distressing condition. We are performing a study to assess these sphincter muscles using a new painless technique that uses sound waves. I am part of a team of surgeons and doctors who have been investigating the causes of faecal incontinence for 30 years and this study will build on the knowledge gained from similar studies in the past.

Why have I been invited?

You have been invited to take part because you are attending the Pelvic Floor Clinic at University Hospital South Manchester. You may have symptoms of faecal incontinence, but not everyone we see in this clinic will have incontinence. Assessment of your sphincter muscles using this new technique will provide valuable information about how the muscles of the back passage work.

What is the purpose of the study?

In this study we are assessing the sphincter muscles using a new technique called AAR (anal acoustic reflectometry). Patients who have incontinence currently have a number of specialist tests performed on their back passage to assess the sphincter muscles. These tests are helpful, but this new sound wave technique will provide us with information on how the sphincter muscles actually work. It is hoped that the additional information gained from this study will improve our understanding of the back passage muscles and help us with the treatment and assessment of patients with the distressing symptoms of incontinence.

Do I have to take part?

No, it is up to you to decide. When you attend the hospital, we will describe the study and go through this information sheet, answering any questions or concerns. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

The study involves measuring pressures in your bottom with the new test (AAR) and the routine test (manometry) in a different order. In this study we want to see if the order of performing the test influences the results.

The standard test (manometry) already in practice throughout the NHS, involves putting a micro-catheter filled with water into the bottom. It measures how strong your sphincter muscles are around the bottom.

The new test (AAR) uses a small collapsed micro-catheter which will be placed inside the back passage (similar in size or smaller than the one used for manometry). The bag inflates and deflates, sending sound wave information to a computer which we can analyse. We will perform the tests twice so we can show whether the order has any effect on the results. Chaperones, usually a member of nursing staff, will be used as appropriate.

The procedure will take about 75 minutes.

You will be asked to complete a short questionnaire on how you found the new test (this will take less than 5 minutes).

What are the possible disadvantages and risks of taking part?

Although some may find the test embarrassing, it will be carried out only by senior health care professionals experienced in this area, and no students will be present. If you find the procedure embarrassing or distressing at any time please inform the doctor who will stop the investigation. This will have no effect on your normal NHS treatment.

The new technique is pain free but you will be aware of the balloon resting in the back passage. There are no risks associated with AAR or manometry.

What are the possible benefits of taking part?

There is no direct benefit to you. We hope to gain more information on the causes of faecal incontinence, and how the new sound wave machine assesses the sphincter muscles. This will allow us to understand and treat patients better in the future.

Harm

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University Hospital South Manchester but you may have to pay your legal cost. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact number below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure, or through the Patient Advice Liaison Service (PALS), which is located Opposite Strollers, East Entrance, New Acute Block, Wythenshawe Hospital, Southmoor Road, For post please put c/o Trust HQ. Telephone Number 0161 291 6611.

Will my taking part in the study be kept confidential?

All study information will be anonymous. However, we will keep a list of those involved in the study, so that if we detect a problem which we think we might be able to help you

with, we can contact you and offer further tests, follow-up or treatment, as appropriate. No one outside the research team will have access to this information.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. If you withdraw from the study you do not have to give a reason and it will not affect your future treatment. You will still be able to access services if you develop bowel problems in the future. If you withdraw, we will, with your consent, use the data collected up to your withdrawal.

What will happen to the results of the research study?

Results of the study will be submitted for publication in the scientific and medical literature. No one will be able to identify you from any data published. If you are interested, we can provide you with a summary of our findings at the end.

Who is organising and funding the research?

The research is being organised and funded by the University Hospital of South Manchester NHS Trust (Wythenshawe Hospital). This study will form part of an educational project by James Nicholson (contact details below), and will be submitted for a Doctor of Medicine (MD/PhD) qualification from the University of Manchester.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the (13/NW/0469) NHS Research Ethics Committee.

Further Information?

Please do not hesitate to contact me if you have any questions/concerns or wish to discuss the above information.

Mr. James Nicholson BSc(Hons) MBChB MRCS
Research Registrar to Miss. Telford MD FRCS Consultant Surgeon
c/o Miss Telford Secretary
2nd floor, Acute block,
Wythenshawe Hospital,
Southmoor Road,
Wythenshawe,
Manchester.
M23 9LT
Direct line 0161 291 5850
Sec 0161 291 6654
Email james.nicholson@manchester.ac.uk

Example of Consent form

University Hospital of South Manchester NHS
NHS Foundation Trust

Patient Consent Form
Study Title – Anal Acoustic Reflectometry (AAR) and Manometry the order of data collection.

Research Project ID:

- I confirm that I have read and understand the information sheet dated 17/04/2013 (Version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

Participant Initials

- I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

Participant Initials

- I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University Hospital of South Manchester NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

Participant Initials

- I am willing to take part in this study using a new technique to assess the function of the anal sphincter muscles.

Participant Initials

Signed: Date:
Name:

Researcher Signature: Date:
Researcher Name: Contact:

Example of Vaizey FI severity score

University Hospital of South Manchester NHS
NHS Foundation Trust

Study Title – Anal Acoustic Reflectometry (AAR) and Manometry the order of data collection.

Vaizey Questionnaire

Thank you for taking part in the study, the following questionnaire should only take a few minutes for you to complete.

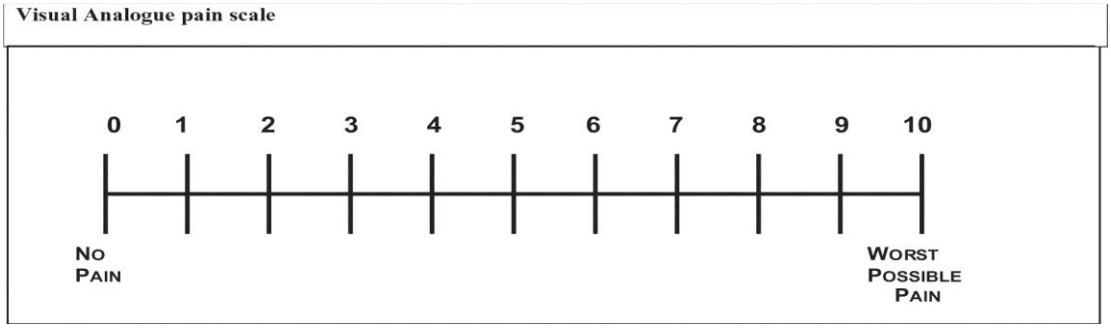
Study ID Number	
Date	

Please answer the following 7 questions by ticking the appropriate box for each question. Please tick only ONE box.

	Never	Rarely	Sometimes	Weekly	Daily
	No episodes in a 4 week period	**1 episode in a 4 week period**	**1 or more episodes in a 4 weeks period but less than once a week**	**1 or more episodes per week but less than once a day**	**1 or more episodes per day**
Do you ever leak solid stools?					
Do you ever leak liquid stools but can hold onto solid stools?					
Do you ever only leak gas but hold onto solid and liquid stools?					
How often does your bowel leakage problem affect your lifestyle?					

	No	Yes
Do you need to wear a pad or plug?		
Do you need to take constipating medicines to make your stools firmer and more controllable?		
If you had the urge to open your bowels would you have had an accident if you could not reach a toilet within 15 minutes?		

8. Please indicate by marking the line below the degree of discomfort experienced with the new test of sphincter muscles. The line represents a scale from the worse discomfort you could ever imagine on the right to no discomfort at all on the left.



Thank you for your time.

Example of data collection proforma

University Hospital of South Manchester NHS
NHS Foundation Trust

Study Title – Filling Rates of the Anal Canal & AAR

Data Collection Proforma **Randomisation:** Fast-Normal Normal-Fast

Demographics

- Study ID.....
- Date of test.....
- Reason for Test
- DOB.....
- Age.....
- Sex (M/F).....
- Weight (Kg).....

Continence

- Faecal Incontinence ☐
- Urinary Incontinence ☐
- Normal ☐

Type of Incontinence

- Urge Incontinence ☐
- Passive Incontinence ☐
- Leakage ☐
- Difficulty in defecation ☐
  (Obstructive defecation).....
- Difficulty in wiping ☐

Gynaecology

- Parity ☐
- No. of vaginal deliveries ☐
- No. of C sections ☐
- Use of forceps Yes/No ☐
- Use of ventouse Yes/No ☐
- Obstetric injuries Yes/No ☐
  Notes (e.g. episiotomy, tear repair)
  .....
- Previous gynaecology surgery Yes/No ☐
  Notes (e.g. TAH BSO, Prolapse)
  .....

Previous Surgery & Bowel Type

- Last bowel movement (Hrs) ☐
- Bristol stool chart (1 hard–7 liquid) ☐
- Previous anorectal surgery Yes/No ☐
  Notes (e.g. haemorrhoidectomy including SNS & PTNS)
  .....
- Abdominal surgery Yes/No ☐
  Notes (e.g. ant resection)
  .....
- Previous rubber band ligation Yes/No ☐

Data Collection Proforma Version 2 04/02/2014

Previous anorectal physiology investigations (ARPS)

- Date.....
- Anal Canal Length (cm).....
- Rectal Sensation (mls)
  - Onset ☐ Call ☐ Urgency ☐
- Right Pudendal Nerve
  - Normal ☐ Prolonged ☐ Not assessed ☐
- Left Pudendal Nerve
  - Normal ☐ Prolonged ☐ Not assessed ☐
- EAUS
  - IAS Intact ☐ Defect ☐
  - EAS Intact ☐ Defect ☐
  - Notes.....
- RAIR Present ☐ Absent ☐ Not assessed ☐
- BET Expelled ☐ Failed ☐ Volume (mls) ☐ Not assessed ☐
- MSP (cmH2O) ☐
- MRP (cmH2O) ☐

Anal Acoustic Reflectometry (AAR)

AAR Bag No.....

• OP1	☐	OP2	☐
• OE1	☐	OE2	☐
• CP1	☐	CP2	☐
• CE1	☐	CE2	☐
• HY1	☐	HY2	☐
• SOP1	☐	SOP2	☐
• SOE1	☐	SOE2	☐

Manometry

MRP1 ☐ MSP1 ☐

MRP2 ☐ MSP2 ☐

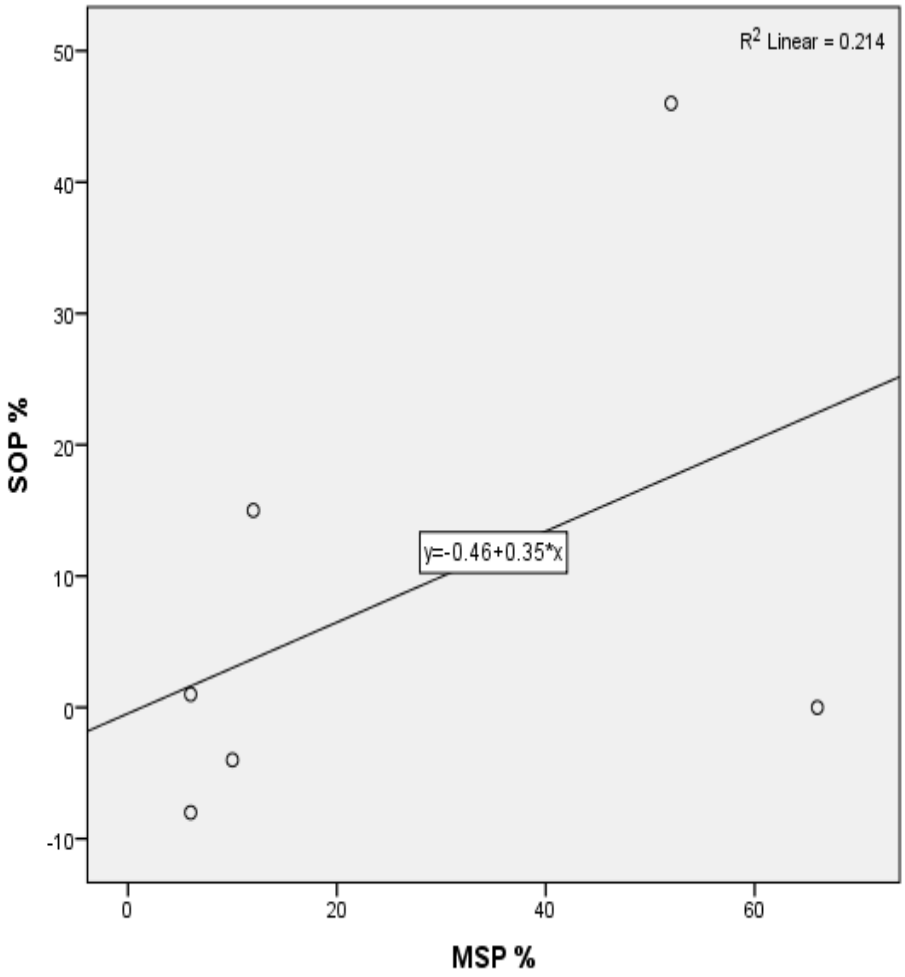
Data Collection Proforma Version 2 04/02/2014

Appendix C

Chapter 13 Additional Analysis

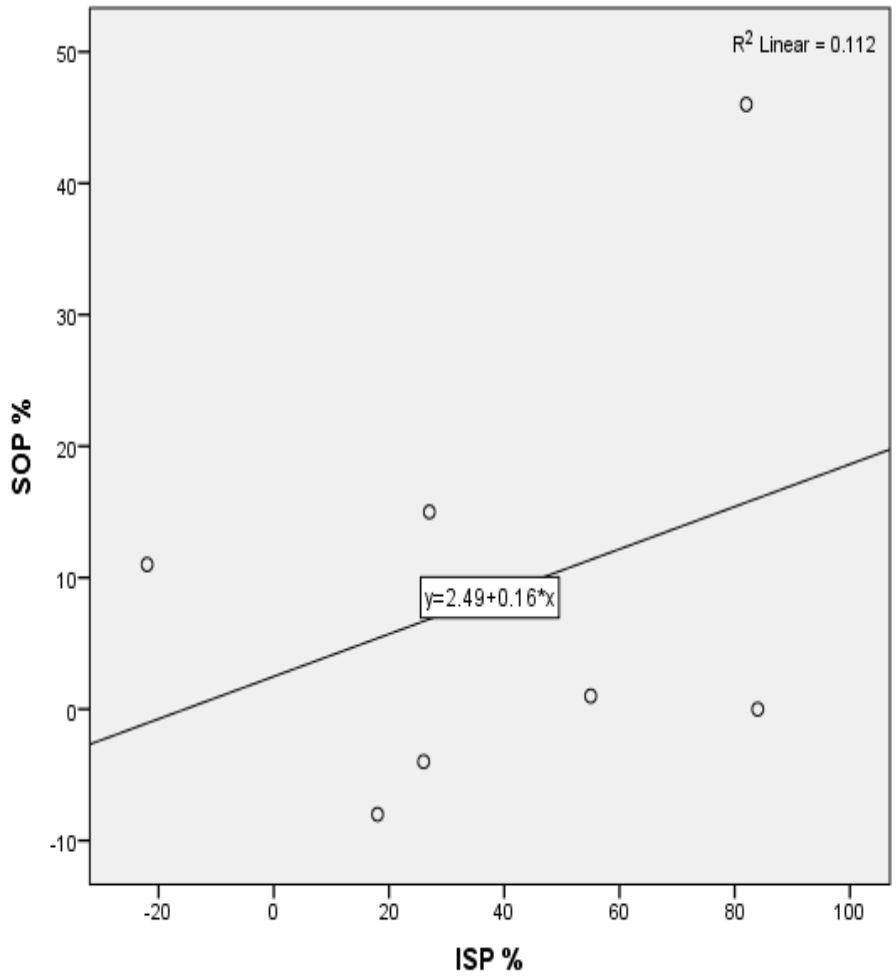
No agreement or correlation was found between SOP and MSP or ISP (see Chapter 13 results section).

Figure 54 Reduction in SOP against the reduction in MSP



Scatter graph showing the reduction in SOP against the reduction in MSP. No agreement found between SOP and MSP (R^2=0.214, where 1 is perfect agreement between the data points and the line of best fit and 0 shows no agreement). Pearson correlation coefficient 0.463 p=0.296, showing poor correlation.

Figure 55 Reduction in SOP against the reduction in ISP



Scatter graph showing the reduction in SOP against the reduction in ISP. No agreement found between SOP and ISP (R^2=0.112, where 1 is perfect agreement between the data points and the line of best fit and 0 shows no agreement). Pearson correlation coefficient 0.334 p=0.464, showing poor correlation.

Appendix D

Chapter 14 Additional Analysis

No significance was found between subjective success and fail in pre-PTNS variables of AAR and manometry.

Table 30 AAR and HRAM variables with subjective success for PTNS

Subjective Success **Variable (n=30)**	**Success (n=20)**	**Fail (n=10)**	**P value**
AAR (pre-PTNS)			
Opening Pressure (cmH_2O)	37 (3-90)$^{\alpha}$	39 (9-67)$^{\alpha}$	0.77*
Opening Elastance (cmH_2O/mm^2)	0.95 (0.45-3.07)	0.86 (0.58-1.90)	0.48
Closing Pressure (cmH_2O)	30 (1-77)$^{\alpha}$	33 (5-67)$^{\alpha}$	0.69*
Closing Elastance (cmH_2O/mm^2)	0.88 (0.46-1.49)	0.8 (0.56-1.47)	0.17
Hysteresis %	18 (5-48)	21 (0-44)	0.78
Squeeze Opening Pressure (cmH_2O)	60 (17-129)$^{\alpha}$	77 (17-162)$^{\alpha}$	0.27*
Squeeze Opening Elastance (cmH_2O/mm^2)	1.17 (0.74-2)	1.18 (0.56-3.42)	0.91
Variable	**Success (n=20)**	**Fail (n=10)**	**P value**
High Resolution Anal Manometry (pre-PTNS)			
Rectal Sensation – onset (mls)	40 (16-100)	35 (17-90)	0.75
Rectal Sensation –call (mls)	83 (40-150)	70 (34-130)	0.35
Rectal Sensation – Urgency (mls)	111 (50-220)	97 (48-240)	0.35
MRP (mmHg)	42 (19-74)	30 (12-55)	0.18
MSP (mmHg)	63 (20-219)	50 (14-195)	0.71
ISP (mmHg)	23 (1-165)	12 (3-93)	0.71

*AAR and HRAM variables with subjective success for PTNS. Subjective success defined as patient stated they derived benefit at the end of treatment and would like to enter top up treatment. Values are medians (ranges) and statistical comparisons made using Mann-Whitney U test unless otherwise stated. $^{\alpha}$Mean (range), *independent samples t-test. Significance level <0.05.*

Agreement between subjective and objective success of PTNS

83% of patients who stated subjective success also had objective success at the 50% threshold. 58% of patients who stated subjective failure of PTNS also had objective failure at the same threshold. When the threshold is raised to 70% the agreement in success increased to 100% (all of the patients with objective success had subjective success), but fell to 53% in failure. As the threshold for success increased the sensitivity improved but the specificity for failure fell (Table 31 Table 32).

Table 31 Subjective and objective agreement at the 50% threshold.

Crosstab

			Patient reported outcome		Total
			Subjective Success	Subjective Fail	
Objective Success >50%	Success	Count	15	3	18
		% within Objective Success >50%	83.3%	16.7%	100.0%
	Fail	Count	5	7	12
		% within Objective Success >50%	41.7%	58.3%	100.0%
Total		Count	20	10	30
		% within Objective Success >50%	66.7%	33.3%	100.0%

Agreement between subjective and objective success at the 50% threshold. Objective success defined as ≥50% improvement in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ).

Table 32 Subjective and objective agreement at the 70% threshold.

Crosstab					
			Patient reported outcome		Total
			Subjective Success	Subjective Fail	
Objective Success >70%	Success	Count	11	0	11
		% within Objective Success >70%	100.0%	0.0%	100.0%
	Fail	Count	9	10	19
		% within Objective Success >70%	47.4%	52.6%	100.0%
Total		Count	20	10	30
		% within Objective Success >70%	66.7%	33.3%	100.0%

Agreement between subjective and objective success at the 70% threshold. Objective success defined as ≥70% improvement in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ).

Predictive factors for the success of posterior tibial nerve stimulation

A predictive factor for success from PTNS was not found using questionnaires or bowel diaries (Table 33 Table 34). The FIQL parameter of embarrassment showed a trend towards significance (p=0.056), suggesting that patients with more embarrassment were more likely to fail PTNS at the 70% threshold of success.

Table 35 below describes the clinical outcome of the 30 patients with regard to their objective and subjective success. 21 patients were entered into top up PTNS therapy following treatment. Six patients had previous PNE or SNS procedures; all but one had a successful objective outcome at 70% and that one had a successful subjective outcome. Five patients had previous sphincter repairs, of these one had objective (50% & 70% thresholds) and subjective success, one objective (50%) success, two had subjective successes and one patient had neither objective nor subjective success.

Two patients with previous spinal surgery had no success however one patient with multiple sclerosis showed complete response on all objective and subjective measures.

Pre PTNS Questionnaire variables	50% Threshold Objective Success			70% Threshold Objective Success			≥50% reduction in FI episodes		
	Success (n=18)	Fail (n=12)	P value	Success (n=11)	Fail (n=19)	P value	Success (n=15)	Fail (n=14)	P value
Vaizey (0-24) lower better	17 (6-23)	20 (6-23)	0.146	19 (6-23)[α]	17 (6-23)[α]	0.995*	17 (6-23)	18 (6-23)	1
GQLI (0-144) higher better	95 (62-120)	90 (51-128)	0.787	91 (62-113)	101 (51-128)	0.145	93 (62-113)	105 (51-128)	0.134
PCO (0-80) lower better	69 (46-80)[α]	63 (32-80)[α]	0.207*	72 (46-80)	66 (32-80)	0.471	70 (46-80)	67 (32-80)	0.505
SF-36 (0-100) higher better									
Physical Functioning	68 (20-100)	58 (5-100)	0.491	59 (20-85)[α]	64 (5-100)[α]	0.575*	61 (20-100)[α]	68 (15-100)[α]	0.517*
Role Limitation due to physical health	63 (0-100)	100 (0-100)	0.491	25 (0-100)	100 (0-100)	0.395	25 (0-100)	100 (0-100)	0.234
Role limitations due to emotional problems	67 (0-100)	100 (0-100)	0.917	100 (0-100)	67 (0-100)	0.767	67 (0-100)	100 (0-100)	0.780
Energy/Fatigue	45 (0-80)[α]	58 (25-85)[α]	0.138*	45 (20-75)[α]	55 (0-85)[α]	0.653*	44 (0-75)[α]	58 (20-85)[α]	0.089*
Emotional well being	64 (20-96)	72 (20-100)	0.305	60 (20-96)[α]	68 (20-100)[α]	0.357*	60 (20-96)	72 (20-100)	0.270
Social Function	69 (0-100)	81 (10-100)	0.632	50 (0-100)	75 (10-100)	0.328	63 (0-100)	75 (10-100)	0.683
Bodily Pain	63 (23-100)	84 (0-100)	0.662	55 (23-100)	80 (0-100)	0.200	58 (23-100)	90 (23-100)	0.158
General Health	53 (15-85)	35 (20-100)	0.755	50 (12-85)	40 (15-100)	0.933	50 (15-85)	48 (20-100)	0.652
FIQL (1-4) higher better									
Lifestyle	3 (1.5-4)	2.9 (1.5-3.9)	0.879	2.5 (1.5-3.9)[α]	2.9 (1.5-4)[α]	0.171*	2.5 (1.5-3.9)	3.1 (1.5-4)	0.352
Coping behaviour	1.7 (0.4-3.2)	1.4 (1-3.4)	0.811	1.6 (1-3.2)	1.4 (0.4-3.4)	0.910	1.6 (0.4-3.2)	1.4 (1-3.4)	0.667
Depression	2.9 (1.4-4)	2.6 (1.1-4)	0.632	2.4 (1.1-4)	3 (1.1-4)	0.395	2.7 (1.4-4)	2.9 (1.1-4)	0.561
Embarrassment	2 (1-3.7)	1.8 (1-3)	0.370	1.5 (1-3.3)	2.7 (1-3.7)	0.056	2 (1-3.3)	2 (1-3.3)	0.667
MHQ (0-100) lower better									
General health	38 (0-75)	25 (0-75)	0.787	50 (25-75)	25 (0-75)	0.287	50 (0-75)	25 (0-75)	0.331
Impact	75 (25-100)	100 (25-100)	0.346	75 (50-100)[α]	75 (25-100)[α]	0.559*	75 (50-100)	88 (25-100)	1
Role	44 (0-75)[α]	53 (13-100)[α]	0.297*	50 (13-75)	50 (0-100)	0.553	50 (13-75)	50 (0-100)	0.847
Physical	50 (0-100)	50 (13-100)	0.950	63 (50-100)	50 (0-100)	0.171	64 (50-100)[α]	49 (0-100)[α]	0.092*
Social	46 (0-83)	46 (0-100)	0.662	50 (8-83)	42 (0-100)	0.345*	50 (8-83)	42 (0-100)	0.533
Personal	38 (0-100)	50 (0-100)	0.573	50 (0-100)	38 (0-100)	0.553	50 (0-100)	31 (0-100)	0.591
Emotions	58 (17-100)	63 (8-100)	0.884	58 (17-100)	42 (8-100)	0.250	58 (17-100)	50 (8-100)	0.533
Sleep	41 (0-100)[α]	41 (0-100)[α]	0.976*	47 (0-100)	38 (0-100)	0.440*	46 (0-100)[α]	34 (0-100)[α]	0.305*
Severity	59 (10-90)[α]	73 (20-100)[α]	0.174*	80 (40-90)	55 (10-100)	0.582	75 (40-90)	68 (10-100)	0.914
Total (0-900)	482 (107-773)	544 (146-783)	0.573	556 (269-773)	463 (107-783)	0.307	532 (269-773)	476 (107-758)	0.400

Table 33 Pre PTNS questionnaire data and objective measures of success.

*Objective success defined as ≥50% or ≥70% in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ) and ≥50% reduction in total FI episodes over 2 weeks. No significant difference found between all pre PTNS questionnaire parameters and success or fail. Values are medians (ranges) and statistical comparisons made using Mann-Whitney U test unless otherwise stated. [α]Mean (range), *independent samples t-test and a significance level of <0.05.*

Table 34 Pre PTNS bowel diary variables and objective success

Pre PTNS 2 week bowel diary variables	50% Threshold Objective Success			70% Threshold Objective Success			≥50% reduction in FI Episodes		
	Success (n=18)	Fail (n=12)	P value	Success (n=11)	Fail (n=19)	P value	Success (n=15)	Fail (n=14)	P value
Total frequency	34 (12-88)	41 (20-87)	0.276	36 (12-63)[α]	44 (14-88)[α]	*0.341	34 (12-88)	40 (14-87)	0.847
Urgency episodes	11 (0-84)	14 (2-35)	0.808	10 (0-67)	14 (2-84)	0.808	14 (0-84)	11 (2-35)	0.914
Urge FI episodes	2 (0-37)	4 (0-26)	0.808	1 (0-37)	4 (0-26)	0.808	1 (0-37)	4 (0-26)	0.914
Passive FI episodes	5 (0-43)	5 (0-32)	0.877	6 (0-43)	4 (0-32)	0.438	5 (0-43)	5 (0-32)	0.914
Staining episodes	7 (0-14)	10 (0-14)	0.188	7 (1-14)	8 (0-14)	0.740	7 (1-14)	9 (0-14)	0.331
Pad use (days)	5 (0-14)	12 (0-14)	0.740	12 (0-14)	4 (0-14)	0.521	7 (0-14)	7 (0-14)	0.683
Enema use (days)	0 (0-2)	0 (0-14)	0.877	0 (0-2)	0 (0-14)	0.912	0 (0-2)	0 (0-14)	1
Effects social life (days)	5 (0-14)	5 (0-14)	0.492	7 (0-14)	4 (0-14)	0.465	5 (0-14)	4 (0-14)	0.914
Bristol Stool Chart	4 (2-6)[α]	4 (2-6)[α]	*0.692	4 (2-6)	4 (2-6)	0.412	4 (2-6)	4 (2-6)	0.780

*Pre PTNS bowel diary variables and objective success. Objective success defined as ≥50% or ≥70% in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ) and ≥50% reduction in total FI episodes per week. No significant difference found between all pre PTNS bowel diary parameters and success or fail. Statistical comparisons made using Mann-Whitney U test unless otherwise stated. [α]Mean (range), *independent samples t-test and a significance level of <0.05.*

Table 35 Success of PTNS with type of incontinence and previous surgery

	≥50% Improvement in total FI episodes	Objective Success >50%	Objective Success >70%	Subjective Success	Clinical Outcome	Type of FI (predominant type if mixed)	Previous SNS	Sphincter Repair	Spinal Surgery	Surgery/relevant diagnosis
1	Yes	Yes	No	Yes	PTNS Top Ups	Mixed				Delormes procedure
2	No	No	No	No	PTQ/Irrigation	Passive				PTQ
3	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed (urge)	PNE (failed)			
4	Yes	Yes	No	Yes	PTNS Top Ups	Urge				Hysterectomy
5	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed	SNS (removed)			SNS removed after trauma and neurological symptoms
6	No	No	No	Yes	PTNS Top Ups	Mixed (passive)		Yes		Perineal reconstruction
7	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed (urge)	PNE (success)			Hysterectomy, patient chose against SNS
8	Yes	Yes	Yes	Yes	PTNS Top Ups	Passive				
9	Yes	Yes	Yes	Yes	PTNS Top Ups	Urge	PNE (failed)	Yes		Hysterectomy
10	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed (passive)				
11	No	No	No	Yes	PTNS Top Ups	Passive	PNE (success)			Hysterectomy, patient chose against SNS
12	Unknown	No	No	Yes	PTNS Top Ups	Mixed (passive)			Yes	Spinal surgery, Colposuspension, hysterectomy
13	No	No	No	No	Referred back to Cons Clinic	Passive			Yes	Extensive spinal surgery (neurogenic bowel & bladder)
14	No	No	No	No	Referred back to Cons Clinic	Urge		Yes (2)		Hysterectomy, multiple laparotomies (7), Levatorpasty
15	No	Yes	No	No	PTNS top Ups (urgency better but not passive) PTQ/Irrigation	Mixed (passive)				PTQ, neonatal bowel surgery
16	Yes	Yes	Yes	Yes	PTNS Top Ups	Urge				Hysterectomy, anal stretch
17	No	No	No	Yes	PTNS Top Ups	Urge				Bowel resection, Haemorrhoidectomy
18	No	No	No	Yes	PTNS Top Ups	Mixed (urge)		Yes		
19	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed (urge)				
20	No	No	No	No	PNE	Mixed (passive)				Transobturator tape, hysterectomy
21	Yes	Yes	Yes	Yes	PTNS Top Ups	Mixed (urge)	PNE (failed)			Hysterectomy
22	Yes	Yes	Yes	Yes	PTNS Top Ups	Urge				
23	No	No	No	No	PNE	Urge				
24	Yes	Yes	No	No	Irrigation	Urge				Haemorrhoidectomy
25	No	Yes	No	Yes	PTNS Top Ups	Mixed (urge)				Fentons procedure
26	Yes	Yes	Yes	Yes	PTNS Top Ups	Urge				Multiple Sclerosis
27	No	No	No	No	Irrigation	Mixed (passive)				Transanal resection of SRUS
28	Yes	Yes	No	No	Referred back to Cons Clinic (?lap VMR)	Mixed (urge)		Yes		Hysterectomy
29	No	Yes	No	Yes	PTNS Top Ups	Urge				
30	No	No	No	No	Irrigation & Loperamide	Urge				Mild ulcerative colitis

Success of PTNS with type of faecal incontinence and previous surgery including neuromodulation. Subjective success defined as patient stated they derived benefit at the end of treatment and would like to enter top up treatment. Objective success defined as ≥50% or ≥70% in 2 or more of 6 variables (FI episodes, urgency, urge FI, passive FI, Vaizey, MHQ) and ≥50% reduction in total FI episodes per week. SNS=sacral nerve stimulation, PNE=peripheral nerve evaluation, PTQ= anal silicone implant to bulk the anal canal and treat passive FI, Lap VMR=laparoscopic ventral mesh rectopexy, SRUS=solitary rectal ulcer syndrome.

References

1. Moore, K.L., *Clinically oriented anatomy*. 2013: Lippincott Williams & Wilkins.
2. Bharucha, A.E., *Pelvic floor: anatomy and function.* Neurogastroenterology & Motility, 2006. **18**(7): p. 507-519.
3. Wester, C. and L. Brubaker, *NORMAL PELVIC FLOOR PHYSIOLOGY.* Obstetrics and Gynecology Clinics of North America, 1998. **25**(4): p. 707-722.
4. Parks, A., *Royal Society of Medicine, Section of Proctology; Meeting 27 November 1974. President's Address. Anorectal incontinence.* Proceedings of the Royal Society of Medicine, 1975. **68**(11): p. 681.
5. Smith, L.E., *Practical guide to anorectal testing*. 1995: Igaku-Shoin Medical Pub.
6. Raizada, V. and R.K. Mittal, *Pelvic Floor Anatomy and Applied Physiology.* Gastroenterology Clinics of North America, 2008. **37**(3): p. 493-509.
7. Salerno, G., et al., *Defining the rectum: surgically, radiologically and anatomically.* Colorectal Disease, 2006. **8**: p. 5-9.
8. Duthie, H., *Dynamics of the rectum and anus.* Clinics in gastroenterology, 1975. **4**(3): p. 467.
9. Lindsey, I., et al., *Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon.* British Journal of Surgery, 2000. **87**(10): p. 1288-1299.
10. Nivatvongs, S., H.S. Stern, and D.S. Fryd, *The length of the anal canal.* Diseases of the Colon & Rectum, 1981. **24**(8): p. 600-601.
11. Phillips, R.K., *Colorectal surgery: a companion to specialist surgical practice*, 2009, Philadelphia: Elsevier Saunders.
12. Thomson, W., *The nature of haemorrhoids.* British Journal of Surgery, 1975. **62**(7): p. 542-552.
13. Haas, P.A., T.A. Fox Jr, and G.P. Haas, *The pathogenesis of hemorrhoids.* Diseases of the Colon & Rectum, 1984. **27**(7): p. 442-450.
14. Lestar, B., et al., *The internal anal sphincter can not close the anal canal completely.* International journal of colorectal disease, 1992. **7**(3): p. 159-161.
15. Lestar, B., F. Penninckx, and R. Kerremans, *The composition of anal basal pressure.* International journal of colorectal disease, 1989. **4**(2): p. 118-122.
16. Netter, F. *The Anal Canal (figure)*. 2013; Available from: http://id.medicine.ucsf.edu/analcancerinfo/diagnosis/anatomy.html.
17. Ward, S.M., K.M. Sanders, and G.D.S. Hirst*, *Role of interstitial cells of Cajal in neural control of gastrointestinal smooth muscles.* Neurogastroenterology & Motility, 2004. **16**: p. 112-117.
18. Rattan, S., *The internal anal sphincter: regulation of smooth muscle tone and relaxation.* Neurogastroenterology & Motility, 2005. **17**: p. 50-59.
19. Goligher, J.C., A.G. Leacock, and J.J. Brossy, *The surgical anatomy of the anal canal.* British Journal of Surgery, 1955. **43**(177): p. 51-61.

20. Sangwan, Y.P. and J.A. Solla, *Internal anal sphincter.* Diseases of the Colon & Rectum, 1998. **41**(10): p. 1297-1311.
21. Bartram, C., *Endoanal Ultrasound*, in *Imaging Pelvic Floor Disorders*. 2008, Springer Berlin Heidelberg. p. 101-114.
22. Lunniss, P. and R. Phillips, *Anatomy and function of the anal longitudinal muscle.* British Journal of Surgery, 1992. **79**(9): p. 882-884.
23. Papachrysostomou, M., et al., *Anal endosonography in asymptomatic subjects.* Scandinavian journal of gastroenterology, 1993. **28**(6): p. 551-556.
24. Chung, E., et al., *Relationship between bladder and bowel filling and the guarding reflex mechanism.* Brit. J. Urol. Int, 2004. **94**: p. 1176.
25. Santorini, G., *Septem decim tabulae edit et explici.* Parone: Mich Gerardi. **1715**.
26. Thompson, P., *The myology of the pelvic floor*. 1899: McCorquodale & Company.
27. Gorsch, R.V., *Proctologic anatomy.* The American Journal of the Medical Sciences, 1956. **231**(3): p. 365.
28. Milligan, E. and C.N. Morgan, *Surgical anatomy of the anal canal.* The Lancet, 1934. **224**(5805): p. 1213-1217.
29. Milligan, E.T.C., et al., *SURGICAL ANATOMY OF THE ANAL CANAL, AND THE OPERATIVE TREATMENT OF HÆMORRHOIDS.* The Lancet, 1937. **230**(5959): p. 1119-1124.
30. Oh, C. and A.E. Kark, *Anatomy of the external anal sphincter.* British Journal of Surgery, 1972. **59**(9): p. 717-723.
31. Ayoub, S.F., *Anatomy of the external anal sphincter in man.* Cells Tissues Organs, 1979. **105**(1): p. 25-36.
32. Lawson, J., *Pelvic anatomy. II. Anal canal and associated sphincters.* Annals of the Royal College of Surgeons of England, 1974. **54**(6): p. 288.
33. Fritsch, H., et al., *Anal sphincter complex.* Diseases of the Colon & Rectum, 2002. **45**(2): p. 188-194.
34. Stoker, J., S. Halligan, and C.I. Bartram, *Pelvic Floor Imaging1.* Radiology, 2001. **218**(3): p. 621-641.
35. Gordon, P.H., *ANORECTAL ANATOMY AND PHYSIOLOGY.* Gastroenterology Clinics of North America, 2001. **30**(1): p. 1-13.
36. Sultan, A., et al., *Endosonography of the anal sphincters: normal anatomy and comparison with manometry.* Clinical Radiology, 1994. **49**(6): p. 368-374.
37. Williams, A., et al., *Gender differences in the longitudinal pressure profile of the anal canal related to anatomical structure as demonstrated on three-dimensional anal endosonography.* British Journal of Surgery, 2000. **87**(12): p. 1674-1679.
38. Rociu, E., et al., *Normal Anal Sphincter Anatomy and Age-and Sex-related Variations at High-Spatial-Resolution Endoanal MR Imaging1.* Radiology, 2000. **217**(2): p. 395-401.
39. Frudinger, A., et al., *Female Anal Sphincter: Age-related Differences in Asymptomatic Volunteers with High-Frequency Endoanal US1.* Radiology, 2002. **224**(2): p. 417-423.

40. Drake, R., A.W. Vogl, and A.W. Mitchell, *Gray's anatomy for students*. 2009: Churchill Livingstone.
41. Gonella, J., M. Bouvier, and F. Blanquet, *Extrinsic nervous control of motility of small and large intestines and related sphincters.* Physiological reviews, 1987. **67**(3): p. 902.
42. Frenckner, B. and T. Ihre, *Influence of autonomic nerves on the internal and sphincter in man.* Gut, 1976. **17**(4): p. 306-12.
43. Carlstedt, A., et al., *Sympathetic nervous influence on the internal anal sphincter and rectum in man.* Int J Colorectal Dis, 1988. **3**(2): p. 90-5.
44. Penninckx, F., B. Lestar, and R. Kerremans, *The internal anal sphincter: mechanisms of control and its role in maintaining anal continence.* Baillieres Clin Gastroenterol, 1992. **6**(1): p. 193-214.
45. Snell, R.S., *Clinical anatomy for medical students*. 6th ed. ed. 1995, Boston ; London: Little, Brown. viiix, 898 p.
46. Shafik, A., et al., *Surgical anatomy of the pudendal nerve and its clinical implications.* Clinical Anatomy, 1995. **8**(2): p. 110-115.
47. Lawson, J.O., *Pelvic anatomy. I. Pelvic floor muscles.* Ann R Coll Surg Engl, 1974. **54**(5): p. 244-52.
48. Percy, J.P., et al., *Electrophysiological study of motor nerve supply of pelvic floor.* Lancet, 1981. **1**(8210): p. 16-7.
49. Duthie, H. and F. Gairns, *Sensory nerve-endings and sensation in the anal region of man.* British Journal of Surgery, 1960. **47**(206): p. 585-595.
50. Maxwell, P., et al., *Anorectal sensation and continence.* Scandinavian Journal of Gastroenterology, 1999. **34**(2): p. 113-116.
51. Christensen, J., *Motility of the colon.* Physiology of the gastrointestinal tract, 1987. **1**: p. 455-471.
52. Brocklehurst, J., et al., *Incidence and correlates of incontinence in stroke patients.* Journal of the American Geriatrics Society, 1985. **33**(8): p. 540.
53. Nakayama, H., et al., *Prevalence and Risk Factors of Incontinence After Stroke The Copenhagen Stroke Study.* Stroke, 1997. **28**(1): p. 58-62.
54. Weber, J., et al., *Anorectal manometric anomalies in seven patients with frontal lobe brain damage.* Digestive diseases and sciences, 1990. **35**(2): p. 225-230.
55. Hinds, J., B. Eidelman, and A. Wald, *Prevalence of bowel dysfunction in multiple sclerosis. A population survey.* Gastroenterology, 1990. **98**(6): p. 1538.
56. Turnbull, G.K., et al., *The cortical topography of human anorectal musculature.* Gastroenterology, 1999. **117**(1): p. 32-39.
57. Talley, N.J., *Clinical gastroenterology*. 2011: Churchill Livingstone.
58. Petersen, O.H., *Human physiology*. 5th ed. Lecture Notes. 2007: London: Blackwell Scientific Publications, 1994.
59. Gowers, W.R., *The autonomic action of the sphincter ani.* Proc R Soc Lond, 1877. **26**: p. 77-84.
60. Denny-Brown, D., Robertson, E.G., *An investigation of the nervous control of defaecation.* Brain, 1935. **58**: p. 256-310.
61. Gaston, E., *The physiology of fecal continence.* Surgery, gynecology & obstetrics, 1948. **87**(3): p. 280.

62. Scharli, A.F. and W.B. Kiesewetter, *Defecation and continence.* Diseases of the Colon & Rectum, 1970. **13**(2): p. 81-107.
63. Lubowski, D.Z., et al., *Neural control of internal anal sphincter function.* Br J Surg, 1987. **74**(8): p. 668-70.
64. Callaghan, R. and H. Nixon, *Megarectum: physiological observations.* Archives of disease in childhood, 1964. **39**(204): p. 153.
65. Lane, R.H. and A.G. Parks, *Function of the anal sphincters following colo-anal anastomosis.* Br J Surg, 1977. **64**(8): p. 596-9.
66. O'Riordain, M.G., et al., *Rectoanal inhibitory reflex following low stapled anterior resection of the rectum.* Diseases of the Colon & Rectum, 1992. **35**(9): p. 874-878.
67. Widmaier, E.P., H. Raff, and K.T. Strang, *Vander's human physiology*. 11th ed. 2008: McGraw-Hill Higher Education.
68. Duthie, H.L. and R.C. Bennett, *The relation of sensation in the anal canal to the functional anal sphincter: a possible factor in anal continence.* Gut, 1963. **4**(2): p. 179-82.
69. Miller, R., D. Bartolo, and F. Cervero, *Anorectal sampling: a comparison of normal and incontinent patients.* British Journal of Surgery, 1988. **75**(1): p. 44-47.
70. Miller, R., et al., *Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique.* British Journal of Surgery, 1988. **75**(10): p. 1003-1007.
71. Porter, N., *A Physiological Study of the Pelvic Floor in Rectal Prolapse: Arris and Gale Lecture delivered at the Royal College of Surgeons of England on 1st November 1960.* Annals of the Royal College of Surgeons of England, 1962. **31**(6): p. 379.
72. Bajwa, A. and A. Emmanuel, *The physiology of continence and evacuation.* Best Pract Res Clin Gastroenterol, 2009. **23**(4): p. 477-85.
73. Dickinson, V.A., *Maintenance of anal continence: a review of pelvic floor physiology.* Gut, 1978. **19**(12): p. 1163-74.
74. Deffieux, X., et al., *External anal sphincter contraction during cough: not a simple spinal reflex.* Neurourol Urodyn, 2006. **25**(7): p. 782-7.
75. Rossolimo, G., *Der Analreflex, seine physiologie und pathologie.* Neurologisches Centralblatt, 1891. **4**: p. 257-9.
76. Pedersen, E., et al., *Anal sphincter responses after perianal electrical stimulation.* J Neurol Neurosurg Psychiatry, 1982. **45**(9): p. 770-3.
77. Frenckner, B., *Function of the anal sphincters in spinal man.* Gut, 1975. **16**(8): p. 638-44.
78. Uher, E.M. and M. Swash, *Sacral reflexes: physiology and clinical application.* Dis Colon Rectum, 1998. **41**(9): p. 1165-77.
79. Chan, C.L., S. Ponsford, and M. Swash, *The anal reflex elicited by cough and sniff: validation of a neglected clinical sign.* J Neurol Neurosurg Psychiatry, 2004. **75**(10): p. 1449-51.
80. Hill, J.R., et al., *Pressure profile of the rectum and anus of healthy persons.* Dis Colon Rectum, 1960. **3**: p. 203-9.
81. Sangwan, Y.P. and J.A. Solla, *Internal anal sphincter: advances and insights.* Dis Colon Rectum, 1998. **41**(10): p. 1297-311.

82. Frenckner, B. and C.V. Euler, *Influence of pudendal block on the function of the anal sphincters.* Gut, 1975. **16**(6): p. 482-489.
83. Engel, A.F., et al., *Relationship of symptoms in faecal incontinence to specific sphincter abnormalities.* Int J Colorectal Dis, 1995. **10**(3): p. 152-5.
84. Sultan, A.H., et al., *Anal-sphincter disruption during vaginal delivery.* N Engl J Med, 1993. **329**(26): p. 1905-11.
85. Preston, D. and J. Lennard-Jones, *Anismus in chronic constipation.* Digestive diseases and sciences, 1985. **30**(5): p. 413-418.
86. Bartolo, D., et al., *Flap-valve theory of anorectal continence.* British Journal of Surgery, 1986. **73**(12): p. 1012-1014.
87. Goei, R., *Anorectal function in patients with defecation disorders and asymptomatic subjects: evaluation with defecography.* Radiology, 1990. **174**(1): p. 121-123.
88. Morgan, C.N., *The Surgical Anatomy of the Ischiorectal Space: President's Address.* Proceedings of the Royal Society of Medicine, 1949. **42**(3): p. 189.
89. Varma, K. and D. Stephens, *Neuromuscular reflexes of rectal continence.* The Australian and New Zealand journal of surgery, 1972. **41**(3): p. 263.
90. Duthie, H.L., *Dynamics of the rectum and anus.* Clin.Gastroenterol., 1975. **4**(3): p. 467-477.
91. Lynn, P.A. and L.A. Blackshaw, *In vitro recordings of afferent fibres with receptive fields in the serosa, muscle and mucosa of rat colon.* The Journal of physiology, 1999. **518**(1): p. 271-282.
92. Lynn, P.A., et al., *Rectal intraganglionic laminar endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum.* Gastroenterology, 2003. **125**(3): p. 786-794.
93. Chan, C.L., N.S. Williams, and P.J. Lunniss, *Rectal hypersensitivity worsens stool frequency, urgency, and lifestyle in patients with urge fecal incontinence.* Diseases of the Colon & Rectum, 2005. **48**(1): p. 134-140.
94. Loening-Baucke, V., A. Metcalf, and S. Shirazi, *Anorectal manometry in active and quiescent ulcerative colitis.* The American journal of gastroenterology, 1989. **84**(8): p. 892.
95. Yeoh, E.E., et al., *Anorectal dysfunction increases with time following radiation therapy for carcinoma of the prostate.* Am J Gastroenterol, 2004. **99**(2): p. 361-9.
96. Jones, J., et al., *British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome.* Gut, 2000. **47**(suppl 2): p. ii1-ii19.
97. Diamant, N.E., et al., *AGA technical review on anorectal testing techniques.* Gastroenterology, 1999. **116**(3): p. 735-60.
98. Siproudhis, L., et al., *Perception of and adaptation to rectal isobaric distension in patients with faecal incontinence.* Gut, 1999. **44**(5): p. 687-692.
99. Siproudhis, L., et al., *Fecal incontinence with normal anal canal pressures: where is the pitfall&quest.* The American journal of gastroenterology, 1999. **94**(6): p. 1556-1563.
100. Berne, R.M. and M.N. Levy, *Principles of physiology*. 2nd ed. ed. 1996, St. Louis ; London: Mosby. xiii, 795 p.

101. Walls, E.W., *Recent observations on the anatomy of the anal canal.* Proc R Soc Med, 1959. **52(Suppl)**: p. 85-7.
102. Chennells, M., Floyd, WF. and Gould, RP., *Muscle spindles in the external anal sphincter of the cat.* J Physiol, 1960. **151**: p. 23P-24P.
103. Li, L., et al., *Sensory nerve endings in the puborectalis and anal region of the fetus and newborn.* Dis Colon Rectum, 1992. **35**(6): p. 552-9.
104. Beersiek, F., A.G. Parks, and M. Swash, *Pathogenesis of ano-rectal incontinence: A histometric study of the anal sphincter musculature.* Journal of the neurological sciences, 1979. **42**(1): p. 111-127.
105. Heit, M., et al., *Levator ani muscle in women with genitourinary prolapse: indirect assessment by muscle histopathology.* Neurourology and urodynamics, 1996. **15**(1): p. 17-29.
106. Parks, A.G., N.H. Porter, and J. Melzak, *Experimental study of the reflex mechanism controlling the muscle of the pelvic floor.* Dis Colon Rectum, 1962. **5**: p. 407-14.
107. MacDonagh, R., et al., *Anorectal function in patients with complete supraconal spinal cord lesions.* Gut, 1992. **33**(11): p. 1532-1538.
108. Phillips, S.F. and J. Giller, *The contribution of the colon to electrolyte and water conservation in man.* J Lab Clin Med, 1973. **81**(5): p. 733-46.
109. Lewis, S. and K. Heaton, *Stool form scale as a useful guide to intestinal transit time.* Scandinavian Journal of Gastroenterology, 1997. **32**(9): p. 920-924.
110. Degen, L. and S. Phillips, *How well does stool form reflect colonic transit?* Gut, 1996. **39**(1): p. 109-113.
111. Heaton, K., S. Ghosh, and F. Braddon, *How bad are the symptoms and bowel dysfunction of patients with the irritable bowel syndrome? A prospective, controlled study with emphasis on stool form.* Gut, 1991. **32**(1): p. 73-79.
112. Heaton, K., et al., *Defecation frequency and timing, and stool form in the general population: a prospective study.* Gut, 1992. **33**(6): p. 818-824.
113. Weaver, L.T., *Bowel habit from birth to old age.* Journal of pediatric gastroenterology and nutrition, 1988. **7**(5): p. 637-640.
114. Lotze, M., et al., *Cerebral activation during anal and rectal stimulation.* Neuroimage, 2001. **14**(5): p. 1027-1034.
115. Tagart, R.E., *The anal canal and rectum.* Diseases of the Colon & Rectum, 1966. **9**(6): p. 449-452.
116. Lynch, A., et al., *Anorectal physiology following spinal cord injury.* Spinal Cord, 2000. **38**(10): p. 573-580.
117. Brookes, S.J., P.G. Dinning, and M.A. Gladman, *Neuroanatomy and physiology of colorectal function and defaecation: from basic science to human clinical studies.* Neurogastroenterol Motil, 2009. **21 Suppl 2**: p. 9-19.
118. Rao, S.S. and A.C.o.G.P.P. Committee, *Diagnosis and management of fecal incontinence.* The American journal of gastroenterology, 2004. **99**(8): p. 1585-1604.
119. Norton, C., et al., *Conservative and pharmacological management of faecal incontinence in adults.* Incontinence, ed. P. Abrams, et al. 2005: Plymouth: Health Publications. 1521–63.

120. Anders Mellgren, M., et al., *Long-term cost of fecal incontinence secondary to obstetric injuries.* Diseases of the Colon & Rectum, 1999. **42**(7): p. 857-865.
121. Crowell, M.D., et al., *Impact of anal incontinence on psychosocial function and health-related quality of life.* Digestive diseases and sciences, 2007. **52**(7): p. 1627-1631.
122. Deutekom, M., et al., *Impact of faecal incontinence severity on health domains.* Colorectal Disease, 2005. **7**(3): p. 263-269.
123. Tariq, S.H., *Geriatric fecal incontinence.* Clinics in geriatric medicine, 2004. **20**(3): p. 571.
124. Miner Jr, P.B., *Economic and personal impact of fecal and urinary incontinence.* Gastroenterology, 2004. **126**: p. S8-S13.
125. Vetter, N., D. Jones, and C. Victor, *Urinary incontinence in the elderly at home.* The Lancet, 1981. **318**(8258): p. 1275-1277.
126. Madoff, R.D., et al., *Faecal incontinence in adults.* The Lancet, 2004. **364**(9434): p. 621-632.
127. Nelson, R.L., *Epidemiology of fecal incontinence.* Gastroenterology, 2004. **126**: p. S3-S7.
128. Szurszewski, J.H., P.R. Holt, and M. Schuster, *Proceedings of a workshop entitled "Neuromuscular function and dysfunction of the gastrointestinal tract in aging".* Digestive diseases and sciences, 1989. **34**(7): p. 1135-1146.
129. Parés, D., et al., *Prevalence of faecal incontinence and analysis of its impact on quality of life and mental health.* Colorectal Disease, 2011. **13**(8): p. 899-905.
130. Thomas, T.M., et al., *The prevalence of faecal and double incontinence.* Journal of Public Health, 1984. **6**(3): p. 216-220.
131. Khullar, V., et al., *Prevalence of faecal incontinence among women with urinary incontinence.* BJOG: An International Journal of Obstetrics & Gynaecology, 1998. **105**(11): p. 1211-1213.
132. Nelson, R., S. Furner, and V. Jesudason, *Fecal incontinence in Wisconsin nursing homes.* Diseases of the Colon & Rectum, 1998. **41**(10): p. 1226-1229.
133. Chiang, L., et al., *Dually incontinent nursing home residents: clinical characteristics and treatment differences.* Journal of the American Geriatrics Society, 2000. **48**(6): p. 673-676.
134. Rao, S. and R. Patel, *How useful are manometric tests of anorectal function in the management of defecation disorders?* The American journal of gastroenterology, 1997. **92**(3): p. 469-475.
135. Chatoor, D.R., et al., *Faecal incontinence.* Br J Surg, 2007. **94**(2): p. 134-44.
136. Allen, R., et al., *Pelvic floor damage and childbirth: a neurophysiological study.* BJOG: An International Journal of Obstetrics & Gynaecology, 1990. **97**(9): p. 770-779.
137. Dietz, H.P., *Pelvic floor trauma following vaginal delivery.* Current Opinion in Obstetrics and Gynecology, 2006. **18**(5): p. 528-537.
138. Dietz, H. and L. Schierlitz, *Pelvic floor trauma in childbirth–Myth or reality?* Australian and New Zealand journal of obstetrics and gynaecology, 2005. **45**(1): p. 3-11.

139. Kamm, M.A., *Obstetric damage and faecal incontinence.* Lancet, 1994. **344**(8924): p. 730-3.
140. Sultan, A.H., et al., *Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair.* Bmj, 1994. **308**(6933): p. 887-91.
141. Groutz, A., et al., *Incidence and obstetric risk factors of postpartum anal incontinence.* Scandinavian Journal of Gastroenterology, 1999. **34**(3): p. 315-318.
142. Brincat, C., et al., *Fecal incontinence in pregnancy and post partum.* International Journal of Gynecology & Obstetrics, 2009. **106**(3): p. 236-238.
143. Eason, E., et al., *Anal incontinence after childbirth.* Canadian Medical Association Journal, 2002. **166**(3): p. 326-330.
144. MacArthur, C., D.E. Bick, and M.R. Keighley, *Faecal incontinence after childbirth.* BJOG: An International Journal of Obstetrics & Gynaecology, 1997. **104**(1): p. 46-50.
145. Ryhammer, A.M., K.M. Bek, and D. Søren Laurberg MD, *Multiple vaginal deliveries increase the risk of permanent incontinence of flatus and urine in normal premenopausal women.* Diseases of the Colon & Rectum, 1995. **38**(11): p. 1206-1209.
146. Hill, J., et al., *History and examination in the assessment of patients with idiopathic fecal incontinence.* Dis Colon Rectum, 1994. **37**(5): p. 473-7.
147. Snooks, S.J., et al., *Injury to innervation of pelvic floor sphincter musculature in childbirth.* Lancet, 1984. **2**(8402): p. 546-50.
148. Parks, A.G., M. Swash, and H. Urich, *Sphincter denervation in anorectal incontinence and rectal prolapse.* Gut, 1977. **18**(8): p. 656-65.
149. Snooks, S., M. Henry, and M. Swash, *Faecal incontinence due to external anal sphincter division in childbirth is associated with damage to the innervation of the pelvic floor musculature: a double pathology.* BJOG: An International Journal of Obstetrics & Gynaecology, 1985. **92**(8): p. 824-828.
150. Kiff, E., P. Barnes, and M. Swash, *Evidence of pudendal neuropathy in patients with perineal descent and chronic straining at stool.* Gut, 1984. **25**: p. 1279 - 1282.
151. Nyam, D.C. and J.H. Pemberton, *Long-term results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of fecal incontinence.* Diseases of the Colon & Rectum, 1999. **42**(10): p. 1306-1310.
152. Garcia-Aguilar, J., et al., *Openvs. closed sphincterotomy for chronic anal fissure.* Diseases of the Colon & Rectum, 1996. **39**(4): p. 440-443.
153. Read, M.G., et al., *A prospective study of the effect of haemorrhoidectomy on sphincter function and faecal continence.* Br J Surg, 1982. **69**(7): p. 396-8.
154. MacIntyre, I. and T. Balfour, *Results of the Lord non-operative treatment for haemorrhoids.* The Lancet, 1972. **299**(7760): p. 1094-1095.
155. Otto, I.C., et al., *Causes of rectal incontinence after sphincter-preserving operations for rectal cancer.* Diseases of the Colon & Rectum, 1996. **39**(12): p. 1423-1427.
156. Ho, M.Y.-H. and F. Seow-Choen, *Anal sphincter injuries from stapling instruments introduced transanally.* Diseases of the Colon & Rectum, 2000. **43**(2): p. 169-173.

157. Pescatori, M., et al., *New grading and scoring for anal incontinence. Evaluation of 335 patients.* Dis Colon Rectum, 1992. **35**(5): p. 482-7.
158. Rockwood, T.H., et al., *Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence.* Dis Colon Rectum, 2000. **43**(1): p. 9-16; discussion 16-7.
159. Jorge, J.M. and S.D. Wexner, *Etiology and management of fecal incontinence.* Dis Colon Rectum, 1993. **36**(1): p. 77-97.
160. Bugg, G.J., ,Kiff, E.S., Hosker, G., *A new condition-specific health-related quality of life questionnaire for the assessment of women with anal incontinence.* Br J Obstet Gynaecol, 2001. **108**: p. 1057-1067.
161. Rockwood, T.H., et al., *Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence.* Diseases of the Colon & Rectum, 1999. **42**(12): p. 1525-1531.
162. Eypasch, E., et al., *Gastrointestinal Quality of Life Index: development, validation and application of a new instrument.* British Journal of Surgery, 1995. **82**(2): p. 216-222.
163. Vaizey, C.J., et al., *Prospective comparison of faecal incontinence grading systems.* Gut, 1999. **44**(1): p. 77-80.
164. Rockwood, T.H., *Incontinence severity and QOL scales for fecal incontinence.* Gastroenterology, 2004. **126, Supplement 1**(0): p. S106-S113.
165. Ware Jr, J.E. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection.* Medical care, 1992: p. 473-483.
166. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatrica Scandinavica, 1983. **67**(6): p. 361-370.
167. Reilly, W.T., et al., *Validation of a questionnaire to assess fecal incontinence and associated risk factors.* Diseases of the Colon & Rectum, 2000. **43**(2): p. 146-153.
168. Baxter, N.N., D.A. Rothenberger, and A.C. Lowry, *Measuring fecal incontinence.* Diseases of the Colon & Rectum, 2003. **46**(12): p. 1591-1605.
169. Wexner, S. and J. Jorge, *Colorectal physiological tests: use or abuse of technology?* The European journal of surgery= Acta chirurgica, 1994. **160**(3): p. 167.
170. Attaluri, A. and S.S. Rao, *Fecal incontinence.* Textbook of Clinical Gastroenterology and Hepatology, 2012: p. 43.
171. Law, P.J. and C.I. Bartram, *Anal endosonography: technique and normal anatomy.* Gastrointest Radiol, 1989. **14**(4): p. 349-53.
172. Abdool, Z., A.H. Sultan, and R. Thakar, *Ultrasound imaging of the anal sphincter complex: a review.* British Journal of Radiology, 2012. **85**(1015): p. 865-875.
173. Savoye-Collet, C., E. Koning, and J.-N. Dacher, *Radiologic evaluation of pelvic floor disorders.* Gastroenterology Clinics of North America, 2008. **37**(3): p. 553-567.
174. Fletcher, J., et al., *Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders.* The American journal of gastroenterology, 2003. **98**(2): p. 399-411.

175. Law, P., M. Kamm, and C. Bartram, *Anal endosonography in the investigation of faecal incontinence.* British Journal of Surgery, 1991. **78**(3): p. 312-314.
176. Sultan, A.H., et al., *Anal endosonography for identifying external sphincter defects confirmed histologically.* Br J Surg, 1994. **81**(3): p. 463-5.
177. Gold, D.M., et al., *Intraobserver and interobserver agreement in anal endosonography.* Br J Surg, 1999. **86**(3): p. 371-5.
178. Konerding, M.A., et al., *Correlation of endoanal sonography with cross-sectional anatomy of the anal sphincter.* Gastrointest Endosc, 1999. **50**(6): p. 804-10.
179. Gold, D.M., et al., *Three-dimensional endoanal sonography in assessing anal canal injury.* Br J Surg, 1999. **86**(3): p. 365-70.
180. Williams, A.B., et al., *Anal sphincter damage after vaginal delivery using three-dimensional endosonography.* Obstet Gynecol, 2001. **97**(5 Pt 1): p. 770-5.
181. deSouza, N.M., et al., *High resolution magnetic resonance imaging of the anal sphincter using an internal coil.* Gut, 1995. **37**(2): p. 284-7.
182. Bartram, C., *Radiologic evaluation of anorectal disorders.* Gastroenterol Clin North Am, 2001. **30**(1): p. 55-75.
183. Briel, J., et al., *External anal sphincter atrophy on endoanal magnetic resonance imaging adversely affects continence after sphincteroplasty.* British Journal of Surgery, 1999. **86**(10): p. 1322-1327.
184. deSouza, N.M., et al., *MR imaging of the anal sphincter in multiparous women using an endoanal coil: correlation with in vitro anatomy and appearances in fecal incontinence.* AJR Am J Roentgenol., 1996. **167**(6): p. 1465-1471.
185. Malouf, A.J., et al., *Prospective assessment of accuracy of endoanal MR imaging and endosonography in patients with fecal incontinence.* AJR Am J Roentgenol, 2000. **175**(3): p. 741-5.
186. Rothholtz, N. and S. Wexner, *Surgical treatment of constipation and faecal incontinence.*, in *Disorders of Anorectum*, S. Rao, Editor. 2001, WB Saunders. p. 131-166.
187. Wald, A., *Colonic and anorectal motility testing in clinical practice.* The American journal of gastroenterology, 1994. **89**(12): p. 2109-2115.
188. Bartram, C.I., G.K. Turnbull, and J.E. Lennard-Jones, *Evacuation proctography: an investigation of rectal expulsion in 20 subjects without defecatory disturbance.* Gastrointestinal radiology, 1988. **13**(1): p. 72-80.
189. Shorvon, P., et al., *Defecography in normal volunteers: results and implications.* Gut, 1989. **30**(12): p. 1737-1749.
190. Rao, S.S., *Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation.* Clinical Gastroenterology and Hepatology, 2010. **8**(11): p. 910-919. e2.
191. Felt-Bersma, R.J., E.C. Klinkenberg-Knol, and S.G. Meuwissen, *Anorectal function investigations in incontinent and continent patients. Differences and discriminatory value.* Dis Colon Rectum, 1990. **33**(6): p. 479-85; discussion 485-6.
192. McHugh, S. and N. Diamant, *Effect of age, gender, and parity on anal canal pressures.* Digestive Diseases and Sciences, 1987. **32**(7): p. 726-736.

193. Rao, S.S., et al., *Manometric tests of anorectal function in healthy adults.* Am J Gastroenterol, 1999. **94**(3): p. 773-83.
194. Lowry, A.C., et al., *Consensus statement of definitions for anorectal physiology and rectal cancer: report of the Tripartite Consensus Conference on Definitions for Anorectal Physiology and Rectal Cancer, Washington, D.C., May 1, 1999.* Dis Colon Rectum, 2001. **44**(7): p. 915-9.
195. Marcello, P.W., et al., *Fatigue rate index as a new measurement of external sphincter function.* Dis Colon Rectum, 1998. **41**(3): p. 336-43.
196. Telford, K.J., et al., *Fatigability of the external anal sphincter in anal incontinence.* Dis Colon Rectum, 2004. **47**(5): p. 746-52; discussion 752.
197. Azpiroz, F., P. Enck, and W.E. Whitehead, *Anorectal functional testing: review of collective experience.* Am J Gastroenterol, 2002. **97**(2): p. 232-40.
198. Felt-Bersma, R.F., E. Klinkenberg-Knol, and S.G.M. Meuwissen, *Anorectal function investigations in incontinent and continent patients.* Diseases of the Colon & Rectum, 1990. **33**(6): p. 479-486.
199. Sun, W., N. Read, and M. Verlinden, *Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence.* Scandinavian Journal of Gastroenterology, 1997. **32**(1): p. 34-38.
200. Rao, S., K. Welcher, and J. Happel, *Can biofeedback therapy improve anorectal function in fecal incontinence?* The American journal of gastroenterology, 1996. **91**(11): p. 2360.
201. Felt-Bersma, R. and M. Cuesta, *Faecal incontinence 1994: which test and which treatment?* The Netherlands journal of medicine, 1994. **44**(5): p. 182.
202. McHugh, S.M. and N.E. Diamant, *Effect of age, gender, and parity on anal canal pressures. Contribution of impaired anal sphincter function to fecal incontinence.* Dig Dis Sci, 1987. **32**(7): p. 726-36.
203. Bordeianou, L., et al., *Anal resting pressures at manometry correlate with the Fecal Incontinence Severity Index and with presence of sphincter defects on ultrasound.* Dis Colon Rectum, 2008. **51**(7): p. 1010-4.
204. Hornung, B.R., et al., *Comparative study of anal acoustic reflectometry and anal manometry in the assessment of faecal incontinence.* British Journal of Surgery, 2012. **99**(12): p. 1718-1724.
205. Zutshi, M., et al., *Anal physiology testing in fecal incontinence: is it of any value?* International Journal of Colorectal Disease, 2010. **25**(2): p. 277-282.
206. McHugh, S.M. and N.E. Diamant, *Anal canal pressure profile: a reappraisal as determined by rapid pullthrough technique.* Gut, 1987. **28**(10): p. 1234-41.
207. Osterberg, A., W. Graf, and L. Pahlman, *The longitudinal high-pressure zone profile in patients with fecal incontinence.* Am J Gastroenterol, 1999. **94**(10): p. 2966-71.
208. Taylor, B.M., R.W. Beart, Jr., and S.F. Phillips, *Longitudinal and radial variations of pressure in the human anal sphincter.* Gastroenterology, 1984. **86**(4): p. 693-7.
209. Rao, S. and W. Sun, *Current techniques of assessing defecation dynamics.* Digestive Diseases, 2008. **15**(Suppl. 1): p. 64-77.

210. Sun, W., T. Donnelly, and N. Read, *Utility of a combined test of anorectal manometry, electromyography, and sensation in determining the mechanism of'idiopathic'faecal incontinence.* Gut, 1992. **33**(6): p. 807-813.
211. Prior, A., D. Maxton, and P. Whorwell, *Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects.* Gut, 1990. **31**(4): p. 458-462.
212. Rao, S., et al., *Anorectal sensitivity and responses to rectal distention in patients with ulcerative colitis.* Gastroenterology, 1987. **93**(6): p. 1270-1275.
213. Caruana, B., et al., *Anorectal sensory and motor function in neurogenic fecal incontinence. Comparison between multiple sclerosis and diabetes mellitus.* Gastroenterology, 1991. **100**(2): p. 465.
214. Sun, W.M., et al., *Disturbances in anorectal function in patients with diabetes mellitus and faecal incontinence.* European journal of gastroenterology & hepatology, 1996. **8**(10): p. 1007-1012.
215. Afd, K., A. Amtssygehus, and T. Hansensgade, *Colorectal function in patients with spinal cord lesions.* Dis Colon Rectum, 1997.
216. Clouse, R.E., et al., *Application of topographical methods to clinical esophageal manometry.* The American journal of gastroenterology, 2000. **95**(10): p. 2720-2730.
217. Ghosh, S.K., et al., *Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers.* American Journal of Physiology-Gastrointestinal and Liver Physiology, 2006. **290**(5): p. G988-G997.
218. Pandolfino, J.E., et al., *Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers.* American Journal of Physiology-Gastrointestinal and Liver Physiology, 2006. **290**(5): p. G1033-G1040.
219. Jones, M.P., J. Post, and M.D. Crowell, *High-resolution manometry in the evaluation of anorectal disorders: a simultaneous comparison with water-perfused manometry.* Am J Gastroenterol, 2007. **102**(4): p. 850-5.
220. Burke, J., et al., *PWE-005 High resolution anorectal manometry: first study establishing normal values in healthy volunteers.* Gut, 2012. **61**(Suppl 2): p. A298-A298.
221. Li, Y., et al., *Normal values and pressure morphology for three-dimensional high-resolution anorectal manometry of asymptomatic adults: a study in 110 subjects.* International journal of colorectal disease, 2013.
222. Noelting, J., et al., *Normal values for high-resolution anorectal manometry in healthy women: effects of age and significance of rectoanal gradient.* The American journal of gastroenterology, 2012.
223. Ratuapli, S.K., et al., *Phenotypic identification and classification of functional defecatory disorders using high resolution anorectal manometry.* Gastroenterology, 2012.
224. Pelsang, R.E., S.S. Rao, and K. Welcher, *FECOM: a new artificial stool for evaluating defecation.* The American journal of gastroenterology, 1999. **94**(1): p. 183-186.
225. Dedeli, O., et al., *Normative values of the balloon expulsion test in healthy adults.* Turk J Gastroenterol, 2007. **18**: p. 177-81.

226. Minguez, M., et al., *Predictive value of the balloon expulsion test for excluding the diagnosis of pelvic floor dyssynergia in constipation.* Gastroenterology, 2004. **126**(1): p. 57-62.
227. Schouten, W.R., et al., *Anismus: Fact or fiction?* Diseases of the Colon & Rectum, 1997. **40**(9): p. 1033-1041.
228. Cheong, D.M.O., et al., *Electrodiagnostic Evaluation of Fecal Incontinence.* Muscle Nerve, 1995. **18**: p. 612-619.
229. Law, P.J., M.A. Kamm, and C.I. Bartram, *A comparison between electromyography and anal endosonography in mapping external anal sphincter defects.* Dis Colon Rectum, 1990. **33**(5): p. 370-3.
230. Tjandra, J.J., et al., *Endoluminal ultrasound is preferable to electromyography in mapping anal sphincteric defects.* Dis Colon Rectum, 1993. **36**(7): p. 689-92.
231. Womack, N., J. Morrison, and N. Williams, *The role of pelvic floor denervation in the aetiology of idiopathic faecal incontinence.* British Journal of Surgery, 1986. **73**(5): p. 404-407.
232. Felt-Bersma, R.J., et al., *The external anal sphincter.* Diseases of the Colon & Rectum, 1989. **32**(2): p. 112-116.
233. Masin, L., *Striated anal sphincter electromyography in idiopathic fecal incontinence.* Diseases of the Colon & Rectum, 1995. **38**(1): p. 27-31.
234. Koch, K.L., M.M. Schuster, and M.D. Crowell, *Schuster Atlas of Gastrointestinal Motility: In Health and Disease*. 2002: PMPH-USA.
235. Podnar, S., et al., *Standardization of anal sphincter EMG: Technique of needle examination.* Muscle & Nerve, 1999. **22**(3): p. 400-403.
236. Podnar, S., M. Mrkaić, and D.B. Vodušek, *Standardization of anal sphincter electromyography: quantification of continuous activity during relaxation.* Neurourology and urodynamics, 2002. **21**(6): p. 540-545.
237. Bischoff, C., et al., *Reference values of motor unit action potentials obtained with multi-MUAP analysis.* Muscle & Nerve, 1994. **17**(8): p. 842-851.
238. Stålberg, E., et al., *Multi-MUP EMG analysis—a two year experience in daily clinical work.* Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control, 1995. **97**(3): p. 145-154.
239. Kiff, E.S. and M. Swash, *Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence.* Br J Surg, 1984. **71**(8): p. 614-6.
240. Snooks, S.J., et al., *Risk factors in childbirth causing damage to the pelvic floor innervation.* Int J Colorectal Dis, 1986. **1**(1): p. 20-4.
241. Donnelly, V., et al., *Obstetric events leading to anal sphincter damage.* Obstetrics & Gynecology, 1998. **92**(6): p. 955-961.
242. Olsen, A.L. and S.S. Rao, *Clinical neurophysiology and electrodiagnostic testing of the pelvic floor.* Gastroenterology Clinics of North America, 2001. **30**(1): p. 33-54.
243. Remes-Troche, J.M. and S.S. Rao, *Neurophysiological testing in anorectal disorders.* Gastroenterol Hepatol, 2008. **2**: p. 323-35.
244. Rao, S.S., et al., *S1826 Translumbar and Transsacral Magnetic Stimulation–a Novel Test of Assessing Anorectal Neuropathy in Fecal Incontinence.* Gastroenterology, 2008. **134**(4): p. A-278-A-278.

245. Tantiphlachiva, K., et al., *S1810 Evaluation of Spino-Anorectal Pathways in Spinal Cord Injury with Bowel Dysfunction Using Magnetic Stimulation: A Novel and Noninvasive Test.* Gastroenterology, 2008. **134**(4): p. A-274-A-274.
246. Sørensen, G., et al., *Distensibility of the anal canal in patients with idiopathic fecal incontinence: a study with the Functional Lumen Imaging Probe.* Neurogastroenterology & Motility, 2014. **26**(2): p. 255-263.
247. Remes-Troche, J.M. and S.S. Rao, *Defecation disorders: neuromuscular aspects and treatment.* Current gastroenterology reports, 2006. **8**(4): p. 291-299.
248. Claerbout, J.F., *Synthesis of a layered medium from its acoustic transmission response.* Geophysics, 1968. **33**(2): p. 264-269.
249. Ware, J.A. and K. Aki, *Continuous and Discrete Inverse-Scattering Problems in a Stratified Elastic Medium. I. Plane Waves at Normal Incidence.* The Journal of the Acoustical Society of America, 1969. **45**: p. 911.
250. Sondhi, M. and B. Gopinath, *Determination of Vocal-Tract Shape from Impulse Response at the Lips.* The Journal of the Acoustical Society of America, 1971. **49**: p. 1867.
251. Jackson, A.C., et al., *Airway geometry by analysis of acoustic pulse response measurements.* Journal of Applied Physiology, 1977. **43**(3): p. 523-536.
252. Fredberg, J.J., et al., *Airway area by acoustic reflections measured at the mouth.* Journal of Applied Physiology, 1980. **48**(5): p. 749-758.
253. Hilberg, O., et al., *Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection.* Journal of Applied Physiology, 1989. **66**(1): p. 295-303.
254. Klarskov, N., S.B. Rasmussen, and G. Lose, *Pressure reflectometry: in vitro recordings with a new technique for simultaneous measurement of cross-sectional area and pressure in a collapsible tube.* Physiological Measurement, 2005. **26**(3): p. 269.
255. Djupesland, P. and B. Lyholm, *Technical abilities and limitations of acoustic rhinometry optimised for infants.* Rhinology, 1998. **36**: p. 104-113.
256. VERSI, E., *Discriminant analysis of urethral pressure profilometry data for the diagnosis of genuine stress incontinence.* BJOG: An International Journal of Obstetrics & Gynaecology, 1990. **97**(3): p. 251-259.
257. Versi, E., et al., *Evaluation of urethral pressure profilometry for the diagnosis of genuine stress incontinence.* World Journal of Urology, 1986. **4**(1): p. 6-9.
258. Weber, A.M., *Is urethral pressure profilometry a useful diagnostic test for stress urinary incontinence?* Obstetrical & gynecological survey, 2001. **56**(11): p. 720-735.
259. Martan, A., et al., *Weak VLPP and MUCP correlation and their relationship with objective and subjective measures of severity of urinary incontinence.* International Urogynecology Journal, 2007. **18**(3): p. 267-271.
260. Nager, C., et al., *Correlation of urethral closure pressure, leak-point pressure and incontinence severity measures.* International Urogynecology Journal, 2001. **12**(6): p. 395-400.
261. Theofrastous, J.P., et al., *Correlation of urodynamic measures of urethral resistance with clinical measures of incontinence severity in women with pure genuine stress incontinence.* American journal of obstetrics and gynecology, 1995. **173**(2): p. 407-414.

262. Zinner, N.R., A.M. Sterling, and R.C. Ritter, *Role of inner urethral softness in urinary continence.* Urology, 1980. **16**(1): p. 115-117.
263. Abrams, P., et al., *Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence.* Neurourology and Urodynamics, 2010. **29**(1): p. 213-240.
264. Perucchini, D., et al., *Standardisation of urethral pressure measurement: report from the Standardisation Sub-Committee of the International Continence Society.* Neurourology and Urodynamics, 2002. **21**: p. 258-260.
265. Griffiths, D., *The pressure within a collapse tube, with special reference to urethral pressure.* Physics in medicine and biology, 1985. **30**(9): p. 951.
266. Klarskov, N. and G. Lose, *Urethral pressure reflectometry; a novel technique for simultaneous recording of pressure and cross-sectional area in the female urethra.* Neurourology and Urodynamics, 2007. **26**(2): p. 254-261.
267. Mitchell, P.J., et al., *Anal acoustic reflectometry: a new technique for assessing anal sphincter function.* Colorectal Disease, 2010. **12**(7): p. 692-697.
268. Proakis, J. and D. Manolakis, *Frequency analysis of signals and systems.* Chapter, 1996. **4**: p. 230-394.
269. Klarskov, N. and G. Lose, *Urethral pressure reflectometry vs urethral pressure profilometry in women: a comparative study of reproducibility and accuracy.* BJU International, 2007. **100**(2): p. 351-356.
270. Klarskov, N. and G. Lose, *Urethral pressure reflectometry and pressure profilometry in healthy volunteers and stress urinary incontinent women.* Neurourology and Urodynamics, 2008. **27**(8): p. 807-812.
271. Mitchell, P.J., et al., *Anal Acoustic Reflectometry: A New Reproducible Technique Providing Physiological Assessment of Anal Sphincter Function.* Diseases of the Colon & Rectum, 2011. **54**(9): p. 1122-1128 10.1097/DCR.0b013e318223fbcb.
272. Berne, R.M. and M.N. Levy, *Principles of physiology*. 1990: Mosby.
273. Mitchell, P.J., et al., *Viscoelastic Assessment of Anal Canal Function Using Acoustic Reflectometry: A Clinically Useful Technique.* Diseases of the Colon & Rectum, 2012. **55**(2): p. 211-217 10.1097/DCR.0b013e31823b2499.
274. Rasmussen, O.O., et al., *A technique for the dynamic assessment of anal sphincter function.* Int J Colorectal Dis, 1990. **5**(3): p. 135-41.
275. Gregersen, H., et al., *Measurement of anal cross-sectional area and pressure during anal distension in healthy volunteers.* Digestion, 1991. **48**(2): p. 61-9.
276. Harris, J., E.E. Therkelsen, and N.R. Zinner, *Electrical measurement of ureteral flow.* Urodynamics, S. Boyarsky et al.,(eds.), Academic Press, London, 1971.
277. Mitchell, P.J., *Investigation of the anal sphincter mechanism and faecal incontinence using acoustic reflectometry*, 2010, The University of Manchester.
278. Swash, M., et al., *Ultrastructural changes in internal anal sphincter in neurogenic faecal incontinence.* Gut, 1988. **29**(12): p. 1692-1698.
279. Horrocks, E., et al., *Systematic review of tibial nerve stimulation to treat faecal incontinence.* British Journal of Surgery, 2014. **101**(5): p. 457-468.

280. Hotouras, A., et al., *Outcome of sacral nerve stimulation for fecal incontinence in patients refractory to percutaneous tibial nerve stimulation.* Diseases of the Colon & Rectum, 2013. **56**(7): p. 915-920.
281. Thin, N., et al., *Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence.* British Journal of Surgery, 2013. **100**(11): p. 1430-1447.
282. Carrington, E., et al., *A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation.* Neurogastroenterology & Motility, 2014. **26**(9): p. 1222-1237.
283. Hornung, B.R., et al., *Anal acoustic reflectometry predicts the outcome of percutaneous nerve evaluation for faecal incontinence.* British Journal of Surgery, 2014. **101**(10): p. 1310-1316.
284. Jarrett, M.E., et al., *Systematic review of sacral nerve stimulation for faecal incontinence and constipation.* Br J Surg, 2004. **91**(12): p. 1559-69.
285. George, A.T., et al., *Long-term outcomes of sacral nerve stimulation for fecal incontinence.* Diseases of the Colon & Rectum, 2012. **55**(3): p. 302-306.
286. Mowatt, G., C. Glazener, and M. Jarrett, *Sacral nerve stimulation for faecal incontinence and constipation in adults.* Cochrane Database Syst Rev, 2007. **3**.
287. Wong, M.T., et al., *Outcome and management of patients in whom sacral nerve stimulation for fecal incontinence failed.* Diseases of the Colon & Rectum, 2011. **54**(4): p. 425-432.
288. Hornung, B.R., *Anal acoustic reflectometry in the evaluation of the anal sphincter and the response to treatment of faecal incontinence.* MD Thesis, University of Manchester, 2012.
289. Sentovich, S.M., et al., *Patterns of male fecal incontinence.* Dis Colon Rectum, 1995. **38**(3): p. 281-5.
290. Titi, M., et al., *Prospective study of the diagnostic evaluation of faecal incontinence and leakage in male patients.* Colorectal Dis, 2007. **9**(7): p. 647-52.
291. Qureshi, M.S., et al., *Male faecal incontinence presents as two separate entities with implications for management.* International journal of colorectal disease, 2011. **26**(12): p. 1589-1594.
292. Parellada, C.M., et al., *Paradoxical high anal resting pressures in men with idiopathic fecal seepage.* Dis Colon Rectum, 1998. **41**(5): p. 593-7.
293. Dibenedetto, M. and S. Yalla, *Electrodiagnosis of striated urethral sphincter dysfunction.* The Journal of urology, 1979. **122**(3): p. 361.
294. Naja, Z., M. Ziade, and P.-A. Lönnqvist, *Nerve stimulator guided pudendal nerve block decreases posthemorrhoidectomy pain.* Canadian Journal of Anesthesia, 2005. **52**(1): p. 62-68.
295. Govaert, B., et al., *A prospective multicentre study to investigate percutaneous tibial nerve stimulation for the treatment of faecal incontinence.* Colorectal Disease, 2010. **12**(12): p. 1236-1241.
296. Boyle, D.J., et al., *Percutaneous tibial nerve stimulation for the treatment of urge fecal incontinence.* Diseases of the Colon & Rectum, 2010. **53**(4): p. 432-437.

297. Peters, K.M., et al., *Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial.* The Journal of urology, 2010. **183**(4): p. 1438-1443.
298. Proakis, J.G. and D.G. Manolakis, *Digital Signal Processsing*, 1996, Prentice Hall.
299. Bordeianou, L., et al., *Anal Resting Pressures at Manometry Correlate with the Fecal Incontinence Severity Index and with Presence of Sphincter Defects on Ultrasound.* Diseases of the Colon & Rectum, 2008. **51**(7): p. 1010-1014.
300. Rao, S., et al., *Minimum standards of anorectal manometry.* Neurogastroenterology & Motility, 2002. **14**(5): p. 553-559.
301. Kepenekci, I., et al., *Prevalence of Pelvic Floor Disorders in the Female Population and the Impact of Age, Mode of Delivery, and Parity.* Diseases of the Colon & Rectum, 2011. **54**(1): p. 85-94 10.1007/DCR.0b013e3181fd2356.
302. Statistics, O.f.N., *Childbearing for Women Born in Different Years, England and Wales, 2013.* Statistical Bulletin, Office for National Statistics, 2014.
303. Kettle, C., et al., *Continuous versus interrupted perineal repair with standard or rapidly absorbed sutures after spontaneous vaginal birth: a randomised controlled trial.* The Lancet, 2002. **359**(9325): p. 2217-2223.
304. Vitton, V., et al., *Water-perfused manometry vs three-dimensional high-resolution manometry: a comparative study on a large patient population with anorectal disorders.* Colorectal Disease, 2013. **15**(12): p. e726-e731.
305. Soubra, M., et al., *A Comparison of Standard Anorectal Manometry and High Resolution Manometry Patterns in Dyssynergic Patients.* Journal of Gastroenterology and Hepatology Research, 2014. **3**(9).
306. Gordon, A.R. and M.J. Siegman, *Mechanical properties of smooth muscle. I. Length-tension and force-velocity relations.* Am J Physiol, 1971. **221**(5): p. 1243-1249.
307. Garry, R., *The nervous control of the caudal region of the large bowel in the cat.* The Journal of physiology, 1933. **77**(4): p. 422-431.
308. Garry, R., *The responses to stimulation of the caudal end of the large bowel in the cat.* The Journal of physiology, 1933. **78**(2): p. 208-224.
309. Bishop, B., et al., *Control of the external sphincter of the anus in the cat.* The Journal of physiology, 1956. **134**(1): p. 229-240.
310. Gowers, W.R., *The automatic action of the sphincter ani.* Proceedings of the Royal Society of Medicine London, 1877. **26**: p. 77-84.
311. Somlyo, A., et al., *Ultrastructure, function and composition of smooth muscle.* Annals of biomedical engineering, 1983. **11**(6): p. 579-588.
312. Sanders, K.M., S.M. Ward, and S.D. Koh, *Interstitial cells: regulators of smooth muscle function.* Physiological reviews, 2014. **94**(3): p. 859-907.
313. Sanders, K.M., et al., *Regulation of gastrointestinal motility—insights from smooth muscle biology.* Nature Reviews Gastroenterology and Hepatology, 2012. **9**(11): p. 633-645.
314. Lestar, B., F. Penninckx, and R. Kerremans, *The composition of anal basal pressure. An in vivo and in vitro study in man.* Int J Colorectal Dis, 1989. **4**(2): p. 118-22.

315. Opazo, A., et al., *Patterns of impaired internal anal sphincter activity in patients with anal fissure.* Colorectal Disease, 2013. **15**(4): p. 492-499.
316. Sørensen, S.M., et al., *Spontaneous anorectal pressure activity: evidence of internal anal sphincter contractions in response to rectal pressure waves.* Scandinavian Journal of Gastroenterology, 1989. **24**(1): p. 115-120.
317. Hill, A., *The viscous elastic properties of smooth muscle.* Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 1926: p. 108-115.
318. Meunier, P. and P. Mollard, *Control of the internal anal sphincter (manometric study with human subjects).* Pflügers Archiv, 1977. **370**(3): p. 233-239.
319. Bharucha, A.E., et al., *Prevalence and Burden of Fecal Incontinence: A Population-Based Study in Women.* Gastroenterology, 2005. **129**(1): p. 42-49.
320. Schweiger, M., *Method for determining individual contributions of voluntary and involuntary anal sphincters to resting tone.* Diseases of the Colon & Rectum, 1979. **22**(6): p. 415-416.
321. Duthie, H.L. and J.M. Watts, *Contribution of the External Anal Sphincter to the Pressure Zone in the Anal Canal.* Gut, 1965. **6**: p. 64-8.
322. Lacima, G., et al., *Is electromyography a predictive test of patient response to biofeedback in the treatment of fecal incontinence?* Neurourology and urodynamics, 2015.
323. Al-Shekhlee, A., B.E. Shapiro, and D.C. Preston, *Iatrogenic complications and risks of nerve conduction studies and needle electromyography.* Muscle & Nerve, 2003. **27**(5): p. 517-526.
324. Lippold, O., *The relation between integrated action potentials in a human muscle and its isometric tension.* The Journal of physiology, 1952. **117**(4): p. 492-499.
325. Scudamore, J.H. and M.J. Yates, *PUDENDAL BLOCK—A MISNOMER?* The Lancet, 1966. **287**(7427): p. 23-24.
326. Wunderlich, M. and M. Swash, *The overlapping innervation of the two sides of the external anal sphincter by the pudendal nerves.* Journal of the neurological sciences, 1983. **59**(1): p. 97-109.
327. Cohen, R. and A. Windsor, *Anus: Surgical Treatment and Pathology*. 2013: Springer Science & Business Media.
328. Lundby, L., et al., *Relief of fecal incontinence by sacral nerve stimulation linked to focal brain activation.* Diseases of the Colon & Rectum, 2011. **54**(3): p. 318-323.
329. Sheldon, R., et al., *Sacral nerve stimulation reduces corticoanal excitability in patients with faecal incontinence.* British Journal of Surgery, 2005. **92**(11): p. 1423-1431.
330. McGuire, E., et al., *Treatment of motor and sensory detrusor instability by electrical stimulation.* The Journal of urology, 1983. **129**(1): p. 78-79.
331. Stoller, M., *Afferent nerve stimulation for pelvic floor dysfunction.* INTERNATIONAL UROGYNECOLOGY JOURNAL, 1999. **10**: p. P99-P99.

332. Shafik, A., et al., *Percutaneous peripheral neuromodulation in the treatment of fecal incontinence.* European surgical research. Europaische chirurgische Forschung. Recherches chirurgicales europeennes, 2002. **35**(2): p. 103-107.
333. George, A.T., et al., *Randomized controlled trial of percutaneous versus transcutaneous posterior tibial nerve stimulation in faecal incontinence.* British Journal of Surgery, 2013. **100**(3): p. 330-338.
334. de la Portilla, F., et al., *Evaluation of the use of posterior tibial nerve stimulation for the treatment of fecal incontinence: preliminary results of a prospective study.* Diseases of the Colon & Rectum, 2009. **52**(8): p. 1427-1433.
335. Findlay, J.M., et al., *Peripheral neuromodulation via posterior tibial nerve stimulation-a potential treatment for faecal incontinence?* Annals of the Royal College of Surgeons of England, 2010. **92**(5): p. 385.
336. López-Delgado, A., et al., *Effect on anal pressure of percutaneous posterior tibial nerve stimulation for faecal incontinence.* Colorectal Disease, 2014. **16**(7): p. 533-537.
337. Thin, N., et al., *Randomized clinical trial of sacral versus percutaneous tibial nerve stimulation in patients with faecal incontinence.* British Journal of Surgery, 2015. **102**(4): p. 349-358.
338. Grossi, U., et al., *Home-Based Percutaneous Tibial Nerve Stimulation for Fecal Incontinence: Is It Feasible?* Annals of surgery, 2015. **261**(1): p. e1.
339. Hotouras, A., et al., *Prospective clinical audit of two neuromodulatory treatments for fecal incontinence: sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS).* Surgery today, 2014. **44**(11): p. 2124-2130.
340. Van Balken, M., H. Vergunst, and B. Bemelmans, *Prognostic factors for successful percutaneous tibial nerve stimulation.* European urology, 2006. **49**(2): p. 360-365.
341. Gallas, S., et al., *Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: results of trial stimulation in 200 patients.* Colorectal Disease, 2011. **13**(6): p. 689-696.
342. Dudding, T., et al., *Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: a 10-year cohort analysis.* Colorectal Disease, 2008. **10**(3): p. 249-256.
343. Maeda, Y., et al., *Predictors of the outcome of percutaneous nerve evaluation for faecal incontinence.* British Journal of Surgery, 2010. **97**(7): p. 1096-1102.
344. Vallet, C., et al., *Sacral nerve stimulation for faecal incontinence: response rate, satisfaction and the value of preoperative investigation in patient selection.* Colorectal Dis, 2010. **12**(3): p. 247-53.
345. Maeda, Y., et al., *Sacral nerve stimulation for faecal incontinence and constipation: a European consensus statement.* Colorectal Disease, 2015.
346. Gourcerol, G., et al., *Sacral nerve stimulation in fecal incontinence: are there factors associated with success?* Diseases of the Colon & Rectum, 2007. **50**(1): p. 3-12.

347. Roman, S., et al., *Sacral nerve stimulation and rectal function: results of a prospective study in faecal incontinence.* Neurogastroenterology & Motility, 2008. **20**(10): p. 1127-1131.
348. Hotouras, A., et al., *Short-term outcome following percutaneous tibial nerve stimulation for faecal incontinence: a single-centre prospective study.* Colorectal Disease, 2012. **14**(9): p. 1101-1105.
349. Hotouras, A., et al., *Percutaneous tibial nerve stimulation (PTNS) in females with faecal incontinence: the impact of sphincter morphology and rectal sensation on the clinical outcome.* International journal of colorectal disease, 2012. **27**(7): p. 927-930.
350. Vaizey, C., *Faecal incontinence: standardizing outcome measures.* Colorectal Disease, 2014. **16**(3): p. 156-158.
351. Straka, R.J., et al., *Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 1997. **17**(1): p. 126-132.
352. Norton, C. and J.D. Cody, *Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults.* The Cochrane Library, 2012.
353. Wexner, S.D., *Commentary on "Home-Based Percutaneous Tibial Nerve Stimulation for Fecal Incontinence: Is It Feasible?".* Annals of surgery, 2015. **261**(1): p. e2.
354. George, A.T., R.K. Maitra, and C. Maxwell-Armstrong, *Posterior tibial nerve stimulation for fecal incontinence: Where are we?* World journal of gastroenterology: WJG, 2013. **19**(48): p. 9139.