The Development of a Patient Reported Outcome Measure and Imaging Modalities in the Evaluation of Haemorrhoidal Disease.

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Abstract

With the advent of DGHAL and PPH, treatments that purport to work by disrupting the arterial supply of haemorrhoids, there has been resurgence in interest in the vascular theory of pathogenesis of haemorrhoids. Despite uncertainty surrounding recurrence and complication rates there has been significant uptake of the new surgical approach due to decreased post-operative pain. However this has not been matched by discussion or evaluation of how haemorrhoidal disease and successful outcome should be evaluated.

This thesis evaluates different approaches to the measurement of the burden of haemorrhoidal disease to the patient. A patient reported outcome measure was designed, administered and evaluated by the investigator. Reliability, reproducibility, validity, responsiveness and acceptability have been demonstrated.

Three-dimensional ultrasound was used to acquire volumetric data and power Doppler angiography from the anal canal, which was shown to be reliable. Measures of power Doppler angiography were shown to be significantly lower in healthy volunteers than in patients. This technique represents promising value as an outcome measure of haemorrhoidal disease.

A dual isotope-surgical nuclear probe technique attempted to measure change in volume of haemorrhoids following rubber band ligation, however consistent results were not obtained. Magnetic resonance imaging was able to demonstrate anal cushions and haemorrhoids, and the feasibility of this method has been demonstrated.

Table of Contents

Declaration

Except where acknowledgement is made by reference, the studies undertaken in this thesis were devised and conducted unaided by the author.

No part of this work has been previously accepted for, or is currently being submitted in candidature for, another degree.

C.S. Parsons

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Lastly but by no means least, thank you so much to Peter, Lily, Frankie and the rest of my family for your incredible support, patience and understanding.

Table of Figures

TABLE OF TABLES

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AES	Anal endosonography
CdTe	Cadmium telluride
DCE	Dynamic contrast enhanced
DGHAL	Doppler-guided haemorrhoidal artery ligation
EAS	External anal sphincter
EDV	End diastolic velocity
fD	Doppler shift frequency
FI	Flow Index
FDA	Food and Drug Administration
FID	Free induction decay
FOV	Field of view
FWHM	Full width at half maximum
G-M	Geiger Muller
HRQL	Health related quality of life
HAS	Human serum albumin
HSI-1	Haemorrhoid Symptom Index-1
IAS	Internal anal sphincter
I_{vc}	Index of volume change
MRI	Magnetic Resonance Imaging
PD	Power Doppler
PDA	Power Doppler angiography
PI	Pulsatility index
PMT	Photomultiplier tube
PSV	Peak systolic velocity
PPH	Procedure for prolapsing haemorrhoids
PRF	Pulse repetition frequency
PRO	Patient reported outcome
PROM	Patient reported outcome measure

PSF	Point spread function
QoL	Quality of life
RBC	Red blood cell
RBL	Rubber band ligation
RF	Radiofrequency
RI	Resistance index
ROI	Region of interest
RTT	Round trip time
SAR	Specific absorption ratio
SC	Sulphur colloid
$t^{1/2}$	Half-life
T	Tesla
TE	Time to echo
TIC	Time intensity curve
TPUS	Transperineal ultrasound
TR	Repetition time
UHN	University Hospital Nottingham
US	Ultrasound
VAS	Visual analogue score
VCI	Volume contrast imaging
V_m	Mean velocity
VFI	Vascularisation Flow Index
VI	Vascularisation Index
VOCAL™	**V**irtual **O**rgan **C**omputer-aided **A**na**L**ysis

1 BACKGROUND & HYPOTHESES

1.1 INTRODUCTION

The word "haemorrhoid" is derived from the Greek: *haima* – blood and *rhoos* – flowing. The word "pile" is derived from the Latin *pila*, meaning a pill or ball. Humans have complained of haemorrhoids since at least biblical times [1], the anatomy of which has only recently been fully described [2]. The evidence for the aetiology and pathogenesis is surprisingly sparse, especially in light of increased interest in the surgical treatment of haemorrhoids. The basis for current treatments of haemorrhoids remains unclear.

The anatomy and pathophysiology of both anal cushions and haemorrhoids will be discussed. Aetiological factors and postulated theories of pathogenesis are examined, with particular reference made to the newest form of treatment, stapled anopexy or procedure for prolapsing haemorrhoids (PPH) and Doppler guided haemorrhoidal artery ligation (DGHAL).

1.2 ANATOMY OF THE ANAL CUSHIONS

The anal canal has a triradiate lumen lined by an irregular layer of fibrovascular tissue. This layer is usually grouped into three anal cushions, which are normal structures, formed early on in embryonic life [3]. They usually occur in the left lateral, right anterior and right posterior positions, and are further subdivided by the columns of Morgagni. The cushions and the columns of Morgagni give the tissue above the dentate line a pleated appearance as the rectum narrows into the anal canal. The exact arrangement of anal cushions often does not follow the textbook arrangement at 3, 7 and 11 o'clock; Thomson reported 19 per cent of normal subjects with this configuration [2].

Anal cushions have three main components: mucosa; stroma containing blood vessels, smooth muscle and supporting connective tissue; and the anchoring smooth muscle fibre network. Beneath the mucosal layer

of the anal canal, there is a dense network of blood vessels. Miles' [4] description of a constant branching pattern of the superior rectal artery, two right and one left, which correspond to the spatial distribution of the anal cushions is discordant with many other descriptions [5, 6]. Following the publication of Thomson's seminal anatomical work, this description of anal arterial supply has been dismissed as erroneous [7].

The blood supply of the anal canal is derived from branches of the superior, middle and inferior rectal arteries. There is a significant variation between individuals in the contribution and branching pattern of each artery. In a study of fifty adult cadavers [2] Thomson demonstrated an average of five (0 – 8) branches of the superior rectal artery reaching the haemorrhoidal zone. There were substantial contributions from the middle rectal artery and inferior rectal artery in 76 and 42 per cent of cases respectively. It is interesting to note that branches of the middle rectal artery pierce the rectal wall anteriorly, whereas branches of the superior rectal artery do so posteriorly and laterally [8].

The anal submucosal venous plexus is characterised by discrete sacculations on the course of veins confined to the lower half of the anal canal, in greater quantity above than below the dentate line. Sections of vein of normal calibre interconnect these sacculations. They are normal structures, found in infants, adolescents and adults [2], although their presence was clearly felt to be the cause of haemorrhoids for nearly a century [8, 9].

Free communications both inferior and through the internal anal sphincter (IAS) have been demonstrated between the superior, middle and inferior rectal veins. Direct arteriovenous communications have been demonstrated histologically [10], radiologically [11] and with latex-injected preparations [2]. The anal canal venous system is more profuse than required for normal tissue nutrition and oxygenation [7], and the blood oxygen tension is arterial [12]. As suggested by several 19th century authors and Stelzner et al [10], anal submucosa may have an erectile property, akin to cavernous tissue, calling it corpus cavernosum recti. The arteriovenous communications may function to allow changes in the size of the cushions depending on whether the anal canal is closed or open. This stimulated the

theory that haemorrhoids may result from hyperplasia of the corpus cavernosum recti.

A network of smooth muscle fibres arises partly from the internal anal sphincter and partly, by passing through the fasciculi of the IAS, from the conjoined longitudinal muscle. The whole component has been called Treitz's muscle, the muscularis submucosae ani, sustentator tunicae mucosae, corrugator cutis ani or the mucosal suspensory ligament. It is distributed around the haemorrhoidal venous plexus, into the perianal skin and back into the longitudinal muscle by passing around the lower border of the internal sphincter. Oblique bundles of IAS smooth muscle run alongside connective tissue and elastic fibres (fig 1-1).

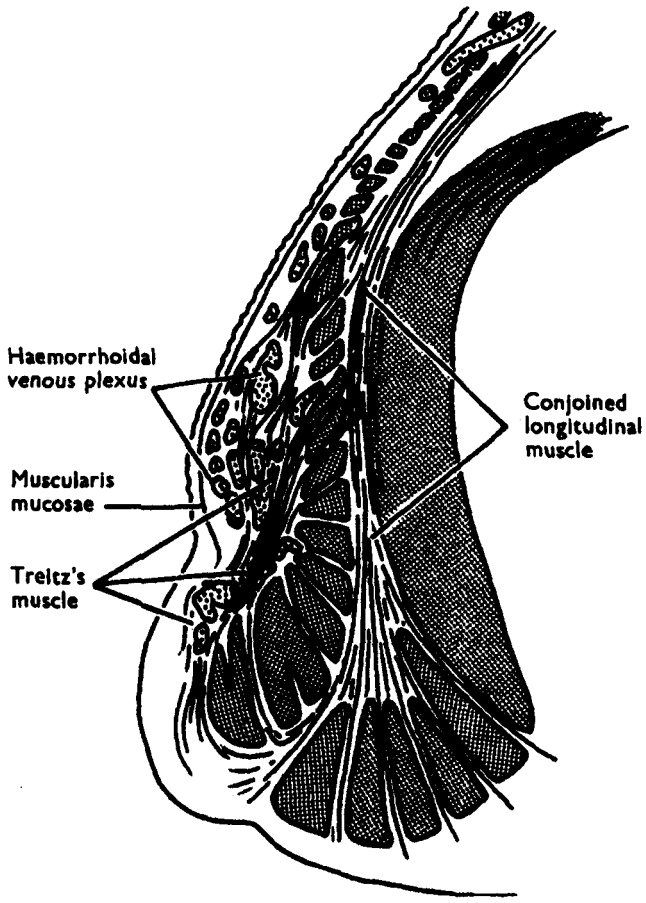

Figure 1-1 Composite diagram of Treitz's muscle.

The cushions drain via veins that pass through the circular muscle layer continuous with the IAS and the conjoined longitudinal muscle. Reproduced from WHF Thomson's The Nature of Haemorrhoids [2], John Wiley and Sons.

Histological studies have shown that with increasing age, the supportive tissue contains an increased proportion of collagen fibres that are fragmented and disorganised. These changes are seen from the third decade of life, and seem to be a part of normal ageing [13]. One of Thomson's most important conclusions was that anal cushions are normal structures, and that haemorrhoids are symptomatic anal cushions that have undergone the degenerative process of ageing.

1.3 FUNCTION OF ANAL CUSHIONS

It has been demonstrated that the IAS cannot fully close the anal canal; the addition of both mucosal folds and venous filling is required. Calculation of tension within the IAS during distension confirms that complete closure of the anal canal is not possible by the IAS alone [14-16]. Based on pressure measurements in patients who underwent abdominoperineal resection, both pre-operatively and in the excised anal canal, vascular filling may contribute fifteen to twenty per cent of resting anal pressure [17]. Anal cushions are likely to act as a compliant plug to the anal canal; haemorrhoidectomy is known to reduce continence to infused saline [18].

The way in which the anal cushions empty prior to defaecation is not known. Active mechanisms include anal dilatation by formed stool, reducing the height of the cushions, and action of the muscularis submucosae displacing the anal cushions. Fibres of the proximal anal canal elevate the cushions, and the arching arrangement of the fibres is likely to cause venous compression [7]. Distally there may be eversion of the IAS causing compression of the vascular spaces. Thus there is an outward rotation of the vascular tissue, as the IAS relaxes during defaecation (see figs 1-2 and 1-3).

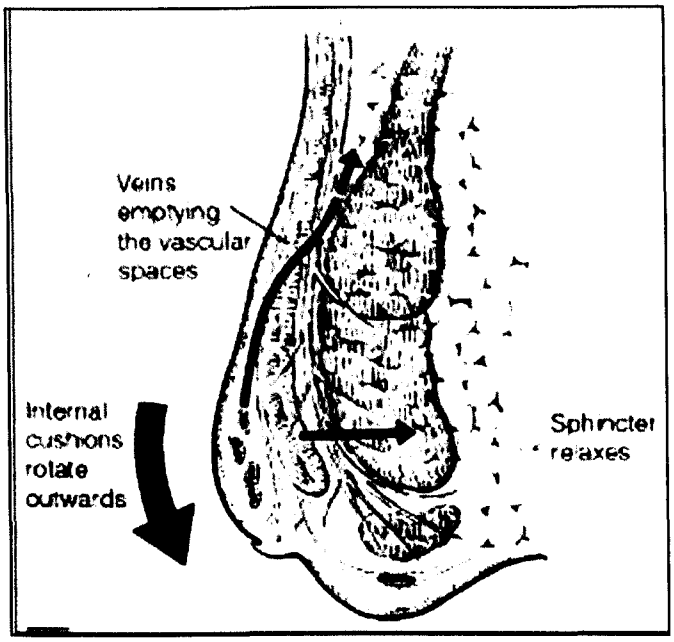

Figure 1-2 The effect of IAS relaxation.

There is an outward rotation of the vascular tissue and the pecten band. Reproduced from Keighley, M.R.B., *Surgery of the anus, rectum & colon.* 3rd ed 2008, Philadelphia: Saunders Elsevier.

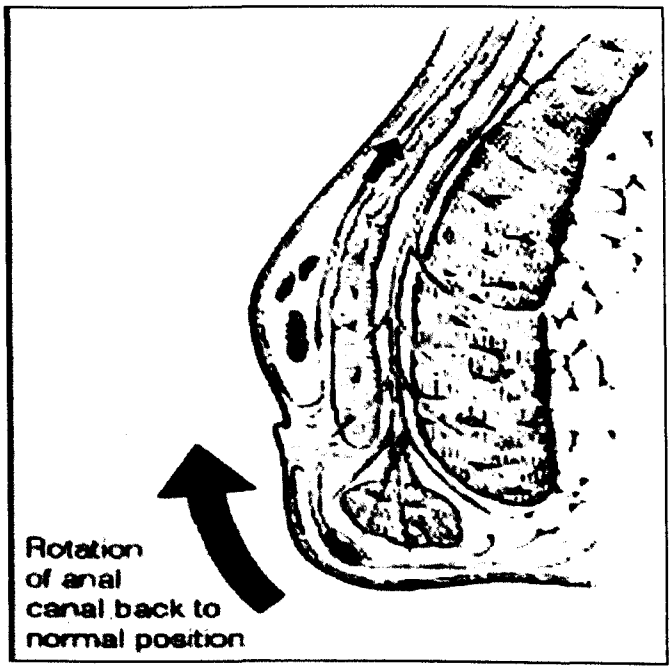

Figure 1-3 The effect of normal defaecation on the anal cushions.

Reproduced from Keighley, M.R.B., *Surgery of the anus, rectum & colon.* 3rd ed 2008, Philadelphia: Saunders Elsevier.

1.4 ANATOMY OF HAEMORRHOIDS

Anatomical assessment of haemorrhoids compared with normal anal cushions is difficult as by definition they only differ in size and symptoms. Haemorrhoidectomy specimens will not represent the full spectrum of haemorrhoidal disease, as surgery is reserved for patients with persistent and marked symptoms associated with significant size and prolapse.

Histological studies of haemorrhoidectomy specimens show squamous metaplasia of the mucosa, probably secondary to prolapse of the haemorrhoids. Chronic inflammatory changes of the stroma and blood vessels associated with mucosal ulceration, ischaemia and thrombosis may also be seen [12, 13]. Disordered, fragmented subepithelial smooth muscle has also been demonstrated in anal cushions during autopsy examination of older patients [13, 19].

Fibrosis of the IAS has been observed more frequently in patients with haemorrhoidal symptoms, than in autopsy specimens of patients without known haemorrhoidal disease. The amount of fibrosis was unrelated to manometry, haemorrhoid size or duration of symptoms [20]. The increased fibrosis in the IAS was felt to be unrelated to ageing because the mean age of the controls was greater than that of the haemorrhoid group. It was postulated that the fibrosis occurs as a result of longstanding venous congestion or repeated traction on the muscularis submucosae.

1.5 PHYSIOLOGICAL STUDIES OF THE ANAL CANAL

Despite differing methods, most studies comparing age and sex-matched controls to patients with symptomatic haemorrhoids have shown a high maximum resting anal pressure in patients with haemorrhoids [21-27]. Prolapsing haemorrhoids are associated with lower resting pressures than non-prolapsing haemorrhoids [28-30].

Hancock [28] concluded that the abnormally high anal pressures are caused by increased tonic activity of both the internal and external sphincters. Such activity may impair venous drainage leading to vascular distension of the anal cushions. This increased tonic activity is abolished by

anal dilatation with associated relief of symptoms, and therefore Hancock postulated that a sphincter abnormality is related to the development of symptoms in patients with haemorrhoids.

Direct pressure measurements in anal cushions of patients with haemorrhoids were significantly higher than in age-matched controls [31, 32]. Endoanal ultrasonographic imaging of the anal canal showed no significant difference in the thickness of the internal sphincter between patients with haemorrhoids and age-matched controls. Sun et al., [31] therefore suggested that the high anal pressure in patients with haemorrhoids is due to hypertensive anal cushions rather than a hypertonic internal anal sphincter.

However there is no test available to directly measure the pressure of the internal sphincter, and therefore it is possible that increased activity of the internal anal sphincter contributes to the pathogenesis of haemorrhoids.

Arabi et al., [22] proposed that there were two quite different groups of haemorrhoidal patients, based on anal pressure measurements. Only young male patients with non-prolapsing haemorrhoids had significantly higher anal pressures than age and sex-matched controls. The other group of patients were mostly multiparous females with prolapsing haemorrhoids and a lax anal canal.

In the anal physiology chapter of the excellent book, The Haemorrhoid Syndrome [8], there is a tantalisingly brief mention of an unpublished study where local blood flow was assessed using ^{133}Xenon. It was injected submucosally over the anal cushions and attempts were made to follow the clearance of the radionuclide. It was not clear where or how measurements were made, but Hancock states that no difference was found between a small group of controls and patients with haemorrhoids. Adrenaline was applied topically to the anal cushions, which reduced clearance time of the radionuclide, implying arteriolar vasoconstriction. Unfortunately reproducibility of the technique was poor and no further details of the study are available.

One other group examined the effect of vasoconstrictors on the local blood flow of the anal canal. Thulesius and Gjöres [12] attempted to change the anal flow by using topical and subcutaneous administration of adrenaline

and a vasoactive polypeptide, ornithine-vasopressin. Blood flow was examined using a thermal conductivity probe [33]. There was a drop (per cent of resting level) in the anal canal blood flow following administration of topical and submucosal adrenaline and topical ornithine-vasopressin, in comparison to a minor increase following submucosal sodium chloride, although there was no analysis of the statistical significance.

1.6 PATHOGENESIS OF HAEMORRHOIDS

1.6.1 Venous Obstruction

Based on the available anatomical and physiological studies, it has been postulated that venous congestion of the anal cushions is the underlying pathological process for haemorrhoidal symptoms. The cushions congest due to failure of emptying during defaecation, the cushions are abnormally mobile, and the cushions may be trapped by a tight IAS. Free venous drainage has been demonstrated through and around the anorectal muscle layers [2]; it has been suggested that impacted faeces in the rectum will compress the veins and impede venous emptying. The act of straining increases intra-abdominal pressure, compressing the submucosal venous plexus, which in turn prevents rapid empting of the cushions.

Other causes of raised intra-abdominal pressure including pregnancy, ascites, and pelvic tumour as well as raised portal venous pressure have been postulated as causative factors [34, 35].

Pregnancy seems to predispose to haemorrhoids [7] and may cause haemorrhoids in three ways. The increased levels of progesterone may relax the submucosal smooth muscle and soften the elastic fibres, which supports the anal cushions. The increased pelvic vascularity may affect the anal cushions, rendering them even more vascular. Women are more likely to suffer from constipation during pregnancy, possibly relating to recommended iron supplementation.

In the past when haemorrhoids were considered to be varicosities of the haemorrhoidal veins, one of the most quoted causes was increased venous pressure due to portal hypertension. There are no valves in the

portal venous system, which in conjunction with the erect position of the human adult should lead one to expect a higher frequency of enlarged, congested haemorrhoids in patients with portal hypertension.

In 1958, Hunt [36] reported that all patients with portal hypertension underwent sigmoidoscopy without the discovery of any haemorrhoidal disease. Jacobs et al. studied the clinical records of 188 patients with portal hypertension at their institution. They found an incidence of 27.6% of symptomatic internal haemorrhoids, as documented by history and examination. The authors and their contemporaries [37] did not consider this to represent a significant difference from the normal population.

A prospective study of 100 patients [38] with cirrhosis showed that the prevalence of anorectal varices increased with the presence of portal hypertension. Haemorrhoids occurred independently of anorectal varices and their presence was unrelated to the degree of portal hypertension.

A prospective study [39] of 60 children with portal hypertension showed a significant incidence of haemorrhoids (33%), anorectal varices (35%) and external anal varices (15%). Children with extrahepatic disease had a higher incidence of both haemorrhoids and anorectal varices. Interestingly only four children (7%) complained of anorectal symptoms, and all were easily managed with conservative therapies.

1.6.2 Prolapse of Anal Cushions

Based on the observation of fragmentation of connective tissue from 200 haemorrhoidectomy specimens, Gass and Adams [40] proposed that haemorrhoids were associated with a lax anus. Thomson [2] suggested that the degeneration of the anchoring smooth muscle leads to distal displacement of the anal cushions, making them more vulnerable to the shearing forces of the passage of hard stools. Straining causes an increase in venous pressure, leading to impaired venous return and stasis of blood within the haemorrhoidal zone. It has been demonstrated that stasis activates white cells to release inflammatory mediators. Inflammation leads to increased permeability, fragility and necrosis of the vessel wall and consequent bleeding. Further impediment of externally prolapsed

haemorrhoids by the anal sphincter leads to thrombosis. This theory proposed in 1975 is now widely accepted.

1.6.3 Alternative Theories of Pathogenesis

1.6.3.1 The Varicose Vein Theory

This theory was based on the observation of the discrete sacculations of the anal submucosal plexus, which was thought to be pathological prior to anatomical studies of infants [41]. The development of these sacculations was explained by increased local venous pressure or by a localised weakness in the vein wall [42]. It appeared to explain the increased frequency of symptoms during pregnancy, as well as constipation and straining as aetiological factors. The absence of valves in the portosystemic anastomoses of the anal canal also seemed to give validity to the venous pressure theory.

1.6.3.2 The Vascular Hyperplasia Theory

The anal submucosal tissue is likened to cavernous tissue and called corpus cavernosum recti, indicating that the tissue might have erectile properties. It has been suggested that haemorrhoids occurred as a result of hyperplasia of the corpus cavernosum recti [43]. This appeared to explain its function as part of the anal continence mechanism.

1.7 AETIOLOGY OF HAEMORRHOIDS

The true prevalence of haemorrhoids is not known; hospital-based studies are not representative, community-based studies rely on self-reporting and inaccuracies arise because patients and some doctors attribute any anorectal symptom to haemorrhoids. This has led to reported prevalence rates of 4.4% amongst adults in the United States [44], 36.4% of patients based at a London general practice [45], and 86% of new patients attending a colorectal surgical clinic [46]. These estimates may or may not be accurate; factors such as self-reporting, and any anorectal symptom being attributed to haemorrhoids by patients or medical practitioners [47] will lead to inaccuracy.

There is a general increase in prevalence with age until the seventh decade, which is equal between the sexes. Men account for approximately 60 % of hospitalised patients with haemorrhoids [22, 48, 49]. In many cases, women present during pregnancy and after childbirth [7]. In the general population the prevalence of haemorrhoids is equal between the genders [44, 45, 48], but women have been found to be more symptomatic on proctoscopic examination [46], and are more likely to have been symptomatic of longer duration [45]. High oestrogen receptor levels have been identified in haemorrhoids [50], which may explain haemorrhoidal symptoms during pregnancy.

It has been stated that haemorrhoids are uncommon in rural Africa in contrast to urban Africa and developed countries. The low prevalence was accounted for by a higher fibre intake; however it could also be related to poor availability and acceptance of medical care. There is an increased prevalence amongst higher socioeconomic groups, but this may reflect health-seeking behaviour [34].

Despite the widely-held beliefs that inadequate fibre intake, prolonged sitting on the toilet and straining lead to the development of symptomatic haemorrhoids, there is little evidence to support this. Fibre -intake and the prevalence of haemorrhoids are not associated. There has not been an overall increase in fibre intake amongst Western populations [51] despite a fall in the prevalence of haemorrhoids [48]. If there is an association between lower incidence of haemorrhoids and rural society, other factors such as squatting position for defaecation, and lack of social restraint with regards to timing and location of defaecation may be just as important as dietary factors [52].

Positive family history is often recorded and treatment for haemorrhoids is more common in the medical history of parents of haemorrhoid patients, however this is just as likely to be related to dietary, cultural or behavioural factors as genetic factors [7].

Unfortunately there is little in the way of evidence with regard to defaecation habits. Anecdotally, the haemorrhoid patient will be one that sits for a longer duration on the lavatory, and may be obsessed by the necessity to open their bowels on a daily basis. Despite the lack of evidence, this

theory forms the basis for conservative management of haemorrhoidal disease [52].

Haemorrhoid sufferers report more constipation [35], lower stool frequency [35] and more straining [27, 28], however researchers have demonstrated normal bowel frequency in their study populations [45]. Indeed haemorrhoids may be the cause of a sense of constipation as a result of pain or mechanical impedance. The concept of constipation requires qualification as the patient's interpretation may relate to infrequent bowel movement, hard stools, which require straining to evacuate or a sensation of incomplete emptying. A history of constipation has been found to follow rather than precede that of haemorrhoids, with resolution of constipation with the onset of prolapse of haemorrhoids, suggesting that haemorrhoids are a cause of constipation.

Further doubt on the causal relationship between constipation and haemorrhoids occurs following review of epidemiological data [44]. Population-based surveys demonstrated an increasing prevalence of constipation from the age of 65 years, and constipation was more common in blacks and families of lower socioeconomic status. This is a significantly different pattern to the haemorrhoid population, where there is peak prevalence in the age range 45 – 65 years, with a subsequent decline after the age of 65 years. Haemorrhoidal disease was a more common complaint in whites of higher socioeconomic status.

1.8 NEW METHODS OF TREATING HAEMORRHOIDS

1.8.1 Doppler-guided haemorrhoidal artery ligation

First described in 1995 [53], DGHAL uses a specially adapted proctoscope with an incorporated Doppler probe. The branches of the superior rectal artery that feed the haemorrhoidal zone are located by the change in the Doppler signal. A "figure of eight" suture is placed in the submucosa to ligate each branch. DGHAL interrupts arterial inflow and tethers the mucosa, causing the haemorrhoids to shrink and retract.

The only randomised controlled trial comparing closed haemorrhoidectomy to DGHAL [54] assessed analgesic requirement, length of post-operative stay, and time taken to return to normal activity all of which were lower in the DGHAL group ($p < 0.01$). Recurrence of symptoms was similar in both groups at 11.7±4.6 months follow-up.

1.8.2 Procedure for Prolapsing Haemorrhoids

Longo first described this alternative approach in 1998 [55]. It is also known as circular stapled anopexy, and stapled haemorrhoidopexy. It has become increasingly popular for the treatment of third and fourth-degree haemorrhoids. A modified circular stapling device, similar to those used for low rectal anastomosis, is used to excise a ring of redundant rectal mucosa 3 – 4 cm above the dentate line and proximal to the haemorrhoids themselves. The aim is to re-suspend the haemorrhoidal cushions back within the anal canal and interrupt the arterial inflow traversing the excised segment.

Complications of PPH include rare cases of severe retroperitoneal and pelvic sepsis, rectal perforation and rectovaginal fistula [56-58]. Following these reports it has been emphasised that care must be taken with the depth of the purse-string suture, to avoid injury to the muscle of the rectal wall and the introduction of bacteria into the perirectal tissues.

In a meta-analysis of fifteen trials including 1077 patients, qualitative analysis showed that PPH is less painful compared with standard haemorrhoidectomy [59]. It also showed a shorter inpatient stay, operative time, and return to normal activity. The same meta-analysis demonstrated significantly worse recurrence rates after PPH. In one of the included trials [60], at a mean of 15.9 months follow-up, recurrence rates were 11.8% after PPH compared to 0% after haemorrhoidectomy for third-degree haemorrhoids, and 50% compared to 0% for fourth-degree haemorrhoids. Further randomised controlled trials with longer follow-up are awaited before a consensus is agreed upon.

1.9 PHARMACOLOGICAL THERAPIES

Micronised purified flavonoid fraction (MPFF) (Daflon®) is a phlebotropic drug, consists of 90% diosmin and 10% flavonoids expressed as hesperidin. It is believed to improve venous tone and lymphatic drainage. It reduces the expression of some endothelial adhesion molecules, thus inhibiting the activation, migration and adhesion of leukocytes. This leads to a reduction in the release of inflammatory mediators and consequent reduction in capillary hyperpermeability [61].

Three randomised double-blinded placebo-controlled trials have investigated the efficacy of flavonoid drugs during an acute episode of haemorrhoids, each of which have demonstrated statistically significant reduction in duration and severity of symptoms [62] , and apparently appeared to prevent relapse of bleeding [63].

1.10 EXPERIMENTAL ANIMAL MODELS

Three different research groups have reported their experience with animal models of haemorrhoidal disease. Myers and Donovan [64] examined porcine rectums, following the induction of cryolesions with a liquid nitrogen probe. Post-mortem angiograms were performed between one hour and fourteen days following induction of the cryolesions. Submucosal vessels at one hour demonstrated marked distortion and hardly any contrast opacification. Submucosal vessels regained patency in lesions of less than 24 hours duration, but after 24 hours there was complete necrosis of the mucosa without any affect on the underlying muscle fibres.

Zmora et al. [65] used a porcine model to examine the possibility of performing PPH on two occasions safely. Concern about potentially reduced blood perfusion to the ring of mucosa and submucosa between the two staple lines was the main reason for performing the study. Interestingly mucosal blood perfusion was assessed using a Laser Doppler Blood Perfusion Monitor, prior to, immediately after the second PPH procedure and one month after the two PPH procedures.

At one month after application, the mean mucosal blood perfusion between the staple lines did not differ significantly from the mean perfusion outside that area.

Mucosal blood perfusion of the distal anorectum was decreased in comparison to higher rectal segments. This phenomenon was found both in baseline measurements before the application of the first PPH suture line and after application of the second.

There was a statistically significant decrease in blood perfusion in the ring between the staple lines compared to the proximal rectum when measured immediately after the procedure ($p = 0.012$, unpaired t-test). This trend was identified in baseline measurements before the application of any sutures, and the authors attributed these findings to the effect of the anoscope in the anal canal rather than the stapler.

All flow measurements taken at one month after PPH were higher than those measured immediately after PPH. The authors cited calibration of the monitor and application of a different pressure on the tissue as possible causes for the differences found.

Plapler [66] examined the effect of ligating the inferior haemorrhoidal vein in a group of *Cebus apella* monkeys. Histological study by the investigator had previously demonstrated similarity of the anal venous drainage in the monkey to that in humans, although this work was not published. The intention was to create hemorrhoids by reducing venous return from the perineal region. The induced haemorrhoids were noted to appear in 50% of the monkeys around the ninth post-operative day, and disappeared within two to three weeks.

It is difficult to assess the value of this study, as no description of the morphological appearance of the pre-procedural anorectum is made. The apparent haemorrhoid was not examined histologically to assess the vasculature of the anorectum. No reference is made to Thomson's work, and the underlying principle that haemorrhoids are essentially enlarged, symptomatic anal cushions. The investigator acknowledged that the cause of haemorrhoids must be multi-factorial and ligation of the inferior haemorrhoidal vein (a term no longer used and presumably the inferior

rectal vein was ligated) is not a full explanation for the appearance of haemorrhoids.

1.11 DISCUSSION AND HYPOTHESES

In summary, although there is a vast amount of literature published on haemorrhoidal disease particularly in the last decade, since the advent of PPH, recent experimental work on the underlying aetiology and pathogenesis is surprisingly sparse. Thomson's anatomical work represented a great advance at the time of publication, and is likely to be partly responsible for the advent of PPH some twenty years later.

Anal cushions are normal structures, found in infants and adults. There is a complex pattern of arterial supply to the anorectum with a varying involvement of the superior, middle and inferior rectal arteries depending on the individual. Direct arteriovenous communications in the anal submucosa have been confirmed by a variety of methods; it has been postulated that these serve an erectile purpose to enable the anal cushions to form a compliant plug to the anal canal. The submucosal venous plexus, characterised by discrete sacculations, is sited within the cushions, and are part of the normal anatomy.

Thomson's work confirmed that the varicose vein theory for the formation of haemorrhoids is invalid. The vascular hyperplasia theory made a resurgence in 1963 [10], albeit acknowledging that the vascular spaces represented a normal part of the anatomy, the corpus cavernosum recti. Thomson rejects this theory for several reasons. First histological examination of haemorrhoidectomy specimens showed no evidence of hyperplasia. Second the haemorrhoids were noted to have a red granular mucosa due to a rich network of dilated capillaries in the lamina propria; bleeding from these vessels was clearly identified on some of the sections. Therefore the classical bleeding of haemorrhoids was deemed to originate from these superficial capillaries rather than the larger vascular spaces separated from the mucosa by connective tissue and the muscularis mucosae.

Finally the results from a verbal survey on the order of occurrence of haemorrhoidal symptoms gave rise to the notion that bleeding was probably a secondary symptom to prolapse. This conclusion was based on the results from 80 consecutive patients admitted to hospital for surgical treatment, who were asked which of their symptoms started first. Thomson reports the results of 66 of these patients, of whom 60% reported prolapse, and 12% bleeding as their first symptom. Unfortunately it is unclear how the other patients are unaccounted for. The study suffers from recall bias, as well as the fact that only patients attending for surgery were included in this survey. These patients were likely to suffer from more advanced prolapsing disease, and therefore recall of other earlier symptoms could have been reduced.

Having rejected the varicose vein and vascular hyperplasia theories, Thomson elaborates on the sliding anal lining theory. His findings confirm that anal cushions are normal structures, specialized highly vascular structures that contribute to the anal continence mechanism. The normal ageing process leading to degeneration of the supporting muscularis submucosae in conjunction with hard, bulky stools and an irregular bowel habit will cause prolapse of the cushions. Straining will lead to engorgement of the cushions making prolapse more likely. Prolapse will further impede venous drainage.

The anatomy of the cushions has been thoroughly studied, however the physiological processes underlying the size and change of size of cushions or haemorrhoids has not been fully examined. Although Thomson states that prolapse is usually the first symptom of haemorrhoids, bleeding without prolapse from first-degree haemorrhoids is an accepted phenomenon [52], and it is possible that venous obstruction may play a greater role in the early stages of haemorrhoid development and symptoms.

There is clinical evidence from newly developed techniques [53, 55] that by disrupting the blood flow in the haemorrhoidal arteries using circular stapling devices or suture ligation a reduction in haemorrhoidal volume and an improvement in symptoms occurs. However, these techniques are invasive, often require general anaesthesia and there is concern regarding the long-term recurrence rate and the risk of incontinence associated with the use of circular stapling devices. It is possible that topical

pharmacological agents may have a less invasive role in the treatment of haemorrhoids by causing vasoconstriction of these arteries and symptomatic improvement. Before pharmacological therapies can even be considered, investigation of the possible vascular aetiology is required. Furthermore objective assessment methods are required if true efficacy of treatment is to be proven. A detailed review of current methods of assessment is presented in chapter 2.

The overall aim of the work described in this thesis is to develop objective measures of the severity of haemorrhoidal disease and their response to treatment, with a view to future evaluation of pharmacological therapies for early stage haemorrhoidal disease.

A secondary aim is to examine the hypothesis that there is a role for abnormal vascularity in the development of haemorrhoids. The following specific objectives will be addressed:

- Develop and validate an index, which measures the symptoms of haemorrhoidal disease, thereby quantifying the effect of treatment on the symptoms of haemorrhoidal disease. (Chapter 2)
- Investigate imaging-techniques that will allow semi-quantification of haemorrhoidal vascularity.
- The techniques to be investigated are:
  - Three-dimensional ultrasound and Doppler imaging (Chapter 3)
  - Nuclear medicine investigations (Chapter 4)
  - Magnetic resonance imaging (Chapter 5)

2 HAEMORRHOID PATIENT REPORTED OUTCOME MEASURE

2.1 INTRODUCTION

The aim of this thesis is to enable the colorectal surgeon and researcher to assess haemorrhoidal disease objectively – investigating the measurement of new parameters that may change after treatment of haemorrhoids. A significant part of this work focuses on various radiological techniques, and their potential use in quantifying the burden of haemorrhoidal disease and the effect of treatment, however this thesis would be incomplete without a more conventional approach to assessment of haemorrhoidal disease using symptoms.

Disease is defined as a specific illness or disorder characterized by a recognizable set of signs and symptoms attributable to heredity, infection, diet, or environment [67]. The World Health Organization defines health as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity [68]. Measuring physiological parameters alone gives an incomplete picture of health when we are attempting to measure the effectiveness of an intervention.

A literature search undertaken in January 2005 showed that although there is considerable interest in and debate on the merits of new surgical interventions for haemorrhoids, very little has been published on how haemorrhoidal disease is assessed or what denotes successful outcome. There are two areas of the literature review that are pertinent to how surgeons currently gauge successful treatment of haemorrhoids. First the literature published on the stapled haemorrhoidopexy operation, and second, a review of available classification systems for haemorrhoids. The latter should enable the surgeon to assess the severity of haemorrhoids, naturally leading to the appropriate choice of management.

2.1.1 Procedure for Prolapsing Haemorrhoids

As this is one of the newer treatment options available with wide uptake across Europe and America, it was important to review the literature; new methods of assessing outcome may have been introduced.

The literature review of the stapled haemorrhoidopexy studies show that although there is great enthusiasm for this operation, there is an absence of standardized outcome measures. There is extensive variation in the choice of outcome measures, and the timing of assessment (see tables 2-1 and 2-2). There is still considerable debate about the long-term recurrence rates, as well as its suitability to fourth-degree haemorrhoids. This situation could be resolved by the use of an instrument using patient reported outcome measures.

2.1.2 Classification Systems

Classification of haemorrhoids should allow the surgeon to assess the severity and the potential impact on the patient. It should also direct the surgeon to the most appropriate treatment for the patient. It is also a tool to aid objective assessment of new treatments.

The most commonly used classification, described by Goligher [69], divides haemorrhoids into four grades. First-degree haemorrhoids project slightly into the lumen of the anal canal when the veins are congested during defaecation. Second-degree haemorrhoids form larger swellings that protrude into the anal canal and descend towards the anal orifice, and may appear externally during straining but will return spontaneously after defaecation. Third-degree haemorrhoids protrude during defaecation and require digital replacement. Fourth-degree haemorrhoids are irreducible. This classification is purely anatomical and does not take into account the symptoms that are associated with haemorrhoids such as bleeding, pruritus, soiling and pain.

Examination of the anal canal shows the mucosa and submucosa above the dentate line to be uneven and arranged into folds, the so-called anal cushions. Sensation of pain in the anal canal can only be attributable to pathologies residing below the dentate line, and therefore pain in most instances should not be attributable to internal haemorrhoids. The

discomfort associated with grade I haemorrhoids is usually associated with anal hypertonicity [70]. The discomfort associated with grade III haemorrhoids is variable, ranging from a dragging sensation to severe proctalgia, and probably arises from sources in the wall of the anal canal and pelvic floor. Pain suffered by patients with grade IV haemorrhoids usually relates to secondary complications such as thrombosis or ulceration.

Thomson *et al.* [71] proposed a modification of Goligher's classification, linking symptoms to the increasing stages of severity. Stage 1 is the same as Goligher's grade I, the symptoms of which are bleeding. Stage 2 haemorrhoids prolapse with bowel movements and reduce spontaneously. Symptoms include bleeding and prolapse. Stage 3 haemorrhoids are divided into minor and major categories. Minor stage 3 haemorrhoids prolapse with bowel movements and require manual reduction, and symptoms include bleeding, prolapse, discharge, discomfort and pruritus. Major stage 3 haemorrhoids prolapse at times other then bowel movements, necessitating frequent attempts to replace the haemorrhoids. Minor stage 4 haemorrhoids are prolapsed and cannot be replaced, and symptoms include pain as well as the others previously mentioned. Major stage 4 haemorrhoids are thrombosed internal and external haemorrhoids, leading to severe pain and sometimes necrosis and ulceration.

Following the introduction of the stapled anopexy technique by Longo [72] in 1998, there has been a deluge of publications surrounding this technique. Unfortunately this has not been mirrored by consistent stratification of results by classification of haemorrhoids (see table 2-1 and 2-2).

In a discussion paper Lunniss and Mann [70] proposed a modification of previously published classifications, based on morphology, that is to say the size and degree of prolapse. Stage 0 refers to anal cushions that may bleed rarely and do not prolapse. Stage 1 refers to small haemorrhoids that bleed intermittently. A minor definite increase in size is visualized during proctoscopy. Stage 2 refers to intermediate haemorrhoids that bleed frequently, sometimes profusely, and also prolapse on defaecation but return to their original position spontaneously. The individual haemorrhoids are described as being moderately increased in size. Stage 3 refers to large

haemorrhoids that bleed frequently and often profusely. They prolapse and require aid to reduce them. Proctoscopy confirms a major increase in size, sometimes circumferential. Stage 4 haemorrhoids are permanently prolapsed and irreducible. They are described as bleeding profusely, with an extreme increase in size, also associated with haemorrhoids in secondary positions.

By linking the degree of bleeding and prolapse, size and possible additional features to haemorrhoidal development, the authors proposed that all haemorrhoids could be placed in one of the stages, therefore allowing accurate comparison of treatments. Additional features mentioned are pruritus, discomfort, skin tags, pain as a result of thrombosis or other complications, and soiling.

Although the authors state that an increase in size cannot be accurately measured, they state that recognizable affects i.e. degree of prolapse are sufficiently associated with size to classify haemorrhoids into separate groups. However it is well known that size may also be affected by day-to-day variation, including pre- and post-defaecation. Manipulation with a proctoscope can cause the haemorrhoids to engorge significantly [52].

The authors aim to have the classification based on the natural history of haemorrhoidal disease, as far as it is known. Normally on defaecation, the anal cushions are flattened and held against the internal anal sphincter by the submucosal smooth muscle fibres. Bright red bleeding arises from damaged capillaries in the lamina propria indicating displacement of the more lax and friable mucosa, such that it becomes pinched between the passing stool and the dentate line. This constitutes first-degree or stage I haemorrhoids.

Prolapse occurs as a result of further and prolonged stresses at defaecation and sitting with an unsupported perineum. Excessive straining causes engorgement of the cushions so that they swell into the lumen of the relaxed anal canal, where they are then subject to the shearing effect of passing stool. Depending on the extent of tissue stretching and fragmentation, the cushions will demonstrate a varying degree of prolapse.

Nevertheless this classification system suffers the same inherent issues that Goligher's does. It does not take into account the burden of other

symptoms; such as discomfort, pruritus and soiling; which anecdotally at least patients find as troublesome as bleeding and prolapse. The Lunniss classification also dictates that bleeding becomes more profuse with increasing severity of prolapse, although it is pointed out that stage 4 haemorrhoids may occasionally cease to bleed if mucosal thickening and squamous metaplasia has occurred. However patients do present with symptoms of intermittent prolapse and no bleeding. Gaj and Trecca [73] have discussed this issue: the difference between haemorrhoids and a possible separate clinical entity of mucosal prolapse.

The other main issue with any classification system for haemorrhoids is that grading is based on the patient's condition at the time of clinical assessment. Very little is known about the natural history of haemorrhoidal disease. It is well known that a significant proportion of patients do not have symptoms on a regular basis. Keighley and Williams state that different degrees of prolapse can occur at different times of the menstrual cycle in women, or even at different times of the day [52].

In 2000 Gaj *et al.,* [74] proposed an alternative classification system for haemorrhoids called PATE 2000. P denotes internal haemorrhoids and for each position the haemorrhoid must be classified as first, second, third or fourth degree. There is also an option for circumferential haemorrhoids, again classified by degree. A refers to the absence or presence of an acute event, either oedema or thrombosis. T refers to anal canal tone and can be hypotonic, normotonic or hypertonic. E refers to the presence of external haemorrhoids and the options for position are left lateral, anterior and right posterior. PATE 2000 was evaluated in 204 consecutive patients from eleven coloproctological centres [75]. Patients with other proctological disease or who had undergone previous proctological surgery were excluded. The examining specialist completed an assessment form on each patient detailing the old and new classification systems. Unfortunately very little information was available on the study population, methodology or results. The authors stated that PATE 2000 was three times superior to the old one, and that a McNemar test was statistically significant.

The only other available classification system is one using endoscopic methods [76]. Haemorrhoids were assessed on the basis of circumferential

distribution of internal haemorrhoids (range), diameter of largest haemorrhoids (form) and the presence of red colour signs in accordance with the general rules for endoscopic findings of oesophagogastric varices. The authors compared endoscopic findings with a simple evaluation of prolapse and bleeding prior to endoscopy and rubber band ligation. They found a significant correlation between bleeding score and range, form and red colour signs. There was also a significant correlation between prolapse score and form. However this study would not be particularly practical for evaluation of patients, with respect to exposure or time required to carry out treatment.

There have been very few recent anatomical studies of haemorrhoidal disease; Thomson's [2] seminal work being the most extensively referenced. Morgado *et al.* [77] examined anal canal sections in 32 foetuses, 20 healthy adult males and 100 haemorrhoidectomy specimens. The anal canal specimens from adult males without anorectal pathology were similar to those of foetuses, but differed in that the submucosal vessels contained a higher ratio of collagen to muscle fibres. The collagen fibres within the submucosa; interdigitating the internal anal sphincter; had a heterogeneous fragmented appearance and again there was a higher ratio of collagen to muscle fibres in the sphincteric muscle mass.

The sphincteric muscle exhibited a greater number of blood vessels with irregular walls and the muscle bundles were less uniform than in the foetal specimens. The intersphincteric groove contained blood vessels with sclerotic walls, some showing signs of long-standing thrombosis. The collagen fibres at this level were particularly fragmented.

Histological study of the haemorrhoidectomy specimens revealed severe inflammation affecting the connective tissue and walls of the arterial and venous blood vessels. Fragmented collagen fibres had replaced muscle tissue. Some cases had ischaemic changes in the mucosa, as a result of local haematoma, leading to ulceration.

The same authors also assessed 816 medical records of patients with haemorrhoidal disease. Standard classification, bowel symptoms and surgical procedures were evaluated. 29.3% of the under 40 years group were operated on for massive thrombosis, in comparison to 5.7% of the over

40 years group. Unfortunately there was no other information available on this large group of patients. On the basis of their review of literature at the time, the authors proposed that a different classification could be used: bleeding haemorrhoidal disease; prolapsing haemorrhoidal disease; thrombotic haemorrhoidal disease; and mixed haemorrhoidal disease.

Essentially the authors argued that classification should be based on symptoms, as a way of choosing the most appropriate treatment. A symptom-based classification should be sufficiently comprehensive to incorporate most, if not all, the principal symptoms that may be attributable to haemorrhoids. It was also unclear from the methodology as to the inclusion and exclusion criteria for the 816 medical records assessed. It appears possible that cases of haemorrhoidal disease occurring as a result of fistulae, fissures, neoplasms or any local pathology that represented part of a systemic disease were included in the cohort studied.

Overall most of the classification systems available are all anatomically based. Correct grading of haemorrhoids is dependent on several factors, all of which are liable to observer error, and possible variation in the natural history of haemorrhoid symptoms.

Differentiating between grade I and II haemorrhoids could be dependent on the assessor's history taking and examination skills. It is not uncommon for a patient to be referred to a surgical clinic, but be asymptomatic at the time of assessment. However based on the history taken the patient may well have had recent episodes of prolapse. In these circumstances patients are often keen to undergo treatment, in an attempt to prevent further symptomatic episodes.

Differentiating between grades II and III haemorrhoids can also be liable to circumstances. The patient may be unwilling to digitally replace haemorrhoids, or they may return to the normal position if given more time. Large haemorrhoids are perhaps more likely to be classified as grade III because of the surgeon's assessment of size. Grade III haemorrhoids may also be incorrectly classified as grade IV if associated with a large external component. Clinical examination can be difficult and the patient themselves may be attempting to replace an external skin tag rather than a prolapsing haemorrhoid.

2.1.3 Patient Reported Outcomes

Prior to considering the design of such an instrument, justification for its design and use is required. More and more medical publications include the keywords quality of life (QoL); a search of the National Library of Medicine's Pub Med database reveals three times as many publications in 2005 as in 1995. QoL is recognized as a major endpoint for phase III randomized clinical trials. A recent systematic review identified 1,275 different instruments measuring health-related quality of life (HRQL) and other related outcomes by the year 2000 [78].

Several clinical trials organizations have introduced the notion of QoL as a standard part of new trials. The European Organization for Research and Treatment of Cancer (EORTC) states that its mission is to "to develop, conduct, coordinate and stimulate translational and clinical research to improve the standards of care by increasing survival and patient quality of life [79]." As far back as 1985 the US Food and Drug Administration (FDA) recognized the benefit of QoL as well as increased survival, as a justification for approval of new anti-cancer drugs [80].

The definition of HRQL and QoL and related concepts such as health status and perceived health has been disputed and elusive, resulting in no single concept being universally adopted [81, 82]. In a recent review of 68 different HRQL models, Taillefer et al. [83] observed that about 25 % of authors did not provide a definition of the concept. When definitions were provided, they differed significantly in their content.

Therefore the FDA has proposed the umbrella term patient reported outcomes (PRO): "a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)" [84].

The importance of assessing health outcomes has become increasingly evident in the practice of medicine. This has been driven both by patients, who are becoming more involved in the decisions affecting their health, and the increased interest in health economics particularly in light of a larger and older population. A better understanding of patient perception of haemorrhoidal disease should optimize clinical decision-making in terms of

achieving outcomes that matter most to patients. Surgeons are well aware that patients' reporting of symptoms, and the degree to which they are affected by the symptoms, vary greatly with similar levels of appearance on examination.

Therefore it is highly desirable for clinicians to have a uniform and reproducible method to assess symptoms. It would enable the clinician to monitor progression of disease for individual patients by providing an objective symptom score to follow. It also facilitates the comparison of results in clinical studies of the outcomes of different treatment modalities conducted at different sites and at different times. This type of clinical information, when combined with physiological measures and other test results, should give a far more detailed picture of disease status in patients with haemorrhoids.

Patient reported outcomes (PRO) are abundant in clinical medicine, and can be used for three purposes: discriminating between subjects, predicting prognosis or the results of a test, and evaluating change over time.

A discriminative measure is used to distinguish between individuals or groups based on an underlying dimension, where there is no external criterion or gold standard available for validating these measures. One of the most useful aspects of discriminative functional status measures is in surveys, which attempt to quantify the burden of illness across different communities [85].

A predictive measure is used to classify individuals into a set of predefined measurement categories when a gold standard is available, either concurrently or prospectively, to determine whether individuals have been classified correctly. This type of index is generally used as a screening or diagnostic instrument to identify which specific individuals have or will develop a target condition or outcome.

An evaluative measure is used to assess the magnitude of longitudinal change in an individual or group on the dimension of interest. The development of evaluative instruments has provided the main focus for those interested in measurement of quality of life. Such instruments are

needed for quantifying the treatment benefit in clinical trials, and for measuring quality adjusted life years in cost-utility analyses.

A number of research groups have developed generic measures, designed for different patient populations. Health profiles such as the SF-36 [86], the Nottingham health profile [87] and the sickness impact profile [88] measure several health domains. More recently the need for disease-specific questionnaires for use in clinical trials has been recognized, leading to the design and validation of instruments for studies in cancer and rheumatology [89].

2.1.4 Gastrointestinal PROMs

Before considering the design and evaluation of a haemorrhoid PROM, it was essential to ensure that other similar measures had not been designed by other researchers. A literature review was undertaken using the National Library of Medicine, Web of Science (ISI) and PubMed Entrez databases, as well as a variety of on-line sources [90-93]. In particular the Patient-Reported Outcome and Quality of Life Instrument Database was carefully perused as its' aims are to identify and describe PRO and QoL instruments to help researchers choose appropriate instruments and facilitate access to them.

The Gastrointestinal Quality of Life Index [94] (GIQLI) was designed to measure quality of life in any patient with gastrointestinal disease. The original intention was also to design several small organ-specific modules, which could be selected for use, dependent upon the site of impairment. The authors were only able to identify a few organ-specific items by their higher prevalence in their item-testing phase. There was no evidence of a haemorrhoid-specific patient reported outcome measure in published literature.

2.2 AIM

The aim of this study is to develop and validate an evaluative PROM to measure the symptoms of patients with haemorrhoids and to evaluate the effect of treatment, with a view to using it as an outcome measure in future clinical trials.

Author	Outcome Measures													
	Pain	Sx	Analg	Ret Work	Satisfn	Comp	Rec	Ret N Activ	QoL	Man	Op Durn	Hosp Durn	Sec Intervn	Proct
Boccasanta[95]	✔	✔								✔				
Brown[96]	✔	✔	✔											
Cheetham[97]	✔	✔		✔	✔									
CorreaRovelo[98]	✔	✔			✔	✔	✔							
Ganio[99]	✔	✔				✔		✔		✔				
Hetzer[100]	✔	✔				✔					✔	✔		
Ho[101]					✔	✔		✔					✔	
Kairaluoma[102]		✔			✔	✔								✔
Krska[103]	✔	✔				✔					✔	✔		
Lau[104]	✔	✔				✔					✔	✔		
Mehigan[105]		✔			✔	✔			✔					

Table 2-1 Assessment of the outcome measures examined in studies comparing PPH to conventional surgery.

Abbreviations are listed below table 2-2.

Author	Outcome Measures													
	Pain	Sx	Analg	Ret Work	Satisfn	Compns	Rec	Ret N Activ	QoL	Man	Op Durn	Hosp Durn	Sec Intervn	Proct
Ortiz[60]	✔	✔	✔		✔	✔		✔			✔			
Palimento[106]		✔			✔	✔								
Pavlidis[107]	✔	✔			✔	✔					✔	✔	✔	
Racalbuto[108]		✔					✔							
Rowsell[109]	✔	✔				✔								
Senagore[110]	✔	✔												
Shalaby[111]	✔		✔		✔	✔		✔		✔	✔	✔		
Wilson[112]			✔			✔		✔			✔	✔		

Table 2-2 Continuation of table 2-1.

Sx – Symptoms

Analg – Analgesic Use

Ret Work – Time to Return to Work

Satisfn – Satisfaction

Compns – Complications

Rec – Recurrence

Ret N Activ – Return to Normal Activity

QoL – Quality of Life

Man – Anorectal Manometry

Op Durn – Operative Duration

Hosp Durn – Hospital Stay Duration

Sec Intervn – Secondary Intervention

Proct – Proctoscopic Appearance

Potential Items To Be Evaluated
Pain or discomfort on defaecation
Pain or discomfort at times other than defaecation
Bleeding on defaecation
Bleeding at times other than defaecation
Prolapse on straining
Prolapse that needs to be manually reduced
Prolapse that cannot be manually reduced
Itch or irritation
Mucus or slime discharge
Soiling of underwear
Feeling of incomplete emptying of the bowel

Table 2-3 Potential items to be evaluated during phase I.

Selection followed literature review and discussion with colleagues.

1A) **How often do you get pain or discomfort on opening your bowels?**

- _ **Never**
- _ **Less than once a month**
- _ **At least once a month, but less than once a week**
- _ **At least once a week, but less than once a day**
- _ **With each motion**

1B) **If you do get pain or discomfort on opening your bowels, how much does this affect your life?**

- _ **Not at all**
- _ **Slightly**
- _ **Moderately**
- _ **Quite a bit**
- _ **A great deal**

Figure 2-1 An example of an item from the HSI-1.

It demonstrates the choices available to the patient when asked to evaluate the frequency of symptoms and the affect on quality of life.

2.3 METHOD

2.3.1 Phase I – Item Selection, Testing & Reduction

The initial item pool was selected after a literature review [7, 13, 34, 41, 113-119], thorough evaluation of established colorectal surgical textbooks [8, 120-123], and discussion with colorectal consultants at Queen's Medical Centre. The final list of items is listed in table 2-3. Phase I was based on work carried out by another clinical research fellow, who had completed his research time at Queen's Medical Centre. The initial haemorrhoid symptom index (HSI-1, figs 8-1 and 8-2 in appendix 8-1) was tested on 60 patients recruited in a general surgical outpatients clinic between March and October 2004. Patients were asked to complete the questionnaire in clinic prior to undergoing treatment if it were deemed appropriate. Informed consent was obtained prior to the patient completing the questionnaire.
The HSI-1 was divided into a section covering patient demographics, and a section covering the patient's symptoms. The patient was questioned on the frequency of each symptom and how much that particular item affected their quality of life. The exact wording for a given item is depicted in figure 2-1.

Each symptom was scored from 0 (never) to 4 (with each motion). The affect of the symptom on the patient's life was also scored from 0 (not at all) to 4 (a great deal). Patient characteristics are shown in table 2-4. The results from the 60 completed questionnaires were assessed, and the current haemorrhoid PROM was based on the selected items. Items were selected if 50% of the patients had experienced the symptom in question. Results of the HSI-1 are summarized in table 2-5.

Each item has been ranked according to how many patients experienced that particular symptom. Bleeding at times other than defaecation, prolapse that requires manual reduction and prolapse that cannot be reduced were all items experienced by less than 50 % of patients, and therefore were not included in the haemorrhoid PROM.

2.3.2 Phase II – Design of a Haemorrhoid PROM

The planned level of observation was the individual patient, in particular the measurement of an individual's change due to treatment by rubber band ligation. This treatment was chosen as the study's setting was in a general surgical clinic. The most frequent treatment for a newly referred patient, diagnosed with grades I to III haemorrhoids is rubber band ligation [124]. This would allow for the greatest number of potential recruits to the study in this setting.

Thus far, the purpose of the study was to use an evaluative instrument to measure the effect of rubber band ligation on symptoms experienced by patients with haemorrhoids. Therefore a high level of responsiveness, as well as validity and reliability, is required for this instrument.

The next point to consider is whether to use a generic or a disease specific instrument. Generic instruments cover a broad range of quality of life dimensions in a single instrument. Including many health related dimensions removes the need to select dimensions for a particular study and allows for the detection of unexpected effects. However a broad approach may reduce responsiveness to the effect of treatment.

Disease specific instruments reduce patient burden and increase acceptability by including only relevant dimensions, which may increase responsiveness. Disadvantages are the lack of comparability of results with those from other disease groups and the possibility of missing effects in dimensions that are not included. One approach, representing a compromise, is to include both disease specific and generic measures in a study.

2.3.2.1 Examining Criterion & Construct Validity

As there is no gold standard criterion for the assessment of treatment for haemorrhoids, a different solution was required for evaluating validity of the proposed haemorrhoid PROM. One option available is to use health-related quality of life measures and examine their relationship to the scores generated by each item in the PROM.

The other option was to use an established measure of health related quality of life such as the SF-36 index [86] or a gastrointestinal quality of life index [94] (GIQLI). The issue here is increased burden for the participant, as well as completing an index that doesn't appear to have any direct relevance to the participant's haemorrhoid symptoms. This could affect the face validity of the haemorrhoid PROM. As neither of these measures has been validated in a haemorrhoid patient population, there is little advantage to using them in this study. Instead the patient was asked about the effect of a particular symptom on HRQL. Symptoms that are scored highly should also have high scores for the HRQL if the PROM has good construct validity.

2.3.2.2 Item Scaling

Given that the symptoms may vary in frequency, the patient was asked to reflect on their symptoms over the previous month, and then quantify the number of days in an average week that they had a particular symptom. The choice ranged from 0 to 7 days per week. The 0 day option was given as the patient may have had symptoms, but less frequently than one day per week. Clearly the patient may not have had the symptom at all, and an option is given to tick a box for "no".

2.3.2.3 Haemorrhoid PROM Construction & Layout

The PROM (figs 8-3 to 8-8 in appendix 8-1) was divided into three sections; the first of which gathered information about the patient including age, gender, occupation, and duration of time that the patient had been aware of having haemorrhoids. Section 2 asked for details of medical history, prescribed medication, and details of previous treatment for haemorrhoids. Patients were also asked about analgesia use and topical treatment for haemorrhoid symptoms, and were asked to quantify how often these therapies had been used over the previous month. Patients were also asked whether any family members also had haemorrhoids, and how badly they were affected. Clearly an adjectival

scale is more appropriate here, and five categories are available to choose from.

Section 3 entitled "Your symptoms now" is divided into ten questions, eight of which ask the same question about each of the final items chosen after evaluation of the results of HSI-1 (table 2-5). The final two questions ask the patient to quantify the effect of pain or discomfort and the other symptoms grouped together on their quality of life. They are asked to make a mark on a VAS. Anchors are placed at each end of the line designating 0 and 10; with an explanation that 0 means no effect whatsoever, and 10 means that their symptoms completely dominate their life.

The patients were given contact details of the researcher on the front cover of the questionnaire, and they were reminded to check that all questions were completed.

2.3.2.4 Administration of Haemorrhoid PROM

Options for administration of the PROM include face-to-face interviews, telephone interviews and mailed questionnaires. The advantages of face-to-face interviewing include absolute certainty that the respondent alone provides the information, and reduction of the number of items omitted by the respondent; it is more difficult to refuse to answer than to simply omit a response to an item on the form. The interviewer can determine if the participant is having any difficulty understanding the items, whether it is the grasp of language, the presence of a learning difficulty, or simply boredom. The interviewer would be able to rephrase the question if necessary. The converse of this is that the interviewer may alter the meaning of the question.

The disadvantages include increased cost and time required to carry out the interview, as well as the effect of the interviewer themselves; biases of the interviewer, and his or her social and ethnic characteristics. It is well known that interviewers can subtly communicate what answers they wish to hear, even if they are not aware of doing so. This can be overcome by training, and regular review by a supervisor, however this entails further expense and time

required. It has been shown that race can have an effect on the responses of the interviewee, and the reasons given include social desirability, interpersonal deference, or courtesy to a polite stranger.

Female interviewers normally have fewer refusers and higher completion rates than males. Responses may be different to female interviewers; Pollner [125] found that both men and women reported more symptoms of depression and substance abuse to female interviewers, and furthermore the difference in response rates are more likely to occur with male interviewees.

It was decided that the PROM should be self-administered. This method was employed for cost effectiveness, ease, efficiency, and privacy and to eliminate interviewer bias.

2.3.3 Ethics

Ethical approval was gained from the North Nottinghamshire Research Ethics Committee (part of the Central Office for Research ethics Committees), and concurrent approval was also given by the Research & Development Department at Nottingham University Hospital NHS Trust. The University of Nottingham Medical School Ethics Committee approved the administration of the questionnaire to healthy volunteers.

2.3.4 Inclusion Criteria

Patients were considered for recruitment to the study if they had haemorrhoidal disease that required rubber-band ligation treatment. Either gender was considered. Healthy volunteers were considered for recruitment to the study provided that there was no history of gastrointestinal disease.

2.3.5 Exclusion Criteria

Patients were excluded from the study based on the following criteria: rectal bleeding that had not been investigated or any other colorectal pathology.

2.3.6 Recruitment

Patients were recruited from a general surgical clinic and had undergone clinical assessment and investigations as appropriate, to exclude other colorectal pathology, before being asked to participate in the study. Patients underwent digital rectal examination, proctoscopy and rigid sigmoidoscopy to allow confirmation of haemorrhoids, and exclude any anal or rectal pathology.

The study was explained to each potential recruit in detail, which was reinforced by an information sheet that was read at the time of assessment. An explanation of the rubber band ligation process was given. If the patient was happy to consent immediately to the study and the treatment, the questionnaire was completed before undergoing rubber band ligation. The patient was left alone in a clinic room to complete the questionnaire.

Some patients preferred to have more time to consider either taking part in the study or having rubber band ligation performed. Patients gave permission to be contacted by telephone, and were contacted 2 to 3 days later. They were given the opportunity to ask further questions. If the patient wished to proceed with rubber band ligation, they were offered an appointment to return to the department of surgery. A letter confirmed this appointment. If the patient had consented to taking part in the study, they were asked to complete the consent form and questionnaire at home and bring the paperwork to the appointment.

All patients gave informed consent. A copy was given to the patient, another copy filed in the hospital medical record and another kept for research documentation.

The first twenty-two patients were asked to complete an extra questionnaire 24 hours after the first pre-treatment questionnaire. Each of these patients had already completed and returned the first questionnaire prior to starting the second pre-treatment questionnaire.

Healthy volunteers were recruited via poster advertisements that were placed around the University of Nottingham medical school. All

volunteers gave informed consent and completed the questionnaire in the absence of the investigator.

2.3.7 Statistical analysis

Distribution of the data, factoring on the basis of degree of haemorrhoids, was examined with the Kolmogorov-Smirnov test. Homogeneity of variance, factoring on the basis of degree of haemorrhoids, of the untransformed data was examined with Levene's test. Differences between the healthy volunteer group and the patient groups were assessed by the Wilcoxon rank-sum test. Validity was assessed by performing the Spearman's correlation coefficient (r) between symptom items and quality of life scores. Reproducibility of the haemorrhoid PROM was assessed by performing intra-class correlations. Internal consistency was assessed with Cronbach's α.

As the data for each variable was not normally distributed and lacked homogeneity of variance, Friedman's ANOVA was used to assess each variable. Wilcoxon signed-rank tests, correcting for the number of tests, was performed to assess the size of effect. A Bonferroni correction was applied and so all effects are reported at a 0.0167 level of significance. The effect size $r = {}^{z}/_{\sqrt{N}}$.

2.4 RESULTS – PHASE II

2.4.1 Recruitment & Retention

One hundred and forty four consecutive patients were asked to participate in this study over a 24-month period. Of these 116 consented to participate in this study. One patient was excluded, after initially being diagnosed with second-degree haemorrhoids, as she developed a posterior anal fissure in between being assessed and returning for the rubber band

Of the remaining 115 patients (see fig 2-2), 72 completed all three questionnaires, 22 completed two questionnaires and 21 completed the first questionnaire only. Of the 22 who completed two questionnaires,

11 completed the first and second, and the other 11 the first and third questionnaires.

2.4.2 Study Group Characteristics: sections 1 and 2.

Overall 55.7 % of the participants were male. There was no significant difference in gender-split based on the degree of haemorrhoids, as shown in table 2-6. The average age of the participant was 51.1 ± 14.4 years (range 20 – 80 years). The participant reported duration of haemorrhoid symptoms for an average of 11.1 ± 1.1 years (range 0 – 50 years). Occupation demographics are set out in table 8-1 of appendix 8-1.

Previous medical history responses were categorized into one of fourteen groups based on the first fourteen categories of the International Classification of Diseases version 10. The majority of conditions declared involved the circulatory or digestive systems (see table 8-2 in appendix 8-1), which did not include colorectal pathology.

Current medication use was categorized in a similar manner to that of medical conditions but also included a further category covering anaesthetic agents. Fifty-two per cent of the participants were not on any regular medication (fig 8-9 in appendix 8-1).

There was no significant difference in use of topical treatment between males and females or between first, second or third degree groups. There was no significant difference in analgesic use between the degree of haemorrhoids or between males and females. Figure 2-3 summarises the participants' previous treatments. Sixty-six per cent of patients had not received treatment of their haemorrhoids prior to entry into the study and the proposed rubber band ligation.

2.4.3 Internal Consistency

Internal consistency of the questionnaire was assessed with Cronbach's α at each time-point in relation to RBL. Results are displayed in table 2-7. The value of Cronbach's α for the total score was calculated at 0.832 prior to rubber band ligation, 0.861 four weeks after RBL and 0.885 eight weeks after rubber band ligation.

Encouragingly it is noted that the values of the item-total correlations are all above 0.3 [126], apart from bleeding at 4 weeks post rubber band ligation, but removal of bleeding as an item does not increase Cronbach's α by a large amount.

2.4.4 Test-Retest Reliability

Test-retest reliability was examined by means of intra-class correlations and is summarised in table 2-8. The average total score of the first test was 22.4 ± 3.1, and the retest score was 22.9± 3.1.The intraclass correlation coefficient for the total score was 0.987 (0.970 – 0.995), and denotes a high level of reliability. The Bland-Altman plot is displayed in fig 2-4.

2.4.5 Validity

2.4.5.1 Healthy volunteers

Twelve healthy volunteers completed the haemorrhoid PROM to allow further assessment of validity. Females accounted for 75% of the group. The mean age was 27.8 (18 – 57) years. The mean total score was 1.58 (0 – 7); the mean quality of life score affected by pain 0.03 (0.0 – 0.4) and the mean quality of life score affected by other symptoms 0.01 (0.0 – 0.1). Four volunteers scored three individual items above zero: one scored 6 days per week for pain when opening bowels, two scored 2 days per week for itch/ irritation, two scored 2 days per week and one scored 1 day per week for the sensation of incomplete emptying.

The healthy volunteer group (Mdn = 0.00) had a significantly lower total symptom score than the pre-RBL patient group (Mdn = 19.00), $W_s = 112.0$, $p < 0.001$, $r = -0.48$; than the 4-week post-RBL patient group (Mdn = 15.00), $W_s = 150.5$, $p < 0.001$, $r = -0.49$, and the 8-week post-RBL patient group (Mdn = 7.50), $W_s = 231.5$, $p < 0.001$, $r = -0.40$.

2.4.5.2 Internal validation

Validity was assessed by correlating the individual scores for each variable against the quality of life scores at each time-point in relation to RBL. Pain when opening bowels and pain when not opening bowels was correlated against quality of life affected by pain. Results are summarised in table 2-9. Based on Cohen's criteria, both variables show a significant correlation at the 0.01 level with a medium to large effect suggesting that the measures have a common underlying dimension.

The other variables were correlated against quality of life affected by other symptoms. Results are summarised in table 2-10. All variables showed a significant correlation with a moderate to large effect size at all time-points in relation to RBL, apart from bleeding and itch/ irritation.

The Spearman correlation of the total score to the quality of life affected by pain score was 0.629 prior to RBL, 0.720 at four weeks post RBL and 0.664 at eight weeks post RBL all with a significance value of < 0.001.

2.4.5.3 Item analysis and effect on validity of total symptom score.

The results reported in the previous section show that the symptom and the total scores correlate significantly with the quality of life scores, however the magnitude of correlations between bleeding, itch/ irritation and quality of life score was lower than in other items. Scores from these items were deleted from the total score to further explore internal validity of the haemorrhoid PROM and are summarised in table 2-11. There was not a significant increase in the correlations at any time-point, when the score for bleeding or itch/ irritation was removed.

Item	Frequency
Mean age (years range)	53 (24 – 88)
Mean duration (years range)	9.7 (0.5 – 42)
Female (%)	27 (45.0)
Analgesic use (%)	6 (10.0)
Ointment use (%)	16 (26.7)
Previous rubber band ligation (%)	14 (23.3)
Previous injection sclerotherapy (%)	9 (15.0)
Previous haemorrhoidectomy (%)	2 (3.33)
Other colorectal conditions (%)	21 (35.0)

Table 2-4 Demographics of patients who completed HSI-1.

Item	Mean Score (Sx)	Pt Score Of 0 (%)	Mean Score (Life)	Pt Score Of 0 (%)
Bleeding on defaecation	2.23	10.00	1.72	20.00
Feeling of incomplete emptying	1.97	18.33	1.35	30.00
Pain or discomfort on defaecation	1.92	23.33	1.17	35.00
Prolapse on straining	1.95	28.33	1.13	40.00
Itch or irritation	1.70	28.33	1.12	40.00
Pain or discomfort at times other than defaecation	1.48	35.00	1.03	41.67
Soiling of underclothes	1.62	35.00	1.35	36.67
Mucus or slime discharge	1.25	41.67	1.00	50.00
Prolapse that needs to be reduced	0.90	63.33	0.58	70.00
Bleeding at times other than defaecation	0.60	66.67	0.65	68.33
Prolapse that cannot be reduced	0.73	76.67	0.38	80.00

Table 2-5 Results of phase I.

The mean score for each item, the mean effect on quality of life and proportion of patients scoring zero are presented.

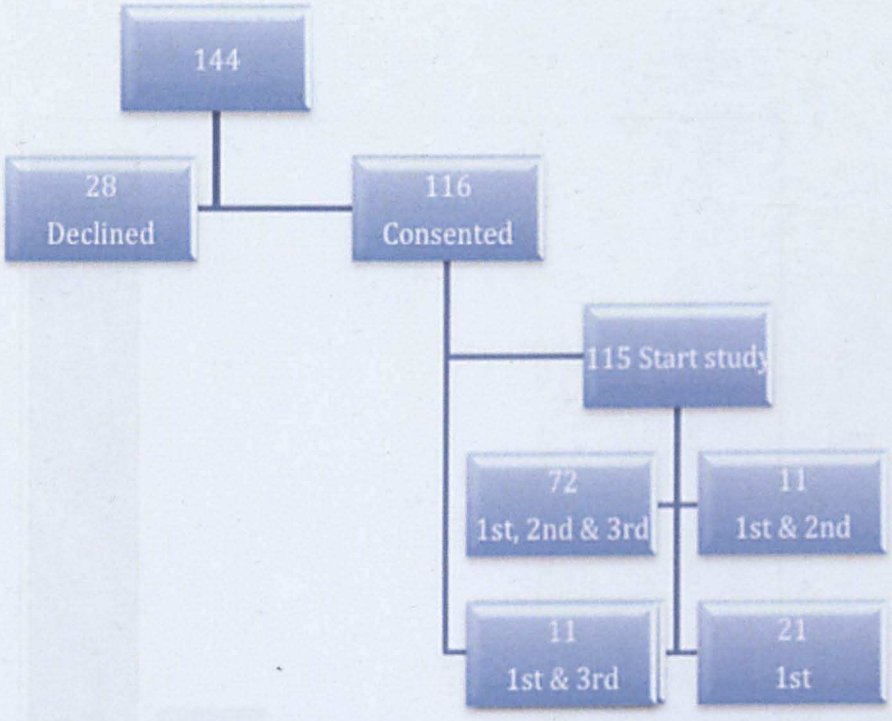

Figure 2-2 Flow-chart demonstrating patient completion of the HS1-2.

Degree	Male (%)	Female (%)
First	52.4	47.6
Second	57.5	42.5
Third	57.6	42.4

Table 2-6 Demographics of participants of HSI-2.

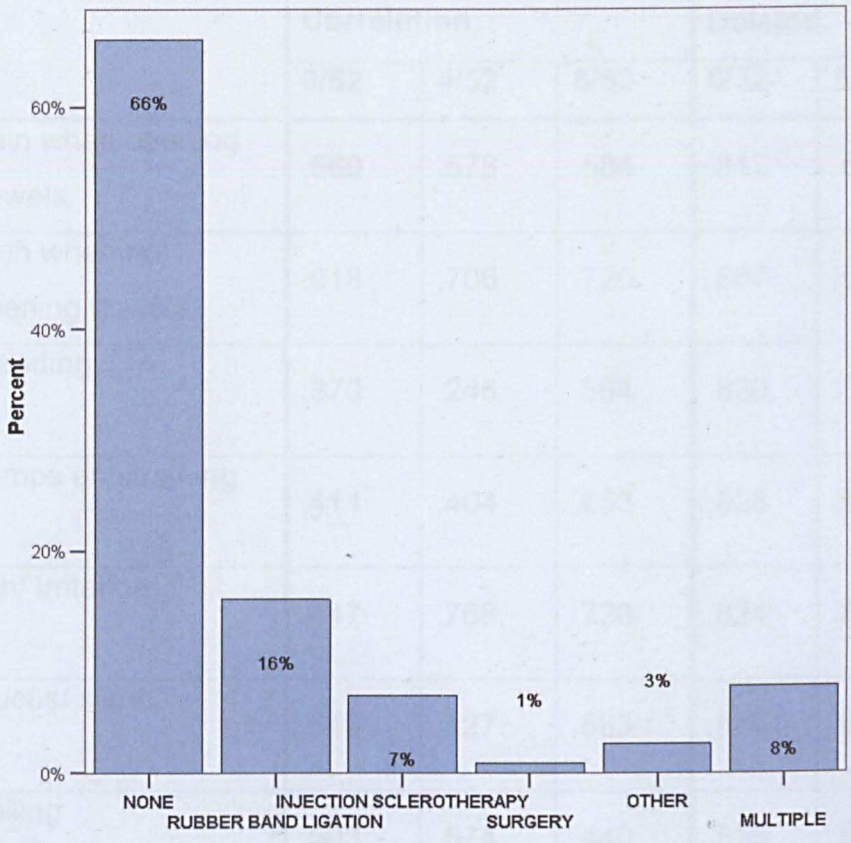

Figure 2-3 Participant's' previous experience of treatment.

Item	Corrected Item-Total Correlation			Cronbach's α If Item Deleted		
	0/52	4/52	8/52	0/52	4/52	8/52
Pain when opening bowels	.560	.573	.584	.812	.847	.877
Pain when not opening bowels	.618	.706	.720	.807	.836	.867
Bleeding	.370	.246	.564	.830	.872	.877
Lumps on straining	.411	.404	.653	.828	.864	.872
Itch/ irritation	.447	.768	.720	.824	.829	.865
Mucus/ slime	.549	.427	.583	.814	.858	.876
Soiling	.503	.574	.440	.818	.847	.885
Incomplete emptying	.534	.561	.503	.815	.849	.881
Pain affecting QoL	.648	.732	.733	.803	.834	.866
Other symptoms affecting QoL	.572	.750	.693	.811	.832	.868

Table 2-7 Internal consistency pre-RBL, four and eight weeks after RBL.

Item	Intra-class Correlation	Range
Pain when opening bowels	.992	(0.980 – 0.997)
Pain when not opening bowels	.855	(0.652 – 0.940)
Bleeding	.852	(0.644 – 0.939)
Lumps on straining	.987	(0.969 – 0.995)
Itch/ irritation	.993	(0.983 – 0.997)
Mucus/ slime	.996	(0.991 – 0.998)
Soiling	.841	(0.616 – 0.934)
Incomplete emptying	.963	(0.910 – 0.984)
Pain affecting QoL	.976	(0.827 – 0.971)
Other symptoms affecting QoL	.987	(0.970 – 0.995)

Table 2-8 Intraclass correlation coefficients for repeatability of individual items.

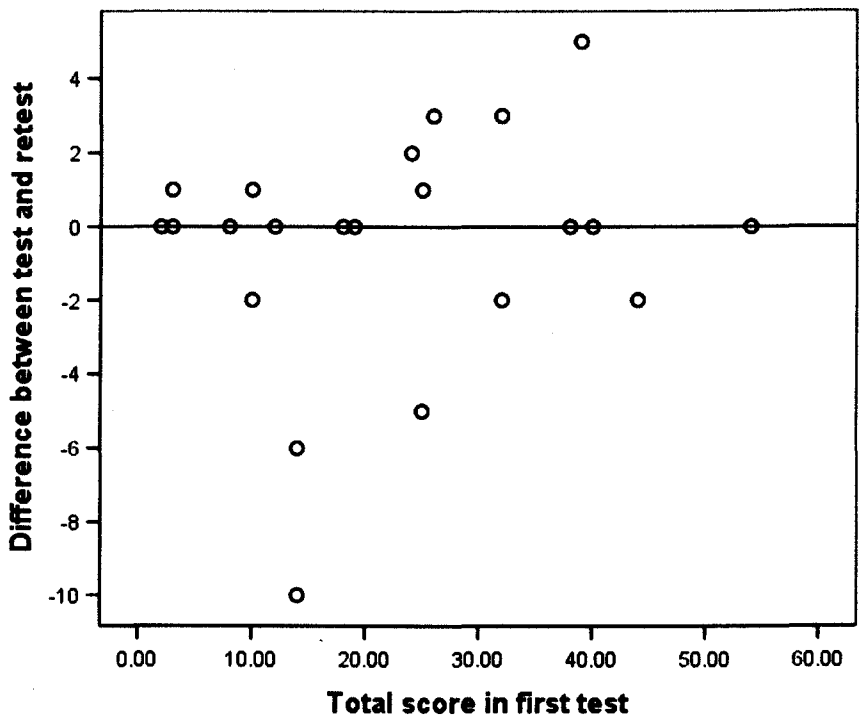

Figure 2-4 Bland-Altman plot of the repeated measurement to test reliability of the haemorrhoid PROM.

Correlation of pain variables to quality of life affected by pain.	Pre – RBL		4/52 post – RBL		8/52 post – RBL	
	r_s	p	r_s	p	r_s	p
Pain when opening bowels	.429	<0.01	.599	<0.01	.559	<0.01
Pain when not opening bowels	.406	<0.01	.677	<0.01	.572	<0.01

Table 2-9 Correlation of pain scores against quality of life affected by pain scores.

Correlation of other variables to quality of life affected by other symptoms.	Pre – RBL		4/52 post – RBL		8/52 post – RBL	
	r_s	p	r_s	p	r_s	p
Bleeding	0.198	0.017	0.171	0.061	0.464	<0.01
Lumps on straining	0.351	<0.01	0.327	0.001	0.423	<0.01
Itch/ Irritation	0.269	0.002	0.716	<0.01	0.532	<0.01
Mucus/ Slime	0.392	<0.01	0.351	0.001	0.451	<0.01
Soiling	0.442	<0.01	0.464	<0.01	0.434	<0.01
Incomplete emptying	0.335	<0.01	0.580	<0.01	0.339	0.001
Total score	0.569	<0.01	0.744	<0.01	0.670	<0.01

Table 2-10 Correlation of variables with QOL affected by other symptoms

Time-point	Item removed	QoL affected by pain	QoL affected by other symptoms
Pre RBL	None	0.629	0.569
	Bleeding	0.632	0.564
	Itch/ irritation	0.603	0.572
4 weeks post RBL	None	0.720	0.740
	Bleeding	0.759	0.763
	Itch/ irritation	0.678	0.700
8 weeks post RBL	None	0.664	0.670
	Bleeding	0.675	0.656
	Itch/ irritation	0.664	0.650

Table 2-11 Effect of item removal on total score correlation with quality of life score.

2.4.6 Responsiveness

Each item changed significantly over the eight-week period and the results are summarised in figs 2-5 to 2-14. Items that changed with a medium size effect (-0.3 ≤ r ≤ -0.5) included bleeding, lumps on straining, itch or irritation and the quality of life scores.

The total score changed significantly over the eight weeks of the questionnaire assessment ($\chi 2(2) = 59.98, p < 0.05$). The scores changed significantly from entry into the study to eight weeks post rubber band ligation, T = 286, r = -0.50, and from four to eight weeks post rubber band ligation, T = 342, r = -0.42 (see fig 2-15).

Although all individual items changed significantly with a graded decrease in score from pre-rubber band ligation to eight weeks, none of the items changed with a large size effect. Significant changes were also identified between pre-rubber band ligation and four week scores, as well as between four and eight week scores, however the majority of these changes were only with a small size effect and are therefore not reported in detail.

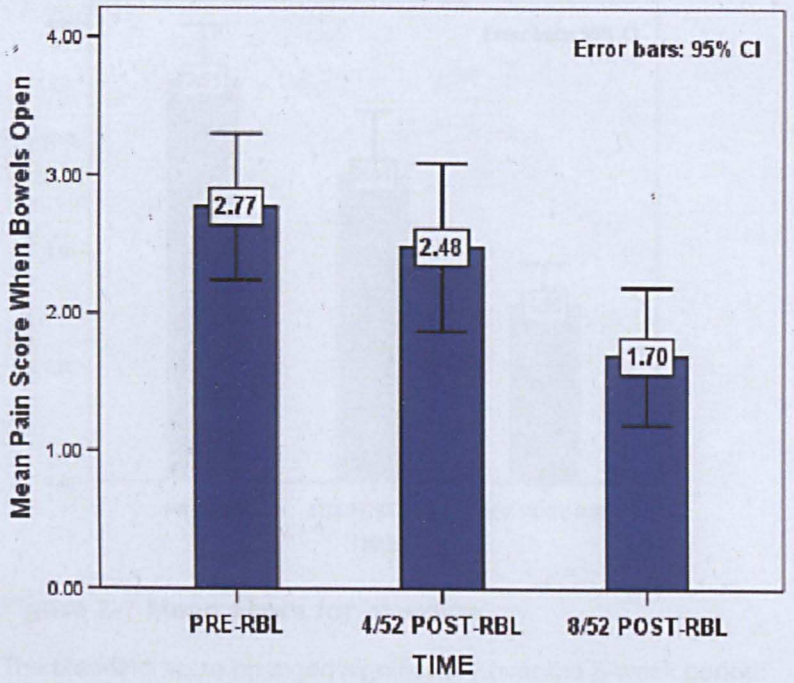

Figure 2-5 Mean score for pain when bowels open.

The score changed significantly over the 8-week period: $\chi 2(2) = 12.07, p < 0.05$, T = 296, r = -0.25.

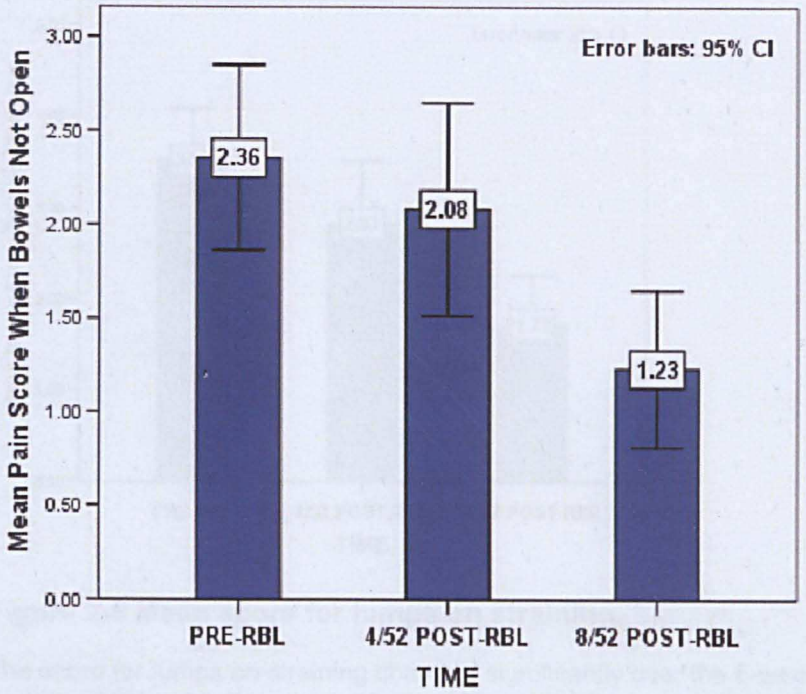

Figure 2-6 Mean score for pain when bowels not open

The score changed significantly over the 8-week period: $\chi 2(2) = 20.19, p < 0.05$), T = 305.5, r = -0.24.

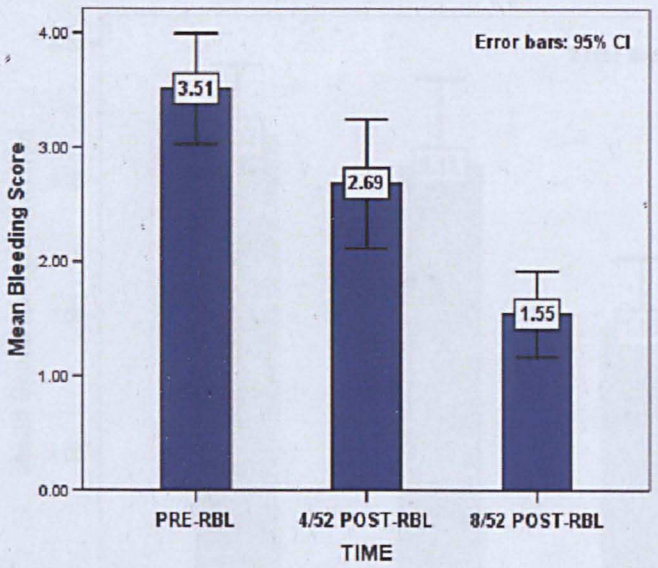

Figure 2-7 Mean score for bleeding.

The bleeding score changed significantly over the 8-week period: $\chi 2(2) = 45.72, p < 0.05$, T = 173, r = -0.45.

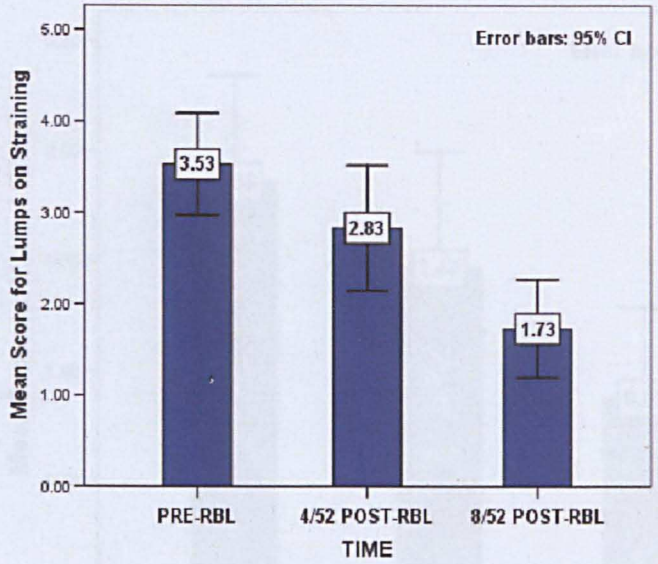

Figure 2-8 Mean score for lumps on straining.

The score for lumps on straining changed significantly over the 8-week period: $\boldsymbol{\chi 2(2) = 32.56, p < 0.05}$: T = 125, r = -0.40.

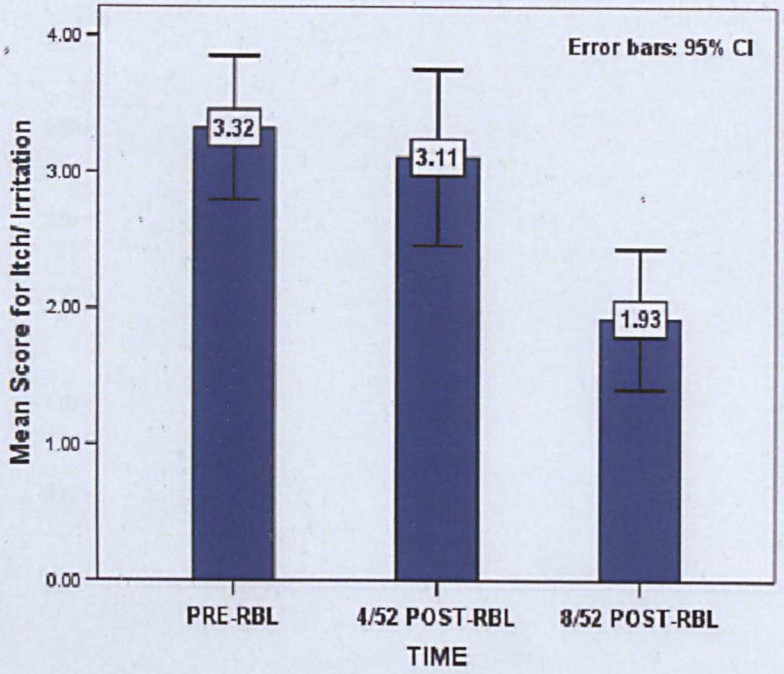

Figure 2-9 Mean score for itch or irritation.

The scores changed significantly over the 8-week period: $\chi 2(2) = 31.30, p < 0.0)$, T = 254, r = -0.40.

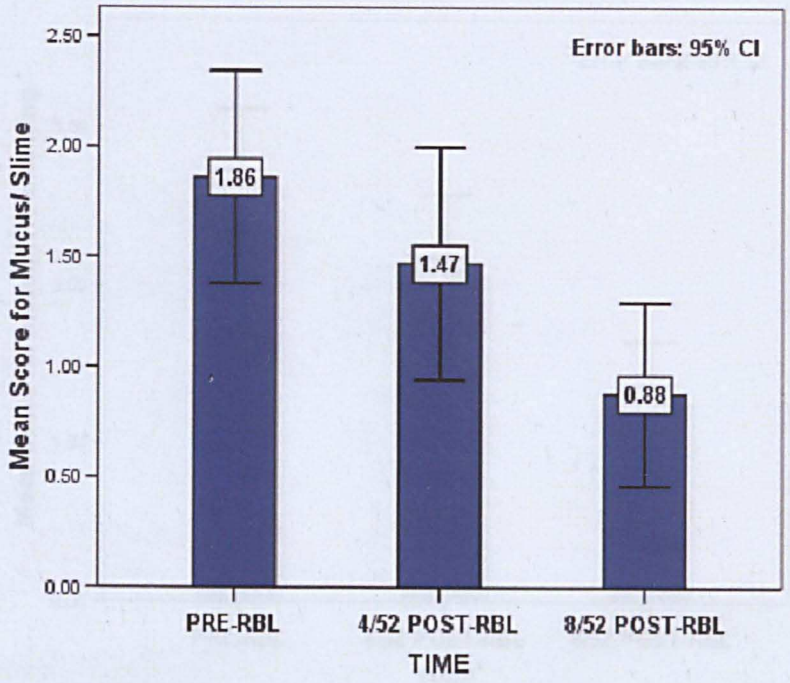

Figure 2-10 Mean score for mucus or slime.

The scores changed significantly over the 8-week period: $\chi 2(2) = 28.25, p < 0.0)$, T = 115, r = -0.31.

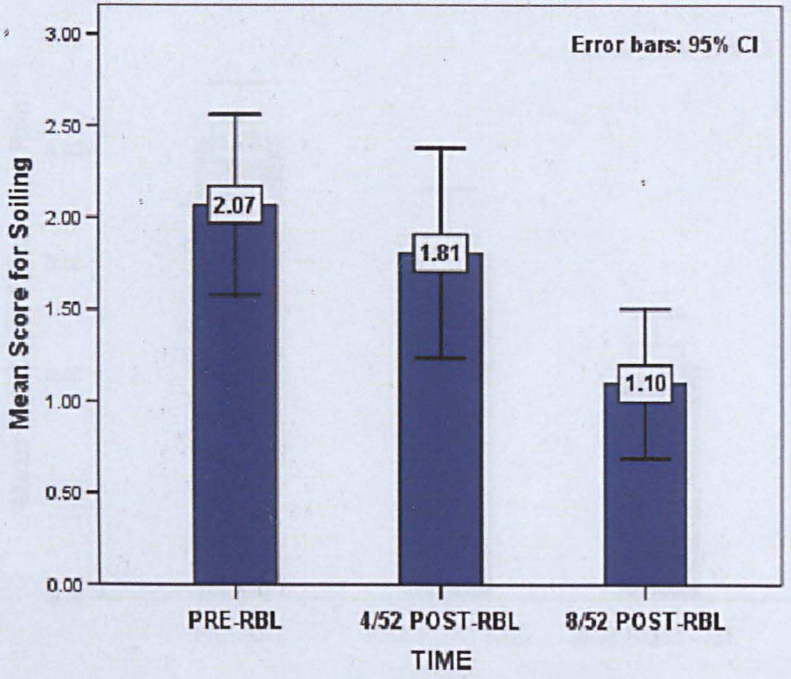

Figure 2-11 Mean score for soiling.

The scores changed significantly over the 8-week period: $\chi 2(2) = 10.56, p < 0.05$, T = 228.5, r = -0.21.

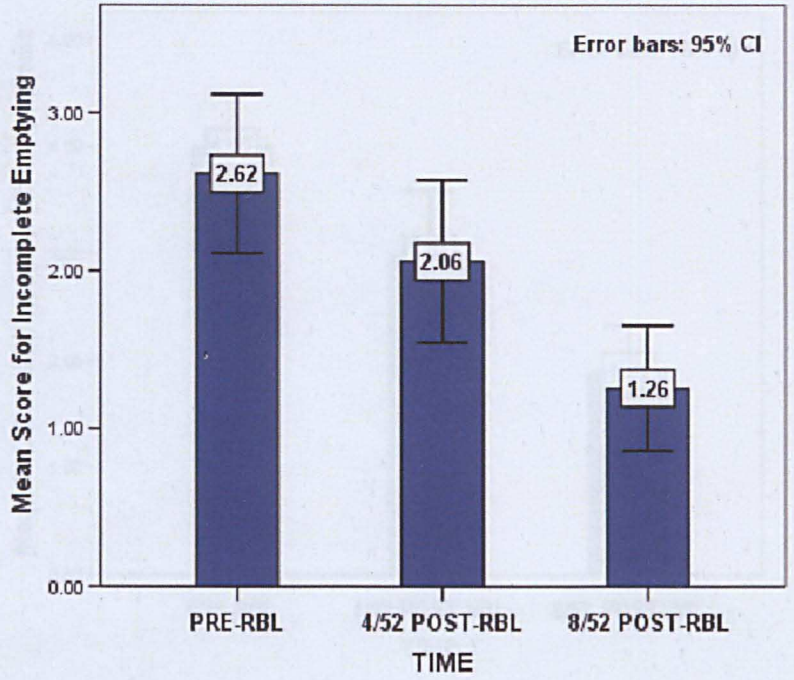

Figure 2-12 Mean score for incomplete emptying.

The scores changed significantly over the 8-week period: $\chi 2(2) = 23.71, p < 0.05$, T = 189, r = -0.32.

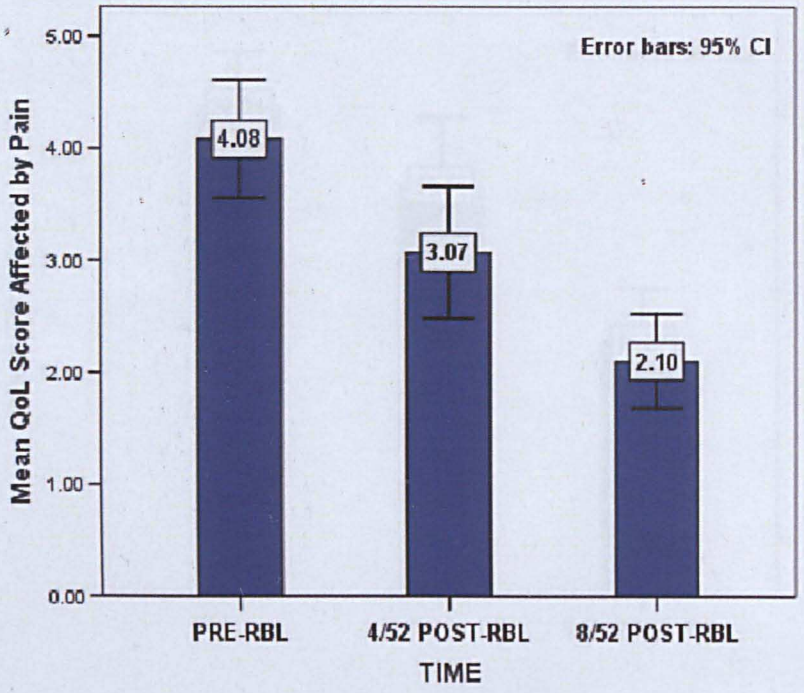

Figure 2-13 Mean score for QOL affected by pain.

The scores changed significantly over the 8-week period: $\chi 2(2) = 34.10, p < 0.05$, T = 391.5, r = -0.39.

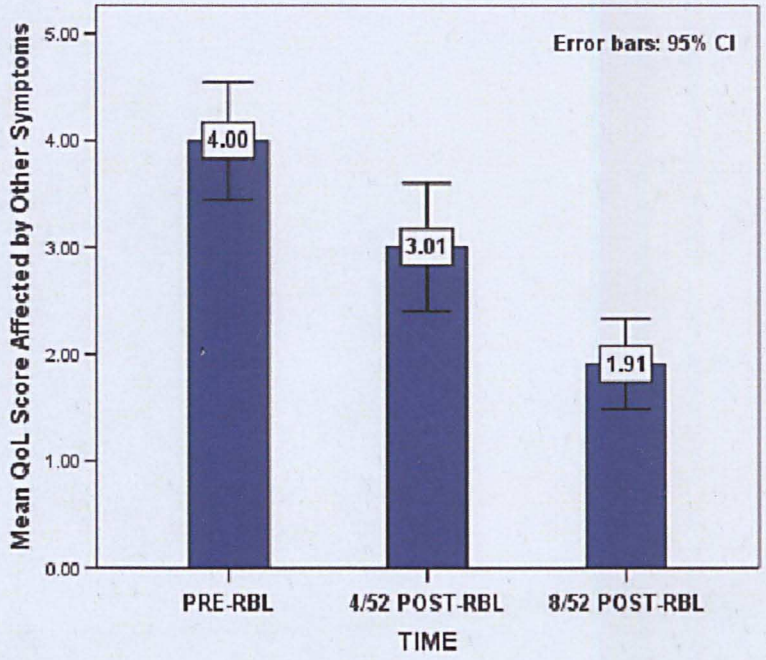

Figure 2-14 Mean score for QOL affected by other symptoms.

The scores changed significantly over the 8-week period: $\chi 2(2) = 39.79, p < 0.05$, T = 877.5, r = -0.41.

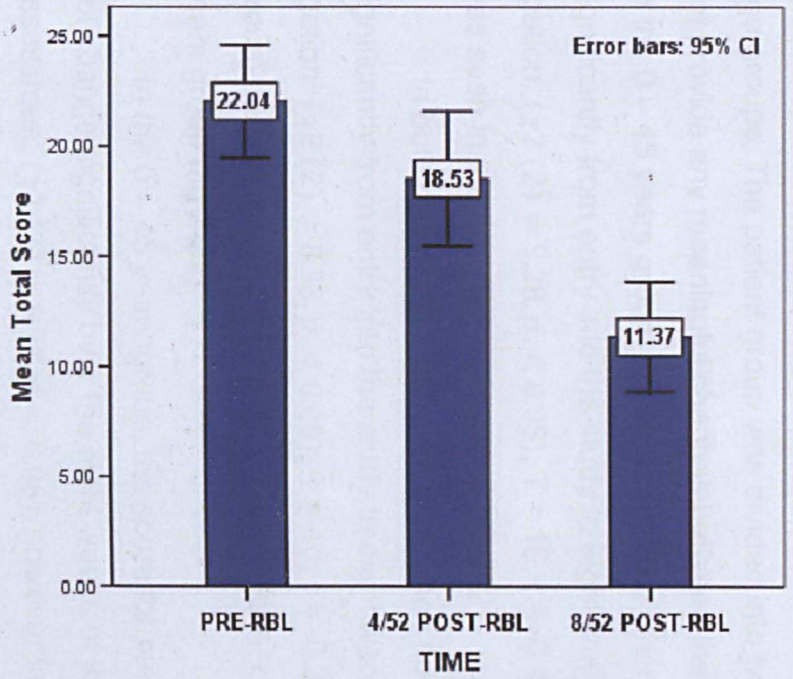

Figure 2-15 Mean total score.

The total score changed significantly over the 8-week period: $\chi 2(2) = 59.98, p < 0.05$, T = 286, r = -0.50.

2.4.6.1 *Analysis of responsiveness by gender.*

The data was analysed for differences in responses between males and females. Females showed a significant decrease for several items where males did not, including the two pain scores (figs 2-16 and 2-17) and soiling (fig 2-18). Females had higher quality of life scores affected by both pain and other symptoms, although males still showed a significant decrease in the effect of pain and other symptoms on their quality of life scores.

The score for other symptoms affecting quality of life significantly changed from entry into the study to eight weeks post rubber band ligation: for males $\chi 2(2) = 9.97, p < 0.05$, T = 183.5, r = -0.32; and for females, $\chi 2(2) = 36.79, p < 0.05$), T = 75, r = -0.49 (fig 2-19).

The score for pain affecting quality of life significantly changed from entry into the study to eight weeks post rubber band ligation: for males $\chi 2(2) = 16.06, p < 0.05$, T = 128.5, r = -0.37; and for females, $\chi 2(2) = 20.24, p < 0.05$), T = 71.5, r = -0.41 (fig 2-20).

2.4.6.2 *Analysis of responsiveness by age.*

The data was analysed for differences in responses between different age groups. The patient group was divided into two, as smaller groups did not provide any meaningful changes between the groups.
In the 0 – 45 years group, the score for pain when opening bowels changed significantly from entry into the study to eight weeks post rubber band ligation, ($\chi 2\ (2) = 9.28, p < 0.05$), T = 16, r = -0.40. No significant change was seen in the 46 – 90 years group (fig 2-21).

In both groups, the score for pain when not opening bowels changed significantly from entry into the study to eight weeks post rubber band ligation: ($\chi 2\ (2) = 8.33, p < 0.05$), T = 10, r = -0.36 for the 0 – 45 years group; and ($\chi 2\ (2) = 15.44, p < 0.05$), T = 64.5, r = -0.33 for the 46 – 90 years group (fig 2-22).

In the 0 – 45 years group, the score for pain affecting quality of life did not change significantly over the eight weeks of the questionnaire assessment ($\chi 2\ (2) = 5.71, p = 0.06$), however in the 46 – 90 years group,

the score for pain affecting quality of life changed significantly from entry into the study to eight weeks post rubber band ligation, ($\chi 2\ (2) = 32.48, p < 0.05$), T = 129, r = -0.43 (fig 2-23).

In the 0 – 45 years group, the score for other symptoms affecting quality of life did not change significantly over the eight weeks of the questionnaire assessment ($\chi 2\ (2) = 5.45, p = 0.067$), however in the 46 – 90 years group, the score for pain affecting quality of life changed significantly from entry into the study to eight weeks post rubber band ligation, ($\chi 2\ (2) = 36.97, p < 0.05$), T = 132.5, r = -0.48 (fig 2-24).

2.4.6.3 Analysis of responsiveness by degree of haemorrhoids

The data was analysed for differences in responses between different degrees of haemorrhoids. In all participants irrespective of degree, the score for bleeding significantly changed over the eight weeks of the questionnaire assessment: for first-degree $\chi 2(2) = 20.86, p < 0.05$, T = 24, r = -0.49; for second-degree $\chi 2(2) = 16.21, p < 0.05$, T = 23.5, r = -0.43; and for third-degree haemorrhoids, $\chi 2(2) = 14.00, p < 0.05$, T = 14.5, r = -0.43 (fig 2-25).

With respect to the items: pain when not opening bowels; lumps on straining; mucus or slime; and sensation of incomplete emptying, there was a difference between the differing degrees. There were no significant changes for participants with first-degree haemorrhoids, whereas participants with second and third-degree haemorrhoids showed significant changes with a medium size effect (figs 2-26 to 2-29).

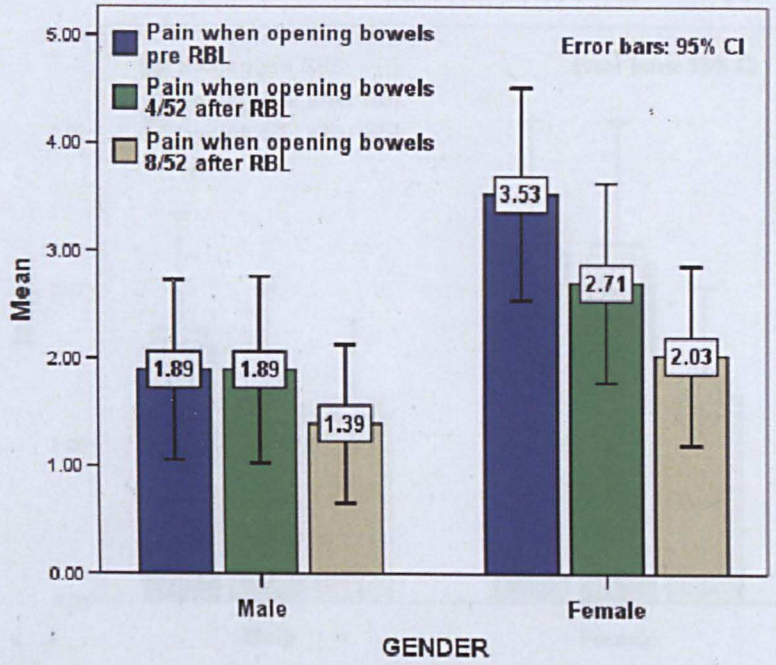

Figure 2-16 Gender differences in pain when opening bowels.

The scores only changed significantly for females: $\chi 2\ (2) = 6.97, p < 0.05$, T = 60, r = -0.32.

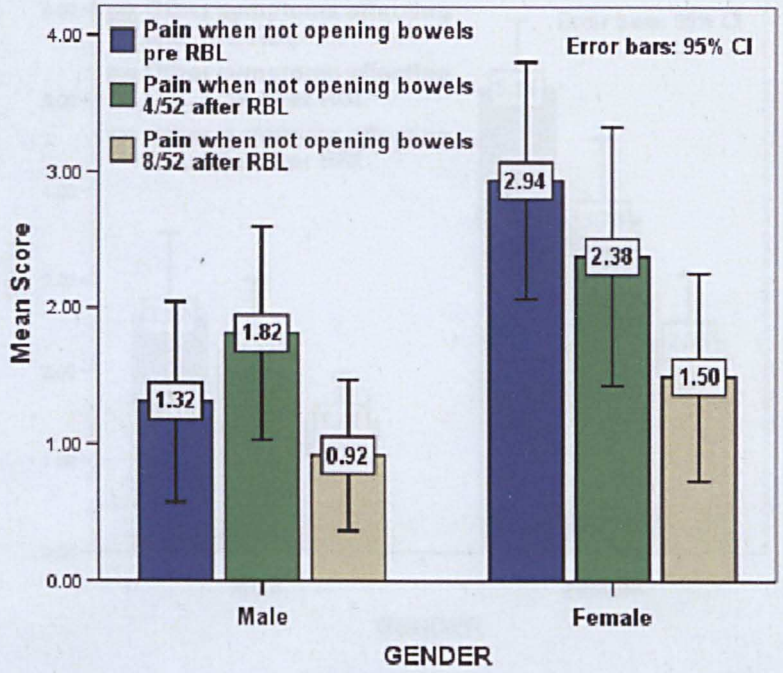

Figure 2-17 Difference in pain when not opening bowels between the genders.

The scores only changed significantly for females: $\chi 2\ (2) = 15.91, p < 0.05$, T = 62.5, r = -0.33.

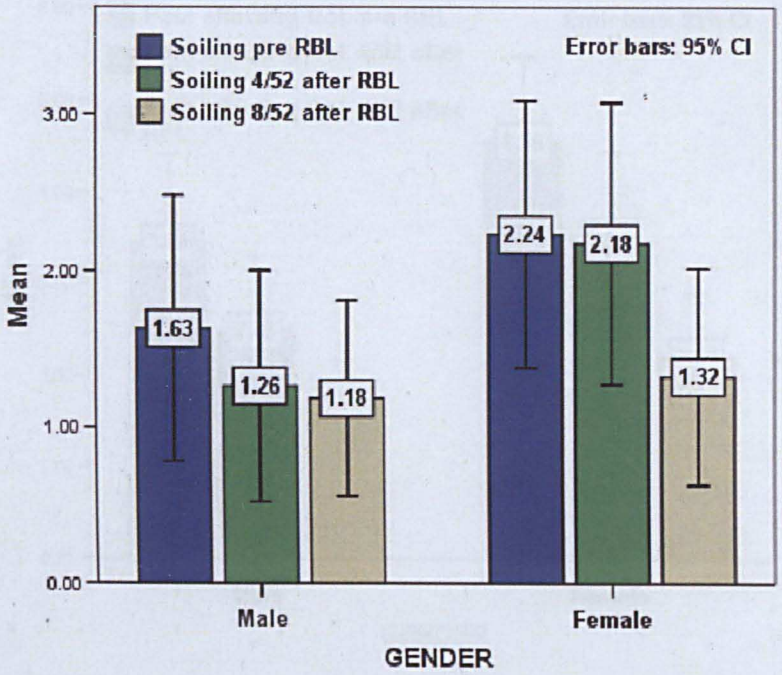

Figure 2-18 Differences in scores for soiling between the genders.

The scores only changed significantly for females: $\chi 2\ (2) = 7.32, p < 0.05$, T = 44.5, r = -0.28

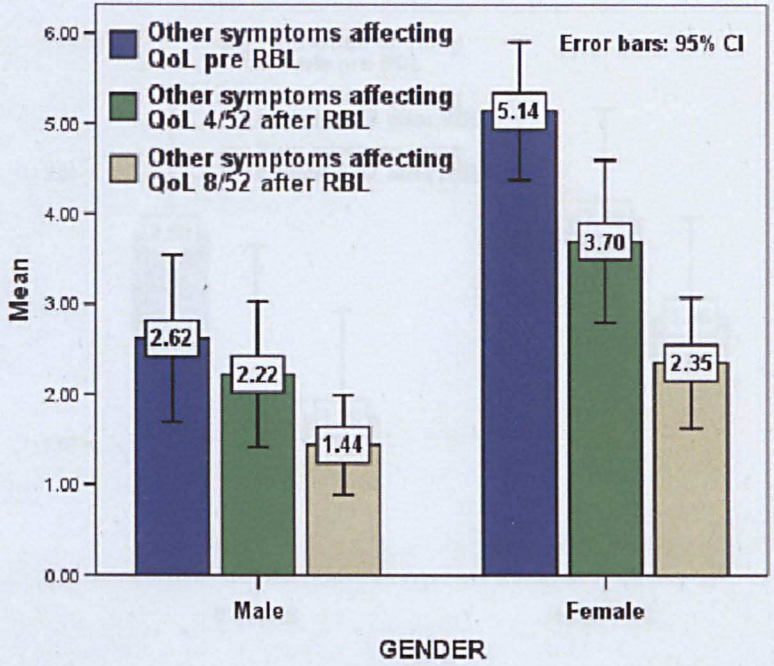

Figure 2-19 Gender differences in scores for quality of life affected by other symptoms.

There was a smaller size effect for males (r = -0.32) than for females (r = -0.49).

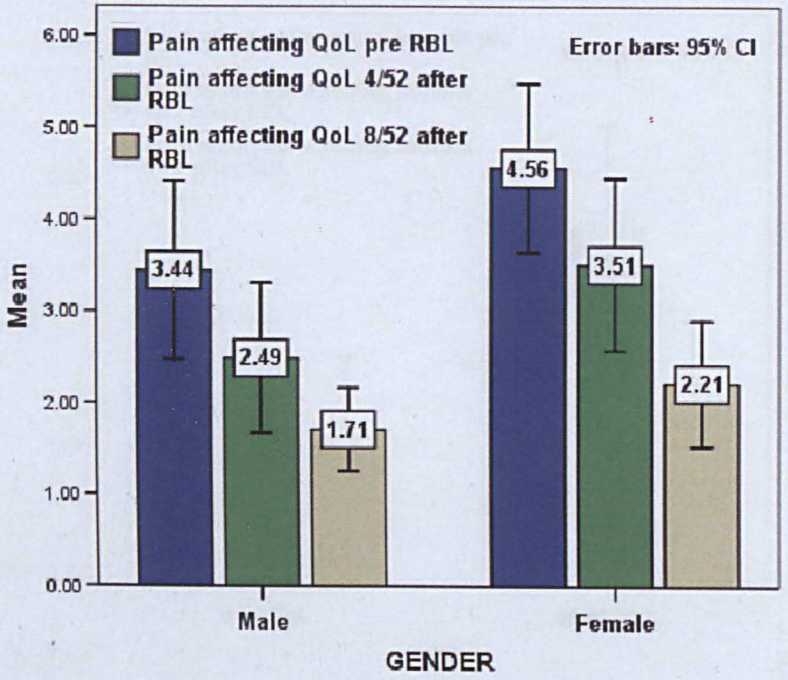

Figure 2-20 Differences between the genders in quality of life scores affected by pain.

Although the scores decreased significantly for both genders, the scores were higher in females at all time-points.

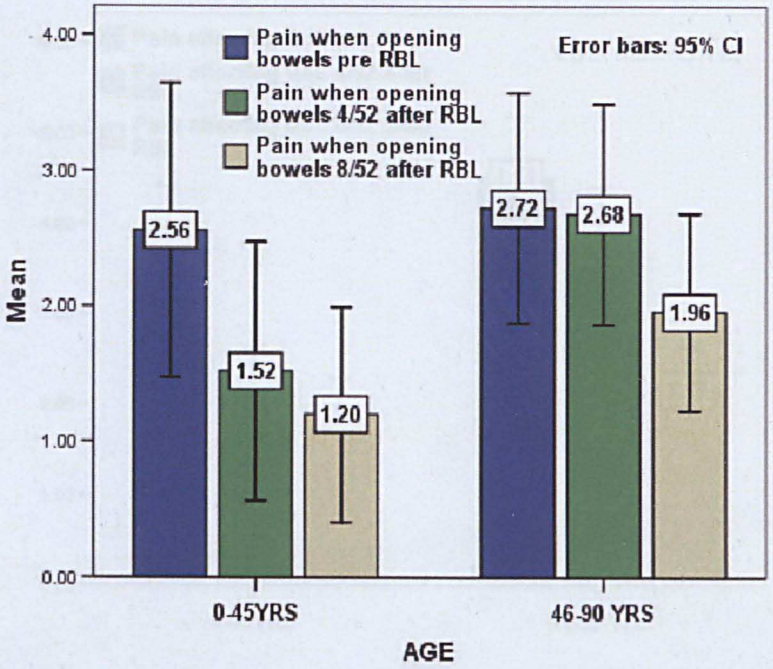

Figure 2-21 Scores for pain when opening bowels by age group.

No significant change for pain when opening bowels is identified for the 46 – 90 years age group compared to the 0 – 45 years group.

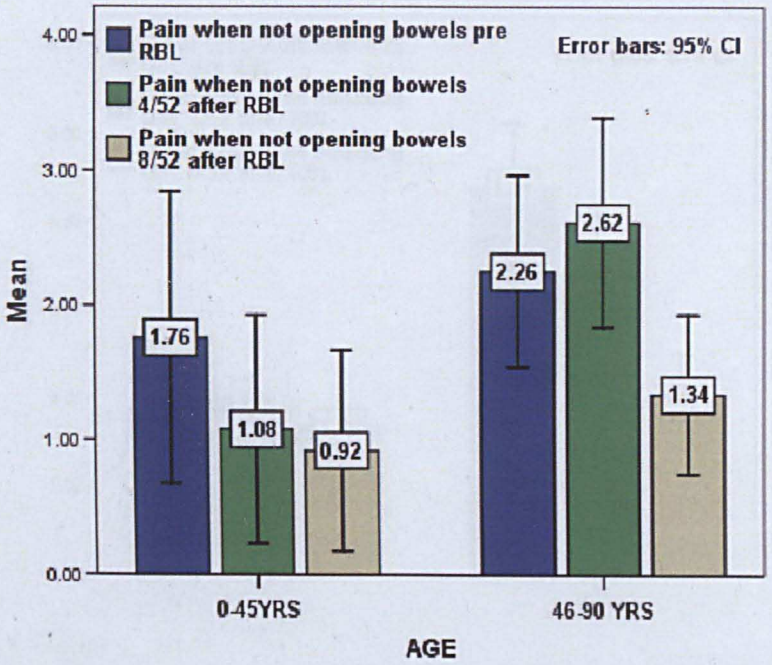

Figure 2-22 Scores for pain when not opening bowels by age group.

Significant changes are identified for both age groups for pain when not opening bowels.

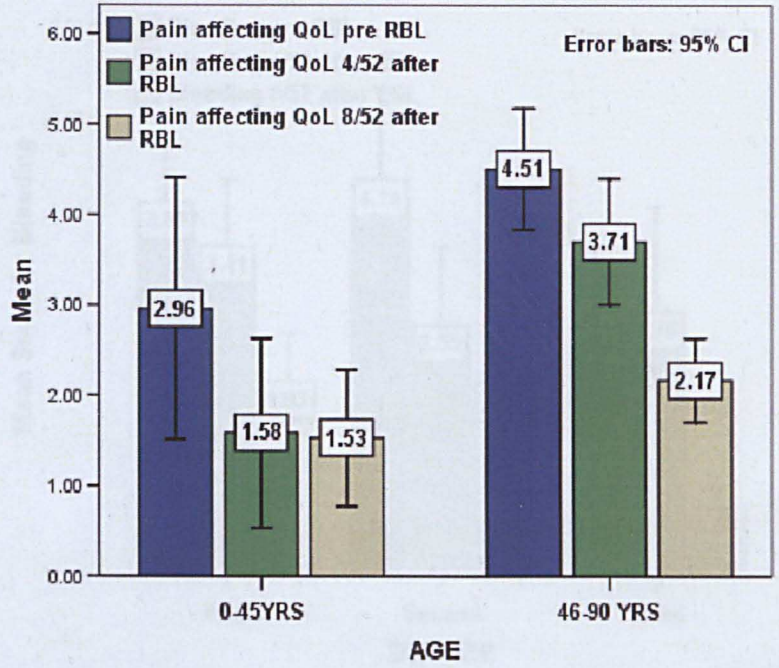

Figure 2-23 Scores for pain affecting QoL by age group.

Significant changes are identified for the 46 – 90 years group for pain affecting quality of life.

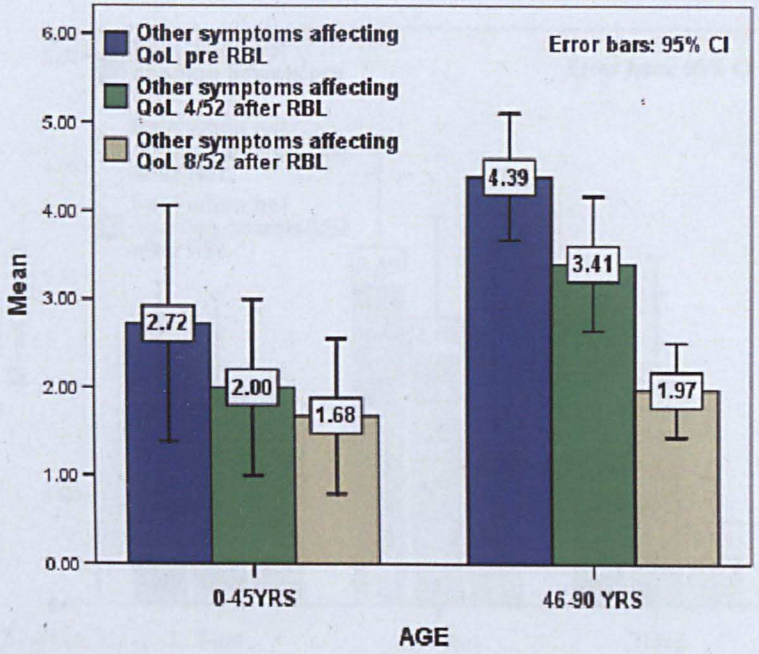

Figure 2-24 Scores for other symptoms affecting QoL by age group.

Significant changes are identified for the 46 – 90 years group for other symptoms affecting quality of life.

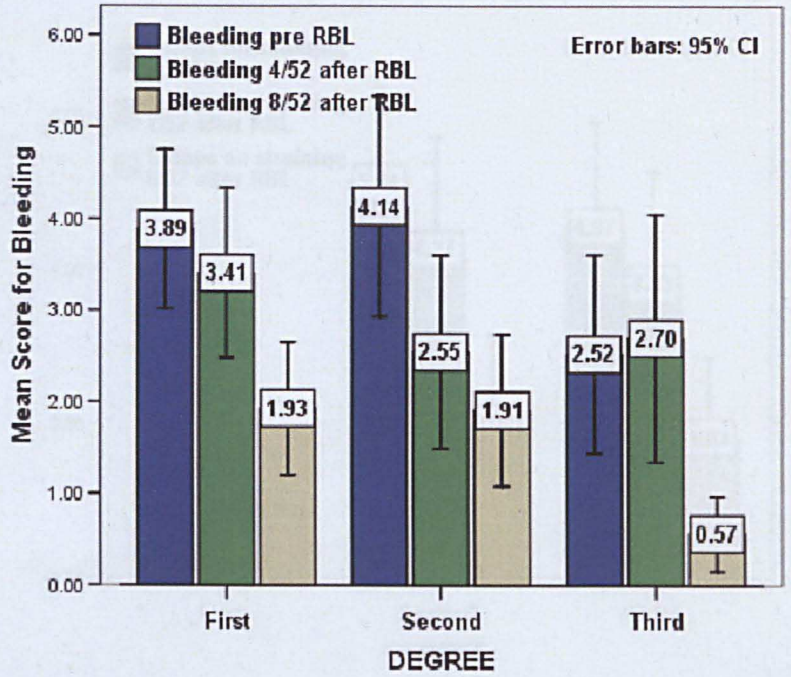

Figure 2-25 Scores for bleeding analysed by degree.

Significant changes for bleeding are identified in all categories of haemorrhoid degree.

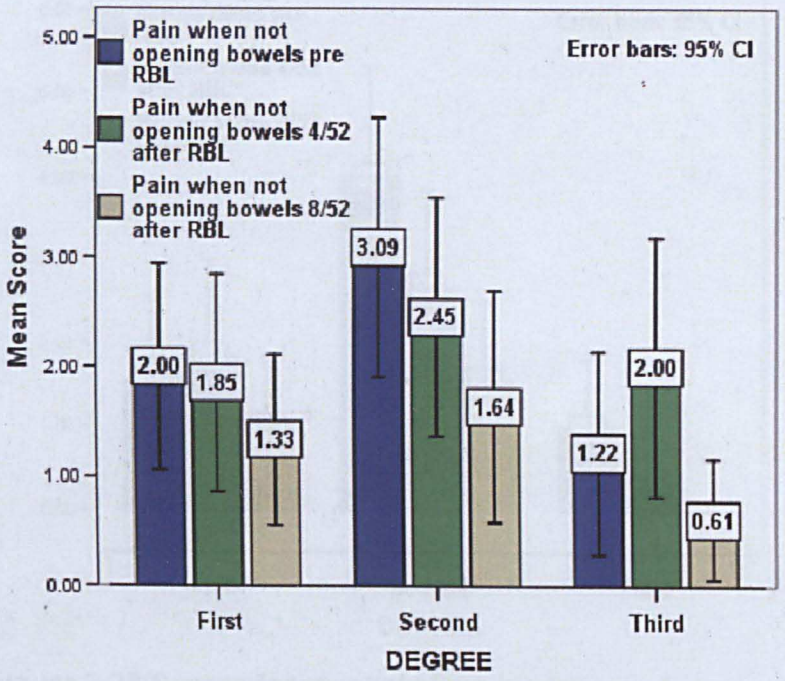

Figure 2-26 Scores for pain when bowels not opening by degree.

Significant changes for 2nd degree from entry to 8-weeks post RBL and 3rd degree from 4 to 8 weeks post RBL.

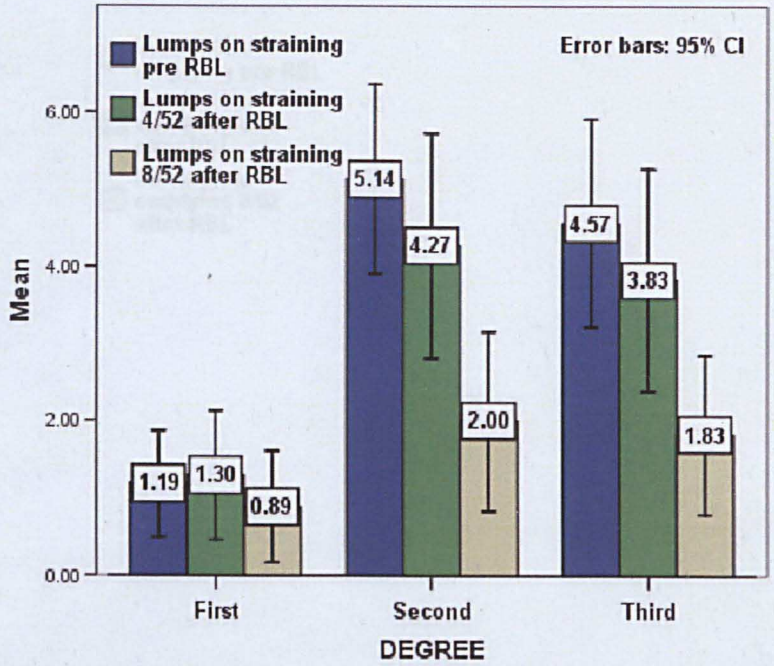

Figure 2-27 Scores for lumps on straining by degree of haemorrhoids.

Significant changes for 2nd and 3rd degree from entry to 8-weeks post RBL.

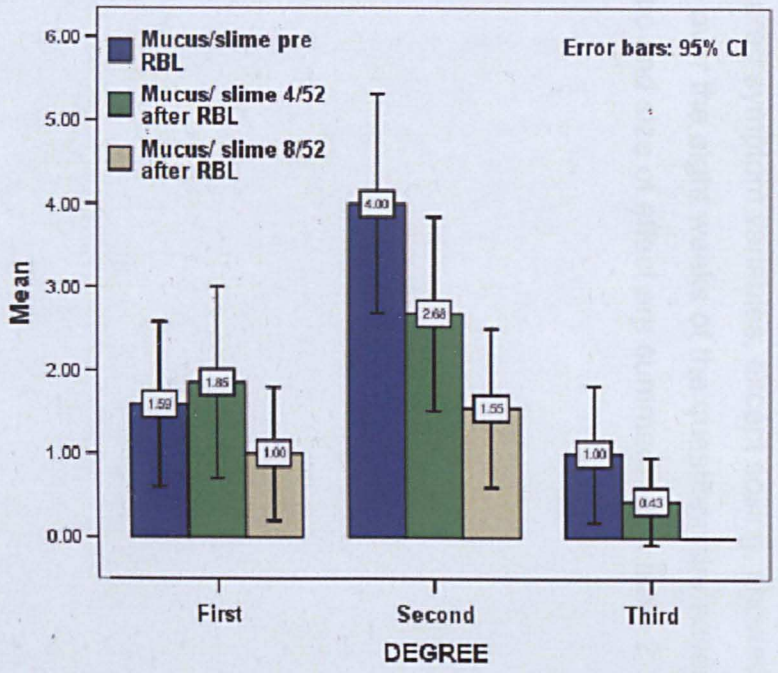

Figure 2-28 Scores for mucus/ slime by degree of haemorrhoids.

Significant changes for 2nd and 3rd degree from entry to 8-weeks post RBL.

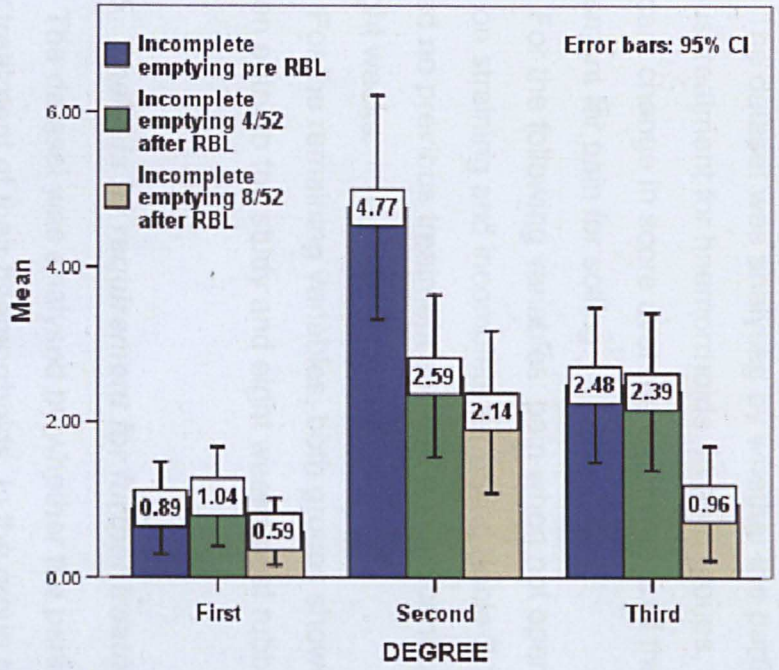

Figure 2-29 Score for sensation of incomplete emptying by degree of haemorrhoids.

Significant changes for 2nd and 3rd degree from entry to 8-weeks post RBL.

2.4.6.4 Analysis by previous treatment

The dataset was analysed by whether the participants had had previous treatment for haemorrhoids. In both groups, there was no significant change in score over the eight weeks of the questionnaire assessment for pain for soiling.

For the following variables: pain when not opening bowels, bleeding, lumps on straining and incomplete emptying (table 2-11), only the group who had had no previous treatment showed a significant change in scores over the eight weeks.

For the remaining variables, both groups showed significant changes between entry to the study and eight weeks post rubber band ligation (table 2-12).

2.4.6.5 Analysis by requirement for further treatment

The dataset was analysed by whether the participants required further treatment of their haemorrhoids. In the group requiring further treatment (n=30) there was no significant change in score for any of the symptom variables.

For the group that did not require further treatment (n =52), all measured symptom variables, except soiling, showed a significant change in score over the eight weeks of the questionnaire assessment. The test statistic and size of effect are summarized in table 2-13.

0 v 8 weeks	No previous treatment N = 76			Previous treatment N = 39		
Degree (%)	38.2	32.9	28.9	33.3	38.5	28.2
Age ± SE (yrs)	49.6 ± 1.7			54.0 ±2.2		
Male (%)	55.3			56.4		
Pain when not opening bowels	$\chi 2\ (2) = 16.91, p < 0.05$ T = 152 r = -0.39			NS		
Bleeding	$\chi 2\ (2) = 46.12, p < 0.05$ T = 40 r = -0.51			NS		
Lumps on straining	$\chi 2\ (2) = 26.95, p < 0.05$ T = 56 r = -0.44			NS		
Incomplete emptying	$\chi 2\ (2) = 26.26, p < 0.05$ T = 56 r = -0.39			NS		

Table 2-11 Comparison of participants by previous treatment

0 v 8 weeks	No previous treatment N = 76	Previous treatment N = 39
Pain on opening bowels	$\chi 2\ (2) = 19.20, p < 0.05$ T = 76 r = -0.33	$\chi 2\ (2) = 6.54, p < 0.05$ r < -0.3
Mucus/ slime	$\chi 2\ (2) = 22.11, p < 0.05$ T = 66.5 r = -0.33	$\chi 2\ (2) = 9.41, p < 0.05$ r < -0.3
Itch/ irritation	$\chi 2\ (2) = 21.16, p < 0.05$ T = 147.5 r = -0.35	$\chi 2\ (2) = 11.65, p < 0.05$ T = 17.5 r = -0.50
Pain affecting QoL	$\chi 2\ (2) = 19.92, p < 0.05$ T = 176.5 r = -0.42	$\chi 2\ (2) = 16.64, p < 0.05$ r < -0.3
Other Sx affecting QoL	$\chi 2\ (2) = 23.23, p < 0.05$ T = 235 r = -0.42	$\chi 2\ (2) = 18.90, p < 0.05$ T = 54 r = -0.36
Total Score	$\chi 2\ (2) = 51.52, p < 0.05$ T = 103 r = -0.54	$\chi 2\ (2) = 9.49, p < 0.05$ T = 43 r = -0.38

Table 2-12 Effect of previous treatment on change in symptom scores

0 v 8 Weeks **n = 52**	$\chi 2(2)$	**Size of effect**
Pain when opening bowels	18.72	T = 68, r = -0.36
Pain when not opening bowels	22.56	T = 48, r = -0.36
Bleeding	46.22	T = 27, r = -0.51
Lumps on straining	33.10	T = 18, r = -0.48
Itch/ irritation	29.57	T = 81, r = -0.42
Mucus/ slime	36.43	T = 14.5, r = -0.40
Incomplete emptying	20.84	T = 39.5, r = -0.35
Total score	65.20	T = 39, r = -0.58
Pain affecting QoL	35.20	T = 41.5, r = -0.51
Other symptoms affecting QoL	39.08	T = 51.5, r = -0.55

Table 2-13 Analysis of group not requiring further treatment.

2.5 *Summary of Results*

The haemorrhoid PROM demonstrated high values of Cronbach's alpha before rubber band ligation (0.832), four (0.862) and eight (0.885) weeks after rubber band ligation; and therefore internal consistency is high. This suggests that the covariation in the items reflects an underlying dimension that may be more important than any single item.

Data from 22 consecutive patients with haemorrhoids, assessed and re-assessed after 24 hours, were used to estimate the test-retest reliability of the haemorrhoid PROM. The intraclass correlation coefficient for the total score was 0.987 (0.970 – 0.995) and denotes a high level of reliability.

Results from the validation studies during phase II, are based on 115 patients completing the 8 symptom items and the 2 quality of life visual analogue scores. The Spearman correlation coefficient of the total score to the quality of life affected by pain score was 0.629 prior to RBL, 0.720 at four weeks post RBL and 0.664 at eight weeks post RBL all with a significance value of < 0.001. The Spearman correlation of the total score to the quality of life affected by other symptoms score was 0.569 prior to RBL, 0.744 at four weeks post RBL and 0.670 at eight weeks post RBL all with a significance value of < 0.001. The moderate to strong correlations suggests that the items have a common underlying dimension.

Validity was further verified by comparing healthy volunteers to the haemorrhoid patient group. The healthy volunteer group (Mdn = 0.00) had a significantly lower total symptom score than the pre-RBL patient group (Mdn = 19.00), $W_s = 112.0$, $p < 0.001$, $r = -0.48$; than the 4-week post-RBL patient group (Mdn = 15.00), $W_s = 150.5$, $p < 0.001$, $r = -0.49$, and the 8-week post-RBL patient group (Mdn = 7.50), $W_s = 231.5$, $p < 0.001$, $r = -0.40$.

All items within the haemorrhoid PROM demonstrated significant changes eight weeks after rubber band ligation, particularly bleeding, lumps on straining, itch or irritation, the quality of life scores and the total score. Analysis by gender demonstrated that the changes in pain scores were more likely to be due to female participants, although males still demonstrated significant changes in the quality of life score affected by pain.

Analysis by degree demonstrated that the changes in bleeding score were significant amongst first, second and third degree haemorrhoid participants. Significant changes were demonstrated for second and third degree haemorrhoids with the lumps on straining, pain when not opening bowels, mucus or slime, or sensation of incomplete emptying items.

In the group of patients that required further treatment after the eight-week period, no significant decrease in any of the item scores was demonstrated.

2.6 DISCUSSION

The aim of this part of the thesis was to develop and validate an evaluative PROM, specifically for haemorrhoidal disease. Phase I of this study was comprised of item selection, item reduction and testing leading to modification of the initial HSI-1. The decision to remove items from HSI-1 if 50% or more of the patients had not experienced the item at all (a score of zero) is an inherently subjective judgement, and was made following discussion with a public health expert. Similar judgements have been made in the development of an irritable bowel syndrome QoL measure [127]. Other investigators [128] have chosen 30% as a cut-off level, in the assessment of patients with oesophageal cancer. Eypasch et al., used 25% in the development of the Gastrointestinal Quality of Life Index [94].

Phase II involved construction, administration and analysis of the haemorrhoid PROM. One of the changes in the content was the approach to scaling of the items; this was extremely important to ensure that the PROM would be able to detect change in the outcome measures following rubber band ligation.

Scaling of the items needed to be decided on the basis of the proposed use of the PROM as well as the natural history of haemorrhoids. Very little is known about the day-to-day changes of symptoms in individuals with haemorrhoids, and therefore the scaling of items was modified, increasing the response options on the scale to increase item responsiveness [85], on the basis that the intended use is evaluative.

Using an adjectival scale is not as reliable as a more objective numerical measure, particularly if the intention is to measure outcomes following an intervention. Interpretation of phrases such as "sometimes" and "frequently" are likely to differ even within the same individual at different times, particularly as symptoms change [129, 130].

To encourage accurate assessment of symptom burden, the items were scaled on the basis of time. The choice to use frequency of symptoms rather than a descriptive response scale has also been made in the investigation of outcomes following haemorrhoidal surgery [131]. This study reported a reduction in symptoms following PPH and diathermy haemorrhoidectomy, however although the investigators stated that the bowel function questionnaire completed by participants was validated [132, 133], no publication was identified in which validation studies were presented.

Internal consistency for the haemorrhoid PROM is high with values of Cronbach's α above 0.8 at all time-points in the study. A more sophisticated method of measuring scale reliability is to use Cronbach's α. According to DeVellis [134], the range of possible values may be interpreted as follows: less than 0.6 is unacceptable; between 0.6 and 0.65 is undesirable; between 0.65 and 0.7 is minimally acceptable; between 0.7 and 0.8 is respectable; and above 0.8 is very good.

Golden *et al.*, [135] advise that α should be calculated on a sample at least twice as large as the number of scale items, however this may not be sufficient if there are only a few scale items. Streiner and Norman [136] suggest that if α is greater than 0.9, there is likely to be items that are duplicating each other. It is argued that in these circumstances the scale can be reduced to improve ease of use by the participant.

However Cortina [137] notes that such general guidelines need to be used with caution because the value of α depends on the number of items in the scale. It is possible to get a large value of α because there are a lot of items in the scale, rather than the scale being reliable in itself.

Kirshner and Guyatt [85] discuss the rationale for performing internal consistency measures in evaluative indexes. Cronbach's α is based on the

assumption that the accuracy of the index will increase with the covariance of the items and the number of items. This is true of a discriminative index but not of an evaluative one. Items in an evaluative index do not need to correlate with each other at a single point in time, but must be consistent in the way they measure change in health status between two points in time. Increasing the number of items in an index, whether they correlate well with each other, can increase the chance of including items that are not sensitive to efficacious treatment. Random error will be introduced, obscuring treatment effect, and increasing participant burden.

All instruments purporting to be measuring aspects of health or disease must produce the same results under the same conditions. Reproducibility assessed by intraclass correlations was high as should be expected, particularly as the PROM was re-administered after one day. The short time period between completion of the PROM is a possible source of bias, as the patient is more likely to recollect their response, but as little is known of the natural history of haemorrhoidal disease, it was deemed to be appropriate to exclude variability due to genuine change in haemorrhoidal disease status.

There is still considerable debate [138] about the choice of method for measuring agreement of continuous data, and therefore both intraclass correlation coefficient and limits of agreement were used to assess reproducibility. The advantage of the ICC is that it measures both the variation between subjects in the study and variation between the observers [139] i.e. the results from the two PROMs.

Validity of a patient based outcome measure is complex because instruments are measuring an inherently subjective phenomenon [140]. Face validity examines whether an instrument appears to be measuring what it is intended to measure [141]. There is no formal method for evaluating face validity [142]. Guyatt and Cook stated that evaluation of the level of relevant expertise involved in generating the content of an instrument is important in the evaluation of face validity [143]. This part of the thesis involved input by a public health physician who has extensive experience of developing and validating outcome measures [144-147] as well as an academic colorectal surgeon with similar experience [148, 149].

The other criterion is the involvement of patients in the generation and confirmation of the instrument's content [150], which was not evaluated in this study. This may represent an area of future development if the haemorrhoid PROM were to be used as a predictive index of measurement, i.e. as a tool in the choice of management modality.

By definition, criterion validity cannot be truly examined because a gold standard is not available for comparison, however it is generally acknowledged that in these circumstances a reference test is one that is generally acknowledged to be the best test available.

Therefore the next step is to examine construct validity, which refers to the extent to which a measuring instrument correlates with measures of other variables that are predicted by, or make sense according to a theory of how the variables are related [142]. This requires examination of the extent of agreement of patient-reported scores with laboratory or clinical measures of disease severity [151], or of the ability of the instrument to distinguish between patient groups [152].

In this study validity was examined in several ways. First, although the haemorrhoid PROM is intended to be an evaluative measure, it is important to verify that healthy volunteers did not score high values in the haemorrhoid PROM. This was confirmed at all time-points of completion of the PROM by the patients, thus confirming that the PROM can also discriminate between patients and healthy volunteers.

The second form of validation was to assess correlation of the individual items with quality of life scores. There are no agreed standards for how high correlations should be between an instrument and other variables in order to establish construct validity [142]. McDowell and Newell have stated that correlation coefficients of 0.60 may be strong enough evidence to support construct validity [153], however validated studies have used a value of 0.40 [127].

Although higher values of correlation coefficient were identified for the pain scores and total scores, the bleeding and itch/ irritation items did not correlate well with the QOL score affected by other symptoms. It appears that although bleeding and itch/ irritation are common symptoms described by haemorrhoid patients, its impact on quality of life is not as significant as

the other symptoms within the haemorrhoid PROM. One can postulate that by placing all symptoms other than pain into one group, the patient is more likely to rank other symptoms such as prolapse as more important to the overall effect on quality of life.

Further validation of the PROM was evaluated by comparing patients who clinically required further treatment with those did not. It is encouraging to note that there was a significant decrease in all items except itch/ irritation with moderate sized effect. Higher sizes of effect ($r > 0.5$) were demonstrated with bleeding, the total score and quality of life scores.

Comparing the item and total scores between varying degrees of haemorrhoids produced some interesting and encouraging trends. As would be expected patients with first-degree haemorrhoids demonstrated both lower scores and low responsiveness to intervention for the items lumps on straining. Similar results for pain when not opening bowels, sensation of incomplete emptying and mucus or slime are all more likely to be related to larger haemorrhoids i.e. ones that prolapse.

Of interest significant decreases in the bleeding scores were identified in all degrees of haemorrhoids, which does not correspond with the majority of previous discussions of classification [69, 74, 77], apart from that reported by Lunniss and Mann [70, 71].

Responsiveness of the entire patient group was also demonstrated for all of the items and the total score with a moderate size effect. This satisfies an important aspect of developing and validating an evaluative measure, which must demonstrate within subject longitudinal change [85]. There are a variety of methods for assessing responsiveness which include, examination of improvement in scores following application of a treatment of known efficacy [85] as used in this study, correlation with change in other scores [89], modified standardized response mean [154], sensitivity and specificity of change scores [155]. The alternative methods require a physiological or other clinical measure to compare to, independent evidence that the patient is clinically stable, or an independent standard to determine true change in a patient [142]. All of these methods require some form of independent measure, which has a similar role to that of a gold standard for evaluating criterion validity.

In conclusion this study represents encouraging findings and the statistical analyses supports preliminary validity of the haemorrhoid PROM, however it is acknowledged that there were weaknesses in the study. The study population was relatively small, and indeed development and validation of a QOL-related PROM can take several years [156] and involve extensive numbers of patients.

3 THREE-DIMENSIONAL ULTRASOUND AND POWER DOPPLER IMAGING

3.1 INTRODUCTION

Before discussing the possible methods of assessing volume and vascularity of haemorrhoids by using three-dimensional (3D) ultrasound (US) and Power Doppler (PD) imaging, it is important to discuss the use of two-dimensional (2D) ultrasound in anal canal imaging, and how it has progressed over the last thirty years.

3.1.1 Two-Dimensional Anal Endosonography

Anal endosonography (AES) was derived from the development of transrectal ultrasound of the prostate [157] and consequent US-guided prostatic biopsy [158]. Over the past thirty years AES has been used with increasing and more widespread skill to evaluate a spectrum of anorectal disorders.

US waves (2.5 – 15 MHz) are emitted from a piezoelectric crystal and depending on tissue characteristics the wave is absorbed, reflected or scattered. The reflected waves are transformed into an image. Transrectal probes designed for the prostate were found to be unsuitable for AES as they caused anatomical distortion and discomfort. Therefore high-frequency rotating probes protected by a sonolucent hard plastic cone with a maximum diameter of 2 cm were designed [159]. This technique gives a series of axial images as the probe is slowly withdrawn from the anal canal.

AES has been thoroughly investigated in healthy volunteers [160-162]. Several studies have established basic anatomy by making comparisons with cadavers [163, 164]. The puborectalis muscle, the medial part of the levator ani muscle, is easily visualized and serves as a point of orientation. It appears as a V-shaped echogenic (white) band, which slings posteriorly around the rectum.

As the probe is withdrawn this band closes anteriorly, thus forming the external anal sphincter (EAS). It takes on a different acoustic pattern, showing mixed echogenicity with a linear pattern, giving it a "streaky"

appearance. The thickness of the EAS is approximately 5–10 mm. In females, the anterior portion of the EAS is shorter and thinner, explaining its vulnerability to damage during childbirth. A negative correlation between age and EAS thickness has been demonstrated in a study of 150 nulliparous women aged between 19 and 80 years [161]. Other studies have failed to show the same results but suffered from significantly smaller numbers of participants [160, 162].

The internal anal sphincter (IAS) lies within the EAS and is seen as a thin homogenous hypoechoic (black) band, of approximately 1–3 mm in width. The IAS increases in thickness with age in both patients and healthy volunteers.

The submucosal layer is of mixed echogenic appearance and is collapsed as a result of the pressure of the endoanal probe. There is some evidence that the submucosal layer is thicker in patients with haemorrhoids [165]. It has also been reported that small hypoechoic areas are seen predominantly at the 3, 7 and 11 o'clock positions, which in the authors' opinion represented venous channels [161]. The mucosa cannot be consistently identified as a separate layer, due to the compression of the probe and the frequencies used.

The longitudinal muscle when seen appears as a mixed echogenic layer. One group were able to distinguish this layer from the EAS in 40 % of women [166]. Frudinger et al did so in 67% of the normal female volunteers studied. There is no correlation between thickness of the longitudinal muscle and age.

3.1.2 Three-Dimensional Ultrasound

Conventional US provides 2D views of 3D structures that an experienced ultrasonographer has to dynamically examine in order to create their own 3D impression of the object of interest [167]. In contrast, 3DUS allows the simultaneous assessment of individual sectional planes, which dependent upon the particular field of interest may be examined in one of several different viewing modalities to maximise the information available and improve spatial awareness [168, 169]. Uniquely, 3D US allows demonstration of the coronal plane perpendicular to the transducer face

facilitating the identification of surface irregularities, which can then be accounted for during volume measurement [170].

3.1.2.1 Data Acquisition

All 3D US techniques rely upon production of a composite of multiple 2D scan images. Computing software is then used to fill in the gaps or 'interpolate' between these images to produce a solid volume. There are several methods available for the acquisition and subsequent display and assessment of 3D US data.

Many commercially available systems (e.g. Siemens SieScape™) and fully freehand image acquisition and offline computer processing techniques are available. These assume that the acquired images are equidistant and parallel, which is rarely true. Alternatively, electromagnetic position sensing devices precisely locate the ultrasound transducer while scanning freehand. This is described as a 'six-degrees-of-freedom' method as it provides three-dimensional co-ordinates in addition to angulation in three dimensions.

Whilst relatively complex, largely due to the need to calibrate the position-sensing device, this method is highly accurate [171, 172]. Mechanical transducer arms (e.g. TomTec™) ensure the acquisition of perfectly parallel images at predefined linear intervals but are less well suited to non-linear objects [173].

Probably the most commonly used and reported technique involves the use of purpose built phased array ultrasound transducers. These transducers fan or rotate the ultrasound beam and acquire two-dimensional images at predefined intervals, described as the 'swept-volume' technique. Abdominal transducers produce a pyramid-shaped volume and vaginal transducers a cone-shaped volume (fig 3-1). This allows the exact spatial co-ordinates of 2D images to be incorporated and an accurate volume to be created. They are easy to use and produce standardised volumes of densely sampled data without irregular gaps. They have been measured to have a mean absolute error of around 1% for distance and 6.4% for volume under experimental conditions using tissue-mimicking ultrasound phantoms in a

water bath [174]. Their main limitation is the maximum volume that can be measured due to the position and size of the transducer.

3.1.2.2 Data Analysis

When one thinks of 3D imaging in terms of its measurement capability the most obvious parameter considered is that of volume. Whilst volume may be estimated from measurements made with conventional 2D US, such measurements use various formulae based upon certain geometric assumptions [175]. Volume estimation based on 3D US still involves a degree of geometric assumption, as data are reconstructed based upon their most probable position within a Cartesian grid system, but utilises much more information. There are two basic methods employed to calculate volume from a 3D dataset: the conventional 'full planar' or 'contour' method and the more recently introduced 'rotational' method possible through Virtual Organ Computer-aided AnaLysis (VOCAL™) which also generates a 3D model of the object of interest [176]. Both techniques involve manual delineation of the object of interest in the multiplanar display that shows the three perpendicular planes characteristic of 3D US.

3D US can also be used to acquire vascular information through the simultaneous application of Doppler US. Conventional colour Doppler is not suited to 3D imaging due to the continual changes in colour induced by variations in blood flow velocity and direction [177]. PD produces a more stable image that facilitates data acquisition and assessment particularly of longer vascular segments, which are displayed continuously on screen [178]. This information is acquired as the US beam is swept through an angle determined by the observer dependent upon the size and position of the object of interest. The Power Doppler signal may then be quantified by one of several currently available software programmes.

The vast majority of the medical literature reports the use of the 'histogram' facility within 3D View and more recently 4D View (GE Kretz, Zipf, Austria) [179] (fig 3-2). This calculates three indices of vascularity based upon the signal intensity within, and distribution of, colour voxels within the defined volume, where a voxel refers to a volume element or three-dimensional pixel. The Vascularisation Index (VI) reflects the ratio of

Power Doppler information within the total dataset relative to both colour and grey information. The Flow Index (FI) represents the mean Power Doppler signal intensity, and the Vascularisation Flow Index represents a combination of the two [180]. The VI is presented as a percentage figure, and although the FI and VFI may range between 0 and 100 they are generally quoted without units.

3.1.3 Transperineal Ultrasonography

First described in 1974 [181] transperineal ultrasonography (TPUS) has been used in a wide variety of clinical settings. These are listed in table 3.1. Several investigators have presented evaluation of anal sphincter anatomy, defects, and perianal pathology through a transperineal approach [182-193]. A selection of transducers have been used including transvaginal, linear and curved linear with varying frequencies, between 3 and 12 MHz.

The transperineal approach has several potential advantages over AES, including absence of distortion of the anal canal by the transducer during examination, visualization of perirectal processes several centimetres from the rectal lumen, multiplanar view if using 3D US or sagittal views by turning the transducer through 90 degrees, and greater acceptability to the patient, especially when pain or diminished size of the anorectal lumen is an issue.

Disadvantages include limited penetration above the caudal 5cm of the rectum and potential contact problems with air, depending on the shape of the transducer. AES may also provide more detailed information because of higher resolution and closer contact to the examined tissue.

The EAS appears as a hyperechoic ring and the proximal part is adjacent to the sling of the puborectalis, which is hyperechoic as well. The mucosa and submucosa are clearly evident as the hyperechoic central portion surrounded by the hypoechoic IAS.

Only one published study has documented the thickness of the IAS and EAS on both TPUS and AES. Females (n = 64) who had been referred for urinary incontinence, with no previous history of anorectal surgery, were scanned by both methods. The mean thickness of the IAS was 2.1 ± 0.8 mm and 2.8 ± 0.7 mm on AES and TPUS respectively. The mean thickness of

the EAS was 6.2 ± 1.5 mm and 5.6 ± 1.8 mm respectively. Statistical analysis by t-test showed a significant difference between EAS and TPUS for both the IAS ($p < 0.0001$) and EAS ($p < 0.039$). TPUS identified two more defects within the sphincters than EAS, but this was not statistically different. These defects were not confirmed surgically and the authors did not question their patients about symptoms of faecal incontinence [194].

Speciality	**Clinical Presentation**
Obstetrics [191]	Placenta praevia Incompetent cervix Preterm labour Presenting part of foetus
Paediatrics [183, 186, 190]	Urethral obstruction Anorectal anomaly Ambiguous genitalia Vaginal anomaly Presacral mass Traumatic priapism
Gynaecology [182, 185, 188, 192, 193, 195]	Pelvic floor (static/ dynamic) Stress incontinence Neoplasia Infertility Sphincter evaluation
Surgery [187, 189, 194]	Perianal fistula disease Sphincter evaluation Distal ureteric calculi

Table 3-1 Indications for transperineal ultrasonography.

3.1.4 The Use of Doppler Ultrasonography

The Doppler effect produced with ultrasonic frequencies has been used in medicine for almost fifty years. In that time, advances in technology have made it possible to use Doppler effect not only to determine whether flow is present but also to visualize flow in two and even three dimensions as well as providing semi-quantitative information.

The shift in frequency is related to the contraction or expansion of wavelengths ahead of or behind the sound-emitting object. Because US is used in a transmit-echo approach, there is a Doppler effect with the sound arriving at the scattering object and a Doppler effect as the sound is reflected from that object back toward the US transducer. In US the round trip for sound is related to the depth and speed of sound in tissue. The Doppler equation is denoted by

$$fD = \Delta f = \frac{2.f_0.v_{rbc}.\cos\theta}{c}$$

Equation 3-1 The Doppler equation.

fD is the Doppler shift frequency, f_0 is the transmitted frequency, v_{rbc} is velocity of the red blood cell, θ is the angle between the direction of sound propagation and the motion of the particle and c is the speed of sound in tissue (assumed to be 1540 msec-1). Hence the velocity of red blood cells can be derived.

The application of this equation in basic US equipment will produce estimates of the blood flow velocity from the frequency shifts within the lumen and the variation of blood flow velocity within the cardiac cycle [196].

3.1.4.1 Continuous Wave Doppler

In this form of Doppler, sound is emitted from a transmitting transducer continuously. A second receiving transducer must detect sound that echoes back. The two transducers are arranged to overlap their beams, resulting in a region of interest (ROI) where the Doppler shifted signals may be detected.

3.1.4.2 Pulsed Wave Doppler

Pulsed sound is used instead of continuous sound. Pulsed wave Doppler US is also referred to as duplex Doppler US. This refers to the fact that the instrument shares time and interrogation of acoustic pulses with a B-mode operation, thereby providing both a B-mode image (2D) and pulsed-wave Doppler information.

A pulsed wave instrument uses a single transducer in pulse echo mode, and this is typically the same transducer used for B-mode imaging. The transducer is used to transmit a pulse down an axis defined by the operator. A train of pulses (8 to 20 pulses sent sequentially) is transmitted down the axis to sample a volume at a depth defined by the transducer beam width and the range gate.

The range gate, which can be adjusted by the operator, is the means by which returning echoes from a particular range in time are separated out for analysis by the Doppler instrumentation. The operator is also able to adjust the angle between the ultrasound beam axis and the primary direction of blood flow in the vessel. There are higher errors in velocity estimation as the angle approaches 90°. This adjustment of the Doppler angle by the operator corrects the calculated velocity. Doppler angles between 30° and 60° are easiest to image while providing velocity estimation with a minimal error.

The returning Doppler frequency shifts are electronically converted by a mathematical technique, fast Fourier transformation, and displayed against time as a waveform. This waveform, which represents changes in blood flow velocity throughout the cardiac cycle, can be analysed to generate indices of blood flow in terms of the absolute flow velocities during peak systole and diastole as well as providing an indication of the resistance to flow over the whole cardiac cycle. Two formulae are used to calculate the degree of resistance to flow: the Resistance Index (RI) and the Pulsatility Index (PI).

$$RI = \frac{PSV - EDV}{PSV}$$

Equation 3-2 The RI or Pourcelot's ratio.

PSV is peak systolic velocity, EDV is end diastolic velocity. The index ranges from 0 to 1.00 with the latter occurring in the absence of end diastolic flow [197].

The RI is easily measured by defining the maximal systolic flow velocity and the end-diastolic flow velocity as two separate points. The PI is calculated by the on-board computer following manual delineation of the complete waveform over three to four consecutive and comparable cardiac cycles.

$$PI = \frac{PSV - EDV}{V_m}$$

Equation 3-3 Calculation of the PI.

PSV is peak systolic velocity, EDV is end diastolic velocity. V_m is the mean velocity [198].

The PI has the advantage therefore of taking into consideration more of the frequencies within any given waveform.

3.1.4.3 Colour Doppler

Colour flow imaging takes the pulsed-wave Doppler concept a step further by using Doppler frequency shift detection over a set of range gates along a number of acoustic lines. The result is a 2D image depicting flow that is superimposed on the 2D grey-scale image generated from backscattered echoes.

It is important to provide real-time colour flow imaging. Shorter interrogation pulses are used to achieve this. Pulsed-wave Doppler uses 8 – 20 pulses, whilst colour Doppler uses 2 – 4 pulses for each line in the colour flow image. This means that colour Doppler is less sensitive to flow, at lower flow rates and in smaller vessels compared to pulsed-wave Doppler ultrasound.

Colour Doppler is a measure of the directional component of the velocity of blood moving through a sample volume. It suffers from inherent limitations including a tendency for noise to overwhelm the flow signal if the

gain is too high or the Doppler display threshold too low, Doppler angle dependence and aliasing.

Aliasing occurs as a result of sampling of data at discrete points in time, in particular when the rate at which interrogating pulses are sent to obtain the phase shift information is less than twice the value of the Doppler shift frequency. The data points in the sample and hold circuit are obtained at specific intervals in time (ΔT). Two samples or less per period of the maximum frequency will result in an erroneous lower frequency being reconstructed from the sample and hold data.

The sampling rate also known as the pulse repetition frequency (PRF) and is dictated by the depth of the range gate in the body, and therefore by the round trip time (RTT) between the transducer and the range gate depth. This is expressed as

$$PRF = \frac{1}{RTT} = \frac{c}{2.range\ gate\ depth}$$

Equation 3-4 Calculation of pulse repetition frequency.

Where PRF is samples per second, RTT is the round trip time in seconds, c is the speed of sound propagation in tissue (1540 msec-1), and range gate depth is in metres.

3.1.4.4 Power Doppler

This is a variation of colour flow imaging, where instead of depicting the mean Doppler frequency shift, the Doppler shift frequencies are summed up. The hue and brightness of the colour signal represents the power in the Doppler signal, which is related to the number of red blood cells producing the Doppler shift. Colour flow imaging depicts both the velocity and direction of flow, but the power mode imaging depicts only the intensity of the Doppler shift. The advantage of power Doppler (PD) is that slow flow rates and small vessels are more easily depicted in comparison to colour flow imaging [199].

Power Doppler displays several advantages over colour Doppler. The main advantage is the increased gain that can be employed. In power Doppler, noise is assigned to a homogeneous background, even when gain is increased greatly over the level at which noise begins to obscure a colour Doppler image. In colour Doppler noise appears as a random colour totally

obscuring any information-containing signal. This is a result of inherent differences in the information being displayed when colour and power Doppler images are produced.

Noise is extraneous, unwanted signal that invade the electrical or optical system in use. Doppler noise is a random process and therefore has a random phase angle. The frequency shift in colour Doppler is dependent on the rate of change of the phase angle, and therefore noise can appear as flow from any direction and of any velocity.

Noise has a very different appearance in power mode. Noise has a very low power when compared to information-containing signal and assumes a uniform appearance, whereas information-containing signal appears as a different colour. Power Doppler uses more of the available dynamic range when producing flow images, thus increasing a machine's flow sensitivity [200].

Another advantage of Power Doppler over colour Doppler is that it is essentially angle independent. Initially this is difficult to understand when studying the Doppler frequency equation (equation 3-1). The number of cells, which cause scatter, at any given location is angle independent. Once the number of cells has been dictated by physiological circumstances, the power Doppler signal appears the same from any direction as long as a Doppler shift is detectable.

Another advantage of power Doppler is that it may also be used to objectively assess vascularity through the quantification of the signal amplitudes following the development of various image analysis computer software programmes [201]. Therefore the main role of power Doppler imaging is to define the position and distribution of vessels within any given field and to demonstrate the presence of flow within them [202]. By displaying background noise as a uniformly colour readily distinguished from true flow the usable dynamic range is extended and the sensitivity enhanced [203]

3.2 AIMS

The aim of this study was three-fold. Primarily it was to establish a reliable method of imaging the anal canal including haemorrhoids in patients and anal cushions in healthy volunteers using three-dimensional Doppler US. The second aim was to assess methods for semi-quantification of vascularity of haemorrhoids and anal cushions. The final aim was to assess the effect of rubber band ligation treatment on the vascularity of the haemorrhoidal zone.

3.3 METHOD

The methods section is divided into three parts. The first phase focuses on early work, which determined the optimum equipment and technique for obtaining US images and Doppler studies of the anal canal, anal cushions and haemorrhoids. The second phase examines the choices available for measurement of volume and vascularity from 3D US datasets. The third phase focuses on analysis of 3D Doppler US studies, including accuracy of software measurement techniques, potential changes in Doppler measures over time, following treatment, and possible correlation with symptom scoring in healthy volunteers and patients.

3.3.1 Ethics

Ethical approval to image thirty patients was gained from the Nottingham Research Ethics Committee 2 (part of the Central Office for Research Ethics Committees). Concurrent approval was also given by the Research & Development Department at Nottingham University Hospital NHS Trust. Approval was given by the University of Nottingham Medical School Ethics Committee to scan healthy volunteers.

3.3.2 Equipment

The choice of Doppler modality was limited to the availability at NUH NHS Trust and the University of Nottingham. Nurture is the infertility treatment centre based in NUH NHS Trust and owns a Voluson 730 Expert® machine capable of 3D US, duplex Doppler and Power Doppler

imaging. I have been very fortunate in having access both to the machine and the time of the staff within Nurture.

At the beginning of the study, there were several questions to be answered. Which of the available modalities are the most appropriate for measuring blood flow in the anal canal: pulsed wave Doppler or power Doppler? Secondly would it be possible to carry out endoanal scanning without compressing the haemorrhoids and therefore altering blood flow in the region? Finally the only probe initially available for use was a transvaginal probe, and the question here was how suitable this would be for endoanal scanning.

All scans have been carried out on the same Voluson® 730 Expert machine and with the help of the senior untrasonographer from Nurture, Jeanette Clewes, and consultant gynaecologist Nicholas Raine-Fenning.

3.4 METHOD PHASE I: Determination Of Approach and Ultrasound Technique

3.4.1 Experimental Design 1

A 47 year-old patient with second-degree haemorrhoids was positioned in the left lateral position, with the hips and knees flexed. An attempt was made to pass an Eisenhammer retractor to allow placement of the endovaginal probe adjacent to each haemorrhoid. Unfortunately the patient could not tolerate this part of the procedure, and therefore the 7.5MHz endovaginal transducer (RIC 5-9) of 2.5cm diameter was inserted into the anal canal without being able to verify it's exact depth.

Angling the thumb depression of the transducer towards the 12, 3, 6 and 9 o'clock lithotomy positions, pulsed wave Doppler was used to assess blood flow in the region.

3.4.2 Experimental Design 2

Three male patients were examined in this experimental design. The first two patients, aged 42 years and 55 years, were undergoing PPH, and

therefore were scanned under a general anaesthetic. The third patient aged 77 years attended prior to undergoing a haemorrhoidectomy.

Prior to scanning the patient a disposable proctoscope had been marked with 1 cm graduations. The distance from the distal level of the haemorrhoids to the anal verge was measured. The sheath covering the endovaginal transducer had also been marked with 1 cm graduations, and therefore the transducer was placed into the anal canal just below the haemorrhoids. The transducer's thumb depression was orientated to the 12 o' clock position. Every effort was made by the researcher to limit movement of the transducer. The third patient was asked to remain as still as possible.

3.4.3 Experimental Design 3

An endoanal probe (RRE 6-10), lent by GE, was trialled in this experimental design. A 48 year-old female with second-degree haemorrhoids was positioned in the left lateral position. The endoanal probe was placed 3cm into the anal canal, at the level of the haemorrhoids at the 3 o'clock lithotomy position. A 3D power Doppler dataset was acquired on the slow speed sweep mode with a pre-determined angle of 120 degrees, with a set depth of 0.5cm. This was repeated at the 7 and 11 o'clock positions. This process was repeated with the endovaginal probe.

3.4.4 Experimental Design 4

A 48 year-old female with second-degree haemorrhoids was scanned in the supine position with the hips flexed and abducted. The endovaginal probe was placed on the perineum of the patient, with the thumb depression in the 6 o'clock position, and the probe angled at approximately seventy degrees to the horizontal.

3D grey-scale datasets were acquired on the medium speed sweep mode, and 3D power Doppler datasets were acquired on the slow speed sweep mode. The probe was removed from the perineum and then replaced, and further acquisitions of grey scale and power Doppler datasets were made.

3.4.5 Determination of power Doppler settings

A further part of the initial study was designed to establish the best power Doppler settings for examination of the anal canal. This was performed by adjusting a single parameter, and maintaining the others at a constant level. The baselines used were the standard abdominal and penetration protocols saved on the Voluson® 730 Expert machine. 3D power Doppler datasets were acquired at each setting and then examined subjectively to determine the settings, which provided the clearest vascular information without creating artefact or exaggerating attenuation.

3.5 RESULTS PHASE I: Determination of approach and ultrasound technique

3.5.1 Experimental design 1

Figures 3-3 and 3-4 are examples of the images acquired using pulsed wave Doppler. A scale with 1 cm markings is present on the left hand side of the screen. The most obvious feature of both images is the presence of gas-filled loops of bowel surrounded by multiple blood vessels, approximately 1 cm from the tip of the transducer.

Another feature is the presence of multiple large vessels that were both arterial and venous in nature (venous trace not shown). Most importantly it was not possible to see any anatomical landmarks such as the pubis and bladder.

In figure 3-4 a range gate had been positioned over one of the larger vessels, and an arterial waveform was clearly evident. To calculate indices of blood flow, the cursor is used to trace the waveform of at least three cycles. Indices of blood flow from pulsed wave Doppler include PSV, EDV, V_m, PI and RI. The values are shown in the bottom right-hand corner.

The process of tracing the waveform must be carried out during the scan. The resulting image and vascular indices must then be stored in Sonoview, the hard-drive of the 730 Expert. It is not possible to calculate the vascular indices once the image has been stored.

3.5.2 Experimental design 2

The aim of this experiment was to position the transducer in the anal canal, without compressing the haemorrhoids, thereby imaging them in a more physiological state. Figures 3-5 and 3-6 show images acquired from pre-operative patients.

On assessing the images acquired from each of the three patients, it became clear that the quality of imaging was poor. It had been difficult to reproduce the same image in each patient. Maintaining the transducer in the anal canal at the required depth (2 – 4 cm) was awkward as the tone of the anal canal naturally ejects the transducer.

Although the transducer may not have been compressing the haemorrhoids, it is logical to assume that its presence will affect blood flow in the region.

3.5.3 Experimental design 3

The endoanal transducer (RRE 6-10) is normally used for imaging the prostate, and hence has a head angled at approximately 30 degrees to the handle. Unfortunately the quality of imaging was very poor, most likely due to malfunction rather than being inappropriate for the desired purpose. Therefore data was acquired using the endovaginal probe (RIC 5-9) (figs 3-7 to 3-9). The aim of this experimental design was to acquire power Doppler information from a ring of submucosa at the level of the haemorrhoids; hence the depth was set to 0.5cm.

Overall, the same problems were encountered as in experimental design 2. Maintaining the transducer within the anal canal at the desired depth was difficult. Angling the transducer, by orientating the thumb depression, to the 3, 7 and 11 o'clock positions was awkward and slightly uncomfortable for the patient. It was likely that there was an overlap of acquisition of data between the three 120-degree sectors.

3.5.4 Experimental design 4

At this point in the study, a literature search using the terms "three-dimensional", "3D", "ultrasonography" and "anal sphincter" produced several papers where the authors[184, 185, 192] had used the transperineal route to examine the pelvic floor and anal sphincters.

This particular technique appeared very attractive with respect to imaging haemorrhoids, as there would be no compression of the haemorrhoids or stretching of the anal canal. The approach was more likely to be acceptable to the patient or volunteer. These images were immediately convincing, particularly when viewing the transverse images (figs 3-10 and 3-11).

3.5.5 Choice of approach and ultrasound technique

On reviewing the experimental designs and the acquired images, the transperineal approach was judged to be the most successful. The axial transperineal images were the most similar to endoanal images, with respect to the surrounding sphincters. The mucosa and submucosa are seen as separate structures, and visual correlation to the proctoscopic appearances of anal cushions or haemorrhoids is apparent. Doppler signal was visualised in the submucosa (fig 3-11) of all the imaged patients. The technique was less invasive and did not involve compression of the haemorrhoids or dilatation of the anal canal.

3.5.6 Final power Doppler settings

When determining the most appropriate settings the three key factors considered were the total amount of power Doppler information within the final 3D dataset, the degree of attenuation, small vessel information at the level of the submucosa and the vessel clarity overall.

A fast acquisition speed was regularly associated with a subjective loss of power Doppler information relative to the medium and slow acquisition speeds. Little difference was seen between the medium and slower acquisition speeds although the latter was associated with a higher incidence of movement artefact.

Factor	Setting
Pulse Repetition Frequency	0.6
Power	100
Gain	-5.6
Wall Motion Filter	Low 1
Acquisition Speed	Medium

Table 3-2 Final settings used for all subsequent patient and volunteer studies.

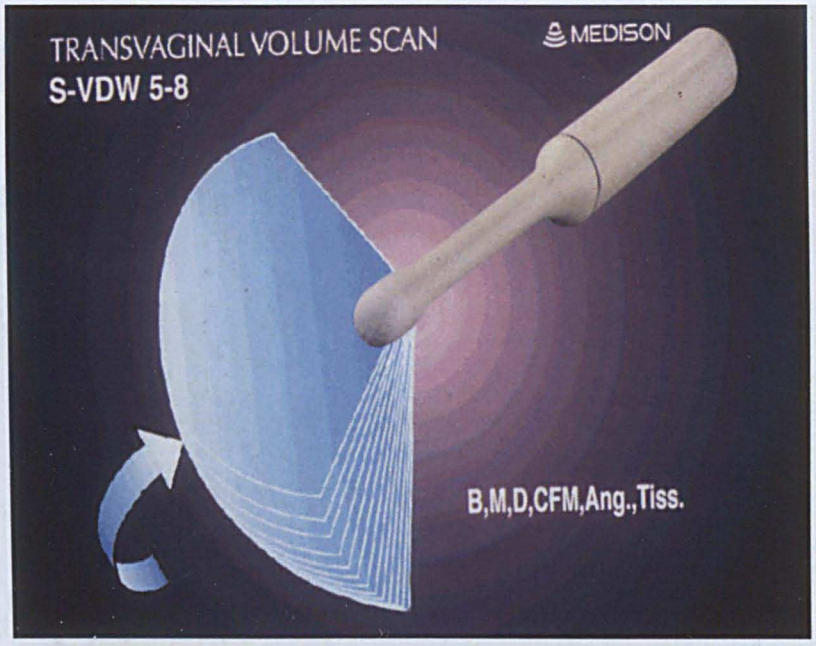

Figure 3-1 Automated method of 3D US data acquisition.

The US beam is directed to a starting point and then swept through an angle defined by the user, who's mid-point is the initial image on the screen. During this 'sweep' a series of 2D planes are acquired each with reference to the adjacent planes and equidistant between them. Image courtesy of Kretztechnik™, Zipf, Austria / Medison™, Seoul, Korea.

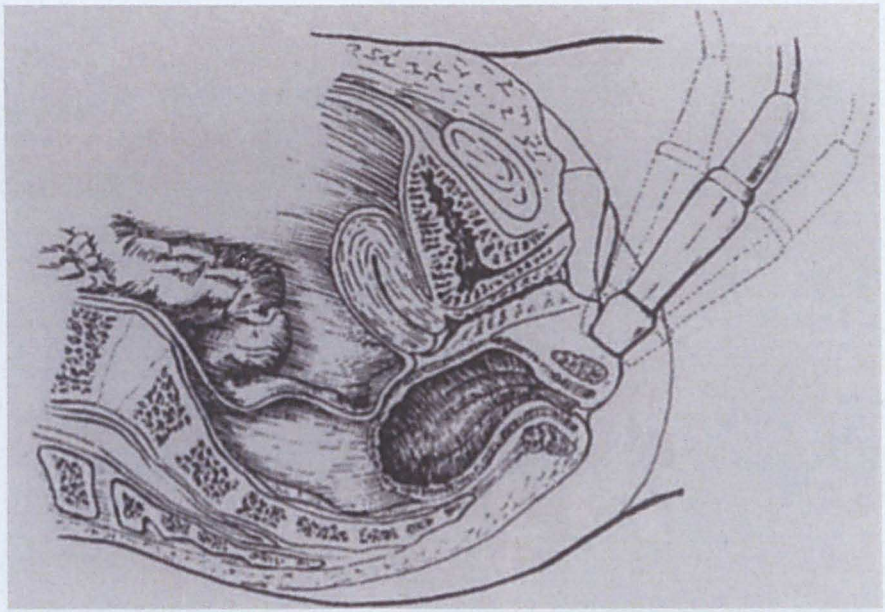

Figure 3-2 Transperineal ultrasound.

Perineal position of the probe to obtain different cross-sections of the anal canal. Reproduced from Kleinubing, H., Jr., et al., *Transperineal ultrasonography: new method to image the anorectal region.* Dis Colon Rectum, 2000. **43**(11): p. 1572-4. Image courtesy of Wolters Kluwer Health.

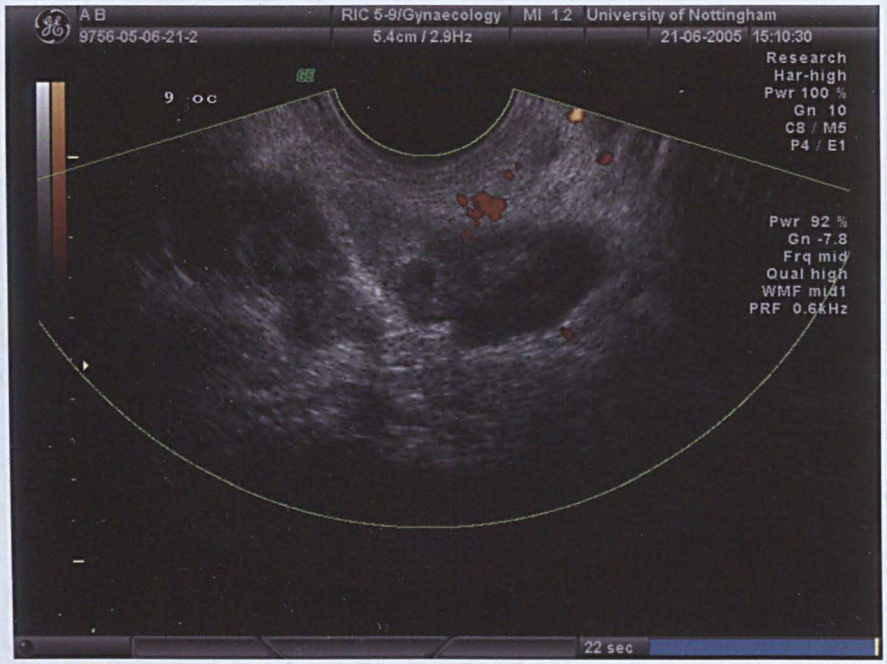

Figure 3-3 Experimental Design 1

Pulsed wave Doppler assessment of anal canal.

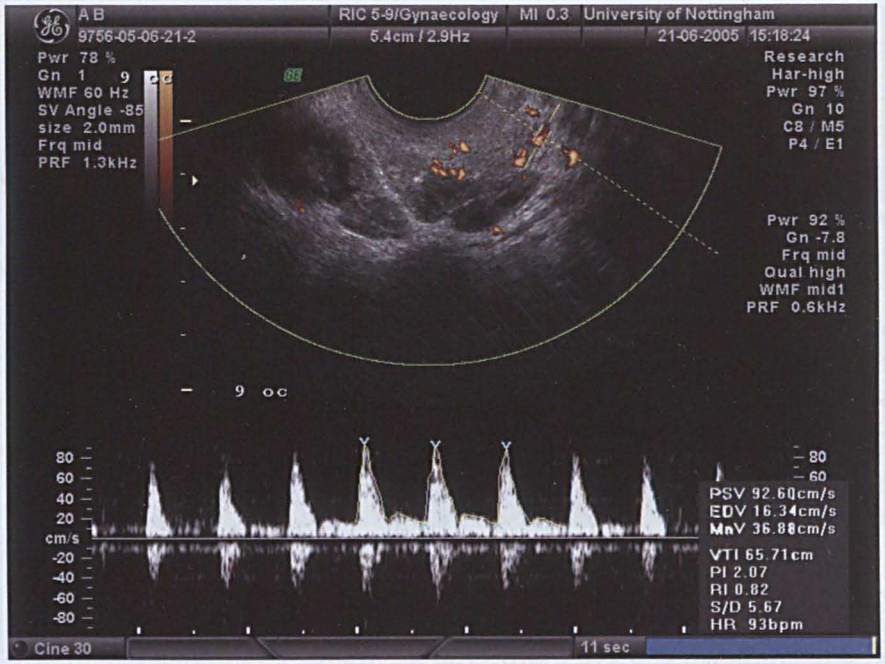

Figure 3-4 Experimental Design 1

Range gate applied to vessel. The waveform represents changes in blood flow velocity through eight cardiac cycles.

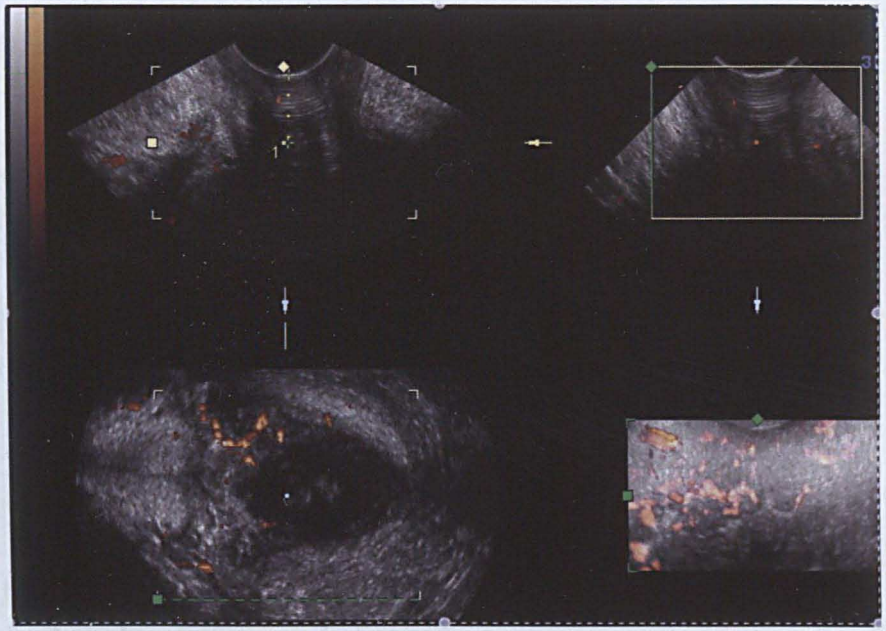

Figure 3-5 Experimental Design 2. 3D image acquired using power Doppler from a pre-operative patient.

The multiplanar display of the 3D ultrasound datasets demonstrates three mutually related orthogonal planes at 90-degrees to one another. The upper left image represents the longitudinal plane, the upper right image the coronal plane and the lower left image the transverse plane. The lower right image represents the amalgamation of all three planes.

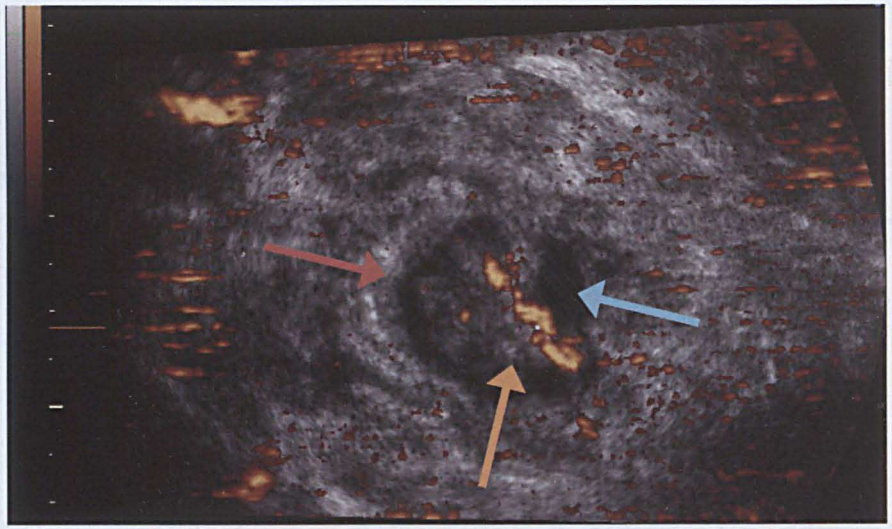

Figure 3-6 Experimental Design 2. Transverse image of third-degree haemorrhoids, acquired using 3D power Doppler.

The mixed echogenic central portion where there is evident blood flow could be interpreted as the mucosa and submucosa (yellow arrow). Therefore the surrounding hypoechoic area could represent the internal anal sphincter (blue arrow). It then follows that the surrounding hyperechoic area could represent the external anal sphincter (red arrow). Significant artefact is also noted.

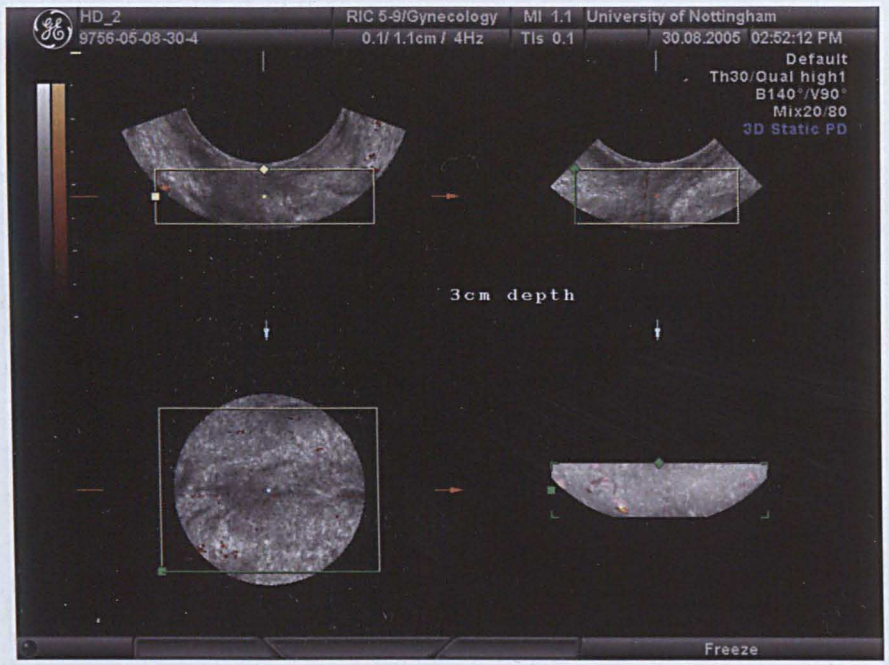

Figure 3-7 Experimental Design 3.

Power Doppler data acquired using a sweep angle of 120-degrees with a set depth of penetration of 0.5cm.

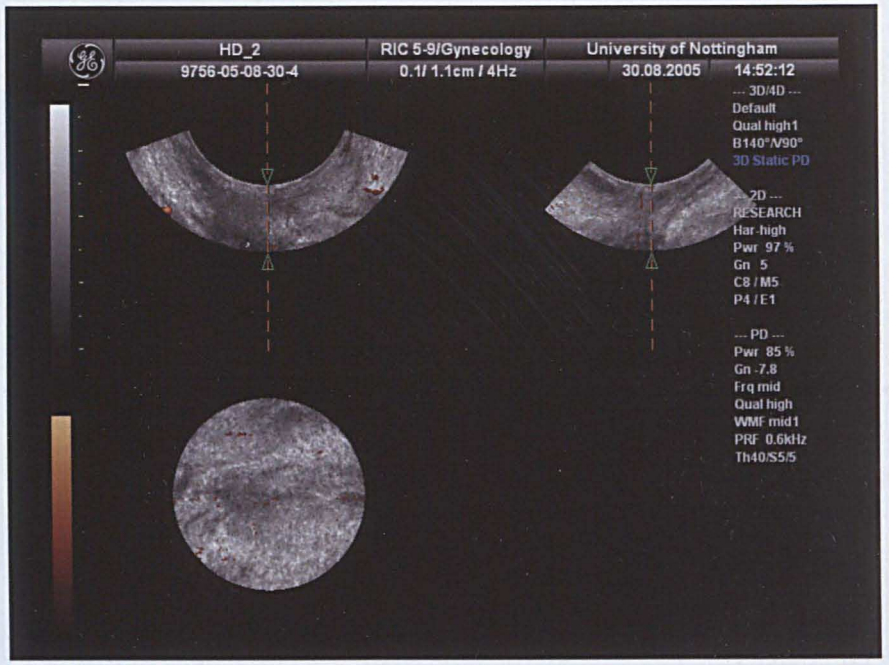

Figure 3-8 Experimental Design 3.

The rotation angle is selected (in the example above, 30 degrees) and the manual mode of measurement entered. The entire sector was then traced using a Graphire4™ pen and tablet until completion of 180 degrees of rotation and the generation of a calculated volume.

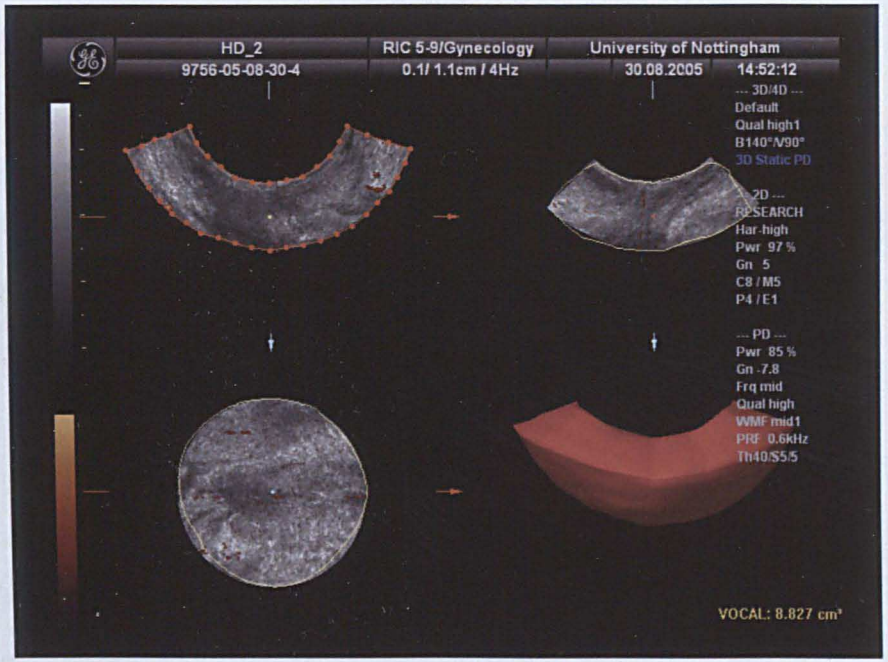

Figure 3-9 Experimental Design 3. The rotational technique of volume calculation.

The dataset has already been rotated through 180 degrees about the central axis. VOCAL gives the user the opportunity to adjust the manually delineated border. The resultant 3D model is shown in the lower right of the image, along with the calculated volume.

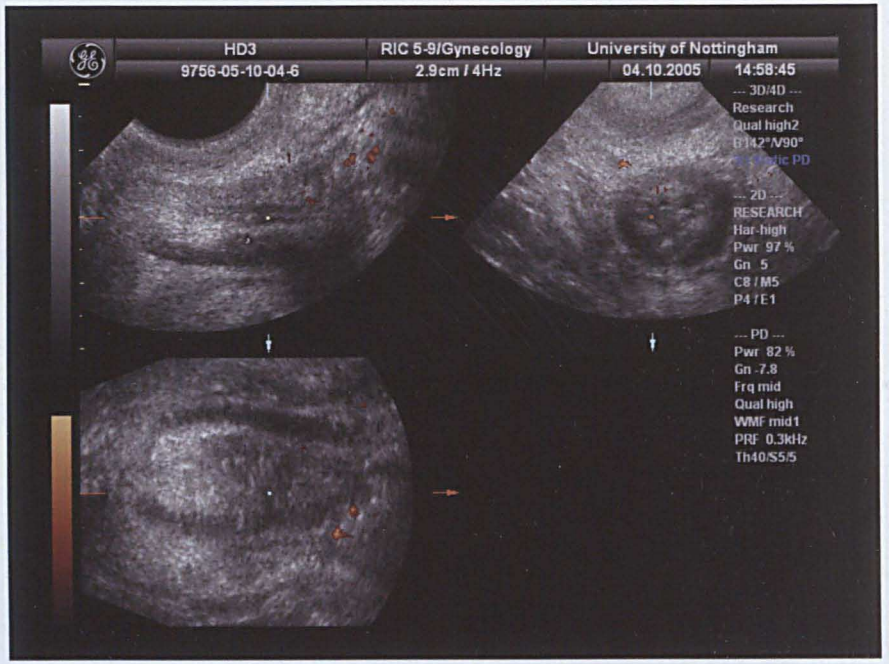

Figure 3-10 Experimental Design 4. Multiplanar view of anal canal using TPUS.

As the thumb depression had been orientated to the 6 o'clock position, the sagittal image is in the top left (A-plane), the transverse image in the top right (B-plane) and the coronal image in the bottom left (C-plane).

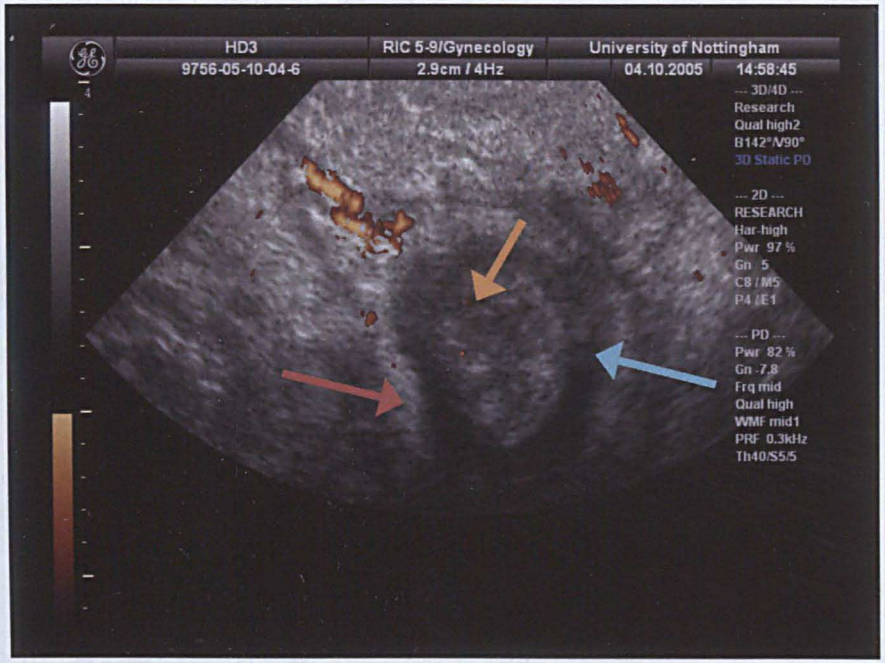

Figure 3-11 Transverse image of the anal canal.

The yellow arrow shows the mixed echogenic central mucosa and submucosa, within which the folds of mucosa can be seen. The blue arrow points to the hypoechoic internal sphincter, and the red arrow to the hyperechoic external sphincter, which is visibly deficient anteriorly.

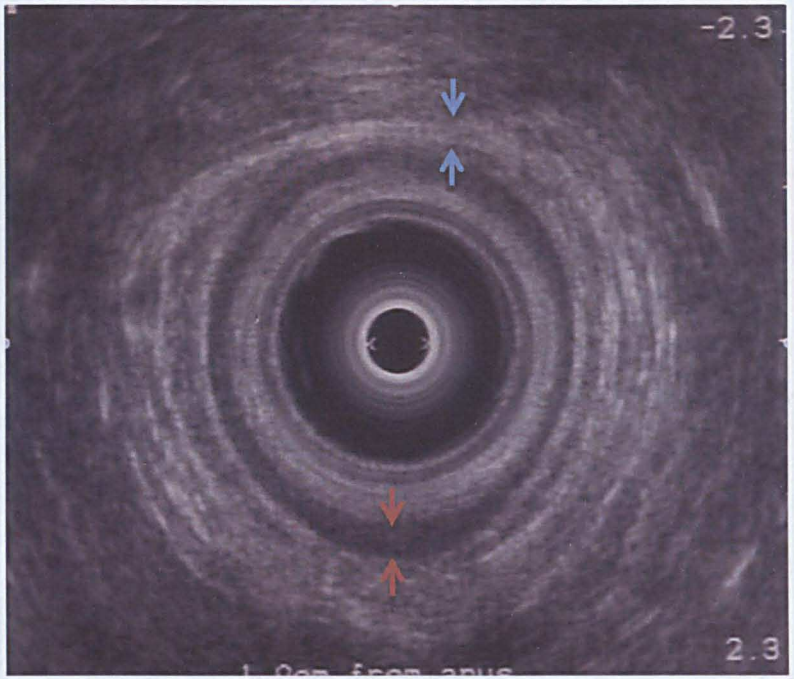

Figure 3-12 Transverse EAS obtained at the level of the middle anal canal.

The external sphincter ring (between blue arrows) is fully formed anteriorly, and the internal sphincter (between red arrows) is intact. The submucosa is the hyperechoic ring internal to the hypoechoic IAS. Image courtesy of Debbie Bush, Department of Surgery, UHN NHS Trust.

3.6 METHOD PHASE II: Data Analysis

Analysis of the US data was conducted using 4D View on a MacBook Pro, running Parallels version 3.0. Volume measurements were largely undertaken using **V**irtual **O**rgan **C**omputer-aided **A**na**L**ysis II (VOCAL™ II) software within 4D View, as this was used to quantify the power Doppler signal within a pre-defined shape. Quantification of power Doppler signal is not possible with conventional volume measurement as this technique does not define a model, and whilst 4D View can be used to examine the power Doppler signal it can only do so through the application of a pre-set or user-defined shape.

Shell imaging facilitates the generation of a parallel contour outside, inside or symmetrically across the originally defined surface contour. For the purposes of examining the surrounding sphincters an 'outside' shell was used so that vascular information from the surrounding smooth muscle could be obtained.

With VOCAL™ II, all of the individual sectional planes within any given volume can be retrieved and displayed as conventional 2D images or as a 3D image. For measurement purposes the multiplanar display was used throughout (fig 3-10). This display allows the three mutually related perpendicular sectional planes to be visualised simultaneously. Because the planes are at 90 degrees to each other, this display is often referred to as the orthogonal image display. The images can be rotated in any direction and if one plane is moved the corresponding planes move in a reciprocal manner. This allows a specific region to be viewed in each of the three planes. Prior to any measurement the multiplanar display was orientated to provide consistent reference to the data acquired. This involved ensuring the sagittal image was shown in the upper left image (the A plane), the transverse image in the upper right image (the B plane) and the coronal view in the lower left image (the C plane). The transducer was always orientated such that the sagittal view of the anorectal angle was on screen at the start of the data acquisition and was thus seen in the A plane following data acquisition with the remaining planes shown as outlined above.

3.6.1 Rotational Volume Measurement

Rotational measurements of regions of interest from the anal canal were undertaken with VOCAL™ II, an extension of 4D View. The basic principle of VOCAL II is the combination of 3D ultrasound tissue presented as voxels and the geometric information of surfaces in a 3D dataset. Calculation of the surface geometry is the first step of VOCAL II. The surface geometry is defined by rotating an image plane around a fixed axis, and defining 2D contours on each plane.

There are four rotation angles to choose from: 30, 15, 9 or 6 degrees. The entire dataset is rotated about 180 degrees and therefore this results in 6, 12, 20 or 30 planes respectively being available for measurement.

The intention of this part of the study was to define a reproducible region of interest (ROI) of the anorectum, which included the haemorrhoids or anal cushions. The power Doppler signal could then be quantified within the ROI, using the 'histogram' facility (fig 3-18), which generates the three indices of vascularity, previously described in section 3.1.2.2. (See appendix 8.2 for a more detailed explanation).

For these rotational measurements two callipers were placed at the superior and inferior aspects of the submucosa on the axial view (fig 3-13). The junction between the submucosa and internal anal sphincter is then traced in a clockwise fashion using a Graphire4™pen and tablet (fig 3-14). The volume is rotated through 9 degrees about the resultant axis; the submucosa-internal anal sphincter interface is again traced to ensure all of the submucosa had been included (figs 3-15 & 3-16). The final volume of interest is accepted (fig 3-17) and the vascular induces are calculated via the histogram facility (fig 3-18).

3.6.2 Sphere as Volume of Interest

For the purposes of this part of the study, the initial multiplanar image (fig 3-19) is magnified by a factor of 1.5. Static volume contrast imaging (VCI) is used to increase the differentiation between the tissue layers (figs 3-20 and 3-21). The cursor is then centred on both the axial and coronal images (fig 3-21). The coronal image is then rotated until the axis runs on a true vertical. The cursor is then moved along the vertical axis of the coronal image until puborectalis is just visualised on the axial image (fig 3-22). VOCAL II was then selected, following which a sphere as the region of interest is selected. Two callipers are placed at the anterior and posterior aspects of the submucosa – internal anal sphincter interface (fig 3-23). The volume is rotated about the resultant axis to ensure they were appropriately sited and that all of the submucosa has been included. The anal canal sphere is defined as the volume defined by the diameter set by the callipers (fig 3-24). The region of interest is accepted and the histogram is then displayed.

3.7 RESULTS PHASE II: Data Analysis

3.7.1 Rotational Volume Measurement

Although this method was initially thought to be promising, difficulties with delineating the ROI soon became apparent. The coronal and sagittal views cannot be defined at the submucosa – IAS interface (see figs 3-16 and 3-17), because the anorectum is a tubular structure with no cranial or caudal limits. The only cranial and caudal limits are those set by the limitations of the volume acquisition of the transperineal transducer.

As seen in figure 3-17 the final ROI is essentially tubular, centred on the anorectal angle. Within VOCAL II whilst manually defining the ROI, there was no available option to measure a set distance from the anorectal angle to produce a three-dimensional tube of set length centred on the anorectal angle. Therefore this method of defining a ROI was rejected.

3.7.2 Sphere as Region of Interest

Alternative methods of analysis of the anal canal were assessed, as the cranial and caudal aspects of an essentially tubular structure were impossible to delineate accurately or with high reproducibility with the rotational method.

VOCAL II also allows the user to use a sphere as a ROI rather than defining the ROI manually on each 2D plane. The diameter of the sphere is set by the callipers, and the position set by the cursor visualised on each of the three orthogonal planes. By positioning the sphere at the anorectal angle, confirmed by visualization of the puborectalis muscle, and by setting the diameter of the sphere by the submucosal axial diameter, a reproducible ROI could be assessed.

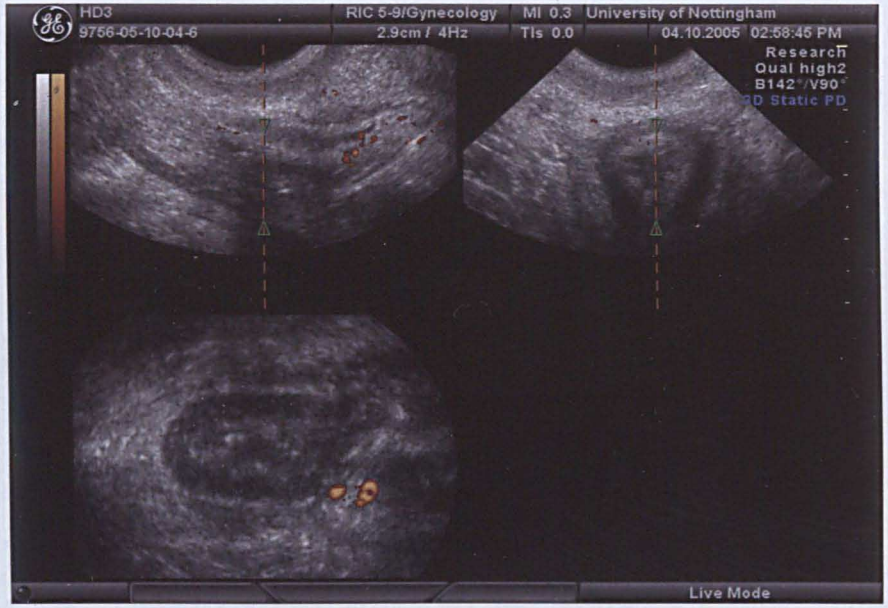

Figure 3-13 Rotational Volume Measurement

Two callipers are placed at the superior and inferior aspects of the submucosa on the transverse view.

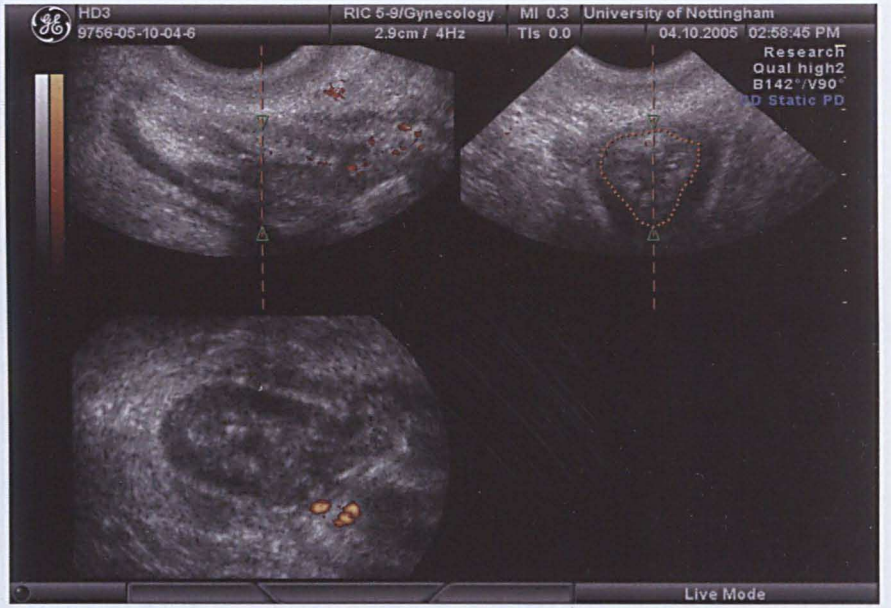

Figure 3-14 Rotational Volume Measurement

This volume has been rotated around the set axis, and then the junction between the submucosa and the internal anal sphincter is traced.

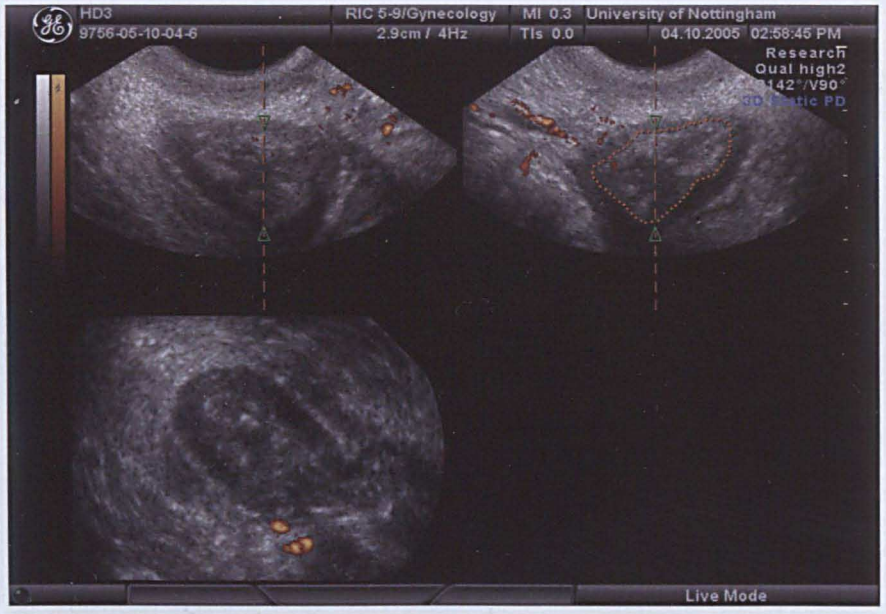

Figure 3-15 Rotational Volume Measurement 1

The volume has been rotated again around the axis. Note the change in orientation of the orthogonal planes.

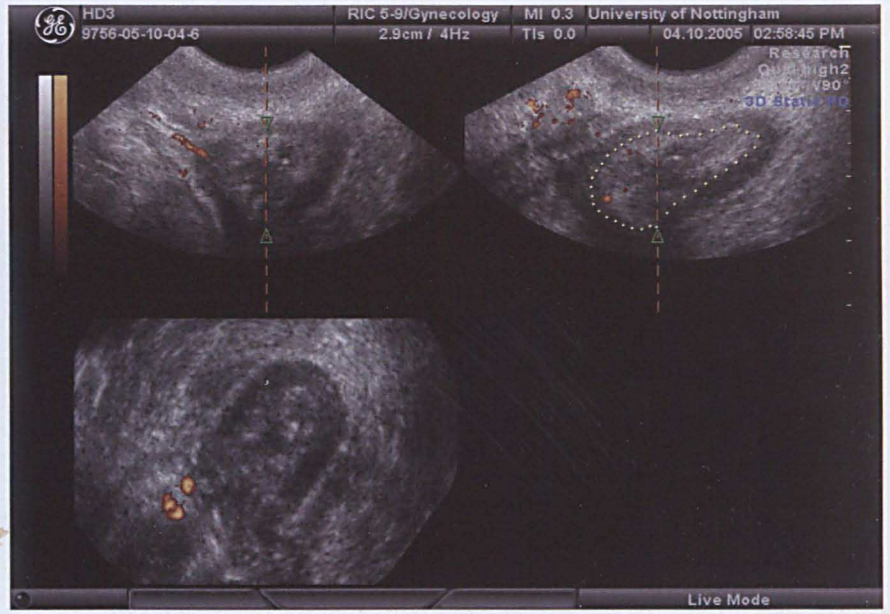

Figure 3-16 Rotational Volume Measurement 2

As the volume is rotated, it becomes more difficult to delineate the interface between the submucosa and the internal anal sphincter, which is unsurprising as there is no anatomical superior limit to the submucosa; it is continuous with that of the rectum.

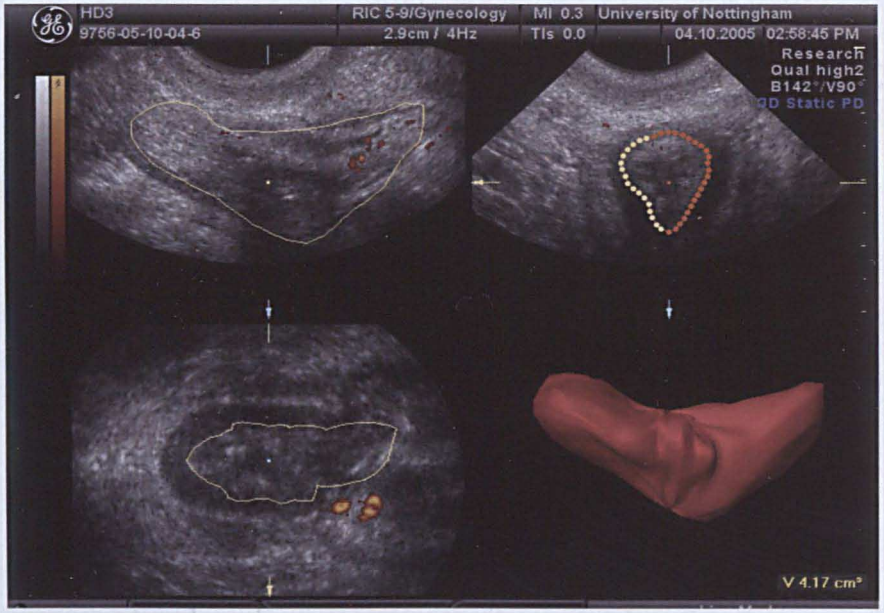

Figure 3-17 Rotational Volume Measurement 3

The volume of interest has been rotated through 180 degrees, and a volume has been generated.

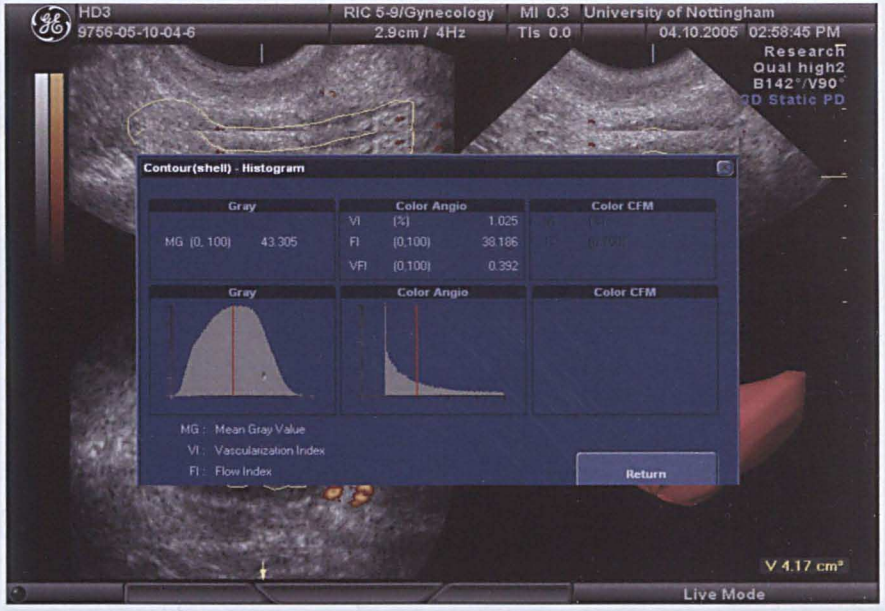

Figure 3-18 Rotational Volume Measurement 4

The histogram facility has been generated, and the results show the three vascular indices.

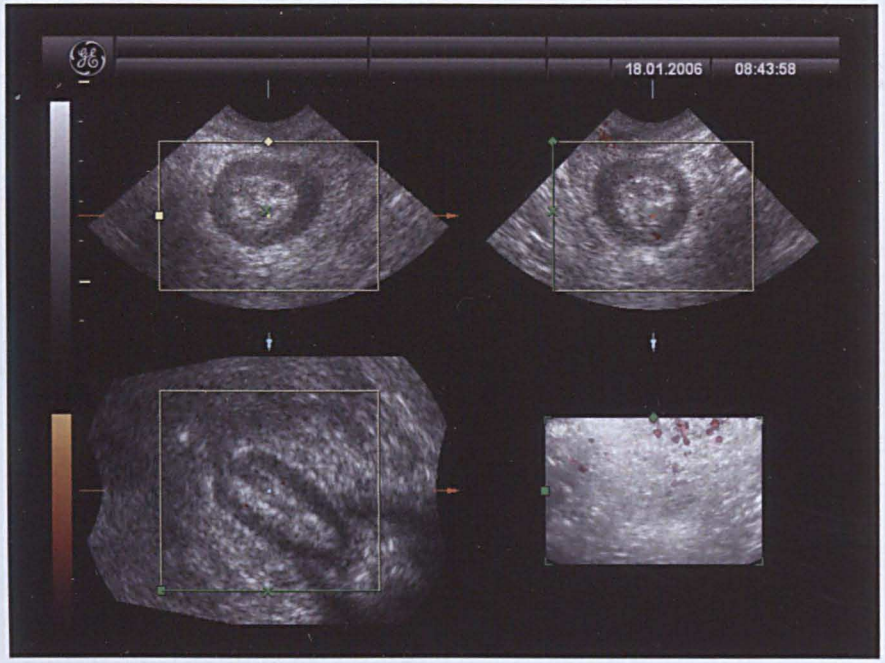

Figure 3-19 Sphere as Region of Interest 1.

Initial volume before adjustments are made for sphere volume analysis.

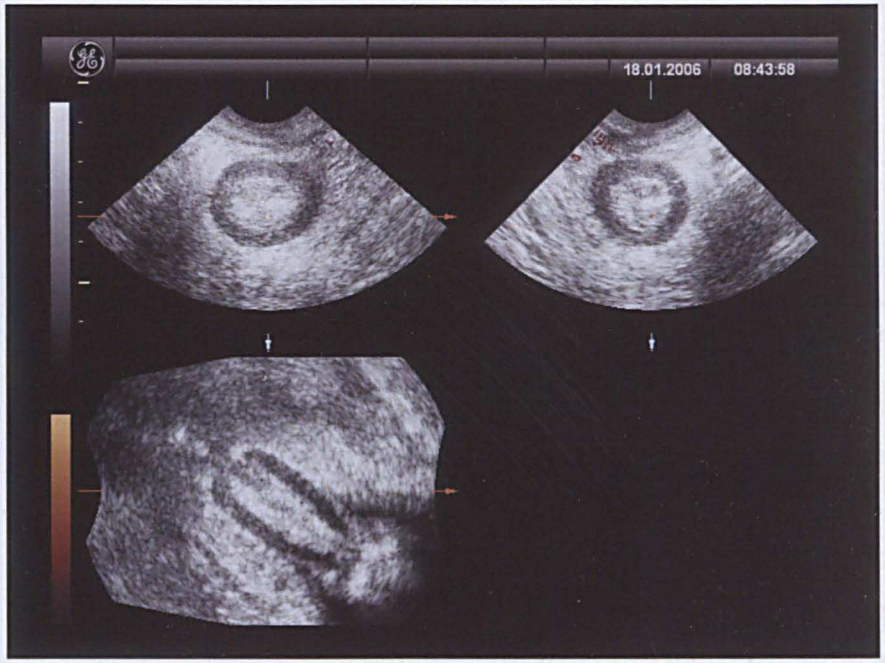

Figure 3-20 Sphere as Region of Interest 2.

Using static VCI to increase differentiation between submucosa and the internal anal sphincter.

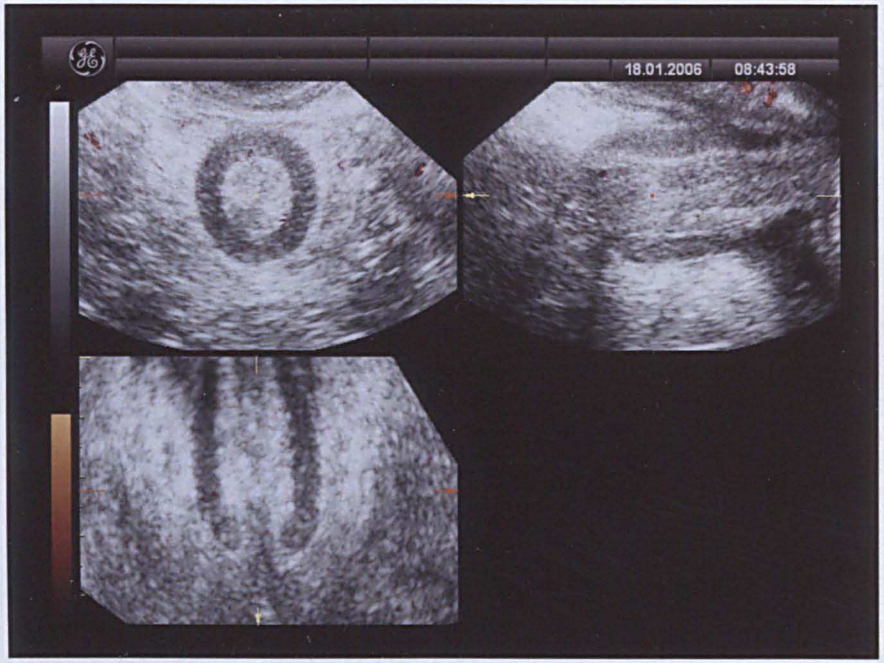

Figure 3-21 Sphere as Region of Interest 3.

Magnification by a factor of 1.5, and centring of cursor on axial and coronal planes. Note the coronal plane is now vertical.

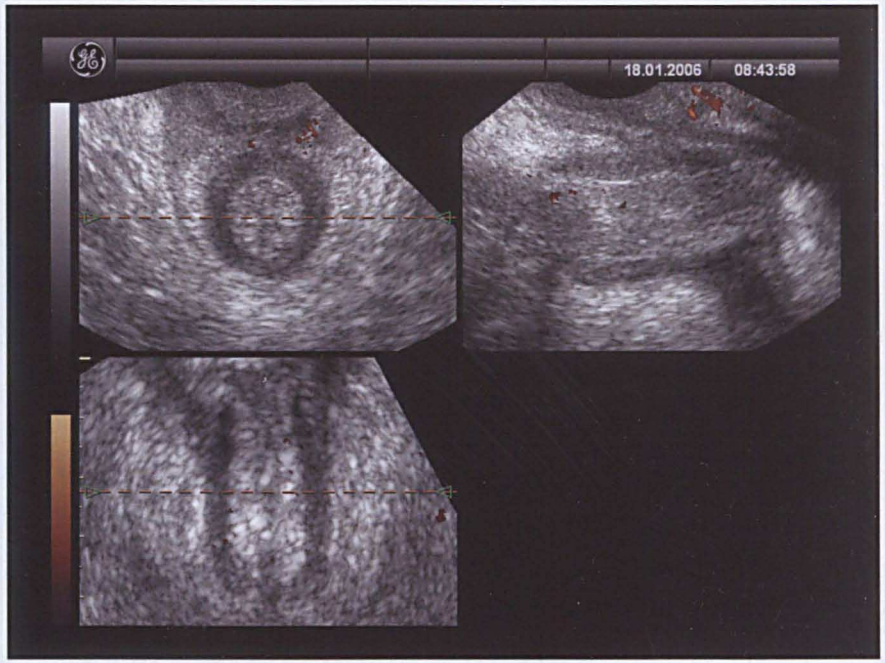

Figure 3-22 Sphere as Region of Interest 4.

The puborectalis sling is identified in the axial image.

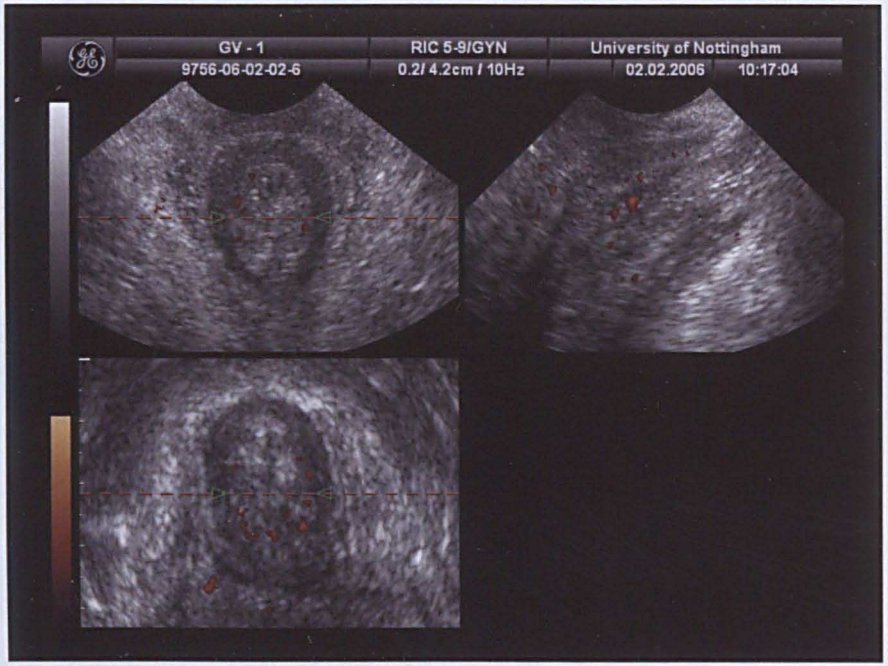

Figure 3-23 Sphere as Region of Interest 5.

Callipers are placed at the submucosa-internal anal sphincter interface.

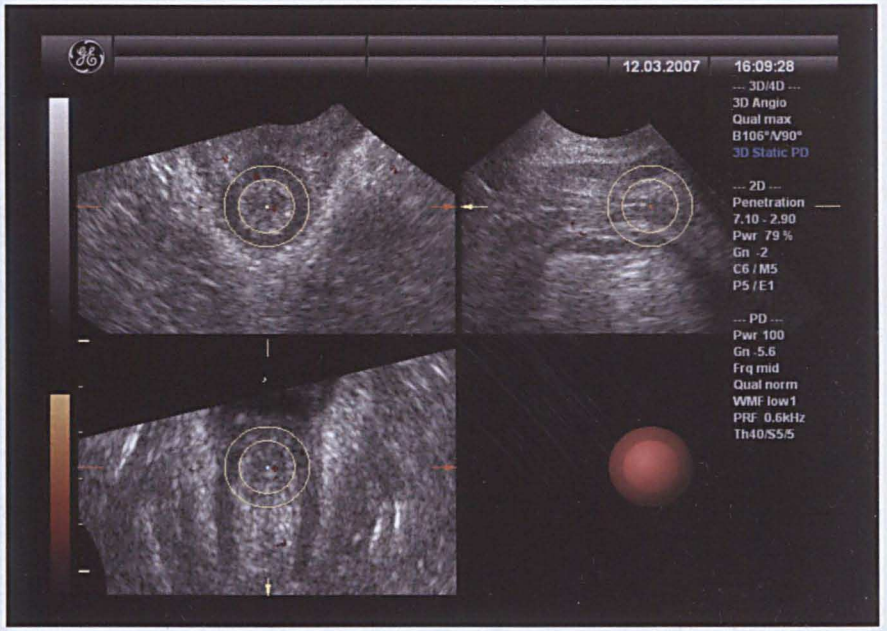

Figure 3-24 Sphere as Region of Interest 6.

VOCAL generates a sphere who's diameter is based on the distance between the calipers. In this example VOCAL has also been used to generate a 2mm shell external to the sphere. A histogram is then applied to generate the vascular indices (not shown).

3.8 METHOD PHASE III: Patient and Healthy Volunteer Studies

3.8.1 Protocol for imaging patients and volunteers.

Following the first and second parts of the study to establish best technique and software analysis, fifteen patients and eleven healthy volunteers were recruited between December 2005 and June 2007. All patients were recruited from a general surgical clinic, following a standard history and examination including proctoscopy and rigid sigmoidoscopy to exclude other colorectal pathology. All patients were diagnosed with haemorrhoids; treatment options were discussed and consent to rubber band ligation was obtained prior to the study being mentioned. Patients were offered time to consider joining the study, and were contacted by telephone to arrange either the first scan or a return to clinic for rubber band ligation if they did not wish to participate in the study.

The same Voluson 730D™ machine (Kretztechnik™, Zipf, Austria / Medison™, Seoul, Korea) and 7.5 MHz transvaginal probe were used throughout. All 3D data was acquired in an identical fashion with the 2D plane being swept through a specific fan plane by automatic rotation of the mechanical transducer (fig 3-2). Ultrasound data analysis was conducted using 4D View (Kretztechnik / Medison) and was performed with Virtual Organ Computer-aided AnaLysis (VOCAL™II) using the anorectal angle sphere method. Each patient was scanned via the transperineal approach immediately before rubber band ligation, two, six and eight weeks after rubber band ligation.

The probe was positioned on the perineum (see fig 3-2) and at least three sets of 3D power Doppler data acquisitions were performed. The probe was removed between each dataset acquisition and the process was repeated at least twice. Immediately after the first scan, rubber band ligation of haemorrhoids was performed.

Eleven healthy volunteers were recruited via posters placed around the University of Nottingham medical school and University Hospital Nottingham. A general history was taken from each volunteer prior to

recruitment and scanning, to exclude any colorectal history. Each volunteer was scanned on days one, three and thirty-five from the start of the study. As for each patient, at least three datasets were acquired during each scan.

Each patient and volunteer was scanned in a supine position with knees flexed and hips abducted. For 3D data acquisition, a sagittal view of the anal canal was obtained and the volume mode entered. The resultant truncated sector defining the area of interest was then centred over the anorectal angle, adjusted accordingly and the sweep angle set to 85° to ensure that the greatest volume was obtained. The patient was asked to remain as still as possible and every effort was made by the ultrasonographer to limit inappropriate movements of the transducer. The 3D dataset was then acquired using the slow sweep mode. The signals are processed and converted into digital information for storage in the computer's random access memory.

The spatial peak temporal average intensity of ultrasound for B-mode and Doppler examinations was maintained at $<80 Wcm^{-2}$, which is well within the safety limits recommended by the Bioeffects Committee of the American Institute of Ultrasound in Medicine [204, 205]. The Thermal Index (TI) and Mechanical Index (MI) were maintained below 0.5 and 0.3 respectively throughout the thesis in keeping with the Guidelines of the British Medical Ultrasound Society [206].

Standardisation of the US settings was ensured by using the same predefined probe programme without adjustment once the programme had been loaded. Prior to each acquisition the power Doppler settings were checked to ensure they had not changed during manipulation of the volume sector, which can lead to an automatic increase or decrease in the settings with larger and smaller volumes respectively.

For both volume and power Doppler acquisitions the resultant multiplanar display was immediately examined to ensure that the complete area had been captured with particular attention being given to the sagittal image in the A plane. If the volume was complete and considered of sufficient quality, with no power Doppler artefact, such as typical 'flash' artefacts seen with bowel movements or patient coughing, the dataset was

then stored to a magnetic optical disk. If there was apparent artefact, the dataset was reacquired until a satisfactory image was obtained. This was readily evident and easily distinguishable from true power Doppler information, as it appeared suddenly and occupied large areas of the screen. In contrast, true information from the anal submucosa was seen as relatively small areas of signal, which remained relatively constant.

4D View was used on a MacBook Pro to receive and store the 3D datasets and for subsequent analysis of vascularity. The volume datasets were first loaded from the magnetic optical disk and, following Cartesian conversion, saved onto a DVD. Cartesian conversion is essential prior to the digital transfer of 3D data to ensure the three coordinates of each pixel are recorded and correctly spatially orientated. The manufacturer recommends that 3D information is stored in this orthogonal grid co-ordinate system as it simplifies the algorithms for visualisation and also reduces image-computing time. The individual units of volume in this Cartesian storage are referred to as voxels (volume elements).

3.8.2 Comparison of Scanning Female and Male Patients and Volunteers.

The entire study group were female; this was related partly to the quality of imaging obtained with the endovaginal probe in males. Maintaining the endovaginal probe in a stable position on the perineal surface of males proved to be more difficult than in females. The average acquisition time for the 3D power Doppler dataset was 42 seconds, during which the transducer must be maintained in a completely stable position.

As the primary aim of the study was to establish a reliable method of imaging haemorrhoids and anal cushions, a decision was made to ultrasound females only for the remainder of this study, and to recruit possible male patient and healthy volunteers to other studies within the thesis. Subjectively it became apparent to the investigator that there was more reluctance from male patients and volunteers to consider taking part in this study, which was more intrusive than the MRI study.

3.8.3 Patient and Volunteer Characteristics

The average age of the patient participant was 46.4 ± 2.1 years (range 35 – 62 years). The participant reported duration of haemorrhoid symptoms for an average of 9.6 ± 2.5years (range 1 – 33years). 42.9% of the patients had 1st degree, 42.9% had 2nd degree and 14.2% had 3rd degree haemorrhoids. The average age of the volunteers was 38.7 ± 3.6 years (21 – 57 years). No significant difference was identified between the age profiles of the patients and healthy volunteers (Independent t-test: t (23) = -1.99 p >.05).

3.8.4 Patient and Volunteer Studies

Prior to making any comparisons between pre and post-treatment datasets, or between patients and healthy volunteers, it was essential to analyse the reproducibility of producing and analysing the anorectal angle sphere. The following separate studies were performed:

1) *Study 1: The reliability of VOCAL II for semi-quantification of anal canal vascularity – serial measurements of the same dataset.*

Repeated measures were made of the same single dataset acquired from both patients and healthy volunteers at the various time-points in the study. Sixty-three individual datasets were assessed by randomising the order of analysis and anonymising the patient or volunteer identification number both on the VOCAL software screen and on the spreadsheet used for data entry. Each dataset was assessed five times.

2) *Study 2: The reliability of VOCAL II for semi-quantification of anal canal vascularity – comparison of serial datasets from the same occasion.*

Three datasets acquired after removing and replacing the transducer from the perineum between each acquisition, from each of eighty-seven scans of patients and healthy volunteers at the various time-points in the study were assessed for agreement. The order of analysis was randomised and the patient or volunteer identification number was anonymised on the VOCAL II software screen and on the spreadsheet used for data entry.

3) *Study 3: Comparison of Volume and Vascularity Measures from Healthy Volunteers Over Time*

Datasets from each time-point (days 1, 3 and 35) were compared for eleven healthy volunteers. An average of three measurements was taken for each time point. The order of analysis was randomised and the volunteer identification number was anonymised on the VOCAL II software screen and on the spreadsheet used for data entry.

4) *Study 4: Comparison of Vascularity Measures from Pre-Rubber Band Ligation Patients with Healthy Volunteers*

Day 1 datasets of fifteen patients were compared to day 1 datasets of eleven healthy volunteers. The order of analysis was randomised and the patient or volunteer identification number was anonymised on the VOCAL software screen and on the spreadsheet used for data entry.

5) *Study 5: Comparison of Vascularity Measures from Pre and Post-Rubber Band Ligation Patients*

Volume and vascular indices from patients were measured and compared over four time-points (days 1, 14, 42 and 56) within an eight-week period, with day 1 representing the pre-rubber band ligation time-point. An average of three measurements was taken for each time point. The order of analysis was randomised and the patient identification number was anonymised on the VOCAL software screen and on the spreadsheet used for data entry.

3.8.5 Statistical Analysis

Distribution of the data was examined with the Kolmogorov-Smirnov test. Homogeneity of variance was examined with Levene's test. Data was not normally distributed and lacked homogeneity of variance and therefore all statistical test were non-parametric. Reproducibility of the vascular indices was assessed by performing intra-class correlations. Differences between the healthy volunteer's data for day 1, day 3 and day 35 was assessed by the Friedman ANOVA test.

Differences between the healthy volunteer group and the patient group was assessed by the Mann-Whitney test. Wilcoxon signed-rank tests, correcting for the number of tests, was performed to assess the size of effect. A Bonferroni correction was applied and so all effects are reported at

a 0.0167 level of significance. The effect size $r = {}^{z}/\sqrt{N}$. A one-tailed assessment was performed as the null hypothesis states that there is no difference between the vascularity indices of pre-treatment patients and healthy volunteers.

Differences between the pre-treatment and post-treatment groups were assessed by the Wilcoxon's signed rank test. The effect size $r = {}^{z}/\sqrt{N}$. A one-tailed assessment was performed as the null hypothesis states that there is no difference between the vascularity indices of pre-treatment patients and post-treatment patients.

3.9 *RESULTS PHASE III: Patient and Healthy Volunteer Studies.*

3.9.1 Study 1: Serial Measurements of the Same Dataset.

The intraobserver ICCs were very high for measurements of both volume and vascularity within the anal canal sphere and the outer 2mm shell, apart from the Flow Index measurement in the 2mm outer shell (table 3-3).

Measurement	Mean ICC ± 95% CI
Sphere Volume	0.968 (0.951 – 0.979)
Sphere VI	0.968 (0.952 – 0.980)
Sphere FI	0.944 (0.914 – 0.964)
Sphere VFI	0.966 (0.948 – 0.978)
Shell Volume	0.978 (0.966 – 0.986)
Shell VI	0.982 (0.973 – 0.989)
Shell FI	0.866 (0.797 – 0.915)
Shell VFI	0.966 (0.948 – 0.978)

Table 3-3 Results of study 1.

The mean intraobserver ICCs ± 95% CI for repeated measures of volume and vascularity of the anal canal sphere and its 2mm outer shell from a single dataset.

3.9.2 Study 2: Serial Measurements of Three Datasets from Same Patient on Same Occasion

The intraobserver ICCs were very high for measurements of both volume and vascularity within the anal canal sphere and the outer 2mm shell, apart from the Flow Index measurement in the 2mm outer shell (table 3-4).

Measurement	Mean ICC ± 95% CI
Sphere Volume	0.963 (0.948 – 0.975)
Sphere VI	0.948 (0.926 – 0.965)
Sphere FI	0.860 (0.800 – 0.905)
Sphere VFI	0.947 (0.924 – 0.964)
Shell Volume	0.965 (0.949 – 0.976)
Shell VI	0.932 (0.903 – 0.954)
Shell FI	0.862 (0.803 – 0.906)
Shell VFI	0.928 (0.897 – 0.951)

Table 3-4 Results of study 2.

The mean intraobserver ICCs± 95% CI for repeated measures of volume and vascularity of the anal canal sphere and its 2mm outer shell from consecutive datasets on the same occasion.

3.9.3 Study 3: Comparison of Measurements from Healthy Volunteers Over Time

Volume and vascular indices were compared from healthy volunteers over three time-points (days 1, 3 and 35) within a five-week period. None of the vascular indices changed significantly over the five weeks (table 3-5 and figs 3-25 to 3-32), and therefore further statistical tests were not performed to assess for size of effect.

Measurement	$\chi 2(2)$	p
Sphere Volume	1.800	0.436
Sphere VI	0.667	0.763
Sphere FI	0.974	0.682
Sphere VFI	0.154	0.947
Shell Volume	1.800	0.436
Shell VI	3.436	0.186
Shell FI	1.897	0.437
Shell VFI	2.263	0.345

Table 3-5 Study 3.

Friedman's ANOVA to assess for change in vascularity measures over a five week period.

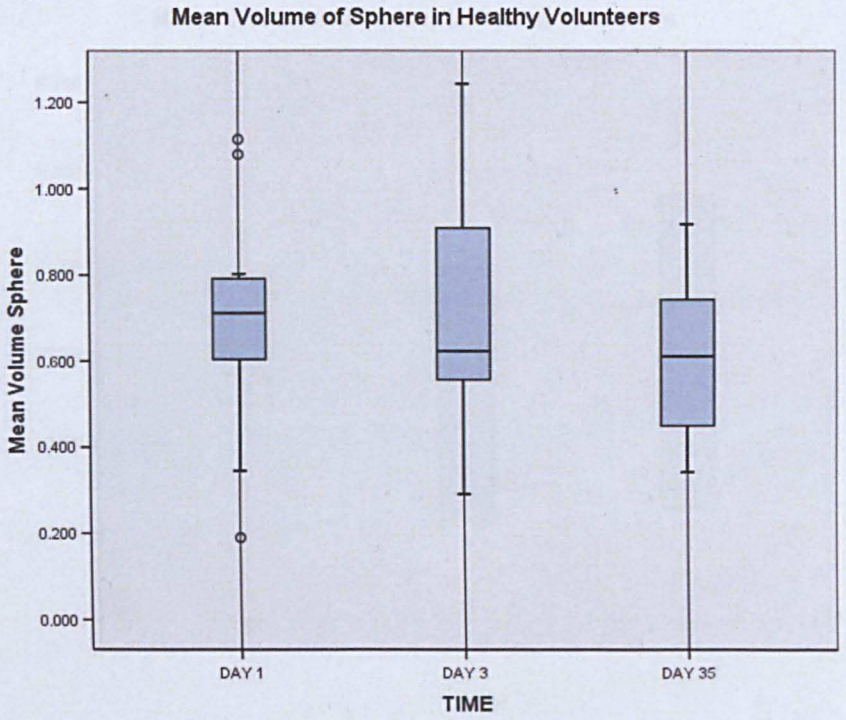

Figure 3-25 Study 3: Mean volume of the anorectal sphere in healthy volunteers over a five-week period.

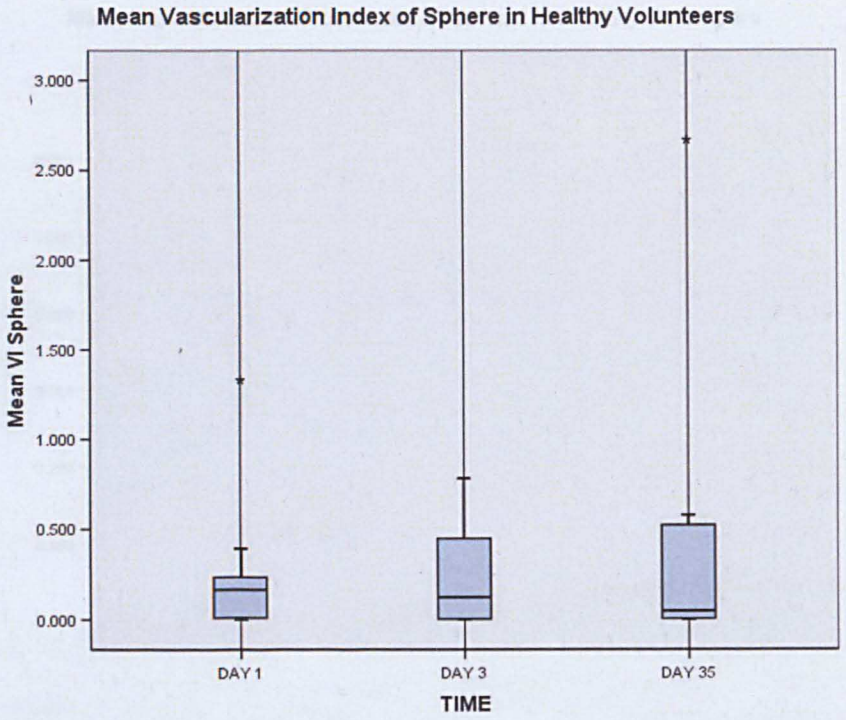

Figure 3-26 Study 3: Mean vascularization index of the anorectal sphere in healthy volunteers over a five-week period.

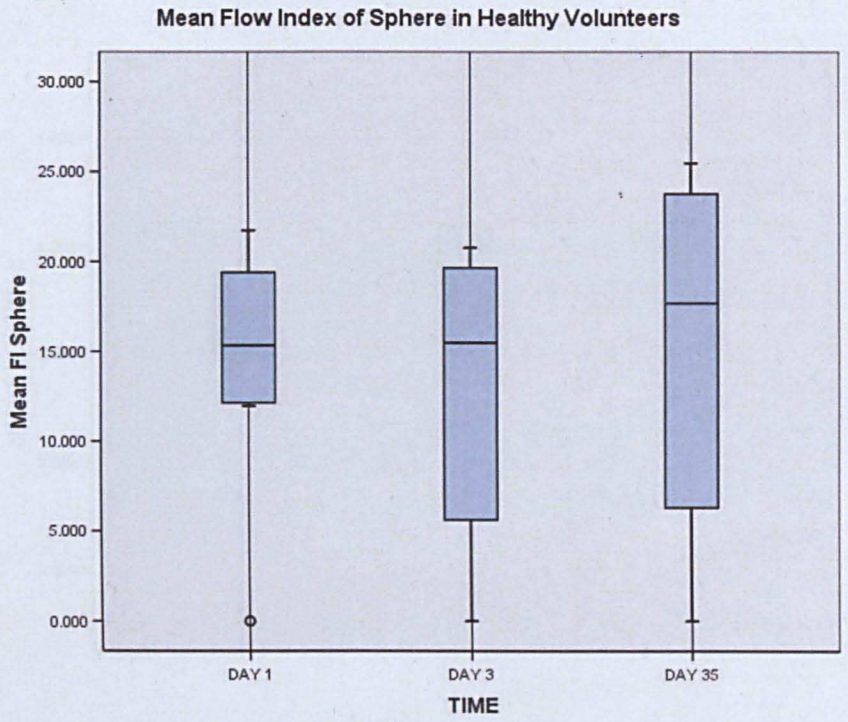

Figure 3-27 Study 3: Mean flow index of the anorectal sphere in healthy volunteers over a five-week period.

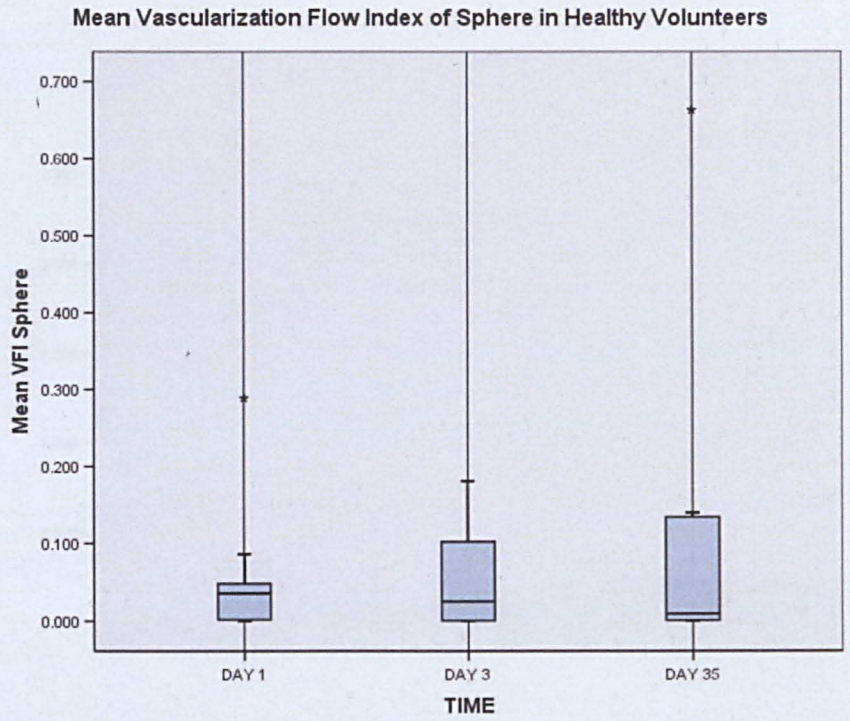

Figure 3-28 Study 3: Mean vascular flow index of the anorectal sphere in healthy volunteers over a five-week period.

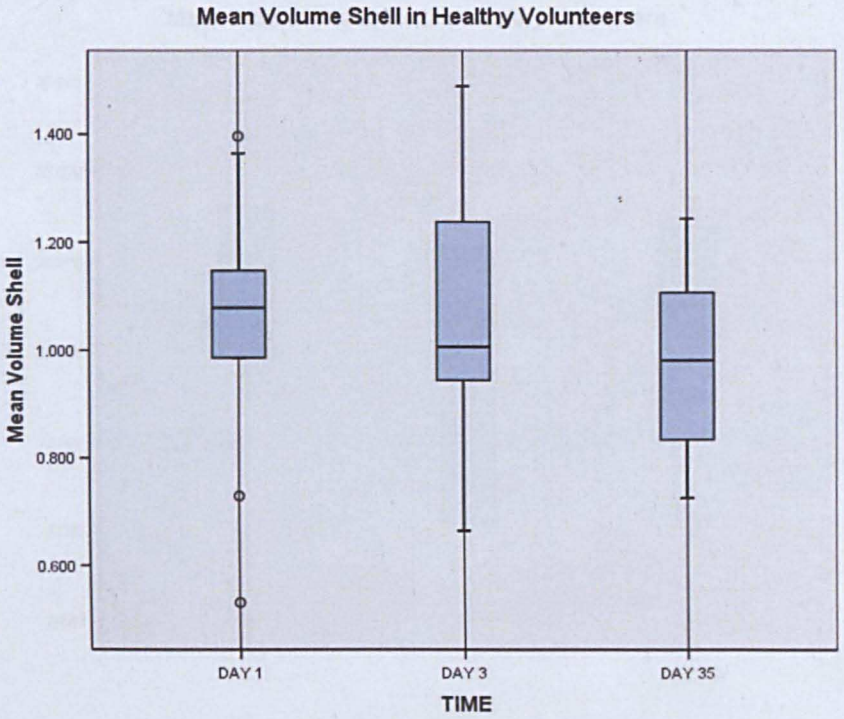

Figure 3-29 Study 3: Mean volume of the anorectal shell in healthy volunteers over a five-week period.

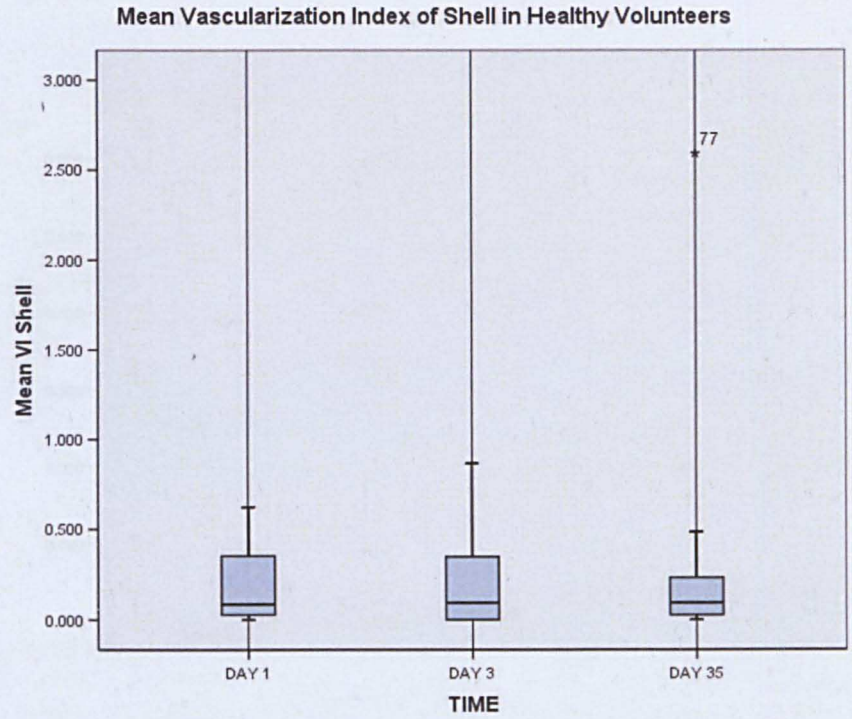

Figure 3-30 Study 3: Mean vascularization index of the anorectal shell in healthy volunteers over a five-week period.

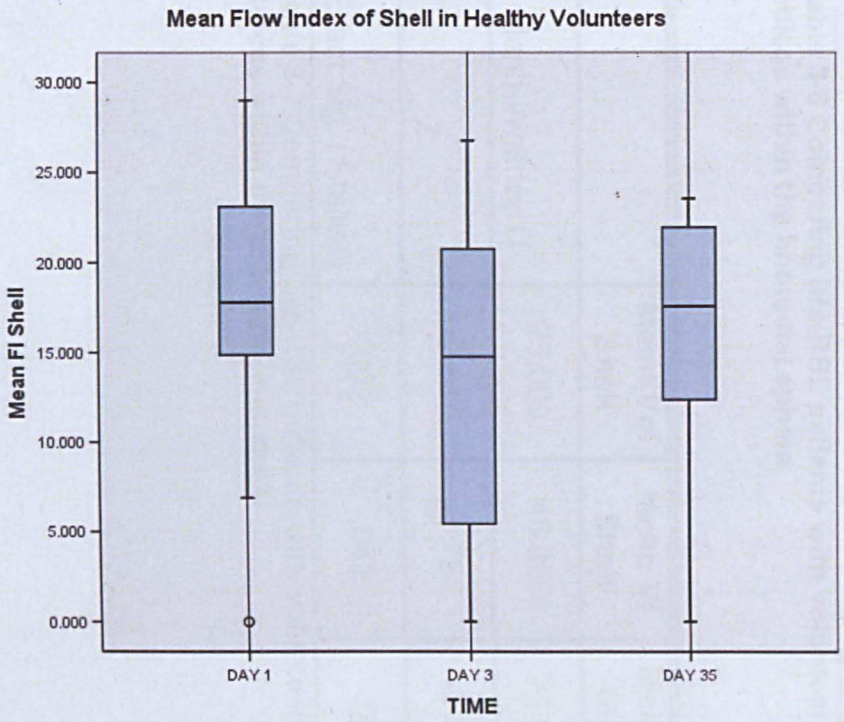

Figure 3-31 Study 3: Mean flow index of the anorectal shell in healthy volunteers over a five-week period.

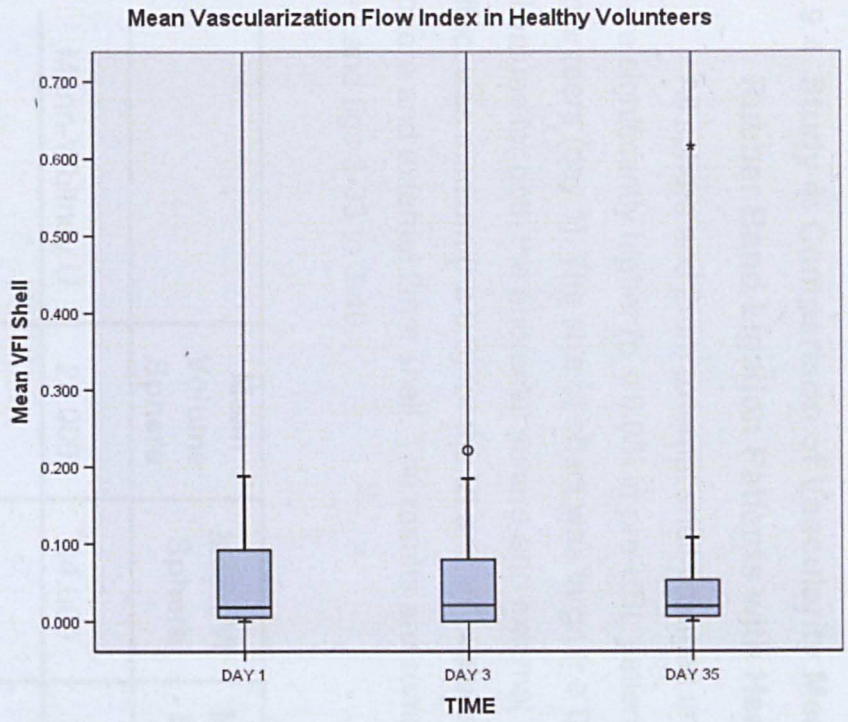

Figure 3-32 Study 3: Mean vascular flow index of the anorectal shell in healthy volunteers over a five-week period.

3.9.4 Study 4: Comparison of Vascularity Measures from Pre-Rubber Band Ligation Patients with Healthy Volunteers

All sphere and 2mm external shell volumes and vascular index values were significantly higher ($p < 0.05$) in pre-RBL patients compared to the volunteers (day 1). The size of effect was large ($r \geq 0.5$) for the volume and FI values for both the anorectal sphere and external 2mm shell. The size of effect was medium ($r \geq 0.3$) for the VI and VFI values of both the anorectal sphere and external 2mm shell. The results are summarised in tables 3-6 to 3-7 and figs 3-33 to 3-40.

	Mean Volume Sphere	Mean VI Sphere	Mean FI Sphere	Mean VFI Sphere
Mann-Whitney U	25.000	44.000	29.000	42.000
Z	-2.847	-1.807	-2.628	-1.916
Exact Sig. (1-tailed)	.002	.036	.004	.028

Table 3-6 Comparing pre-RBL patients with volunteers: results for vascular indices within the anorectal sphere.

	Mean Vol Shell	Mean VI Shell	Mean FI Shell	Mean VFI Shell
Mann-Whitney U	25.000	45.000	31.000	45.500
Z	-2.847	-1.752	-2.518	-1.725
Exact Sig. (1-tailed)	.002	.042	.005	.043

Table 3-7 Comparing pre-RBL patients with volunteers: results for vascular indices within the external 2mm shell.

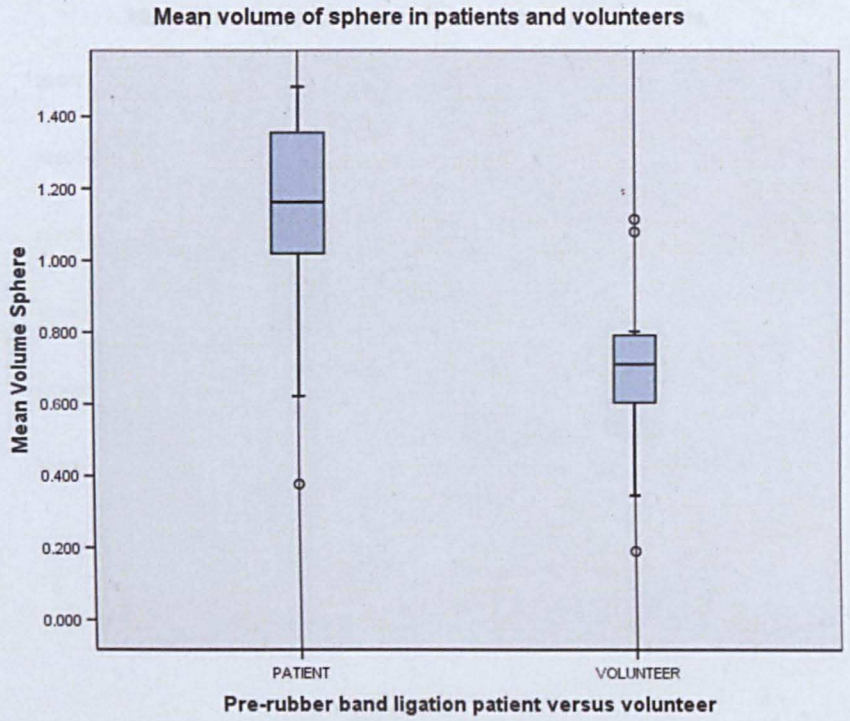

Figure 3-33 Study 4: Sphere volume

Pre-RBL patient sphere volume (Mdn = 1.16) differed significantly from that of volunteers (Mdn = 0.71).

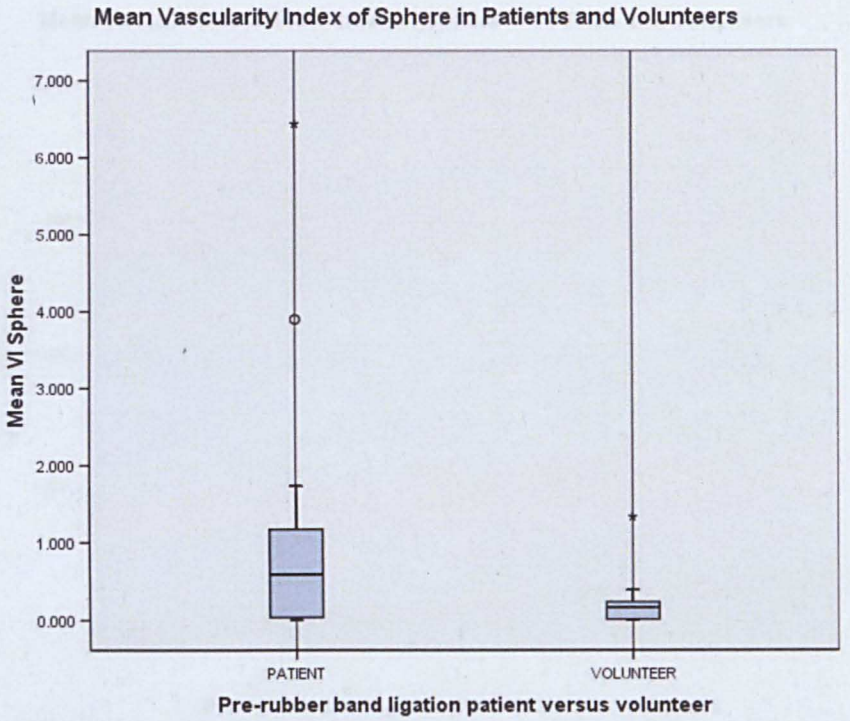

Figure 3-34 Study 4: Sphere VI.

Pre-RBL patient sphere VI (Mdn = 0.59 differed significantly from that of volunteers (Mdn = 0.17).

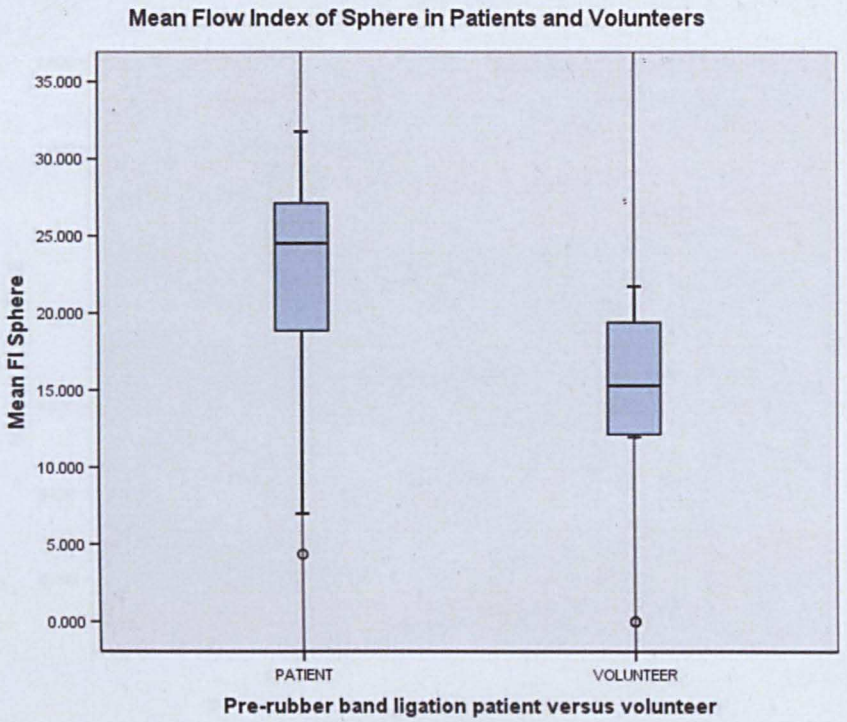

Figure 3-35 Study 4: Sphere FI.

Pre-RBL patient sphere FI (Mdn = 24.51) differed significantly from that of volunteers (Mdn = 15.32).

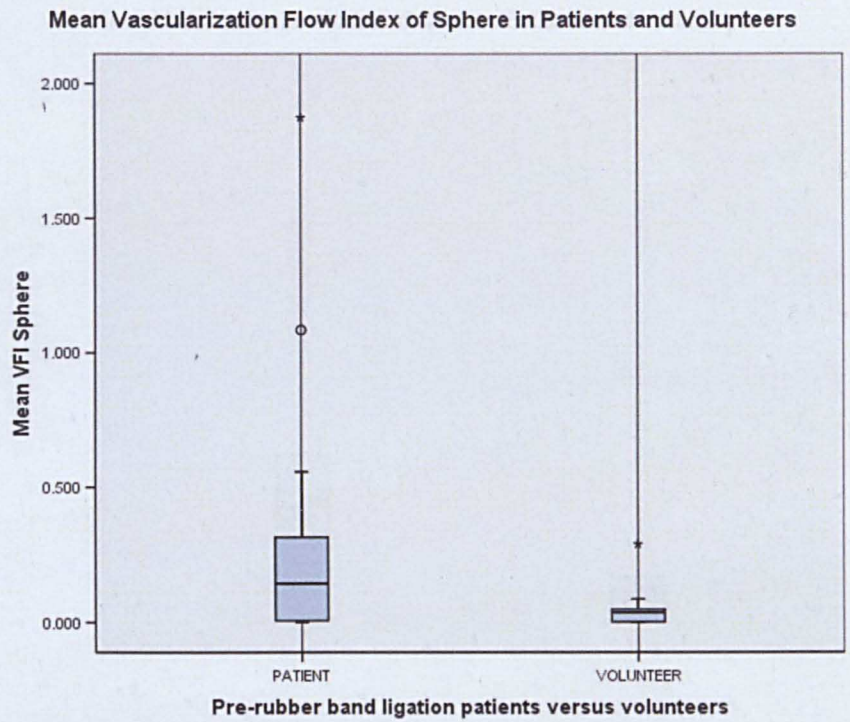

Figure 3-36 Study 4: Sphere VFI.

Pre-RBL patient sphere VFI (Mdn = 0.15) differed significantly from that of volunteers (Mdn = 0.04).

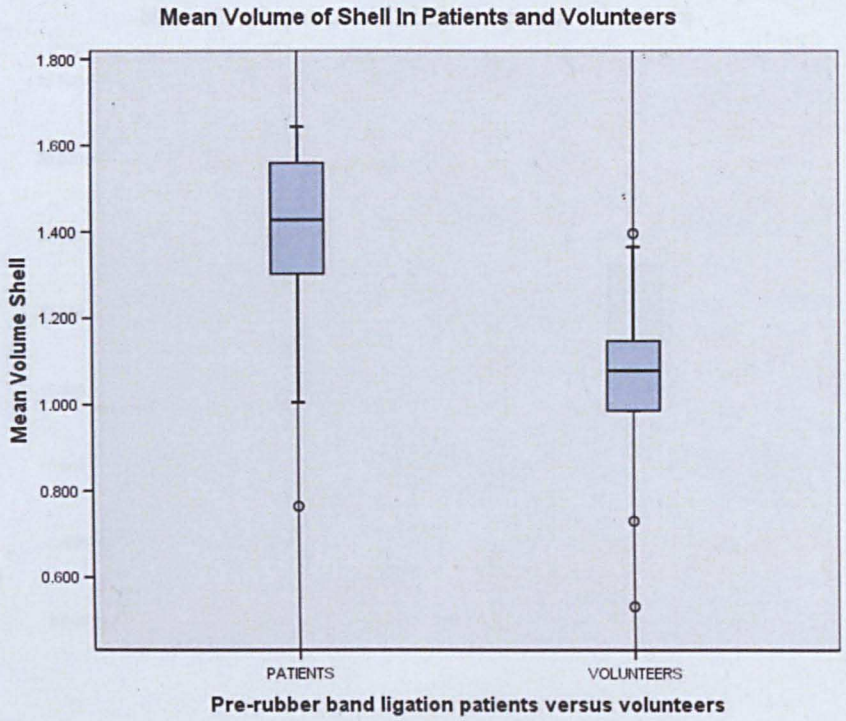

Figure 3-37 Study 4: Shell volume.

Pre-RBL patient external shell volume (Mdn = 1.43) differed significantly from that of volunteers (Mdn = 1.08).

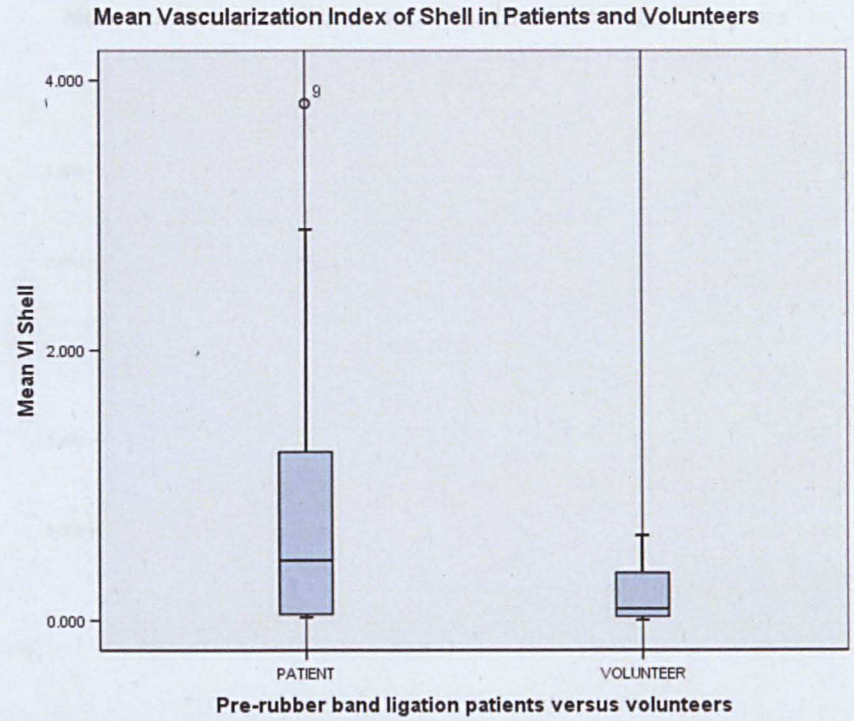

Figure 3-38 Study 4: Shell VI.

Pre-RBL patient external shell VI (Mdn = 0.44) differed significantly from that of volunteers (Mdn = 0.09).

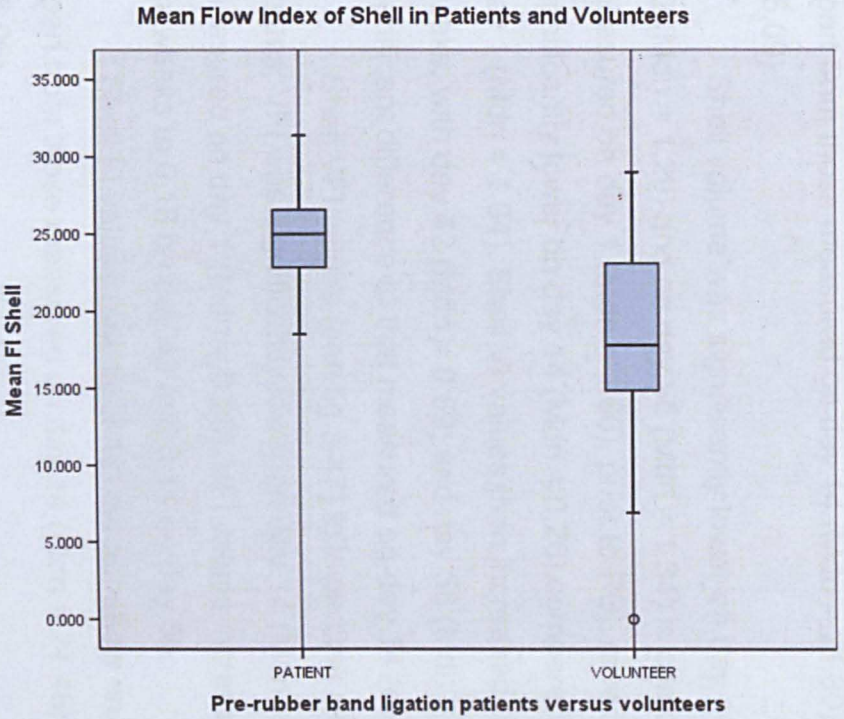

Figure 3-39 Study 4: Shell FI.

Pre-RBL patient external shell FI (Mdn = 25.00) differed significantly from that of volunteers (Mdn = 17.82).

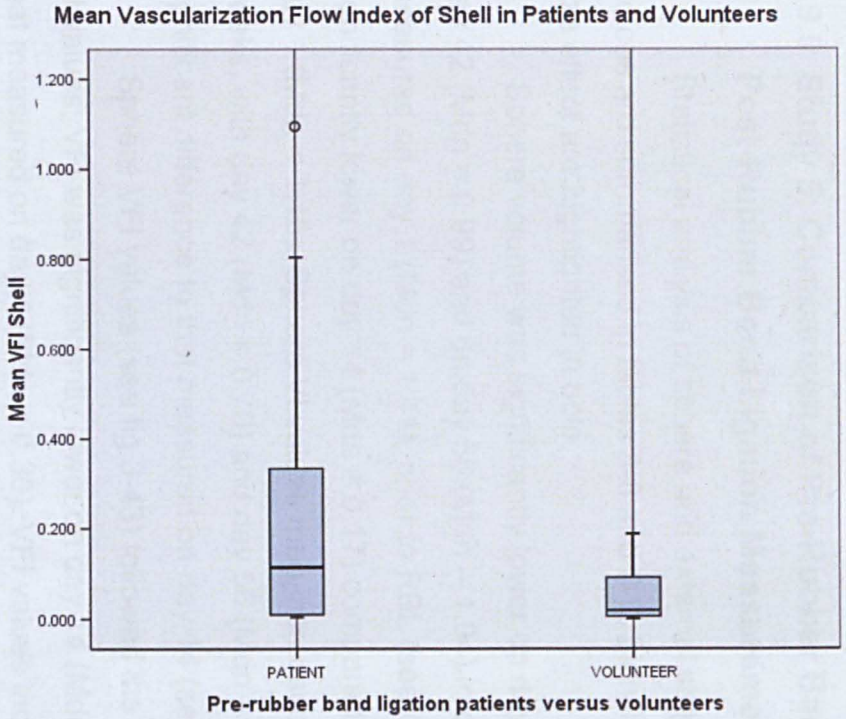

Figure 3-40 Study 4: Shell VFI.

Pre-RBL patient external shell VFI (Mdn = 0.11) differed significantly from that of volunteers (Mdn = 0.02).

3.9.5 Study 5: Comparison of Pre-Rubber Band Ligation and Post-Rubber Band Ligation Measurements

Statistical analysis of sphere and external shell volume and vascular indices are summarised in tables 3-8 and 3-9. Significant changes with their size effect are highlighted in bold.

Sphere volume was significantly lower on day 14 (Mdn = 1.11), on day 42 (Mdn = 0.99) and on day 56 (Mdn = 1.04) in comparison to that measured on day 1 (Mdn = 1.41), prior to RBL (see fig 3-41). Sphere VI was significantly lower on day 14 (Mdn = 0.17) compared to that measured on day 1 (Mdn = 1.16). Sphere VI values then increased over the remaining six weeks, with day 42 (Mdn = 0.70) and day 56 (Mdn = 0.45) values showing a significant difference to that measured on day 14 (see fig 3-42).

Sphere VFI values (see fig 3-43) followed the same pattern to that of VI values; VFI was significantly lower on day 14 (Mdn = 0.04) compared to that measured on day 1 (Mdn = 0.30). VFI values increased over the remaining six weeks to 0.18 on day 42 and 0.11 on day 56.

Sphere FI values (see fig 3-44) did not show any significant changes apart from those measured on day 14 (Mdn = 21.80) and day 42 (Mdn = 25.09).

Shell volume was significantly lower on day 14 (Mdn = 1.39), on day 42 (Mdn = 1.29) and on day 56 (Mdn = 1.34) in comparison to that measured on day 1 (Mdn = 1.60), prior to RBL (see fig 3-45). Shell VI was significantly lower on day 14 (Mdn = 0.26) compared to that measured on day 1 (Mdn = 1.04). Shell VI values then increased over the remaining six weeks, with day 42 (Mdn = 0.69) and day 56 (Mdn = 0.44) values showing a significant difference to that measured on day 14 (see fig 3-46).

Shell VFI values (see fig 3-47) followed the same pattern to that of VI values; VFI was significantly lower on day 14 (Mdn = 0.07) compared to that measured on day 1 (Mdn = 0.28). VFI values increased over the remaining six weeks to 0.18 on day 42 and 0.11 on day 56.

Shell FI values (see fig 3-48) did not show any significant changes apart from those measured on day 14 (Mdn = 24.46) and day 42 (Mdn = 26.06).

Day	Sphere Volume	Sphere VI	Sphere FI	Sphere VFI
1 v 14	***T = 10.00*** ***p = 0.021*** ***r = -0.44***	***T = 5.00*** ***p = 0.005*** ***r = -0.53***	T = 19.00 p = 0.120	***T = 5.00*** ***p = 0.005*** ***r = -0.53***
1 v 42	***T = 8.00*** ***p = 0.003*** ***r = -0.51***	T = 39.00 p = 0.342	T = 44.00 p = 0.473	T = 40.00 p = 0.368
1 v 56	***T = 16.00*** ***p = 0.02*** ***r = -0.44***	T = 27.00 p = 0.108	T = 38.00 p = 0.318	T = 28.00 p = 0.122
14 v 42	T = 32.00 p = 0.483	***T = 10.00*** ***p = 0.021*** ***r = -0.44***	***T = 12.00*** ***p = 0.034*** ***r = -0.40***	***T = 11.00*** ***p = 0.027*** ***r = -0.42***
14 v 56	T = 29.00 p = 0.382	***T = 11.00*** ***p = 0.027*** ***r = -0.42***	T = 16.00 p = 0.074	***T = 12.00*** ***p = 0.034*** ***r = -0.37***
42 v 56	T = 45.00 p = 0.500	***T = 8.00*** ***p = 0.006*** ***r = -0.48***	T = 29.00 p = 0.137	***T = 16.00*** ***p = 0.020*** ***r = -0.40***

Table 3-8 Wilcoxon signed rank test of sphere volume and vascular indices .

Day	Shell Volume	Shell VI	Shell FI	Shell VFI
1 v 14	***T = 10.00*** ***p = 0.021*** ***r = -0.44***	***T = 6.00*** ***p = 0.007*** ***r = -0.51***	***T = 5.00*** ***p = 0.005***	***T = 6.00*** ***p = 0.007*** ***r = -0.51***
1 v 42	***T = 8.00*** ***p = 0.003*** ***r = -0.51***	T = 38.00 p = 0.318	T = 42.00 p = 0.420	T = 39.00 p = 0.342
1 v 56	***T = 16.00*** ***p = 0.02*** ***r = -0.51***	T = 23.00 p = 0.064	T = 30.00 p = 0.153	T = 25.00 p = 0.084
14 v 42	T = 32.00 p = 0.483	***T = 7.00*** ***p = 0.009*** ***r = -0.49***	***T = 13.00*** ***p = 0.042*** ***r = -0.38***	***T = 7.00*** ***p = 0.009*** ***r = -0.49***
14 v 56	T = 29.00 p = 0.382	***T = 9.00*** ***p = 0.016*** ***r = -0.45***	T = 20.00 p = 0.139	***T = 11.00*** ***p = 0.027*** ***r = -0.42***
42 v 56	T = 29.00 p = 0.382	***T = 8.00*** ***p = 0.003*** ***r = -0.51***	T = 32.00 p = 0.188	***T = 14.00*** ***p = 0.013*** ***r = -0.42***

Table 3-9 Wilcoxon signed rank test of shell volume and vascular indices.

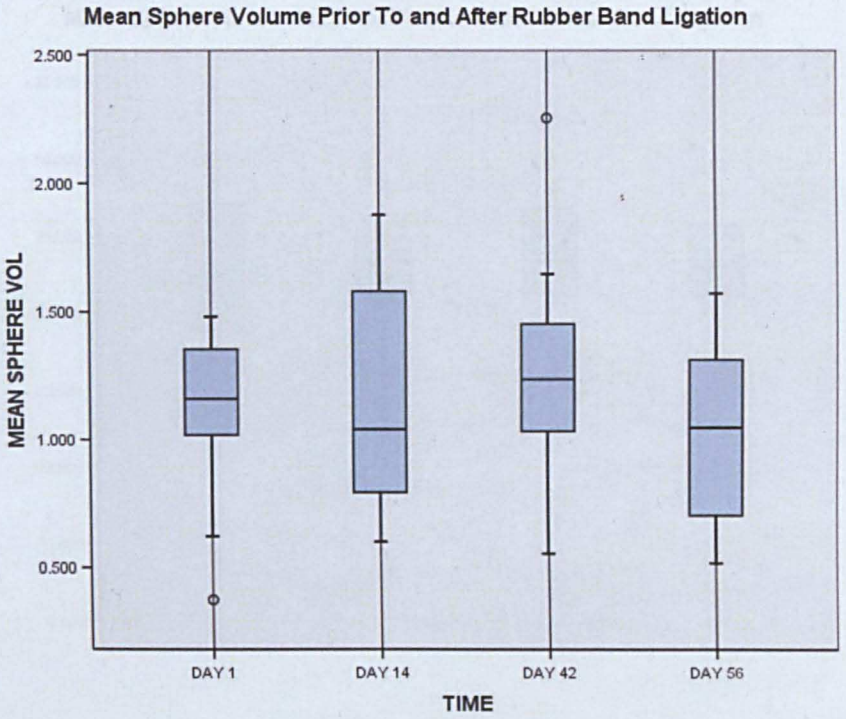

Figure 3-41 Study 5: Changes in sphere volume prior to and after rubber band ligation.

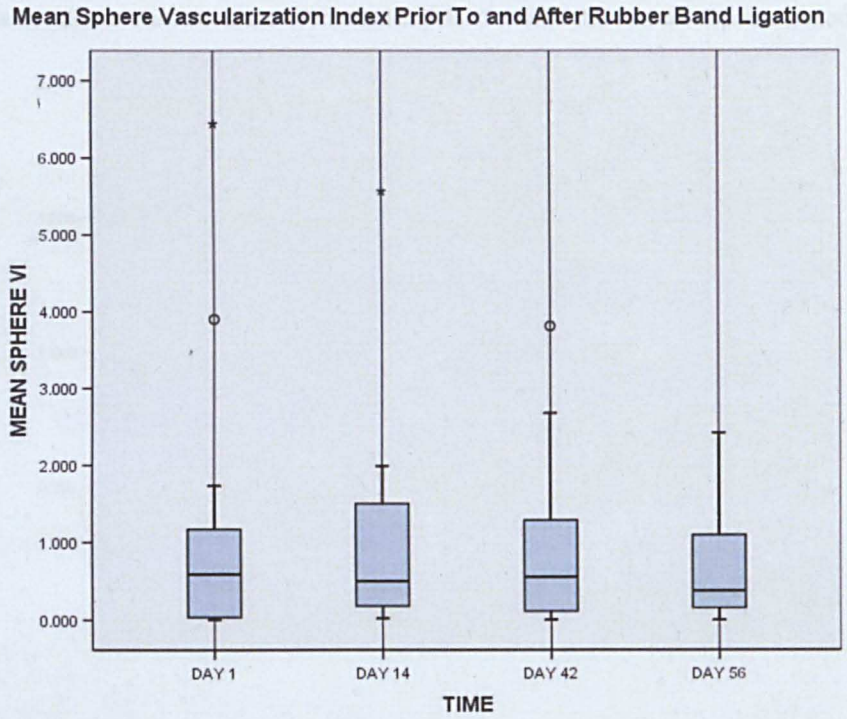

Figure 3-42 Study 5: Changes in sphere VI prior to and after rubber band ligation.

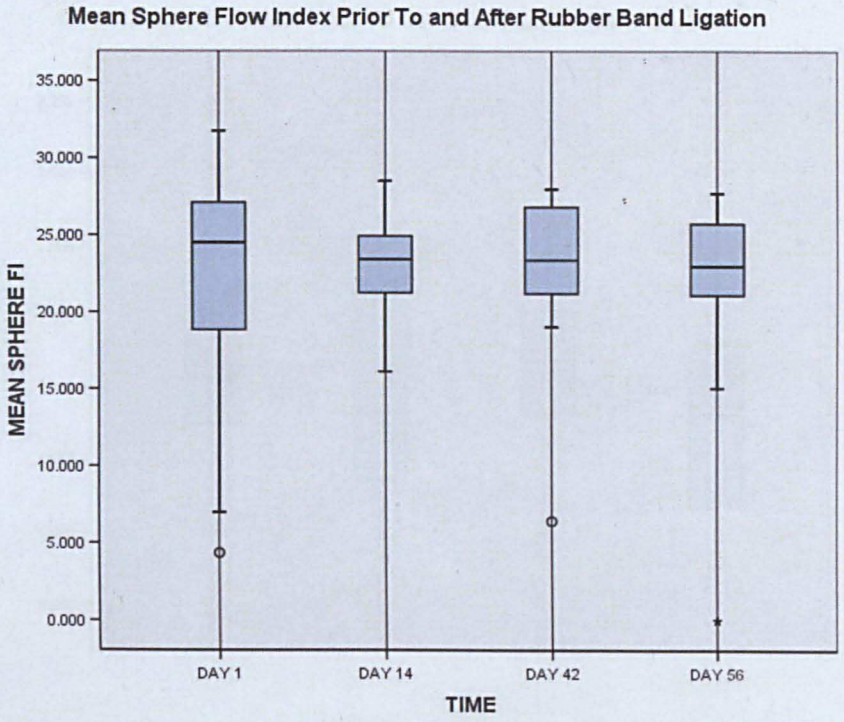

Figure 3-43 Study 5: Changes in sphere FI prior to and after rubber band ligation.

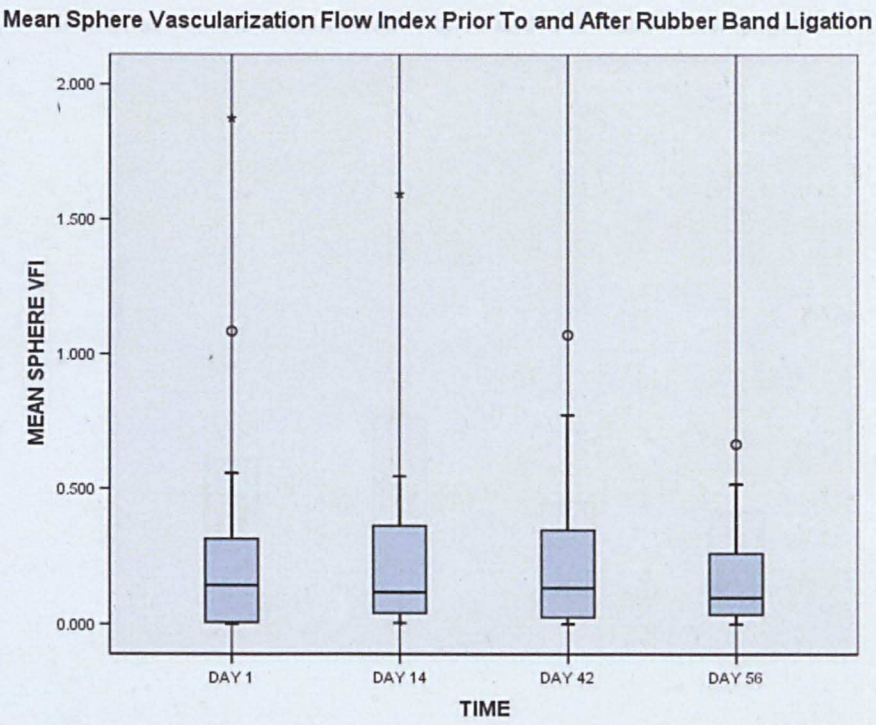

Figure 3-44 Study 5: Changes in sphere VFI prior to and after rubber band ligation.

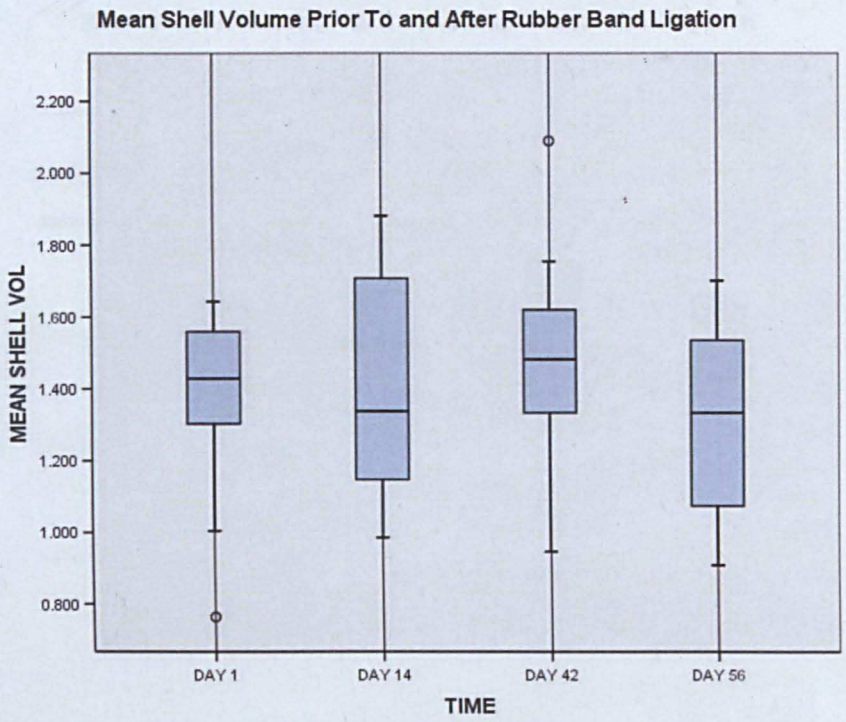

Figure 3-45 Study 5: Changes in shell volume prior to and after rubber band ligation.

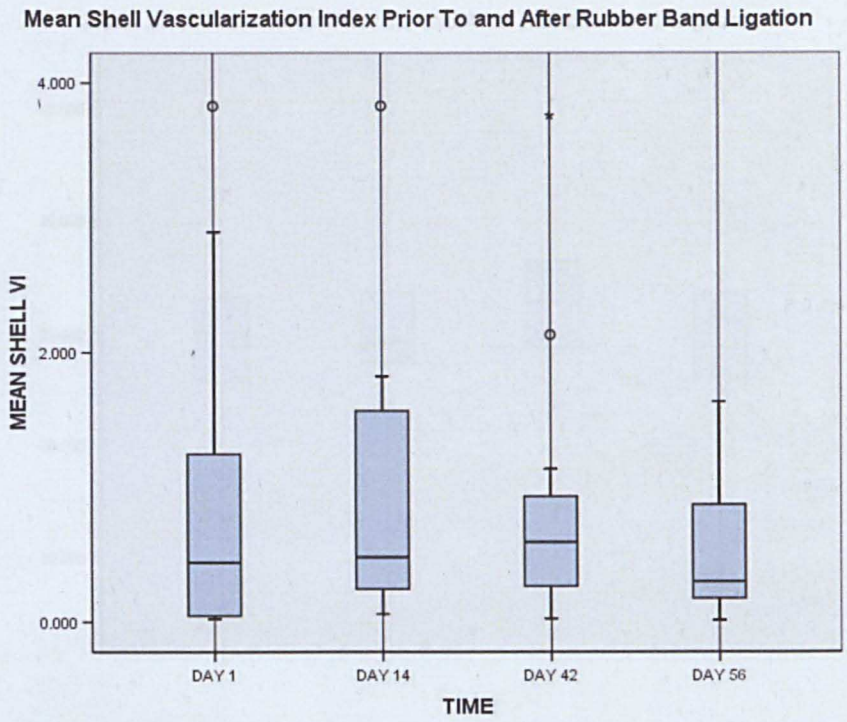

Figure 3-46 Study 5: Changes in shell VI prior to and after rubber band ligation.

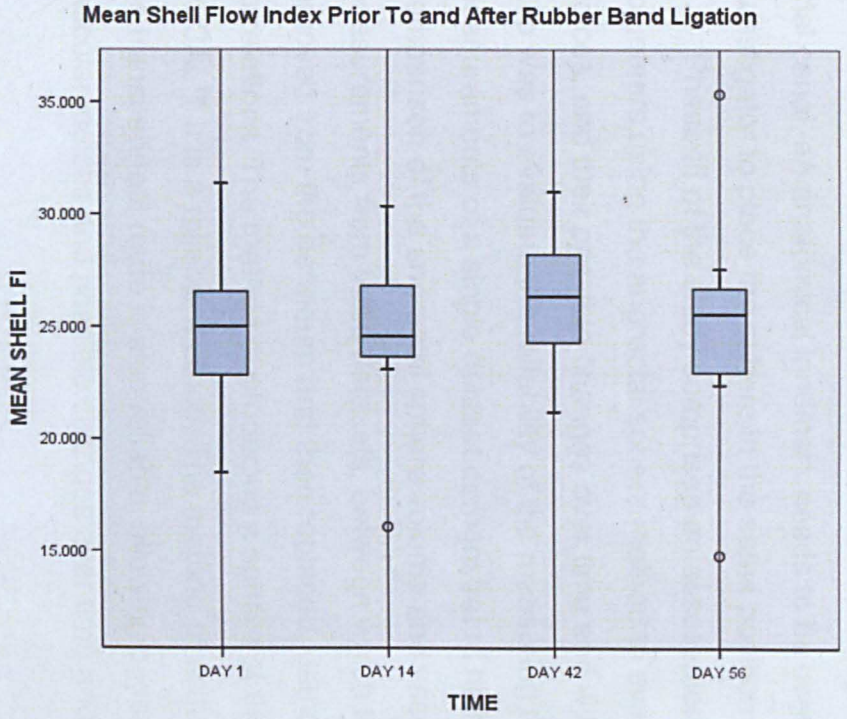

Figure 3-47 Study 5: Changes in shell FI prior to and after rubber band ligation.

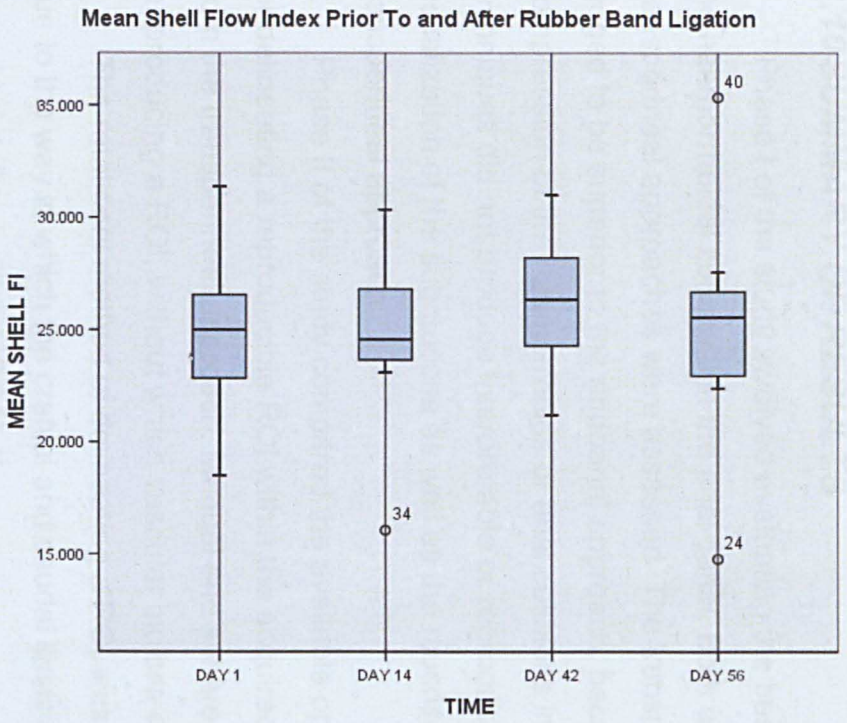

Figure 3-48 Study 5: Changes in shell VFI prior to and after rubber band ligation.

3.10 SUMMARY OF RESULTS

Phase I of the study involved evaluating the best technique for imaging the haemorrhoidal zone within the anal canal. Both endoanal and transperineal approaches were assessed. The transperineal approach was judged to be superior to the endoanal approach, because of lack of compression of the haemorrhoids or anal cushions in volunteers. Endoanal techniques did not produce interpretable or reproducible images. There was visualization of the submucosa as well as the mucosal folds with the transperineal approach.

Phase II of the study compared the available options within VOCAL II for delineating a reproducible ROI within the acquired 3D volume dataset from the transperineal approach. Manual and sphere options are available for producing a ROI, without which vascular indices cannot be measured.

The rotational method of delineating a ROI was found to be unreliable due to the way in which the cranial and caudal limits of the anorectum cannot be defined within VOCAL II.

The only other available option within VOCAL II was to set a sphere as the ROI. To allow a reproducible method of placing the sphere within the anal canal, an anatomical landmark needs to be used to allow the investigator to place the sphere in the same position in the anal canal.

Phase III of the study comprised an assessment of patients and volunteers using the anorectal sphere method to evaluate the vascular indices, and their possible changes over time and with treatment. The initial step was to evaluate the reliability of the measuring technique. Multiple measurements of a single dataset demonstrated high intraclass correlations. Comparison of the anorectal sphere volume and vascular index measurements from three datasets, between which the transducer had been removed from the perineum and then replaced, demonstrated high intraclass correlations. The method of producing a sphere at the anorectal angle from VOCAL™ II is a reliable method. The method of acquiring the 3D volume by the transperineal route is also reliable, allowing consequent evaluation of the vascular indices and possible changes over time and with treatment.

Evaluation of the anorectal angle sphere volume and vascular indices from healthy volunteers over a five-week period showed no significant differences between any of the three time-points.

Comparison between pre-treatment patients and healthy volunteers showed significant differences between the two groups for both sphere and shell volume and vascular indices, apart from the flow index measures.

Comparison between pre and post treatment sphere and shell volume and vascular indices showed significant differences for both sphere and shell volume, VI and VFI measures.

3.11 DISCUSSION

The first aim of the study was to establish a reliable method of acquiring an ultrasound based dataset including Doppler information, to enable assessment of vascularity of the anal cushions in subjects without haemorrhoidal symptoms, and in patients with haemorrhoidal symptoms.

Early on in the thesis period it became clear that anal cushions or haemorrhoids could not be imaged with an endoanal approach, due to the compressive effect of the transducer. Attempts to insert the transducer just distal to the haemorrhoids did not produce images with identifiable anatomy, partly due to artefact secondary to movement of the transducer and anal tone, which naturally expelled the transducer. Other authors confirm that anal cushions or the submucosa cannot be visualised or measured [207, 208] via the endoanal route.

In this study the transperineal route produced images, in all scanned patients and volunteers, which identified anatomical landmarks such as the IAS, EAS and the puborectalis at the anorectal junction. These findings are supported by recent publications, which evaluated anal cushions in the context of faecal incontinence and haemorrhoids by the transvaginal and transperineal routes [207, 209, 210].

In each of these studies two-dimensional ultrasound was employed to measure the cross-sectional area enclosed by the IAS, and the area enclosed by the anal cushions at the level of the mid-anal canal. The cushion to canal (C:C) ratio was derived from these measurements. A greater value of C:C ratio indicated larger anal cushions. The level of the canal was confirmed by visualising the U-shaped EAS [207], which the authors stated was indistinguishable from the puborectalis.

Rather than assessing 2-D ultrasound, this part of the thesis evaluated the acquisition of transperineal 3-D ultrasound datasets. This has been evaluated by other investigators in the dynamics of the pelvic floor [182], but not with respect to haemorrhoids. The phased array transducer employed in this study acquires 2-D images at pre-defined intervals, ensuring that the exact spatial co-ordinates of 2-D images are reconstructed

into a Cartesian based-grid system. 3-D US potentially allows for more accurate and reproducible volume measurements because the various display modalities allow the observer to correct for any surface irregularities [211]. Demonstration of the coronal image is specific to 3-D US and this plane provides more spatial information than either the transverse or longitudinal images, both of which are obtainable with conventional 2-D ultrasonography through a simple rotation of the transducer [169].

The second aim of the study was to assess methods for semi-quantification of vascularity of haemorrhoids and anal cushions. Therefore the next logical step was to decide which Doppler method was most suitable.

Due to the method in which pulsed Doppler information is obtained, it cannot be acquired from a 3D dataset. Although transperineal evaluation of pulsed Doppler information was not evaluated in this study, pulsed Doppler was rejected as a method of evaluating vascularity of the anal canal due to operator dependent error, experience of the operator and Doppler angle reliance [212, 213].

Generally if flow within individual vessels is to be examined, the combination of colour and duplex Doppler provides better information, however solid organs are often better assessed with power Doppler as it provides an overall view of the vascularity of the entire organ [214]. Given that the calibre of branches of the supplying rectal arteries (average diameter of 1.7mm [215]) and the haemorrhoidal venous plexus is small, and that flow is directly proportional to the fourth power of the radius according to Poiseuille's law [216], one can calculate that there is low velocity of flow within these vessels. Features of power Doppler include the ability to display the distribution of the strength of the returning Doppler signal, increased sensitivity to low flow, and reduction of noise in the image [199].

The most obvious advantage of the GE 730 Expert is the opportunity to evaluate the potential the combination of power Doppler angiography, VOCAL™ II and it's histogram facility. This software has been used in the evaluation of endometrial and subendometrial volume and blood flow of

apparently fertile and infertile females [217]; with some studies showing reduced VI, FI and VFI in women with unexplained subfertility [218].

The rotational method of volume calculation is well suited to solid organs such as the uterus and ovary, with the shell feature enabling calculation of vascular indices within tissues such as the endometrium. Within respect to the anorectum, which is a tubular structure, there is no method available within VOCAL II to measure and accurately mark the cranial and caudal limits of the ROI, thereby allowing accurate and reproducible assessment of the vascular indices.

The anorectal angle sphere was therefore used as a marker of vascularity in the anorectum, rather than as a true measurement of volume or vascularity. The high intraobserver ICCs obtained from studies one and two confirm that the transperineal 3D volume acquisition and the placement of the anorectal angle sphere are reliable tests. The ICC values were lower for the FI measurements than for those of volume, VI or VFI. FI is the average colour value of all colour voxels, representing average colour intensity. Other investigators have reported low FI ICCs for measurements of ovarian vascularity [219-221].

It is likely that the fluctuations in blood flow cause greater changes in the colour voxels than the gray-scale index, which remains nearly constant. The variation in the measurements of colour indices maybe partly due to the artifacts produced by power Doppler. Amso et al. quantified power Doppler energy images on 2D real-time scanning and observed a significant image-to-image variation [222].

Nelson et al. categorized power Doppler artifacts relating to gain and motion [223]. In this study there were pre-defined settings for each scan, which should have excluded any effects caused by gain. Motion artifact is caused by external movement, which causes colour in places where there is no flow, showing streaks and pseudo-vessels in the image. It is feasible that smooth muscle contractions in the rectal wall caused motion artifact that was not obvious on evaluation of the 3D volume during acquisition.

Unfortunately there was no option available for testing either the interobserver reliability of obtaining the datasets or of analysing the 3D-PDA data. This was related both to available funding, and the time required to

analyse the data. The approximate duration of data analysis for the entire study was three months.

It is promising that no significant changes of volume or vascularity indices were identified amongst the group of healthy volunteers over a five-week period. There are limitations to study three including small group size, and the lack of a gold-standard outcome measure to compare to.

At each ultrasound appointment, the volunteer was questioned about possible haemorrhoidal symptoms. Prior to the first ultrasound, the entire group completed the symptom questionnaire and scored zero in all parts of section 3 (see appendix 8-1, figs 8-7 and 8-8).

The results of study 4 are also encouraging; the patients' volume and vascular indices were significantly higher than those of the volunteers, particularly the volume and FI ($r > 0.5$). It is acknowledged however that these were essentially pilot studies and no attempt was made to control for differences between patients and volunteers. The numbers included in the study are too small to assess for effect of grade of haemorrhoid, or other surgical factors such as previous treatment. Apart from the small numbers in each group, other factors that may account for the higher volumes and vascular indices in patients include hormonal factors [224].

Aigner et al. used transperineal 2D US and duplex Doppler to evaluate the supplying branches of the superior rectal artery in groups of patients with haemorrhoids and healthy volunteers [225-228]. All the studies involved measurement of the calibre and peak velocities of the supplying vessels, and in each study, these were significantly lower in the healthy volunteer group compared to the patient group.

The investigators stated that did not study the middle or inferior rectal arteries and their branches, as they did not supply the corpus cavernosum recti [226]. This decision was also based on their macroscopic evaluation of five cadaveric rectal specimens in which the middle rectal artery was not identified. This conflicts with the findings of Thomson, who found that the middle rectal artery contributed to the blood supply of the anal canal in 76% ($n = 50$) of anorectal specimens [8].

Despite the factors described above, and although the acquisition of Doppler information was different to 3D-power Doppler angiography (PDA),

there are similarities in the findings of the current study and those of Aigner et al. All vascularity measures were lower in age-matched healthy volunteers compared to patients.

The final aim of this study was to assess the effect of rubber band ligation treatment on the vascularity of the haemorrhoidal zone. Significant changes were identified post rubber band ligation with a decrease in volume, VI and VFI. Aigner et al. failed to show a difference between pre-treatment and post-treatment measures of supplying vessel calibre and maximum velocity, in all grades of haemorrhoids and following PPH treatment [225, 227]. Therefore the authors concluded that PPH has little impact on the cause of haemorrhoids (hypertrophied arterial supply of the anorectal vascular plexus), thus explaining the higher recurrence rates in comparison to conventional haemorrhoidectomy [59, 229, 230].

Although the current study showed a decrease in volume, VI and VFI post rubber band ligation, the results should be interpreted with caution due to the small numbers involved. It should be noted that the anorectal sphere is possible a more global measure of vascularity as power Doppler signal from arterial, arteriovenous communications and the submucosal venous plexus are all included depending on the relative size of the sphere, the length of the anal canal and the exact position of the haemorrhoids with relation to the anorectal angle.

The choice of the anorectal sphere was dictated by the options available in VOCAL II; discussion with the designers of the software could lead to other options for setting a ROI, or indeed placing a grid system over the multiplanar display to allow accurate positioning of a ROI.

At the start of the thesis research period, a literature search performed in December 2004 using the terms "anal", "cushions", "haemorrhoids", "measurement", and "ultrasound" produced only one publication with direct reference to ultrasound assessment of anal cushions or haemorrhoids [226]. Since that time there have been two different approaches to assessing anal cushions or haemorrhoids: the cushion to canal ratio calculated from transvaginal 2D analysis of the mid anal canal [207, 209, 210], and 2D transperineal Doppler analysis of the feeding vessels to the haemorrhoidal zone [225-228, 231]. Further larger studies are

required to assess the impact on our understanding of the pathogenesis of haemorrhoids and the clinical role of these approaches. No other group has performed 3D transperineal PDA of the haemorrhoidal zone; this approach requires further studies to evaluate its role in the understanding of pathogenesis, but the preliminary results overlap with the findings of other groups. A role for vascular congestion in the haemorrhoidal zone requires further debate and investigation.

4 SURGICAL NUCLEAR PROBES

4.1 INTRODUCTION

Nuclear medicine has the potential to offer a different approach to the possibility of semi-quantifying the haemorrhoid complex. Before reviewing radionuclide studies where a quantitative approach is utilized, a general overview was carried out. This provided a summary of the types of study that could be undertaken using radionuclides, and aided in determination of the most suitable methodology.

4.1.1 Nuclear Imaging Modalities

4.1.1.1 Gamma Camera

The gamma camera, invented in the late 1950s by Hal Anger [232], is used to generate a two-dimensional projected image of a three-dimensional distribution of radioactivity. The gamma camera or scintillation camera is based on a large scintillation crystal coupled to an array of photomultiplier tubes to record the distribution of gamma-emitting radiopharmaceuticals. The main components are a large scintillation crystal, often sodium iodide (NaI) doped with a small amount of thallium, a bank of photomultiplier tubes which detect the scintillation light emitted from the NaI crystal, and a collimator in front of the NaI crystal to localize radiation.

The collimator is normally made out of a plate of lead or tungsten in which a large array of apertures are placed close to each other with a narrow septal thickness. The collimator mechanically confines the direction of incident photons reaching the scintillation crystal, thereby providing a means of localizing the site of the emitting sources. The scintillation crystal is highly efficient at converting the incident gamma rays or photons into visible radiation. These photons deposit energy within the scintillation crystal by a photoelectric or a Compton scattering interaction.

In a photoelectric interaction, the entire energy of the photon is transferred to an electron and the photon ceases to exist. In a Compton scattering interaction, only a partial amount of the photon's energy is

transferred to an electron, and the photon continues to travel at an angle to its initial direction. Approximately 10% of the incident photon's energy deposited in the scintillation crystal is converted into visible light photons (»3eV energy). These visible light photons are guided towards the photocathodes of the photomultiplier tubes, where they are converted into an electrical signal at the anode of each photomultiplier tube. The amplitudes of the signals from each anode are then examined by either an analogue or digital positioning circuitry to estimate the x and y coordinates of the scintillation event on the crystal. The apertures of the collimator physically restricts the gamma radiation, thereby ensuring that the x and y coordinate of the events on the scintillation crystal matches the x and y coordinates of the two-dimensional projection image of the object of interest.

Most clinical examinations are carried out with a parallel hole collimator (apertures parallel to each other) since it provides a good combination of resolution and sensitivity for most regions of the body with no geometrical distortion. The spatial resolution of scintillation imaging is determined by the intrinsic resolution of the camera and the resolution of the collimator. The intrinsic resolution indicates the ability of the camera to locate the point at which the incoming photon interacts with the scintillation crystal. This is approximately 2 – 3 mm in modern scintillation cameras. The collimator's contribution to the resolution can be much larger. The collimator resolution depends on its design; shape, diameter and length of apertures; and the distance between the region being imaged and the collimator. Typically, the collimator resolution is 1 cm at a distance of 10 cm from the region of interest, although detail in the image ultimately depends upon uptake of the radiopharmaceutical.

4.1.1.2 Geiger-Muller Probes

Nuclear medicine originated with the use of probe detectors, primarily for tumour localization; the majority of current research concentrates on probes used intra-operatively; but the first relevant probe work used external detectors. In 1942 Marinelli and Goldschmidt [233] used a hand-held Geiger-Muller (G-M) tube to compare phosphate-32 (32P) labelled sodium

phosphate uptake in melanoma, mycosis fungoides and normal skin. Uptake and turnover was higher in melanoma than in normal skin. It was also noted that probe counts were higher over bone than elsewhere. This demonstrated that probes detect counts from surrounding tissue, not just from the volume immediately adjacent to the detector. This will be considered later in the discussion on probe design.

In 1946 Low-Beer et al [234]., correctly classified 24 of 25 breast lesions in preoperative patients as benign or malignant using a hand-held G-M tube with 32P. Axillary and supraclavicular lymph nodes were also evaluated, but the results were equivocal. It is now well accepted that external imaging is unsatisfactory with respect to localizing soft-tissue tumours smaller than 2 cm in diameter [235, 236].

Selverstone et al., were the first to report the intra-operative use of a probe in 1949 [237]. Cylindrical G-M tubes, 3 and 5mm in diameter, were employed to localize and in some cases demarcate cerebral tumours. The patients were given 32P-buffered sodium phosphate prior to operation. Tumours were correctly localized in 29 of 33 cases. There were two false-negative cases in which the probe was not adequately employed. The probe gave a false-positive result in one, a case of diffuse gliomatosis, and a true-negative result in another. This study demonstrated the issues with using 32P as a tumour-seeking tracer. Its maximum beta particle range is in the range of 2 – 8 mm in soft tissue [236, 238], and therefore the probe must be within this distance of the tumour. 32P is a non-specific tracer, and any cause of increased metabolic activity such as inflammation, will cause false-positive results. Finally, the radiation dose from 32P is not insignificant.

The early work with 32P and G-M counters worked because the GM tube had very high detection efficiency for beta particles, and the relative high energy of the beta particles allowed penetration of up 8mm of tissue to reach the G-M tube. The success of this approach was limited in part by the absorbed dose per unit activity for 32P. It is 300 – 600 times greater than that of the currently most frequently used isotope, technetium-99m (99mTc). Between 1.2 and 2.4 MBq of 32P is equivalent in dose to the 740 MBq of 99mTc that is typical in diagnostic nuclear medicine. This meant that there would be very low count rates from the tumour or larger doses would need

to be administered. In the early work with 32P [237], 37 – 148 MBq doses were injected for intra-operative probe-assisted surgery. It should be added that these studies were carried out before guidelines had been established for medical applications of radiation.

4.1.1.3 Scintillation Detectors

G-M counters have low sensitivity to gamma rays, and therefore other alternatives have been examined. The only readily available solution for a gamma ray-sensitive probe in the 1950s was the scintillation detector. Harris et al., reported the use of a thallium-activated caesium iodide scintillation detector coupled to a rigid Lucite light pipe with iodine-131 (131I) to localize thyroid tissue and recurrent thyroid carcinoma in patients undergoing neck exploration [239]. Unlike G-M counters the gamma ray-detector probe is not limited by distance from the volume of interest, but it is limited by its detection of distant background activity. Thus, a large volume of low activity may obscure a small tumour with increased radionuclide activity, and a more distant hot source may be interpreted as a nearby tumour.

Woolfenden et al., used a 2.5 mm x 9 mm NaI detector passed through the channel of a fibreoptic bronchoscope to assess the bronchial tree for cobalt-57 bleomycin activity in lung tumours [240]. Sensitivity, specificity, accuracy and predictive values were compared for the NaI detector, chest X-ray film and bronchoscopy alone in a group of 34 patients. The NaI detector performed satisfactorily, but was limited by its inability to detect tumours smaller than 6mm adjacent to the detector leading to the lowest sensitivity of the three modalities. This is a result of the activity level in the tumour and the tumour-to-background activity ratio.

4.1.1.4 Solid State Detectors

The reduction in the use of G-M tubes and scintillation detectors was due in part to the introduction of solid state detectors, which are essentially solid versions of gas-filled ionization chambers. They have several advantages over G-M detectors, including better energy resolution allowing reduction of the background count. They can be manufactured in very small

sizes and in a variety of shapes, and therefore they can be used for counting radioactivity in small superficial lesions such as those of the skin and eye. Also they may be introduced through catheters into body cavities such as those of gastrointestinal and genitourinary tracts, the cardiac chambers and great vessels, or they may be implanted into tissue through trochar needles [241]. They can take narrow entry windows to allow the counting of very low energy beta and gamma rays [242]

The earliest use of solid state probes was as direct replacements for G-M tubes to detect 32P in eye tumours [243, 244]. Pircher et al., examined 32P uptake in melanomas of the anterior hemisphere of the eye and in lesions of the skin [243]. In four cases of skin lesions metastatic from carcinoma of the breast, the investigators were able to show a decrease in differential uptake of 32P one week after initiation of radiotherapy, albeit statistical significance was not assessed.

The possibility for miniaturization was demonstrated by Lauber, who placed a detector inside a needle with an outside diameter of 1.1mm and multiple detectors inside a 1.5mm diameter needle [245].

Marcus evaluated lithium-drifted silicon probes [Si (Li)] for gamma-ray detection of 87m-strontium and 99mTc-polyphosphate in healing periodontal lesions, and 67-gallium citrate in prostatic cancer [246]. Problems with the study included the low stopping power for Si (Li) for gamma rays and the lack of tumour specificity of 67-gallium citrate.

Further work on periodontal lesions was reported by Garcia et al., who used a cadmium telluride (CdTe) probe; the counting efficiency of CdTe for 99mTc was comparable to that of a rectilinear scanner with a NaI (Tl) crystal [247]. Lennquist et al., used a CdTe probe with iodine-125 in thyroid cancer surgery [248].

Scintillation and semiconductor probes have been used inside the body for a variety of applications other than tumour detection. Most of these involve localization of abnormalities that are already known to be present. The most common intra-operative application has been in the localization of osteoid osteoma, not visible with naked eye examination of the surgical field, which concentrates 99mTc [249-251]. Kirchner et al., demonstrated the reliability of the procedure after follow-up in 12 cases [252]. The nidus of the

tumour is successfully removed, and normal bone tissue is spared. Perkins and Hardy [253] presented a case series of 68 procedures undertaken over 15 years. This included excision of osteoid osteoma, osteoblastoma, hamartoma, Brodie's abscess, chronic bone infection, ectopic parathyroid adenoma and metastatic neuroblastoma. In the majority of cases a CdTe probe was used, in conjunction with 99mTc-hydroxymethylene diphosphonate for bony lesions, 201Tl-thallous chloride for examination of ectopic parathyroid adenoma, and 123I-MIBG for examination of metastatic neuroblastoma. In all these cases, the lesions were successfully excised with confirmation of complete excision.

Aslam et al., used 123I-MIBG pre-operatively in two children with neuroblastoma [254]. 123I-MIBG is a low-energy emitter, and therefore extensive shielding of the detector was not required. It was more appropriate in children because of the lower radiation dose.

4.1.2 Radiopharmaceuticals

The rate of colloid transport and movement through lymphatic pathways is strongly related to the particle size of the colloid [255, 256]. Particles larger than 0.004 – 0.005 mm are preferred, as smaller particles have been reported to penetrate the capillary membranes and therefore may be unavailable to migrate through the lymphatic channel. Particles that are smaller than 0.1mm show the most rapid disappearance from the interstitial space into the lymphatic vessels, and yet have significant retention in the lymph node. Larger colloid particles, approximately 500mm, showed a much slower rate of clearance from the interstitial space with significantly less accumulation in the lymph node.

A gold-198 colloid [257] has been evaluated. It has a relatively uniform particle size of 3 – 5 mm, with a 2.7 day physical half-life and emits a 412 keV gamma photon and beta particles. This radionuclide delivers a high radiation dose at the injection site, and the (412 keV) gamma photon is not suitable for scintillation camera imaging.

Various 99mTc-labelled colloids and albumin agents have also been assessed. 99mTc nanocolloid, a labelled human albumin colloid, is used in Europe. Ninety five per cent of the colloidal albumin particles that comprise

this agent are smaller than 0.8 mm [258]. Although 99mTc human serum albumin successfully images flow, it is not particulate in nature and shows poor retention within the lymph nodes [255], and therefore delayed images or gamma probe intra-operative explorations may miss the sentinel node.

4.1.3 Choice of Radionuclide

An important consideration in the methodology and choice of nuclear medicine imaging modality is the selection of radionuclide, and therefore the radiation energies, with which it is used. Ideal characteristics of a radionuclide in a diagnostic arena include:

- Gamma radiation suitable for imaging (in terms of energy and abundance).
- A half-life of appropriate length, long enough to allow optimal localization and imaging but not unnecessarily long such that an unsuitable radiation dose is given.
- Absence of particulate emissions to substantially reduce the radiation dose.
- High specific activity (a high radioactivity-to-mass ratio provides sufficient gamma radiation with negligible mass effect i.e. the radionuclide behaves as a tracer of physiologic function.
- Absence of pharmacologic and toxic effects.
- A biodistribution suitable for the intended procedure, i.e. localization only in the tissue of interest.
- Availability at a reasonable cost.
- If the radionuclide is to be prepared on-site, the procedure should be as simple as possible and there should be a radiopharmaceutical quality control program implemented on site.

4.1.4 Radionuclides and γ-Cameras

Radionuclides used in gamma camera imaging include technetium-99m, indium-111, iodine-123, iodine-131, thallium-201, gallium-67 and selenium-53 [259]. ^{99m}Tc is the most widely used as it has favourable emission energy of 140 keV, is cheap, easily available and can be bound to

many ligands. The half-life of 6.02 hours is excellent for same-day imaging, but is inadequate if imaging is requires for a period of 24 hours or more. ^{111}In is more expensive, but has a favourable emission spectrum (173 keV and 247 keV), good binding characteristics and a longer half-life allowing delayed imaging.

^{131}I has a long half-life of 8 days and can be bound to many ligands including proteins. It emits a gamma photon (364 keV) which is only moderately favourable for imaging, and also emits a beta particle resulting in increased patient radiation absorbed dose, hence its use as a therapeutic radiopharmaceutical in thyroid and other cancers. ^{123}I has a more suitable profile, with a favourable half-life and gamma-emission energy, resulting in better imaging and a reduced radiation dose to the patient, but is much more expensive.

^{67}Ga is used when delayed imaging is necessary. It has a complex emission spectrum, which leads to some loss of image quality. ^{53}Se has limited use with its long half-life of 50 days, leading to high radiation doses and poor counting statistics.

4.1.5 Radionuclides and γ-Probes

The major factors affecting the choice of radionuclide are photon energy and physical half-life. For accurate localization, e.g. with sentinel lymph node detection, it is more appropriate to use low-energy radionuclides [260, 261]. The effect of attenuation of the low energy gamma photon by tissue is minimal since the gamma probe is in direct contact with tissue of interest during the procedure. Low radioactivity concentration in distant organs will improve detection efficiency of the gamma probe when used with a low-energy radionuclide. The use of a lower energy photon emitter also reduces the problem of radiation exposure to staff.

The use of high-energy radionuclides reduces the specificity of the procedure, such as scattered radiation from sites of high normal uptake, such as the liver [262]. Medium to high-energy emitters such as ^{111}In and 131I, require increased shielding around the detector element making the probe heavy and bulky, thereby reducing acceptability to the user [263].

Virtually all current lymph node-avid radiopharmaceuticals are labelled with ^{99m}Tc, whereas tumour-avid radiopharmaceuticals, such as monoclonal antibodies and antibody fragments, may be labelled with ^{99m}Tc, ^{111}In, ^{125}I, ^{123}I or ^{131}I. Most available probe detectors appear to have reasonably high intrinsic efficiency for ^{123}I, ^{125}I (35 keV), ^{99m}Tc, and other low-energy photon emitters [264].

The use of ^{131}I and ^{111}In is not ideal because of their high-energy spectrum, and although the use of ^{125}I is attractive from a physical point of view, it would appear to be contraindicated for routine use because of its high patient radiation absorbed dose.

Most intra-operative procedures have been carried out using 99mTc. It is a safe, inexpensive readily available radionuclide with excellent imaging characteristics, which can be readily bound to many proteins. Given the above attributes it seems necessary to consider ^{99m}Tc before any other radionuclide for gamma probe studies.

4.1.6 Functional Studies

Other chapters in this thesis focus on imaging modalities where anatomical structure is the basis on which measurements are taken. Nuclear medicine investigations essentially measure organ perfusion and functional uptake of a suitable tracer. All of the studies mentioned so far have focused on localization of pathology, but organ function has also been studied.

4.1.6.1 Dual Isotope Techniques

Quantitative approaches to measuring vascular permeability in adult respiratory distress syndrome have been examined in the intensive care setting. Cardiologists and nuclear medicine physicians have measured cardiac output and ejection fraction [265].

The principle of such studies is to use two radiolabelled tracers that act in different ways at the site of interest. In 1957 Aviado and Scmidt [266] summarized a series of investigations in which they used diffusible ^{131}I-albumin and non-diffusible ^{32}P-labelled red blood cell tracers to study the development of pulmonary oedema in dogs. Emissions from the radiotracers were measured with a Geiger counter inserted into the pleural space.

Technical limitations only allowed the use of one radiotracer per animal, however the authors did observe an increase in ^{131}I counts in lung occurring agonally, at a time when ^{32}P counts were known to fall. This may have reflected increased extravasation of plasma albumin into the lung parenchyma.

Potchen and Welch [267] suggested a modification of the two-tracer approach to study regional lymph transport of proteins. A pulse-height analyser distinguished between gamma emissions from a diffusible ^{131}I-albumin and a non-diffusible ^{51}Cr-RBC tracer administered simultaneously. The rate of albumin accumulation in leg muscles of intact animals was only assessed indirectly.

Basran et al., studied lung vascular permeability in ten patients with ARDS [268]. The authors anticipated that monitoring in patients on intensive care units would have to occur simultaneously to therapeutic procedures, such as drug administration. Therefore anticipated changes in circulating blood distribution were corrected for by simultaneously monitoring the distribution of ^{99m}Tc-labelled red blood cells. Radiolabelled ^{113m}In-transferrin was used as the protein marker. The study used a NaI thallium activated crystal-probe detector system; with a dual channel analyser to detect and record ^{99m}Tc and ^{113m}In counts simultaneously and separately.

Indium count rates recorded over the lung field provided a measure of the circulating and extravascular radiolabelled transferrin. To correct for normal clearance from the circulation and for radioactive decay, the lung count rates were divided by the cardiac blood pool count rates. If there were no accumulation of protein, the indium rates of lung count rates to heart count rates would remain constant throughout the study. Extravasation within the lung would result in the increase of this ratio with time. To allow for changes in thoracic blood distribution radioactive decay and loss of transferring to other extravascular compartments, it was necessary to correct using a marker that is confined to the intravascular space, such as ^{99m}Tc-labelled red blood cells. Simultaneous recordings over the lung and cardiac blood pools, and dividing the indium ratio by the technetium ratio, allows the investigator to calculate the lung transferring index:

The rate of change of the lung transferrin index provides a plasma protein accumulation (PPA) index for the lung. PPA index values were compared between an ARDS group (1.83) and a healthy volunteer group (0.1). ARDS patients were clearly distinguished from the volunteers ($p < 0.001$).

Bedside probe studies have proven to be useful in the management of patients in intensive care. Perkins et al., demonstrated the value of assessing renal and hepatobiliary function, gastric emptying and lung vascular permeability in an adult intensive care unit [269].

4.1.6.2 Washout Techniques

Although myocardial perfusion imaging is now generally performed using positron emission tomography (PET) or single photon emission computed tomography (SPECT), earlier researchers assessed myocardial viability using thallium-201 scintigraphy, using gamma cameras [270] as well as gamma-detecting probes [271]. Viability of myocardium is assessed by measuring the washout rate of 201Tl from the myocardium after intravenous administration. The distribution of ^{201}Tl within the myocardium is a complex mechanism. Interventions such as ischaemia with reperfusion, ouabain and hypoxia have only modest effects on ^{201}Tl uptake and retention by the myocardium. Under clinically relevant conditions the principle factor determining the rate of ^{201}Tl washout from the myocardium appears to be the rate of decline in ^{201}Tl levels in the blood. Marked decreases or increases in myocardial blood flow have little impact on net loss of isotope from the heart.

Differential thallium washout, known as redistribution, occurs in clinical scans because regions with normal perfusion lose thallium faster than regions in which flow is reduced. The lower initial concentration in the low flow region permits extraction and retention of thallium for longer against rapidly declining levels in the blood. In contrast a normally perfused region obtains a higher initial concentration of the radioisotope and thus is less able to maintain those levels as blood activity falls. Therefore thallium redistribution is widely regarded as evidence of myocardial viability.

4.1.7 Choice of Methodology

4.1.7.1 γ-Camera versus Intraoperative Probe

A single-head g camera was available for research purposes, at the time of planning the study protocol, in the Medical Physics department at Queen's Medical Centre. The main concern with using the g camera was the issue of resolution, the ability to distinguish the haemorrhoidal zone from the surrounding tissue. Spatial resolution depends on the intrinsic resolution of the g camera, the resolution of the collimator and the regional uptake of radiopharmaceuticals.

A literature search failed to find any studies of g camera imaging of the rectum or anal canal where an attempt is made to quantify the volume of a section of the lower gastrointestinal tract. Although small volumes of tissue are visible as discrete entities, for example in lymph node scintigraphy, no attempt is made to measure size or volume, only to distinguish between normal and tumour-laden lymph nodes.

The advantage of the intraoperative probe is that it is small and can be positioned on the haemorrhoid itself via a proctoscope. Its field of view is much smaller than that of the g camera, such that it should be able to distinguish between haemorrhoid and surrounding tissue, purely on the basis of the positioning of the probe. Given the importance of the directional properties of the detector, care must be taken in the positioning of the probe.

4.1.7.2 Dual Isotope versus Washout Method

Although these methods are discussed as options for the methodology of assessing change in haemorrhoids before and after treatment, they are measuring different entities, and therefore it is pertinent to discuss what should be measured when assessing the success of treatment.

These issues are discussed in the haemorrhoid symptom index chapter. After review of the literature, it becomes clear that success of treatment is assessed subjectively by the surgeon and the patient. Most classification systems divide the disease into stages of increasing severity

as denoted by degree of prolapse. Lunniss and Mann [70] relate increasing severity of prolapse to increasing size of the haemorrhoids, which again is assessed subjectively.

With respect to assessing change in the haemorrhoid complex after treatment, it is logical to attempt to measure size or volume of the haemorrhoids before and after treatment.

Given that the washout technique measures perfusion, resulting in a $t^{1/2}$ measurement for a radioisotope in the region of interest, it is essential to consider what perfusion is, and its relationship to the volume or size of the region of interest.

In physiology perfusion is the delivery of arterial blood to a capillary bed in the biological tissue. Tissue perfusion can be defined as the volume of blood that flows through a unit quantity of tissue and can be expressed in the unit ml blood /100g tissue. In this case distribution of radioisotope to the region of interest is the result of both blood flow delivery of radioisotope and extraction of the radioisotope by the biological tissue.

Application of the washout technique to assessing change before and after treatment of haemorrhoids increases the complexity of the study by performing two sets of measurements. Even if a radioisotope with a short half-life were used such as ^{99m}Tc (6.02 hours), the study would have to be carried out on two separate days, to allow time for the ^{99m}Tc to decay. The results will be affected by variation in positioning of the patient and positioning of the probe. There is also the logistical consideration of having patients returning on consecutive days to the medical physics department.

The dual isotope technique is simpler to carry out. Patients would only need to attend on one occasion, and changes in the experimental set-up would be less of an issue i.e. positioning of the patient. The dual isotope technique is also semi-quantitatively measuring volume, since the number of gamma photons measured is related to the number of blood components labelled by radioisotope in the set region of interest.

4.1.8 Radioisotope Choice

^{99m}Tc was chosen as it is safe, inexpensive, readily available and has excellent imaging characteristics. ^{123}I was also an attractive option as it is also a low energy emitter (27 keV & 159 keV) and obviously has a different peak energy profile from ^{99m}Tc. At the time of planning the methodology, ^{123}I was difficult to purchase and more expensive than the alternative option of ^{111}In. Although the gamma probe is not ideally suited to the ^{111}In profile, the dual isotope technique was still the most attractive method for investigating change in haemorrhoids after treatment, and therefore this was decided to be the best compromise.

4.1.9 Labelling Issues

Fundamental to the procurement of high-quality blood pool studies, whether for nuclear cardiac imaging studies or gastrointestinal haemorrhage, is the use of a suitable radiopharmaceutical that remains within the vascular space. There are three major categories of radiopharmaceutical available for blood pool imaging: labelled red blood cells (RBCs), labelled human serum albumin (HSA) and labelled sulphur colloid (SC).

In the main ^{99m}Tc SC was used in scintigraphy of gastrointestinal haemorrhage, where its advocates theorized an improved contrast between the exponentially diminishing background activity and areas of extravasated radiopharmaceutical. ^{99m}Tc SC, with a half-life of two minutes in patients with normal liver function, is rapidly extracted from the circulation. Thus, detectable activity with this agent is removed from the circulation in 5 – 10 minutes. Advocates recommended repeated administrations of 370 MBq doses as a way of expanding the time frame of this radiopharmaceutical. The radiation exposure to the liver and spleen is substantial. Each 370 MBq of ^{99m}Tc SC delivers 3.4 rad to the liver. Given the radiation exposure and that no advantage has been found for ^{99m}Tc SC over 9^{9m}Tc RBCs, either clinically or in experimental models, it is inappropriate to consider using this radiopharmaceutical.

Imaging of the cardiac blood pool has been compared using ^{99m}Tc HSA and 99mTc RBCs. Thrall et al., analysed the relative distributions of ^{99m}Tc RBCs and ^{99m}Tc HSA on end-diastolic frames of gated blood-pool studies and on whole-body anterior pinhole images [272]. ^{99m}Tc RBCs demonstrated greater relative percentage localization in the cardiac blood pool, higher target-to-background ratios in the left ventricle, and less liver concentration. Several other investigators have suggested that ^{99m}Tc RBCs might be superior to ^{99m}Tc HAS because of the in vivo stability of ^{99m}Tc RBCs and the observation that albumin leaks from the vascular space with time [273, 274]. Such leakage reduces effective tracer activity and the target-to-background ratio.

4.1.10 Methods of Labelling Ted Blood Cells with ^{99m}Tc

The ability of ^{99m}Tc pertechnetate to become attached to RBCs that have been exposed to stannous ion has been known for almost four decades [275]. The labelling methods outlined in the literature involved in vitro methods using stannous chloride, with repeated centrifugations and washing steps before and after addition of ^{99m}Tc-pertechnetate. The procedure was cumbersome and time-consuming. Stannous pyrophosphate was introduced as the reducing agent, which increased labelling efficiency and reduced the number of manipulations required in the labelling sequence [276]. Clinical application was limited until the introduction of a relatively simple in vitro kit for ^{99m}Tc RBC labelling by Smith and Richards in 1975 [273].

In 1974, McRae et al., observed that the tissue distribution of ^{99m}Tc pertechnetate in rats was altered for up to thirteen weeks following administration of stannous ion [277]. The tin prolonged the clearance of technetium from the blood. Chandler and Shuck observed similar effects; they noticed increased intravascular radioactivity on brain scans performed with pertechnetate following ^{99m}Tc pyrophosphate bone scan [278]. These observations led Pavel et al [279]., and Stokely et al [274]., to suggest that red blood cells could be intentionally labelled in vivo by intravenous injection of stannous pyrophosphate 20 minutes to 24 hours before the administration of ^{99m}Tc. Pavel et al., administered the stannous ion 20 minutes before the

^{99m}Tc pertechnetate, reported in vivo labelling efficiency of 96%, which persisted for up to 60 minutes after ^{99m}Tc pertechnetate injection [279].

4.2 AIMS

The hypothesis states that radionuclide probe investigations can identify a semi-quantitative reduction in haemorrhoidal volume following rubber band ligation of haemorrhoids. Comparison between volume reduction and change in symptom scores will also be made.

Prior to the clinical evaluation of patients, the surgical probe needed evaluation to ensure accuracy and reproducibility of radionuclide counts, which is presented in phase I. The clinical evaluation of patients with haemorrhoids is presented in phase II.

4.3 METHOD PHASE I

4.3.1 Evaluation of Equipment

Before starting the recruitment phase of this project, two second-hand probes had been acquired by the Medical Physics department at Queen's Medical Centre. The department already owned one surgical probe; but it could not be used for the haemorrhoid research, as it had to be kept in reserve for any potential clinical work. Therefore the probes' operational characteristics were examined, to determine suitability for the haemorrhoid research. This was carried out with the help of a trainee medical physicist.

In order to distinguish between ^{99m}Tc and ^{111}In, different energy windows are set on the CTC4 electronics box. This particular model does not provide a display of the energy spectrum, and therefore it was not possible to check visually whether the photopeak coincides with the pre-set photopeak energy window. As the results were critically dependent on the accurate and reproducible performance of radionuclide counting, it was essential to assess the performance of the probes with a known amount of radiopharmaceutical.

4.3.2 Equipment

Each of the second-hand probes was compared to the working surgical probe. Low activity (~ 1MBq) point sources of ^{99m}Tc and ^{111}In in syringes were placed on a piece of benchkote. The control probe and one of the second-hand probes were clamped 1 cm above the source, as shown in figure 4-1. The energy window was set by two potentiometers, calibrated in arbitrary units from 0.0 to 10.0. The energy range switch determined whether the range was 0 – 200 keV for use with ^{99m}Tc, or 0 – 1 MeV for use with ^{111}In.

To reduce radiation exposure, the source was shielded by lead blocks. After use the sources were disposed of in the relevant shielded sharps bin. The surgical probe equipment consists of three main items, as shown in figure 4-7: the handheld probe, the counting electronics and a count rate meter. All are manufactured by Radiation Monitoring Devices (Watertown, MA, USA). The handheld probe contains a solid-state cadmium telluride detector surrounded by tungsten for collimation. The remainder of the probe was made from surgical stainless steel and contained the pre-amplifier electronics. The probe was connected to a CTC4 electronics box, which enabled the user to set the counting window to be used. There is also an option to display the number of counts detected in a given time period. The box shown on top of this was the count rate meter that displayed the counts detected per second in the selected window.

There were two different sizes of probe tip available for use with the probe as shown in figure 4-7. The left hand probe contains a 5mm diameter detector, whereas the right hand one contains a 10mm diameter detector. The tungsten collimation can clearly be seen on both the probes. The smaller detector improves the ability to localise the source of γ-rays, whereas the larger detector increases the sensitivity of the probe; hence the choice of detector was dependent upon its intended use as well as ergonomic considerations.

4.3.3 Examination of the Surgical Nuclear Probes

Dead time was examined by placing each probe immediately adjacent to the source and obtaining a 10 second count. This was repeated at set distances up to 20 cm from the source. The measurements were found to obey the inverse square law in both probes, and therefore neither probe had any significant dead time when used with low activity sources. This was checked with both ^{99m}Tc and ^{111}In.

Probe 1 and the working surgical probe were clamped at a set distance above a 1 MBq source of ^{99m}Tc. The energy window was set at its lowest setting (0 – 3 keV), and the counts detected by each probe in a 10 second period were recorded; this was repeated three times for each energy window. The fixed width energy window was increased in steps of 3 keV, and for each step the aforementioned process was repeated, until measurements had been recorded over the whole energy range (0 – 198 keV). The whole process was repeated with probe 2.

As the electronics boxes were interchangeable, the experiments were repeated, as set out in table 5-1 (experiments 2 and 4), in an attempt to distinguish whether any problems were due to either the probe or the electronics box.

The detected counts were corrected for decay. Interpreting the results of experiments 1 – 4 using ^{99m}Tc dictated that only probe 2 needed comparison to the surgical probe for ^{111}In. In order to detect the second peak of ^{111}In, the energy range had to be changed to 0 – 1 MeV and the window width widened to 10 keV. This led to some loss of energy resolution in the results.

4.4 RESULTS PHASE I

The results are displayed in figures 4-2 to 4-6. The mean of the three counts recorded per energy window is plotted against the detected energy. Each figure compares the energy spectrum of one of the second-hand probes to that of the working surgical probe.

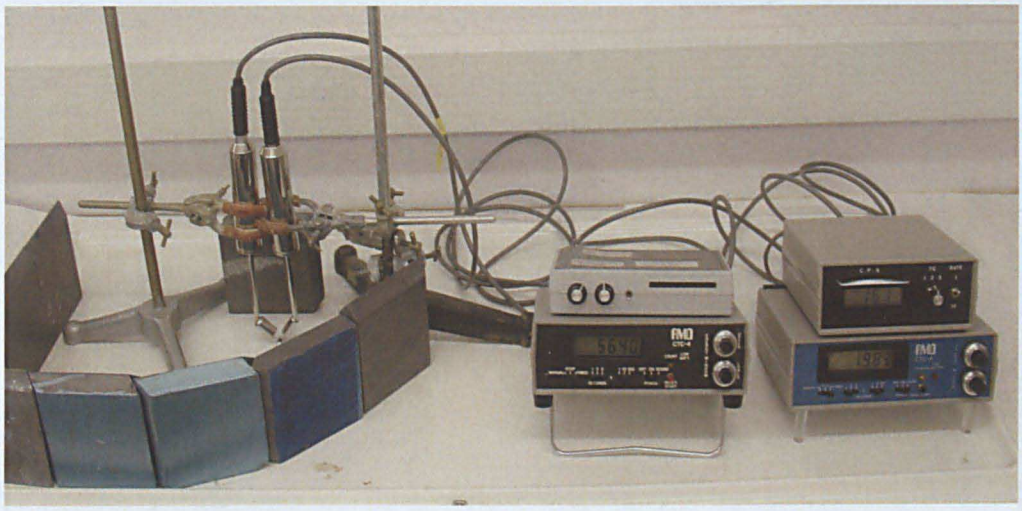

Figure 4-1 Testing of the working surgical probe.

The radiation source was placed behind the lead blocks. The electronic boxes are seen on the right of the image.

Experiment	Spectrum Analysed	Combination A		Combination B	
		Probe	Box	Probe	Box
1	^{99m}Tc	Surgical	Surgical	1	1
2	^{99m}Tc	Surgical	1	1	Surgical
3	^{99m}Tc	Surgical	Surgical	2	2
4	^{99m}Tc	Surgical	2	2	Surgical
5	^{111}In	Surgical	Surgical	2	2

Table 4-1 Combination of probe and box experiments.

This allowed comparison of both components of probes 1 and 2 with the surgical probe, which was known to be accurate and reproducible.

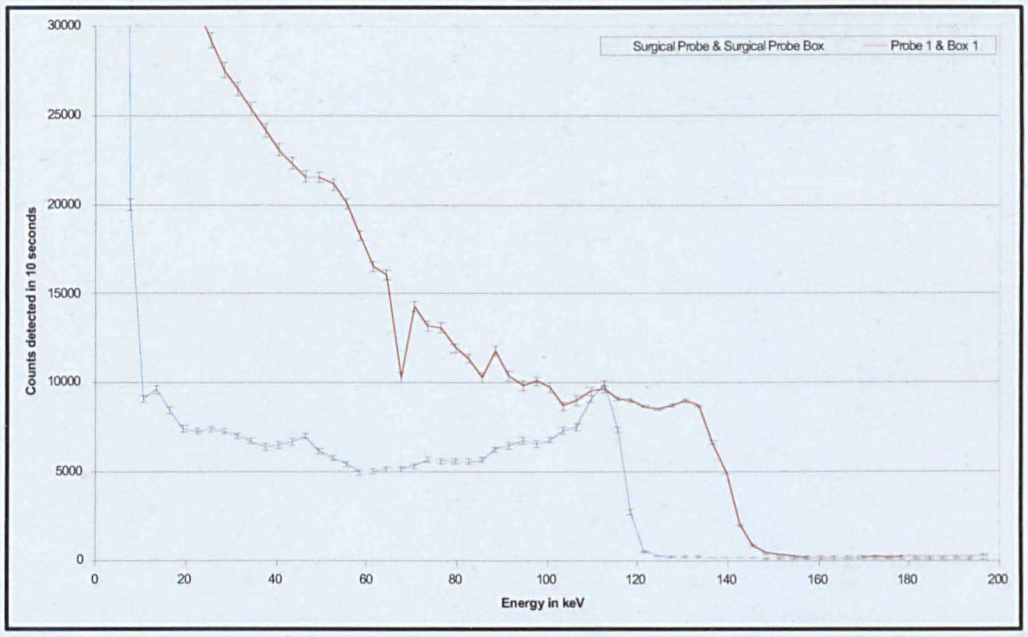

Figure 4-2 Experiment 1.

Probe 1 clearly does not show a peal for ^{99m}Tc; its energy spectrum shows Compton scattering.

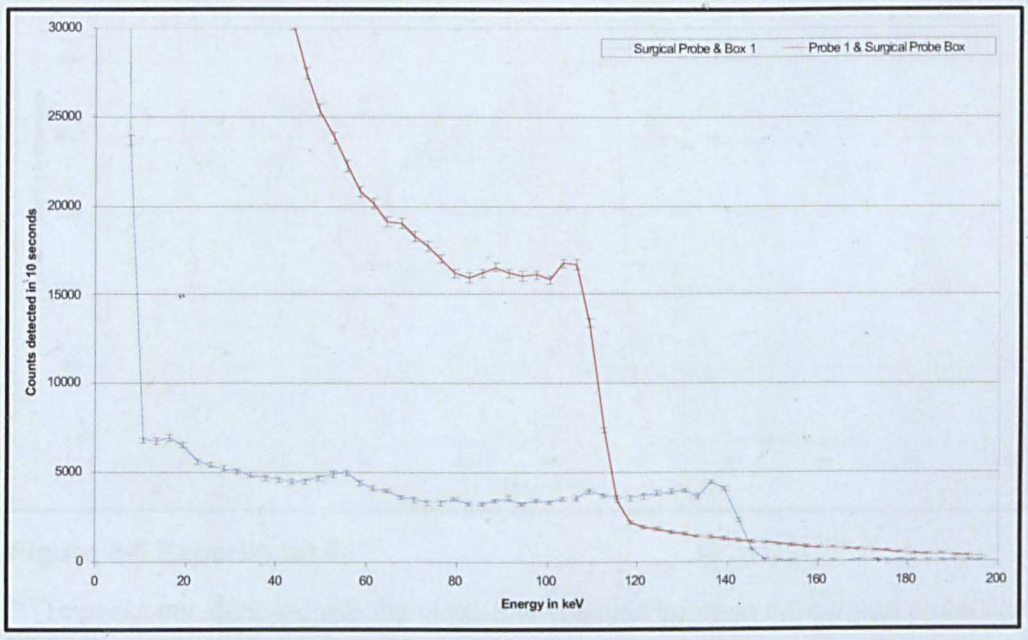

Figure 4-3 Experiment 2.

No improvement is identified in the energy spectrum when the boxes are interchanged between the surgical probe and probe 1.

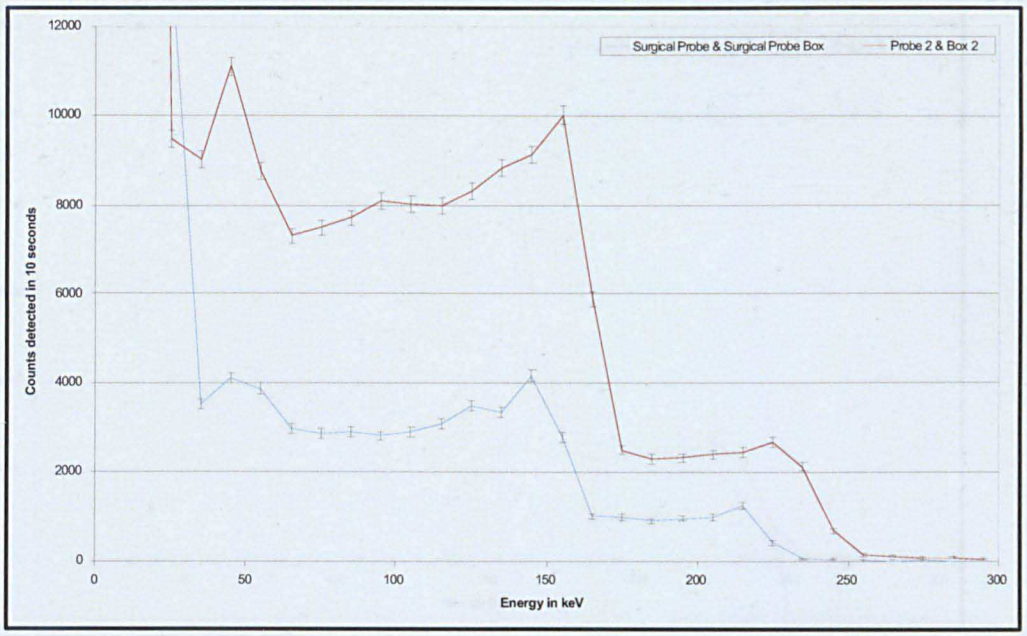

Figure 4-4 Experiment 3.

^{99m}Tc peaks are identified for both the surgical probe and probe 2.

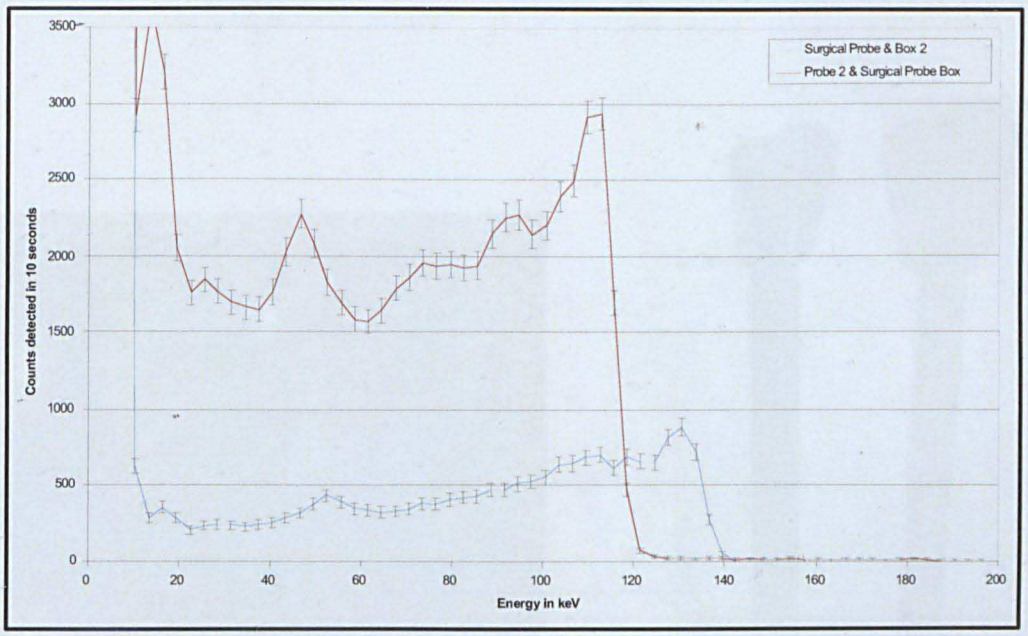

Figure 4-5 Experiment 4.

^{99m}Tc peaks are identified with the boxes interchanged between the surgical probe and probe 2.

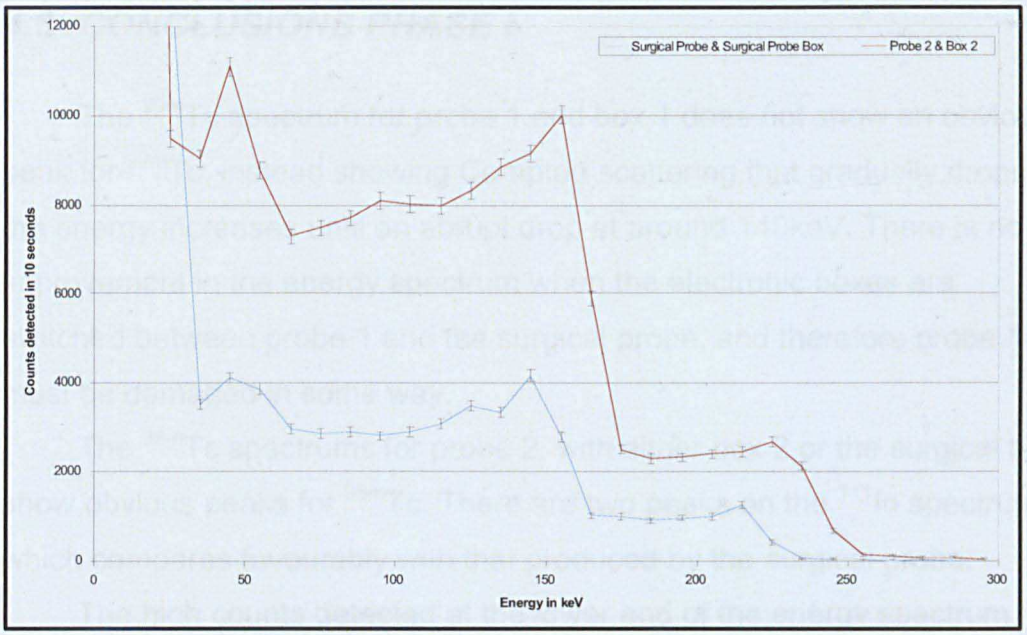

Figure 4-6 Experiment 5.

Both probes demonstrated two peaks corresponding to the photon energies emitted by ^{111}In (173 keV and 246 keV).

Figure 4-7 CTC4 electronics box and γ-probes.

On the right, the smaller detector improves the ability to localise the source of γ-rays, whereas the larger detector increases the sensitivity of the probe.

4.5 CONCLUSIONS PHASE I

The ^{99m}Tc spectrum for probe 1 and box 1 does not show an obvious peak for ^{99m}Tc, instead showing Compton scattering that gradually drops as the energy increases until an abrupt drop at around 140keV. There is no improvement in the energy spectrum when the electronic boxes are switched between probe 1 and the surgical probe, and therefore probe 1 must be damaged in some way.

The ^{99m}Tc spectrums for probe 2, with either box 2 or the surgical box, show obvious peaks for ^{99m}Tc. There are two peaks on the ^{111}In spectrum, which compares favourably with that produced by the surgical probe.

The high counts detected at the lower end of the energy spectrum for all experiments are the result of noise. A peak is visible on some of the spectra at ~ 50 keV which is consistent with Compton scattering.
As a result of the aforementioned experiments, probe 2 and its box was used for the haemorrhoid research, because adequate spectra had been obtained for both ^{99m}Tc and ^{111}In, comparing favourably with those obtained using the surgical probe.

4.6 METHOD PHASE II

4.6.1 Ethics

Ethical approval was gained from the designated NHS research ethics committee, and the research & development committee at Queen's Medical Centre also gave concurrent approval. A certificate to administer radioactive medicinal products was approved by the Administration of Radioactive Substances Advisory Committee (ARSAC).

4.6.2 Inclusion Criteria

Patients were considered for recruitment to the study if they had haemorrhoidal disease that required rubber-band ligation treatment. Either gender was considered. An age limit was set such that only patients over the age of 55 years were considered.

4.6.3 Exclusion Criteria

Patients were excluded from the study based on the following criteria: rectal bleeding that had not been investigated; any other colorectal pathology; and pregnancy. Pregnant patients were excluded on the basis that we were only investigating patients over the age of 55 years.

4.6.4 Study Group

Patients were recruited from a general surgical clinic and had undergone clinical assessment and investigations as necessary before being asked to participate in the study. The study was explained to each recruit in detail, which was reinforced by an information sheet that was taken home. Patients gave permission to be contacted by telephone. Patients were contacted and given the opportunity to ask further questions. At this point patients were given an appointment for the study, which was confirmed by letter. All patients gave informed consent. A copy was given to the patient, another copy filed in the hospital medical record and another kept for research documentation.

4.6.5 Procedure

Corrections were applied for background counts and radioactive decay. The basic procedure was that counts were measured over 50 second periods, however a variety of time intervals and durations were assessed. Each patient was asked to complete the haemorrhoid PROM prior to the study, four and eight weeks after rubber band ligation.

The procedure steps were:

- The patient was asked to empty their bladder immediately before starting the procedure.
- A 16G butterfly was sited in a vein of the right hand or arm of each participant.
- A mark was made over the right radial artery.
- The patient was placed in the left lateral position.
- The patient was examined using a proctoscope, documenting the position and degree of the haemorrhoids.

- The proctoscope was marked with indelible ink to mark the corresponding position of the haemorrhoids. The proctoscope was inserted into the anal canal in the same position each time. This was verified by ensuring that the handle of the proctoscope was in alignment with the natal cleft.
- Markings at 0.5cm intervals were also made with indelible ink along the barrel of the proctoscope, and therefore depth of insertion was kept constant by placing the distal edge of the proctoscope at the dentate line. The length from the anal margin to the dentate line was recorded in each patient. Each time that the proctoscope was reinserted into the anal canal, this distance was used to maintain the accuracy of positioning the probe.
- Non-radioactive stannous pyrophosphate was injected via a metal needle at a dose of 0.5mg/ kg (for in vivo radiolabelling of red blood cells) and flushed with 10mls of 0.9% saline.
- Wait 10 minutes.
- 10 MBq ^{99m}Tc -pertechnetate was injected intravenously and flushed with 10mls 0.9% saline.
- The energy range was set at 10% below and above the value for the ^{99m}Tc peak as measured by the phase I experiments.
- Wait 5 minutes.
- The probe was positioned directly over the distal aspect of each haemorrhoid, and 50-second counts were recorded manually.
- 50-second counts were then recorded over the reference points: 12 o'clock position 3 cm from the anal verge, and over the right radial artery.
- Rubber-band ligation of the haemorrhoids was carried out using suction banding equipment.
- 5 MBq of ^{111}In -chloride was injected and flushed with 10mls normal saline.
- The energy range was set at 10% above and below the value for the ^{111}In peak as measured by the previous probe experiments.
- Wait 10 minutes.

- The probe was re-positioned to monitor counts for 50 seconds over each haemorrhoid and at each reference point.

A venous blood sample was taken after completion of the experiment to check the extent of labelling.

4.6.6 Calculation of Index of Volume Change

The index of volume change (Ivc) is defined by the following equation:

$$I_{vc} = \frac{^{111}In^{H} / ^{111}In^{R}}{^{99m}Tc^{H} / ^{99m}Tc^{R}}$$

Equation 4-1 Index of volume change.

H is the count from the haemorrhoids. R is the count from the reference point.

Therefore if I_{vc} has a value of ≥ 1, this would indicate that no change in volume has occurred after rubber band ligation. If I_{vc} has a value < 1, this would indicate a reduction in volume.

4.6.7 Radiation Dosimetry

The effective dose for the procedure from 10 MBq of ^{99m}Tc was 0.1 mSV and from 5MBq of ^{111}In was 1.0 mSV. This gave a total dose of 1.1 mSV per patient; equivalent to less than 6 months exposure from background radiation [280].

4.7 RESULTS PHASE II

4.7.1 Study Group Characteristics

Twelve patients were recruited to the study over a 12-month period. There were 7 males and 5 females aged between 56 and 81 years. Of these, three of the females changed their minds about taking part in the study. In each case this was because of concerns about the radiation dose.

Of the remaining nine patients, one did not complete the study. In this case there was a fault with the charging of the counting electronics box. Therefore there were eight patients who completed the study, of which seven were male and one female aged between 56 and 75 years. Adjustments were made to the method after the first experiment and therefore there are results for seven patients.

4.7.2 Initial Results

The results of the first participant (NM2) (see table 5-2) are discussed separately, because modifications were made to the protocol as a consequence of carrying out the first experiment and the results obtained. The left half of table 5-2 shows the actual results obtained during the experiment. The top half shows the ^{99m}Tc counts, and the times at which they were obtained, over the reference point and haemorrhoids. The bottom half shows the same for the 1^{111}In counts. The right half of the table shows from left to right:

- correction for decay from the time of injection of the radioisotope (highlighted in yellow).
- mean of the corrected counts obtained from the reference point (highlighted in green) and from the haemorrhoids (highlighted in dark pink).
- the counts per second (cps) for the reference point (highlighted in blue) and each haemorrhoid (highlighted in orange).
- the haemorrhoid cps divided by the reference point cps (highlighted in light pink).

The indium values in the final column are divided by the corresponding technetium values to give the result of the index of volume change for each haemorrhoid. In this participant the results are set out in table 5-3.
The counts obtained from the reference point were quite low and varied quite significantly particularly for ^{111}In. There was a significant degree of variability between the counts for each haemorrhoid, both for ^{99m}Tc and ^{111}In. The variation in counts between haemorrhoids could have been due to a genuine difference in the size, but it could also have been due to small changes in the position of the probe.

Therefore, two changes were made to the protocol. It had been hoped that one count over each haemorrhoid would be enough to obtain interpretable results, in order to minimize the time that the proctoscope was in the anal canal. Due to statistical considerations, it seemed essential to obtain three counts over each haemorrhoid. The other change was to move the reference point from the radial artery to the skin overlying the common carotid artery in the right carotid triangle. Again this reference point was marked prior to starting the study.

	ACTUAL TIME	
	HRS	MINS
^{99m}Tc INJECTION	11	3
^{111}In INJECTION	11	45

	^{99m}Tc	^{111}In
T1/2	6.030	67.200
DECAY FACTOR	0.115	0.010

TECHNETIUM

REFERENCE CTS	^{99m}Tc CTS	CT TIME	ACTUAL	TIME
1	88	50	11	23
2	83	50	11	24
3	65	50	11	25

HROID POSN	^{99m}Tc CTS	CT TIME	ACTUAL	TIME
12	604	50	11	27
9	458	50	11	29
5	448	50	11	30

CORRECTED

TIME DIFF (Hrs)	^{99m}Tc CTS	MEAN OF CTS	CORR CTS/CT TIME
0.333	91.437	81.881	1.638
0.350	86.407		
0.367	67.798		

	^{99m}Tc CTS	MEAN OF CTS	CORR CTS/CT TIME	HROID/REF
0.400	632.420	632.420	12.648	7.724
0.433	481.391	481.391	9.628	5.879
0.450	471.784	471.784	9.436	5.762

INDIUM

REFERENCE CTS	^{111}In CTS	CT TIME	ACTUAL	TIME
1	223	50	11	56
2	92	50	11	58
3	49	50	11	59

HROID POSN	^{111}In CTS	CT TIME	ACTUAL	TIME
12	1052	50	12	4
9	796	50	12	6
5	1209	50	12	7

CORRECTED

	^{111}In CTS	MEAN OF CTS	CORR CTS/CT TIME
0.183	223.422	121.582	2.432
0.217	92.206		
0.233	49.118		

	^{111}In CTS	MEAN OF CTS	CORR CTS/CT TIME	HROID/REF
0.317	1,055.442	1,055.442	21.109	8.681
0.350	798.879	798.879	15.978	6.571
0.367	1,213.581	1,213.581	24.272	9.982

Table 4-2 Results from first patient (NM2).

Technetium counts are presented in the top half and indium counts in the lower half of the table. Corrected values are presented in the right half of the table. The index is calculated from the values in the columns highlighted in light pink.

Haemorrhoid	Banded	I_{vc}
12	Yes	1.12
5	No	1.12
9	No	1.73

Table 4-3 Initial results from the first participant. No change in the index of volume change was identified.

PT ID	Deg	Lab (%)	Haem 1 Ivc	RBL	Haem 2 Ivc	RBL	Haem 3 Ivc	RBL
NM1	3	10.6	0.37	Y	0.77	Y	1.10	N
NM3	1	93.9	0.72	Y	0.97	Y	1.12	N
NM4	2	38.4	1.06	Y	1.44	Y	1.13	N
NM5	1	42.7	0.41	Y	0.27	Y	0.34	N
NM6	2	82.8	1.45	Y	1.67	Y	1.38	N
NM11	2	66.4	0.63	Y	0.51	N	0.76	N
NM12	3	66.5	0.49	Y	0.89	Y	0.59	N

Table 4-4 Summary of the outcome for the participants examined under the modified protocol.

Deg – degree Lab – Extent of red blood cell labelling
Haem – haemorrhoid

PT ID	DEG	Lumps	Bleeding	Total	QOL Pain	QOL Other	Dec in I_{vc}
NM1	3	-2	0	-3	-3.2	-0.1	Yes
NM3	1	DNC	DNC	DNC	DNC	DNC	Yes
NM4	2	-1	0	-29	-4.1	-3.4	No
NM5	1	-5	0	-6	-1.9	-2.3	Yes
NM6	2	-1	-5	-7	-1.4	-1.9	No
NM11	2	DNC	DNC	DNC	DNC	DNC	Yes
NM12	3	0	-3	1	-0.9	0.4	Yes

Table 4-5 Summary of change in the symptom score prior to and after rubber band ligation.

DNC – Did not complete haemorrhoid PROM.

4.8 SUMMARY OF RESULTS

Modifications to the initial protocol increased the number of counts over the reference points and the haemorrhoids for both ^{99m}Tc and ^{111}In. There was less variability between the three counts obtained over the four measured points.

Overall only the results of two patients (NM1 and NM3) completely fulfilled the expectations of the hypothesis i.e. that there would be an Ivc of less than 1 for the ligated haemorrhoids and also an Ivc for the haemorrhoids that were not ligated.

In three patients (NM5, NM11 and NM12) there was a reduction of Ivc for all three haemorrhoids, not just the two that were ligated. In the remaining two patients (NM4 and NM6) there was no reduction in Ivc for any of the haemorrhoids whether ligated or not.

There was a large degree of variability in the extent of red blood cell labelling by ^{99m}Tc -pertechnetate, from 10.6 to 93.9%. It is noted that in only one (NM4) of the three patients with labelling of less than 65%, was there a failure to show a change in the following rubber band ligation.

There was no obvious relationship between Ivc and the change in symptom scores, whether one assessed the individual items, the total scores or the quality of life scores. Formal statistical analysis was not performed as the number of participants involved was too small to attain any meaningful significance.

4.9 DISCUSSION

The choice of methodology was partly based on equipment available for use at the time of planning the study, which was the γ-camera or the surgical solid state cadmium telluride detector. The total spatial resolution of a gamma camera is approximately 10mm depending on the model and purpose of use [281]. The spatial resolution of a gamma camera will also reduce the further the ROI is placed from the camera head. Given that the average length of the anal canal is 2.5 – 4cm depending on the measurement modality [282] and gender, the task of differentiating haemorrhoids from surrounding tissue is likely to be difficult.

The choice of surgical probe overcomes the issue with spatial resolution because of its design and the ability to position it directly on the haemorrhoid or reference point. The dual radioisotope technique allows the investigator to indirectly semi-quantitatively measure volume change by acquiring counts from ^{99m}Tc labelled red blood cells pre rubber band ligation and ^{111}In bound transferrin, an intravascular protein, post rubber band ligation. The reference point measurements are used to correct for normal clearance from the circulation and for radioactive decay.

This technique is attempting to calculate an index of volume change by measuring the counts from radioisotope bound components of blood, the presumption being that less blood components will reach the haemorrhoidal zone after rubber band ligation. The results of the technique showed a reduced I_{vc} for some of the participants, however there were several sources of possible error within this technique.

Woolfenden and Barber [238] found that minor changes in the angle of surgical probes could have a significant effect on the count rate. These counts were arising from distant sources in the volume of tissue in front of the detector. A change of angle might bring a high-activity source, for example the kidney or urinary bladder, into view. Even when distant hot sources were not present, they found that changes in probe angle or position could cause changes in count rate because of differences in the volume of tissue assessed by the probe. All patients were asked to empty

their bladder prior to the beginning of the study to eliminate this possibility, however positioning of the probe was certainly difficult.

Despite marking the position of the haemorrhoids and the dentate line on the distal end of the barrel of the proctoscope, it was difficult to maintain the barrel within the anal canal, which is unsurprising as counting time totalled 450 seconds prior to and post rubber band ligation for each patient. The morphology of the haemorrhoids obviously changed post rubber band ligation, with swelling of the ligated areas, thus making exact positioning of the probe more difficult.

Another factor to be considered is the interaction of the x- and γ-ray energies emitted by radionuclides with matter by the photoelectric effect and Compton scatter. Compton-scattered photons that are scattered in a patient's body and then absorbed in the detector appear to originate from a direction different to that of the incident photon. This represents one of the major difficulties in accurate spatial localization and high-contrast detection of radionuclides.

Energy-selective counting is used to reject Compton-scattered photons and accept primary photons. For 140-keV technetium-99m γ- rays, even sharply scattered photons would be included in the standard 20% photopeak energy window. Narrowing the energy window to ±10%, as was the case in the described methodology, will result in less scattered radiation being detected but at the cost of significantly reduced sensitivity [264], thus explaining the requirement for three counts at each measured region.

The low levels (≤ 65 % [283]) of red blood cell binding identified in three of the patients (NM1, NM4 and NM5), could explain some of the variation in the results. Although in vitro RBC labelling is recommended for use in cardiac imaging, many centres prefer to use in vivo tagging because of its ease of use and the reduction in time consumption [284]. Since the description of the method for in vivo red blood cell labelling by Pavel et al., [279], it has been widely applied all over the world, using different stannous compounds for the tinning procedure, with reported labelling values from 60% to 90% [285].

Recommendations from Hambye et al., were followed in this methodology including the use of weight appropriate doses of stannous pyrophosphate and a metal needle for its injection. None of the patients were on heparin [286] or chemotherapeutic agents [287], however two (NM1 and NM4) of the three patients were taking cardiac medication (digoxin and nifedipine), which have been shown to interfere with in vivo red blood cell labelling [288].

If the results from the three patients with poor red blood cell labelling are set aside and the remaining participants are evaluated, the values obtained cannot be explained on the basis of which haemorrhoids were ligated.

For the purpose of Ivc calculation, it is assumed that all externally detected radioactivity originated from the haemorrhoids. In Gorin's [289] sheep model of pulmonary oedema and calculation of transvascular protein flux, using diffusible 113mIn-transferrin and non-diffusible ^{99m}Tc -RBC, there was an assumption that all the externally detected activity originated from the lung. By studying pneumonectomy patients using Na^{125}I, other investigators showed that up to 30 % of counts originated in the chest wall, which would be expected with a small highly diffusible, low-energy tracer [290]. Although there are obvious differences between placing an external detector on the chest wall and within the anal canal, the underlying principle is applicable to this technique.

Accuracy of measurement is also affected by the fact that a proportion of the gamma radiation will be absorbed before it can be detected, the extent of which is proportional to the gamma ray energy, tissue path length and tissue densities.

From a logistical point of view, this study was difficult to organize and there were surprising numbers of patients who declined to take part in the study. This included the three patients who initially entered the study before changing their minds. Despite the patient information sheet and the investigator explaining that the dose involved was very small, half that of the UK yearly background dose, there appeared to be genuine reluctance to receive any radioactive dose whatsoever.

The underlying principles of the dual radioisotope technique are simple, and had the study produced reliable results this technique would have been an elegant way of demonstrating volume change after a surgical or even future pharmacological intervention.

5 MAGNETIC RESONANCE IMAGING

5.1 INTRODUCTION

5.1.1 Physics of Magnetic Resonance Imaging

The nucleus of the hydrogen atom is a single positively charged proton. As a fundamental particle, the proton spins on its own axis, generating its own magnetic field, which is known as its magnetic moment. If the proton is placed in an external magnetic field, it experiences torque and the protons attempt to align themselves parallel and anti-parallel to the magnetic field, The torque causes the protons to precess around the direction of the magnetic field. The precessional frequency of the proton is proportional to the external magnetic field strength, and is described by the Lamor equation.

$$\omega_0 = \gamma B_0$$

Equation 5-1 The Lamor equation where ω_0 is the Lamor frequency,

γ is the gyromagnetic ratio and B_0 is the strength of the external magnetic field.

The protons can only precess in one of two orientations known as states: spin-up or parallel and spin-down or anti-parallel. The spin-down state requires slightly more energy than the spin-up state, and protons interchange between the two by gaining or losing a photon, a packet of electromagnetic radiation. In the human body there are millions of protons, and in a set external magnetic field strength, there will be a set distribution between the spin-up and spin-down states. In a 1.5 Tesla (T) scanner for every million protons in the spin-down state, there will be a million and four in the spin-up state. For a large number of protons the distribution is described by the Boltzmann distribution, and from this the net magnetization M_0 can be calculated as depicted in equation 5.2 below.

$$M_0 = \frac{\rho\gamma^2 h^2 B_0}{4K_B T}$$

Equation 5-2. The net magnetization M_0.

ρ is proton density, γ is the gyromagnetic ratio, h is Planck's constant divided by 2π, B_0 is the strength of the external magnetic field, K_B is the Boltzmann constant and T is body temperature.

Water contains 6.67 x 1022 protons ml^{-1}, and from equation 5-2, at body temperature and 1.5T, M_0 is calculated at 0.02μTml^{-1}. The calculated magnetization of the body is very small compared to the main magnetic field, and therefore almost impossible to measure while it is at equilibrium, lying parallel to B_0.

If the body's magnetization is tipped through 90° into the transverse plane, a detector which only measures magnetic field in the transverse plane will be able to record a significant signal. This is achieved by applying a 90° radiofrequency (RF) pulse, which must be at the Lamor frequency. The flip angle (α) is determined by the strength of the RF magnetic field (B_1) and the duration of the pulse (t_p). As time is a crucial factor in magnetic resonance imaging (MRI), the strength of the pulse is altered to produce different flip angles.

The RF pulse also brings the spins into phase coherence, such that they all point to the same position on the precession circle. With M_0 in the transverse plane, it can be measured by detecting the voltage it induces in the receive coil, which can only detect magnetization perpendicular to B_0.

The amplitude of the signal undergoes Free Induction Decay (FID), dropping exponentially to zero, because the protons rapidly dephase with respect to each other. As soon as the protons have been flipped into the transverse plane, they start to relax back to the equilibrium position when the RF pulse is switched off. Relaxation involves dephasing of the spins and realignment along the z-axis as the protons lose energy absorbed from the RF pulse.

The spins dephase due to small differences in their precessional frequencies. The main factor causing FID is the inhomogeneity in the

external magnetic field. A second factor is the interaction between spins as they move within the tissues. This is known as spin-spin interaction and is denoted by the T2 relaxation time, which is independent of the magnet and its field strength.

As two protons come close together, they experience a change in the magnetic field strength, which changes their precessional frequency. Therefore each proton will dephase with respect to the Lamor frequency. When the two protons move apart, they both return to precessing at the Lamor frequency, but the newly acquired phase angle is irreversible. Over time there will be thousands of proton-proton interactions until all the protons are out of phase with each other. The transverse magnetization vector decays exponentially to zero, and T2 is the time taken for it to drop to 37% of its original value.

Although transverse magnetization decays, there is no loss of energy in spin-spin interaction. To lose energy the protons interact with the surrounding tissue known as the lattice. The lattice can absorb energy and disperses it via blood flow. The protons lose the extra energy by attaining thermal equilibrium with the lattice. This is known as spin-lattice relaxation characterised by T1, the time taken for magnetization to recover to 63% of its equilibrium value. T1 increases proportionally with field strength. In human tissues T1 is always longer than T2.

The time difference between T1 and T2 is essential to the formation of the MR image. There is always a series of repeated RF and gradient pulses, with a repetition time (TR). In a simple spin echo sequence, 90°-TR-90°-TR, provided the TR is at least five times longer than the longest T1 of the imaged tissues, M_z will have recovered to M_0. All tissues will have returned to equilibrium before the next 90° RF pulse. Signal in the transverse plane will depend only on proton density.

5.1.2 Magnetic Resonance Equipment

The magnet is the main component of the magnetic resonance (MR) system. The static magnetic field is inherently non-uniform. Its homogeneity is optimized by a process called shimming. Pieces of steel or electric coils are incorporated into the magnet to improve uniformity.

Magnetic field strength is measures in tesla (T). Strengths vary from 0.02 – 8T, however most clinical systems operate in the 0.5 – 3.0T range. The advantages of higher field strengths are a better signal to noise ratio (SNR) and increased chemical shift artefact. Improvement in SNR can be traded for increased spatial resolution or decreased imaging time.

There are four types of MR magnet, the most up-to-date version of which is the superconducting magnet. They are composed of certain materials which at temperatures approaching absolute zero (-273.16°C, 0K) have zero electrical resistance. Electric current in a loop of superconducting wire, held below its transition temperature will continue to circulate indefinitely.

The MR signal that provides diagnostic information is produced within the patient's tissue in response to RF pulses. These are produced by a transmitter coil, which surrounds the whole or a part of the body. A body coil is usually built into the construction of the magnet.
The MR signals produced in the body are detected using a receiver coil. The MR signals are very weak and sensitive to electrical interference. Special shielding known as a Faraday cage is built into the magnet room.

5.1.3 Obtaining the Magnetic Resonance Image

All magnetic resonance (MR) images are produced using a pulse sequence, which contains radiofrequency (RF) pulses and gradient pulses. The timing and duration of these pulses are precisely controlled to obtain images of tissues with specific characteristics.

The most important properties of magnetic resonance imaging (MRI) are the proton density (PD), the spin-lattice relaxation time (T1) and spin-spin relaxation time (T2). PD relates to the number of hydrogen atoms in a particular volume. Relaxation times refer to the time taken for a tissue to return to equilibrium after an RF pulse. Contrast of an MR image is determined by the PD, T1 and T2. High PDs produce high signal intensities and appear bright on the image. In T2-weighted images, tissues with long T2 have high signal intensities. In contrast, T1-weighted images and tissues with long T1 have low signal intensities.

There are two main types of pulse sequence, spin echo (SE) and gradient echo (GE). SE sequences use two RF pulses to produce the echo, which measures the signal intensity. T1, T2 or PD weighted images can be acquired with SE sequences dependent on the TR and TE used. SE images are of higher quality but acquisition time is generally longer.

GE sequences use a single RF pulse followed by a gradient pulse to create the echo, which measures signal intensity. Again T1, T2 or PD weighting is obtained by changing the TR and TE. Generally the TR is much shorter than in SE imaging, and therefore scan times are much shorter. GE images are affected by the external magnetic field, which affects the spin-spin relaxation or T2 time, which becomes shorter. This combination is known as T2*.

T1-weighted images are obtained by using short TR and TE times to enhance the T1 differences between tissues. Fluid appears dark, fluid-based tissues are grey and fat-based tissues are very bright. T1-weighted images are often called "anatomy" images.

T2-weighted images are generally obtained following a SE pulse sequence, and require longer acquisition times due to the long TR. Fluid appears very bright, water and fat-based tissues are of intermediate signal. T2 images are often considered to be "pathology" scans. Oedema is often associated with pathology, and will appear bright against the darker normal tissue.

PD images are formed by creating a second echo at a shorter TE during a T2 SE acquisition. This produces an image at the same slice location and within the same scan time, but with PD weighting.

A gradient refers to an additional spatially linear variation in the static field strength in the z direction (B_0). An x-gradient (Gx) adds to or subtract from the magnitude of the static field at different points along the x-axis. The protons resonate faster or slower than the Lamor frequency depending upon their position. Faster or slower precession is detected as higher or lower frequencies in the MR signal. Therefore frequency measurements may be used to distinguish between MR signals at different positions in space.

Slice selection is the process by which MR signals are restricted to a two-dimensional plane or slab within the patient. The operator can control all

the position, width and orientation of the slice. A specially designed RF excitation pulse is applied at the same time as a gradient. The special RF pulse contains a narrow range of frequencies of RF centred about the Lamor frequency. The presence of the gradient causes the resonant frequency to vary with position.

Gradient pulses are applied in a controlled fashion to form a pulse sequence. An RF pulse is applied simultaneously with a slice selective gradient. The RF pulse stimulates the MR interactions in tissues, which leads to the MR signal. By combining the RF excitation with a gradient, the MR interactions are restricted to a two-dimensional plane, slab or slice. Any physical gradient G_x, G_y, G_z or combinations of these can be used, producing transverse, sagittal, coronal or oblique slices.

Next phase encoding is applied in a direction orthogonal to the slice selection. This encodes the MR signal in the phase encode direction. The frequency-encode or readout gradient is applied in the third direction. Finally the MR signal is then acquired, which actually occurs during the frequency-encode gradient and after phase encoding.

The whole sequence is repeated for each line of data, corresponding to a different value of phase encode gradient until the k-space matrix is filled. Once the data is acquired a two-dimensional Fourier transformation is applied. The data, already encoded as spatial frequencies, is converted into an image.

5.1.4 Contrast Agents

MR imaging is considered to be very sensitive, making pathology very conspicuous, but not very specific. It is poor at distinguishing different pathologies. Contrast agents help to improve the specificity by producing an extra sequence of images with differing contrast; they also increase SNR improving image quality.

The most commonly used contrast agents are based on gadolinium, which has a strong paramagnetic susceptibility. When it is injected, it initially is taken up into the arterial system, but rapidly redistributes into the extracellular fluid space. It is then gradually excreted via the kidneys. It

shortens T1 in tissues where it accumulates, such that on post-contrast T1-weighted images these tissues have enhanced signal.

The super-paramagnetic iron oxide (SPIO) group of contrast agents reduce the T2 of tissues in which they accumulate, causing lower signal intensities on T2 and T2* weighted images post contrast.
Gadolinium does affect T2 as well as T1, and similarly SPIOs have a T1-shortening effect as well as reducing T2 and T2*. The exact effect of contrast depends on their concentration in the tissue of interest, and also on the imaging sequence being used. At high concentrations and sequences with long TEs, gadolinium may reduce the signal intensity of the tissues due to shortening of T2.

5.1.5 History of Abdominal and Pelvic MRI

Before discussing the possible methods of assessing volume and blood flow within haemorrhoids using MRI, it is important to discuss the advent of medical MRI and its progression since the 1980s.

Early MR evaluation of the abdomen [291] used systems with a 0.15T resistive magnet or a 0.3T-superconducting magnet. A whole body coil was used, allowing transverse, sagittal and coronal image acquisition. Slice thickness varied between 11 and 15mm with a resolution of two line pairs per cm in the plane. Acquisition time varied between 4 and 9 minutes per slice.
Different pulse techniques were used to acquire images of different PD, T1 and T2 weighting. Focal liver abnormalities such as metastatic deposits, haemangiomas and cysts were imaged with both MRI and computed tomography (CT). In nineteen out of twenty-two cases MRI detected all liver lesions.

Failure to depict the focal lesion in the three cases was thought to be related to the long scanning times required for T2 weighted imaging, poor spatial resolution and poor SNR when compared to T1 weighted imaging. Other early research [292, 293] evaluated the quality of images of the pelvic organs in males and females, as well as the T1 and T2 relaxation times of tissues, such as the myometrium and endometrium. MR anatomical appearances were described on T1 and T2 sequences. Basic evaluation of

bladder and prostate tumour appearances on T1 and T2 sequences were described, and compared to clinical and CT appearances.

At this point MR technology was limited in the spatial resolution available, and certainly could not distinguish between different layers of the rectal wall for example.

Improvements in hardware, spatial and contrast resolution and faster scanning techniques meant that by the 1990s, MR was being evaluated for the clinical assessment of anal fistulae [294-296] and faecal incontinence. A few studies have evaluated and compared the use of a body wrap-around coil [297, 298] to endoanal coil imaging [296], however the majority of researchers used endoanal coils because of insufficient spatial resolution for differentiating the individual small muscles of the anal sphincter [299-301].

Typical signal intensities of the submucosa, internal anal sphincter, conjoined longitudinal muscle and external anal sphincter were characterised on T1, T2, short tau inversion recovery and post contrast sequences, as detailed in table 5-1 [302]. Correlation with cadaveric cross-sections confirmed the morphology of the sphincters, and correlation with clinical and surgical findings confirmed that endoanal MR could accurately assess anal fistulae. Although the use of rigid endoanal coils allows high-resolution thin MR images, there is compression of the epithelium and subepithelial tissue [303].

	Submucosa	Internal Anal Sphincter	Conjoined Longitudinal Muscle	External Anal Sphincter
T1	↑↑	→	↓	↓
T1 & Contrast	↑↑	↑	↓	↓
T2	↑↑	↑	↓	↓
STIR	↑↑	↑	↓	↓

Table 5-1 Typical signal intensities from the layers of the anorectum

PD-weighted GRE and T2-weighted TSE MR images clearly demonstrate normal anal anatomy and disease [295, 296, 304], including faecal incontinence and anorectal tumours. Fat suppression techniques such as fat saturation, spectral inversion recovery and short tau inversion recovery (STIR) may help to increase the level of confidence in difficult cases, facilitating identification of small amounts of fluid [305].

In anorectal tumour imaging, contrast between tumour and the rectal wall is optimal on T2-weighted TSE images. PD-weighted GRE images are too susceptible to motion artefact caused by rectal contractions. Characterization of tumour extension into perirectal fat or anal sphincter is best achieved with T1-weighting. The use of contrast can help determine tumour extent [305]. Dynamic MR imaging has been advocated to improve the differentiation between T2 and T3 tumour.

Imaging planes used are off-axis orientated orthogonal or parallel to the coil and anorectum, thereby reducing partial volume effects. The axial plane is optimal in the evaluation of anorectal disease. Longitudinal sequences allow better appreciation of the craniocaudal extent of disease [306]. A radial sequence has the theoretical advantage that all sections are perpendicular to the coil and anorectum resulting in fewer partial volume effects. Superior evaluation, in terms of multiplanar capability, of the external anal sphincter has increased the understanding of the external anal sphincter anatomy.

5.1.6 Relaxometry

Much of the early work carried out by MR researchers focused on measurement of relaxation times in vitro and in vivo. The working theory was that normal tissue and pathologies could be characterized on the basis of relaxation times. This has proved to be impossible for a number of reasons.

There is a substantial overlap of T1 and T2 values due to biological variability. As shown in table 5-2 [307, 308], grey matter, white matter and cerebrospinal fluid have distinct T1 and T2 values, which allows for good anatomical imaging. Various brain lesions including tumours [309], infarction and multiple sclerosis plaques have T2 values in a narrow range (170 – 200 msec), which is distinct from the T2 values of grey and white matter, but not

uniquely distinctive from each other [310, 311]. MRI is very sensitive but less specific based on relaxation times only, unless other features such as contrast uptake, presence of oedema, degree of vascularity and blood breakdown products are taken into account.

Tissue	T1 (msec)	T2 (msec)
White Matter	832	110
Grey Matter	1331	80
CSF	3700	
Fat	382	68
Muscle	898	29
Liver	809	34
Spleen	1328	61

Table 5-3 Selection of T1 and T2 values for tissues at 3.0T.

All values are measured in vivo from human tissues.

So far tissues have been considered to have single T1 and T2 values. In practice the situation is usually more complex. Tissues are formed of various components including parenchymal cells, the interstitial space and the microvascular space. Relaxation characteristics of each of these may differ significantly from each other, and thus the measured T1 and T2 will be a weighted average of the components.

When considering relaxation mechanisms, water molecules reside in three states: free, bound and structured. Water molecules, free in solution, consist of a uniform number of protons moving over a wide range of frequencies. There will only be a small number moving at the Lamor frequency, so T1 relaxation is relatively inefficient and T1 times are long. Similarly only a small number are moving at very low frequencies, and therefore T2 relaxation time is also inefficient leading to long T2 values.

With water molecules bound to larger macromolecules through the formation of a hydration layer, there are a large number of protons moving at very low frequencies because the binding to macromolecules restricts their motion. T2 relaxation is very efficient and T1 relaxation inefficient.

Protons can also be in the intermediate stage, between bound and free states. There are a large number of protons moving at the Lamor frequency, and T1 relaxation will be the most efficient. T2 relaxation is intermediate between bound (short T2) and free (long T2). The measured T1 and T2 relaxation times will be a weighted average of the three states.
As well as mixing of tissues at the cellular level, there is mixing of the tissue types within a voxel due to the relatively low spatial resolution of MRI.
T1 has a marked dependence on the field strength B0, which is described by the mathematical relationship in equation 5.3.

$$T1 \propto B_0^b$$

Equation 5-3 The relationship between field strength and the T1 relaxation time.

The constant b lies in the 0.3 – 0.4 range.

As there are many different MR scanners with carrying field strengths, it is difficult to directly compare relaxation measurements from different sites or models. T2 is largely independent of field strength. The observed MR signal, and therefore the T1 and T2 relaxation time can be influenced by magnetization transfer. This occurs when there is fast exchange between bound and free protons. The bound or restricted pool has such a short T2 relaxation time that the molecules are invisible to standard MR imaging, as their signals decay before the echo can collect the signal. However the bound pool has a broad resonance and therefore can be excited by an RF pulse at a frequency several kilohertz away from the free water frequency, which therefore has no effect on the free protons.

Exchange of protons between the bound and free pools means that saturated magnetization from the invisible bound pool will move into the free pool, this reducing the total MR signal that can be observed.

Apart from biological variability, multi-exponential behaviour (exchange between states), tissue mixing, field strength dependence and magnetization transfer there are a number of other sources of error in relaxometry. These include poor sequence parameter choice, particularly too short a TR for a PD-weighted image, inhomogeneous RF pulses,

contrast effects in multiple slice acquisitions arising from selective pulses intended for other pulses and slice profile distributions. All of these problems dictate that T1 and T2 measurement is not at present a useful tool.

5.1.7 Dynamic contrast enhanced imaging

Development of DCE imaging arose in response to the development of antiangiogenic agents, which are selectively targeted to the endothelial cells of tumour neovasculature. Unlike traditional cytotoxic drugs, these new agents induce a rapid shutdown of tumour blood supply. Their cytostatic nature precludes normal tumour size measurement as a marker for response evaluation [312]. It has been used in multiple oncological settings including tumour grading and clinical outcome prediction [313, 314].

In solid tumours the neovasculature is abnormal in structure with defects in the walls that make them more permeable than normal vessels. Low molecular weight contrast agent molecules will leak into the interstitial space, and interaction with adjacent water protons will increase the tissue longitudinal relaxation time, generating a brighter signal in T1 weighted images [315], producing a more rapid and intense washout of contrast. The change in contrast agent concentration can be described by a variety of model-free parameters [316, 317] or fitted to a pharmacokinetic model [318], which enables quantification of tumour vascular heterogeneity [313].

5.2 AIM

The aim of this study is to evaluate the feasibility of using MRI and in particular DCE-MRI to evaluate vascular measures in haemorrhoidal disease.

5.3 METHOD

5.3.1 Ethics

Ethical approval to image fifteen patients was gained from the Nottingham Research Ethics Committee 2 (part of the Central Office for Research Ethics Committee). Concurrent approval was also given by the

Research & Development Department at Nottingham University Hospital NHS Trust. Approval was given by the University of Nottingham Medical School Ethics Committee to scan four healthy volunteers.

5.3.2 Inclusion and Exclusion Criteria

Patients were considered for recruitment to the study if they had haemorrhoidal disease that required rubber-band ligation treatment. Either gender was considered. Healthy volunteers were considered for recruitment to the study provided that there was no history of gastrointestinal disease. Patients were excluded from the study if they had rectal bleeding that had not been investigated or any other colorectal pathology. Patients were also asked specifically about MRI exclusion criteria, including a known metal implant or pacemaker, known allergy to intravenous contrast, pregnancy or claustrophobia (see appendix 10.4).

5.3.3 Recruitment

Patients were recruited from a general surgical clinic and had undergone clinical assessment and investigations as appropriate, to exclude other colorectal pathology, before being asked to participate in the study. Patients underwent digital rectal examination, proctoscopy and rigid sigmoidoscopy to allow confirmation of haemorrhoids, and exclude any anal or rectal pathology.

The study was explained to each potential recruit in detail, which was reinforced by an information sheet that was read at the time of assessment. A safety check was carried out to ensure that the potential participants did not have a contraindication to undergoing MRI. An explanation of the rubber band ligation process was given.

Some patients preferred to have more time to consider either taking part in the study or having rubber band ligation performed. Patients gave permission to be contacted by telephone, and were contacted two to three days later. They were given the opportunity to ask further questions. If the patient did not wish to take part in the study but wished to proceed with rubber band ligation, they were offered an appointment to return to the department of surgery. If the patient had consented to taking part in the

study, they were asked to complete the consent form and questionnaire at home and bring the paperwork to the appointment.

All patients and healthy volunteers gave informed consent. A copy was given to the patient, another copy filed in the hospital medical record and another kept for research documentation. Both patients and healthy volunteers completed a safety screening form prior to entry into the study (see appendix 8.3).

5.3.4 Equipment

All patients and healthy volunteers were imaged at the Sir Peter Mansfield Magnetic Resonance Centre. They were scanned on a Philips Medical Systems™ Intera Achieva 3T machine, with a phased array body coil centred at the hips. An intravenous cannula was inserted into the antecubital fossa for administration of gadolinium-based contrast. Each patient was weighed and a dose of $0.1 mmol kg^{-1}$ of Prohance™ (Gadoteridol) was calculated. The gadolinium was hand injected through a 20G cannula with an approximate flow rate of 1.1 ml/sec, followed by 20mls of saline flush. The first sequence was acquired without contrast, followed by acquisition at 30, 60, 90 and 120 seconds.

5.3.5 Determination of Sequences

Four healthy volunteers and two patients were each scanned once to establish the best sequences for imaging the anal canal. The details of each and a summary of the sequences trialled are summarised in table 5-3. Axial and sagittal planes were acquired; the sagittal images were used to plan the axial imaging such that true axial views were obtained, orthogonal to the anal canal.

ID	Age	Gender	Degree	T1	T2	PD	STIR	SE	GE	T1C
MV1	36	F	0	✓	✓		✓	✓	✓	
MV2	46	F	0	✓	✓	✓		✓		
M3	52	F	2	✓	✓			✓		
M4	37	F	2	✓	✓			✓		✓
MV4	30	F	0	✓	✓			✓	✓	
MV3	22	M	0	✓	✓			✓		✓

Table 5-2 Overview of demographics and sequences trialled on each patient and volunteer in phase 1.

5.3.6 Protocol for Imaging Patients and Healthy Volunteers

The final choice of sequences consisted of a high-resolution sagittal T2 to allow planning of the axial sequences, followed by a true axial T2 weighted sequence, a DCE axial T1 weighted sequence, and lastly another axial T2 sequence. These are summarised in table 5-4. Six patients were scanned with the finalised protocol, one of who withdrew after the first scan. The remaining five patients were scanned immediately prior to and two days after rubber band ligation.

ID	Age	Gender	Degree
M5	35	M	2
M6	46	F	1
M8	33	M	3
M9	54	F	1
M11	66	F	2

Table 5-3 Demographics of patients in phase II of MRI study.

Property	Sag T2	Axial T2	Axial T1
TE	80	55	10
TR	1910.5	1500	164.3
Angle	90	90	90
Slice Thickness (mm)	1.5	2.0	2.0
Slice Spacing (mm)	1.6	2.2	3.0
NSA	4	8	4
ETL	14	7	3
Matrix	256 x 256	256 x 256	256 x 256
Duration (secs)	114.6	702	557.1
No of slices	14	16	6

Table 5-4 Summary of finalised sequences used for assessing patients and healthy volunteers.

The same axial T2 sequence was repeated immediately after the axial DCE T1 sequence.

5.3.7 Image Analysis

Analyses of regions of interest were carried out on OsiriX™, version 4.0 (32-bit), on a 15-inch MacBook Pro (Intel Core Duo). OsiriX™ is an image processing software application dedicated to DICOM images produced by imaging equipment. It is fully compliant with the DICOM standard for image communication and image file formats. It is able to receive images transferred by DICOM communication protocol from any PACS or imaging modality. It has been specifically designed for navigation and visualization of multimodality and multi-dimensional images.

Each dynamic image was evaluated for signal intensity values. The regions encapsulated by the IAS and by the submucosa were selected for signal intensity calculations obtained with the oval ROIs (see figs 5-1 and 5-2). Time-intensity curves were constructed from signal intensity values calculated at the 30-second intervals over the 120-second duration. To compare the relative enhancement differences between pelvic tissues, additional measurements were taken from a major artery and a reference muscle (gluteus maximus) in all patients in each slice.

The percentage of enhancement for each time-intensity curve was calculated from the formula:

$$E = \frac{(I_{max} - I_{pre})}{I_{pre}} \, x \, 100$$

Equation 5-4 Calculation of percentage enhancement from time-intensity curve.

I_{max} is the peak signal intensity during the post contrast dynamic sequence. I_{pre} is the signal intensity at the base of the curve [319].

The acceleration rate on a time-intensity curve was used as a measure of perfusion of the imaged anorectum. This is defined as the steepest slope of gadolinium uptake and is expressed by the following equation:

$$AR = \frac{(I_{end} - I_{pre}) x \, 100}{I_{pre} \, x \, (T_{end} - T_{prev})}$$

Equation 5-5 Calculation of acceleration rate on a time-intensity curve.

I_{end} and I_{pre} are the values on the time-intensity curve at the corresponding time points T_{end} and T_{prev} [320].

To compensate for differences in contrast injection rate and variations in vasculature the ratio $\frac{I_h}{I_{a60}}$ was used where I_H is the signal intensity of the haemorrhoids, I_A is the signal intensity of a reference artery, and 60 refers to the time-point at which the measurements were taken.

5.4 RESULTS

5.4.1 Choice of Sequences

Attempts to image patients and volunteers using gradient echo technique failed to produce images with adequate detail of the submucosa (compare fig 5-1 to 5-2), and therefore spin echo images were used, which have a longer duration of acquisition, but better spatial resolution. T2 weighted imaging produced anatomical images, whilst T1 images were required for the DCE imaging.

5.4.2 Qualitative Evaluation of Imaging

All T1-DCE and T2-images were evaluated for the presence of artefact. The submucosa-IAS and the IAS-EAS interfaces were either recorded as adequate or inadequate for ROI analysis. Pre and post rubber band ligation images were synchronised within OsiriX™ and viewed simultaneously for objective differences within the submucosa.

Motion artefact affected the pre and post rubber band ligation images of M11 and the post rubber band ligation images of M8. Peristalsis artefact was identified on the pre-RBL images of M6, however this did not preclude ROI analysis. The submucosa-IAS and the IAS-EAS interfaces were easily discerned in the lower and mid-anal canal (fig 5-2) allowing easy placement of the ROIs (fig 5-3), however as the axial plane of imaging approached the anorectal angle the interfaces became less distinct (fig 5-4) in all patients.

Review of the T2 weighted images also demonstrated a high signal trefoil appearance within the centre of the low signal submucosa, which is likely to represent the mucosal folds of the anal canal. This was evident in the single healthy volunteer (fig 5-5) and all the patients that were scanned under the finalised protocol (fig 5-6).

The DCE images were difficult to assess initially; there was no inherent tissue contrast identified at the first time-point, which made placement of an ROI virtually impossible (fig 5-7). However this issue was overcome by propagating ROIs from images of the same slice acquired at 60 or 90 seconds, which is possible within the OsiriX ™software (fig 5-8).

No discernible difference was identified between pre and post rubber band ligation images on T2 images (fig 5-9 & 5-10), however comparing the patient (M8) with third-degree haemorrhoids to the other patients showed a difference on the final post contrast T2 images (fig 5-11 & 5-12). There was an area of high signal intensity identified at the 6 o'clock position, which was also identified on the post rubber band ligation images (fig 5-13).

5.4.3 Semi-Quantitative Analysis of DCE Imaging

Although all slices were analysed a representative selection of the data is presented. The most proximal of the six slices (slices 5 and 6) are presented, as these are in closest proximity to the anorectal angle, an easily identifiable landmark. No results are presented for the patient M5, as there was an error with the timing of the MR acquisition in relation to the contrast such that the upward slope of the time-intensity curve was not acquired at all.

It became clear on evaluating the time intensity curves (see fig 5-14 and 5-15) of all scanned patients that the contrast enhancement curve had not demonstrated a complete plateau, however this did not preclude the calculation of values for E, AR or $\frac{I_h}{I_{a60}}$. The values for the IAS ROI are presented below in tables 5-6 to 5-8.

Comparison of the healthy volunteer's time intensity curve (fig 5-16) demonstrated a faster attainment of peak contrast enhancement at 30 seconds, compared to that of 90 seconds for the pre and post rubber band ligation curves.

Unsurprisingly due to the small numbers involved, the Wilcoxon signed rank test showed no significant difference between pre and post rubber band ligation values of the IAS ROI values of E (T = 15.00 p = .742), AR of the time intensity curve (T = 10.00 p = .313) or of $\frac{I_h}{I_{a60}}$ (T = 14.50 p = .491).

Similar results were identified for the submucosal ROI signal intensity values.

PT ID	SLICE 5		SLICE 6	
	Pre-RBL	2/7	Pre-RBL	2/7
M5	-	-	-	-
M6	85.71	137.84	125.27	92.6
M8	118.42	85.98	74.19	111.0
M9	183.53	155.68	182.76	240
M11	186.27	25.76	229.17	114.29
MV11	121.62	-	146.77	-

Table 5-5 Percentage enhancement E within IAS ROI

PT ID	Deg	SLICE 5		SLICE 6	
		Pre-RBL	2/7	Pre-RBL	2/7
M5	2	-	-	-	-
M6	1	2.95	2.3	1.39	1.54
M8	3	0.99	2.87	0.82	1.88
M9	1	6.12	1.3	3.05	2.0
M11	2	3.1	0.43	7.64	1.29
MV11	-	1.01	-	1.22	-

Table 5-6 Acceleration rate of time intensity curve for the IAS ROI.

PT ID	SLICE 5		SLICE 6	
	Pre-RBL	2/7	Pre-RBL	2/7
M5	-	-	-	-
M6	0.36	0.46	0.40	0.56
M8	0.36	0.43	0.38	0.44
M9	0.32	0.28	0.47	0.38
M11	0.21	0.15	0.22	0.14
MV11	0.22	-	0.23	-

Table 5-7 $\frac{I_h}{I_{a60}}$ **for the IAS ROI.**

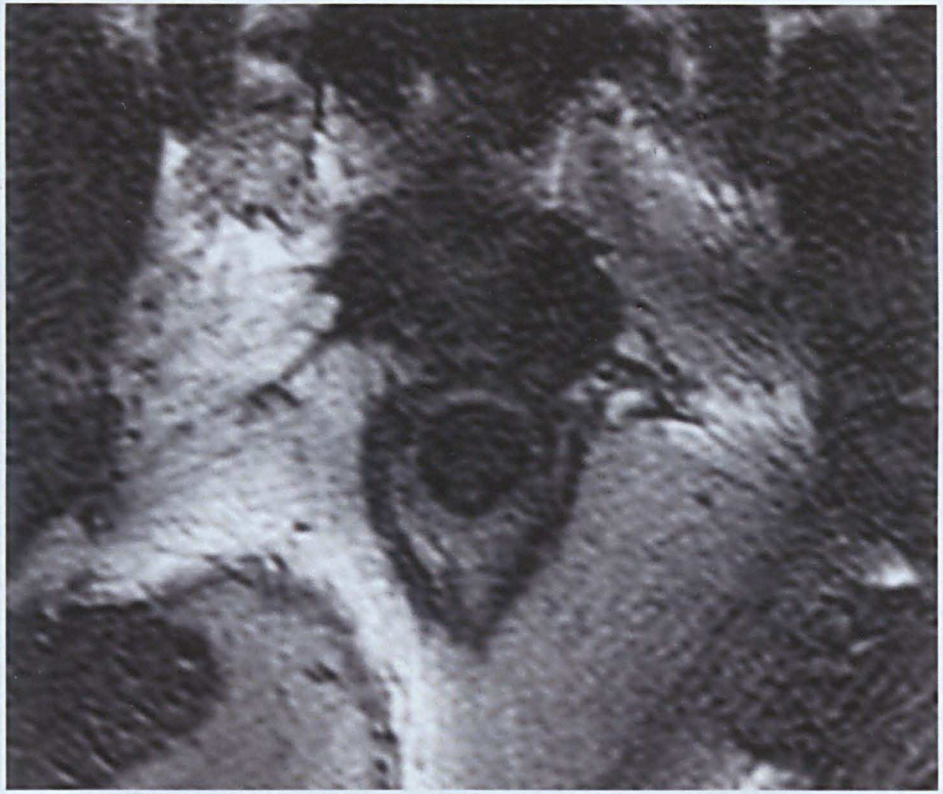

Figure 5-1 Spin echo based image demonstrating poor spatial and contrast resolution.

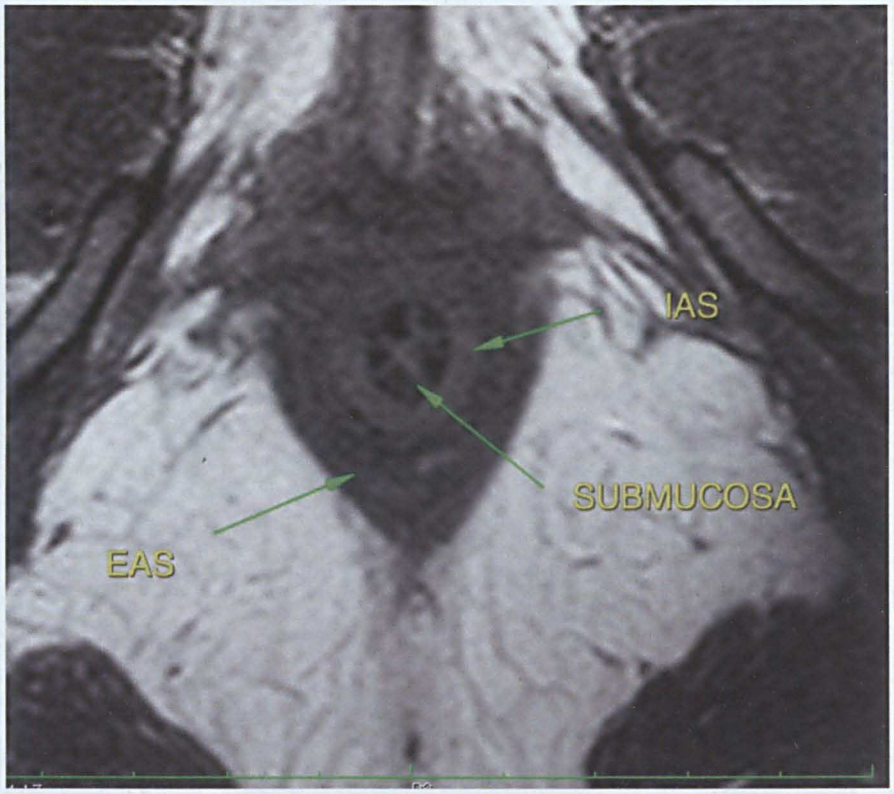

Figure 5-2 T2 weighted image of lower anal canal.

The submucosa-IAS and IAS-EAS interfaces are well demonstrated.

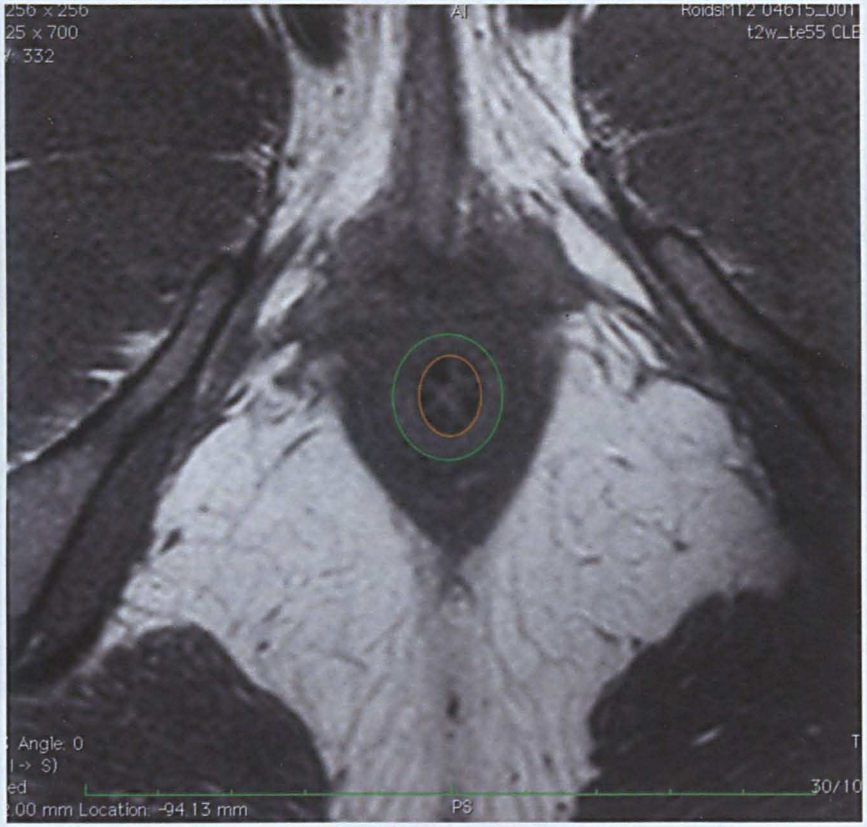

Figure 5-3 Demonstration of placement of ROIs.

T2 weighted image.

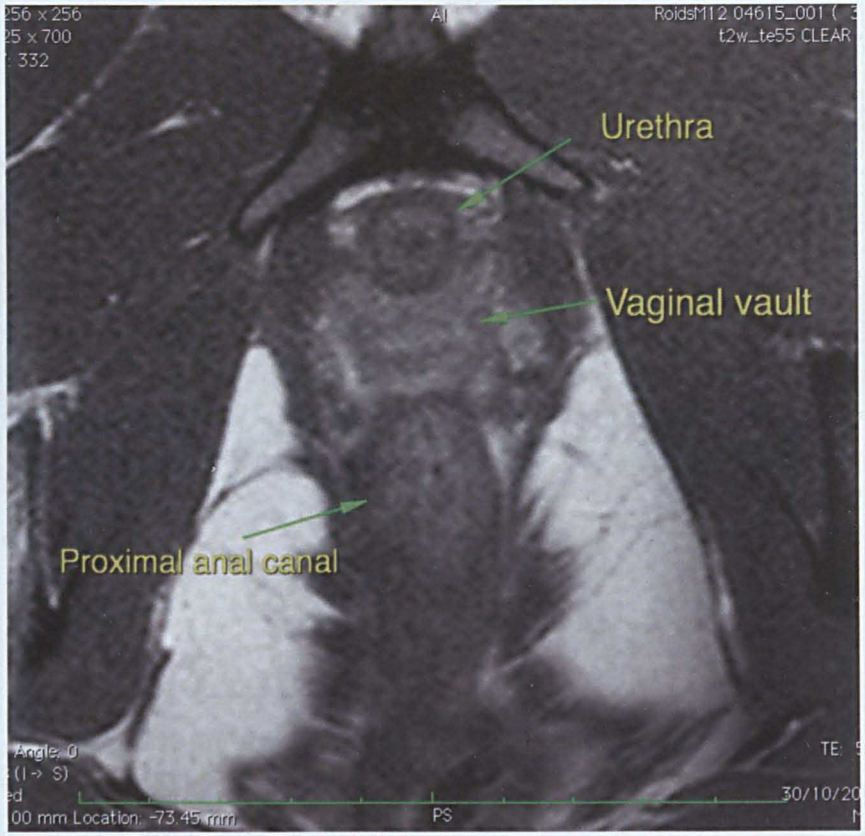

Figure 5-4 Axial image of proximal anal canal.

Images are from the same patient as in figs 5-1 and 5-2.

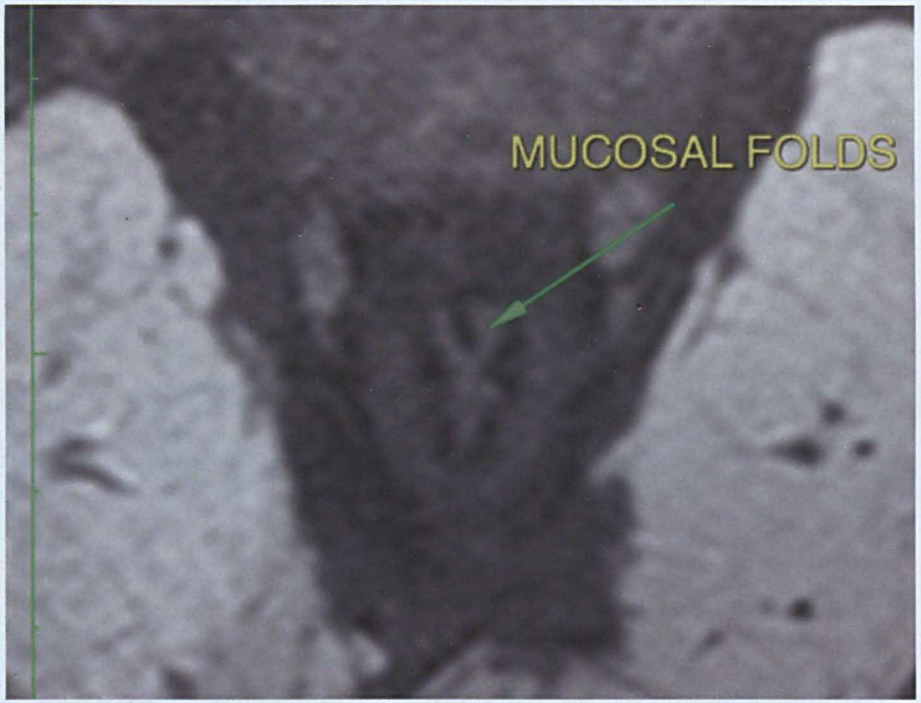

Figure 5-5 High signal intensity of mucosal folds in a healthy volunteer.

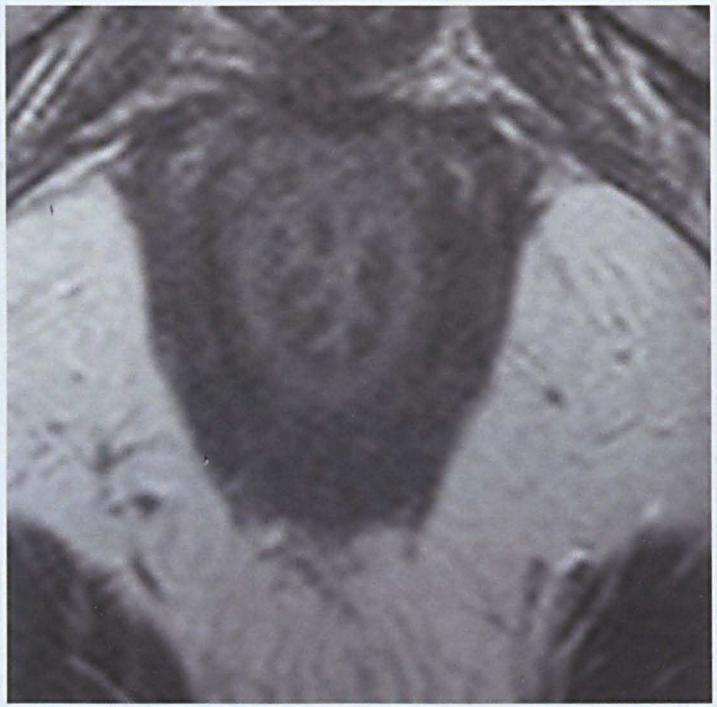

Figure 5-6 High signal intensity of mucosal folds in a patient.

Similar appearance in a patient with second-degree haemorrhoids at mid-anal canal level.

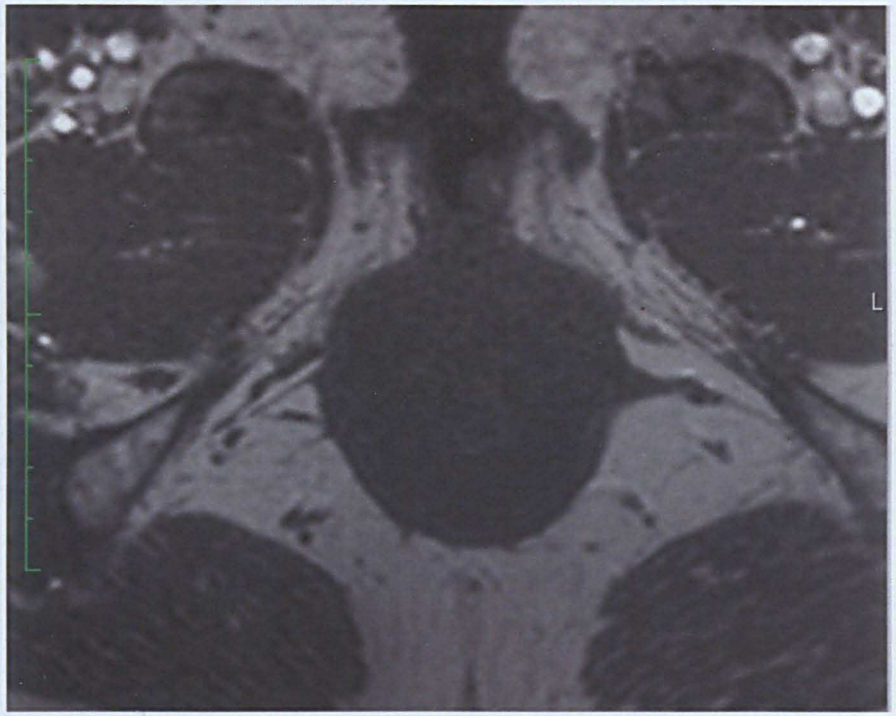

Figure 5-7 T1 weighted image DCE.

Proximal slice from a patient prior to rubber band ligation at start of DCE scanning.

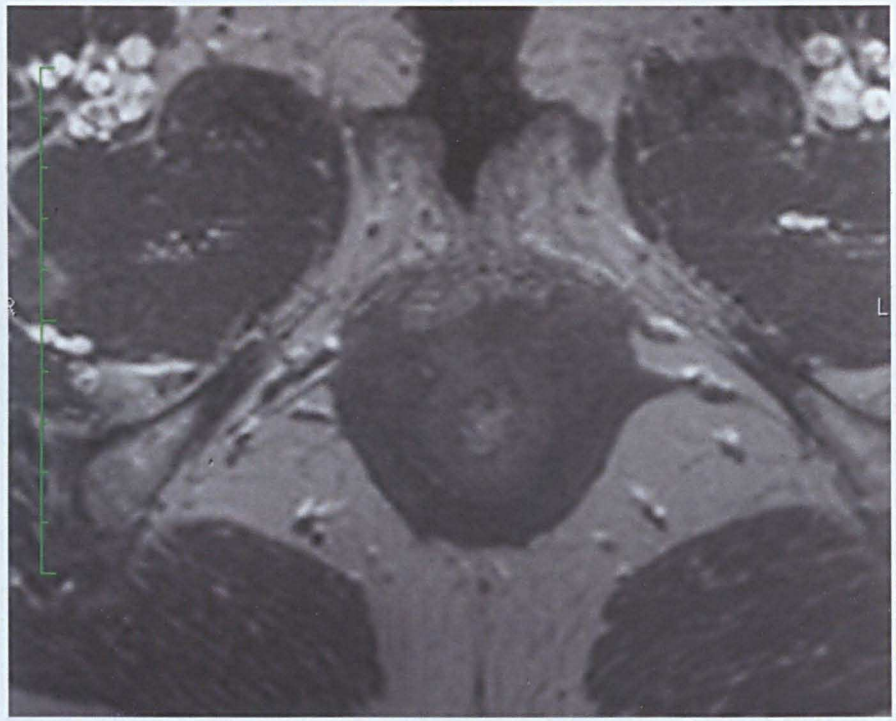

Figure 5-8 Image acquired at 60 seconds post contrast injection.

The same slice as in fig 5-5 now shows contrast-enhanced delineation between the submucosa and IAS, thereby allowing placement of ROIs and propagation to other slices.

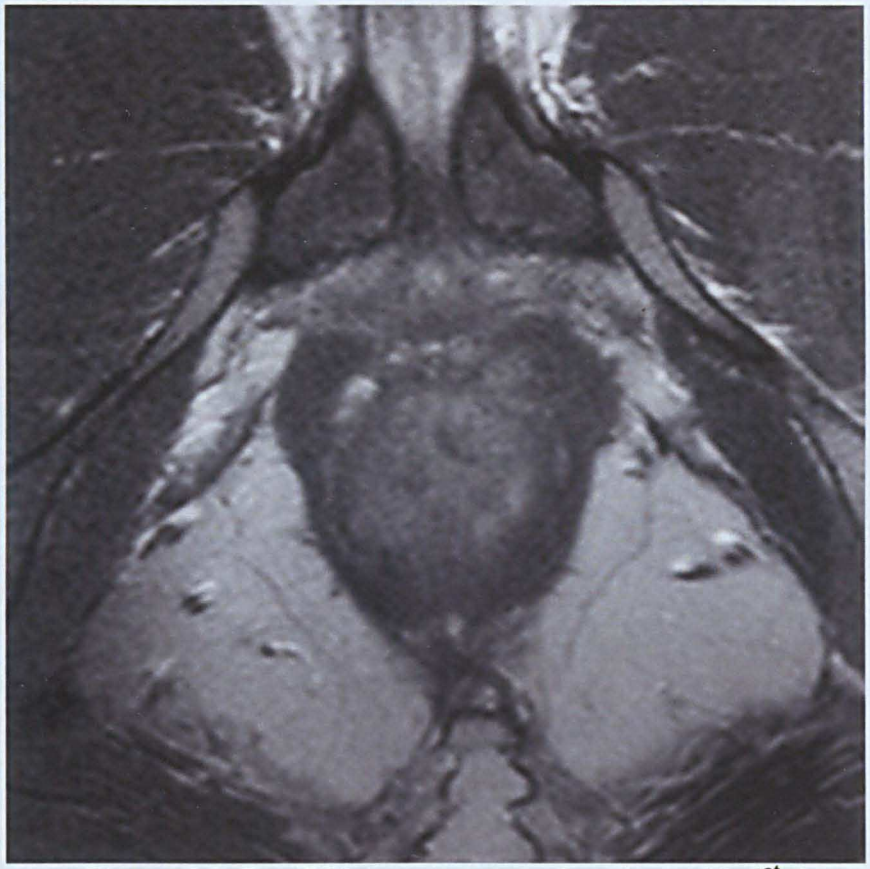

Figure 5-9 Pre-RBL appearance of patient with 1st degree haemorrhoids.

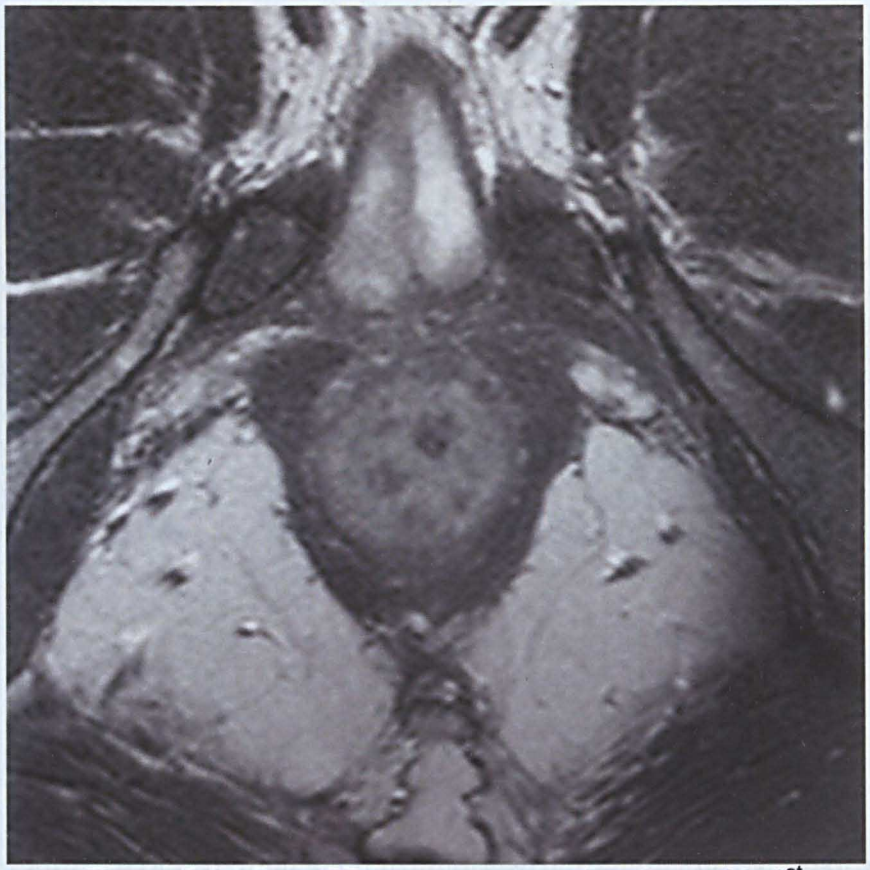

Figure 5-10 Post-RBL appearance of patient with 1st degree haemorrhoids

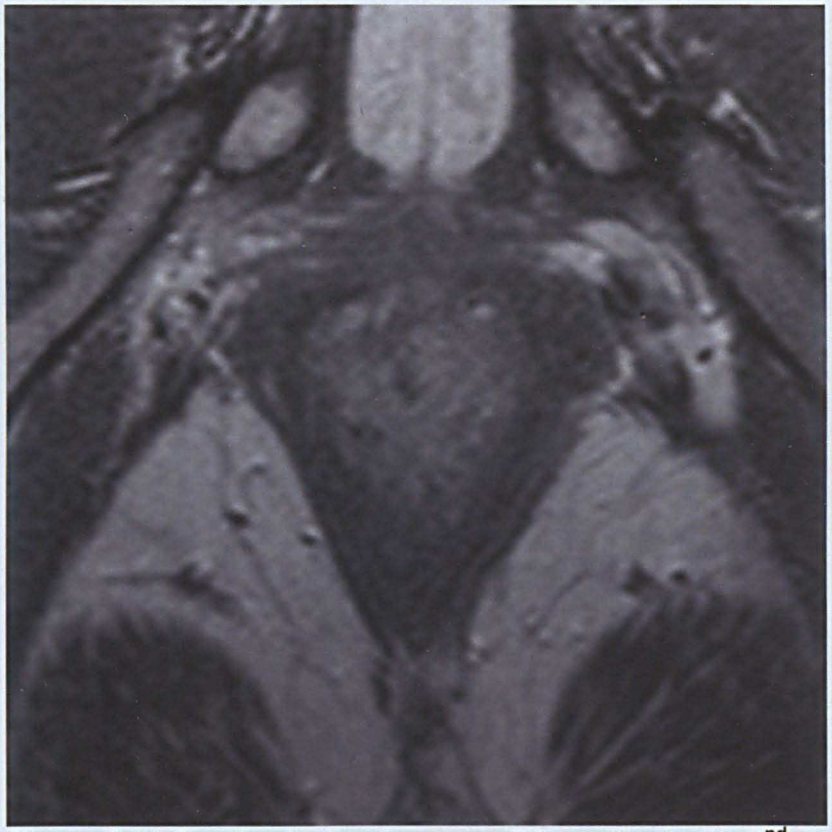

Figure 5-11 Proximal slice from pre-RBL patient with 2nd degree haemorrhoids.

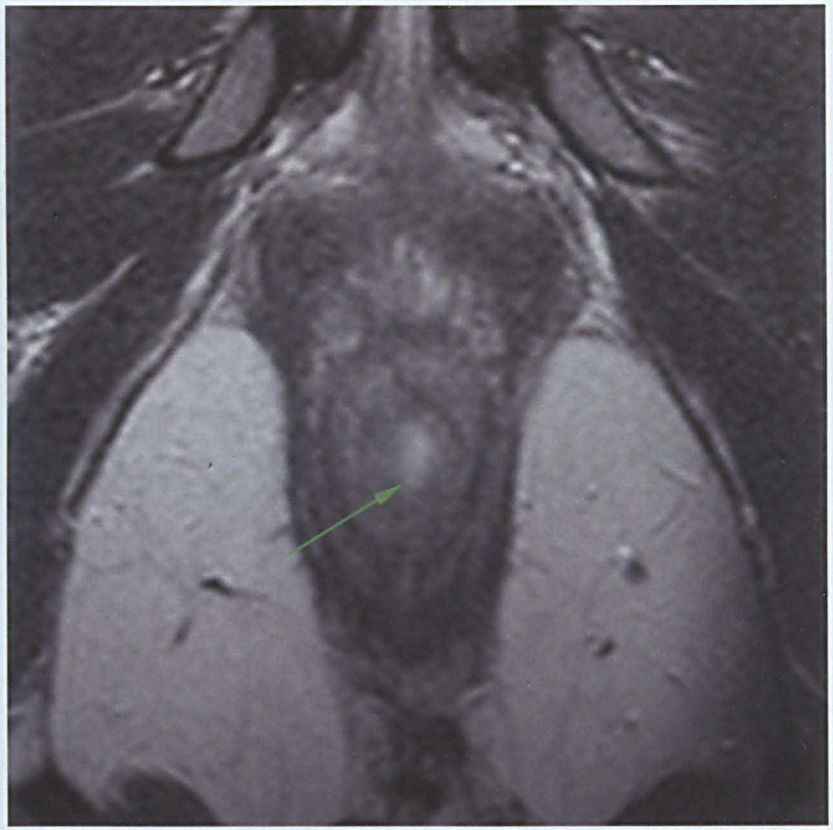

Figure 5-12 Proximal slice from pre-RBL patient with 3rd degree haemorrhoids.

An area of high signal intensity is identified at the six o'clock position.

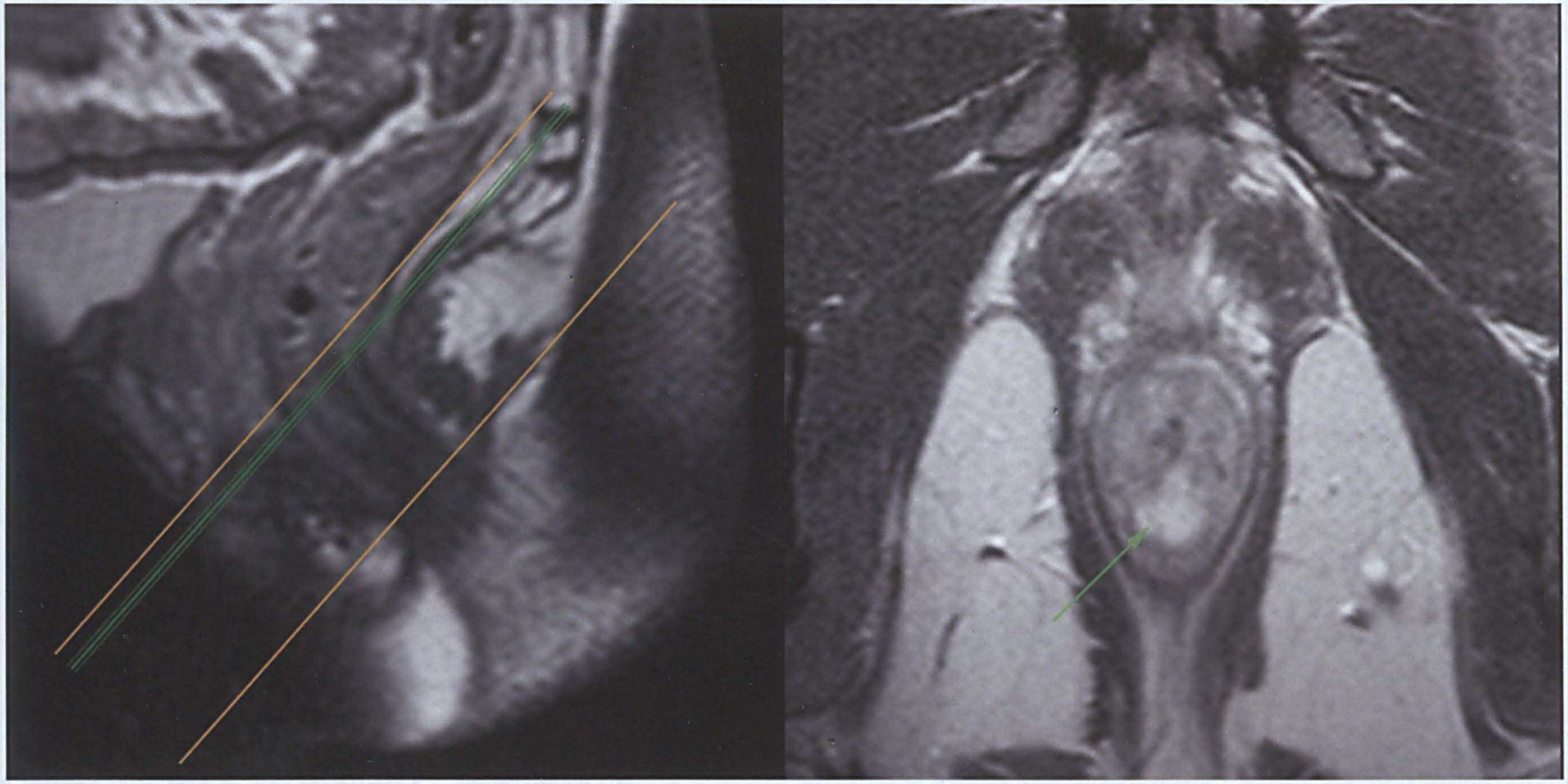

Figure 5-13 Axial slice from post-RBL patient with third-degree haemorrhoids and concurrent position on sagittal image

The green line on the left image denotes the exact position of the axial slice. The area of high signal intensity is unchanged visually from that in fig 5-12.

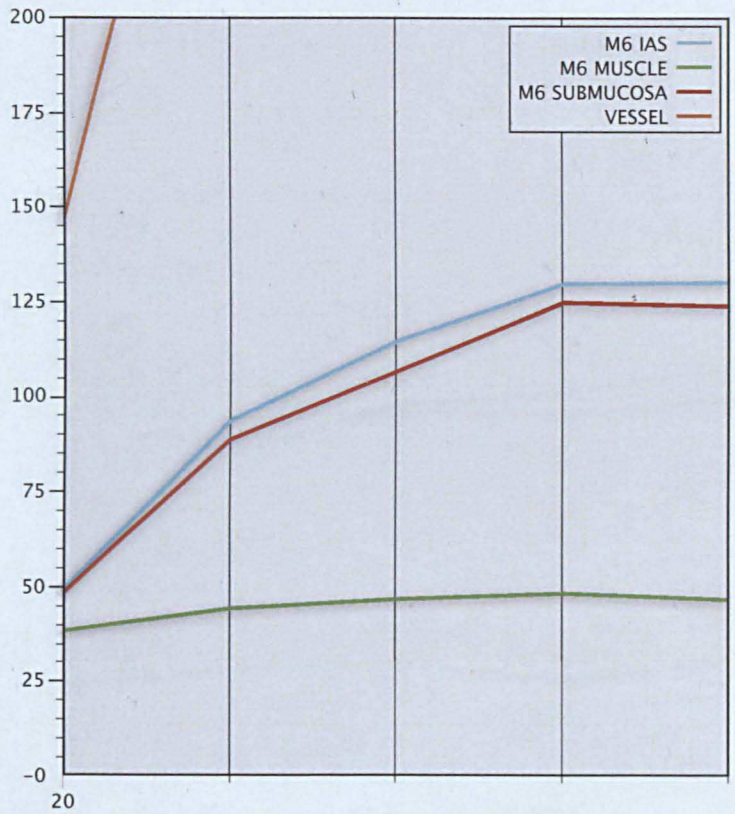

Figure 5-14 Time intensity curve for M6 prior to RBL.

Each gridline on the x-axis represents a 30-second interval.

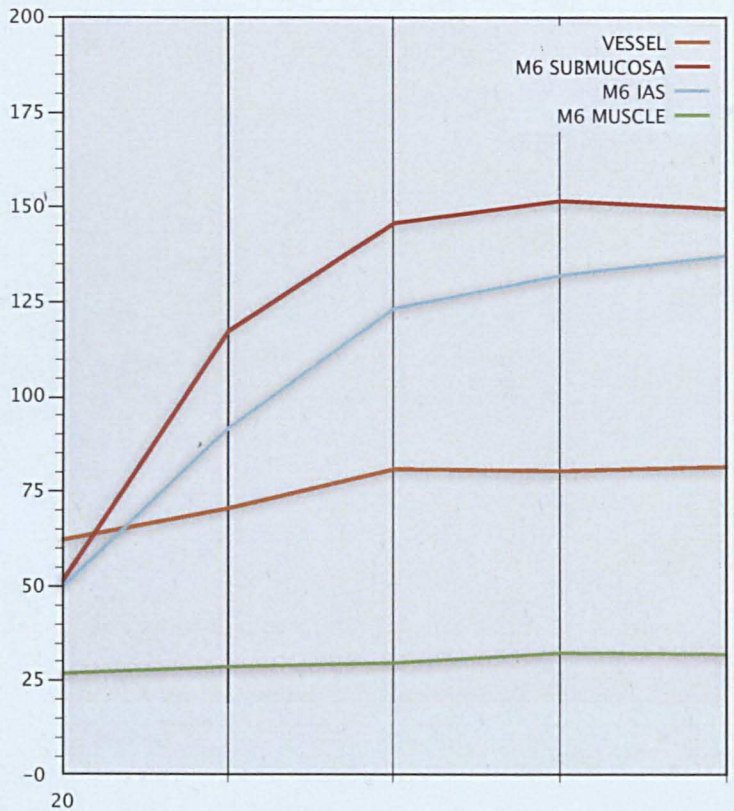

Figure 5-15 Time intensity curve for M6 2 days after RBL.

No significant difference was identified between the measures of perfusion pre and post rubber band ligation.

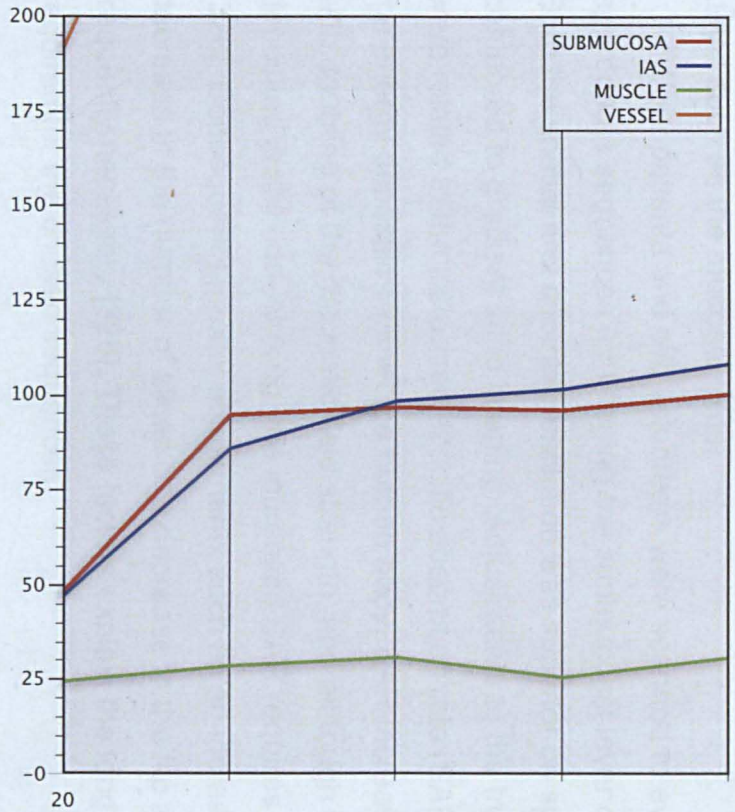

Figure 5-16 Time intensity curve of a healthy volunteer.

This demonstrates attainment of peak enhancement at 30 seconds, which is of shorter duration than in the pre or post RBL time intensity curves

5.5 DISCUSSION

The aim of this study was to evaluate the feasibility of both acquiring MR images of haemorrhoids and the evaluation of perfusion calculations as a possible parameter for haemorrhoidal vascularity. There is an extensive amount of research on the role of both endoanal and external phased array MRI in the evaluation of faecal incontinence and perianal fistulae. This is supported by numerous studies on the morphology of anal sphincters in patients and healthy volunteers [283, 297, 298, 305, 306, 321]. There is, however, no formal evaluation of the submucosal layer in any of these studies. Review of images from groups evaluating the role of external phased array MRI of the anal sphincter complex [322-324], show that the submucosa is isointense in comparison to the hypointense IAS. There was no morphological detail such as the hyperintense mucosal folds identified in this study. This is likely to be related to the use of a 3T magnet, with its increased intrinsic SNR proportional to the main magnetic field strength, B_0 (equation 5-1). The SNR is not however twice of that obtained in a 1.5T magnet due to factors such as increased longitudinal relaxation time [307, 325] and decreased transverse relaxation time [307]. Nevertheless qualitative analysis of the images demonstrated improved morphological detail such as the mucosal folds.

Four patients and two volunteers were scanned to evaluate the most appropriate sequences for imaging the submucosal layer of the anal canal. Both the spatial and contrast resolution was superior on spin echo imaging, compared to gradient echo imaging. Adjustments to the trialled sequences were related to the increased specific absorption rate (SAR), a measure of the energy deposition within the human body. SAR increases by a factor of 4 with doubling of the magnetic field strength, and although the energy deposited is still non-ionizing, the increased SAR requires careful monitoring [326]. Consequent protocol adjustments such as an increase in the TR, a decrease in the number of slices or a decrease in the flip angle are frequently necessary [326]. These factors explain the long durations required for the chosen sequences.

There were a number of limitations in this study, which should be taken into account. The qualitative analysis demonstrated that images were affected by artefact due to motion, peristalsis and flow. Although these artefacts did not preclude the placement of the IAS and submucosa ROIs, accuracy of replicating this process in the images acquired after rubber band ligation is likely to have been affected. This could be improved by administration of an anti-spasmodic such as buscopan™ (Boehringer Ingelheim, GmbH) in possible future studies.

Following on from the last point, there will have been errors relating to the placement of the orthogonal planes on the planning sagittal sequence (fig 5-13). Measurement errors are related to the inherent discriminatory capability of the imaging method, as well as the ability of the observer to perform a consistent reading [298]. Due to the pilot nature of this study and the small sample size, formal evaluation of reproducibility was not performed. Difficulty with placement of the ROIs was noted for the proximal slices at the anorectal angle; this was likely to be related to the change in orientation of the orthogonal plane at the anorectal angle. In possible future studies modification of the technique may include acquiring two sets of axial images, orthogonal to the mid and distal anal canal, and orthogonal to the proximal anal canal at the anorectal angle.

Technical limitation of the DCE MRI component of the study was demonstrated on review of the time intensity curves, where the contrast enhancement curve had not yet completed a full plateau. If further investigation of DCE-MRI is to be performed, further evaluation of the T1 sequence parameters will be necessary to reduce acquisition time.

It was possible and simple to evaluate three model-free parameters describing the DCE-MRI dynamic curve, however no meaningful statistical analysis could be performed due to the small number of patients involved. The choice to use the model-free parameters is related to the simplicity of application and calculation.

In the research field of recurrent rectal cancer, investigators have emphasised the need to evaluate diagnostic criteria for categorization of recurrent tumour [327, 328]. Therefore qualitative analysis of pre and post

rubber band ligation images was performed in this study. The appearance of pre and post rubber band ligation images did not differ, with no difference in overall or focal signal intensity identified. It is acknowledged that analysis of signal intensity was not performed, however this choice is related to the errors inherent in relaxometry, including biological variability, multi-exponential behaviour, tissue mixing, field strength dependence and magnetization transfer.

Pre rubber band ligation T2 images from the patient with third-degree haemorrhoids showed a focal area of high signal at the six o'clock position. This appearance became slightly more prominent on the second set of T2 post DCE image acquisition, and was still present at the time of post rubber band ligation image acquisition. It was documented at the time of MR examination that the patient was in considerable discomfort prior to rubber band ligation, and one possible interpretation of this appearance is that of thrombosis present within the haemorrhoidal venous plexus.

At the time of writing (January 2012) the investigator is not aware of any MRI studies performed by other groups to examine anal canal cushions or haemorrhoids. This was a feasibility study, and I would recommend the following alterations to the study protocol: the use of buscopan to reduce motion and peristalsis artefact; longer duration of acquisition of DCE images; acquisition of two sets of axial images, orthogonal to the mid-to-distal anal canal and orthogonal to the proximal anal canal as it approaches the anorectal angle; and lastly to image patients with third and fourth-degree haemorrhoids.

There are multiple parameters available for evaluation of DCE MRI images, and if there are greater numbers of patients involved, then these could be compared formally. It is noted that the model-free parameters have shown poor reproducibility and do not distinguish the effects of blood flow, blood volume or contrast agent leakage [329]. Nevertheless, given that haemorrhoidal vascularity has not been evaluated in any great depth, simple measures, which can be easily replicated by multiple groups, are likely to represent a more pragmatic approach to further research.

6 DISCUSSION

6.1 Development of objective measures of haemorrhoidal disease and response to treatment.

At the start of the research period the underlying theme to the proposed investigations was that if new surgical treatments, DGHAL and PPH purported to affect haemorrhoids by interrupting arterial supply, then it might be possible to replicate the effect pharmacologically. A literature review at this time demonstrated a paucity of research evaluating changes in vascularity as a cause of haemorrhoids, despite enthusiastic and extensive publication of trials evaluating the effectiveness of DGHAL and PPH.

There has been very little objective assessment of the relationship between development of symptoms and the change from normal anal cushions to pathological haemorrhoids. Little is known of the natural history or symptom progression of patients with haemorrhoids. Although there has been enthusiastic uptake of PPH and DGHAL, this has not been mirrored by investigation of pathogenesis or objective evaluation of outcome.

The testing of pharmacological agents often requires a biomarker; which can be defined as a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathological process or pharmacological response to a therapeutic intervention [330]. The requirement for objective outcome measures or biomarkers in the evaluation of treatment of haemorrhoids is clear; there are no validated or even standardised methods for evaluation of treatment efficacy, as discussed in the introduction to chapter two.

Therefore the primary aim of the thesis is to investigate and develop different modalities to assess efficacy of treatment, with a view to producing a biomarker of haemorrhoidal disease. A secondary aim is to evaluate whether pathological change in vascularity of the normal anal cushions is at least partly responsible for the development of haemorrhoidal disease.

6.1.1 Haemorrhoid PROM

At the time of starting the thesis research period, there had been no significant discussion of how surgeons should compare the success of different treatment modalities for haemorrhoidal disease. The advent of PPH and DGHAL stimulated re-evaluation of the role of abnormal vascularity in the pathogenesis of haemorrhoids.

Patient reported outcome measures and quality of life measures have become a significant, and sometimes essential, part of assessment of treatment efficacy in clinical trials, in a variety of clinical settings.
There are a wide variety of measures reported in the literature, which are used to compare treatment modalities and verify successful outcome. These include surgeon-assessed clinical outcomes such as symptoms and proctoscopic appearance, complications and requirement for re-intervention, patient satisfaction and return to work, and recurrence rates at varying post-operative time intervals.

In the early stages of the thesis research period, it became clear that there is no consensus on a gold standard criterion for evaluation of the efficacy of any treatment modality. Therefore validation of any outcome measure was always going to be difficult. It was postulated that health-related quality of life could be correlated to responses to individual items and a total score, allowing self-validation. This has been used in the early stages of development of other PROMs to assess validity.

The development of the haemorrhoid PROM comprised an initial phase of item selection, reduction and scaling. Analysis of the responses to the initial symptom index (HSI-1) was used to develop a second PROM. Differences included reduced number of items, different scaling, altered formatting to improve ease of use, and the use of visual analogue scales to assess HRQL.

The choice of a general surgical outpatient clinic for recruitment of patients was inherent to the nature of the study, i.e. evaluation of a treatment. One hundred and fifteen patients with first to third degree haemorrhoids were recruited to the study. Early on in the study, reproducibility was assessed by asking the first twenty-two participants to

complete a second PROM, once the first had been completed and returned. The intraclass correlation was 0.987 (0.970 – 0.995). Reliability was further assessed by analysing internal consistency. Values of Cronbach's α were higher than 0.80 for all items at all time-points. This indicates that the covariance of the items reflects an underlying dimension that may be more important than any single item.

Validity was assessed in several ways: completion by healthy volunteers, and correlation of the item and total scores to the quality of life scores. Healthy volunteers scored a mean value of 1.58 compared to patients who scored a mean value of 22.04 prior to, 18.53 four weeks after and 11.37 eight weeks after rubber band ligation.

Spearman's rho for correlation of the total score to quality of life score affected by pain ranged between 0.629 and 0.720 depending on the time-point of assessment, and for correlation to quality of life affected by other symptoms ranged between 0.569 and 0.744. Correlation values of less than 0.300 were obtained for the bleeding and itch/ irritation items, which suggest that these items are less important to the overall construct. Removal of these items did not make a significant difference to the overall correlation of the total score to the quality of life scores.

Responsiveness was verified by demonstrating a significant decrease with a moderate size effect in the total score, and in most individual items apart from the pain and soiling items. Further proof of validity was demonstrated by comparing patients who did and did not require further treatment. At no point in the study was reference made to the scores with respect to making decisions about the requirement for further treatment. A significant decrease with medium to high size of effect was identified for all items, except itch/ irritation. As this item did not correlate well with quality of life scores either, it is suggested that in any future work, the investigator considers removal of this item completely or analysis of validity with the item included and excluded from the total score.

Evaluation of the patient group by degree of haemorrhoid demonstrated significant differences between first-degree haemorrhoids and second or third-degree haemorrhoids. Patients with first-degree

haemorrhoids demonstrated low responsiveness for pain, lumps, sensation of incomplete emptying and mucus/ slime. This pattern of response is in keeping with currently used classification systems, however the decrease in score of the bleeding item for first, second and third-degree haemorrhoids does not correlate well with Goligher's classification [331].

Acceptability of the PROM can be evaluated by the recruitment rate, which was good (80.6%) and moderate retention rate (72.2%) for each time-point. It is suggested that if future studies are carried out, then only the 8-week questionnaire is sent out to reduce the burden on the patient. Statistical analysis of missing data was handled in a consistent manner for every study, and data was excluded in a list-wise manner. This may explain the low values for the correlation of some items to the quality of life scores.

Although most of the requirements [332] for a clinically appropriate PROM have been fulfilled, it is acknowledged that there were limitations to the study. Most importantly patients were not directly involved in the item selection process. The study group was relatively small, and with respect to validity, further studies are required. Nevertheless the haemorrhoid PROM has fulfilled many of the appraisal criteria to merit further development and analysis.

This study evaluated patients with first to third degree haemorrhoids requiring rubber band ligation as the chosen method of treatment, and therefore although there is promising evidence of validity, it cannot be used directly in the evaluation of fourth-degree haemorrhoids. Recruitment to all studies proved difficult, which may be related to the strict adherence to exclusion criteria. The study population was relatively small, and further analysis of validation sets of patients is required before the PROM can be applied to a clinical setting, Future work should focus on direct involvement of patients in further generation of quality of life related items. Expansion of the study population to include fourth-degree haemorrhoids will require modification of the PROM to include relevant items.

6.1.2 3D PDA – Anorectal Angle Sphere Measurements of Vascular Indices.

An endoanal approach was rejected as a possible route to imaging haemorrhoids because of the compressive effect of the probe. Duplex Doppler was rejected as a means of analysing vascularity because of Doppler angle reliance, operator dependent error and aliasing. It should also be noted that there was no significant ultrasound training available for the investigator, and that this was also a factor in rejecting the duplex Doppler approach to analysing vascularity. The decision to use power Doppler was also based on the fact that all vessels, including arteriovenous communications and the venous plexus would be assessed.

The other pragmatic decision was related to the probes available for use with the GE 730 Expert based at Nurture, the fertility treatment centre based at University Hospital Nottingham. An abdominal probe (RAB 2-5) and an endovaginal probe (RIC 5-9) were available for use. The frequency range of the abdominal probe is 2.0 – 5.0 MHz, which was too low for the application of interest. Several of the healthy volunteers were also scanned with the abdominal probe, and the 3D grey-scale datasets and power Doppler datasets were found to be of much lower quality in comparison to those obtained with the endovaginal probe. An issue with the endovaginal probe was the ergonomics of supporting the probe on the perineum whilst the datasets were acquired.

Transperineal 3D ultrasound was established as a reliable method of acquiring images of the anal canal that did not compress the haemorrhoids or anal cushions. Evaluation of all datasets showed that the anorectal angle was captured within the acquired volume. Optimum power Doppler settings were established prior to starting the clinical part of the study.

Early on in the study, it was important to decide the means of evaluating the 3D power Doppler information available within the scanned volumes. Delineating a region of interest by rotating it around an axis was not feasible as the cranial and caudal limits could not be defined accurately. Therefore the anorectal angle sphere was assessed for feasibility and

reliability. Once the centre-point of the sphere had been positioned.at the anorectal angle, the sphere was automatically generated by VOCAL.

Therefore there is less of a margin for the introduction of measurement error, which was evaluated by studies 1 and 2. These studies established the reliability of obtaining the 3D-PDA volumes from patients and healthy volunteers. Very high intraclass correlations were obtained for volume and vascular indices when analysing a single dataset and three datasets acquired within the same scanning session.

At this stage in the research, reliability of the transperineal technique and the anorectal angle sphere measurement technique had shown high reliability. The establishment of validity as discussed previously is inherently a difficult task, with the lack of an available gold standard. Therefore construct validity had to be assessed; in these circumstances based on the theory of a vascular element to the pathogenesis. It was postulated that the vascular indices of healthy volunteers should not change significantly over time, and that the vascular indices of patients should be higher than those of healthy volunteers.

There was no significant difference between patients and healthy volunteers with respect to age or current medication use. Study 3 assessed the possible change in the vascular indices of healthy volunteers over time. Friedman's ANOVA did not identify any significant difference between the values, and therefore further analysis with the Wilcoxon signed rank test was not performed. Study 4 compared the vascular indices of healthy volunteers to patients at all time-points. The Mann-Whitney test identified that the pre-rubber band ligation patients' sphere volumes and vascular indices were significantly higher than those of the healthy volunteers.

Responsiveness of the volume and vascular indices was analysed over an eight week time period. Although significant decreases were identified between day 1 and day 14 scores, the study size limited its strength to assess responsiveness.

Aigner et al., assessed the branches of the superior rectal artery with duplex Doppler, and was able to show significant differences between an age and gender matched groups of patients and healthy volunteers [228].

This group was unable to show a statistically significant difference between pre and post DGHAL measurements, which was thought to be related to failure to ligate all branches of the superior rectal artery, thus explaining the recurrence rates for DGHAL. To the best of the author's knowledge, this group has not published any data on the reliability of measurement of the flow and diameter of vessels assessed, and this may represent an alternative explanation for failure to show a difference between patients and volunteers.

6.1.3 Surgical Nuclear Probe

The nuclear medicine study evaluated the feasibility of measuring a change in volume of haemorrhoids following rubber band ligation. The underlying principle of the dual radioisotope technique was simple: g-rays emitted by the ^{99m}Tc labelled red blood cells and counted by the surgical probe represented volume prior to rubber band ligation; and similarly counts from ^{111}In labelled transferring represented post rubber band ligation volume. Calculations were corrected for decay and reference counts corrected for normal clearance from the circulation.

Consistent results were not identified across the study participants, and there are various sources of error that could account for this. Patient related characteristics included cardiac medication that affected in vivo ^{99m}Tc labelling of the red blood cells. Reproducibility of positioning the patient and placing the probe on the haemorrhoids is difficult to verify. Changes in the morphology of the haemorrhoids following rubber band ligation would also make accurate probe positioning difficult. Error relating to the measurement of the photons should also be considered, including γ-rays that are absorbed before they can be detected and Compton-scattered γ-rays contributing to the acquired counts.

6.1.4 Dynamic Contrast Enhanced Magnetic Resonance Imaging

This study firstly evaluated the feasibility of imaging anal cushions and haemorrhoids with enough spatial and contrast resolution to allow for potential image analysis. Having identified appropriate sequences, DCE-MRI and signal intensity curves were used to assess potential measures of

vascularity. Software analysis of images and regions of interest were simple to perform.

Qualitative analysis of images from healthy volunteers and patients did not show any discernible differences. Similarities included the high signal mucosal folds on T2 weighted images. The only difference identified was that of high signal change within the submucosa of one patient with third-degree haemorrhoids, who from the history taken and examination performed obviously had thrombosis of an internal haemorrhoid.

6.2 Choice of Modality for Future Studies

Overall comparison of the three imaging modalities is difficult because they are all measuring different factors, relating to vascularity. However the surgical nuclear probe is not recommended as a modality to be further assessed, even if one discounts the issues with reliability. Of the three studies, the surgical nuclear probe was the most difficult to recruit to, with poor patient understanding of relative risks of radiation doses. The procedure itself was of relatively long duration with periods of inconvenience or discomfort when the proctoscope is inserted. The feasibility study failed to demonstrate consistent results in the patients where in-vivo 99mTc-red blood cell labelling had been adequate.

To a certain extent, the choice of outcome measure has to be a pragmatic one. Many centres do not have access to ultrasound equipment capable of 3D volume acquisition, and post-procedural analysis of Doppler data. The same applies to a certain extent with 3T MRI however these magnets have become much more common in the last few years.
The Doppler technique has been shown to be reliable, and the significant differences between patient and healthy volunteers are suggestive of validity. Although statistically significant differences were identified in the analysis of responsiveness, the study size precludes use of this study clinically without further analysis of validity and responsiveness.

It is important to remember that these indices are unitless and do not represent true measurements of flow, vascularity or perfusion. They may still be used, however, to differentiate between patient populations or quantify

the effect of a treatment in the same way that resistance and pulsatility indices are. If one accepts that power Doppler quantification has a clinical role then one of the most important issues to address in its application is standardisation of measurements.

The effect of machine settings on the power Doppler signal has been recognised by most authors who report the maintenance of settings throughout the study period. However, power Doppler is not only highly dependent upon the machine settings but is also significantly affected by attenuation.

Ensuring consistency of the power Doppler settings is insufficient, therefore, if variation in the patient population is not considered. The effect of haematocrit on the power Doppler signal might be considered to be relatively constant across a patient population, but the effect of signal attenuation by excess subcutaneous tissue and fat can have an effect on the acquired Doppler signal. Attenuation will also be aggravated if the object of interest is at a considerable depth from the transducer, which may explain the difficulties with imaging male patients. Time-gain-compensation can be used, but has limitations and may be unable to compensate for large changes in depth encountered in some patients.

Once the sequences had been finalised, the DCE-MRI study was relatively easy to perform. As this was a feasibility study, further work is required to establish reliability and validity, including reproducibility of T2 weighted image acquisition by repeated scanning of the patient or volunteer, intra-observer and inter-observer reliability of region of interest deployment, and assessment of other model-free parameters and possibly pharmacokinetic models.

The time required to analyse the data was much shorter in comparison to the Doppler study. Disadvantages of the modality include the exclusion criteria inherent to MRI, such as patient-related factors including the presence of pacemakers, neurosurgical coils and claustrophobia. Estimates of patient refusal for MRI due to claustrophobia vary between 4% [333] and 37% [334].

Whether future investigators choose to evaluate 3D power Doppler ultrasound, duplex Doppler ultrasound or DCE-MRI or other unexplored modalities, it is essential that other markers of outcome such as the haemorrhoid PROM, be used in parallel to allow evaluation of correlation, and possible confirmation of validity.

6.3 Examination of the vascular theory of pathogenesis

Prior to the advent of DGHAL and PPH, the accepted theory of pathogenesis is that haemorrhoids arise as a consequence of degeneration of stromal or submucosal connective tissue and of the supportive smooth muscle network arising from the internal anal sphincter and the conjoined longitudinal muscle [2, 13]. Venous obstruction due to straining [335], constipation [34], pregnancy [52] or portal hypertension [336] is another well accepted pathological factor [52]. The final proposed theory of pathogenesis is hyperplasia of the arteriovenous communications in the submucosa, or the corpus cavernosum recti [10].

There is an unusual and extensive vascular network within the haemorrhoidal zone composed of a varying branching network of the superior, middle and inferior rectal arteries, the direct arteriovenous communications and the distinctive sacculated submucosal venous plexus [337]. How these components are related to the pathogenesis of haemorrhoids is unknown. Anal cushions are considered to be normal structures and part of the anal continence mechanism [17] by forming a compliant plug in the anal canal. As the cushions reduce and increase in size for the purposes of defaecation, it is logical to consider that pathological change in the vascular network is at least partly responsible for the onset of haemorrhoids.

Part of this thesis studied the effect of treatment on indirect vascularity measures, and differences between patients and healthy volunteers. Although significant differences were measured, vascularity measures were not assessed over time to identify if the measures were stable without treatment or without any change in the level of disease. Patients and healthy

volunteers were not formally age-matched, although there was no statistically significant difference between the two groups.

Therefore although the three-dimensional power Doppler angiography technique is promising, one can only continue to speculate that pathological change in the vascular network has a role in the pathogenesis of haemorrhoids.

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8 APPENDIX

8.1 HAEMORRHOID PROM

Study number ☐☐☐☐☐☐☐

QUEEN'S MEDICAL CENTRE UNIVERSITY HOSPITAL NHS TRUST

Today's Date: / /

Section 1

Please answer the following questions by ticking the boxes or writing your answers in the space provided:

1. Are you **Male** ☐ **or** **Female** ☐ **?**

2. How old are you? _____ **years**

3. How long have you had piles (haemorrhoids)? ____ **years or** ____ **months or** _____ **weeks**

4. Are you using any **painkillers** for your piles eg. paracetamol, ibuprofen?

   Yes ☐ **No** ☐

5. If you answered Yes to Question 4 please write the **name and dose** of medicine.

_____

6. Are you using any **ointment or suppositories** for your piles eg. Anusol, Anugesic, Anacal, Preparation H ?

   Yes ☐ **No** ☐

7. If you answered Yes to Question 6 please write the **name and dose** of medicine.

_____

8. What made you see your GP **about your piles**?

_____

_____

Figure 8-1 Section 1 of Haemorrhoid Symptom Index-1

Your Symptoms

Please **answer all of the following questions** on the current state of your symptoms.

This will help us determine if any improvement has occurred after treating your piles.

Please tick the box you feel most appropriate.

1A) How often do you get pain or discomfort on opening your bowels?

- ☐ **Never**
- ☐ **Less than once a month**
- ☐ **At least once a month, but less than once a week**
- ☐ **At least once a week, but less than once a day**
- ☐ **With each motion**

1B) If you do get pain or discomfort on opening your bowels, how much does this affect your life?

- ☐ **Not at all**
- ☐ **Slightly**
- ☐ **Moderately**
- ☐ **Quite a bit**
- ☐ **A great deal**

2A) How often do you get bleeding on opening your bowels?

- ☐ **Never**
- ☐ **Less than once a month**
- ☐ **At least once a month, but less than once a week**
- ☐ **At least once a week, but less than once a day**
- ☐ **With each motion**

2B) If you do get bleeding on opening your bowels, how much does this affect your life?

- ☐ **Not at all**
- ☐ **Slightly**
- ☐ **Moderately**
- ☐ **Quite a bit**
- ☐ **A great deal**

Figure 8-2 Selected page from section 2 of Haemorrhoid Symptom Index-1

Queen's Medical Centre Nottingham NHS
University Hospital NHS Trust

HAEMORRHOID (PILES) SYMPTOM QUESTIONNAIRE

STUDY NO:

DATE OF COMPLETION:

(PLEASE FILL IN ON DATE SPECIFIED, OR IF BLANK THE DAY THAT YOU COMPLETED THE QUESTIONNAIRE)

Please complete all three sections of the questionnaire.

If you have any difficulty completing the questionnaire, please contact us.

Dr Caron Parsons
Department of Surgery
E Floor West Block
University Hospital
Nottingham
NG7 2UH

0115 8231144
Email: caron.parsons@nottingham.ac.uk

Version 1.6
19th August 2005

Figure 8-3 Haemorrhoid PROM Front Cover Page

VERSION 1.6
19th AUGUST 2005

Section 1: About You

1. Are you? ☐ Male ☐ Female

2. How old are you? ..... Years

3. What is your current occupation? If you are retired, please state your occupation prior to retirement?
.....
.....
.....

4. How long have you had piles (haemorrhoids)?

..... Years **OR** ..... Months

Section 2: About Your Health

1. Do you have any serious medical problems, including other bowel problems?

☐ No ☐ Yes

If YES, please give details.
.....
.....
.....
.....
.....

2. Are you currently taking any prescribed medication?

☐ No ☐ Yes

If YES, please give names of the medicines.
.....
.....
.....
.....

Figure 8-4 Haemorrhoid PROM section 2 continued

3. In the last month, have you used any ointment or suppositories for your piles e.g. anusol, anugesic, anacal, preparation H etc?

☐ No ☐ Yes If YES, how often per week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

4. In the last month, have you used any painkillers for your piles e.g. paracetamol, ibuprofen?

☐ No ☐ Yes If YES, how often per week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

5. Have you had any previous treatment for your piles before today?

☐ No.
☐ Yes, rubber bands in clinic. In.....
☐ Yes, injections in clinic. In.....
☐ Yes, surgery under an anaesthetic. In.....
☐ Yes, other In.....

6. Do you have any relatives with piles?

☐ No ☐ Yes

If YES, how badly were they affected?

☐ Not at all ☐ Slightly ☐ Moderately

☐ Quite a bit ☐ A great deal

Figure 8-5 Haemorrhoid PROM sections 1 and 2

VERSION 1.6
19th AUGUST 2005

Section 3: Your Symptoms Now

- This study is investigating the symptoms of piles.
- Please answer the following questions about your symptoms **OVER THE LAST MONTH.**
- Please tick the box that best applies to you. If you are not sure, please make a best guess.

1. Do you get pain or discomfort on opening your bowels?
   ☐ No ☐ Yes

   If **YES**, how often in a **TYPICAL** week?

   ☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

   ☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

2. Do you get pain or discomfort around the anus **without** opening your bowels?
   ☐ No ☐ Yes

   If **YES**, how often in a **TYPICAL** week?

   ☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

   ☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

3. Do you get bleeding on opening your bowels?
   ☐ No ☐ Yes

   If **YES**, how often in a **TYPICAL** week?

   ☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

   ☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

4

Figure 8-6 Haemorrhoid PROM section 3

4. Do you get lumps (piles) around the anus, on straining to open your bowels?

☐ No ☐ Yes

If **YES**, how often in a **TYPICAL** week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

5. Do you experience itch or irritation around the anus?

☐ No ☐ Yes

If **YES**, how often in a **TYPICAL** week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

6. Do you experience any mucus or slime discharge from the anus?

☐ No ☐ Yes

If **YES**, how often in a **TYPICAL** week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

7. Do you experience soiling of your underclothes?

☐ No ☐ Yes

If **YES**, how often in a **TYPICAL** week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

Figure 8-7 Haemorrhoid PROM section 3 continued

8. Do you experience the feeling of incomplete emptying after opening your bowels?

☐ No ☐ Yes

If **YES**, how often in a **TYPICAL** week?

☐ 0 days ☐ 1 day ☐ 2 days ☐ 3 days

☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days

9. How much does the pain and discomfort affect the quality of your life?

Please make a MARK on the line below.

0 = NO AFFECT WHATSOEVER

10 = COMPETELY DOMINATES YOUR LIFE

0 _____ **10**

10. How much do the other symptoms from your piles affect the quality of your life?

Please make a MARK on the line below.

0 = NO AFFECT WHATSOEVER

10 = COMPETELY DOMINATES YOUR LIFE

0 _____ **10**

Please check that you have completed all the questions.

Thank you very much for completing the questionnaire.

Figure 8-8 Haemorrhoid PROM section 3 continued

Occupation Category	%
Managers	8.7%
Professionals	20.0%
Technicians & associate professionals	14.8%
Clerical support workers	2.6%
Service & sales workers	11.3%
Skilled agricultural, forestry & fishery workers	1.7%
Crafts & related trades workers	9.6%
Plant & machinery operators & assemblers	7.8%
Elementary occupations	5.2%
Retired/ housewife/ single parent/ student	18.3%

Table 8-1 Occupation demographics of the 115 participants in the haemorrhoid PROM.

Category	Number of patients (%)
1. Infections	0
2. Neoplasms	2 (1.74)
3. Blood & blood forming organs	2 (1.74)
4. Endocrine, nutritional & metabolic	6 (5.22)
5. Mental & behavioural	5 (4.35)
6. Nervous system	0
7. Eye	2 (1.74)
8. Ear	0
9. Circulatory system	20 (17.40)
10. Respiratory	3 (2.61)
11. Digestive	21 (18.26)
12. Skin & subcutaneous tissue	0
13. Musculoskeletal	3 (2.61)
14. Genitourinary	1 (0.87)

Table 8-2 Summary of medical conditions declared by participants completing the haemorrhoid PROM in phase II

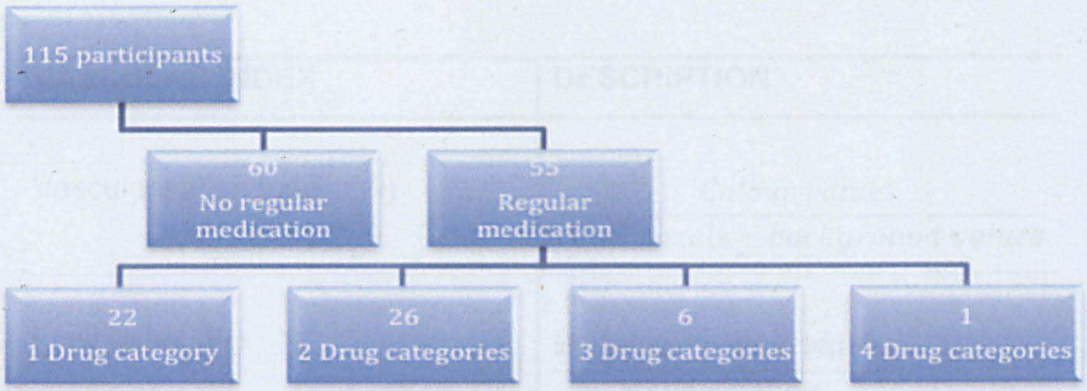

Figure 8-9 Medication use of patients in phase II.

8.2 THREE-DIMENSIONAL ULTRASOUND AND POWER DOPPLER

VASCULAR INDEX	DESCRIPTION
Vascularisation Index (VI)	$\frac{Colour\ values}{Total\ voxels - background\ values}$
Flow Index (FI)	$\frac{Weighted\ colour\ values}{Colour\ values}$
Vascularisation Flow Index (VFI)	$\frac{Weighted\ colour\ values}{Total\ voxels - background\ values}$

Table 8-3 Explanation of calculation of the vascular indices in VOCAL

g = grey-scale value in ultrasound image normalised to 0 – 100

Low Intensity = 1, High Intensity = 100

hg(x) = frequency of grey value x in ultrasound image

c = colour value in ultrasound image normalised to 0 – 100

Low Intensity = 1, High Intensity = 100

hg(c) = frequency of colour value x in ultrasound image

$$MG = \frac{\sum_{g=1}^{100} g.hg(g)}{\sum_{g=1}^{100} hg(g)}$$

$$VI = \frac{\sum_{c=1}^{100} hc(c)}{\sum_{g=1}^{100} hg(g) + \sum_{c=0}^{100} hc(c)}$$

$$FI = \frac{\sum_{c=1}^{100} c.hc(c)}{\sum_{c=1}^{100} hc(c)}$$

$$VFI = \frac{\sum_{c=1}^{100} c.hc(c)}{\sum_{g=1}^{100} hg(g) + \sum_{c=0}^{100} hc(c)}$$

8.3 MAGNETIC RESONACE IMAGING

The University of Nottingham

Sir Peter Mansfield Magnetic Resonance Centre
and the **Brain & Body Centre**

Safety Screening Questionnaire

For ANYONE entering the INNER CONTROLLED AREA marked by red and white tape on the doors (Magnetic field safety information is available in the SPMMRC website)

>> Shaded boxes to be filled in by scan volunteers and patients only <<

NAME	Date of Visit	Phone Number
ADDRESS	Volunteer Number	
	Date of Birth	
Study Ethics Code (or reason for visit)	Hospital No (if applicable)	
	Weight (Philips scanners only)	

MR scanning uses strong magnetic fields, for your own safety and the safety of others it is **very important** that you do not go into the magnet halls with any metal in or on your body or clothing.

Please answer the following questions carefully and ask if anything is not clear.
All information is held in the strictest confidence.

1. Do you have any implants in your body? e.g. replacement joints, drug pumps Y/N
2. Do you have aneurysm clips (clips put around blood vessels during surgery)? Y/N
3. Do you have a pacemaker or artificial heart valve? *(These stop working near MR Scanners)* Y/N
4. Have you ever had any surgery? Please give brief details* Y/N

*(*We do not need to know about uncomplicated caesarian delivery, vasectomy or termination of pregnancy)*

5. Do you have any foreign bodies in your body (e.g. shrapnel)? Y/N
6. Have you ever worked in a machine tool shop without eye protection? Y/N
7. Do you wear a hearing aid or cochlear implant? Y/N
8. Could you be pregnant? You must use the pregnancy tests available in the female toilets if you are unsure. Y/N
9. Have you ever suffered from tinnitus? Y/N
10. Do you wear dentures, a dental plate or a brace? Y/N
11. Are you susceptible to claustrophobia? Y/N
12. Do you suffer from blackouts, epilepsy or fits? Y/N
13. Do you have any trans-dermal patches (skin patches)? Y/N
14. Do you have any tattoos? Y/N
15. Will you remove all metal including coins, body-piercing jewellery, false-teeth, hearing aids etc before entering the magnet hall.? *(lockers available by the changing rooms)* Y/N
16. Is there anything else you think we should know? Y/N

I have read, understood, and answered all questions **Signature:**	**Date:**
Verified by: **SPMMRC/B&BC Staff Signature:**	**Date:**

Figure 8-10 Safety screening form completed by all patients and healthy volunteers at the Sir Peter Mansfield Magnetic Resonance Centre.