Combined Stimulation of Afferent and Efferent Sacral Nerves for Bladder Control in Spinal Cord Injury.

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Abstract

Aims The Finetech-Brindley Sacral Anterior Root Stimulator is an effective method for achieving bladder emptying in patients with spinal cord injury (SCI). It is usually combined with a posterior rhizotomy of sacral roots 2 to 4 to increase bladder capacity and reduce detrusor-external sphincter dyssynergia (DSD). Although effective, rhizotomy abolishes reflex erections and is unacceptable to many patients. Neuromodulation, by stimulation of pudendal nerve afferents, has been shown to increase bladder capacity in SCI patients. The aim of this work was to develop an implant capable of bladder emptying (by high-level stimulation to activate the detrusor) and neuromodulation (by continuous low-level stimulation) to increase bladder capacity, while preserving the sacral roots.

Methods The response to neuromodulation was assessed preoperatively by stimulation of the dorsal penile nerve during serial cystometry in 17 patients. Conditional stimulation (where 1 minute periods of neuromodulation are repeatedly triggered by a rise in detrusor pressure) was compared with continuous, and a microtip transducer catheter used to measure urethral sphincter pressure. Five patients were implanted with a device capable of stimulating both anterior and posterior sacral roots (SPARS). Bladder emptying was assessed using interval voiding programs in the laboratory; neuromodulation was assessed both in the laboratory and in the long term at home.

Results Conditional neuromodulation was of similar efficacy to continuous: both significantly increased bladder capacity but neither markedly reduced DSD. In three patients with persisting postoperative detrusor hyperreflexia, neuromodulation was effective in the laboratory in two, and at home in one. In 3 out of 4 patients, bladder emptying was incomplete, with evidence of persisting DSD in the gaps between stimulations.

Conclusion Neuromodulation by continuous stimulation through the SPARS may be effective enough to replace posterior rhizotomy in some patients, but if DSD is present preoperatively it is likely to persist, preventing complete bladder emptying.

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Acknowledgements

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1. Introduction

Publications: two papers arising from work in this thesis

- note: 'The acute effects of conditional and continuous neuromodulation on the bladder in spinal cord injury' also contains data from continuous neuromodulation experiments by N.C. Shah.

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List of abbreviations

BCR   Bulbocavernosus reflex

DH   Detrusor hyperreflexia

DPN   Dorsal penile nerve

DSD   Detrusor-external urethral sphincter dyssynergia

ISC   Intermittent self catheterisation

NM   Neuromodulation

SARS   Sacral anterior root stimulator

SCI   Spinal cord injury

SPARS   Sacral posterior and anterior root stimulator

S2   The second sacral nerve root (mixed anterior and posterior fibres unless

specified)

S23   The second and third sacral nerve roots

Glossary

Detrusor Hyperreflexia	Bladder overactivity due to disturbance of the nervous control mechanisms (Abrams *et al.* 1988).
Detrusor-sphincter Dyssynergia	Detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle (Abrams *et al.* 1988).
Firing off	Leak of urine per urethra associated with detrusor hyperreflexia.
Habituation	A decline in the successive responses to a stimulus that is repeatedly applied (Carpenter 1990).
Neuromodulation	The process by which 'the influence of activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction' (Craggs & McFarlane 1999).

1.1 *Background and general introduction*

Every year in the USA, approximately 10,000 people are admitted to hospital with an acute spinal cord injury (accurate figures for the UK are not available), and just under half of these patients have neurologically complete lesions. With improved acute and chronic treatment, survival in spinal cord injury has improved markedly over the last century, and life expectancy is now close to normal in those with paraplegia (Go *et al.* 1995). However, urinary tract problems still have an enormous impact on the lives of these patients, and are an important cause of morbidity and mortality. Incontinence, urinary tract infection and stones are common, and the frequent combination of detrusor hyperreflexia and detrusor-external sphincter dyssynergia leads to high bladder pressures, which, if untreated, can cause vesicoureteric reflux and renal impairment (van Kerrebroeck *et al.* 1993b).

Better monitoring and treatment of urinary tract pathology has reaped great benefits, but there are disadvantages – in terms of both safety and convenience – to each of the current ways of managing the bladder in SCI. Anticholinergics have significant side effects and may not be fully effective, intermittent self-catheterisation can be time consuming and introduce infection, reflex voiding works well only in a minority of patients and it is generally agreed that indwelling catheters should be avoided if at all possible (Rudy 1997).

The development, by Brindley, Craggs, Rushton and others of the Sacral Anterior Root Stimulator (SARS) in the late 1970s was an important advance in the management of the hyperreflexic bladder, enabling stimulator-driven 'interval voiding' with low residuals in the great majority of patients (Brindley 1994). It is usually combined with a rhizotomy of the posterior roots, a procedure that has been performed by some centres since the 1950s.

The rhizotomy has the great advantage of markedly reducing detrusor hyperreflexia in almost every case, producing a compliant, high capacity bladder and reducing incontinence (Koldewijn *et al.* 1994b). Combined with a stimulator, rhizotomy also reduces external urethral sphincter dyssynergia and improves emptying.

The SARS is in many ways an excellent solution: it reduces infections, protects the kidneys and is convenient for the patient. Although it entails a long operation and is a fairly expensive device, it is also probably the most *economic* method of bladder management in the long term (Wieling *et al.* 1997). However, posterior rhizotomy abolishes reflex erections in men, may predispose to stress incontinence and is destructive (MacDonagh *et al.* 1990). For these reasons, it is becoming increasingly unpopular with patients as prospects for spinal cord regeneration improve. Unfortunately, a SARS stimulator *without* rhizotomy is often less satisfactory: emptying is of less benefit if the bladder still has a small capacity and is prone to hyperreflexia which causes incontinence. A device capable of emptying the bladder and increasing capacity without rhizotomy would be almost ideal.

It has been known for some time that stimulation of pudendal afferents can suppress bladder activity and increase capacity in SCI. This can be achieved with anal, vaginal, dorsal penile nerve or sacral root stimulation, and can be termed *neuromodulation*, in which 'activity in one neural pathway influences the pre-existing activity in another' (Craggs & McFarlane 1999). The Finetech-Brindley device is capable of delivering low-level continuous pulses to activate myelinated afferents in the sacral roots for neuromodulation, and several groups have previously shown that chronic sacral root stimulation can increase bladder capacity in SCI. The primary aim of the work described in this thesis is to establish whether effective neuromodulation and bladder emptying can

be achieved in one device, using the Finetech-Brindley stimulator as a Sacral Posterior (for neuromodulation) *and* Anterior (for bladder emptying) Root Stimulator.

The mechanism of neuromodulation is uncertain, and in particular there is some disagreement about whether contraction of the urethral sphincter is central to it. Detailed information about the behaviour of the urethral sphincter during neuromodulation would help to resolve this issue, but it is an area that has received little attention in human studies. The effect of neuromodulation on detrusor-external sphincter dyssynergia is also uncertain. This study aims to address some of these issues, using microtip catheters to measure urethral sphincter pressure directly.

For future devices, continuous stimulation for neuromodulation may not be ideal: reflex urethral sphincter contraction rapidly diminishes, there are implications for battery life, and the long-term efficacy of continuous stimulation is uncertain. A more elegant solution would be suppression of hyperreflexic contractions as they occur - 'conditional' neuromodulation. Recent work in animals and humans has demonstrated that bladder contractions can be suppressed conditionally (Jezernik *et al.* 2001), but it is not know whether this method is as effective for increasing bladder capacity as continuous stimulation. A further aim of this study is to establish the efficacy of conditional stimulation during slow fill cystometry

It is hoped that this work will contribute towards the development of a fully implanted device, capable of neuromodulation and bladder emptying, that will be suitable for a larger proportion of spinal cord injured patients.

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1.2 Structure and function of the lower urinary tract

A detailed discussion of the structure and function of the lower urinary tract is beyond the scope of this section. Instead, some areas of anatomy relevant to the project are described in detail – in particular, the physiological mechanisms of urinary continence, the bulbocavernosus reflex and the innervation of the bladder and external urethral sphincter. A schematic summary is shown in Figure 1

Continence: In both sexes, there are four important mechanisms for urethral continence :

1. The urethral lamina propria, consisting of a glandular mucosa and submucosa. The submucosa is highly vascular, but the filling of the vessels is probably not under direct nervous control (Brading 1999). In both sexes, the lamina propria forms folds which completely occlude the urethral lumen at rest.

2. Smooth muscle: continuous with the smooth muscle of the bladder neck and in the female present in the whole length of the urethra. In the male it is found as far as the distal membranous urethra. It consists of a thin layer of circular smooth muscle, inside which is a thicker layer of longitudinally oriented fibres. Both layers function as sphincters, but contraction of the longitudinal layer may also contribute to opening of the bladder neck, by shortening the urethra (Brading 1999).

3. The striated external urethral sphincter. This is structurally and developmentally distinct from the muscles of the urogenital diaphragm, and consists of relatively small (15-20μm diameter) fibres. In the male it extends from the bladder base and anterior prostate to the full length of the membranous urethra, and consists of (in one study) 65% fast twitch and 35% slow twitch fibres (Ho *et al.* 1997b). In the female, it extends distally from the proximal urethra, with only 13% of fibres fast twitch (Ho *et al.* 1997a).

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Figure 1
A schematic diagram of the innervation of the bladder, urethral sphincter and pelvic floor

sympathetic fibres
-inhibition of parasympathetics
at the pelvic ganglion
& bladder neck + urethral
smooth muscle contraction

thoracolumbar
cord

interneurones
(very simplified)

sensory fibres
from bladder
& urethra
S234, A∂ & C

sacral
cord

pelvic
ganglion

pre & post
ganglionic
parasympathetics
-detrusor
contraction
S234, but S3
component
largest

detrusor

bladder
neck

pudendal
nerve, S234
external urethral
sphincter & pelvic
floor contraction
(S3 most important
for sphincter)
afferents from pelvic
floor & penis

pelvic floor

external urethral
sphincter

urethral smooth
muscle

note: no muscle
spindles in the
external urethral
sphincter

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4. The periurethral muscles of the pelvic floor, in particular the transversus perinei and

levator ani (Juenemann *et al.* 1987). Contraction of these muscles is particularly

important for continence during brief rises in intra-abdominal pressure.

Innervation of the lower urinary tract

Efferents run to the lower urinary tract in three sets of nerves:

1. The sacral parasympathetics, arising as the nervi erigentes from Sacral roots 2, 3 and 4.

These nerves pass through the pelvic ganglion (or *inferior hypogastric plexus*), and may

synapse here, although many parasympathetic postganglionic fibres arise in the

intramural ganglia of the bladder and urethra. They have several functions:

a) Detrusor contraction: the S3 component usually has the largest contribution, with

stimulation of S4 producing a significant, but smaller contraction and S2 in most cases

the smallest, although there is considerable variation between patients (Brindley *et al.*

1982, Chang & Hou 2000). The parasympathetic detrusor motorneurones lie in the

intermediolateral region of the sacral cord.

b) Relaxation of the urethra. There is little evidence for autonomic control of the

striated urethral sphincter (Brading 1999), but there is some evidence to suggest that

parasympathetic pathways produce smooth muscle relaxation in humans directly

(Torrens 1978). This relaxation is abolished by ß-blockade, and acetylcholine causes

contraction of the human urethra; therefore, it may be a peripheral reflex effect

(Morrison 1987). In any case, the main control of urethral smooth muscle is by the

sympathetic system, and parasympathetic nerves are also believed to inhibit sympathetically-mediated closure at the bladder neck (Lincoln & Bernstock 1993).

2. Sympathetic nerves. Preganglionic neurones arise in the intermediolateral segments of the low thoracic and upper lumbar segments of the spinal cord, and reach the pelvic plexus either via the inferior mesenteric plexus and hypogastric nerve or the sacral sympathetic chain and pelvic nerves. Their main function is to maintain contraction of smooth muscle in the bladder neck and urethra, but there is evidence that sympathetic innervation inhibits bladder contraction during the stable phase of filling, both at the pelvic ganglion and by direct innervation of the bladder (de Groat & Saum 1972, Blaivas 1982, Lindström *et al.* 1983)

3. The pudendal nerve and fibres that run to levator ani. Although there has been some disagreement about the innervation of the urethral rhabdosphincter, by far the most important contribution is from the pudendal nerve (Rossier *et al.* 1982), with as much as 70% of maximum closure pressure produced by S3 stimulation (Juenemann *et al.* 1988), and the rest variably by S2 and S4. Motorneurones lie in Onuf's nucleus: together with the parasympathetic nucleus in the intermediolateral cord, this forms the *sacral micturition centre.*

The relative contributions of smooth and striated muscle to maximum urethral closure pressure vary along the proximal urethra, with approximately equal contributions at the point of maximum pressure (Rossier *et al.* 1982).

Afferents

Afferents from S2 to S4 dorsal root ganglia project both to the bladder (in particular the base) and the urethra, travelling mainly via the pelvic nerves; a smaller number arise in the thoracolumbar dorsal roots and run with sympathetic fibres in the hypogastric nerves, tending to supply the trigone. The fibres split into two main groups: C-fibres supplying temperature-sensitive and nociceptor endings that do not fire under most physiological conditions (Mazières *et al.* 1998), and A∂ fibres that respond in a graded fashion to rises in bladder pressure of 5 to 15mmHg (Habler *et al.* 1993). Less is known about urethral receptors, although there are receptors in the proximal urethra that respond to low-level mechanical stimulation (Bahns *et al.* 1987) and C-fibre afferents are certainly found here (de Groat *et al.* 2001).

Afferents from the periurethral muscles run in the pudendal nerve and project centrally to the same regions as bladder afferents, allowing the integration of somatic and visceral motor activity (Lincoln & Bernstock 1993). However, it should be noted that the external urethral sphincter itself lacks muscle spindles (Williams *et al.* 1989).

The bulbocavernosus reflex: The bulbocavernosus, pudendo-urethral and pudendo-anal reflexes are different names for the reflex muscle contractions produced by stimulation of the clitoris or glans penis (Yalla *et al.* 1978). Both limbs of this reflex lie in the pudendal nerve, with the afferents probably medium or small diameter myelinated fibres (Ertekin & Reel 1976, Vodusek *et al.* 1983) and the efferents large myelinated fibres supplying striated muscles innervated by the pudendal nerve (Uher & Swash 1998).

Storage and Micturition

The co-ordinated control of storage and micturition can be thought of as a set of reflexes that enable switching between storage and voiding, and can be modulated by voluntary control. Centres in the pons – in particular, the lateral pontine centre and the pontine micturition centre (PMC) project to the sacral and lumbar cord and are responsible for co-ordinated voiding. A detailed discussion of the anatomy of central pathways and neurotransmitters is beyond the scope of this section, and the reader is referred to two excellent reviews (de Groat 1993, 1997).

1.3 *Spinal cord injury: effects on the bladder and urethral sphincters*

Historically, the concept of the sacral micturition centre (SMC) has been central to many of the theories about the effects of spinal cord injury over the last century. One of the first detailed studies of the effects of spinal cord injury on the lower urinary tract in 1933 postulated that this area was fundamentally overactive, and required constant suppression by 'corticoregulatory tracts' until micturition (Denny-Brown & Robertson 1933). This is at best an oversimplification, and in particular there is little evidence for a spinal detrusor reflex in normal humans (de Groat 1997).

The lower urinary tract immediately after spinal cord injury

Immediately after complete spinal cord injury, and after the majority of incomplete lesions, spinal shock is present. Somatic and visceral reflexes are absent, and the bladder is areflexic. In about 95% of patients with suprasacral injuries (Light & Beric 1992, Weld & Dmochowski 2000), bladder activity will eventually return, but after a very variable time: between one week and six moths in one study (Butler 1978), and after a year or

more in rare cases (Light *et al.* 1985). In contrast, the bulbocavernosus reflex usually

returns within hours or days after the injury (Nanninga & Meyer 1980), even while

tendon reflexes of the lower limbs are abolished (Curt & Dietz 1999).

During the areflexic phase, urethral sphincter activity is relatively high. This is partly

because sympathetic activity is usually preserved in spinal cord injury (McGuire *et al.*

1976), so that smooth muscle tone in the bladder neck and urethra remains (Downie &

Awad 1979) and may increase during bladder filling (Rossier *et al.* 1979). However,

striated muscle activity is also often detectable by electromyography (EMG), and even

during the spinal shock phase the guarding reflex is demonstrable in many patients, with

an increase in sphincter EMG during filling (Nanninga & Meyer 1980). Others, however,

have found a *decrease* in sphincter EMG during filling (Butler 1978). In either case,

striated sphincter tone is usually relatively low and will rise when the shock phase ends

(Thomas *et al.* 1975).

The development and aetiology of detrusor hyperreflexia.

When bladder activity returns, it is usually seen as a gradual increase in detrusor tone,

followed by spontaneous organised and sharply rising bladder contractions (Butler 1978).

This can be termed *detrusor hyperreflexia* and is often heralded by incontinence between

intermittent catheterisations.

In normal cats and humans, the afferent limb of the micturition reflex is mediated by A∂

afferents via spino-bulbo-spinal pathways, and there is little evidence of a spinal

micturition reflex (Mahony *et al.* 1977), especially in humans.

In normal cats, the spino-bulbo-spinal micturition reflex has a long central delay (60-

75ms), is unaffected by capsaicin (a neurotoxin which disrupts C-fibre afferents

(Dasgupta & Fowler 1997)) and is abolished by spinal transection, producing an areflexic bladder. However, several weeks after transection, a new micturition reflex appears with a much shorter central delay (15-40ms), which can be abolished by the administration of capsaicin (de Groat *et al.* 1990).

These findings suggest that *in the cat* there is a reorganisation of the spinal centres after spinal cord injury in which the absent A∂ dependent spino-bulbo-spinal reflex is replaced by a C-fibre dependent spinal micturition reflex. However, C fibres in the cat do not normally respond to distension (Habler *et al.* 1990), so that it is also necessary to postulate a change in the properties of these receptors after spinal cord injury.

A subpopulation of C-fibres responds to cold, and it is worth noting that cold water instillation often produces a micturition reflex in humans with spinal cord injury (Geirsson *et al.* 1995) and in normal infants (Geirsson *et al.* 1995) but not in normal adults. This supports the hypothesis that the changes in humans after SCI are similar to those seen in cats, but the effect of capsaicin on detrusor hyperreflexia has not been as dramatic as was hoped (Dasgupta & Fowler 1997).

The behaviour of the urethral sphincter after spinal cord injury

Voiding in normal subjects is synergic: the urethra relaxes before contraction of the detrusor, and is relatively inhibited during micturition. This orderly sequence of events is usually lost in SCI (Blaivas 1982), with dyssynergic contractions of the urethral sphincter occuring in most patients during detrusor hyperreflexia. Estimates of the prevalence of detrusor-external sphincter dyssynergia (DSD) vary widely, from 36% (Chancellor *et al.* 1990) to 100% (Thomas *et al.* 1975, Bary *et al.* 1982), depending on the population

studied and methods of measurement. Although detrusor hyperreflexia occurs in patients with suprapontine lesions, DSD very rarely does (Blaivas 1982, Siroky & Krane 1982).

DSD has been classified by Blaivas into three types using electromyography (Blaivas *et al.* 1981):

1. A simultaneous increase of detrusor and urethral sphincter pressure, with urethral pressure suddenly dropping and in most cases, voiding (30% of patients).

2. Intermittent, clonic contractions of the urethral spincter throughout voiding (15% of patients).

3. Fluctuating detrusor pressure, with urethral pressure following that of the detrusor, but little or no voiding (55% of patients).

There is some disagreement about whether distinct types actually exist: most of the behaviour of the urethral sphincter can be explained by the observation that it is closely related to detrusor pressure and its rate of rise: urethral pressure always falls as detrusor pressure does (Rudy *et al.* 1988). Contractions of the urethral sphincter may begin before bladder pressure rises, as a 'pre detrusor kick' (Bary *et al.* 1982), but a characteristic feature of DSD is that it does not occur a significant length of time *after* detrusor pressure has started to rise (Blaivas 1984).

In a valuable study using a microtip pressure transducer catheter, Rossier et al showed that pudendal nerve blockade completely abolished DSD in 3 out of 3 patients, while phentolamine had little effect in 2 out of 2 (Rossier *et al.* 1982). This provides compelling evidence that DSD is a spinal reflex mediated by the pudendal nerve, and

given the innervation of the urethral smooth muscle (described in section 1.2), that DSD is mainly a phenomenon of the striated sphincter.

Consistent with the finding that a significant urethral sphincter pressure persists during the shock phase, the bladder neck remains closed in most patients with spinal cord injury during filling (Light & Beric 1992). A recent study of the bladder neck using pressure-tipped transducers provided convincing evidence of *bladder neck* dyssynergia in a majority of SCI patients, but *not* in those with lesions below the sympathetic outflow (Schurch *et al.* 1994). This was not synchronous with external sphincter DSD and was unaffected by pudendal nerve blockade. Phentolamine, an alpha adrenergic antagonist, abolished the bladder neck dyssynergia in patients who had autonomic dysreflexia. These findings indicate that the two types of dyssynergia are to some extent independent, and are consistent with the finding that alpha blockade improves voiding in many cases of SCI (Awad & Downie 1977). Because bladder neck dyssynergia will not be apparent on EMG recordings, it is still relatively unstudied.

The aetiology of dyssynergia

According to de Groat (discussion in (Chancellor *et al.* 1990)), DSD and bladder neck dyssynergia can be explained by postulating a lack of inhibition of two spinal reflexes:

a) The guarding reflex. Barrington demonstrated that this reflex was inhibited during voiding in normal cats (Barrington 1928). A similar inhibition can be demonstrated in normal humans by eliciting the bulbocavernosus (or pudendo-urethral) reflex with electrical stimulation: greater amounts of afferent stimulation are required for the reflex during voiding (Yalla *et al.* 1978). In contrast, the reflex

is not suppressed in the detrusor hyperreflexia of spinal cord injury: small levels of

afferent stimulation produce contraction of the urethral sphincter strong enough to

stop the flow of urine (Dyro & Yalla 1986, Sethi *et al.* 1989).

b) The sympathetic response to filling. There is less direct evidence for this in

humans, but in cats this reflex is suppressed during voiding (Sogbein *et al.* 1984).

The lack of bladder neck dyssynergia in patients with lesions below the

sympathetic outflow suggests that bladder neck dyssynergia is closely related to

this sympathetic reflex.

Some aspects of de Groat's hypothesis do not fit with experimental observations.

Although the striated sphincter guarding reflex is preserved in spinal cats (Galeano *et al.*

1986), it is *lost* in most patients with complete SCI, but preserved in many with

incomplete lesions (Siroky & Krane 1982). This led the authors of the latter study to

conclude that the reflex involves the pons in humans, and that DSD is either an abnormal

flexor response to bladder contraction or caused by new reflex connections in the sacral

cord after spinal cord injury. There is now some evidence for such connections (Kruse *et*

al. 1995).

1.4 *The urological management of patients with SCI*

Survival rates in SCI improved markedly between World Wars One and Two, but in the

two decades that followed the urinary tract was still a cause of death in over 50% of

paraplegics (Barber & Cross 1952, Hackler 1977). The aetiology was usually raised

bladder pressures and incomplete emptying leading to bladder and kidney stones,

infection, vesicoureteric reflux and renal failure. Modern urological management has

been a major contributor to greatly improved survival rates (Stover *et al.* 1995), so that

the life expectancy of a 20 year old paraplegic is now 64 years, and that of a tetraplegic

53 years (Go *et al.* 1995), but urological morbidity is still common (van Kerrebroeck *et*

al. 1993b).

Treatment has two key objectives: a) the maintenance of a low bladder pressure, and b)

complete bladder emptying. Each of the current methods has important potential

drawbacks, summarised in table 1.1. An ideal solution would result in a high capacity,

low pressure bladder that can be emptied when convenient. With this in mind, several

further alternatives - neuromodulation, posterior sacral rhizotomy and the Sacral Anterior

Root Stimulator (SARS) will be discussed in detail in the sections that follow.

1.5 *Sacral nerve stimulation for bladder emptying*

It was known one hundred years ago that the denervated bladder responded to direct

electrical stimulation in the same way as the normal bladder (Stewart 1900), and it was

appreciated in the 1960s that stimulation of sacral nerves was unlikely to produce

complete bladder emptying because of pelvic floor and urethral sphincter contraction

(Susset & Boctor 1968). The first implanted devices designed to empty the bladder were

therefore mostly direct vesical stimulators, which were only partly successful in upper

and lower motor neurone lesions (see (Susset & Boctor 1968) for a review). As well as

incomplete emptying, rejection due to infection and electrode migration were serious

difficulties.

In the early 1970s, Brindley made a crucial insight that enabled the emptying of the

bladder of a baboon by sacral root stimulation (Brindley 1974). Instead of continuous

Method of management	Disadvantages
Reflex voiding	High incidence of vesicoureteric reflux, making regular monitoring mandatory to prevent nephropathy. Incomplete emptying (Rudy 1997).
External urethral sphincterotomy + reflex voiding or external urethral sphincter stent (McFarlane et al. 1996)	Although there is less chance of vesicoureteric reflux, patients usually become incontinent and a sheath is needed: only suitable for men (Vapnek et al. 1994).
Intermittent self catheterisation, usually combined with anticholinergic medication.	Side effects of anticholinergics. ISC difficult for patients with cervical injuries & may introduce infection. Anticholinergics ineffective in a minority (Blaivas et al. 1980).
Bladder augmentation (eg clam enterocystoplasty)	Self catheterisation necessary. Mucus & stone formation, possible metabolic derangements and risk of malignancy (Murray et al. 1995, Chartier-Kastler et al. 2000a).
Indwelling catheters	Possible permanent reduction in bladder capacity. Upper tracts may not be protected unless combined with anticholinergics (Kim et al. 1997). Focus for infection.
Intrathecal baclofen	Only moderately effective at suppressing hyperreflexia (Leyson et al. 1980). Self catheterisation still necessary.
Botulinum toxin injections to bladder +/- trigone, external urethral sphincter	Temporary effects. Long term results unknown. Self catheterisation necessary (Dykstra 2003).

Table 1.1
Some current methods of bladder management, and their drawbacks.

stimulation, bursts of pulses were used. The bladder, being a smooth muscle, responds

slowly to these bursts and continues to contract for several seconds after they have been

stopped. The skeletal muscles of the pelvic floor and external sphincter relax

immediately, so that emptying occurs in the gaps: *interval voiding*. The first implant of a

sacral root stimulator into a human patient was in 1976, which met with limited success,

but in subsequent patients good bladder emptying was achieved and by 1985, 50 patients

with neurogenic bladders had received the device (Brindley *et al.* 1986). All of the early

stimulators has 3 or 4 radiolinked channels and electrodes that were applied intrathecally

to the separated anterior nerve roots S2 to S4. This is a technically demanding procedure,

and in many cases separation was not possible, so that mixed roots were trapped in the

electrodes and anterior and posterior root damage was common; although neurapraxia of

the anterior roots usually recovered, the posterior roots often did not. 44 out of the first 50

patients could achieve bladder emptying with low residuals, and sacral root stimulation

could also be used to improve bowel function and achieve stimulator driven erections.

It was noted early on that patients whose posterior roots were damaged often had large

increases in bladder capacity, and this led to the practice of cutting S3 and sometimes S2

roots in some patients. Although rhizotomy often markedly improved incontinence and

increased capacity, in most cases it abolished reflex erections. It is discussed in the next

section: further development of sacral root stimulation will be discussed in the section

that follows.

1.6 *Rhizotomy of the sacral roots*

Observations at the start of this century suggested that even in complete sacral cord,

cauda equina (Denny-Brown & Robertson 1933) or pelvic nerve lesions (Elliot 1907),

spontaneous bladder contractions would occur and result in emptying with low residuals.

Several reports of either anterior, posterior or combined rhizotomies of the sacral cord

improving bladder capacity followed (summarised in (Misak et al. 1962)). In these cases,

although detrusor hyperreflexia was reduced, many patients developed efficient

'automatic' bladder emptying. In a 1963 study of 28 patients with complete and

incomplete lesions subjected to sacral rhizotomy, 25 out of 28 had a good capacity

bladder with 'good voiding potential' (Misak et al. 1962): the procedure markedly

increased the proportion of patients whose bladders emptied with low residual. Although

there were temporary derangements in bowel function, it returned to normal in a few

months. Autonomic dysreflexia was markedly improved but reflex erections were

generally impaired or abolished.

Subsequent attempts at selective neurectomy of roots innervating the bladder alone had

somewhat less success, because of the recurrence of hyperreflexia (Lucas et al. 1988).

However, later reports of selective dorsal rhizotomy have confirmed that it increases

bladder capacity and compliance in virtually all patients, although this may take several

months to become apparent (Gasparini et al. 1992, Koldewijn et al. 1994b). Reflex

erections are always abolished if S2 to S5 roots are included (Koldewijn et al. 1994b),

but may be preserved if the procedure is more selective (Gasparini et al. 1992).

Consistent with the earlier findings, detrusor contractions are abolished only in a minority

of patients, but are of markedly lower strength after rhizotomy.

Continence after rhizotomy is markedly improved because hyperreflexia is controlled,

but there is a suspicion amongst some workers that stress incontinence becomes more

common after the procedure, because of urethral sphincter and pelvic floor weakness.

Although Gasparini et al did not find that rhizotomy significantly reduced urethral

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closure pressure, others have found that if patients have an open bladder neck on videourodynamics before the procedure, they are very likely to experience stress incontinence after it (MacDonagh *et al*. 1990). Similarly, previous external urethral sphincterotomy markedly increases the chances of stress incontinence (Barat *et al*. 1993). Conversely, patients who are not in these categories are unlikely to experience stress incontinence.

As well as reducing hyperreflexia, posterior rhizotomy also reduces or abolishes a number of other spinal reflexes mediated by bladder and sphincter afferents. In particular, detrusor-external sphincter dyssynergia is abolished in most cases. This is consistent with the hypothesis that it is a reflex whose afferent limb is 'driven' by increases in bladder volume or pressure (see section 1.3), and indeed sphincter contractions very rarely occur in the absence of either raised intravesical pressure or volume (Rudy *et al*. 1988). The elimination of DSD explains why sacral rhizotomy can improve bladder emptying in spite of reducing hyperreflexia (Misak *et al*. 1962, Schmidt 1988).

1.7 *Further development of the SARS and alternative approaches*

The realisation that rhizotomy was likely to improve emptying as well as capacity meant that from 1986 most SARS patients had a complete posterior rhizotomy from S2 to S4 (Madersbacher & Fischer 1993, Brindley 1994). To perform a complete root separation for rhizotomy is to further risk posterior root damage, and it may be that a combination of intradural deafferentation at the conus (where identification and separation of the posterior roots is easiest) with extradural electrode placement (minimising the risk of

CSF leak and infection) is safest for the patient (Hohenfellner *et al.* 1992, Sarrias *et al.* 1993).

Brindley and van Kerrebroeck have have produced summaries of the benefits of the SARS implant (van Kerrebroeck *et al.* 1993a, Brindley 1994). Complete bladder emptying was achieved in over 80%, bladder capacity increases markedly and vesicoureteric reflux is uncommon. Bowel function is very often improved, and in some patients effective programs can be set for stimulator-driven evacuation. Erections can be generated by intense stimulation of S2 in some patients, although this is at odds with our experience at the RNOH, where of 16 patients who have been asked the question, none use the device regularly for this purpose. Another study has recently suggested that there is a significant increase in quality of life with the SARS compared to alternative bladder managements (Vastenholt *et al.* 2003).

Although the figures for the number of patients using the device for micturition are impressive, some patients are never able to empty their bladders adequately. This is due to a variety of factors, but it seems that in many, persistently high urethral sphincter pressure is a factor, with or without active DSD. Van Kerrebroeck reported that 4 out of 26 patients with incomplete voiding were treated by sphincterotomy. It is surprising that Brindley did not have more such problems in his early, non-rhizotomy patients (Brindley *et al.* 1986), which may be partly due to root damage with the intrathecal technique.

1.8 *The disadvantages of rhizotomy: the need for SPARS*

Although nearly 3000 stimulators have been implanted, this is a small fraction of those who would benefit from a SARS. Patients may be wary of a big operation, but in most cases their main reason for not proceeding is the posterior rhizotomy (G. Creasey, D. Thomas, personal communication). As well as the small risk of stress incontinence, reflex erections are important to many. 70% will recover erectile function after SCI (Smith & Bodner 1993), and the majority of these will be able to have penetrative sex. The situation has improved further with the use of sildenafil (Giuliano *et al*. 1999, Langtry & Markham 1999). Although partial rhizotomy may preserve some erectile function (Gasparini *et al*. 1992), the benefits of rhizotomy may well be partial as well, making a secondary deafferentation necessary. Therefore, patients who have marked DSD or a low bladder capacity must be prepared to lose reflex erections with a SARS.

However, the biggest problem with posterior rhizotomy may be that it is destructive. As prospects for spinal regeneration improve, many patients are not willing to undergo any procedure that might prejudice future recovery. Some surgeons maintain that with the information presented clearly, most patients will not decline the operation for this reason (H. Madersbacher, personal communication), but the situation may well be different in the next few years, particularly in the USA.

It is clear that an implant that combined the benefits of sacral root stimulation for emptying with a method for suppressing detrusor hyperreflexia without rhizotomy would be close to ideal, and be acceptable to a greater number of patients than the SARS. Neuromodulation has the potential for this, and will be discussed after a brief summary of alternative approaches to sacral root stimulation.

Other Methods of Sacral Root Stimulation

Tanagho's group in San Fransisco have developed a sacral root stimulator for use in SCI, and at the last formal publication, 22 patients had received the device. Together with variable posterior rhizotomy, pudendal neurectomy, sphincterotomy and levatorotomy, they achieved complete voiding in 8 patients (Tanagho *et al.* 1989). Although there were few complications in the 22 patients, elective ventral rhizotomy, pudendal neurectomy and sphincterotomy are to some extent equivalent solutions to high urethral resistance during voiding, and each has the potential to worsen stress incontinence, so that patients must be selected carefully. They have also investigated the effects in dogs of selective neurotomy of fibres supplying the external sphincter, either at the sacral root by microdissection (Probst *et al.* 1997) or by pudendal neurectomy (Bosch, R. J. L. H. *et al.* 1992).

Several other methods for synchronous voiding (urine flow at the same time as the stimulated detrusor contraction) have been tried. Anodal blockade (Brindley & Craggs 1980) has been shown to be effective at blocking large nerve fibres in monkeys and acutely in humans (Rijkhoff *et al.* 1997a), and high frequency stimulation and depolarising prepulses are other techniques to achieve selective activation of small fibres that have been successful in the laboratory. Alternatively, the pudendal nerve could be blocked electrically, either by high frequency or collision block. None of these has yet proved sufficiently safe and reliable to use in a human implant (reviewed by (Rijkhoff *et al.* 1997b)). Pre-stimulation fatigue of the external urethral sphincter was tried by Brindley in baboons twenty years ago and found to be relatively ineffective (Brindley *et al.* 1982); there are no published reports of its successful use in humans, although the Finetech-Brindley control box is capable of generating the necessary pattern of pulses.

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1.9 Neuromodulation: early results using anal and vaginal stimulation

Stress and urge incontinence

The first devices using electrical stimulation to treat urinary incontinence appeared in the early 1960s, and were at first used to treat stress incontinence. They either consisted of external anal (Hopkinson & Lightwood 1967) or vaginal (Alexander & Rowan 1968) plug electrodes, or implanted radiolinked stimulators with electrodes in the anal sphincter (Caldwell 1963), and stimulation was usually intermittent . Hopkinson and Lightwood noted that their anal plug stimulator was effective for both faecal and urinary incontinence, with a 'tetanic' stimulation of the sphincters, but it was shown convincingly several years later that their device, even using a high level of stimulation, did not directly stimulate the pudendal nerve branches innervating the urethral sphincter: even at a very high level of stimulation, urethral sphincter contraction was *reflex*, with a latency of >60ms, rather than direct (Brindley *et al.* 1974).

Although the early focus of stimulation was on stress incontinence, beneficial effects of intermittent stimulation were also noted in patients with urge incontinence (Alexander & Rowan 1968, Fall *et al.* 1978b). Subsequent studies have shown symptomatic improvements in most patients who have urge incontinence associated with idiopathic detrusor instability (Plevnik & Janez 1979, Eriksen *et al.* 1989, Ohlsson *et al.* 1989, Fossberg *et al.* 1990, Primus & Kramer 1996).

Spinal Cord Injury

In spinal cord injury, Vereeken et al showed that hyperreflexic contractions could be suppressed by strong anal stimulation applied as they began (Vereecken *et al.* 1984), and Sheriff has similar sucess with functional magnetic stimulation of the sacral roots (Sheriff *et al.* 1996). Others have demonstrated a marked increase in bladder capacity during anal stimulation (Godec & Cass 1979). However, the *therapeutic* results of intermittent stimulation for neurogenic detrusor hyperreflexia are not impressive. In most patients, both the subjective and objective cystometric effects of 'maximal stimulation' are small (Sotiropoulos *et al.* 1976, Petersen *et al.* 1994, Primus & Kramer 1996, Prévinaire *et al.* 1998), and other studies must be interpreted with caution, because the patient group is often heterogeneous, including patients with intact sensation and detrusor instability as well as those with detrusor hyperreflexia (Ohlsson *et al.* 1989). However, intermittent pelvic floor stimulation by implanted electrodes was effective in the majority of SCI patients in one small study, roughly doubling bladder capacity, although the extent of the neurological deficit was not stated (Ishigooka *et al.* 1994).

1.10 *Neuromodulation by stimulation of the dorsal penile nerve*

In one of the first studies of the effects of spinal cord injury on the bladder, it was noted that although light stimuli to the glans penis or perineum often resulted in a vesical contraction, stronger stimuli produced 'a more powerful inhibitory effect which accompanies contraction of the external sphincter' (Denny-Brown & Robertson 1933). Several decades later, it was noted again that stimulation of the glans penis resulted in

suppression of detrusor hyperreflexia in most patients (Kondo *et al.* 1982), and since then

there have been four studies of the acute urodynamic effects of stimulating the dorsal

penile nerve (DPN) in spinal cord injured patients, summarised in Table 1.2.

1.11 *Neuromodulation: continuous stimulation for treating detrusor*

instability and hyperreflexia

In contrast to the results with intermittent stimulation, long-term continuous stimulation

of pudendal afferents appears to be effective in the detrusor hyperreflexia that results

from spinal cord injury, as well as in idiopathic detrusor instability. Anal and vaginal

stimulation, and long term dorsal penile nerve stimulation, have been tried with some

success (Godec & Cass 1979, Wheeler, J. S.,Jr & Walter 1993), but the stimulation

method is unwieldy and the most reliable data is from stimulation via an implanted neural

stimulator:

Sacral nerve root stimulation

Since the 1960s (Habib 1967), stimulation of the sacral roots at the sacral foramina has

been used to treat a variety of lower urinary tract dysfunctions. An implanted device for

unilateral sacral foramen stimulation is commercially available - the *Interstim*

(Medtronic, Minneapolis, MN) - and has been used in several thousand patients. Here, a

period of trial stimulation of S3 or S4 using a percutaneous wire is followed, if

successful, by implantation (van Kerrebroeck *et al.* 1993b). Others have modified this

technique to enable bilateral stimulation (Hohenfeller *et al.* 1998) or percutaneous

implantation of electrodes (Ishigooka *et al.* 1998).

Study	Number of patients	Injury	Stimulation intensity & (frequency)	Number of patients responding	Mean % increase in bladder capacity
Vodusek et al. 1986	10	4 complete SCI 6 incomplete SCI	2 to 3.5x threshold for BCR (5 to 10Hz)	10/10	177
Wheeler, J. S. et al. 1992	6	3 complete SCI 3 incomplete SCI	'above pelvic twitch threshold [probably low]' (5Hz)	6/6	76
Prévinaire et al. 1996	10	6 complete SCI 4 incomplete SCI	2x BCR threshold (5Hz)	9/10	105
N.M Shah: Kirkham et al. 2001	6	5 complete SCI 1 incomplete SCI	2x BCR threshold (15Hz)	6/6	110

Table 1.2 Results of studies examining the acute cystometric effects of continuous DPN stimulation. BCR = bulbocavernosus reflex. Note that the intensity of stimulation correlates with the mean increase in capacity.

Study	Number of patients implanted with device (number tested acutely to determine suitability)	Injuries	Proportion whose CMG capacity increased	Mean % increase in capacity	Proportion whose symptoms improved
Bosch & Groen 1998	5 (7)	4 M.S. 1 Incomplete SCI	2/5	39	3-5/5 (depends on criteria)
Ishigooka et al 1998	4 (no acute tests to select patients before final implantation)	2 Incomplete SCI 2 Complete SCI	3/4	180	3/4
Chartier-Kastler et al 2000	9 (23)	5 M.S. 2 Myelitis 2 SCI (?complete)	6/9	54	9/9

Table 1.3 Effect of long-term sacral root neuromodulation in neurogenic detrusor hyperreflexia: 3 studies. None of these studies attempted to determine optimum stimulation parameters.

Continuous stimulation of the sacral roots has been used most commonly to treat urge

incontinence and idiopathic instability. Approximately 60-75% of patients respond to

trial stimulation (van Kerrebroeck 1998), and 60 to 80% of these patients will have a

good result with long-term stimulation (Koldewijn *et al.* 1994a, Bosch, J. L. H. R. &

Groen 1995, Shaker & Hassouna 1998).

There are three studies of the effects of chronic stimulation in patients with detrusor

hyperreflexia, summarised in Table 1.3. The results are particularly encouraging because,

in all 3 studies, the patients had failed to respond to 'conservative' treatment (in most

cases oral anticholinergics).

1.12 *The mechanism of neuromodulation.*

The diversity of conditions that are improved by neuromodulation – including both

detrusor hypoactivity (urinary retention) (Goodwin *et al.* 1998) and hyperactivity

(detrusor instability and hyperreflexia) means that there may be several different

mechanisms for the response (Craggs & McFarlane 1999). In particular, sensory effects –

including 're-education' may be important in conditions such as chronic pelvic pain and

urgency. The evidence for this is well summarised by Wyndaele (Wyndaele *et al.* 2000),

and will not be discussed further, as it is probably not relevant to the detrusor

hyperreflexia of spinal cord injury (except, possibly, in patients with incomplete lesions).

Apart from McGuire's results with stimulation of branches of the sciatic nerve (McGuire

et al. 1983), each of the methods of neuromodulation that have been effective in SCI

have activated afferent fibres of the pudendal nerve. This almost always results in

contraction of anal and urethral sphincters, bulbocavernosus and muscles of the pelvic

floor – the bulbocavernosus reflex, which has already been described. Contraction of

these muscles results in further afferent activity in the pudendal nerve. There are at least

two possible mechanisms for the resulting suppression of detrusor activity.

Mechanism 1 – Pudendal afferent activity essential:

Pudendal afferent activity (for instance from DPN or anal sphincter stimulation) might

cause, via interneurones in the spinal cord

a) a decrease in parasympathetic efferent activity to the bladder, and

b) an increase in efferent sympathetic activity, resulting in inhibition either in the pelvic

ganglion or bladder wall.

There is good evidence for both *a* and *b* in cats (Lindström *et al.* 1983), with the

sympathetic effects predominating at low bladder volumes, and parasympathetic effects

at high bladder volumes when efferent activity is high (almost always the case in DH).

The sympathetic effects are less certain in humans, and the effect of pharmacological

manipulation of alpha and beta receptors relatively small (Norlen & Sundin 1982), so that

the parasympathetic almost certainly predominate in DH. The mechanism by which

parasympathetic efferent activity is reduced is uncertain, although the GABA agonist

Baclofen administered intrathecally does reduce detrusor hyperreflexia (Gardner *et al.*

1995). Also, intrathecal morphine reduces DH in dogs (Magora *et al.* 1989).

Mechanism 2 – Urethral sphincter contraction essential:

Pudendal afferent activity results in reflex contraction of the pelvic floor and sphincters,

causing a *local* effect (the mechanism of which is uncertain) which inhibits detrusor

hyperreflexia. In this case, as Tanagho and Schmidt assert, 'the key to control of the bladder lies in control of the sphincter' (Schmidt 1988). Similarly, others have asserted that contraction of the pelvic floor is important for neuromodulation (Vereecken *et al.* 1984). Of course, contraction of the sphincters and pelvic floor may result in increased pelvic afferent activity (for example from pelvic floor muscle spindles), but this effect, if important, is essentially Mechanism 1, above. There are two important pieces of evidence suggesting that although sphincter contraction may be a *marker* for adequate pelvic afferent stimulation, it may not be necessary for neuromodulation.

i) Blockade of the striated urethral sphincter does not abolish the effect of pudendal afferent stimulation on the bladder in cats (Fall *et al.* 1978a).

ii) Lindström has examined the effect of stimulating different afferent fibres of the cat pudendal nerve. Stimulation of dorsal penile or clitoral branches strongly inhibits the bladder but stimulation of pelvic floor fibres has little effect. Stimulation of urethral rhabdosphincter branches *increases* bladder activity (Lindström & Sudsuand 1989).

1.13 *Aims of the work in this thesis*

The main aim of the work in this thesis is the implantation and testing of a device capable of neuromodulation (for increasing bladder capacity) and neurostimulation (for bladder emptying) in a group of patients with spinal cord injury. This should be achieved without nerve damage – either planned (rhizotomy) or accidental (intraoperative neurapraxia).

Such a device is subsequently termed a SPARS – Sacral Posterior and Anterior Root Stimulator.

The aim of the preoperative tests (described in chapter 3) was to establish the response to neuromodulation by pudendal afferent stimulation in a group of spinal cord injured patients, some of whom might be suitable for such a device. This also allowed the testing of several key hypotheses which have important implications for the way neurostimulation and neuromodulation would be applied with the implanted device.

Preoperative tests:

i) The response to pudendal afferent stimulation

The primary aim of the preoperative tests was to identify a group of patients who responded to dorsal penile nerve stimulation. A positive response was expected in most patients – the efficacy of DPN stimulation has been tested previously – and was necessary for progression to implantation. The hypothesis that DPN stimulation increases bladder capacity in spinal cord injured patients was tested in the two years before this project by N. Shah at the Royal National Orthopaedic Hospital and the results are described in his thesis and in part of a subsequent paper (Kirkham et al. 2001); this hypothesis was not explicitly tested again.

ii) The effect of different modes of neuromodulation on bladder capacity.

We planned to used continuous low-level stimulation to achieve neuromodulation in the SPARS device. However, it may be that other, intermittent, modes of stimulation are more effective and could be used to optimise the response to neuromodulation in an

implanted device. In particular, Shah has shown that provoked hyperreflexic contractions can be reliably suppressed with *conditional* stimulation, triggered by a rise in detrusor pressure of 15cm water (Kirkham *et al.* 2001). It is possible that bladder capacity can be significantly increased by suppressing hyperreflexic contractions as they occur, and that this method might be as effective or more effective than continuous stimulation. Experiments in cats have demonstrated conditional suppression of bladder contractions with sacral nerve root stimulation (Jezernik *et al.* 2001), although there is little data on the increases in bladder capacity that are possible with this technique, either in animals or humans. Whether conditional stimulation is a promising technique depends critically on the following hypothesis, which has not yet been tested:

Hypothesis 1: Conditional stimulation is at least as effective as continuous stimulation for increasing bladder capacity in spinal cord injury.

This type of neuromodulation would require a reliable method for detecting the start of hyperreflexic detrusor contractions, making it unsuitable (at least initially) for use in the SPARS implant. It might, however, prove a valuable technique in the future – either to improve response or to save battery power by reducing stimulation time.

iii) The effect of neuromodulation on DSD.

As described in sections 1.5 to 1.7, it was suspected that DSD might be a significant problem when trying to achieve bladder emptying by sacral root stimulation without rhizotomy in a SPARS implant. If neuromodulation has a significant effect on

dyssynergia, it might be a useful strategy to improve emptying in an implanted device, and in patients in whom DSD prevents efficient spontaneous voiding.

It is well known that neuromodulation can reduce detrusor hyperreflexia, and one way of thinking of this effect is that neuromodulation reduces (or 'gates') the amount of reflex DH caused by activity in the bladder afferent nerves. If bladder afferent activity is also necessary for DSD, it might well be that neuromodulation can reduce – or 'gate' – DSD as well.

In one sense neuromodulation does reduce DSD: it suppresses detrusor hyperreflexia, and thereby reduces the DSD that accompanies it. However, the most important question for *voiding* in SCI (whether reflex or stimulator-driven), where detrusor activity is high, is:

> Does neuromodulation reduce DSD when detrusor pressure is raised by
>
> activation of motor pathways? Such activation includes spontaneous
>
> detrusor hyperreflexia and stimulated voiding.

Schmidt et al assert that it does, stating that 'neuromodulation can stabilise the sphincter by eliminating much of the random clonic activity behind dyssynergic voiding in spinal injury patients' (Schmidt 1986). However, although attractive theoretically, there is no published evidence for this statement. If it is true, neuromodulation might be an important method for reducing dyssynergia and improving reflex voiding. It might also be used to reduce DSD during stimulator-driven voiding. Therefore, a one aim of the preoperative tests was to test the following hypothesis:

Hypothesis 2: Neuromodulation at a level which significantly increases bladder capacity also reduces DSD during DH.

Postoperative tests

i) The effect of neuromodulation

That neuromodulation by sacral foramen stimulation appears to be effective suggests that stimulation of multiple roots via a Finetech-Brindley device might increase bladder capacity enough to eliminate the need for posterior rhizotomy. Indeed, the Finetech-Brindley stimulator can be implanted in a configuration that allows stimulation of S2 to S4 bilaterally, and it may be that stimulation of multiple roots produces a more powerful inhibitory effect on the bladder than the single foramen conventionally used with the Medtronic *Interstim*. The afferent fibres responsible for neuromodulation are type A myelinated (Yalla *et al.* 1978, Craggs & McFarlane 1999) and can therefore be activated at lower level of stimulation than the preganglionic parasympathetic B fibres that are the motor supply to the bladder. A central aim of the work in this thesis is to test the following hypothesis:

Hypothesis 3: Stimulation of the sacral afferents at a low level with a Finetech-Brindley stimulator can increase bladder capacity enough to eliminate the need for posterior rhizotomy.

ii) Bladder emptying without rhizotomy

Even if the above hypothesis is true, it is possible that stimulator-driven emptying will be less effective than with a conventional SARS + rhizotomy, because of intact sacral afferent pathways. These might lead to increased resistance to flow in the gaps between stimulation, analogous to DSD. It is therefore necessary to test a further hypothesis:

Hypothesis 4: Bladder emptying by intense sacral root stimulation and an interval voiding technique is possible without rhizotomy of the posterior roots.

This includes the use of several techniques which might be used to improve emptying in the presence of DSD, including different stimulation techniques and pharmacological and surgical approaches.

2. General Methods

Project approval: Local ethics committee approval was obtained for this project. The application was later modified (with the approval of the committee) to include some additional diagnostic tests. The final patient information sheet is shown in appendix 1.

Recruitment: Adult male patients at least six months after upper motor neuron spinal cord injury were recruited. For participation in initial testing, neither detrusor hyperreflexia nor detrusor-external sphincter dyssynergia were necessary, although these were present in the majority of patients. Exclusion criteria were:

1) Any condition making repeated cystometry hazardous to the patient – for instance urinary tract infection or high pressure vesicoureteric reflux.

2) Any contraindication to stopping anticholinergic medication – in particular severe autonomic dysreflexia.

Patients gave fully informed, written consent to testing and anonymous publication of results. A summary of the participants is given in Table 2.1.

Anticholinergic medication: This was stopped at least three days before each test, with the exception of one patient (PtX). He had high pressure DH and DSD while on oxybutinin and to stop the medication for several days would not have been safe. He was keen to participate in the project and because his detrusor hyperreflexia on oxybutinin was reliably >60cm water in amplitude, he was included in the testing. The results of neuromodulation on bladder capacity in PtX were *not* included in the statistical analysis.

Patient	Age /y	Neurological Level & Frankel Grade	Date of Injury	Bladder Management	Daily Dose of Oxybutinin	Protocol used for DPN tests
PtA	32	T6 complete	1983	condom	none	
PtB	34	T4 complete	Oct 1995	ISC	30mg	i
PtC	38	T10 complete	Jan 1995	ISC, condom	15mg	i
PtD	46	T3 complete	Jun 1995	ISC	30mg	iv
PtE	36	T6 complete	Oct 1995	ISC	30mg	iv
PtF	34	T6 complete	Jun 1995	ISC	30mg	iv
PtG	42	C6 complete	1982	condom	none	iii*
PtH	49	T4 complete	Nov 1996	ISC, condom	none	iii
PtI	20	T6 incomplete C	Oct 1998	ISC	30mg	iii
PtJ	48	L1 incomplete B	1973	ISC, condom	none	iii
PtK	29	T2 incomplete B	1990	ISC	none	ii
PtL	32	T3 complete	1994	ISC, condom	15mg	ii
PtM	29	T4 complete	Jul 1998	ISC	7.5mg	iii
PtN	37	T5 complete	Mar 1999	ISC, condom	4mg tolt.	iii
PtO	42	T7 complete	Feb 1997	SPC	10mg	ii
PtP	29	T7 complete	Apr 1999	ISC	22.5mg	
PtQ	59	C5 complete	June 1994	SPC	5mg	iii
PtR	33	T6 complete	1995	ISC	30mg	iii*
PtS	43	C7 complete	1993	SPC	5mg	
PtT	42	T5 complete	Nov 1999	ISC	20mg	
PtU	40	C45 complete	1982	SPC	5mg	
PtV	30	T10 complete	Mar 1994	ISC	30mg	
PtW	43	T10complete	Oct 1994	SARS 8/96	none	
PtX	24	C6 incomplete B	July 1999	ISC	30mg	iii

ISC = intermittent self catheterisation   SPC = suprapubic catheter   complete = Frankel D
tolt = tolterodine   * = incomplete tests

Table 2.1 The patients involved in the study, and some relevant demographic details.

Cystometry: All cystometry was in the supine position. Patients were always given one dose of ciprofloxacin 500mg orally as prophylaxis against urinary tract infections. Two main catheter configurations were used:

1. A solid state microtip transducer catheter system (Gaeltech, Isle of Skye, UK) – Figures 2.1, 2.3. This configuration enabled simultaneous recording of urethral pressure (3 transducers), bladder pressure and anal sphincter pressure (1 transducer each).

Two transducers were used, and each was calibrated using a column of water. In each case, the catheters were zeroed to air before placement. Several other studies were performed to validate this method of pressure recording:

i)   The position of the catheters was determined during videourodynamics in 7 patients (Table 2.2 and Figure 2.4). In each, the external urethral sphincter was assumed to be the point of narrowing below the prostatic fossa during voiding. In six out of seven patients, at least the most distal urethral transducer was at the external urethral sphincter (Table 2.2). In one patient, gentle pulling on the catheter lodged its asymmetric balloon in the prostatic fossa, but this did not result in any signs of urethral trauma. Importantly, one urethral transducer still lay at the position of the external sphincter.

Medtronic[1] 9013L0451 self-adhesive Ag/AgCl skin electrodes (cathode placed proximally)

Gaeltec[4] anal sphincter and urethral multitip transducer catheters

Digitimer[2] DS7 electrically isolated constant current stimulator

Lectromed[4] Ambulatory recorder (output to PC serial interface)

Thurlby Thandar[3] TGP 110 pulse generator (triggered manually)

manual coordination

Personal Computer running Gaeltech[4] 5p1d software in DOS

Figure 2.1 (above). Microtip transducer catheter setup for experiments using DPN stimulation
Figure 2.2 (below). Urodynamic system using standard water-filled catheters.

Anal sphincter balloon, bladder filling and pressure lines

standard self-adhesive Ag/AgCl skin electrodes[1] (anode placed proximally)

Digitimer[2] DS7 electrically isolated constant current stimulator

Lectromed[4] MT8P electrically isolated amplifier

SensoNor[6] 840 pressure domes

CED 1401 Analogue to Digital Converter[5] & interface

Personal Computer running Spike2[5] software in Windows 95

1. Dantec Medical A/S, Skovlunde, DK-2740, Denmark
2. Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK
3. Thurlby Thandar Ltd, Huntingdon, Cambridgeshire, UK
4. Gaeltec Ltd., Isle of Skye, UK
5. Cambridge Electronic Design Ltd., Cambridge, UK
6. SensoNor asa., Horten, Norway

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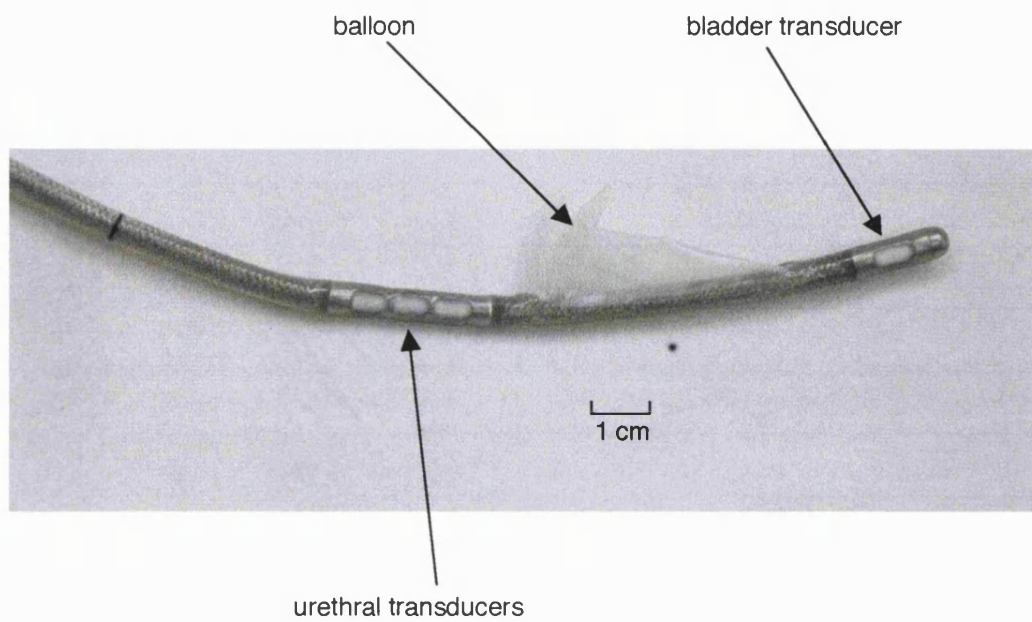
Figure 2.3 Close up of urethral sphincter pressure tip catheter, and (below), the ideal catheter position.

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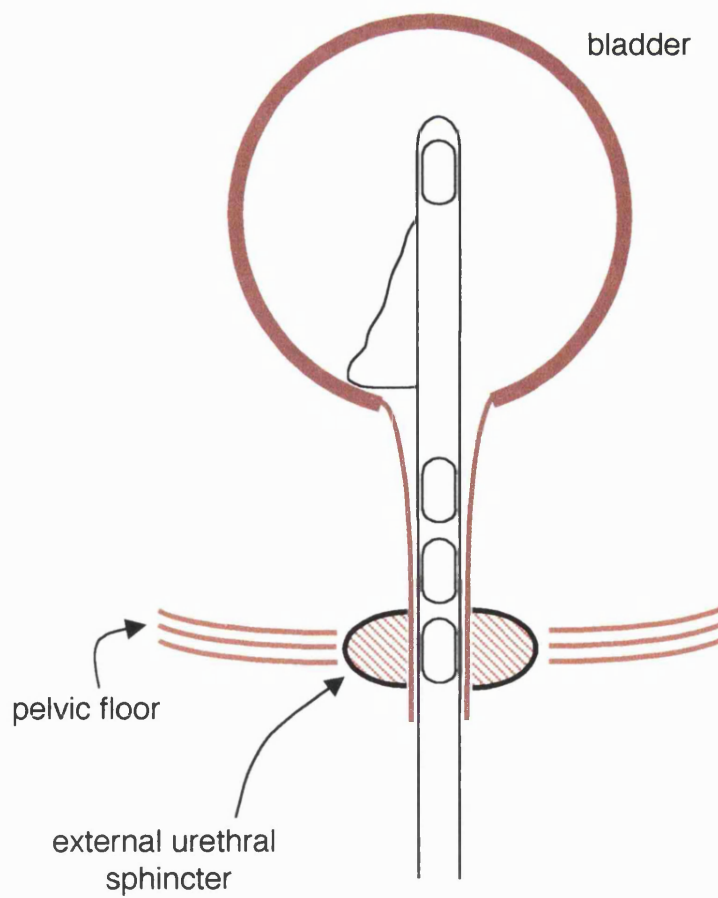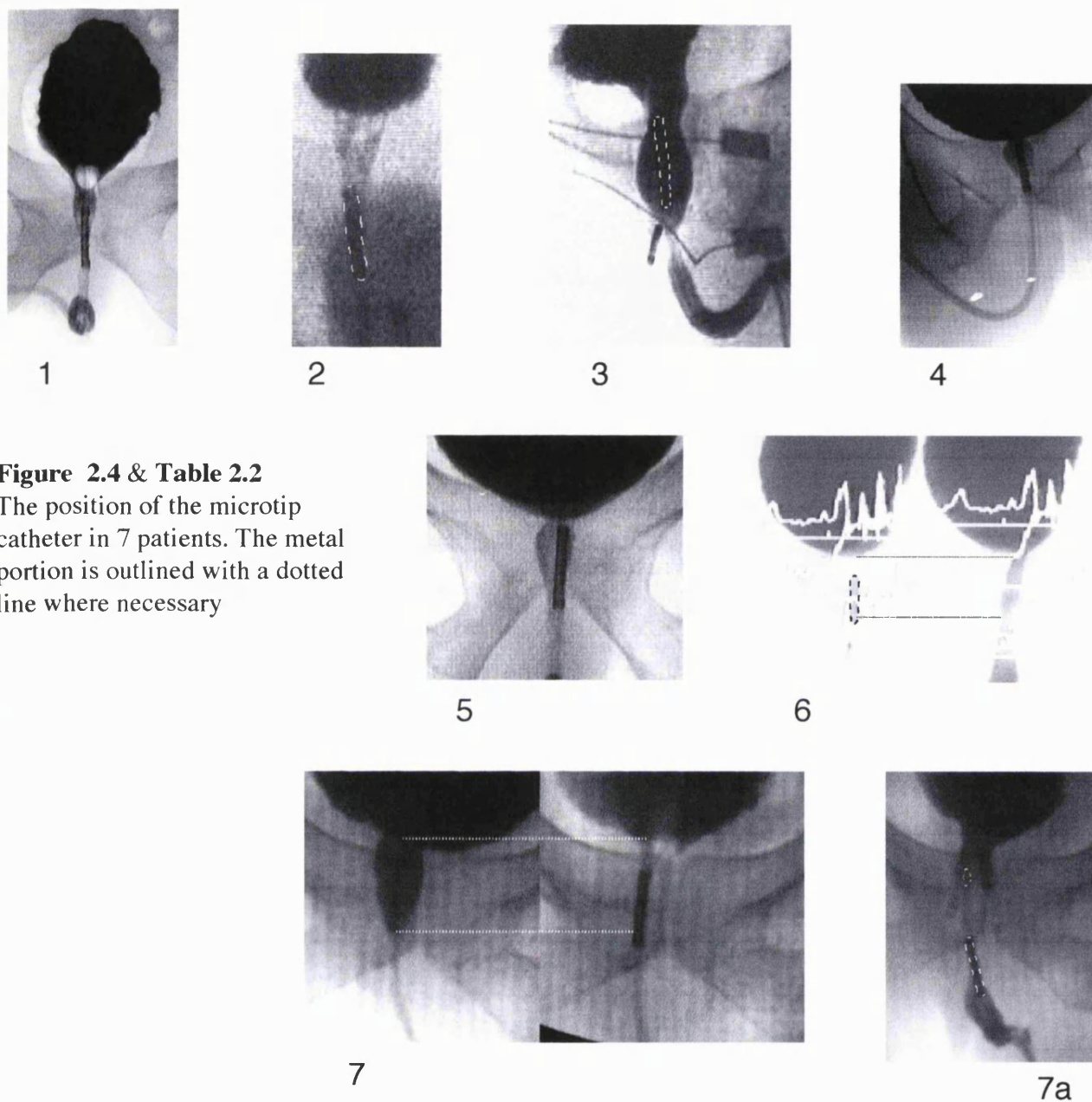
Figure 2.4 & Table 2.2
The position of the microtip catheter in 7 patients. The metal portion is outlined with a dotted line where necessary

Patient	Number	Catheter positioned at external urethral sphincter?	Age	Injury
PtY	1	yes	38	T8 complete
PtZ	2	yes	21	T8 incomplete
PtB	3	no (but large pressure rises with sacral nerve stimulation)	36	T4 complete
PtE	4	yes	37	T6 complete
PtAA	5	yes	38	C6 incomplete
PtC	6	yes	39	T10 complete
PtD	7	yes	47	T3 complete
PtD (after pulling catheter)	7a	yes	47	T3 complete

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ii)   It was not practical to determine the position of the catheter radiologically in

every patient, or in every test. To do so would have resulted in unjustifiable

exposure to radiation. Instead, each time the microtip catheter was used,

positioning was confirmed by observing large (>50cm water) and rapid (<0.5

sec) rises in at least one of the urethral pressure records, characteristic of

skeletal muscle contraction. Importantly, in the one patient in whom the

radiographic position was imperfect, rapid urethral pressure rises of >150cm

water could be recorded after sacral nerve stimulation.

For two reasons, *changes* in urethral pressure are more reliable in this study than absolute

values. Firstly, it was not certain that any transducer was positioned at the area of

maximum pressure in the external urethral sphincter; the balloon on the catheter would

have made repeated urethral pressure profiles by gradual withdrawal impractical and

potentially traumatic. Secondly, anteroposterior orientation of the catheter transducers

was not controlled, and there is evidence that this can affect *absolute* pressure

measurements by up to 30% (Rossier & Fam 1986).

ii) In 6 patients, the catheter was pulled once or repeatedly to identify the artefact

produced by movement and in 8 patients the effect of a large cough was recorded (Figure

2.5). Importantly, those patients who had significant DSD showed large responses,

usually in both anal and urethral sphincters, and usually to both coughing and pulling the

catheter. Patients who had undergone rhizotomy showed much smaller responses. This

suggests that as well as a direct mechanical effect, coughing or catheter movement caused

reflex contraction of the sphincters.

Mechanical increases in intravesical pressure due to coughing would have been reduced by using a standard subtraction cystometry technique (where rectal pressure is subtracted from bladder pressure to determine detrusor pressure), but in this case recording of anal sphincter pressure would not have been possible because of the limited number of channels on our recording equipment. For several reasons, subtraction during cystometry of spinal cord injured patients is probably less important than in a neurologically normal population:

- detrusor hyperreflexia is involuntary and there is little reason to suppose that it is associated with rises in intra-abdominal pressure – or 'straining'.

- coughing is often of reduced amplitude in SCI patients, and can be marked on the pressure trace when it occurs.

- changes in posture were very uncommon: testing was performed with the patients lying on a mattress in the same position (often with rolling between tests to relieve pressure areas). If significant changes in posture occurred, this could again be marked.

In addition, use of the Finetech-Brindley stimulator produces rectal contractions with a latency of about 6 seconds (Brindley 1998). This will invalidate the subtraction technique for the calculation of detrusor pressure during stimulated emptying.

Figure 2.5 Two examples of the effect of coughing and movement with the microtransducer catheter system. P = pulling on the catheter. C = cough.
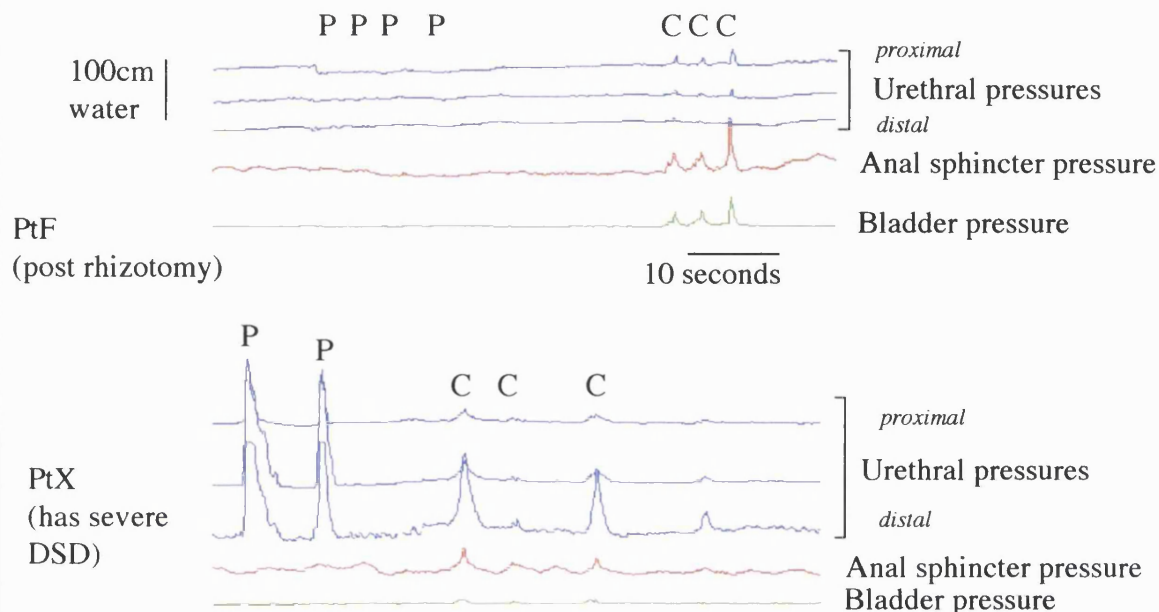
Table 2.3 responses to *a)* coughing and *b)* pulling the urethral catheter in 8 patients. The grading system (which is arbitrary) is explained below.

Name	DPN response*	Degree of DSD**	Response to cough*** (Urethral / Anal)	Response to urethral catheter movement*** (Urethral / Anal)
PtW (post rhizotomy)	-	-	+ / ++	
PtF (post rhizotomy)	-	-	+ / ++	- / -
PtK	+	+	+ / +	+ / +
PtC (pre SPARS)	+	+	+++	+++
PtD	++	+	- / -	+ / -
PtB (post SPARS)	++	++	+++ / +++	- / -
PtR	++	++	+ / -	+++ / -
PtX	++	++	+++ / ++	+++ / ++
PtT	+++	+++	+++ / +++	

* The DPN response is graded as follows:
  + Response <100 cm water in urethral catheter or threshold pulse width for stimulation >70mA (these terms are explained in the *methods* section)
  +++ Response >160cm water or threshold <25mA

** The degree of dyssynergia is graded as follows:
  + small (<100 cm water) rises in urethral pressure over bladder pressure or occasional rapid and short-lived spikes
  ++ dyssynergia during firing off only
  +++ dyssynergia during firing off *and* large rises in urethral pressure during filling

*** The response to cough or catheter movement is graded as follows:
  + <20 cm water
  +++ >100cm water

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The terms *bladder pressure* and *intravesical pressure* are used interchangeably. Where *rises in detrusor pressure* are referred to (for instance during the emptying experiments), such figures are derived by subtracting the peak intravesical pressure from the baseline intravesical pressure at the start of filling.

Microtip transducers are well-established and their use for the measurement of DH and DSD and have been used in this capacity before (Bary *et al.* 1982, Rossier & Fam 1986).

2. The second configuration of catheters was used for intraoperative monitoring and in situations where the microtip configuration was impractical:

-for accurate determination of residual volume in any situation – for instance during neuromodulation when bladder volume is small (<150ml). The small calibre of the filling line and the asymetric balloon on the microtip system sometimes made aspiration of residual urine difficult.

- in assessing the efficiency of emptying. The balloon on the microtip system was considered likely to obstruct flow.

-when the balloon on the microtip system itself provoked detrusor hyperreflexia, or when catheterisation was difficult.

A 10 french urethral catheter was used for filling, with a standard urodynamic pressure line. An anal sphincter balloon was positioned by attaching it to the side of a foley catheter with its balloon in the rectum, and signals processed and recorded as in Figure 2.2.

The ability to measure anal sphincter pressure has several advantages. In most patients, detrusor-external urethral sphincter dysssynergia is reflected in anal sphincter contractions of similar morphology (Perkash 1980). In the microtip system described above, observing similar contractions in anal and urethral sphincters confirms that the pattern of dyssynergia is not simply due to mechanical movement of the catheter. Also, in the water-filled catheter setup, contraction of the anal sphincter can be used as a marker for the start of dorsal penile nerve stimulation, allowing accurate measurement of the time course for the effects of neuromodulation.

Filling Rates: Unless stated, the bladder was filled with room temperature normal saline at a rate of 10ml/min using a pump (Lectromed, UK). The filling rate was chosen to be as close as possible to normal physiological filling while allowing a large number of fills in one day.

Measurement of bladder volume: In all cases, bladder filling was stopped when there was a leak of urine ('firing off') or a sustained (>10 sec) rise in bladder pressure of >35cm water. The residual urine was aspirated and its volume added to the amount fired off to determine bladder capacity.

Measurement of bladder compliance: Compliance may be defined as the mean increase in bladder volume per centimetre of water increase in pressure (Abrams 1997). It was measured by dividing the bladder capacity by Δp, where Δp = (intravesical pressure just before the start of detrusor hyperreflexia *minus* starting intravesical pressure).

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Stimulation of the Dorsal Penile Nerve: The stimulator was a constant current device, connected as in Figures 2.1 and 2.2. Self-adhesive Ag/AgCl electrodes (see Figure 2.1) were placed 1cm apart on the dorsum of the penis, as near to the base as possible.

Asessment of the bulbocavernosus (or pudendo-urethral and pudendo-anal) reflexes: These reflexes were elicited by electrical stimulation of the dorsal penile nerve. The threshold for the pudendo-anal and pudendo-urethral sphincter reflexes was defined as the minimum stimulus intensity that reliably produced a greater than 5cm water contraction of the respective sphincters.

Stimulation parameters for neuromodulation by DPN stimulation:

i) Electrical current

The current was set at twice the threshold for the bulbocavernosus reflex, a level derived from Shah's optimisation work using provoked hyperreflexic contractions (Shah *et al.* 1999). Prévinaire showed convincingly that stimulation *at* the bulbocavernosus reflex threshold has little effect on the bladder, with a level of twice the threshold producing reliable suppression of hyperreflexia (Prévinaire *et al.* 1996).

ii) Frequency and pulse width

A frequency of 15Hz and a pulse width of 200μs was used for all experiments. Lindström showed in non-spinal cats that inhibition of bladder activity by the sympathetic nervous system was maximal with stimulation of pudendal afferents at 5Hz, and diminished rapidly at higher frequencies, while central inhibition of parasympathetic

activity was maximal at 5-10Hz, with the effect diminishing by only 25% at 50Hz

(Lindström *et al.* 1983). Because the central effects probably predominate when the

bladder is full (and parasympathetic efferent activity high), this is consistent with Shah's

finding that 15Hz was optimal in humans (Shah *et al.* 1999). Two groups have

investigated the relationship between current intensity, total charge delivery and pulse

width for afferent pudendal stimulation in either in cats (Ohlsson *et al.* 1986) or humans

(Plevnik *et al.* 1986), and found 500μs or 200μs respectively to be optimal.

Statistical analysis: Several different statistical tests were used for the data in chapters 3

to 6, and they are stated where they are occur. For some data, a normal distribution was

assumed; for others, non-parametric tests were used. This can be summarised as follows:

Normal distribution assumed: Data closely distributed around a non-zero mean.

This includes most of the timings in chapter 3 – for instance, the time for a

suppressed contraction to decay by 50%.

Non-parametric data: Increases in bladder capacity in chapters 3 and 5, and the

pulse width threshold for neuromodulation in chapter 5 cannot be assumed to be

normally distributed. Here, a two-tailed Wilcoxon matched pairs test or a Mann-

Whitney U test was used, with a significance level of 95%.

Figures in brackets represent standard deviations. The data was analysed, and all graphs

drawn, with a commercially available Macintosh program (Prism 3, Graphpad Software,

Inc. – *www.graphpad.com*).

3 Preoperative neuromodulation using dorsal penile nerve stimulation.

3.1 *Aims*

The first aim of these tests was to establish that patients responded to neuromodulation before implantation of a SPARS device. In particular, it was essential to confirm that neuromodulation significantly increased bladder capacity. It was also important to determine the degree of dyssynergia, and efficiency of reflex voiding, in prospective SPARS patients. These studies also provided the opportunity to examine several other areas in detail:

1. An examination of the efficacy of conditional neuromodulation. The reasons for investigating this technique have been described in chapter 1. DPN stimulation is a particularly attractive way to apply conditional neuromodulation, because it is safe, non-invasive and easy to stop and start.

2. Further characterisation of the pudendo-anal and pudendo-urethral reflexes, and their behaviour over time. Tanagho and Schmidt's view of the mechanism of neuromodulation is that 'Detrusor activity is suppressed by sphincter contractions. Thus, enhancing tone within the external sphincter suppresses the detrusor and improves storage' (Schmidt 1986). A major problem with this hypothesis is that it is *not known* whether sphincter pressure is significantly raised when pudendal *afferent* stimulation is used for neuromodulation. The Medtronic *Interstim* has been used sucessfully to increase bladder

capacity in spinal cord injury (see the introduction to this thesis), and chronic stimulation probably does increase sphincter tone by continuous activation of slow-twitch sphincter fibres (Brindley *et al.* 1974), but this increase in pressure is probably due to *efferent* stimulation. DPN stimulation activates no efferent fibres directly, and yet is highly effective for neuromodulation. The observation that neuromodulation was occurring without significant sphincter contraction would have important implications for the likely mechanism.

3. A characterisation of detrusor-sphincter dyssynergia, and the effects of neuromodulation upon it. This was an important part of the project for several reasons:

a) It was likely that detrusor-external sphincter dyssynergia would occur in the gaps between stimulations in patients implanted with SPARS stimulators. If a pattern of phase relationships that characterises DSD could be established preoperatively, it might also help to characterise rises in urethral sphincter pressure occurring during stimulated voiding, identifying them either as DSD or as a different phenomenon.

b) Schmidt states that 'neuromodulation can stabilise the sphincter by eliminating much of the random clonic activity behind dyssynergic voiding in spinal injury patients' (Schmidt 1986), although he does not provide convincing evidence of this. If he is right, however, neuromodulation might be used beneficially in the SPARS stimulator to reduce urethral sphincter activity in the gaps between stimulations. Secondly, neuromodulation would be a potentially useful therapy

(applied cutaneously or via implant) in a large group of spinal cord injured

patients in whom dyssynergic voiding prevents adequate emptying. Although

unlikely, we considered it important to investigate such a possibility.

3.2 *Methods*

After determination of the threshold for the pudendo-anal and (in most cases) the

pudendo-urethral reflexes, neuromodulation was performed during slow fill cystometry

using several different protocols, summarised in Figure 3.1. The patients investigated

with each protocol are shown in Table 2.1.

1. *Conditional and continuous neuromodulation:* In the continuous fills, DPN stimulation

was applied throughout filling, at a frequency of 15Hz, pulse width $200\mu s$ and current

twice the threshold for the pudendo-anal reflex. In the conditional fills, a one minute

period of neuromodulation *using the same parameters* was triggered manually by a rise

in bladder pressure of 10cm water occuring in less than 20 seconds (so that gradual rises

in bladder pressure due to low compliance never triggered a period of neuromodulation)

(Figure 3.2). If the hyperreflexic contraction was not suppressed to within 10% of

baseline within one minute, a further one minute period of neuromodulation was applied.

End fill was defined in exactly the same way as during the continuous stimulation fills.

During the conditional neuromodulation fills, three suppressed contractions were

analysed in detail for each patient (at the beginning of the neuromodulation period, in the

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middle, and just before 'escape' from neuromodulation at end fill). Time to peak of contraction, time to decay to within 50% of maximum and time to decay to within 10% of baseline were determined for each suppressed hyper-reflexic contraction (Figures 3.2, 3.3). In addition, the gaps between suppressed contractions were measured for each patient.

As well as measuring the increase in bladder capacity using serial measurements of bladder volume, a further method of analysis was used:

In patients in whom the first fill with neuromodulation was with conditional stimulation (in which case there would be no carry over effect from previous neuromodulation), a time-based method was used. Assuming a constant rate of filling (justified because 10ml/min was likely to be much higher than the patient's urine output), the time from the start of filling to the first hyperreflexic contraction (c in Figure 3.2) and the period of sucessful conditional suppression (n in Figure 3.2) were measured. The fraction n/c then represents the proportional increase in bladder capacity due to neuromodulation. This method has the great benefit of eliminating the variation in control fill volume between fills, and the tendency for bladder capacity to gradually increase in serial fills (Kirkham *et al.* 2001). However, it may, for the same reason , underestimate the potential increases possible in a series of fills with neuromodulation: the first fill of the series tends to show the smallest increase over controls.

Protocol i.

Protocol ii.

Protocol iii. The order of continuous and conditional fills was reversed in several patients, and is specified in the text.

☐ Control

▦ Continuous Neuromodulation

▤ Conditional Neuromodulation

{ } Denotes fills which were sometimes omitted

Figure 3.1
Protocols used for the investigation of the effects of neuromodulation, and number of patients tested with each.

One minute periods of neuromodulation

End fill

Start of fill

intravesical pressure

100cm water

c

n
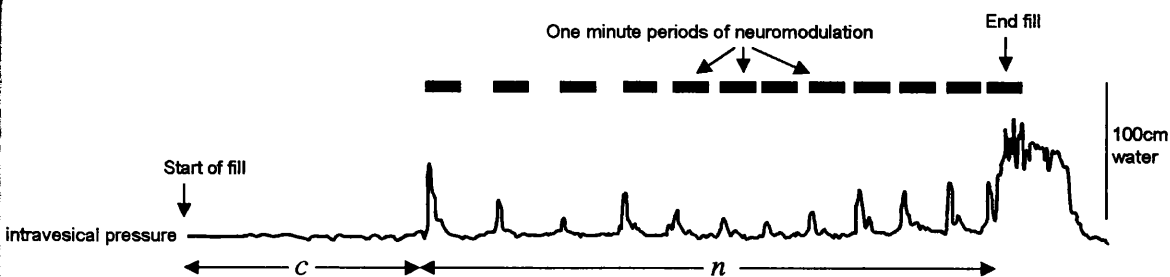
Figure 3.2

A typical fill with conditional neuromodulation, showing the definition of control (c) and neuromodulation (n) periods. This analysis was only used in the first neuromodulation fill.

PtD
PtF
PtE

50cm water

30 seconds

PtN

PtH
PtX
PtI
PtT

PtO

PtQ
PtM

PtJ

stimulation

d
c
b
a

x

1

10cm water

x

2

intravesical pressure

y

5 seconds
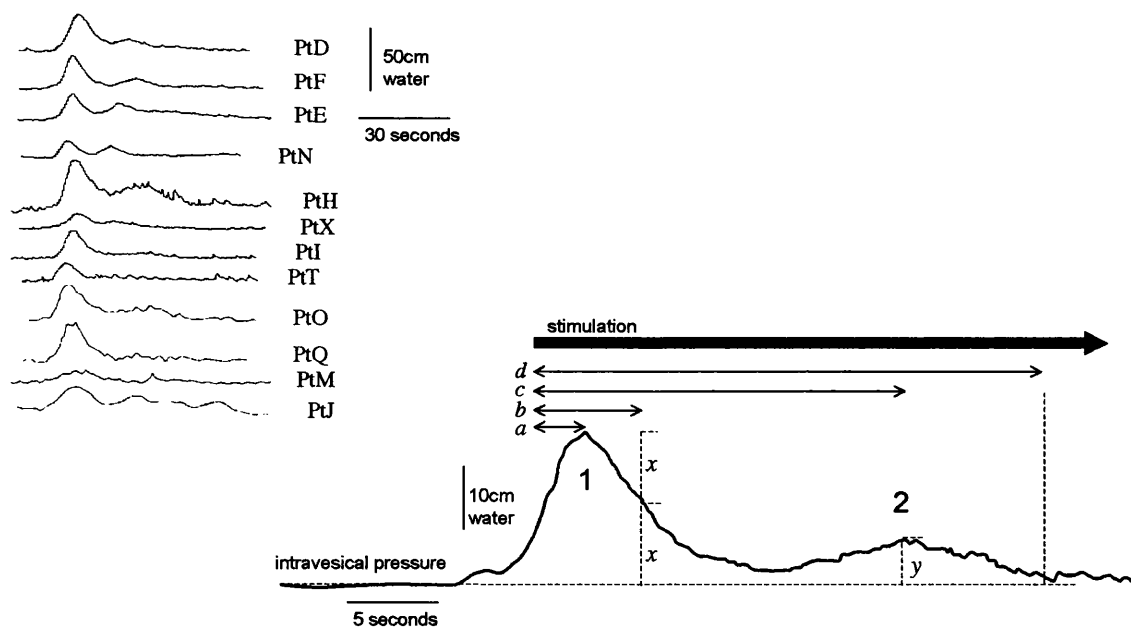
Figure 3.3

A suppressed hyperreflexic contraction during conditional neuromodulation. The parameters a, b, c, d, $2x$ and y are discussed in chapter 3. Traces from twelve patients are shown on the left.

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Where conditional and continuous techniques were compared, the *mean* of an equal number of fills for each technique was calculated for each patient. However, because the last fill in a series of fills with neuromodulation is often the largest (Kirkham *et al.* 2001), when assessing the effect of conditional neuromodulation alone the *greatest* control bladder volume (at least two were always performed) was compared with the *greatest* bladder volume with neuromodulation. This more accurately reflects the increases achievable with the technique.

2. *Characteristics of the pudendo-urethral reflex*:

a) *Morphology of the reflex.* In 11 patients, good quality recordings of the urethral pressure during continuous stimulation were obtained over a period of at least 4 minutes.

b) *Change in the reflex after repeated periods of continuous stimulation.* In 7 patients, the rise in urethral pressure on stimulating at twice the original threshold for the PUR was determined a) at the start of the day's experiments and b) after at least two fills with neuromodulation had taken place. The threshold for the PUR was then determined again. It should be noted that the stimulator was a constant current device, with visible warning when compliance was inadequate, so that changes in electrode – skin impedance (for instance from drying of the electrode electrolyte) should have had a minimal effect. This was *not* a detailed study of the habituation of the pudendo-urethral reflex; rather, it simply aimed to establish whether the threshold for (and the strength of) the pudendo-urethral reflex was reproducible throughout a day's testing.

2. *Detrusor-external urethral sphincter dyssynergia:* DSD was recorded during the initial control fills in 11 patients. It was analysed in the following way, with the urethral channel showing the highest rises in pressure again assumed to be closest to the external urethral sphincter. (Figure 3.4):

-at up to five peaks in urethral pressure during DSD, bladder pressure rise and *rate* of bladder pressure rise (in cm water/sec) were calculated.

-at up to five peaks in bladder pressure associated with dysynergic sphincter contractions, urethral pressure rise and *rate* of rise were calculated.

-the time between these urethral and bladder pressure peaks was measured.

The same parameters were measured, where possible, during i) two control fills, ii) one continuous neuromodulation fill and iii) one conditional neuromodulation fill.

3.3 Results *(Tables 3.1 to 3.5)*

1. *Continuous and conditional neuromodulation.*

Conditional neuromodulation increased bladder capacity in 13 out of 15 patients; in PtG and PtR it was not possible to suppress DH conditionally and any increases in capacity were likely to be due to the tendency for bladder volume to increase during serial fills noted by Shah (Kirkham *et al.* 2001).

g_b = rate of change of bladder pressure at urethral pressure peak

urethral pressure

bladder pressure

g_u = rate of change of urethral pressure at bladder pressure peak
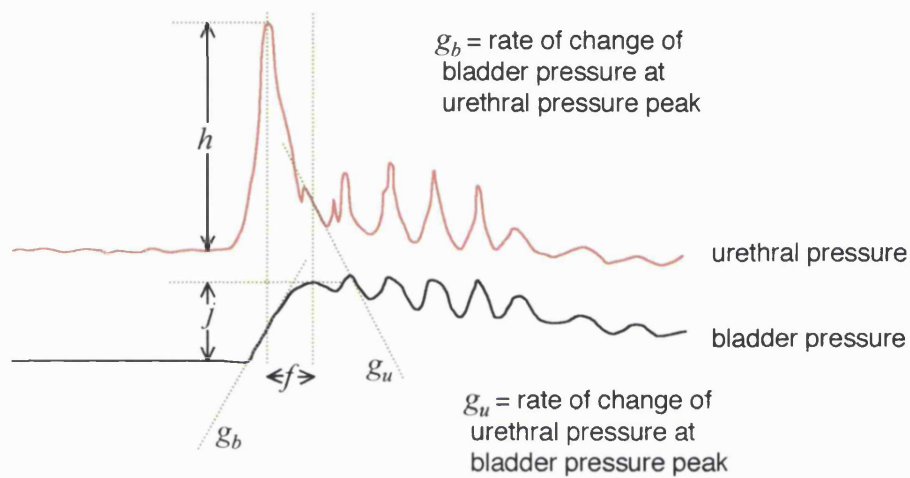
Figure 3.4   The parameters measured for the analysis of DSD in 10 patients

h = height of urethral pressure peak
j = height of bladder pressure peak
f = time between bladder and urethral pressure peaks

Patient protocol	Control Fills /ml	Volumes with Continuous Stimulation /ml	Mean Increase /ml (%)
PtB i	133, 155, 171	260, 286, 512	200 (131)
PtC i	181, 195, 210	288, 330, 360	131 (67)

Table 3.1
Results using protocol *i*: a series of fills with *continuous* neuromodulation

Patient protocol	Control Fills /ml	Volumes with Conditional Stimulation /ml	Mean Increase /ml (%)
PtK ii	240, 290	400,410	140 (53)
PtL ii	182, 170	365, 330	172 (97)
PtO ii	110, 100	480, 500	385 (367)

Table 3.2
Results using protocol ii: a series of fills with *conditional* neuromodulation.

Patient protocol	Control fill Volumes /ml	Volumes with Continuous /ml	Volumes with Conditional /ml	Mean Increase with Continuous /ml (%)	Mean Increase with Conditional /ml (%)
PtH iii (conditional first)	255, 255, 260	315, 330	293, 360	66 (26)	70 (27)
PtI iii (continuous first)	190, 210, 210	340, 265	310, 285	99 (49)	94 (46)
PtJ iii (continuous first)	380, 380	460, 470, 405	470, 500, 450	65 (17)	93 (25)
PtM iii (continuous first)	160, 170	190, 260	215, 280	60 (36)	83 (50)
PtN iii (conditional first)	230, 270	>650	>650	>450 (>225)	>450 (>225)
PtQ iii (conditional first)	87, 88, 93	126, 140, 146	135, 135, 142	48 (54)	48 (54)

Table 3.3

Results using protocol iii: alternating *continuous* and *conditional* fills.

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Patient protocol	Control Fills (Continuous day) /ml	Volumes with Continuous Stimulation /ml	Control Fills (Conditional day) /ml	Volumes with Conditional Stimulation /ml		Mean Increase with Continuous /ml (%)	Mean Increase with Conditional /ml (%)
PtD iv	146, 170	280, 320, 480	105, 100	215, 510, 460		202 (128)	309 (301)
PtE iv	160, 150, 270	265, 320, 329	182, 180, 220	380, 370, 385		111 (58)	184 (95)
PtF iv	75, 81	143, 150	125, 125	185, 222		69 (88)	79 (63)

Table 3.4
Results in patients investigated with both protocols *i* and *ii*: a series of *continuous* fills on one day, a series of *conditional* fills on another.

Patient	Reason for not including in protocols i to iv	Results
*PtA**	Control fill volumes 400-500ml	Provocation of DH by rapid instillation of 60ml used instead: successful conditional suppression observed.
PtP	Limited time for tests: 1 conditional and 1 continuous fill	Useful microtip catheter data obtained. Bladder capacity increased from 30ml to >170ml with each technique.
PtG, *PtR*	No response to DPN stimulation	Could not suppress DH conditionally. Capacity with continuous stimulation similar to controls.
*PtS**, *PtU**, *PtV**	Did not have reproducible DH, but DPN response measured.	
*PtT**	Very variable control volume (first fill 650ml)	Conditional suppression of DH still possible (4 contractions suppressed). Microtip catheter data obtained for this.

* These patients were not included in the analysis of the results of neuromodulation.
All other patients were.

Table 3.5 Patients not included in protocols i to iv

The mean increase with conditional neuromodulation (*including* two figures of zero for PtG and PtR) was 158ml (±132ml) or 125% (±145%), with the median values 94ml and 53%. The maximum rises seen for each patient are shown in Figure 3.5. Those patients who had stopped oxybutinin for the tests had significantly greater percentage increases in capacity with neuromodulation than those who were not managed with anticholinergics (mean 175% *vs* 33%, p=0.012, Mann-Witney U test).

Using the time technique (and including PtG and PtR), the mean percentage increase in the first conditional fill was 86% (±83%), and the median 56%.

In the comparison of the two techniques:

> In the three patients in whom the two techniques were used on separate days (protocols *i* and *ii*), the conditional neuromodulation resulted in the largest volume increase in all 3, and in the greatest percentage increase in 2 out of 3.

> In the patients investigated using the alternating technique (protocol *iii*), there was never a large difference between the two types of neuromodulation. In 3 out of 7, conditional stimulation was more effective (in 2 out of 3, the order was with continuous fill first), and in 2 continuous was a little better (one with continuous stimulation first). The mean increase with continuous was 70%, and with conditional 72%, but the difference was not significant.
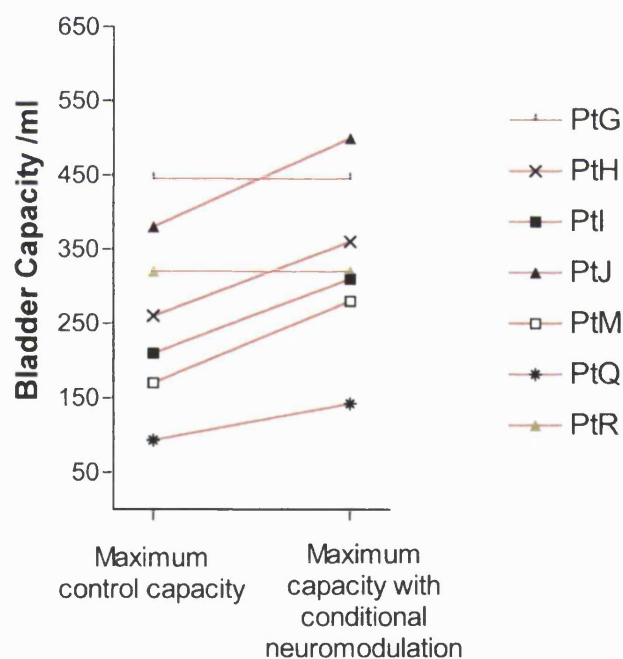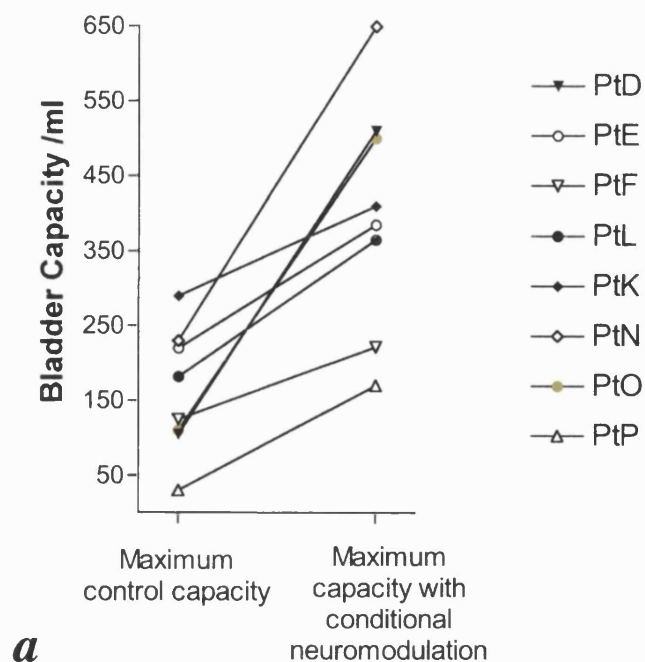
Figure 3.5

The maximum control fill volume, and the maximum conditional
neuromodulation fill volume in fifteen patients. The top graph (3.5a) shows
the best result with conditional neuromodulation when a series of serial
conditional fills was performed (protocols ii, iv). The bottom graph shows
the maximum volume fill with conditional neuromodulation during an
alternating conditional / continuous series (protocol iii).

There was a significantly larger increase (Mann-Whitney U test, p=0.002) in bladder volume in patients in whom a series of conditional fills (protocol *ii*) was performed, compared to those in whom the conditional fills were alternated with continuous (protocol *iii*).

The time between suppressed hyperreflexic contractions fell reliably with increasing volume in every patient (Figure 3.6), although the absolute time varied widely between patients.

Two patients (PtN and PtJ) were excluded from the further analysis of conditional neuromodulation in Figure 3.3 because the tracings were not of sufficient quality, leaving 13 patients who were investigated with protocols *ii* or *iii*.

The peak of the suppressed contraction ($2x$ in Figure 3.3) was on average 35cm water (± 11cm water) above baseline. Several parameters were strikingly similar between patients, and are shown in Figures 3.7 and 3.8. The mean time from start of stimulation to peak of suppressed contraction, and time for the contraction to fall to 50% of peak were 3.0s (± 0.5s, range 2.3 to 3.7s) and 7.6s (± 1.0s, range 6.7 to 10.3s) respectively (*a* and *b* in Figure 3.3). The initial decay of the suppressed hyperreflexic contraction was approximately fitted by a single exponential function [$y = A + Be^{-t/k}$], with a time constant (k) of 7.1s (± 1.9s).

In all cases, the first peak in intravesical pressure was followed by a second, smaller peak after 21.0s (± 4.7s) (*c* in Figure 3.3). The rise in intravesical pressure over baseline at the
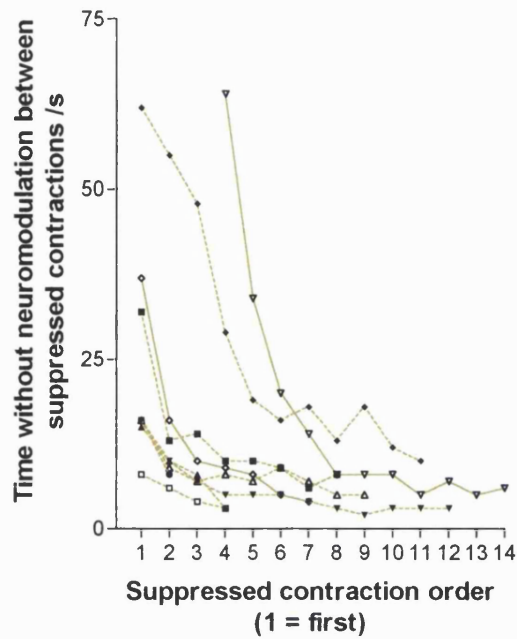
Figure 3.6

The gaps between suppressed contractions during conditional neuromodulation in nine patients.
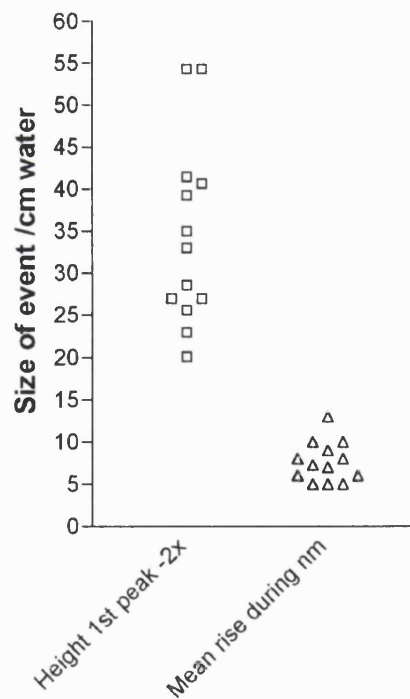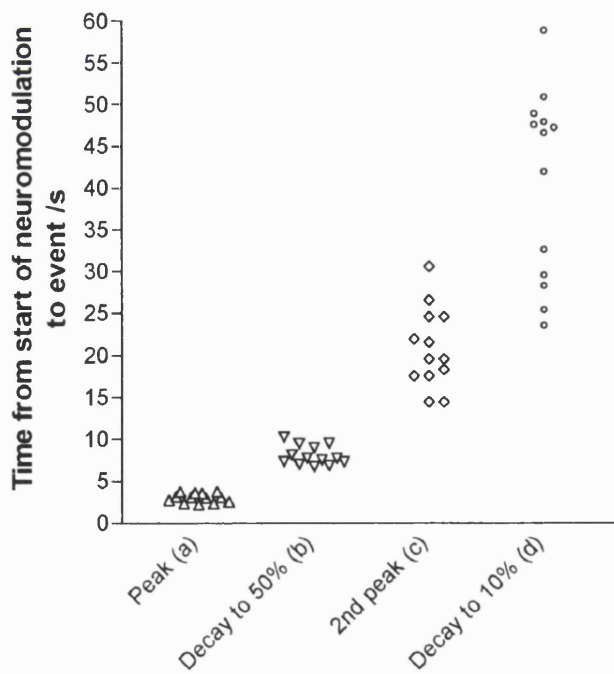
Figures 3.7 (left) and 3.8 (right)

Various parameters during conditional neuromodulation in 13 patients. Each point represents one patient: the mean of values derived from the start, middle and final suppressed contraction. The letters in brackets refer to Figure 3.3

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height of this second peak (y in Figure 3.3) was on average 44% ($\pm$15%) of the size of the

initial peak.

The mean time taken for the intravesical pressure to decline to within 10% of pre

hyperreflexic contraction baseline (d in Figure 3.3) was 41s ($\pm$11s) with only 1 of 29

measurements longer than one minute. The *mean* intravesical pressure during the

neuromodulation period was 7.6cmH$_2$O ($\pm$ 2.4cm water, range 5 to 13cmH$_2$O) higher

than the baseline at the end of the control period.

2. *The pudendo-urethral reflex.*

Tracings of the reflex with continuous stimulation at twice the threshold current were

possible in 11 patients (those who underwent neuromodulation with the microtip

transducer system) and are shown in Figure 3.9. In no patients did the urethral pressure

remain 30cm water above baseline after 4 minutes, and in 7 out of 11, the pressure

decayed to within 10cm water of the baseline during this period. The peak height of the

reflex did not correlate significantly with the efficacy of neuromodulation (Spearman's

rank correlation coefficient r = 0.26 and 0.37 for percentage increases and volume

increases respectively).

The behaviour of the reflex also changed over hours with repeated stimulation. In the

seven patients in whom the threshold for the pudendo-urethral reflex was tested more

than once, it increased significantly (Wilcoxon matched pairs test, p=0.016) as the

experiments progressed (Figure 3.10). Similarly, the urethral contraction resulting from

PtE

PtD

PtI

PtV

PtS

PtT

PtH

Upper limit of
← microtip
transducer
system

PtF

←

PtN

PtX

PtR

100 cm
water
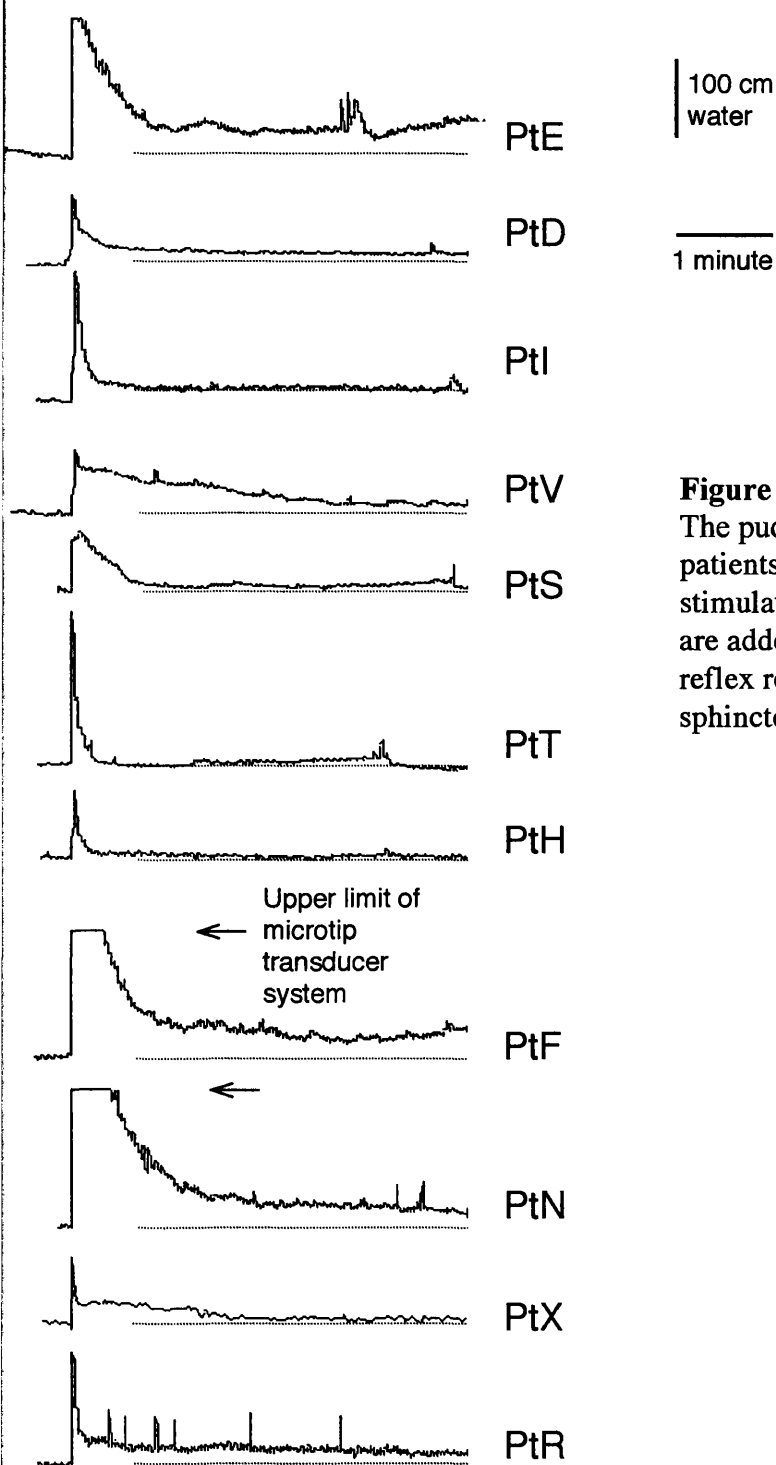
1 minute

Figure 3.9
The pudendo-urethral reflex in 11
patients:behaviour in the first 4 minutes of
stimulation. The dotted lines under each trace
are added to illustrate the rapid decay of the
reflex response towards the resting urethral
sphincter pressure.

Patient	E	D	I	V	S	T	H	F	N	X	R
Rise above baseline at 4 min /cm water	30	11	0	7	3	0	2	24	15	1	10

79
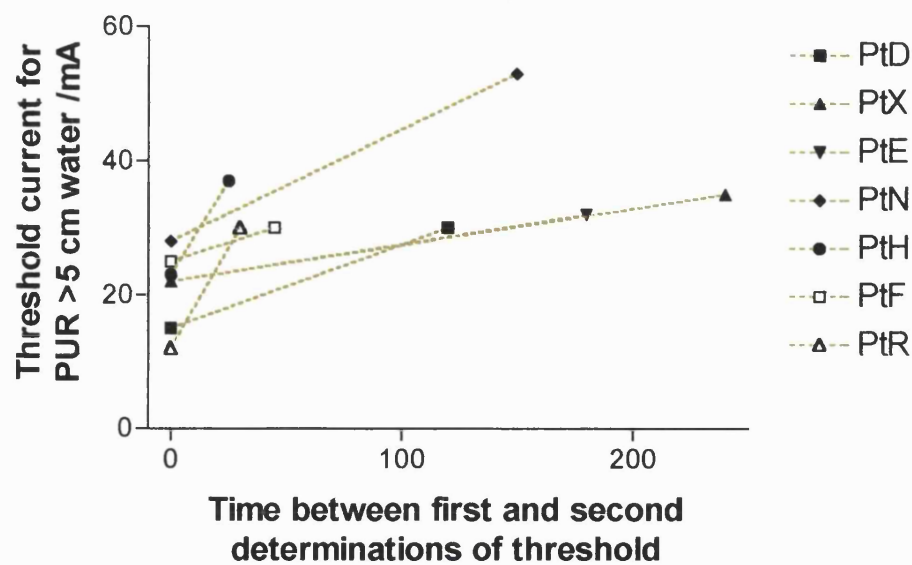
Figure 3.10
The change in the threshold for the pudendo-urethral reflex after fills with
neuromodulation have taken place (seven patients).
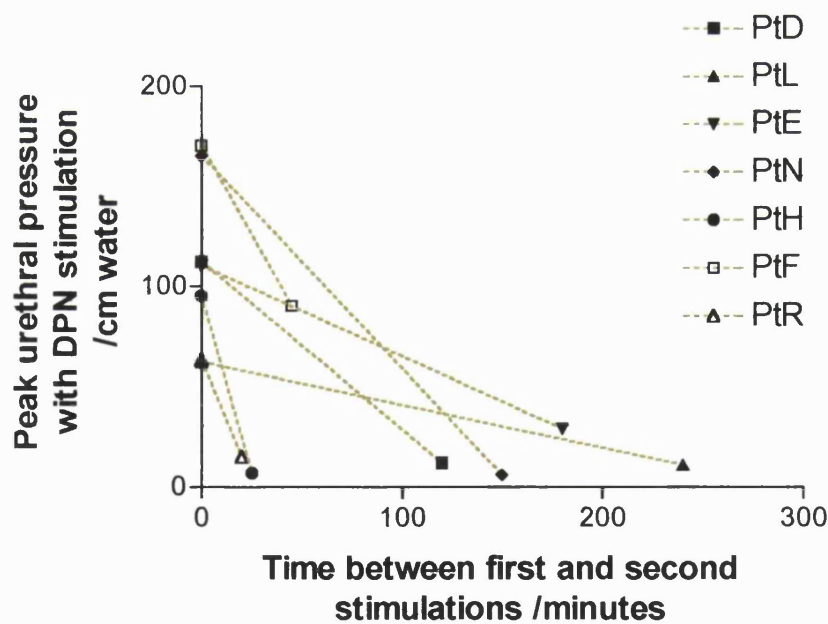
Figure 3.11
The change in the size of the pudendo-urethral reflex after fills with
neuromodulation have taken place (seven patients). There was no change in DPN
stimulation current between first and second stimulations.

DPN stimulation at twice the *initial* threshold for the reflex declined by a mean of 79%

(±16%) (p=0.016) (Figure 3.11).

3. *Detrusor-sphincter dyssynergia*

Significant DSD was recorded in 11 patients, 10 of whom responded to neuromodulation

(Figure 3.12). The patterns were very variable, and it was not possible to include urethral

responses occurring before or after detrusor hyperreflexia in the analysis that follows.

Such responses were mainly 'pre-detrusor kicks' (Bary *et al.* 1982) and occurred in 4

cases: PtN, PtP, PtH and PtF. These rapid and short-lived (<2 sec) contractions occurred

3s, 7s, 1min and 2 min before the start of detrusor hyperreflexia respectively.

In most patients the pattern of detrusor-sphincter dyssynergia was markedly different in

the periods before and during firing off. Certain generalisations could be made about the

relationship between bladder and urethral pressure:

   Before firing off:

   a) In the great majority of cases, peaks in urethral pressure occurred as bladder

   pressure was rising. Sometimes bladder and urethral peaks occurred at the same

   time, but only very rarely did a peak in urethral pressure occur as bladder pressure

   was declining. This is shown in Figure 3.13, where the size of the urethral peak (h

   in Figure 3.4) is plotted against the rate of change of bladder pressure when it

   occurred (g_b in Figure 3.4). The relationship was not obviously affected by

   neuromodulation.

PtN   PtP   PtE

1 minute | 100cm water

Red = urethral pressure
Black = bladder pressure

F denotes urine per urethra

PtH   PtI   PtD

PtF   PtX   PtK   PtL
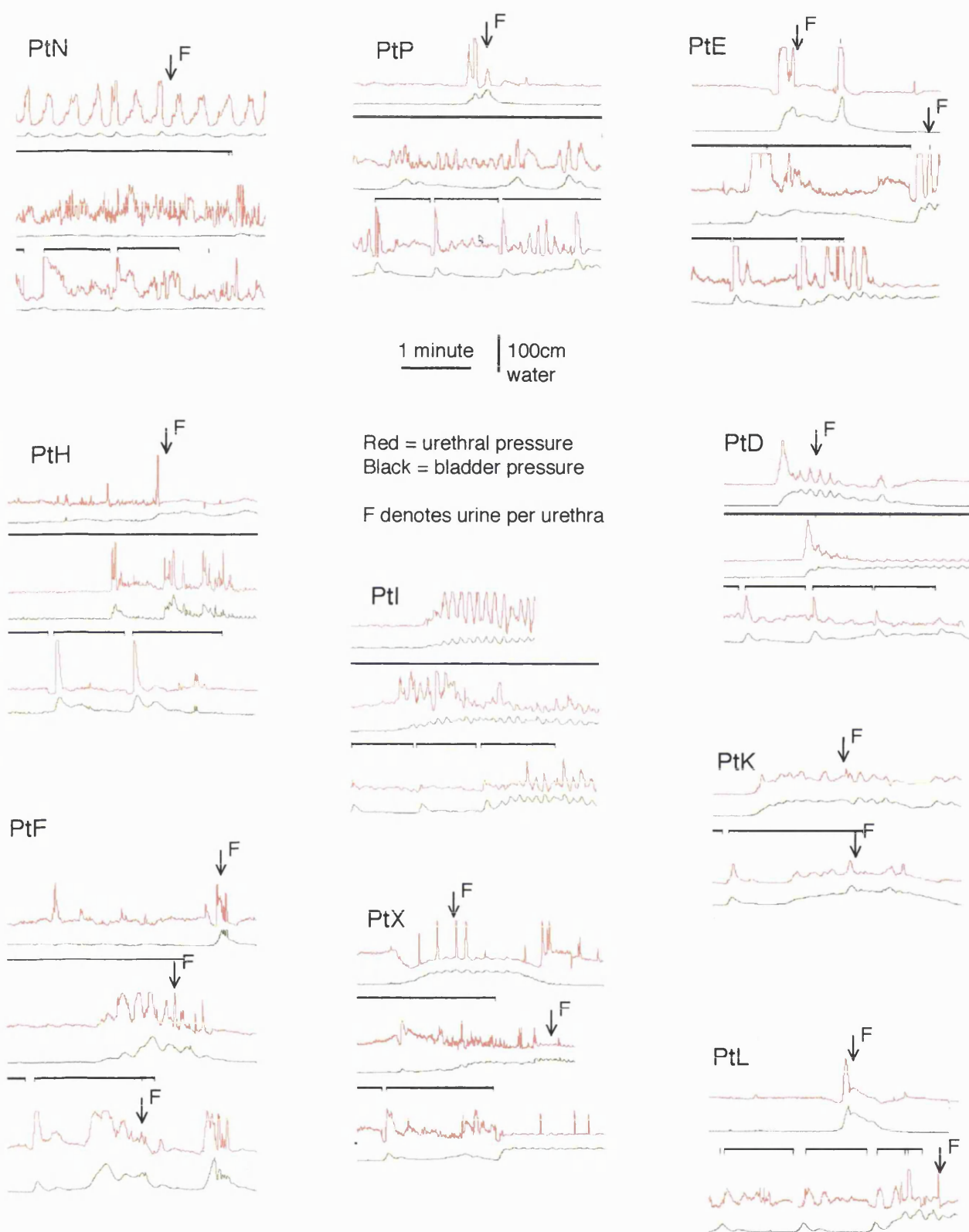
Figure 3.12 The urethral pressure during control (top), continuous neuromodulation (middle) and conditional neuromodulation (bottom) fills in 10 patients. In PtL and PtK, continuous stimulation was not used. The black bars above the traces signify neuromodulation.
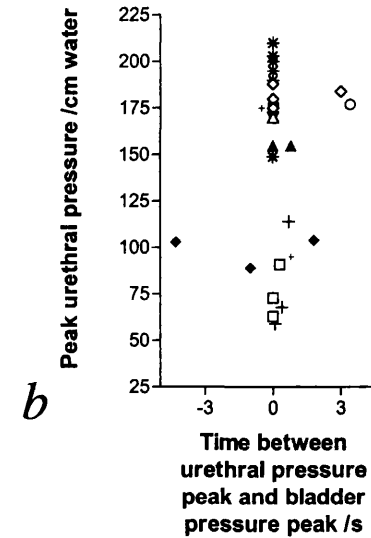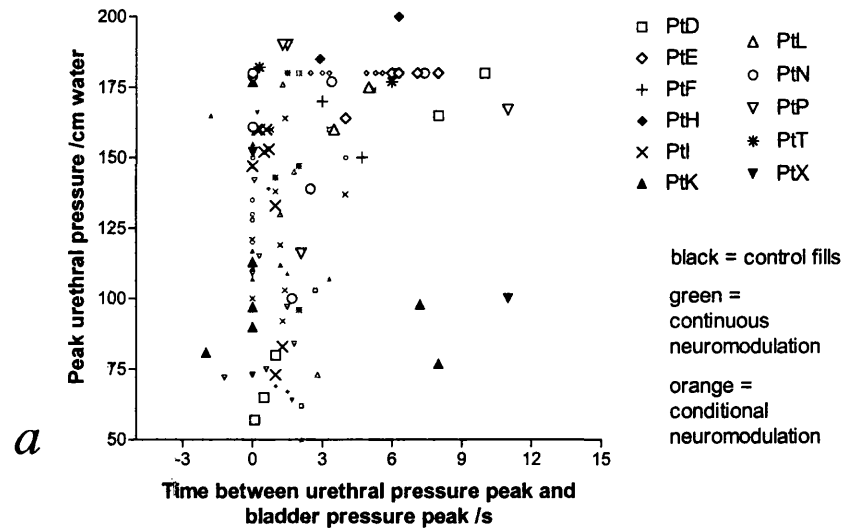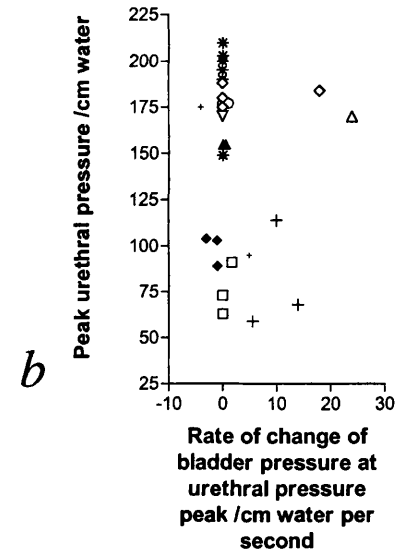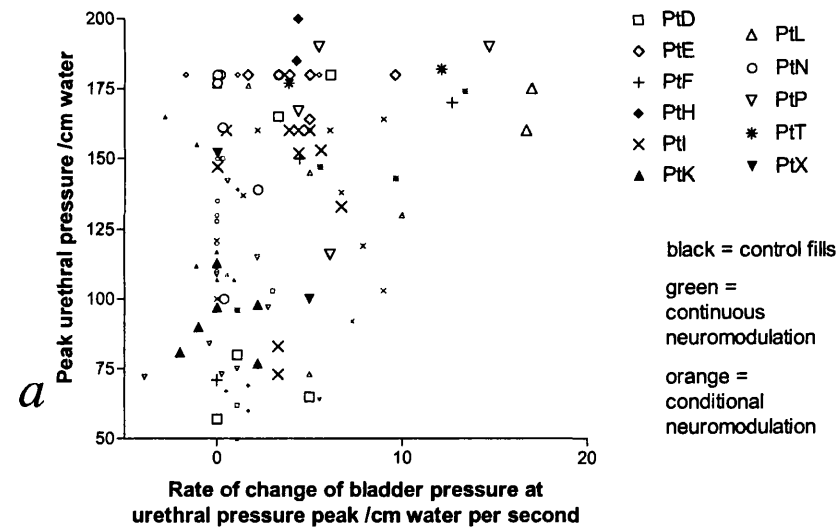
Figures 3.13 (top), 3.14 (bottom)

Two relationships between bladder and urethral pressure during detrusor-sphincter dyssynergia. The graphs on the left (*a*) show data derived from eleven patients before firing off. Those on the right (*b*) show data from the same patients during firing off.

b) Consistent with *(a)*, in most cases the urethral pressure peak occurred before

the bladder pressure peak; the difference was significant (P<<0.01, Wilcoxon

signed rank test). This is shown in Figure 3.14, where the time between peaks (*f* in

Figure 3.4) is plotted against the size of the urethral peak. Again, the relationship

was not affected by neuromodulation.

During firing off:

The relationships described in *(a)* and *(b)* were still present, but to a much smaller

degree. In particular (as shown in Figures 3.13 and 3.14), in the majority of cases,

bladder pressure peaked *at the same time* as urethral pressure.

A statistical evaluation of the effect of neuromodulation on the size of the urethral

contractions during DSD was impossible because:

- neuromodulation affected bladder pressure during detrusor hyperreflexia,

usually reducing but sometimes increasing it.

- detrusor hyperreflexia usually occurred at a higher bladder volume during

neuromodulation than in control fills.

However, comparing the patterns of DSD at end fill with or without conditional and

continuous neuromodulation (as in Figure 3.12), some generalisations are possible:

- neuromodulation did *not* markedly reduce DSD, except when it considerably

reduced the size of detrusor hyperreflexia.

- several patients (PtD, PtL, PtP, PtE, PtK, PtX) voided volumes >20ml during

control fills, but *did not* fire off when the neuromodulation stimulus was on

(Table 3.6). When it was stopped, the detrusor hyperreflexia usually 'rebounded'

and there was voiding

The patterns of DSD during conditional neuromodulation in particular warranted cautious

comparison. At first sight, it may appear that DSD was reduced during stimulation, but

this is usually misleading. Peaks of DSD often occured at the start of DH (as in patient

PtD in Figure 3.12), but it is at this point that conditional neuromodulation is triggered.

The reflex urethral pressure rise from starting the one minute period of neuromodulation

therefore masks the initial DSD, and makes comparisons difficult.

4. *The results of neuromodulation in the patients who elected to receive SPARS implants.*

These are summarised in Table 3.7, and will be discussed in detail and compared with

postoperative results in chapter 5. PtA, PtB and PtC were implanted with stimulators

before we had begun to use conditional neuromodulation for preoperative testing. In PtA,

the effects of continuous neuromodulation were not tested because his control bladder

capacity was between 400 and 500ml in the laboratory. Instead, DH was provoked using

the technique described by McFarlane (McFarlane *et al.* 1997), and successful

suppression observed.

Patient	Highest rise in detrusor pressure: no neuromodulation (fill1, fill2) /cm water	Highest rise in detrusor pressure: neuromodulation (continuous, conditional) /cm water	Voiding in no n-m fills?	Voiding with n-m in 1st minute?
PtD	68, 69	32, 26	yes	no
PtE	85, 105	57, 62	yes	no
PtF	71, 64	105	yes	yes (later, less)
PtH	55, 48	39, -	yes	no
PtI	44, 46	36, 79	no	no
PtK	63, 59	55, 83	yes	yes
PtL	99, 108	-, 85	yes	no
PtN	18, 19	10, 18	yes	no
PtP	48, 38	59, 39	yes	no
PtT	75, 51	21, 12	yes	no
PtX	86, 83	40, 34	yes	no

Table 3.6
Detrusor pressures and voiding behaviour with and without neuromodulation.

Patient	*Preoperative Investigations*	*Result*
PtA	Suppression of provoked contractions using percutaneous electrodes*	Successful suppression
PtB	Continuous DPN neuromodulation	Capacity increased from 172 ml to a maximum of 512 ml
PtC	Continuous DPN neuromodulation	Capacity increased from 210 to 360ml
PtD	Continuous and conditional DPN neuromodulation	Continuous: 170ml increased to 480ml Conditional: 105ml increased to 510ml
PtE	Continuous and conditional DPN neuromodulation	Continuous: 270ml increased to 330ml Conditional:220ml increased to 385ml

* PtA emptied his bladder by reflex voiding at a volume of approximately 400ml. In a previous study at the Royal National Orthopaedic Hospital using percutaneous stimulation of the sacral roots, provoked contractions at this volume could be suppressed. This experiment was not repeated.

Table 3.7

Tests confirming the effect of neuromodulation in the five patients who elected to receive a SPARS device. The results are described in more detail, and compared to those using sacral root stimulation, in chapter 5.

3.4 Discussion

Neuromodulation was effective in 13 out of 15 patients, and in all five who elected to receive a SPARS implant. Shah has shown that bladder capacity increases significantly as a series of fills with continuous neuromodulation is performed (Kirkham *et al.* 2001), so that there was some reason to expect that modest acute rises seen in some patients might be translated into larger long term effects with continuous stimulation. Only one group has examined both the acute and chronic effects of neuromodulation on bladder capacity, using the Medtronic *Interstim*, and they did not find that chronic rises were markedly larger (Chartier-Kastler *et al.* 2000b). For several reasons, however, these results do not necessarily apply to the current group of patients. Their subjects consisted mainly of patients refractory to pharmacological bladder suppression, and it is not clear what drugs were stopped before testing. Our subjects had in most cases responded to anticholinergics (although often with significant side effects); neuromodulation was in the context of a device also capable of bladder emptying rather than as a last resort, so that one might expect increases in capacity to be more easily achieved. Also, the *Interstim* is a relatively inflexible device, prone to displacement of the stimulating electrode and usually applied to only one sacral root. The facility to easily vary all of the stimulation parameters and to stimulate up to six sacral roots at the same time was expected to have a greater effect than simple stimulation of the dorsal penile nerve, so that a moderate (50% or greater) increase in bladder capacity was considered a positive response, justifying the implantation of a Finetech-Brindley device in SPARS configuration.

There is another reason to suppose that chronic rises in capacity might be larger than those seen during acute tests. The bladder capacity after posterior rhizotomy usually increases immediately, but further large rises are often observed over subsequent months (Koldewijn et al. 1994b), and it might be that a similar increase would occur with chronic neuromodulation.

The largest rises in bladder capacity in this study occurred in patients who had stopped anticholinergics before the tests. On stopping these drugs, they often had hyperreflexia at low bladder volumes during control fills. This was effectively suppressed by neuromodulation, enabling them to return to their previously high bladder capacity. As expected, patients who were not previously on anticholinergics had significantly smaller increases, as there is a limit to the distension that can be achieved in a chronically small bladder during one day. It is clear that the selection of patients critically affects the results of neuromodulation studies and means that caution is necessary in comparing results from different centres.

Conditional neuromodulation.

The combination of slow fill rates and the ability to rapidly switch on stimulation is essential for establishing how effective conditional neuromodulation might be in everyday use, and these conditions have not been present in most previous studies, which have used conventional (and more provocative) filling rates of around 50ml/min.

Filling at 10ml/min, conditional neuromodulation increased bladder 9 out of 11 patients. As with continuous stimulation, the range of increases was wide, so that unless

randomised groups with large numbers of patients are used, conditional and continuous modes should be examined in the same patients to compare efficacy. The results of this study suggest that conditional stimulation is as effective as continuous, and it is possible that it is slightly more so, but the numbers are too small to answer the question definitively. It was difficult to devise an adequate protocol for comparing the two modes of stimulation: the alternating continuous/conditional strategy for comparison is flawed because it is impossible to eliminate the effects of 'carry over' in a series of CMGs. Comparing results from two different days' testing eliminates the carry over effect but introduces other sources of variation – in particular, varying capacity on the control CMGs (which can be seen in Table 3.4), and differing electrode position and stimulation parameters. The 'time' method of analysis (as described in Figure 3.2) also provides valuable evidence (free of 'carry over' effect if it is the first fill with neuromodulation) of the efficacy of conditional neuromodulation.

The finding that *of* significantly higher rises in bladder capacity when a series of pure conditional fills were performed compared to an alternating protocol is interesting but should be interpreted with great caution: the patients were *not* randomised and there may well be a selection effect so that the best responders were entered into protocol *ii*. However, this may be a fruitful area for future study.

The gap between suppressed hyperreflexic contractions almost always decreased progressively with increasing bladder volume. This effect resembles the finding that unstable contraction frequency increases with volume in the spinal cat (Sasaki 1998), and may well be useful for the estimation of bladder volume in an implanted system for

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conditional neuromodulation, because bladder pressure often rises only a small amount during the stable phase of filling.

Although bladder volume increases with neuromodulation varied widely, the time to peak of suppressed contractions and time to 50% decline were strikingly similar between patients, suggesting a common mechanism. A mean of 3 seconds from start of stimulation to peak of DH is consistent with a previous observation that the effects of neuromodulation occur after a latency of '1 to 3 seconds' (Vereecken et al. 1984). The time constant of 7.1s(±1.9s) for the decay of the suppressed pressure is less than the Figure of 9.9s(±2.6s) seen with magnetic stimulation of the sacral roots in healthy men (Craggs et al. 1997), but in the latter study stimulation was for 2 seconds only. The mean rise in intravesical pressure of 7.6cm water during conditional neuromodulation suggests that this technique will be safe: in no patient was the rise greater than 10cm water. The second peak that occurred in the intravesical pressure as it was declining was present in every patient (although only just detectable in some), and has not been described before. It may reflect episodic activity in bladder or pudendal motor nuclei (Rudy et al. 1988).

The pressure rise of 10cm water chosen as a trigger for conditional neuromodulation is necessarily somewhat arbitrary but is similar to the smallest intravesical pressure rises that can currently be detected in animals by recording from the sacral roots (Jezernik et al. 2000, 2001).

The stimulation period of one minute was sufficient to bring intravesical pressure to within 10% of baseline in almost all cases (the Figure of 10% was chosen to allow for

any rises due to low compliance or signal noise). This confirms the results of provocation experiments, where 60-70s was found to be best for minimising the area under the intravesical pressure-time curve (Shah *et al.* 1999), and suggests that one minute is an appropriate 'on' time for conditional neuromodulation.

The pudendo-urethral reflex during continuous stimulation.

Although the electromyographic behaviour of the urethral sphincter in normal and spinal cord injury have been extensively studied (Ertekin & Reel 1976, Vodusek *et al.* 1983, Dyro & Yalla 1986, Sethi *et al.* 1989), this is the first time that the pressure response to purely afferent continuous stimulation has been studied in humans.

In the 12 patients studied, the sphincter contraction from continuous stimulation of the dorsal penile nerve declined rapidly, in most cases almost to baseline. Several of the results in this study suggest that this decline is mainly due to *habituation* of the reflex, rather than fatigue of the urethral sphincter. Firstly, the morphology of the reflex changes markedly during conditional neuromodulation after the first successful suppression. Secondly, we found that the response to dorsal penile nerve stimulation declines over hours of intermittent periods of stimulation, with threshold for the reflex *always* increasing and the response diminishing, suggesting habituation affects lasting several hours. Lastly, the urethral sphincter consists of fast and slow twitch fibres, with approximately three quarters of the maximum contraction being fatiguable (Brindley *et al.* 1974). The return *to baseline* seen in several subjects here must be due to more than muscle fatigue.

The lack of reproducibility in the threshold and strength of the DPN response seen during

a day's testing implies that caution is necessary when analysing changes in these

parameters (for instance, before and after SPARS implantation). For this reason, in

subsequent chapters a single figure from the start of the day's testing is used, rather than

mean or median values.

Implications for the mechanism of neuromodulation: Because of the filling rate used in

this study, each cystometrogram usually took between 10 and 50 minutes to perform. For

most of this time, the urethral pressure rise from neuromodulation would in most patients

have been close to zero, and yet continuous neuromodulation very often markedly

increased bladder capacity. If the assertion by Schmidt and Tanagho that 'the key to

control of the bladder lies in control of the sphincter' (Schmidt 1988) is true, then there is

only one possible explanation for this effect: the sphincter contraction early on in filling

has a persisting effect that lasts for up to 40 minutes and is powerful enough to markedly

increase bladder capacity. Shah has shown that control fills performed *after*

neuromodulation *are* of increased capacity, and that it may take several hours for this

effect to diminish (Kirkham *et al.* 2001). His findings are consistent with a persisting

effect from previous sphincter contraction, although they certainly do not imply it.

However, the experiments with conditional neuromodulation are much less consistent

with Schmidt and Tanagho's hypothesis. The reasoning is as follows:

1. Conditional neuromodulation is probably at least as effective as continuous.

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2. Most of the sphincter contraction during continuous neuromodulation occurs during the first minute. Therefore, if it is true that 'control of the sphincter' is key, the effect on the bladder of one minute of stimulation during the conditional experiments should be similar to the effect of continuous stimulation throughout bladder filling. In this case, one would expect the one minute of conditional neuromodulation to be followed by a long period of bladder suppression.

3. In the conditional stimulation experiments, one minute periods of neuromodulation *are not* followed by long periods of suppression (this is shown clearly in Figure 3.6)

The implication from these results is that contraction of the external urethral sphincter is unlikely to be central to the mechanism of neuromodulation.

Detrusor-sphincter dyssynergia

This study found that the pattern of DSD, as measured with a urethral pressure transducer, was different before and during voiding (or 'firing off'). When there was no flow (or a small amount), urethral pressure peaks usually occurred before bladder pressure peaks, and urethral pressure was usually declining when bladder pressure was at a maximum. Another way of describing this association is that urethral pressure correlated with *rate of change* of bladder pressure as well as its absolute value. These findings are somewhat different to those of Rudy, who found in a detailed study of 14 patients that *a)* increasing external urethral sphincter pressure and EMG activity

correlated with a positive slope of the intravesical pressure trace and *b)* urethral pressure

and EMG activity declined whenever bladder pressure did (Rudy *et al.* 1988). Rudy's

findings – that bladder pressure and urethral pressure tended to rise, peak and fall

together – are much more consistent with the pattern observed in the current study when

there was urine flow.

There is a simple explanation for the difference between the patterns observed before and

during flow, that holds for studies using either EMG or pressure transducers:

> The intravesical pressure depends mainly on two things: *a)* The strength of
>
> detrusor contraction and *b)* The outflow resistance, of which a major determinant
>
> is contraction of the external urethral sphincter. When there is little or no flow, the
>
> influence of *(b)* is insignificant, but during firing off, changes in outflow
>
> resistance may be the main determinants of *changes* in intravesical pressure. In
>
> the latter case (the most extreme example of which is the 'stop' test (Blaivas
>
> 1982) (Blaivas 1982)), rises in bladder pressure will always occur at the same
>
> time as the rises in urethral pressure causing them.

Rudy considers that each of the three patterns of DSD described by Blaivas (Blaivas *et al.*

1981) are consistent with his description of the relationship between urethral and bladder

pressure. The same is true of the current study, where the distinction between types I, II

and III of DSD does not affect the fundamental relationship between bladder and urethral

pressure. Others prefer to describe DSD as 'sustained' or 'unsustained' (Bary *et al.*

1982).

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There are several other pieces of evidence to suggest that in DSD, urethral sphincter

activity is closely related to bladder pressure. Galeano found in spinalised cats that

manipulations which increased bladder pressure worsened DSD (Galeano *et al*. 1986),

and Yalla describes similar findings in humans with Credé, Valsalva and suprapubic

tapping manoeuvres (Yalla *et al*. 1976). Siroky hypothesises that DSD is an 'abnormal

flexor response of the perineal musculature to bladder contraction' based on observations

of groups of patients with and without DSD (Siroky & Krane 1982).

This evidence suggests that DSD is a reflex response to increases in bladder pressure,

although bladder volume also appears to be important: the pre-detrusor 'kick' is common,

and DSD may persist when bladder contractions are suppressed by propantheline (Rudy

et al. 1988).

In one study of bladder afferents in the cat, bladder efferent activity behaved as a slowly

and incompletely adapting response to bladder pressure, with a stimulus-response

function such that small rises in pressure during slow filling produced relatively large

changes in activity (Habler *et al*. 1993). This means that the small increases in bladder

pressure during filling have a relatively large effect on bladder afferent activity. Thus, if

DSD were a response to this activity, it might behave in a way similar to that observed in

the current study: a function of both *rate of change* and *absolute* bladder pressure, and

sometimes occurring before DH.

These results suggested that DSD was likely in the gaps between stimulations in SPARS patients – who were expected to have intact bladder afferents. The characteristics of detrusor smooth muscle mean that the rate of rise of bladder pressure is likely to be high when stimulation is stopped, and to be positive for a significant proportion of the gap between stimulations in an interval voiding program. This is discussed further in chapter 6.

DSD and neuromodulation

Apart from Schmidt's assertion that 'neuromodulation can stabilise the sphincter by eliminating much of the random clonic activity behind dyssynergic voiding in spinal injury patients' (Schmidt 1986), little is known about the influence of neuromodulation on DSD. The finding in this study that in most cases it persisted and was of similar pattern and intensity during neuromodulation is supported by the observation that in six patients it *prevented* reflex voiding. This was probably due to a combination of detrusor inhibition and the small residual increase in urethral pressure seen with continuous stimulation.

These findings suggest that neuromodulation is unlikely to result in more synergic voiding: although it may effectively suppress the detrusor, this is of little use in the context of bladder emptying. They suggest that neuromodulation is unlikely to be a useful technique for reducing DSD in the gaps between stimulation in the SPARS device.

In summary

1. 14 out of 16 SCI patients (including those who opted for a SPARS implant) responded to neuromodulation.

2. Conditional neuromodulation was of similar (or better) efficacy to continuous.

3. Reflex urethral sphincter activity fell rapidly during continuous neuromodulation.

4. DSD behaved as if 'driven' by both the rate of change and absolute level of bladder pressure.

5. Neuromodulation did not make dyssynergic voiding markedly more synergic.

If it do cause problems, the extramural procedure will not work —

4. Implantatation of the SPARS & testing of root integrity

4.1 *Aims*

The central aim of the SPARS project is the restoration of bladder function without damage to the sacral roots. As well as not performing a surgical rhizotomy, this means avoiding damage to the sacral roots intraoperatively. Neurapraxia is a common consequence of implantation, and Brindley's early patients – who often did not have a rhizotomy – often had signs of damage to both anterior and posterior roots (Brindley *et al.* 1986). While motor root damage is likely to recover eventually, sensory nerve damage may well be permanent. Indeed, it is likely that some of the early SARS patients benefited from this difference: their anterior root neurapraxia recovered, but persistent posterior root damage resulted in the functional equivalent of a posterior rhizotomy.

The decision about what type of implant to use was therefore crucial. There is good evidence that the extradural approach is less traumatic, with a lower incidence of postoperative neurapraxia. It is probably also an easier procedure (Sarrias *et al.* 1993). However, intradural stimulation also has some important advantages. Separation of the anterior and posterior roots would enable the separate stimulation of anterior and posterior roots with a device that can have up to 4 channels (Brindley 1998). The effect of intense posterior root stimulation on the behaviour of bladder and sphincters is relatively unknown (especially during voiding programs), and were it to cause problems with bladder emptying the ability to stimulate anterior roots alone might be a major

advantage. Similarly, it may be that neuromodulation by purely sensory stimulation (as in the DPN experiments) is preferable to mixed root stimulation – either because it has less side-effects or is more effective. Intradural implantation might help to resolve these issues.

A further aim of this section was to discover the effect of SPARS implantation on bowel and erectile function. It is known that posterior rhizotomy transiently slows bowel transit, and that this usually recovers over several months (Misak et al. 1962, Koldewijn et al. 1994b). Such effects should be avoided in an implant without rhizotomy, and in addition, stimulation of the anterior sacral roots has a definitely beneficial effect on the slow transit times (Binnie et al. 1991). While patients undergoing SARS often have to change their method of bowel emptying after rhizotomy (for instance from digitally stimulating a reflex rectal contraction to manual evacuation (Varma et al. 1986)), this should be unnecessary if sensory pathways are preserved.

Sexual function, however, is more precarious. Complete posterior rhizotomy will abolish reflex erections, which are important to patients with spinal cord injury, and there is some evidence that it is section of S2 that is most critical (Gasparini et al. 1992). In contrast to the situation with bowel function, damage to the posterior roots is likely to have a direct impact on sexual function. For this reason, the pre and postoperative asessment of sexual function was an important aim of this part of the project.

Minimum requirements for the SPARS implants: The ability to stimulate S3 and S4 motor nerve roots was considered essential for bladder emptying; the S2 motor roots sometimes

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contribute usefully to bladder contraction and this can be discovered during intraoperative stimulation (Brindley 1998). For neuromodulation, there is evidence that S3 stimulation (for instance with the Medtronic *Interstim*) can be used for long term stimulation, but there is also evidence that S2 stimulation is effective; it may innervate part of the area of the penis stimulated during the DPN experiments in chapter 3. With very little known about which roots are *most* effective for neuromodulation, we considered it desirable to include as many of the sensory roots from S2 to S4 as possible, and ideally to be able to stimulate them separately.

4.2 *Implantation*

Five patients underwent implantation of a SPARS device. In four (PtA, PtB, PtC, PtD), the device was a 2 channel extradural implant, with the following configuration:

Channel A: S2 mixed roots bilaterally

Channel B: S3 and S4 mixed roots bilaterally

In one patient (PtE), a three channel intrathecal stimulator was used, in the following configuration:

Channel A: S3 anterior roots bilaterally

Channel B: S3 posterior roots bilaterally

Channel C: S4 mixed roots bilaterally

The decision to implant an intrathecal device in PtE was made in the middle of the project, after 3 patients had received extradural devices. As described in chapters 4 and 5, it was becoming apparent that detrusor-external sphincter dyssynergia was likely to impair stimulator-driven emptying in some patients, and it was hypothesised that this might be due to simultaneous stimulation of the sensory and motor roots. Because PtE showed considerable DSD on preoperative testing (see Figure 3.4), the flexibilty to stimulate sensory and motor roots separately was considered to be especially important in him. The decision to separate the S3 root was made at operation: the greatest bladder contraction was produced by S3 stimulation bilaterally, so that it was likely that stimulation of these roots alone would be sufficient for bladder emptying. S4 was not separated because it was considerably smaller than S3, and the likelihood of neurapraxia greater. S2 stimulation did not result in significant bladder contraction, so that it was left undisturbed to ensure that reflex erections (which were important to the patient) were preserved.

The method for implantation was as described in the Finetech-Brindley *Notes to Surgeons* (Brindley 1998). In each patient, the procedure and postoperative period were uncomplicated.

In several patients, including those who received SARS rather than SPARS implants, the dimensions of the sacral nerve roots, and the space available for possible future electrode designs was recorded. The results are shown in appendix 2.

Evidence for preservation of sensory and motor function

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Although clinical tests such as the bulbocavernosus and anal skin reflexes are useful for determining the integrity of sensory and motor sacral roots, we studied in particular those reflexes which could be quantified:

i) The volume at which detrusor hyperreflexia occurred, and the maximum rise in bladder pressure that occurred during it (pudendal nerve fibres, S3 most important, S2 and S4 variable) (Brindley *et al.* 1982, Chang & Hou 2000)

ii) The threshold for the pudendo urethral reflex, and its size (afferent limb S2, some S3 and efferent limb S3 and some S2, S4) (Ertekin & Reel 1976, Vodusek *et al.* 1983, Uher & Swash 1998).

iii) The subjective quality of reflex erections (dependent on S2 integrity (Brindley *et al.* 1986, Gasparini *et al.* 1992))

Reflex erections were asessed pre and postoperatively using a questionnaire, which included several visual-analogue scales and is reproduced in appendix 3. Bowel function was assessed by direct questioning as part of the clinical history before and after implantation. Skeletal muscle responses were also measured for stimulation of each channel.

4.3 *Results*

The results of postoperative tests are shown in Tables 4.1 to 4.4 and Figure 4.1.
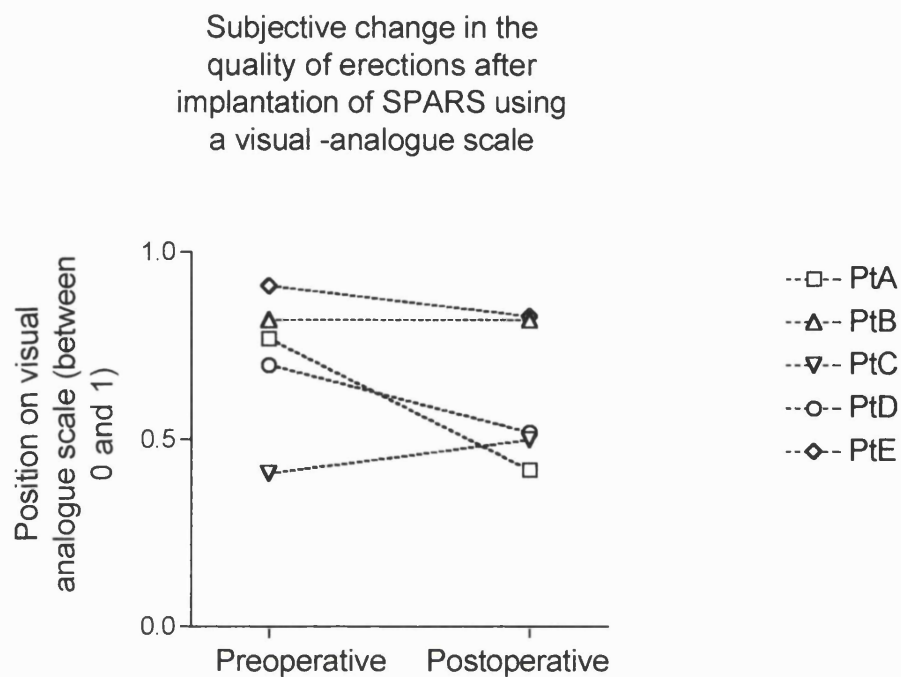
Figure 4.1

Pre and postoperative scores on the visual-analogue scale for quality of erection in the 5 SPARS patients (the full questionnaire is reproduced in appendix 3).

Patient	Pharmacological assistance Pre / Postoperatively?	Frequency of spontaneous erections Pre / Post operatively	Ejaculation Pre / Postoperatively	Significant change in erectile function?
PtA	papaverine / sildenafil	3x a day / 2 x a day	yes / yes (unchanged)	poorer quality erections*
PtB	caverject / caverject	5x a week / 10x a week	no / no	no
PtC	caverject & sildenafil / caverject & sildenafil	daily / daily	occasionally (unchanged)	no
PtE	caverject / caverject	daily / daily	no / no	no
PtD	caverject & sildenafil / caverject & sildenafil	weekly / weekly	no / no	no

* confounding factor: total hip replacement 6 months postop., altering pelvic reflexes

Table 4.1 Erectile function before and after SPARS implantation.

Patient	Time of assessment /months postoperatively	Frequency of bowel emptying Pre / Postoperatively?	Frequency of incontinence Pre / Postoperatively	Significant change?
PtA	1 year	every 2 days / every day	none / none	increased anal sphincter tone (resolved at 2 years)
PtB	2 years	every 2 days / every 3 days	2 times a year / 15 times a year	slightly reduced frequency, increased incontinence
PtC	1 year	every 1-2 days	none / none	no
PtD	6 months	every day / every day	none / none	no
PtE	6 months	every 1-2 days / every 1-2 days	none / none	slightly less constipation after SPARS

Table 4.2 Bowel function before and after SPARS implantation.

Patient	Preoperative threshold for the pudendo-urethral reflex /mA	Postoperative threshold for the pudendo-urethral reflex /mA	Maximum size of the pudendo-urethral reflex Preoperatively /cm water	Maximum size of the pudendo-urethral reflex Postoperatively /cm water	Volume at first detrusor hyperreflexia Preoperatively /ml	Volume at first detrusor hyperreflexia Postoperatively /ml	Maximum detrusor contraction on 'firing off' Preop. /cm water	Maximum detrusor contraction on 'firing off' Postop. /cm water
PtA	40 (pudendo-anal)**	64 (pudendo-anal)	No P$_{ur}$ investigations	19	490	No detrusor hyperreflexia	75, 80, 45	No detrusor hyperreflexia
PtB	40 (pudendo-anal)**	45	No P$_{ur}$ investigations	23	133,155,171	216, 290, 92 (3 days)*	132, 108, 112	96, 97, 78 (3 days)*
PtC	20	45	72	58	181, 195, 210	195, 240, 100 (3 days)*	51, 27, 71	57, 29, 32 (3 days)*
PtD	13	30	>140	14	146, 170, 105 (2 days)*	108,120, 175 (2 days)*	69, 69, 66 (2 days)*	77, 76, 72 (2 days)*
PtE	22	60	>190	10	135, 145, 95	250, >500, >500 (variable) (2 days)*	138, 106, 88	78, 20,0 (2 days)*

*Where '2 days' or '3 days' is stated, figures represent the first fills from separate days, to give an indication of the variability between tests.

** These patients were not tested with the microtip pressure transducer catheter system before SPARS implantation. However, the threshold for the pudendo-anal reflex is likely to be similar to that for the pudendo-urethral.

Table 4.3 The characteristics of the pre and postoperative detrusor hyperreflexia and the pudendo-urethral reflex in five SPARS patients

Patient	S2 response	S34 response
PtA	R=L plantarflexion	R=L toe flexion
PtD	R>L toe flexion & R>L plantarflexion	R=L toe flexion, abdominal spasm
PtB	L=R plantarflexion, R=L gluteal contraction	R=L toe flexion
PtC	L=R plantarflexion, R gluteal contraction	R=L toe flexion

Patient	S3 anterior response	S3 posterior respoonse	S4 mixed response
PtE	marked abdominal spasm variable R & L toe, knee movement	R>L toe flexion	L toe & plantarflexion

L = left   R = right

Table 4.4 Skeletal muscle responses using the SPARS stimulator.

In each patient the results of the tests used to determine sacral root integrity were as follows:

PtA (2 channel extradural implant): Preoperatively, this patient had DH at a volume of between 400 and 500ml, with maximum detrusor pressure of 50-70cm water. This usually resulted in reflex voiding of over 50% of his bladder volume, implying that he did not have severe DSD.

Postoperatively, it was not possible to reliably produce DH, even using a provocation technique, suggesting a degree of root damage - although his pudendo-urethral reflex was intact and good detrusor pressure rises were produced by stimulation. This situation was unchanged after two years. Spontaneous erections were unchanged, but reflex erections (which depend on afferent signals from the penile skin) impaired compared to preoperatively. The skeletal muscle responses did not suggest severe efferent nerve damage. *Impression: some degree of damage to the sensory sacral roots.*

PtB (2 channel extradural implant): Preoperatively, DH with DSD at low bladder volumes.

This situation was essentially unchanged postoperatively, with an intact pudendo-urethral reflex and unchanged reflex erections. *Impression: no evidence of marked root damage.*

PtC (2 channel extradural implant): Preoperatively, DH with a small degree of DSD. Similar postoperatively, with preservation of reflex erections and intact pudendo-urethral reflex. *Impression: no evidence of marked root damage.*

PtD (2 channel extradural implant): Preoperatively, DH with moderate DSD. Similar postoperatively, with intact pudendo-urethral reflex. Anal and urethral sphincter contraction on low-level stimulation but *no* detrusor contraction with intense stimulation of either channel. It was not easy to explain these findings straightforwardly, but some conclusions could be drawn:

- the S34 and S2 electrodes were sited near *either* S2, S3 or S4 on *at least* one side, because low-level stimulation of each channel resulted in sphincter contraction. However, this does not necessarily mean that the S34 electrodes are situated next to the S34 roots.

- intraoperatively, only S3 and S4 stimulation resulted in rises in bladder pressure. DH and DSD were still present postoperatively, implying that some motor pathways in the S3 or S4 roots were intact.

Because DH was still present, neurapraxia was not an adequate explanation for these results. The only explanation that fitted was that the S34 channel was intact electrically but malpositioned – either closer to the S2 roots than the S34 roots, or sufficiently distant from each root so that large, but not small-diameter fibres could be stimulated. However, the position of the electrodes was not abnormal on the post-operative antero-posterior radiograph. *Impression: Probable malposition of S34 electrodes*

PtE (3 channel intrathecal implant): Preoperatively, DH with marked DSD at low bladder volumes. Postoperatively reflex erections were preserved (the S2 root was left

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undisturbed at operation), but there was severe neurapraxia of the S3 anterior root. DH

not present reproducibly postoperatively. The results of stimulation immmediately post

implantation were as follows:

S3 anterior roots: little function (probable severe neurapraxia), with <10cm water

rise in intavesical pressure and a small sphincter response on intense stimulation.

S3 posterior roots: virtually no rise in detrusor pressure on intense stimulation.

Marked abdominal wall muscle and pelvic muscle spasm at low level stimulation,

with large urethral and anal sphincter contractions. These were probably reflex.

S4 mixed roots: intravesical pressure rise of >50cm water on intense stimulation.

Anal and urethral sphincter contractions on low level stimulation.

Impression: Nearly complete S3 anterior root neurapraxia. Reduced (or absent) DH,

with intact pudendo-urethral reflex and erections may be due to a) S3anterior root

neurapraxia or b) Partial sensory root damage (either S3 or S4).

4.4 *Discussion*

Although there was evidence of root damage in PtA, and electrode malposition in PtD,

the most severe root damage occurred in PtE (who received an intrathecal implant). This

is not a surprising result, as the nerves are more fragile where they lie intrathecally, and

the separation procedure always involves a degree of traction. This damage was probably

neurapraxia (the nerve was intact at operation) and was expected to recover.

In three patients, DH was still present postoperatively, and low level stimulation of the S2 and S34 channels produced anal and urethral sphincter contractions. It was in these patients that the initial experiments with neuromodulation (as described in chapter 5) were performed.

In four patients (all except PtD), a detrusor pressure pressure >50cm water could be generated by intense stimulation of the sacral roots. In each, intermittent stimulation programs for bladder voiding were tried, and the results described in chapter 6.

A rise in the threshold for the pudendo-urethral reflex, and the reduction in the maximum size of the urethral contraction, occurred in each patient. This could be due to partial sensory or motor root neurapraxia; it may be that the DPN reflex is the first to be affected detectably by partial root damage. An alternative explanation is a change in the reflex pathways in the spinal cord as a result of SPARS implantation or use, but this is less likely; in all patients except PtA, the tests were performed several months after implantation, and when the stimulator was *not* being used regularly.

Reflex erections were preserved in each patient, suggesting that the S2 afferent and efferent roots were intact. This is expected: the S2 root was always larger than S3 or S4, and was trapped next to its own electrode, or in the case of PtE left untouched. Thus, one of the primary aims of this project was achieved. The questionnaire used has not been validated, which is a weakness of the study, but existing scales of erectile function do not apply specifically to spinal cord injury and were considered insufficiently sensitive (and

partly irrelevant) to SCI patients. Considerable use was made of visual analogue scales

(see appendix 3) in order to reduce bias.

As expected, bowel function was unaffected by the implants, except for the transient

rise in anal sphincter tone described by PtA.

5. Neuromodulation Using a Sacral Posterior and Anterior Root Stimulator.

5.1 *Aims*

The first aim of this section of the project was to establish that neuromodulation was effective in the laboratory, the first step being the determination of optimum stimulation parameters for each channel. Data from these experiments might also provide valuable information about which nerve roots are best used for neuromodulation in humans.

A further aim was to compare the efficacy of DPN and SPARS stimulation in increasing bladder capacity, and to establish whether the nature of the neuromodulatory effect was the same. This could be studied using both continuous and conditional stimulation, and many of the same methods of analysis that were used in chapter 3.

Next, it was necessary to establish the efficacy of long-term neuromodulation using the SPARS. Because components of the Finetech-Brindley device can be replaced (ideally without cutting wires: the *Craggs* connectors in the implants can be unplugged after a simple manoeuvre to remove the silicone glue), they can also be upgraded, and it was envisaged that patients who responded to long-term neuromodulation could eventually be fitted with a fully implanted device capable of long-term continous low-level stimulation.

Programs for voiding are discussed in the next chapter (6).

5.2 Methods

The initial postoperative testing is described in chapter 4. Once the presence of detrusor

hyperreflexia was confirmed, and at least a month after implantation (to allow for the

behaviour of the detrusor to stabilise, and the surgical wounds to heal), initial

experiments with neuromodulation were performed in those patients who had

reproducible detrusor hyperreflexia (PtB, PtC and PtE)

Provocation experiments: To set stimulation parameters, a provocation technique was

used. The bladder capacity was determined by an initial cystometrogram, and the bladder

then filled to within 100ml of this control volume. As in previous studies (McFarlane *et*

al. 1997), repeated provocations with 60ml room temperature normal saline were used to

provoke a hyperreflexic contraction. Although the instillation always produced a transient

rise in intravesical pressure, when the rise exceeded 15cm water it almost always

heralded the start of DH. The provocations were repeated until DH occurred; it was then

either observed (control provocations), or suppressed with neuromodulation. Firing off

often occurred with the provoked contractions, but if not (or if the volume voided was

low), 60ml saline was aspirated from the bladder after 1 min. An example of the

technique is shown in Figure 5.1.

In each case, control and neuromodulation provocations were interleaved. However, in each patient it was found that the bladder capacity (and, possibly because of this, the response to neuromodulation) changed after repeated provocations. For this reason, to minimise changes due to repeated fills, control provocations were on several days were not performed after *every* provocation with neuromodulation; in all cases, however, at least one out of every four provocations was a control. At least three minutes of recovery was allowed between provocations.

It was possible to vary 4 parameters for each suppressed contraction: stimulation channel (S2, S34 or both), intensity (set as an integer from 1 to 4 on the Fintech digital control box), pulse width and pulse frequency (Figure 5.2). It would have been impossible to find the optimum for each parameter without many days testing, so that it was necessary to fix some and vary others:

-the frequency of stimulation was fixed at 15Hz. This is based on previous work in both animals (Lindström *et al.* 1983) and humans (Shah *et al.* 1999).

-the intensity of stimulation was fixed at 1. In each patient, this was sufficient to produce skeletal muscle contraction at low pulse widths. Having only 4 possible intensity settings made it impossible to perform meaningful experiments by varying this parameter.

Figure 5.1
An example of the method used to derive the threshold pulse width for neuromodulation for each channel.

amplitude

1

1
2
3
4

4 amplitude levels,
but the box is
designed for bladder
emptying. Only 1
and possibly 2
usable for
neuromodulation

frequency

2

2
3
↓
105

Frequency (cycles per
second) variable as an
integer from 2 to 105

pulse width

3

(4)
8
↓
800

Continuously
variable from 4 (8
on amplitude 1) to
800 μs in steps of 4

channel

4

A = S34
B = S2
A, B or both (with
different frequency,
amplitude, pulse width)
channels may be
stimulated.

Figure 5.2

The parameters that can be varied in the Finetech-Brindley digital control box.

-changes in pulse width were used as the main way of varying stimulation intensity. Assuming that the impedance at the electrode did not change significantly during stimulation, charge delivered was proportional to pulse width. This is not exactly the same as varying stimulation current, but at the parameters we used, has a similar physiological effect (Bostock 1983).

-each series of experiments using different pulse widths was performed with S2 and S34 channels separately, enabling a comparison of the efficacy of neuromodulation via each.

The area under one minute of each suppressed hyperreflexic contraction was measured for each successful provocation, and the results plotted against pulse width for each channel. Where the results of neuromodulation were equivocal (for instance at near the threshold pulse width for neuromodulation), suppression using the same parameter was attempted up to 3 times. This experiment was repeated on a separate day for each patient, so that there were 6 such graphs. In all cases, it was possible to fit the data to a Boltzmann sigmoidal curve, and thereby derive a pulse width for each channel that gave 50% of the maximum neuromodulatory effect; this was defined as the *threshold pulse width for neuromodulation*.

Conditional and continuous neuromodulation in the laboratory. In these tests, the S2 and S34 channels were stimulated at between 2 and 5 times the thresholds derived from the provocation experiments. This never resulted in bladder contraction, or inconvenient skeletal muscle side effects. As in the preoperative experiments with DPN stimulation,

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two control fills were followed by two or three fills with continuous neuromodulation for each patient.

The parameters measured in chapter 3 for the bladder pressure during conditional neuromodulation (time to peak of contraction, decay to within 50% and 10% of baseline, and time to second peak) were measured in exactly the same way for conditional neuromodulation via the SPARS in PtC and PtD.

If possible, the effect of varying the stimulation pulse width, and of single channel and combined stimulation were examined. However, as before, it was difficult to derive reliable quantitative data about increases in bladder capacity for each group of settings because of the carry-over effect that occurs during multiple fills.

Neuromodulation at home. In the two patients who responded well to conditional neuromodulation in the laboratory, continuous neuromodulation was used at home over periods lasting between 3 days and 3 weeks. The stimulation level was set at between 3 and 6 times the threshold for neuromodulation on each channel, to allow for some change in transmitter coil position. Bladder capacity was estimated as follows:

> PtC: unable to wear a conveen. Bladder volume was documented at each self-catheterisation. If firing off occurred before catheterisation, an attempt was made to estimate its volume. Bladder capacity could be inferred from the maximum bladder volumes achieved without firing off.

PtD: was able to wear a conveen, and documented the time of any reflex voiding, and its volume. He was asked to self-catheterise as soon as possible after this.

Neuromodulation and the urethral sphincter. Urethral sphincter traces from continuous stimulation in were recorded in all except PtA. They were compared with the pudendo-urethral reflex in PtE and PtD; in PtB and PtC this comparison was impossible because there were not good preoperative recordings of the pudendo-urethral reflex with the microtip system.

5.3 Results

Postoperative tests using provoked contractions. In each of the three patients, it was possible to determine thresholds for suppression of provoked contractions using each channel of the stimulator. A sample series of provocations (with controls) is shown in Figure 5.1, and the graphs in Figure 5.3 show the method for determination of threshold in each case.

There was considerable variation between days 1 and 2 in the calculated thresholds for neuromodulation (Table 5.1). In four out of six tests, the threshold pulse width for suppression of provoked contractions was lower with the S2 channel, and the mean threshold for the 2 days testing was lower with S2 in 2 out of 3 patients.

Patient & root	Threshold pulse width for NM /μs day1 / day 2 (mean)	Threshold. for urethral sphincter /μs*	Urethral sphincter pressure rise at mean threshold for NM /cm H_2O	Threshold. for anal sphincter /μs*	Anal sphincter pressure rise at mean threshold for NM /cm H_2O	Threshold for NM as a multiple of urethral sphincter threshold	Threshold for NM as a multiple of anal sphincter threshold
PtB							
S2	16.3 / 124 (**70**)	14	152	15	92	**5**	**4.7**
S34	33 / 62 (47)	6.5	27	7	95	**7.2**	**6.7**
PtC							
S2	24 / 56 (**40**)	6.5	68	7	170	**6.1**	**5.7**
S34	37 / 54 (**46**)	7	79	8	195	**6.6**	**5.8**
PtD							
S2	8 / 9.3 (**8.6**)	7	9	7	8	**1.2**	**1.2**
S34	26 / 30 (**28**)	7	>170	7	110	**4**	**4**

* = figures derived by extrapolation and therefore not precise   NM = neuromodulation

Table 5.1   Thresholds for neuromodulation using S2 and S34 channels, and associated urethral and anal sphincter pressure rises.
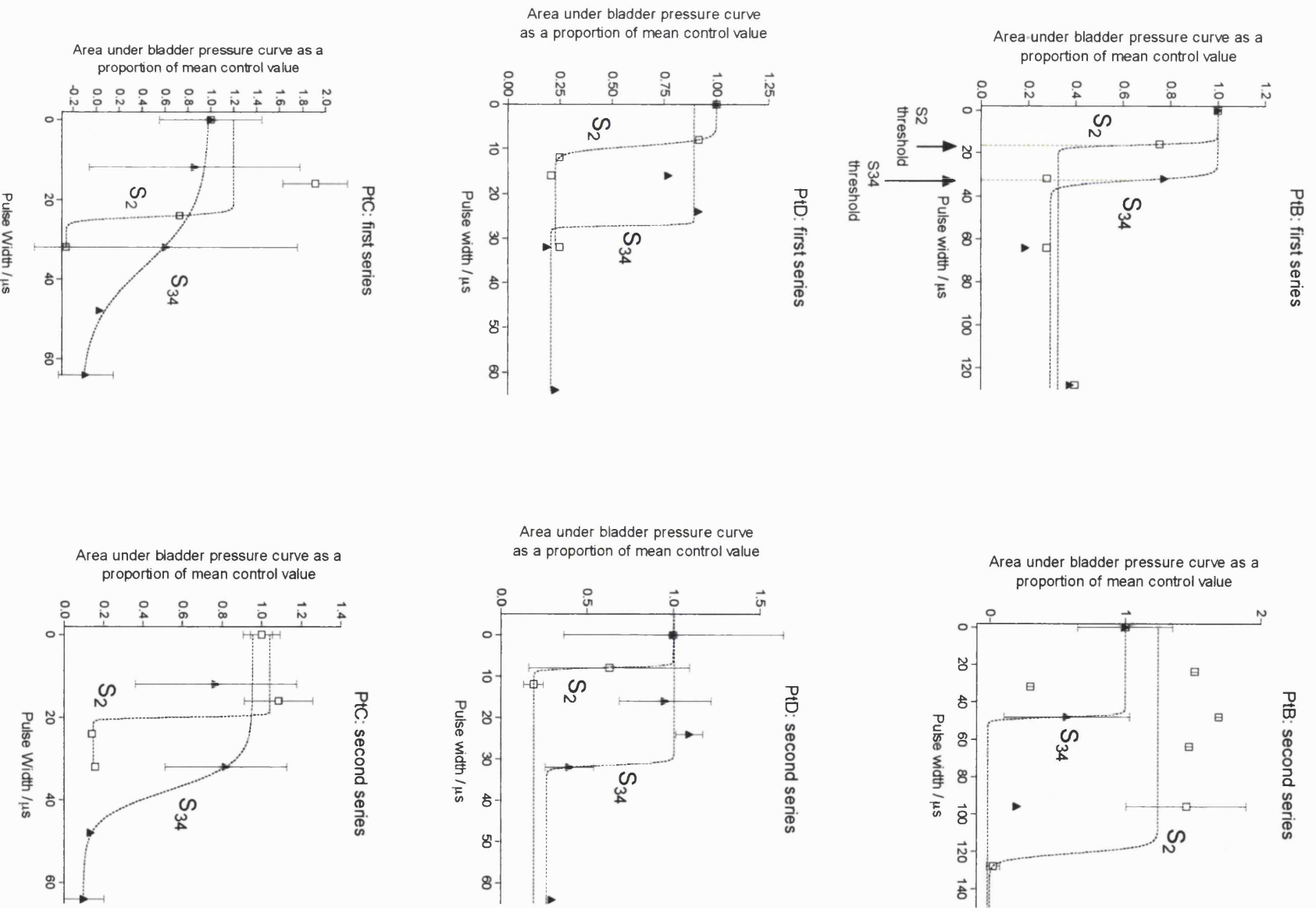
Figure 5.3
Calculation of the threshold pulse width for neuromodulation in 3 patients.

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The threshold for neuromodulation was also expressed as a multiple of the threshold for

urethral or anal sphincter contraction. Adjusted in this way, the mean S2 threshold is

lower than the mean S34 threshold in each patient (Table 5.1). Anal and urethral

sphincter pressure rises *at* the threshold for neuromodulation were not consistently higher

with S2 or S34.

Slow fill cystometry with neuromodulation.

In each patient, neuromodulation increased bladder capacity. PtB has high pressure

detrusor hyperreflexia, and neuromodulation on three occasions has increased his

capacity by no more than 35%; indeed, on two out of three tests it had little effect.

Results in PtC and PtD are better; the results are shown in Figure 5.4, together with the

equivalent results of properative testing using DPN stimulation. In both patients, bladder

capacity was more than doubled using neuromodulation via the SPARS.

The bladder compliance showed increases with neuromodulation in each patient

preoperatively (Figure 5.5). Postoperatively, it was normal (defined as >40ml/cm water

(Abrams 1997)) in PtC (apart from one result – the second control fill - which was not

replicated subsequently) and PtD, and increased compared to preoperatively in PtB. No

definite effect of neuromodulation on compliace was seen postoperatively, but these

results are prone to considerable error, as rises in intravesical pressure were almost

always <7cm water during fills.
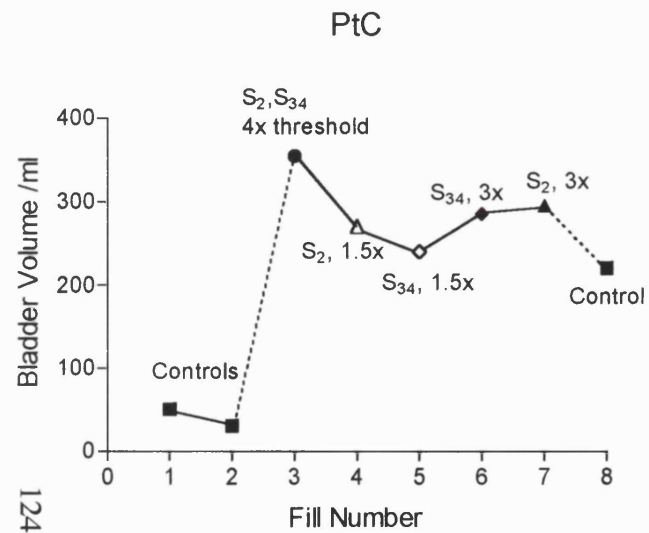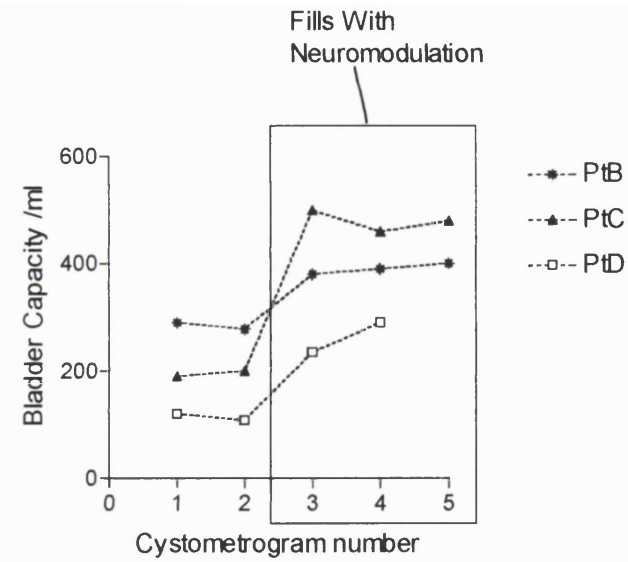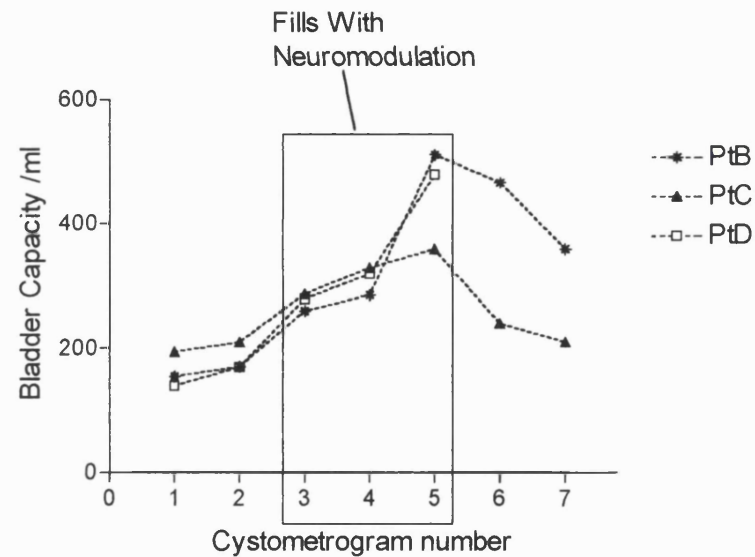
Figure 5.4
Preoperative (top left) and postoperative (top right) bladder capacity with DPN and SPARS neuromodulation respectively in the three patients with persisting DH after implantation. The graph on the bottom left illustrates the effect of changing the pulse width on the bladder volumes achieved in PtC. A similar graph for PtD is shown in Figure 5.6.
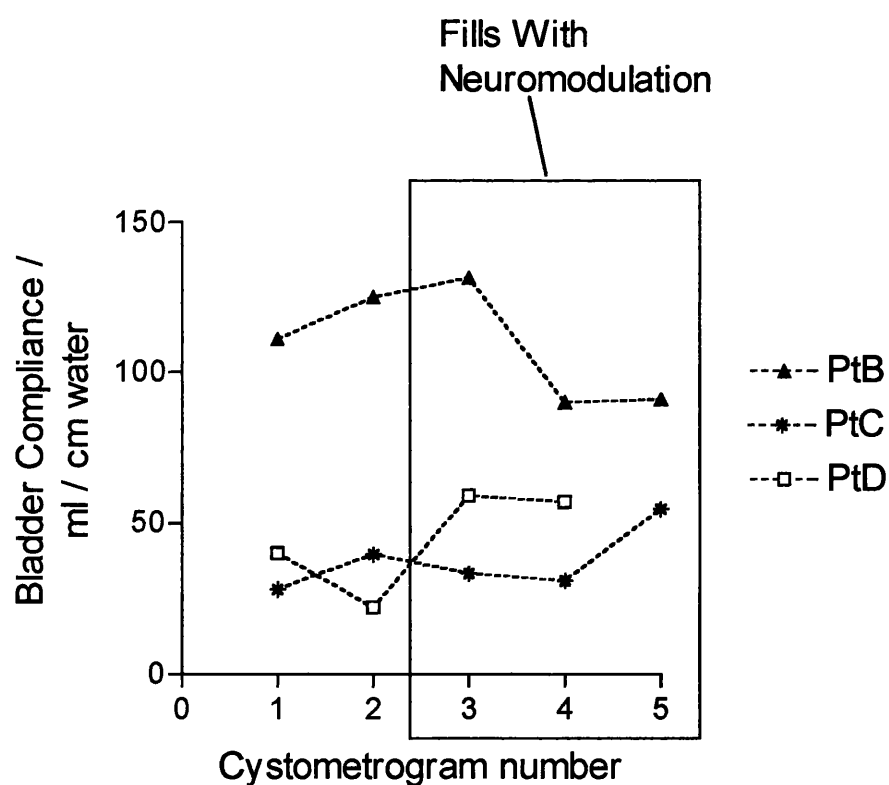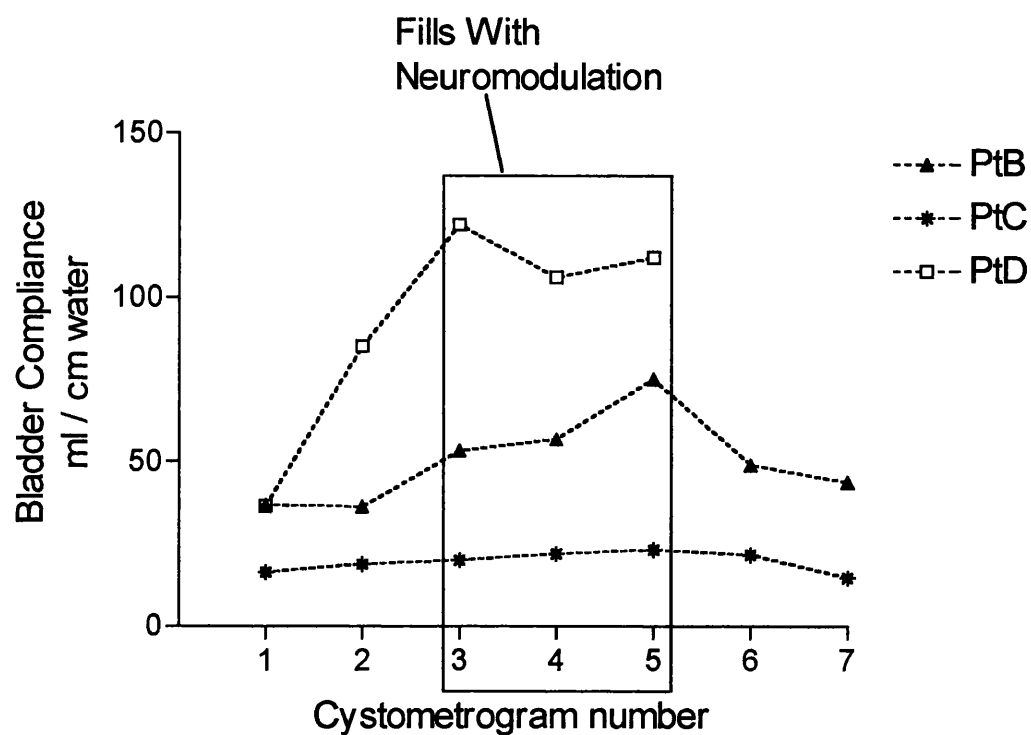
Figure 5.5

Preoperative (top) and postoperative (bottom) compliance with DPN and SPARS neuromodulation respectively in the three patients with persisting DH after implantation.

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Conditional neuromodulation.

This was highly effective in PtC and PtD; in PtB, it was not possible to suppress detrusor hyperreflexia conditionally, consistent with the modest increases in bladder capacity seen with continuous stimulation. Although the effects of conditional and continuous stimulation were not compared statistically (to do so while eliminating the effects of carry over and order would have required many day's testing), fills using each technique were alternated (Figure 5.6), and as in the preoperative tests, the conditional mode appeared to be as least as effective as the continuous.

The times to peak bladder pressure and its subsequent fall lay well within the range observed with dorsal penile nerve stimulation (Figure 5.7), suggesting a common mechanism.

Long term neuromodulation.

PtC: Neuromodulation was used intermittently at home for a period of four months. He was not able to use it continuously for two reasons. Firstly, affixing the transmitter to the skin resulted in transient erythema after aproximately two weeks, making it necessary to 'rest' the receiver site. Secondly, he often used an indwelling catheter when urine output was likely to be high, or self-catheterisation difficult (as he had done before implantation of the SPARS).

The median volume at self-catheterisation (excluding volume fired off) was 100ml in the control period, and 250ml in the continuous, on/off and oxybutinin periods. The difference between control and all other periods was highly significant (p<0.0001, Mann-
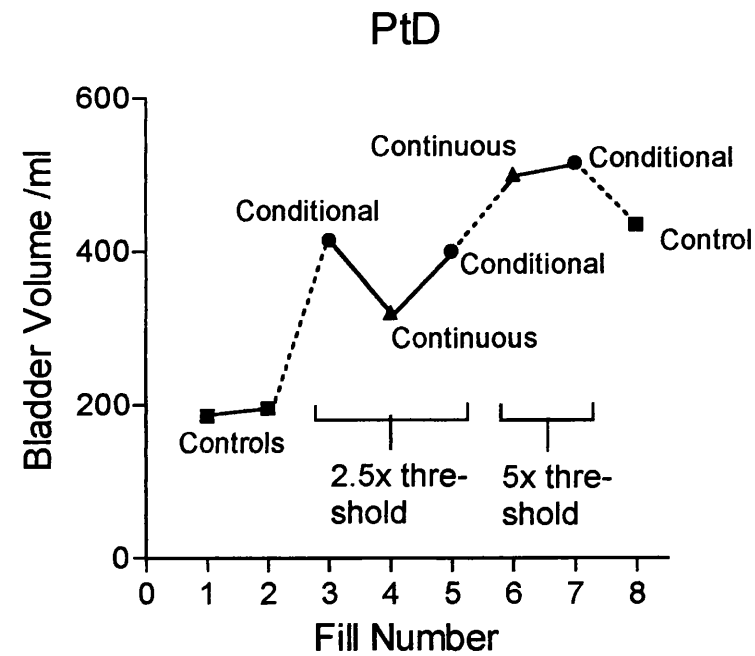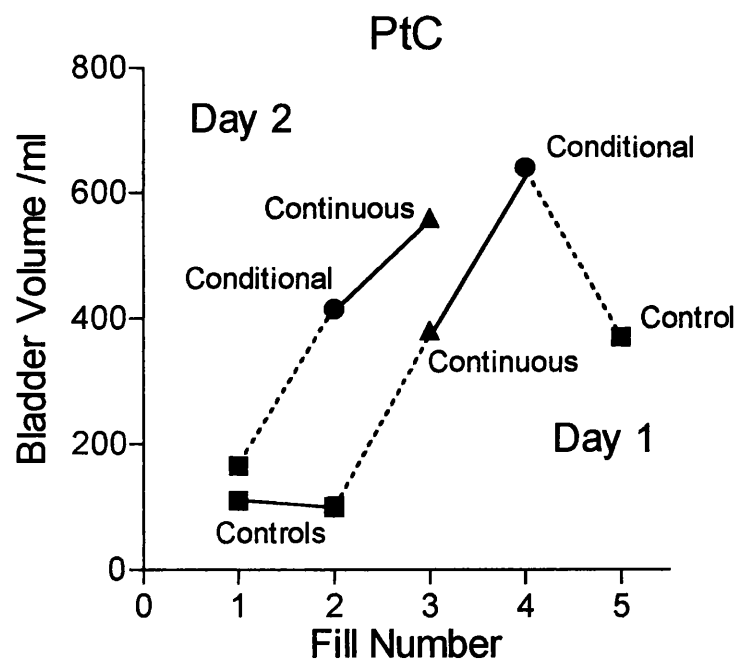
Figure 5.6
The results of alternating continuous and conditional fills in PtC and PtD, using stimulation of both channels of the SPARS stimulator for neuromodulation.
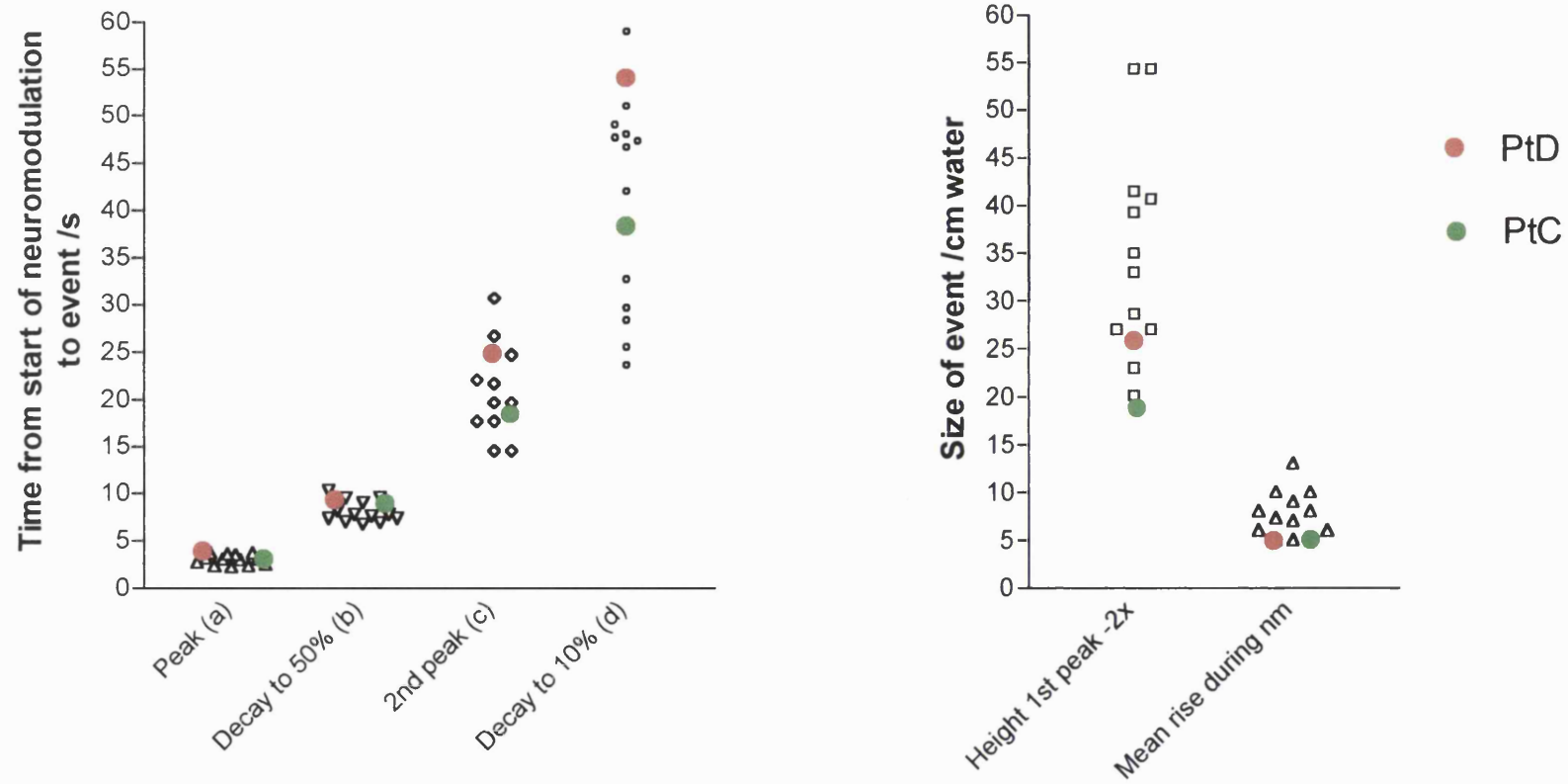
Figure 5.7
The parameters (the derivation of which is shown in figure 3.3) of the suppressed contractions during conditional neuromodulation in PtC and PtD using the SPARS, superimposed on the results derived using DPN neuromodulation in 13 patients (Figures 3.7 and 3.8).

Whitney U test) in each case. There was not a significant difference between continuous, on/off and oxybutinin periods (Figure 5.8 and appendix 5).

Incontinence was subjectively improved with long-term neuromodulation, but, as shown in Figure 5.8, was still present most days (although stress incontinence was improved with neuromodulation, probably because of persistent urethral sphincter contraction). Volumes with the 50s on/ 50s off program were no worse than with the continuous pattern, and indeed PtD felt strongly that this pattern was more effective than continuous stimulation. He preferred neuromodulation to oxybutinin.

PtD: In contrast to the findings in the laboratory (which were reproducible), there was no convincing evidence that neuromodulation increased bladder capacity (Figure 5.9 and appendix 6).

Neuromodulation and the urethral sphincter. Urethral pressure traces from each patient are shown in Figure 5.10. In PtC and PtB, there was a sustained increase in the urethral sphincter pressure during the first 5 minutes of neuromodulation, in contrast to the results of dorsal penile nerve stimulation. In PtE and PtD there was a more rapid and complete decay.
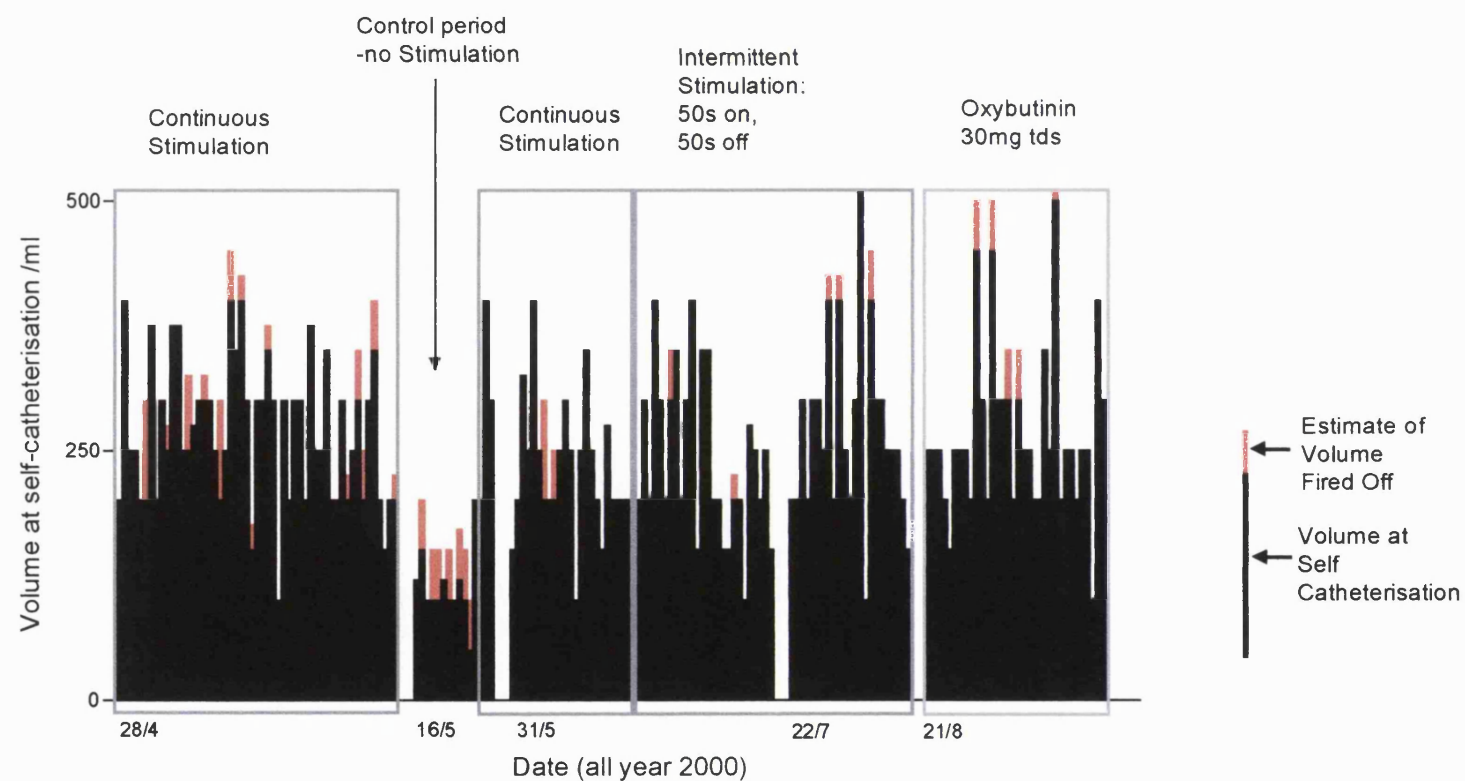
Figure 5.8
Volumes at self catheterisation (black) and estimated volume fired off (red) in PtC during several periods when the SPARS device was used for neuromodulation. The data is listed numerically in appendix 5.
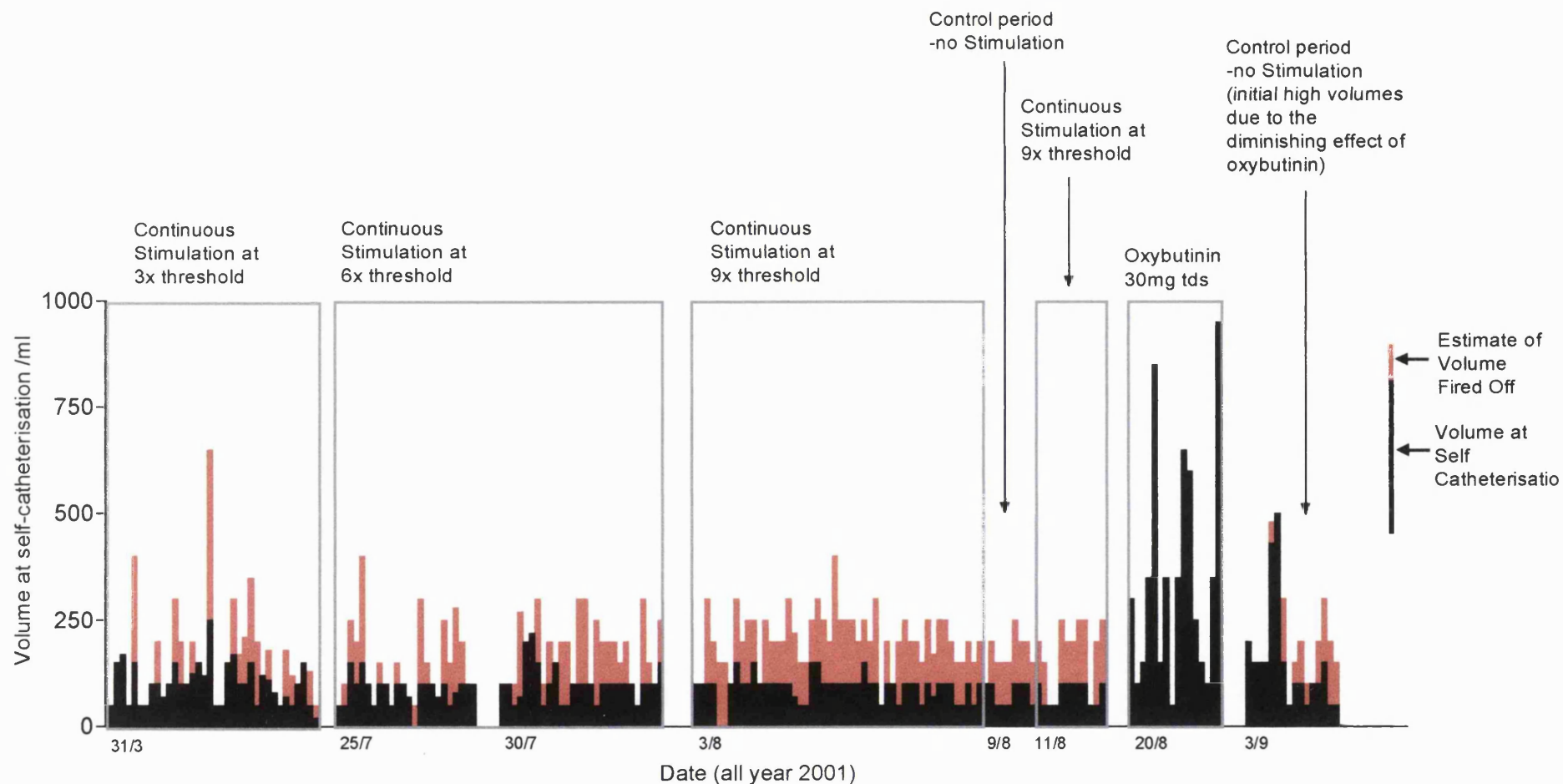
Figure 5.9
Volumes at self catheterisation (black) and volume fired off (red) in PtD during several periods when the SPARS device was used for neuromodulation. The stimulation intensity for neuromodulation is given as a multiple of the thresholds derived using provocations (see figure 5.3). This data is presented in numerical form in appendix 6.

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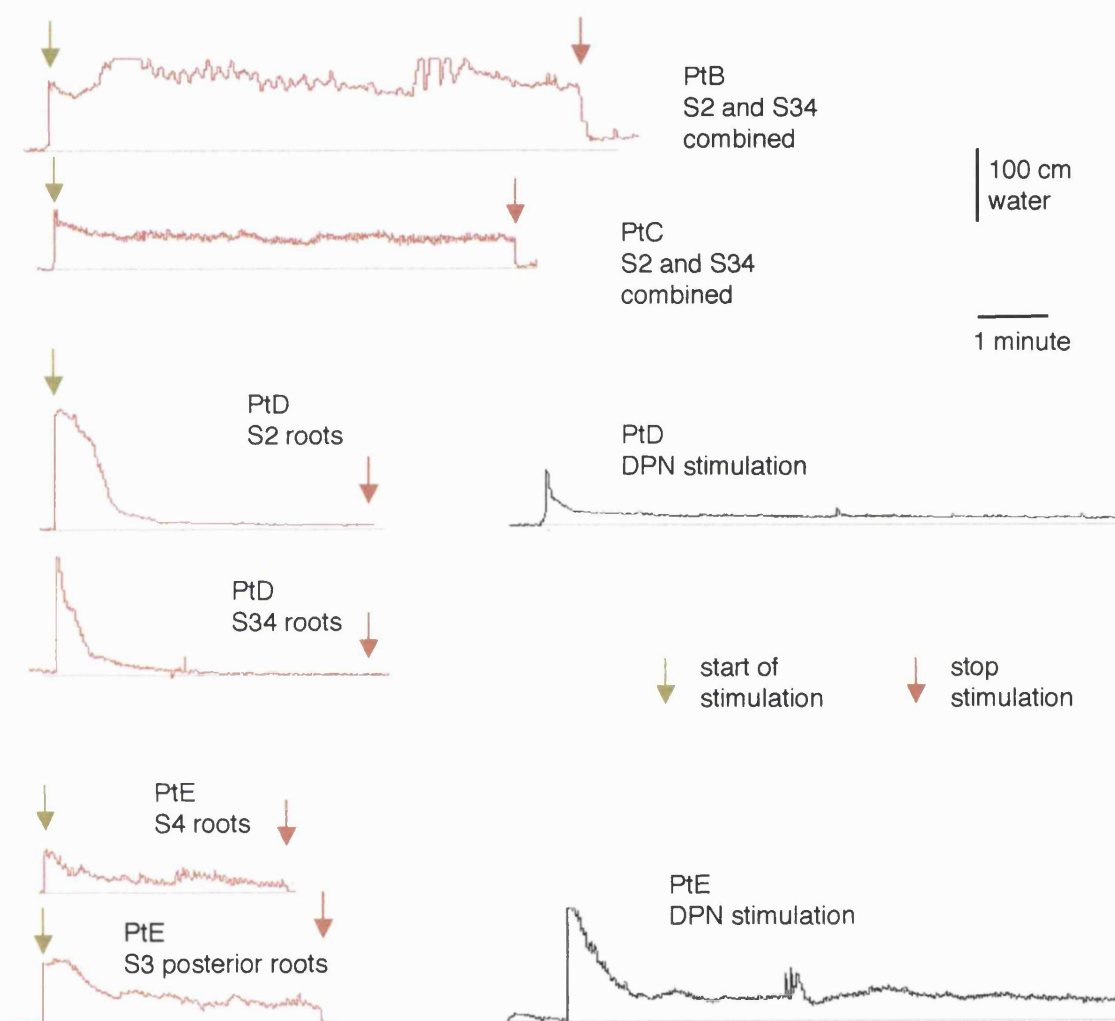
Figure 5.10
Urethral sphincter responses to sacral root stimulation and DPN neuromodulation in 4 patients.

5.4 Discussion

Detrusor hyperreflexia could be reliably provoked many times in all 3 patients, with a gap of only three minutes between episodes of neuromodulation. That the residual effect of neuromodulation after several minutes was not sufficient to prevent a hyperreflexic contraction contrasts with the persistent effects seen during repeated slow fills with continuous neuromodulation, where the effects on bladder volume seem to persist for several hours (Shah et al. 1998). The likely explanation is that the inhibition of the detrusor reflex gradually diminishes: after 3 minutes it can be overcome by an intense stimulus (such as the rapid instillation of 60ml of saline), but a smaller inhibition can influence the threshold for detrusor hyperreflexia during slow bladder filling. The aim of interleaving of provocations with and without neuromodulation during this study was to minimise the influence of such carry over effects. In all three patients, we found that the area under the detrusor pressure curve for control provocations was not markedly affected by preceding neuromodulation.

The variability in both bladder capacities and the effect of neuromodulation between patients seen in chapter 3 and elsewhere (Vodusek et al. 1986, Wheeler, J. S. et al. 1992, Prévinaire et al. 1996) means that any attempt to compare the efficacy of neuromodulation via different sacral roots should either involve large numbers of patients, or a method where different roots may be stimulated in the same patient. Although the current series consisted of only three patients, it presented a valuable opportunity for the latter. Provocation of unstable contractions is quick and reproducible

(McFarlane *et al.* 1997, Shah *et al.* 1998), allowing the evaluation of a large number of parameter changes during one day's testing.

Although the results of each day's testing allowed calculation of threshold pulse widths, agreement *between* the 2 days was poor in PtB and only fair in PtC. PtB has never had marked increases in bladder capacity with neuromodulation via the SPARS, implying that the effect of sacral root stimulation is weak in him, and this may be reflected in the variability of the results with provocation. In PtC and PtD, S2 stimulation produced neuromodulation at a lower (3 out of 4 tests) or similar (one test) threshold compared to S34, and normalisation of the neuromodulation threshold to the threshold for anal and urethral sphincter contraction did not markedly affect the findings. In PtD, however, where the difference is largest, there is certainly a degree of neurapraxia of the S34 roots, because bladder contractions cannot be achieved. It is therefore likely that there is some neurapraxia of the S34 fibres responsible for neuromodulation, which may account for some of the difference between S2 and S34. This, and other potential biases means that the only reliable conclusion is that the S2 root *could* be used for effective neuromodulation in all three patients.

It is likely that S3 was chosen for the *Interstim* device (and for a previous trials of long-term stimulation in spinal cord injury) because it produces less skeletal muscle contraction than S2 (Schmidt 1986). In neurologically intact patients this may make S3 or S4 preferable, but none of the SCI patients in this study experienced inconvenient skeletal muscle contractions with either S2 or S34 stimulation. Also, one might expect chronic stimulation of the glutei to have a beneficial effect on muscle bulk.

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Neuromodulation and bladder capacity: Neuromodulation via the SPARS during slow filling markedly increased bladder capacity in two out of three patients (PtC and PtD), and was of similar efficacy to preoperative DPN stimulation. There is no simple explanation for the loss of efficacy of neuromodulation in PtB, especially since contraction of his anal and urethral sphincters (S2 and S34 channels) and bladder (S34 channel) could be achieved easily.

Conditional stimulation in the two patients who did respond well to continuous stimulation was highly effective, consistent with the finding in chapter 3 that conditional stimulation via the DPN is probably at least as effective as continuous. It was also striking that the parameters of the suppressed bladder contraction curve lay well within the values observed with DPN stimulation; statistical analysis was impossible because of the small numbers, but the findings do suggest a common mechanism.

In previous studies with implanted stimulators for long-term neuromodulation in SCI (Ishigooka *et al.* 1998, Chartier-Kastler *et al.* 2000b), cystometry was performed at predefined intervals after implantation to assess the effect of neuromodulation. Especially with the filling rates used (50ml/min or greater), this does not necessarily reflect the bladder capacity that the patient experiences at home. Also, it was not applicable in the case of PtC, as he used stimulation for variable periods of 4 days to 2 weeks. Instead, volume at self catheterisation was the primary outcome variable. Recording the volume leaked with a pad and adding this to catheterised volume would have increased the complexity of the measurements and is not necessarily informative: if the patient does not

self catheterise immediately after 'firing off', bladder capacity will be overestimated. We considered it more reliable (and easier for the patient) to record bladder volumes at self catheterisation for a long period, and to infer the bladder capacity from the *maximum* volumes achieved without incontinence. Measuring frequency of self-catheterisation is unreliable, as the decision to catheterise is a subjective one, and patients may alter their fluid intake according to their bladder management.

The current method for long term stimulation is not ideal: it is necessary to fix the transmitter coils to the skin over the subcutaneous receiver for all but the first 30 to 60 minutes after bladder emptying. However, PtC used the device intermittently at home over a period of four months, and the results show a marked increase in bladder capacity. When stimulation is stopped, this returns in less than a day to a much smaller baseline capacity. The effect of neuromodulation was comparable with oxybutinin, although PtC stated that incontinence on filling past bladder capacity was generally of larger volume with neuromodulation – when the bladder 'escapes' from electrical suppression, it contracts at close to full force. We did not find that the effect of neuromodulation diminished with time, or that there was a need to increase the stimulation parameters.

The lack of efficacy of neuromodulation in PtD is puzzling, given the good results obtained in the laboratory. In spite of repeated checks of transmitter coil positioning and the electrical integrity of the implant, there were neither subjective nor objective increases in capacity.

In total, two out of three patients failed to respond to continuous stimulation. As described in the introduction (section 1.11), other groups have had mixed results, with 40 to 75% of patients responding (defined as a significant increase in bladder capacity) to long term sacral nerve stimulation. The current results suggest that *long term* neuromodulation is more difficult to achieve than suppression of provoked contractions or end-fill hyperreflexia in the laboratory.

There are several possible explanations for the discrepancy in short and long term results. Firstly, it may be that the response to neuromodulation habituates, just as the reflex urethral sphincter contraction does during continuous neuromodulation. In this case suppression of provoked contractions would be the most powerful effect, and long term continuous stimulation the weakest, which correlates with the observations in this chapter.

Secondly, the environment during home use may be more provocative, with changes in posture occurring more frequently, such that the stimulus for hyperreflexia cannot be suppressed by neuromodulation. Lastly, coil malposition may be more likely during home use, and it is difficult to rule out changes at the electrode / nerve interface, although Brindley found that stimulation parameters rarely changed over many years (Brindley 1994). We attempted to reduce the effects of coil malposition by setting stimulation parameters at several times the threshold for urethral sphincter contraction (thus allowing moderate malposition), and stimulating all available channels. The position was checked in PtC and PtD when they attended the laboratory, and was almost always found to be adequate.

Bladder compliance. Bladder compliance is an important parameter to measure and has

important implications for the probability of vesicoureteric reflux (van Kerrebroeck *et al.*

1993b). However, its measurement is problematical in detrusor hyperreflexia, and

especially during conditional neuromodulation. The problem is in defining the end-point:

there are often relatively large rises in intravesical pressure in the last minute of filling

before the defined end point (a rise in intravesical pressure of >35cm water or firing off).

Defining the *start* of a hyperreflexic contraction, as opposed to end-fill poor compliance,

is difficult and a subjective judgement. For this reason, figures for compliance are

presented only once in the current work and should be interpreted with caution.

The urethral sphincter. It is notable that the two patients in whom the urethral sphincter

pressure rise was relatively sustained during continuous neuromodulation are those in

whom there is least evidence for postoperative root damage (PtC and PtB). The decay

seen in PtE and PtD is more similar to that seen with the DPN reflex, and it may be that

low-level stimulation is activating mainly *afferent* pathways in these patients; the

efferent roots may have a higher threshold for stimulation or may have been partly

damaged. That there is some root damage is suggested by the reduced pudendo-urethral

reflex in each patient (described in chapter 4)

While it would have been worthwhile to record long-term changes in the urethral

sphincter in PtC, the variability in positioning and performance of the microtip system

meant that small changes in absolute pressures over time would not have been detected;

similarly, small changes in the contractile behaviour of the sphincter would have been

likely to be much less than the variability between different day's testing.

In summary:

1. Hypothesis 3

Stimulation of the sacral afferents at a low level with a Finetech-Brindley stimulator can increase bladder capacity enough to eliminate the need for posterior rhizotomy.

may be true in *some cases*, in particular PtC. In two further patients with intact sphincter responses, long term neuromodulation was ineffective.

2. It is likely that neuromodulation can be achieved by stimulation of S2, instead of or in addition to the S3 stimulation used in current implanted devices.

6. Bladder emptying using a Sacral Posterior and Anterior Root Stimulator.

6.1 *Aims*

The aim of this part of the project was to achieve bladder emptying in the five SPARS patients. In one (PtD), it was not possible to obtain significant bladder pressure rises with intense stimulation of any channel, but in the other four subjects good bladder pressures could be produced.

There are historical reasons for supposing that bladder emptying without dorsal rhizotomy is possible. Many of Brindley's early patients had intact posterior roots, and in only 17 out of the first 50 patients was there an intentional (and almost always incomplete) posterior rhizotomy. Bladder emptying, however, was excellent, with 43 out of 49 able to use the implants for micturition (Brindley *et al.* 1986). A possible explanation for the early success in bladder emptying without rhizotomy is accidental damage to the posterior roots, and indeed Brindley found this in 4 out of 13 patients in whom it could be measured. Similarly, a urodynamic study of 13 of the first SARS patients (two of whom had had a partial rhizotomy) found significant (>50%) increases in bladder capacity in 7, and in 3 patients previous detrusor hyperreflexia was abolished (Cardozo *et al.* 1984). At a later follow up of the first 500 patients with SARS implants, 25 out of 143 patients who had partial (79) or no (64) deafferentation at implantation

required secondary deafferentation later (Brindley 1994). Although all of these results aH

suggest a degree of posterior root damage associated with the early intrathecal technique,

such damage cannot fully explain the success with voiding and there are many examples

of patients with intact posterior roots who voided well. An additional factor in this study

is that 4 out of 5 patients had extradural implants, and the effect of concurrent stimulation

of the sensory (posterior) sacral nerve roots during an interval voiding program is not

known.

It was therefore was expected that some of the SPARS patients would achieve voiding

after the initial implantation, but that in others further procedures (to the sphincters or

sacral nerves) or novel stimulation techniques might be necessary. A further aim was to

use several techniques to gain more insight into DSD that did occur, and to treat it if

possible. These included:

i) Fatigue: Approximately three quarters of the initial urethral sphincter contraction that

occurs with maximal stimulation is fatiguable by high frequency stimulation (Brindley *et*

al. 1974). Although the interval voiding technique has proved a more robust method for

eliminating active sphincter contraction during stimulator voiding (Brindley *et al.* 1982),

it is possible that fatigue, followed by either continuous or interval stimulation, might be

a useful additional technique.

ii) Anodal blockade: this has the potential to selectively activate small fibres and has been

effective in humans during implantation of an intrathecal SARS device (Rijkhoff *et al.*

1998), but it probably requires special electrodes and special pulse shapes (Brindley &

Craggs 1980). A degree of anodal blockade, however, might be seen with the extradural implant and evidence for it was sought.

iii) Alpha blockade: as much as 50% of resting urethral sphincter tone in the urethra is due to smooth muscle (Rossier *et al.* 1982), and there is evidence of detrusor – *bladder neck* dyssynergia in some patients with SCI, as discussed in section 1.3 of the introduction. Also, oral and intravenous alpha blockade has been used with success to improve reflex voiding in SCI patients (Awad & Downie 1977, Hachen 1980, Rudy *et al.* 1988). It is possible, then, that alpha blockade would improve stimulator-driven voiding by reducing background smooth muscle tone and possibly reducing detrusor-bladder neck dyssynergia.

Other techniques (for instance, pudendal nerve blockade (Rossier *et al.* 1982) and temporary urethral stent placement (McFarlane *et al.* 1996)) have the potential to determine the influence of active DSD on bladder emptying and are discussed in the last section of this chapter.

6.2 Methods

Testing of stimulation for bladder emptying was deferred for at least three weeks, to allow for wound healing and so that the effect of any postoperative neurapraxia was apparent. The procedure for devising a bladder emptying program was similar to that

described in the Finetech-Brindley *Notes to Surgeons* (Brindley 1998), and this basic

information will not be reprised. The steps in setting up an emptying program were:

1. At least two control cystometrograms before any stimulation to determine

bladder capacity, size of detrusor hyperreflexia and degree of detrusor-sphincter

dyssynergia. For these the microtip catheter system was used if possible.

2. Determination of the threshold current for muscular, urethral sphincter and

detrusor contraction *for each channel,* with bladder filled to within 100ml of its

capacity.

3. Determination of the maximum detrusor contraction for each channel, and the

maximum contraction strength using all channels simultaneously.

A program was then set using conventional timings, beginning with 4s on, 8s off.

Volume voided was measured together with residual bladder volume obtained by

aspiration. Stimulation was stopped when there was no longer significant urine flow.

There was at least a 5 minute gap between trial stimulations. Stimulation frequency was

set at 25 cycles per second; intensity, pulse width, channel and on/off timings were varied

according to the timing of urine flow and the strength of the detrusor contractions. If

voiding was incomplete, either a narrow bore catheter system (8 French filling line,

converted to pressure line at for voiding) and balloon anal sphincter catheter were used,

or the catheters were removed entirely and the residual measured by self catheterisation.

In the patients in whom there was persisting DSD, the behaviour of the urethral spincter
during the gaps between stimulation was analysed in the same way as the DSD in chapter
3, and its characteristics compared to the dyssynergia seen in control fills.

Further manoeuvres: stimulation programs.

Fatigue: a 2 minute 'prefatigue' period is available in the digital Finetech-Brindley
control box, and was used to stimulate the urethral sphincter *on all channels* at a
frequency of 105Hz (the maximum allowed). The intensity was set to maximally activate
the urethral sphincter, but was below the threshold for detrusor contraction. The
prefatigue period was followed by:

    i)   a conventional interval voiding program, or

    ii)   3 to 10s of intense stimulation on the channels which produced

              detrusor contraction, with a continued lower level stimulation of

              the urethral sphincter at 105Hz. This was possible using the

              'interleave' function of the digital control box.

Anodal blockade: evidence for anodal blockade was sought in two patients (PtC and
PtB), using the microtip catheter system. Maximal urethral and anal sphincter contraction
at a pulse width of between 50 and 200μs (too low for anodal blockade) was measured at
amplitudes 1 to 4. This was compared stimulation at 800μs (the maximum allowed),
which may be sufficient for anodal blockade (Brindley & Craggs 1980), at amplitudes 1

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to 4. If there was any evidence of anodal blockade, the longer pulse width was incorporated into the voiding program and the effect on DSD examined.

Further manoeuvres: alpha blockade. The approval of the local ethics committee for this part of the project was obtained and is included in the proposal in appendix 1. The procedure was as follows, with pulse rate and pulse oximetry measured continuously and blood pressure recorded every minute.

i)   Control cystometry; bladder volume measured by aspiration.

       Position of the microtip catheter checked using 1s periods of low-level stimulation to elicit urethral sphincter contractions.

       Size of maximum urethral sphincter contraction determined.

       Optimised (in previous experiments) bladder emptying program used.

ii)   Injection into a fast-running intravenous line (containing Hartmann's solution) of 10mg phentolamine maleate (Raja *et al.* 1991).

iii)   Changes in blood pressure and resting sphincter tone recorded.

iv)   *Identical* bladder emptying program compared to preoperatively, repeated with changes if necessary.

       Maximum urethral sphincter contraction measured

       Cystometrogram.

Nt very much neuropraxia - else he
would not still have hyperreflexia!
→

The maximal effect of phentolamine is relatively short-lived (15min), so that stages *iii*

and *iv* were performed as quickly as possible. Only one injection was used for the

experiment.

6.3 Results

The bladder pressures achieved on stimulation of each channel are shown in Table 6.1,

together with the degree of postoperative detrusor hyperreflexia and DSD.

Emptying results for individual patients:

PtA: Emptying was rapid and complete using an interval voiding program, with maximal

detrusor pressure <80cm water (Figure 6.1, Table 6.2). However, the postoperative

picture suggested at least partial damage to the posterior roots; detrusor hyperreflexia and

DSD are absent although reflex erections were intact. The detrusor and urethral sphincter

pressure trace was very similar to that seen in a patient with an established SARS implant

and complete posterior rhizotomy (*PtW*) (Figure 6.1).

PtD Bladder emptying was not possible in PtD because it was impossible to generate a

detrusor contraction with intense stimulation. This is discussed in chapter 4. Because he

still has detrusor hyperreflexia (which can be suppressed with neuromodulation), it is

likely that the stimulating electrodes were malpositioned (although this is not apparent on

postoperative radiographs), and it is also possible that there was a degree of postoperative

neurapraxia.

Patient	Maximum S2 response /cm water (date)	Maximum S34 response /cm water (date)	Maximum combined response /cm water (date)	Size of detrusor hyperreflexia /cm water (date)	Bladder capacity /ml (without neuromodulation)	Detrusor-sphincter dyssynergia?	Evidence of vesicoureteric reflux or renal impairment?
PtA	not tested	not tested	100	absent	>600	no	no
PtB	0	137	not tested	118	290	yes	no
PtC	4	42	64	63	165	yes	no
PtD	none	none	none	77	175	does not apply - no DH	no

Patient	Maximum S3 anterior response /cm water	Maximum S3 posterior response /cm water	Maximum S4 response /cm water	Maximum combined response /cm water	Size of detrusor hyperreflexia /cm water	Bladder capacity /ml	Detrusor –sphincter dyssynergia?	Evidence of vesicoureteric reflux or renal impairment?
PtE	120	0	120	138	not reliably reproduced postop, 78 preop	>500	yes	reflux (see text)

Table 6.1   Stimulator-driven detrusor contractions, detrusor hyperreflexia and detrusor-sphincter dyssynergia in the five SPARS patients.

Patient	Mean volume fired off in control fills / residual/ml (date)	Mean peak detrusor contraction in control fills /cm water	Best volume voided using interval program / residual [if measured accurately] /ml (date)	Peak detrusor pressure during voiding program
PtA	no DH	no DH	375/0 (12.10.99) 600/0 (6.3.00)	100 (12.10.99) 67 (6.3.00)
PtB*	50/150 (2/12/99) 140/75 (13/1/00) 105/57 (10/5/00) 124/92 (14/6/00)	90 (2/12/99) 115(13/1/00) 85 (10/5/00) 90 (14/6/00)	82/160 (12/10/99) 100/80 (13/1/00)	119 (12/10/99) 135 (13/1/00)
PtC*	80/85 (18.5.00) 50/150 (27.4.00) 90/45 (12.2.01)	60 (18.5.00) 50 (27.4.00) 40 (12.2.01)	70/190 (13.12.99) 20/300 (17.7.00) 0/400 (16.2.01)	52 (13.12.99) 63 (17.7.00) 47 (16.2.01)
PtE	no DH postop	no DH postop	30 (9.8.00) <5 (21.9.00) 0 (29.4.01)	83 (9.8.00) 78 (21.9.00) 138 (29.4.01)

Table 6.2 The results of bladder emptying programs in three patients in whom stimulator-driven voiding was possible, and the same figures for spontaneous detrusor hyperreflexia.
* In PtC and PtB, voiding was attempted on many different days of testing. The results here are from experiments with the water-filled (not microtip) catheter system, which has a larger lumen for aspiration and no balloon.
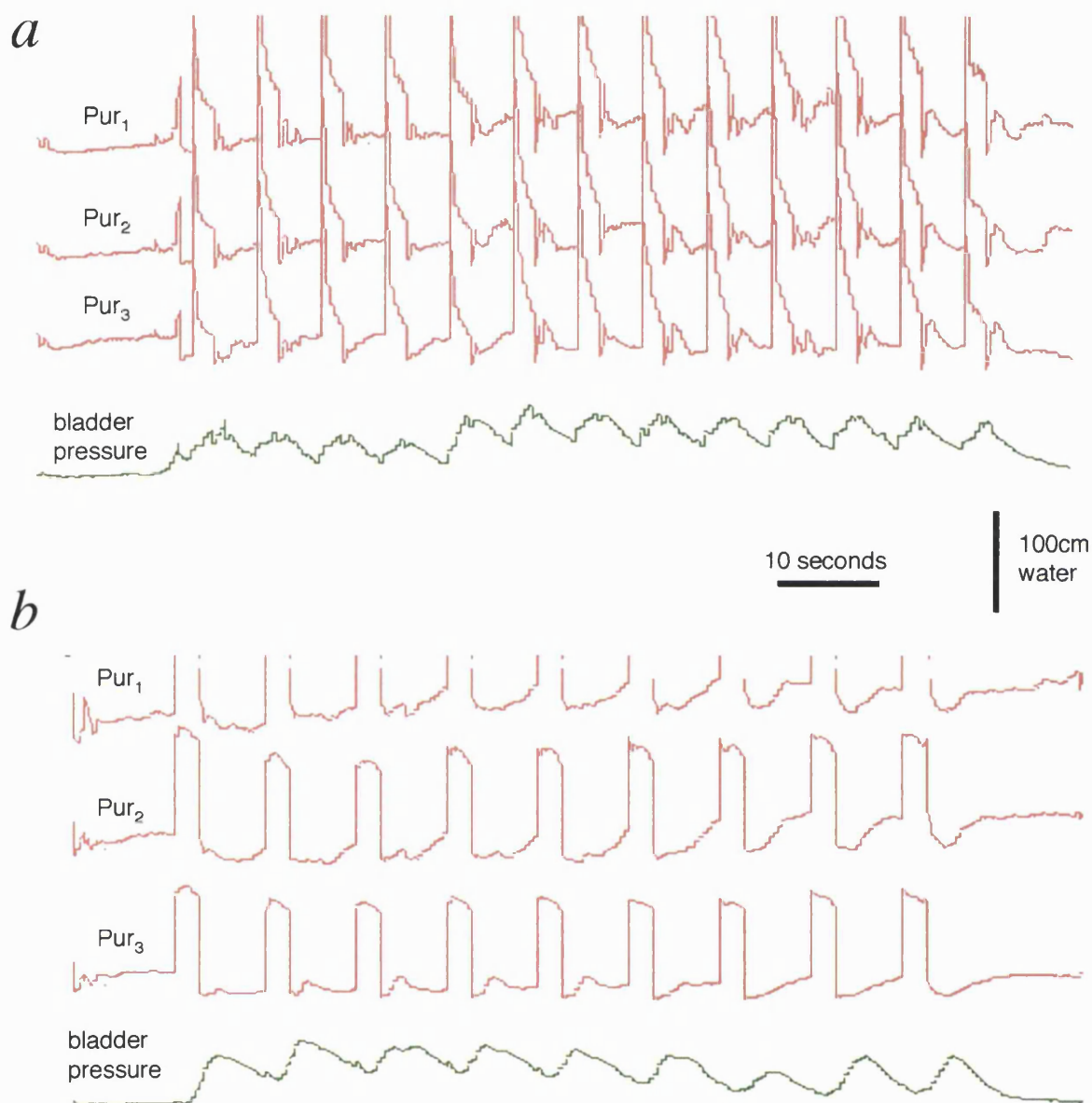
Figure 6.1

Voiding traces in PtA (*a*), and PtW (*b*) who has a SARS implant with complete rhizotomy. In each case, the rapid rises in urethral pressure indicate the start of a stimulation period, and rapid falls the end. Both patients emptied completely with these programs. Pur_1=proximal, Pur_3=distal urethral pressure.

In each, in spite of peak detrusor pressures >50cm water, emptying was incomplete, and never reliably more than 50% of bladder volume. In all, there was persisting detrusor-sphincter dyssynergia in control fills, with incomplete reflex voiding. A striking result was that in each patient reflex voiding was *more complete than stimulator-driven voiding*, and associated with *lower or similar* peak detrusor pressure (Table 6.2). This result persisted in spite of all changes in stimulation intensity, timing and channel balance. Detrusor and urethral sphincter traces from the three patients, together with images from videocystometry, are shown in Figures 6.2 and 6.3 (PtB and PtE), and Figures 6.4 and 6.5 (PtC).

In each patient, there was evidence for two types of dyssynergia:

> *active DSD:* the expected rises in urethral sphincter pressure that occur during stimulation, and are avoided by the interval voiding technique

> *passive DSD:* contractions of the urethral sphincter *between* stimulation periods that impair stimulator-driven voiding.

In PtB and PtE the characteristics of the DSD observed in the gaps between stimulation are similar to those seen in chapter 3 (Figure 6.6)
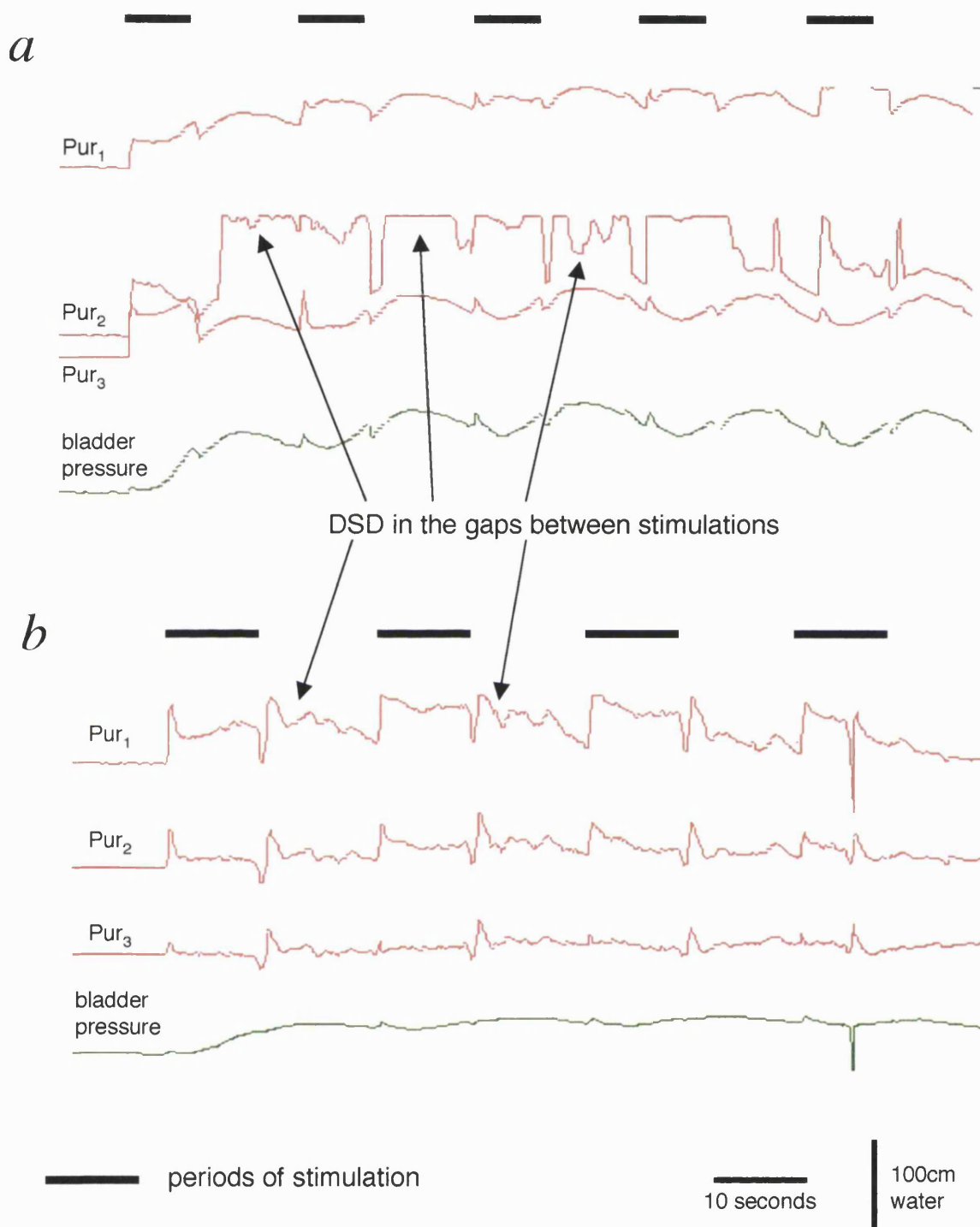
Figure 6.2
Intravesical and urethral pressures during voiding programs in PtB (*a*) and
PtE (*b*). In both cases there is evidence of severe detrusor-urethral
sphincter dyssynergia in the gaps between stimulation. Pur_1=proximal,
Pur_3=distal urethral pressure

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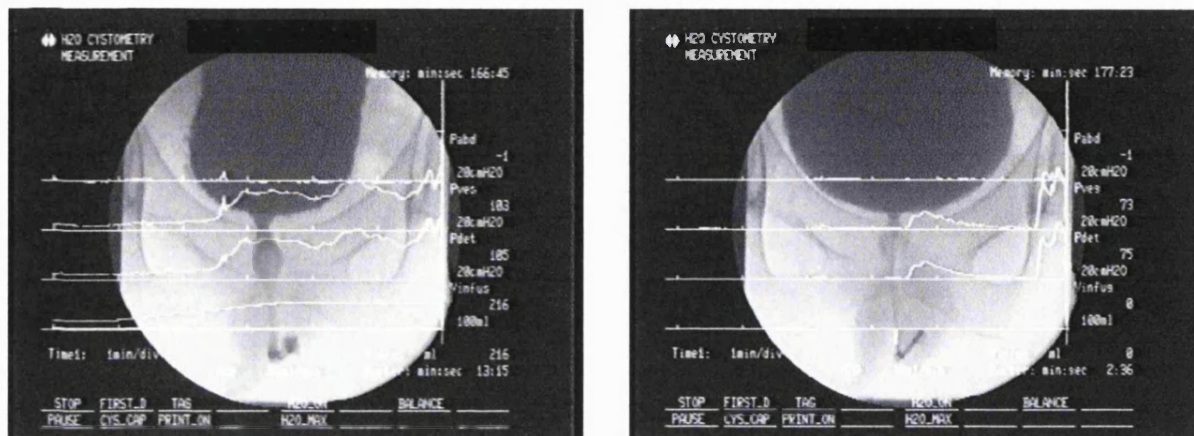
Figure 6.3

Detrusor-external sphincter dyssynergia in the gaps between voiding in SPARS patients. The upper two traces show contraction of the external spincter during voiding in PtB. On the left, there is a small amont of flow; this is interrupted by forceful external sphincter contraction (right).

Below is a capture from PtE, in a gap between stimulations when the detrusor pressure is 60cm water. Again, the external urethral sphincter is obstructing flow.
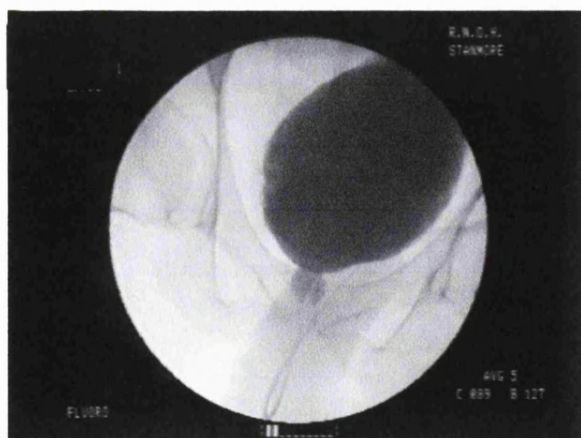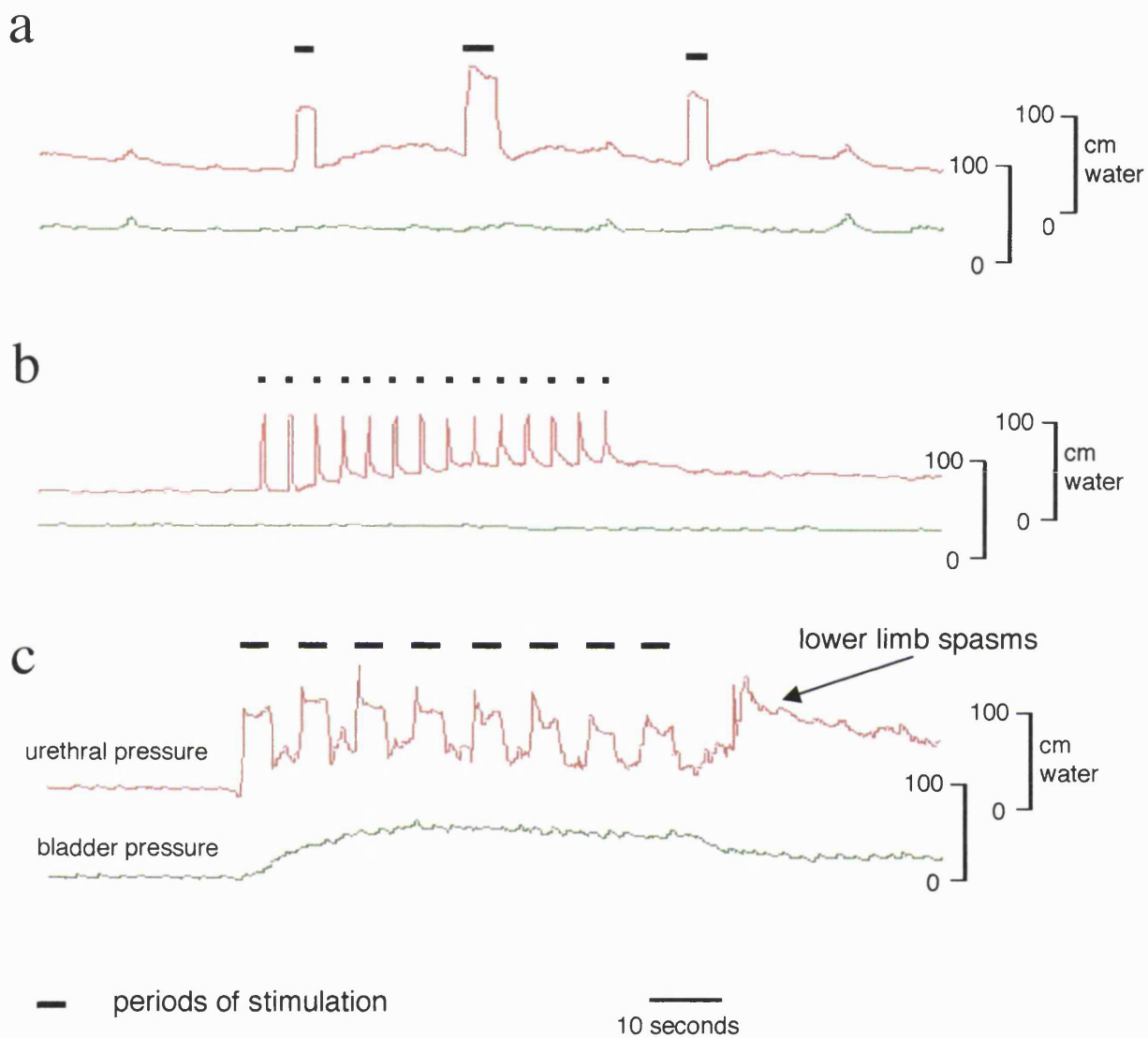
Figure 6.4

The response of the urethral sphincter during 3 different patterns of stimulation in PtC, as follows:

a) Stimulation of the S34 channel for periods of 3 to 7 seconds at a level below the threshold for bladder contraction

b) 1 second stimulations of the S34 channel at a level just below the threshold for bladder contraction

c) An interval voiding program with maximal stimulation of the S34 channel.

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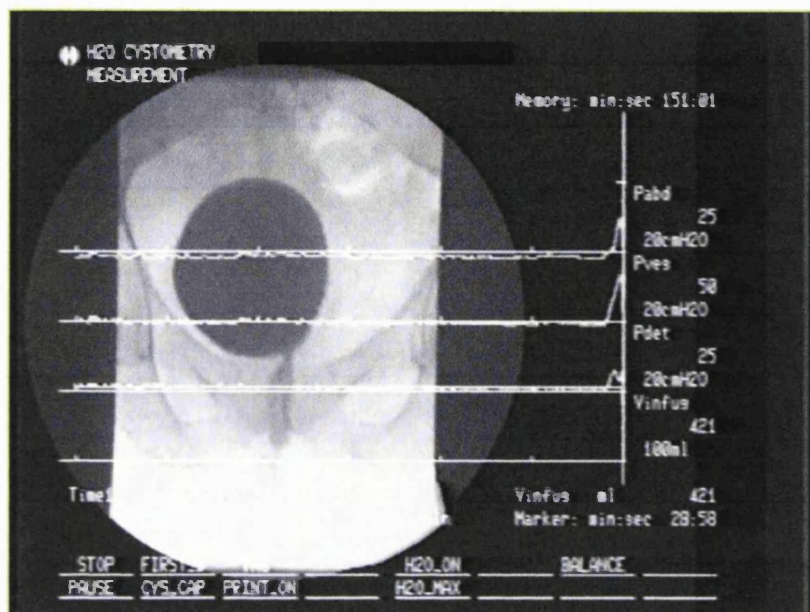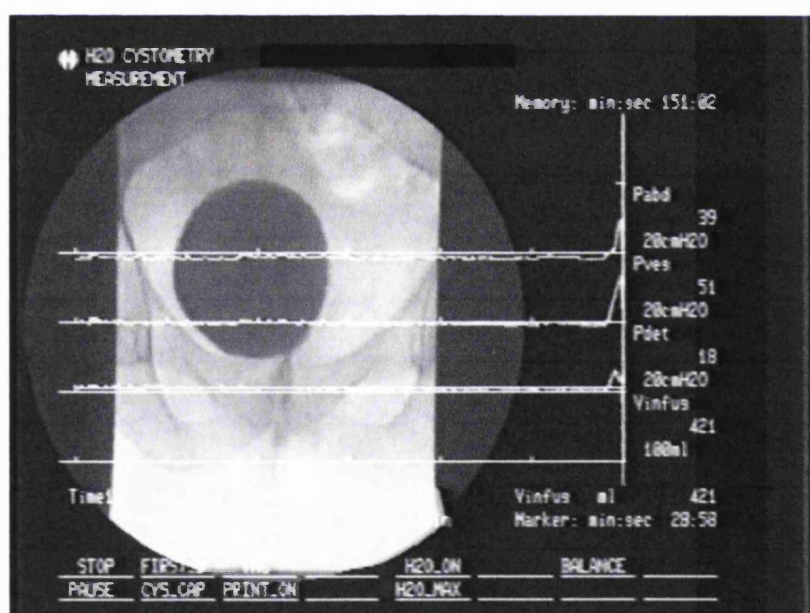
Figure 6.5
Two captures from videourodynamics studies in PtC. *a* shows flow in the gap between stimulations during a voiding program, while *b* shows the effect of repeated rhythmic contractions of the external urethral sphincter that begin in the second gap and precede lower limb spasms by 20-30 seconds, interrupting flow.
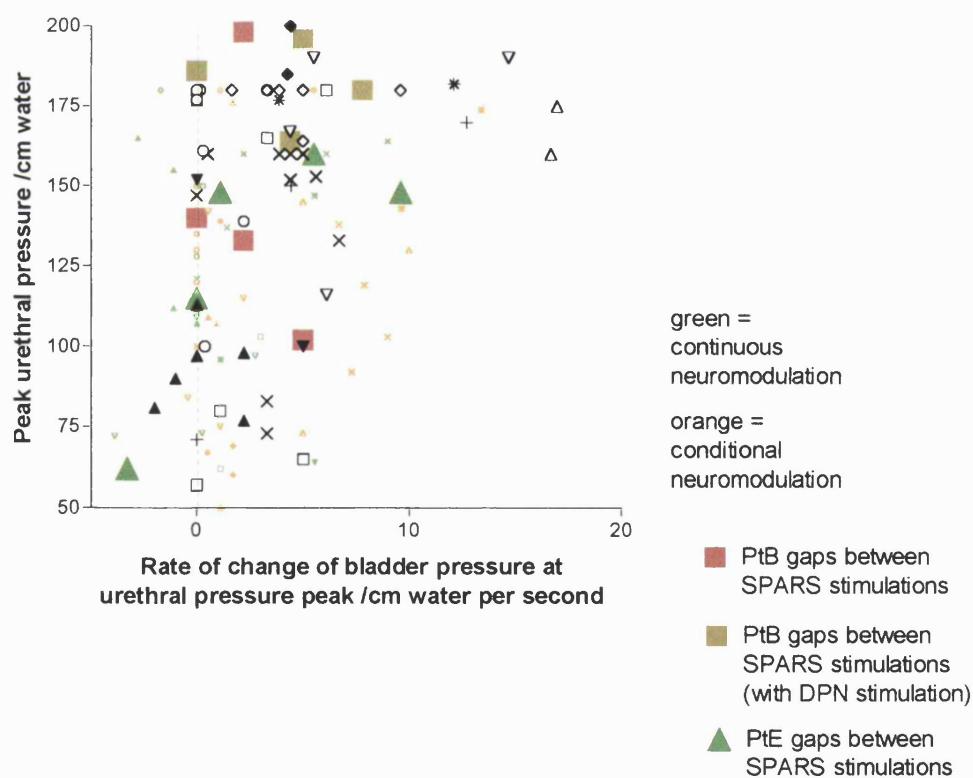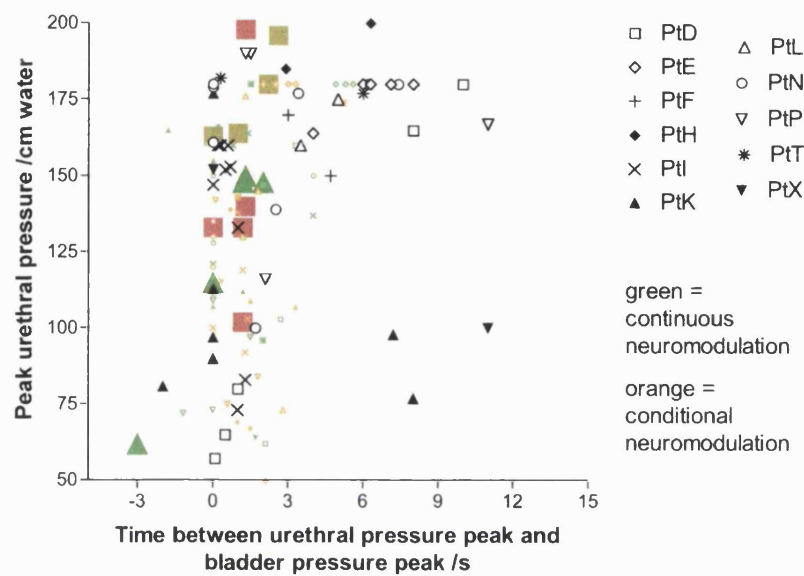
Figure 6.6

A comparison of the properties of the urethral sphincter contractions in the
gaps between stimulations in PtB and PtE, and the equivalent figures for
DSD presented in chapter 3

-rapidly oscillating changes in urethral sphincter pressure suggested striated muscle contraction

-peaks in urethral sphincter pressure occurred before the post-stimulation peak in bladder pressure.

-as bladder pressure started to decline, urethral pressure generally fell, but not sufficiently to allow good voiding

In both patients, videourodynamic studies confirmed that the main site of obstruction was at the external urethral sphincter.

In PtC, the DSD, although still present, was less marked when measured with the microtip catheter . The obstruction to voiding could be attributed to three main factors:

a) Videourodynamics demonstrated that the urethra at the level of the external spincter was occluded by rhythmic (2-3 per second) muscular contractions in the gaps between stimulations, usually from the second gap onwards. This may have been due to both external urethral sphincter and pelvic floor contraction. It was *always* followed, after an interval of 10-30 seconds, by intense gluteal and lower limb spasms. These made the use of a voiding program very difficult for the patient.

b) A more gradual rise in urethral sphincter pressure over 10 to 20 seconds, sufficient to prevent voiding, was apparent when using the microtip catheter. A similar rise was noted after short stimulations of the urethral sphincter at a level just below the

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Should the sphincter - fatiguing 105 Hz
stim's be simultaneous with the
bursts of bladder stim — to relax
sphincter at end of burst ??

→

threshold for a bladder contraction (Figure 6.4). This was a result specific to PtC; neither PtE nor PtB showed similar post-stimulation rises in urethral pressure when there was not a bladder contraction.

c) As shown in Figure 6.4, detrusor pressure during a voiding program in PtC was 40-50cm water, which is at the lower limit of the optimal range. The contraction of the bladder was markedly asymmetrical, suggesting that some damage had occurred to the S34 motor roots on the right

Further investigations:

PtA No further tests indicated.

PtB Fatigue programs: Programs with 2 minutes of maximal sphincter contraction using stimulation of both channels at a frequency of 105Hz were used to fatigue the sphincter before a voiding sequence. By the end of this period, urethral sphincter contraction had declined from 200cm water to 8 cm water (Figure 6.7). This fatigue was relatively short-lived, however, so that after a single 5 second gap the urethral sphincter contraction was 90cm water. Two strategies for emptying were tried:

i) A fatigue period of 2 minutes followed by continuous stimulation of the bladder at 30 cycles per second. Between each of these cycles, two lower-level (using the same parameters as in the fatigue period) stimulations

1 second periods of stimulation
using the same parameters as in the
fatigue period, 5 second gaps with no stimulation

100 cm water

1 minute

urethral pressure

bladder pressure

Prefatigue period
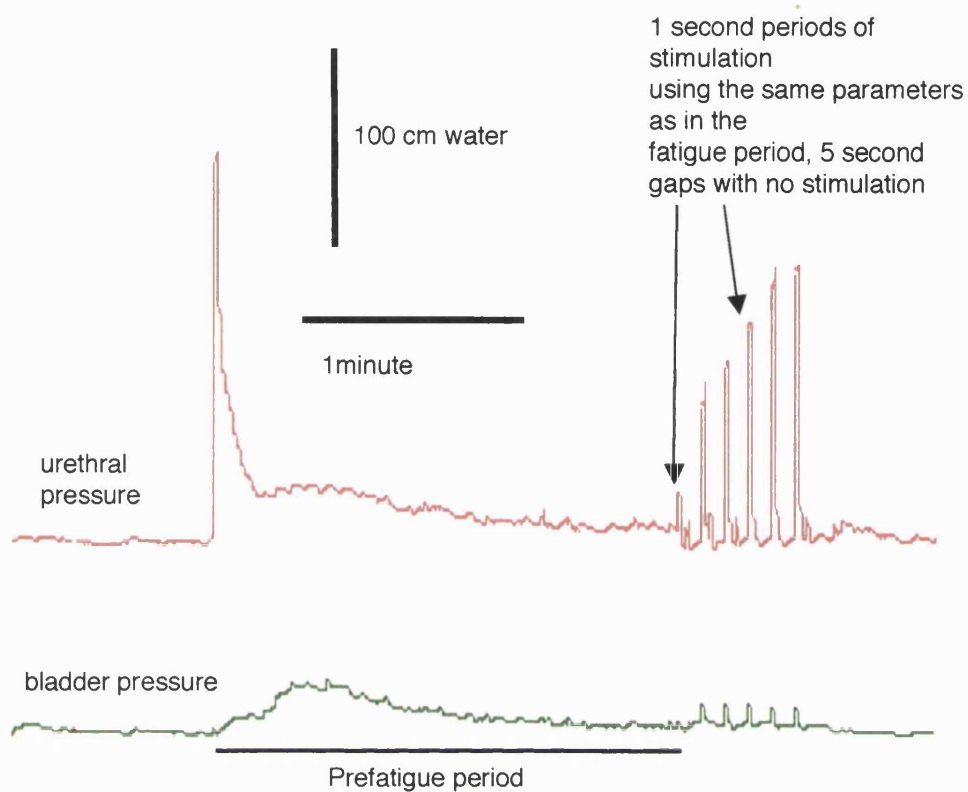
Figure 6.7

The behaviour of the urethral sphincter during a fatigue program in PtB, and its recovery tested by 1 second stimulations every 5 seconds.

100 cm water

1 minute

urethral pressure

bladder pressure

fatigue period
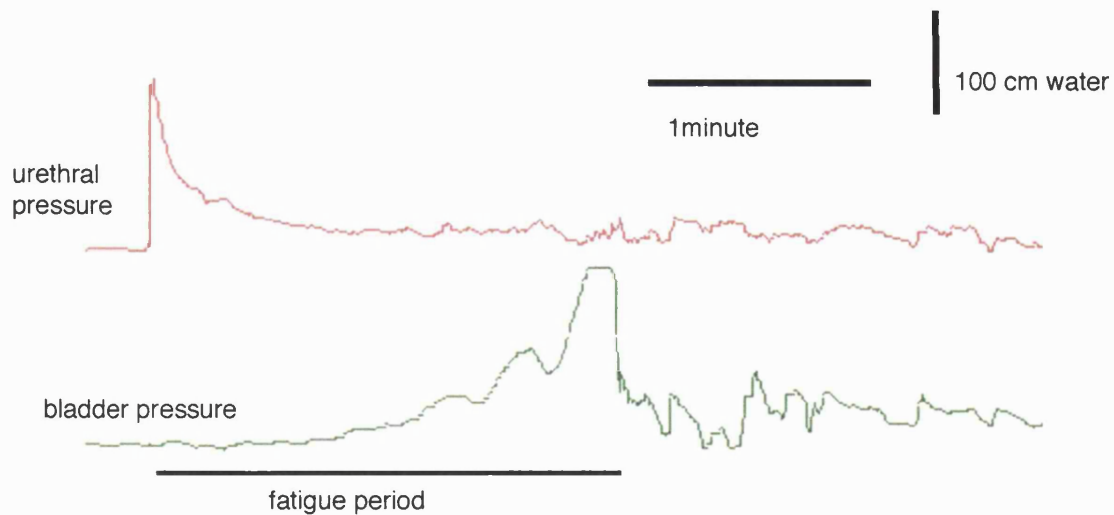
Figure 6.8

The behaviour of the urethral sphincter during a fatigue program in PtC. The lower limb spasms begin after 40 seconds and are reflected in the intravesical pressure trace.

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were interleaved. Thus, urethral sphincter stimulation was at 90Hz, to maintain the fatigue, and the bladder was stimulated at 30Hz. This method *never* resulted in significant bladder emptying.

ii)   A fatigue period of 2 minutes followed by a standard interval voiding program. Again, the fatigue program did not improve voiding, probably because the urethral sphincter recovered quickly in the gaps between stimulation.

Alpha blockade: As shown in Figure 6.3, the bladder neck was narrow in the gaps between stimulations, *but never completely obscured.* This suggested that the most important site of obstruction was the external urethral sphincter, but we considered it important to assess the effect of reducing smooth muscle tone in the urethra.

The injection of 10mg phentolamine resulted in a subjective sensation of heavy eyes, blocked nose and tiredness, and an increase in pulse rate from a mean of 45 to 55 per minute. However, there was no definite change in the resting urethral sphincter pressure: the small (2-5cm water) changes that were observed are well within the limits of the gradual changes seen as the catheter changes position. Similarly, *no* improvement was seen in the voiding pattern, with <5ml voided both before and after injection on an identical program.

Anodal blockade: The first results using this technique were obtained with the microtip anal sphincter catheter when a *Memokath* (Engineers & Doctors, Kvistgård, Denmark)

temporary urethral stent was in place, so that there is not corresponding urethral sphincter data. However, the evidence of anodal blockade is convincing: the degree of contraction of the urethral sphincter was markedly smaller with pulse widths of 800μs compared to 200-400μs (which is too short for anodal blockade), but only at current levels 3 or 4 (Figure 6.9). Subsequent experiments in which the urethral sphincter was also examined provide less marked, but still convincing, evidence of blockade. However, voiding programs incorporating the longer pulse width were *not* demonstrably more effective.

PtC Fatigue : Pelvic floor and lower limb spasms were markedly precipitated by continuous stimulation: at about 1 minute into the fatigue program, severe spasms occurred (Figure 6.8) and we were not able to overcome this with variations in stimulation parameters.

Anodal Blockade: No evidence for anodal blockade at high pulse widths was found in PtC.

PtE: At videourodynamics 8 months post implantation the effect of gradually increasing single bladder contractions was examined by increasing pulse width and time of stimulation. In spite of large detrusor pressures, no significant emptying was observed; the site of obstruction was clearly at the external urethral sphincter. No vesicoureteric reflux was present during control filling and on stimulating the detrusor to produce a rise in intravesical pressure of 60cm water. However, after a pressure rise of 120cm water there was clear reflux to the left kidney (Figure 6.3), which could subsequently be reproduced by much smaller rises in bladder pressure. Testing was therefore
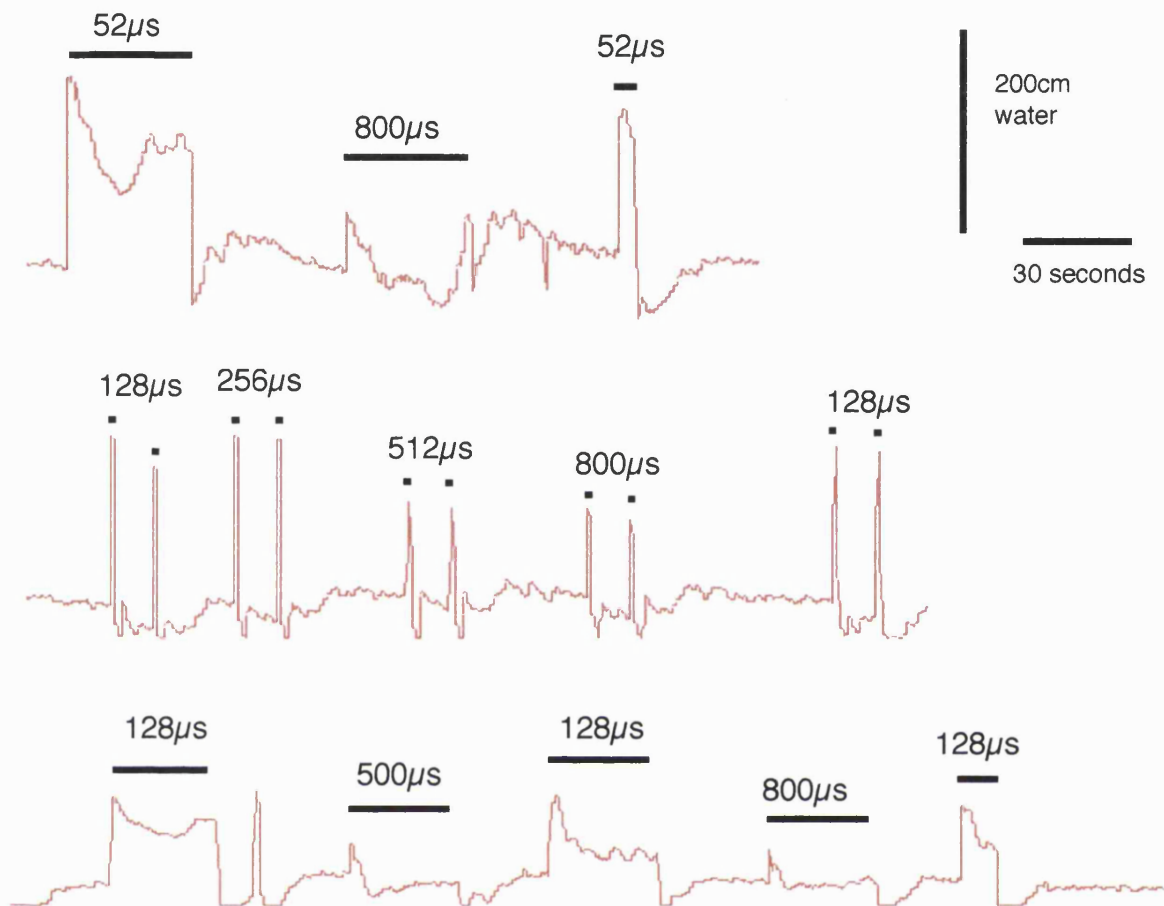
Figure 6.9

Three traces of anal sphincter pressure during stimulation with the S34 channel of the SPARS in PtB, at an amplitude setting of 3. Each shows reduced sphincter contraction at high pulse widths, suggesting that a degree of anodal blockade is occurring.

What about DSD?

You can cope with DM!

(Le cut S34 Ps, SPARS S2 Ps)

discontinued, and the patient restarted high dose oxybutinin and intermittent self-

catheterisation. It was not considered safe to prduce high intravesical pressures in the

presence of the vesico-ureteric reflux demonstrated on videourodynamics. A subtrigonal

injection of macroplastique (STING) is planned, with follow up videourodynamics 1-3

months later.

6.4 Discussion

Results in individuals: Emptying was successful in one patient who did not have severe

DH or DSD preoperatively, and had no evidence of either postoperatively (PtA). The

success in emptying can almost certainly be attributed to the lack of DSD and DH, and

means that the appearance of the urodynamic trace during voiding is similar to that seen

in SARS (with rhizotomy) patients. It is likely that some degree of posterior root damage

occurred at implantation, reducing his already small DSD and DH, but insufficient to

abolish erections. Although this clinical picture is highly desirable, it is unlikely to be

achievable in patients with severe DSD or DH; it is known that recurrence of DH is

common after rhizotomy of S3 and S4 without S2 (which might be expected to preserve

reflex erections) (Lucas *et al.* 1988).

The lack of detrusor contraction on intense stimulation in PtD is difficult to explain,

given that reflex voiding is intact and the urethral sphincter can be activated with low

level stimulation of the S34 channel. One possibility is malposition of the S34 electrodes,

such that the S2 roots are stimulated before the S34 roots, and the latter never intensely.

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Another benefit of shizoturg??

how?

However, it is also possible that there is a degree of neurapraxia in the nerves of the S3 and 4 roots closest to the electrodes, so that it would be sensible to defer any invasive attempt at repair (for instance operative exploration of the electrodes) until this has had a full chance to recover – at least 2 years post implantation.

In PtE, although the urethral pressure traces and videourodynamics suggest DSD, it has not yet been possible to perform further experiments because of the vesicoureteric reflux observed 8 months postoperatively.

In PtC, there is not a complete obstruction either at the bladder neck or the external urethral sphincter on videourodynamics, and experiments with the microtip transducer catheter system confirm that there are not always large amplitude rises in the urethral sphincter pressure in the gaps between stimulations. However, the 'rhythmic' narrowing of the urethra at the external urethral sphincter before the onset of lower limb spasms suggests either DSD or pelvic floor contractions, and in addition the slow rises in urethral pressure seen with repeated stimulations might be due to smooth muscle contraction.

It is of note that Tanagho has observed reduced detrusor pressures on stimulation of the mixed sacral roots, with improvements in some patients after rhizotomy (Tanagho *et al.* 1989), and it is possible that concurrent afferent stimulation reduces the efferent signal to the bladder in a manner analogous to neuromodulation. An additional problem is of severe lower limb spasms post stimulation; even if emptying was complete, these would currently prevent everyday use of the device for bladder emptying.

In PtB, the videourodynamic and microtip catheter data suggest that the primary site of obstruction during interval voiding is at the external urethral sphincter. It is not, therefore, surprising that alpha blockade failed to improve emptying. Whether a rhizotomy of the posterior S2 to S4 roots would result in complete emptying is uncertain. A complete rhizotomy has abolished DSD in the great majority of patients in previous series (Gasparini *et al.* 1992, van Kerrebroeck *et al.* 1993a), and the voiding pressures in PtB are up to 120cm water, which should be adequate even given the narrowed bladder neck observed in the voiding programs.

Pudendal nerve blockade. There is, unfortunately, no established method for reversibly simulating a posterior rhizotomy (for instance with local anaesthetic) without affecting the motor roots. However, if DSD is a phenomenon of the external urethral spincter, it should be abolished by pudendal nerve blockade (Rossier *et al.* 1982), and this would be a valuable technique to determine the likely response to posterior rhizotomy, and the degree to which contraction of striated muscle fibres was inhibiting emptying. Pudendal nerve blockade was attempted in PtB (twice) and PtC, using both Computed Tomography and a stimulating needle to guide anaesthetic placement, but the evidence of full blockade was on each occasion equivocal and the results are therefore not presented here. This was unfortunate, and it may be that better technique in the future may provide diagnostic results.

The passive DSD during stimulation.

The rapidly changing urethral sphincter contractions in the gaps between stimulation in PtB and PtE had similar phase characteristics to the DSD observed in a group of patients

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in preoperative experiments, and as with those results, suggests that the urethral sphincter

contraction is an aberrant response to rate of rise and absolute bladder pressure.

The failure to empty in PtC, PtE and PtB is in contrast to Brindley's early results

(Brindley *et al.* 1986), and this will be addressed further in the general discussion

(Chapter 7). Two possible explanations for the discrepancy are as follows:

i)   Damage to posterior sacral roots during implantation in Brindley's

         patients, resulting in reduced or absent afferent signals from the bladder,

         and reduced DSD. This is likely, as implantation was universally

         intrathecal.

ii)   Concurrent stimulation of the posterior roots during an emptying program

         has a delayed effect on the urethral sphincter, either increasing the size of

         dyssynergic contractions or causing a more prolonged increase in urethral

         sphincter pressure post-stimulation. Although some evidence was found

         for the latter in PtC (Figure 6.4), it *was not* found in PtB and PtE, in spite

         of several similar experiments.

The methods used to investigate incomplete voiding

Urethral pressure measurement: As discussed in chapter 2, the microtip catheter system

is theoretically capable of measuring pressure both at the external urethral sphincter and

at two points closer to the bladder neck. This would ideally enable pressure rises at or

near the bladder neck (which would be due mainly to smooth muscle) to be distinguished from those due to striated muscle in the region of the external urethral sphincter. In practice, the three channel data did not reliably provide this information, for two main reasons:

i) As described in chapter 2 (and illustrated in Figure 2.4), the positioning of the urethral pressure tip system was variable, and liable to change through a day's experiments. This was especially true when voiding occurred; both the resting urethral pressure and the response to short periods of stimulation were often different before and after voiding.

ii) The variable position of the catheter meant that the channel with the highest rapid rises in urethral pressure on short intense stimulation (assumed to be closest to the striated muscle of the external urethral sphincter) was sometimes that of the middle or proximal pressure tip transducer. In this situation, it was not certain that pressure at the bladder neck was being recorded at all.

iii) When the pressure at the bladder neck falls below the intravesical pressure, urine flows into the proximal urethra and the pressure in the column of fluid now represents bladder pressure. This obscures the pressure exerted by urethral striated and smooth muscle when it falls below that of the detrusor.

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Alpha adrenergic blockade: The dose of phentolamine used has markedly reduced resting urethral sphincter pressure in previous studies, and did have a definite effect on pulse rate in PtB. Therefore, the failure to improve emptying after alpha blockade can be taken as good evidence that urethral smooth muscle activity is not the *main* contributor to outflow obstruction during an intermittent voiding program. This is consistent with the rapid and large rises in urethral pressure visible on the microtip catheter trace in the gaps between stimulation, indicative of striated muscle contraction.

In summary: Of five patients with a SPARS implant, emptying was impaired in 4. The probable reasons for this appear to be:

- Inability to stimulate the nerves supplying the detrusor (1 patient)

- Low detrusor pressure with probable obstruction at the external urethral sphincter (1 patient)

- Severe DSD (2 patients)

In the three patients with intact detrusor hyperreflexia in whom implant-driven bladder detrusor contraction could be achieved, emptying with the SPARS was less efficient at emptying the bladder than spontaneous 'firing off'.

The only patient in whom voiding was efficient showed no evidence of DH or DSD; although the outcome is a clinical success, intact posterior roots cannot be assumed.

Therefore, the following hypothesis:

Bladder emptying by intense sacral root stimulation and an interval voiding technique is possible without rhizotomy of the posterior roots.

has not been proven, and is indeed unlikely to be true in most cases.

7. General discussion.

The central aim of the work in this thesis was to implant a device that could achieve neuromodulation (to increase bladder capacity) and neurostimulation (to empty the bladder) in a group of paraplegic patients, without significant damage to the sacral roots. Although successful bladder emptying was achieved in one patient, the combination of neurostimulation and neuromodulation was not achieved successfully in any, and several results suggest that the SPARS device as currently configured will not be suitable for the majority of patients. This will be discussed after the preoperative neuromodulation results.

A secondary aim was to examine the efficacy of conditional neuromodulation. A more general question, which remains, is whether *intermittent* modes of stimulation are more effective than continuous. The results in chapter 3 do suggest that conditional neuromodulation is effective, but the statistical analysis is difficult for several reasons, especially as the distribution of bladder volumes cannot be assumed to be parametric, and the numbers are too small to test for normality. Faster filling rates would have generated more testable data, but would not have been physiological. In some individual experiments, the conditional mode appeared to be superior, but this was not testable. The question is raised: 'why perform the comparison between the two modes if statistical analysis is unlikely to be possible?'. The answer is that although order effects are possible biases, and the non-parametric distribution makes finding significance difficult,

they do not prevent these results from implying that the two techniques are of *similar* efficacy. Future studies – of both conditional and intermittent stimulation – are needed, but must be designed carefully to ensure that the results are robust. Whether the complexity of a conditional stimulator is justified will depend on how effective such stimulation is *in the long term*, which has not been addressed by the current work.

The methods used for measurement of urethral pressure

The microtip catheters used in the current study have not proved ideal. Firstly, they are prone to zeroing error, so that it is mandatory to use changes in, rather than absolute urethral sphincter pressure. Similarly, the transducer closest to the urethral sphincter could not be inferred from the absolute pressures recorded, but was instead assumed to be that which showed the largest rapid rises in urethral sphincter on stimulation. The catheter also gradually changed in position in almost every patient. These sources of error mean that considerably less evidence was gained about the behaviour of the bladder neck and external urethral sphincter than was theoretically possible. In addition, aspiration through the small central lumen was difficult, and probably less accurate than in the water-filled system (where the bladder can be allowed to drain by a siphon effect). The balloon at the bladder neck, while helpful for positioning, is another potential source of artefact. A better system would have:

- a larger central lumen for filling

- a less sharp and angulated positioning balloon that could be inflated for positioning, and then deflated during filling, together with:

- more pressure transducers (including some at the bladder neck and at the distal external urethral sphincter)

- (possibly) electrodes for the measurement of striated sphincter EMG

Electromyography would have been useful both in the measurement of DSD in chapter 3 and in the determination of striated sphincter activity in the gaps in voiding in chapter 6. It might also have provided information about fatigue and habituation during long-term neuromodulation. Its use should be considered for future experiments.

The urethral sphincter during DH, and the effect of neuromodulation.

Although the response of the urethral sphincter to several minutes of continuous DPN stimulation varied between patients, the persisting increase in sphincter activity with this purely *afferent* pudendal nerve stimulation was in most cases small. The fall of urethral pressure close to baseline has implications (as discussed in chapter 3) for the mechanism of neuromodulation, but will not necessarily generalise to a system that stimulates mixed roots, where concurrent stimulation of efferents may result in more sustained urethral sphincter contraction. Unfortunately, we were not able to document long-term effects on the urethral sphincter in this study because neuromodulation was used by PtC and PtD for a limited period, and intermittently. In future studies, however, it will be important to document resting urethral pressure, sphincter fatigue characteristics and possibly urethral sphincter volume before and during long-term neuromodulation. The current microtip catheter system is not adequate to detect the small changes that would result, and it might be that measurement of urethral pressure profile would be more sensitive.

The phase characteristics of the urethral and bladder pressure traces are examined here in closer detail than in previous studies, and it does seem that in most cases urethral sphincter contraction behaves as a complex response to both the absolute bladder pressure and its rate of rise. The method of deriving the data (choosing the five largest peaks in urethral pressure, and deciding with which bladder pressure rise they are associated) is somewhat subjective, and the results again difficult to analyse statistically, apart from showing that the urethral peak usually arrives significantly before that of the bladder. Although the phase characteristics may be similar, there is considerable heterogeneity between patients in the extent to which DSD impairs voiding, and it may be that Blaivas's classification into 3 types is more clinically relevant. The phase characteristics may be more useful in the identification of DSD – and were used in the current study in the analysis of urethral contractions during SPARS voiding programs.

The finding that DPN neuromodulation did not markedly reduce DSD or change its phase characteristics is not surprising, as in spite of assertions that it does, firm evidence showing an effect has never been published. This was an key hypothesis to test, however, because the converse finding would have had important potential clinical applications (not least as a method of reducing the DSD seen during stimulated voiding in the SPARS patients).

SPARS and long-term neuromodulation.

This study showed that in one patient neuromodulation was a feasible method for suppressing hyperreflexic bladder contractions and increasing capacity. However, there were several significant obstacles to continuous neuromodulation via the SPARS. Firstly, the device could not be used for bladder emptying in any patient. Secondly, fixation to the skin was problematic, with the transmitter easy to dislodge and erythema at the fixation site after several weeks in PtC. To overcome these problems it will probably be necessary to engineer a larger, more flexible stimulator coil (precise localisation over S2 or S34 being unimportant) and lead. A final problem is the 'escape' from bladder control. With anticholinergics this often occurs as an overflow dribble, but with neuromodulation a large detrusor contraction may occur with a large volume voided. This also makes it mandatory to check that 'escape' from neuromodulation does result in voiding or detectable sensation of fullness, to avoid dangerous detrusor contraction against a closed sphincter.

There is a definite difference in the short and long-term results of neuromodulation in SCI patients in previous studies (as shown in the tables in chapter 1), with the acute experiments successful in a higher proportion of patients, although it may be that some of this is due to publication bias, differing anticholinergic use and patient selection. However, it may also be that neuromodulation is easier to achieve acutely: as discussed in chapter 6, just as the bulbocavernosus reflex appears to habituate, the inhibitory effect of neuromodulation may decrease over an unknown period ranging from hours to months. There are no reliable studies examining this issue, and a major shortcoming of the current study is that difficulties in applying neuromodulation continuously in our patients prevented such an assessment. The issue of continuous vs intermittent

stimulation may be important here: it may be that intermittent stimulation programs result

in less habituation, and this is an important area for future studies. Stimulation programs

with fixed on and off periods would be simpler to apply than conditional

neuromodulation and it is possible that they would provide some of its benefits without

the inevitable complexity of detecting bladder contractions.

SPARS and voiding

The results of the current work suggest that detrusor-external urethral sphincter

dyssynergia will be a major problem for bladder emptying in devices where rhizotomy

has not been performed. In PtC, the dyssynergia was not typical, but rhythmic sphincter

or pelvic floor contractions were observed on videourodynamics and severe lower limb

spasms followed stimulation.

Whether PtE, PtB and PtC would have achieved voiding had they undergone posterior

rhizotomy is unknown, but the results of previous studies suggest that a successful

outcome is very likely (van Kerrebroeck *et al.* 1993a, Brindley 1994), especially given

the adequate bladder pressures in the first two. In PtC, it is at least possible that a

rhizotomy would reduce the lower limb and pelvic floor spasms that followed

stimulation.

The results in Brindley's early patients, many of whom did not undergo rhizotomy,

remain puzzling (Brindley *et al.* 1986), although *a*) in relatively few were the posterior

roots completely preserved, *b*) some may not have had significant DSD and *c*) in many

there was evidence of posterior root damage. The poor emptying in the SPARS project

may in a sense be a consequence of the success in preserving the posterior roots and with

them DSD. One significant difference in the groups of patients is in the roots stimulated:

the first Brindley stimulators often enclosed only the anterior roots, and the SPARS in

four patients enclosed the mixed sacral roots. It is difficult to determine whether posterior

root stimulation is an important cause of urethral sphincter contraction during interval

voiding, although PtE has a stimulator configuration that might enable experiments to

determine this. It will be important to determine the effect of posterior root stimulation

when his vesicoureteric reflux has been treated, and this will be investigated as the

SPARS project is continued at the Royal National Orthopaedic Hospital.

It may be that there is a group of patients (probably a minority) with DSD in whom

bladder emptying will be successful, but currently the only reliable method of identifying

them is to perform a SPARS implant and proceed to a rhizotomy later if necessary. An

alternative might be percutaneous stimulation of the sacral roots preoperatively, but this

is technically demanding, and we have failed to produce large rises in bladder pressure in

two out of two patients tested with the technique. The finding that stimulated emptying

(with the SPARS) is in most cases less efficient than spontaneous detrusor hyperreflexia

at emptying the bladder is cautionary.

It seems then that sacral root stimulation for bladder emptying without rhizotomy

requires in most cases a method for dealing with DSD. This has been the finding of

Tanagho's group in San Francisco, who have used combinations of urethral

sphincterotomy, rhizotomy and pudendal neurectomy to achieve bladder emptying

without incontinence in about half of their patients, although the numbers are small (Tanagho *et al.* 1989). However, the fundamental drawback to these techniques is that they are destructive, and they are unlikely to be more acceptable to patients than rhizotomy. Electrical blockade of the pudendal or sacral nerves in the gaps between stimulations or during continuous stimulation is promising, and there have been encouraging results in animals, but no practical solution currently exists for human use (Rijkhoff *et al.* 1997b). Anodal blockade via the Finetech-Brindley electrodes may be difficult because of field inhomogeneity and current leak, but has proved promising intraoperatively in humans with the intrathecal electrodes (Rijkhoff *et al.* 1997a). It is encouraging that some evidence of successful anodal blockade was found in PtB in this study, but the extradural electrodes will probably require considerable modification for a reliable effect. To completely block afferent signals from the bladder or efferents to the urethral sphincter would require effective anodal blockade of six nerves (S2,3 and 4 bilaterally) – a daunting technical challenge.

The SPARS and future stimulators.

Because of his mild pre-existing DH and DSD, and the evidence of partial root damage, the successful clinical outcome of the SPARS stimulator in PtA is not directly relevant to the SPARS project. It was already known that patients with large bladder capacities and no evidence of dyssynergia may not require rhizotomy, and this group of patients has two generally satisfactory methods for bladder management (condom drainage and self-catheterisation).

The small number of patients in this study makes it difficult to generalise about the outcome of a SPARS implant without rhizotomy in future patients, and the current results anyway mean that further recruitment into the study is likely to be small. The only way in which experimental implantation could now be justified in a patient with DSD would be as part of a two-stage procedure. The initial extradural implant would be followed by several months of testing, and a conus rhizotomy performed if the results were unsatisfactory. Such a sequence is only a modification of the established 'Barcelona' technique, where the two procedures are performed at the same time (Sarrias *et al.* 1993), and is the basis of a flowchart for enrolment into the SPARS project that was devised after four patients had received implants; it is shown in appendix 4.

On this basis, there are several possible areas for future study. These include

i) Further diagnostic tests to determine the cause of incomplete emptying in SPARS patients. Pudendal nerve blockade is potentially highly informative and alternatives such as botulinum toxin injection and temporary urethral stent placement might be both diagnostic and therapeutic.

ii) Novel stimulation techniques to block efferent signals to the urethral sphincter during stimulation. Anodal blockade is a promising technique but will probably require special electrodes. Blockade does not necessarily have to be complete: any reduction in striated sphincter tone is likely to improve emptying

iii) Improvements in stimulation for neuromodulation. There are many important issues

for optimising neuromodulation – both general (the effect of intermittent *vs* continuous

stimulation, the efficacy of neuromodulation over weeks to years) and specific to the

SPARS project (optimisation of pulse width and channel mix for long term stimulation).

As well as the development of a more manageable and easily positioned stimulator coil,

an implanted device for long term stimulation might be considered.

The SPARS project is being continued at the Royal National Orthopaedic Hospital, where

many of these issues will be addressed.

The final conclusion of this project is that a stimulation of the sacral roots for both

bladder emptying and neuromodulation is *currently* unlikely to succeed in patients with

significant detrusor-sphincter dyssynergia.

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Appendix 1
Patient information leaflet and consent form for the SPARS project

CLINICAL INVESTIGATION OF AN IMPLANTABLE DEVICE FOR COMBINED NEUROSTIMULATION AND NEUROMODULATION OF THE SACRAL ROOTS FOR COMPLETE CONTROL OF BLADDER FUNCTION

PATIENT INFORMATION SHEET

You have been invited to participate in this clinical investigation because you have expressed an interest in receiving a *Finetech-Brindley SARS* (Sacral Anterior Root Stimulator) to improve your bladder management and your doctor considers that this would be an appropriate treatment option.

The Finetech-Brindley SARS has been used successfully in over 2,000 patients world-wide. As you are probably aware from the literature regarding the Finetech-Brindley SARS, the implantation of the device is usually accompanied by a technique known as a *posterior rhizotomy*. This technique means that the sensory nerve roots at the S2-S4 level are cut to prevent your bladder from having *hyper-reflexic* contractions. These hyper-reflexic contractions are what make your bladder 'jittery' and cause you to 'fire-off'. Normally they are controlled with drugs such as Oxybutynin, but this method is not compatible with the current Finetech-Brindley SARS.

We have developed an alternative method of using the Finetech-Brindley SARS, which would mean that it would suppress your unwanted contractions as well as allowing bladder emptying, without the need for destructive surgery to cut your sensory nerves. The method that we would use to do this is called *neuromodulation*. Neuromodulation (low level electrical stimulation of the sensory or posterior nerves) has been used successfully in the past in other patient groups, to prevent hyper-reflexia and we have done a number of years of research at Stanmore in spinally injured patients. We have called this new use of the device the SPARSI (Sacral Posterior and Anterior Root Stimulator Implant.).

The aim of this investigation is to determine whether the SPARSI can be used in the long term bladder management of patients with a spinal injury who have a Fintech-Brindley SARS implanted without having a posterior rhizotomy. The Royal National Orthopaedic Hospital Trust Joint Research and Ethics Committee has given approval for this work.

The actual implant and implantation procedure for the SPARSI are identical to that of the SARS. The only difference in use is that neuromodulation will be applied continuously, and therefore the external control box will have to be worn for longer than when it is used for just bladder emptying. The exact length of time it is necessary to be worn will be investigated as part of the study.

If you agree to take part in the study you will be asked to come to the hospital for a number of visits, including pre-operative assessments, the operation itself and post-

operative follow-up visits to see how the implant is working. The schedule of these visits is detailed below:

Pre-operative Assessment

During the pre-operative assessments we will need to carry out standard urodynamics tests, similar to those which you have previously had. These tests involve having a small flexible tube passed into the bladder and a second tube passed into the rectum. This technique will allow us to measure the pressure in your bladder, the capacity and the degree of hyper-reflexia. We will give you an antibiotic injection or tablets as there is a small risk (1-2%) of you developing a urine infection. During the urodynamics we will measure:

In order for us to establish whether the technique of neuromodulation will work in suppressing your hyper-reflexic contractions before we implant the SPARSI device we will carry out assessments using a technique called *Dorsal Penile Nerve Stimulation*. This involves having surface skin electrodes placed at the base of the penis, through these electrodes we can stimulate the same nerves which would be stimulated by the implant to provide neuromodulation; this procedure is painless. Once we have The assessments will be as follows:

1ˢᵗ Assessment – Acute Stimulation

We will try and provoke a hyper-reflexic contraction by rapidly introducing 60 ml of saline into your bladder. If we can reliably provoke contractions we will use various stimulation parameters to determine whether we can suppress these contractions using neuromodulation. If we are successful you will be allowed to undergo the second assessment. This assessment will take approximately 2 hours.

2ⁿᵈ Assessment – Chronic Stimulation

We will allow your bladder to fill naturally by asking you to drink the appropriate volume of fluid. Whilst your bladder is filling we will apply the dorsal penile nerve stimulation to see if your bladder capacity increases with neuromodulation and the hyper-reflexia is reduced. This assessment will take a few hours, depending on how quickly your bladder can be filled. It may be necessary to keep you in over night in a hospital research bed to investigate whether the neuromodulation will work over an extended period of time.

If your bladder responds well to neuromodulation you will be put forward for implantation of the SPARSI device

Implantation

The implantation procedure of the SPARSI is identical as that for the Finetech-Brindley SARS. The electrodes will be placed around the sacral nerves, but of course the sensory nerves will not be cut. A receiver block which receivers the signal from the external control box will be implanted under the skin in the optimum position either on the chest wall, the abdominal wall or the upper thigh.

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Following the operation you will be an in-patient for a period of 1 week, during which time we will check whether the implant is working properly and will instruct you on how to use it effectively.

Post-operative Follow-up

In order for us to fully understand if the SPARSI device is successful in suppressing hyper-reflexia in spinal cord injured patients, we will need to carry out a number of follow-up investigations. We will ask you to attend the hospital for 6 follow-up visits at intervals of 1, 2, 4, 8, 12 and 24 months after the operation. Each visit will take approximately 2 hours and all your expenses will be paid. Prior to each visit we will ask you to fill in a voiding and symptom diary for 1 week. During the visits we will carry out routine urodynamics and check that you are using the device effectively. The information collected from these investigations will help us understand how the device is performing.

To improve the emptying of your bladder with the device, it may be necessary to perform two further tests during these visits:

i) An injection of local anaesthetic around the nerves that supply the urethral
   sphincter. The effects of this injection wear off completely after a few
   hours. The test allows us to see if the sphincter is slowing the flow of urine
   from your bladder. The dose of local anaesthetic is the same as that used
   for minor surgical procedures, and side effects (such as dizziness) are rare.
   More serious side effects that affect the heart or brain are very rare. To
   inject the anaesthetic into the right place, we would use either CT scanning
   or fluoroscopy (both are methods of taking Xray picures of the pelvis). The
   level of Xrays that this involves would be similar to one videourodynamics
   test. If the test was successful, we could consider going on to block your
   sphincter in ways that would give a longer lasting improvement in bladder
   emptying (for instance an injection of botulinum toxin – 'botox', which
   lasts for several months, or eventually cutting part of the sphincter –
   sphincterotomy).

ii) An intravenous injection of a drug (phentolamine) that relaxes the neck of your bladder. The effects of this drug would wear off completely after a few hours. This often causes a small drop in blood pressure and may cause minor side effects , such as blocked nose, dizziness and headache. Very rarely, it causes a drop in blood pressure that can affect the heart or brain, so we would monitor blood pressure constantly during the test. If the test was successful, we could consider starting a course of tablets ('alpha blockers') that would improve bladder emptying in a similar way to the injection.

Any possible side effects resulting from this implant would be the same as those described for the Finetech-Brindley SARS (see information sheet), there are no known harmful side effects of the process of neuromodulation itself.

In the event of the SPARSI device not being successful at suppressing detrusor hyper-reflexia you will be given a number of options:

- A posterior rhizotomy which will prevent the hyper-reflexia and allow you to continue using the bladder emptying device.
- Continue using the bladder emptying device but try to treat the hyper-reflexia with pharmacotherapy
- Return to your previous method of bladder management but leave device in situ.

You are free to withdraw from this study at any time, without this affecting the care that you receive. All information will be treated confidentially. The study results may be published in scientific journals, however, you will not be identified in person.

If you have any questions regarding this investigation please contact:
Dr Michael Craggs,
Mr Alex Kirkham or
Dr Sarah Knight
at the Royal National Orthopaedic Hospital
☎ 020 8909 5343 or 020 8954 2300 ext 5606 or 0793 9116779

Appendix 2

Root measurements in 4 patients undergoing implantation of extradural stimulators, and demographic information.

Patient procedure		S2 left	S2 right	S3 left	S3 right	S4 left	S4 right
PtF SARS	exposed length /cm	2	2.2	2.5	2.4	2	2
	width /mm	5	5	3.5	3	2	2.5
PtA SPARS	exposed length /cm	2	2	3.5	4	4	4
	width /mm	5	4	3.5	3	2.5	2
PtD SPARS	exposed length /cm	all>2					
	width /mm	5	5.5	3.5	4	2	1.5
PtAB SARS	exposed length /cm	2.5	2.5	3	3	3	3
	width /mm	4	4.5	3	3	1.5	1.5

Initials	Age /y	Neurological Level & Frankel Grade	Date of Injury	Bladder Management	Daily Dose of Oxybutinin
PtF	34	T6 complete	Jun 1995	ISC	30mg
PtA	38	T10 complete	Jan 1995	ISC, condom	15mg
PtD	46	T3 complete	Jun 1995	ISC	30mg
PtAB	42	T5 complete	1974	ISC	none

Appendix 3
The erectile function questionnaire used to assess patients before and after SPARS implantation.

The Stanmore Erectile Function Questionnaire

Name: _____
Date of birth: _____
Date of injury: _____
Level of neurological injury: _____
Complete? _____

Date of SPARSI: _____

After your injury:

How long before some erections returned? _____
Have you used (please give dates and frequency eg. 5 times between 1994 and
1996, or once a week)
        -vacuum device _____
        -caverject or other intracavernosal injections _____
        -MUSE _____
        -viagra _____

Did you have any sensation in the genital area
        a) before the SPARSI operation? _____
        b) after the SPARSI operation? _____

Note:
With questions that involve putting a cross on a line: the line is a scale between
one extreme and another. For instance, for warm water:

cold water   ✗   hot water
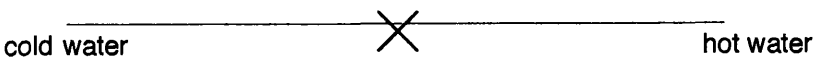
Before SPARSI (eg a month before the operation):

How often did you think about sex? (put a cross on the line)

_____
never   all the time

How often (on average) did you get a spontaneous erection (without the area being touched)? _____
        - and how long did it last (give a range & average eg. 2 to 10 mins, average 5mins) _____

Did you always get an erection when
        a) you stimulated/touched the genital area ? _____
        b) your partner did? _____
(if you didn't, give a fraction eg 'half the time')

Your best erections before the operation (without using caverject/ viagra/ MUSE/ vacuum device):

_____
completely flaccid/soft   completely rigid

Your average erection before the operation

_____
completely flaccid/soft   completely rigid

About one month before SPARSI, were you able to have penetrative sex with your partner without using caverject/ viagra/ MUSE/ vacuum device? _____

How long were you able to have sex for?   a) maximum _____
                                                                           b) average _____

Did you use caverject/ viagra/ MUSE/ vacuum device (which?) _____
How long are you able to have sex for? a) maximum _____
                                                               b) average _____
Did you ever ejaculate?

_____
never   a fifth of the time   always

At any time since your injury:

Have you had a partner since your injury? _____
When were you most active sexually before the implant (eg. '3 years ago')? ____

At this time were you able to have penetrative sex with your partner?
- and how often did you have it? _____
- how long were you able to have it for: a) maximum _____
b) average _____
- did you need to use caverject/ viagra/ MUSE/ vacuum device? _____
(if so, which?) _____

After SPARSI (eg a two months after the operation):

How often do you think about sex? (put a cross on the line)

_____
never   all the time

How often (on average) do you get a spontaneous erection (without the area
being touched)? _____
- and how long does it last (give a range & average eg. 2 to 10 mins,
average 5mins) _____

Do you always get an erection when
a) you stimulate/touch the genital area ? _____
b) your partner does? _____
(if you don't, give a fraction eg 'half the time')

Your best erections after the operation (without using caverject/ viagra/ MUSE/
vacuum device):

_____
completely flaccid/soft   completely rigid

Your average erection after the operation

_____
completely flaccid/soft   completely rigid

About two months after SPARSI, are you able to have penetrative sex with your
partner without using caverject/ viagra/ MUSE/ vacuum device? _____

How long are you able to have sex for? a) maximum _____
b) average _____

Do you use caverject/ viagra/ MUSE/ vacuum device (which?) _____
- and is this always successful? _____
- and how often do you use it? _____

Do you ever ejaculate?

never   a fifth of the time   always

Finally, has the implant changed your thinking about sex? Are you more or less confident? Would you be more or less likely to have sex? Also write any comments here that you feel the questionnaire has missed out.

Appendix 4,
page 1
Figures in red refer
to *notes*, page 2

A decision tree for participation in the SPARS project

Start: patient interested in & suitable for SARS/SPARS?

↓

detailed vidourodynamics (ideally with sphincter EMG or sphincter pressure measurement)[1]

↓

bladder capacity without anticholinergics >300-400ml? — no → **is neuromodulation effective and attractive to the patient?[2]** — no →

- yes ↓ (from bladder capacity)
- yes ↓ (from neuromodulation)

fires off >100ml at detrusor pressure <80cm water [3] — no →

- yes ↓

is there DSD? [4] — yes → **Good Emptying on PNE? [5]** — no → **willing to have a rhizotomy if necessary ?** — no → **abandon implant**

- no ↓ (from is there DSD)
- yes (handwritten, arrow pointing down-left)

willing to have a rhizotomy if necessary? — yes ↓

extradural implant without rhizotomy - +/- neuromodulation ← yes — **happy with a 2 stage procedure?** — no → **extradural implant with rhizotomy**

↓ (from extradural implant)

is bladder capacity poor in spite of neuro-modulation? — yes → **conus rhizotomy [7]**

- no ↓

does DSD prevent good emptying? — yes → **willing to undergo further procedures? (eg sphincterotomy, α blockade) [6]** — yes → **sucessful emptying?**

- no (from willing to undergo) → **conus rhizotomy [7]**
- no (from sucessful emptying) → **conus rhizotomy [7]**

- no ↓ (from does DSD prevent good emptying)
- yes ↓ (from sucessful emptying)

succesful SPARS implant

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[1] This protocol sheet assumes that the patient can generate detrusor pressures of >50cm water (see the Finetech-Brindley notes for surgeons). If they do not, a percutaneous nerve evaluation test is advised to establish the integrity of the motor nerve supply to the bladder.

[2] The practicalities and uncertainty involved with neuromodulation must be discussed with the patient. Although the initial results are encouraging, there is not enough data to be confident that successful Dorsal Penile Nerve Neuromodulation implies successful long term implant-driven neuromodulation. Also, neuromodulation will inevitably require more frequent postoperative follow-up. Patients must be aware of the currently unwieldy method of continuous stimulation using skin fixation of the transmitter; however, they can be reassured that the current electrodes should be compatible with future fully implanted devices capable of continuous stimulation.

[3] These figures are necessarily arbitrary. Current experience with implants without rhizotomy (n=4) suggests that for a given detrusor pressure, implant-driven emptying will be roughly as effective (at best) as spontaneous emptying ('firing off') . Therefore, efficient spontaneous voiding is a good prognostic sign. Also, if firing off occurs at low pressures, there is the potential to achieve better emptying with the stimulator by increasing detrusor pressure. Therefore, firing off at low pressures is a good prognostic sign.

[4] After the initial VCMG, further tests may not be necessary. However, DSD is likely to be an important factor for bladder emptying and should be examined in detail. If there is doubt about whether a small degree of DSD is significant, a percutaneous nerve evaluation test may be worthwhile.

[5] Although percutaneous nerve stimulation is a good test for neuromodulation (for instance with the Medtronic Interstm), in our experience it is much more technically challenging to simulate implant-driven emptying (2 out of 3 tests inconclusive). Therefore, if good bladder pressures cannot be achived with the test, the patient should be counselled about the potential need for rhizotomy as a second procedure. It is extremely difficult to estimate the probability that rhizotomy will actually be necessary; current work at the RNOHT should lead to the identification of prognostic factors.

[6] Initial results suggest that incomplete emptying is likely to be associated with detrusor-sphincter dyssynergia. This may have smooth muscle and striated muscle components. To distinguish between these the two, alpha blockade and local anaesthetic bilateral pudendal nerve blocks may be used. Obstruction from the smooth muscle component would be reduced by oral alpha blockade; striated sphincter obstruction would be reduced by botulinum toxin injection or sphincterotomy.

[7] Conus rhizotomy is very likely to abolish active DSD and increase bladder capacity. However, neither of these is certain, and it should be borne in mind that not all conventional SARS operations are successful (see the Finetech-Brindley notes for surgeons and Brindley GS, Rushton DN. Long term follow up of patients with sacral anterior root stimulator implants. *Paraplegia* 1990; 28: 469

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Appendix 5
Catheterisation volumes for PtC (see figure 5.8)

red: neuromodulation
green: oxybutinin
black: control

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
28/4/00	200	
	400	
	250	
	250	
	200	
	200	100
	375	
	200	
	300	
	250	25
	375	
	375	
	250	
	250	75
	275	
	300	
	300	25
	300	
	250	
	200	100
	250	
	400	50
	350	
	400	25
	300	
	150	25
	300	
	300	
	350	25
	300	
	100	
	300	
	200	
	300	
	300	

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
28/4/00	200	
cont.	375	
	250	
	250	
	350	
	200	
	200	
	300	
	200	25
	250	
	300	50
	200	50
	300	
	350	50
	200	
	150	
	200	
	200	25
16/5/02	120	
	150	50
	100	
	100	50
	100	50
	120	
	100	50
	100	
	120	50
	100	50
	50	50
	200	
	200	
	400	
	300	
31/5/02	150	
	200	
	325	
	250	
	400	
	250	
	200	100
	200	
	200	50
	250	
	300	
	250	
	100	

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
31/5/02	250	
cont.	350	
	250	
	200	
	150	
	275	
	200	
	200	
	200	
	200	
	150	
	200	
	300	
	200	
	400	
	300	
	200	
	300	50
	350	
	200	
	300	
	400	
	150	
	350	
	350	
	200	
	200	
	150	
	150	
	200	25
	200	
	100	
	275	
	250	
	200	
	250	
	150	
22/7/02	200	
	200	
	300	
	200	
	300	
	300	
	250	
	400	25
	200	
	400	25

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
22/7/02	250	
cont.	200	
	300	
	600	
	100	
	400	50
	300	
	300	
	250	
	250	
	250	
	200	
	150	
21/8/02	250	
	250	
	250	
	200	
	150	
	250	
	250	
	250	
	200	
	450	50
	300	
	200	
	450	50
	300	
	300	
	300	50
	200	
	300	50
	250	
	250	
	200	
	200	
	350	
	250	
	500	100
	200	
	250	
	250	
	200	
	250	
	250	
	100	
	400	
	300	

Appendix 6
Catheterisation volumes for PtD (see figure 5.9)

red: neuromodulation
green: oxybutinin
black: control

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
31/3/01	50	
	150	
	170	
	50	
	150	250
	50	
	50	
	100	
	100	100
	70	
	100	
	150	150
	100	100
	100	
	125	75
	150	
	120	
	250	400
	50	
	50	
	150	
	170	130
	100	70
	100	110
	150	200
	50	150
	120	
	110	70
	80	
	50	
	70	110

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
31/3/01	50	70
cont.	100	
	150	
	50	80
	20	30
25/7/01	50	
	50	50
	150	100
	100	100
	150	250
	100	
	50	
	100	50
	100	
	50	
	100	50
	100	
	70	
	0	50
	100	200
	100	50
	100	
	70	
	100	150
	50	100
	80	200
	100	100
	100	
	100	
30/7/01	100	
	100	
	50	50
	70	200
	200	
	220	
	150	150
	50	50
	100	100
	150	
	50	150

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
30/7/01	50	150
cont.	100	
	100	200
	100	200
	100	
	50	200
	100	100
	100	100
	100	100
	100	50
	100	100
	100	
	50	
	100	200
	100	50
	100	0
	150	100
3/8/01	100	0
	100	0
	100	200
	100	100
	0	150
	0	150
	100	0
	150	150
	100	100
	100	150
	150	100
	100	0
	100	150
	100	100
	100	100
	100	100
	100	200
	70	150
	50	100
	50	100
	150	100
	150	150
	100	150
	100	150
	100	100

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
3/8/01	100	300
cont.	100	150
	100	150
	100	150
	100	100
	150	100
	100	100
	100	200
	50	0
	100	100
	100	0
	50	150
	100	150
	100	100
	100	100
	50	100
	100	150
	70	100
	100	150
	100	150
	100	100
	50	100
	100	100
	100	0
	100	100
	50	100
	50	100
	50	100
	100	150
	100	100
	100	100
	50	100
	100	100
	50	100
	100	100
	50	0
	50	0
	100	150
	100	100
	100	100

Start date of measurement period	Vol. at self-catheterisation /ml	Vol. fired off /ml
3/8/01	100	150
cont.	100	150
	50	0
	50	150
	100	150
20/8/01	300	0
	100	0
	150	0
	350	0
	850	0
	150	0
	350	0
	50	0
	350	0
	650	0
	600	0
	250	0
	150	0
	100	0
	350	0
	950	0
3/9/01	200	0
	150	0
	150	0
	150	0
	430	50
	500	0
	150	150
	50	0
	100	50
	100	100
	50	50
	100	0
	100	100
	150	150
	50	150
	50	100

Untreated detrusor hyperreflexia may cause incontinence – and when it occurs with detrusor-external sphincter dyssynergia, high bladder pressures and, if untreated, vesicoureteric reflux leading to renal impairment. Preventing this sequence of events is a primary aim of bladder management in those with spinal cord injury.

Initial experiments with anal stimulation[5] and penile squeeze[6] demonstrated bladder suppression in SCI patients, and over the last 20 years four centres have shown that skin stimulation of the Dorsal Penile Nerve can reliably increase bladder capacity.[3,7–9] Stimulation of the sacral roots, whether magnetically[10] or by percutaneous[11] or implanted electrode,[12] is probably at least as effective. However, although there is now a large quantity of data about the short term effects of neuromodulation, it has been more difficult to apply it in the long term. Two groups have shown that application of sacral root stimulation via implanted electrodes can increase capacity to a functionally useful degree,[12,13] but the situation in spinal cord injury lags behind the treatment of the urinary urge group, where the Medtronic Interstim is an accepted and effective implant.[2]

The Finetech-Brindley Sacral Anterior Root Stimulator (SARS or Vocare, Neurocontrol, USA) is an established and successful device for bladder and bowel emptying in Spinal Cord Injury, and is usually accompanied by a rhizotomy of the posterior (sensory) sacral roots. Although the early SARS devices were often implanted without rhizotomy, the procedure became standard as its great benefits were realised: a low pressure, high capacity bladder and elimination of active detrusor-external urethral sphincter dyssynergia.[14] However, rhizotomy is unacceptable to many patients because it abolishes reflex erection and ejaculation, and is destructive – the latter becoming an increasingly important factor as the prospects for spinal cord regeneration improve. It may also cause sphincter and pelvic floor weakness, and in a minority of patients, stress incontinence.[15]

Without rhizotomy, a SARS device has the potential to be used for neuromodulation to increase bladder capacity, and neurostimulation for bladder and bowel emptying. It is then a Sacral Posterior and Anterior Root Stimulator – SPARS. Because the effects of neuromodulation are mediated by myelinated A afferent fibres,[16] it can be achieved by low-level stimulation of the mixed sacral roots, with more

intense stimulation to activate preganglionic efferent B fibres to empty the bladder and bowel when required. Use of an extradural device to stimulate the mixed nerves is simpler and probably safer than intradural separation into anterior and posterior roots.

The aim of this study was to establish the efficacy of both acute and chronic neuromodulation via a Finetech-Brindley stimulator in SPARS configuration. We describe three patients in which neuromodulation and bladder stimulation have been achieved with this device.

Materials and Methods

Local ethics committee approval and informed consent were obtained. Five patients were implanted with SPARS devices. All had detrusor hyperreflexia (as defined by International Continence Society[17]) preoperatively, but in two patients this was not present postoperatively. The patients are listed in Table 1.

Cystometry
Anticholinergic medication was stopped at least 4 days before cystometry. In all tests, a filling rate of 10 ml/min was used. This was chosen to be as close as possible to natural filling while allowing a sufficient number of cystometrograms to be performed on one day. Filling was stopped when there was a sustained rise in bladder pressure of > 35 cm water, or incontinence – 'firing off'. Bladder capacity was calculated by adding the volume fired off to the residual measured by aspiration. Two types of urethral catheter were used: either standard urodynamics catheters (10 French filling and small bore pressure catheter) or a four channel microtip pressure transducer (Gaeltech, Isle of Skye, UK). The latter has three urethral and one bladder pressure transducer; between them is an asymmetric balloon which, with gentle pulling, lodges in the bladder neck. The position of the catheter was confirmed by observing rapid, large pressure rises with SPARS stimulation at the urethral transducers, characteristic of external urethral sphincter contraction. All tests were conducted in the supine position.

Preoperative tests
In each patient, two control cystometrograms were performed to establish baseline bladder capacity. The

Table 1 Patient details and preoperative management

Initials	Age (years)	Neurological deficit	Date of injury	Bladder management	Daily dose of oxybutinin (mg)
GD	46	T3 complete	Jun 1995	ISC	30
DL	34	T4 complete	Oct 1995	ISC	30
PG	38	T10 complete	Jan 1995	ISC, condom	15
AS	32	T6 complete	1983	condom	none
SN	36	T6 complete	Oct 1995	ISC	30

ISC = intermittent self catheterisation; complete = Frankel A

Original Article

Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator

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Study design: Investigation of five patients receiving an implant, using laboratory cystometry and self-catheterisation at home.

Objectives: To use the established Finetech-Brindley sacral root stimulator to increase bladder capacity by neuromodulation, eliminating the need for posterior rhizotomy, as well as achieving bladder emptying by neurostimulation.

Setting: Spinal Injuries Unit, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK.

Methods: Five patients underwent implantation of a Finetech-Brindley stimulator without rhizotomy of the posterior roots. This was either a two channel extradural device (four cases) or a three channel intrathecal device (one case). In each patient, the implant was configured as a Sacral Posterior and Anterior Root Stimulator (SPARS). Postoperatively, repeated provocations using rapid instillation of 60 ml saline were used to determine the relative thresholds for neuromodulation using each channel. The effect of continuous neuromodulation was examined in the laboratory using slow fill cystometrograms, and conditional stimulation was also studied (neuromodulation for 1 min to suppress hyperreflexic contractions as they occurred). In one patient, neuromodulation was applied continuously at home, and volumes at self catheterisation recorded in a diary.

Results: Reflex erections were preserved in each patient. In three patients, detrusor hyperreflexia persisted postoperatively and neuromodulation via the implant was studied. In these three patients, the configuration was: S2 mixed roots bilaterally (channel B), and S34 bilaterally (channel A). Both channels could be used to suppress provoked hyperreflexic contractions, with the S2 channel effective at a shorter pulse width than S34 in a majority of cases. Continuous stimulation more than doubled bladder capacity in two out of three patients during slow fill cystometry. Conditional stimulation was highly effective. In the one patient who used continuous stimulation at home, bladder capacity was more than doubled and the effect was comparable with anticholinergic medication. Bladder pressures > 70 cm water could be achieved with intense stimulation in three patients, but detrusor-external urethral sphincter dyssynergia (DSD) prevented complete emptying.

Conclusions: Neuromodulation via a SPARS was effective and may replace the need for posterior rhizotomy. However, persisting DSD may prevent complete bladder emptying and warrants further investigation.

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Keywords: male; human; bladder; neurogenic, therapy; spinal cord injury

Introduction

It has been known for some time that stimulation of the pudendal afferents or sacral nerve roots suppresses bladder activity. This effect is observed in normal subjects,[1] idiopathic bladder instability,[2] and in the detrusor hyperreflexia that is the likely consequence of spinal cord injury.[3] It can be termed neuromodulation, where 'the influence of activity in one neural pathway affects the pre-existing activity in another by synaptic interaction.[4]

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In the home experiments, bladder volume at self catheterisation was the primary measure. Results were compared using a two-tailed Mann-Whitney U test with a significance level of 95%.

Results

Preoperative neuromodulation with dorsal penile nerve stimulation

This resulted in at least a 70% increase in bladder capacity in four patients (GD, DL, SN, PG). In AS, detrusor hyperreflexia occurred at a bladder volume of 400–500 ml, so that continuous neuromodulation was not tried; previous experiments had demonstrated suppression of provoked hyperreflexic contractions with dorsal penile nerve stimulation. The results are shown in Figure 1. Volume increased progressively with each neuromodulation fill.

Postoperative findings

In all five patients, reflex erections were preserved. In four patients, they were 'no different' compared to

preoperatively, and in AS (who had other evidence of damage to the posterior roots) they were still present but less frequent than before implantation.

In two patients (AS and SN), detrusor hyperreflexia was present preoperatively but was not reproducible postoperatively either during slow filling or on provocation with rapid instillation of saline. In both cases, changes in the threshold for the DPN reflex and skeletal muscle and bladder responses to stimulation suggested partial sacral root damage. These patients will not be described in the sections on postoperative neuromodulation that follow.

Postoperative tests using provoked contractions

In each of the three patients, it was possible to determine thresholds for suppression of provoked contractions using each channel of the stimulator. A sample series of provocations (with controls) is shown in Figure 2, and the method for calculation in Figure 3.

There was considerable variation between days 1 and 2 in the calculated thresholds for neuromodulation (Table 2). In four out of six tests, the threshold pulse width for suppression of provoked contractions was lower with the S2 channel, and the mean threshold for the 2 days testing was lower with S2 in two out of three patients.

The threshold for neuromodulation was also expressed as a multiple of the threshold for urethral or anal sphincter contraction. adjusted in this way, the mean S2 threshold is lower than the mean S34 threshold in each patient (Table 2). Anal and urethral sphincter pressure rises at the threshold for neuromodulation were not consistently higher with S2 or S34.

The degree of skeletal muscle contraction at the threshold for neuromodulation using each channel is shown in Table 3.

Figure 1 Results of preoperative Dorsal Penile Nerve neuromodulation in each patient

Slow fill cystometry with neuromodulation

In each patient, neuromodulation increased bladder capacity. DL has high pressure detrusor hyperreflexia, and neuromodulation on three occasions has increased his capacity by no more than 35%. Results in PG and GD are better (Figure 4). Conditional
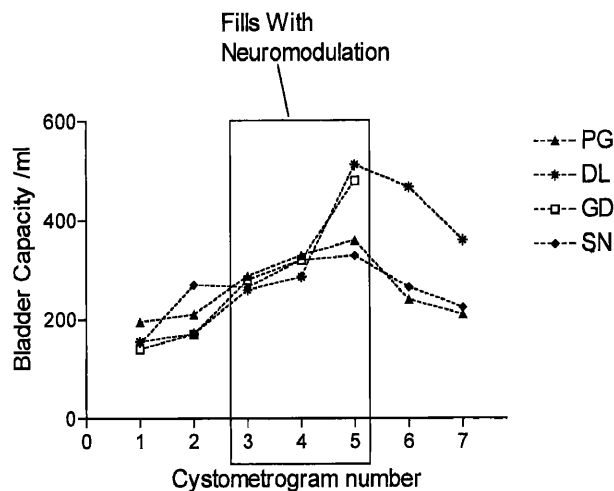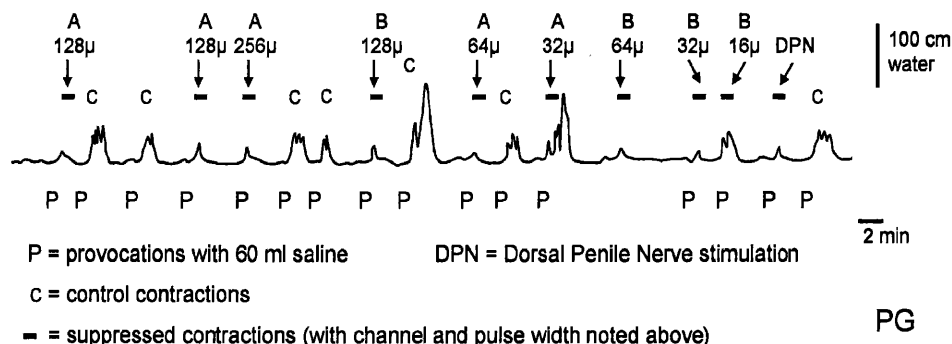

Figure 2 Tracing showing method for determination of threshold for suppression of provoked hyperreflexic contractions (in this case in DL). Channel B = S$_2$, Channel A = S$_{34}$

effects of neuromodulation via Dorsal Penile Nerve stimulation were then studied. Stimulation was via Ag/AgCl self-adhesive electrodes, at a frequency of 15 Hz, pulse width 200 μs and current set at twice the threshold for the pudendo-anal reflex. The parameters used were derived from previous work at our institution using provoked contractions.[18] Bladder capacity with continuous stimulation was measured during three fills with neuromodulation. If possible, a final control fill was performed to assess the residual effects of neuromodulation.

Implantation
In four patients (AS, GD, DL, PG), a laminectomy from L_5 to S_2 was performed. Standard Finetech-Brindley extradural electrodes (Neurocontrol, Cleveland, USA) were placed bilaterally on the mixed S_2 roots (channel B) and bilaterally on the mixed S_3 and S_4 roots (channel A). In one patient (SN), a three channel intrathecal implant was used, with electrodes placed bilaterally on S3 anterior roots (channel A), S3 posterior roots (channel B) and S4 mixed roots (channel C).

Postoperative tests
Postoperative cystometry was used to confirm hyperreflexia and record baseline bladder capacity. The effects of sacral root stimulation were then examined in detail, as follows:

Provocations Repeated rapid instillations of 60 ml Normal Saline over 5–10 s at room temperature were used to provoke hyperreflexic contractions. Provocation was deemed successful if detrusor pressure rose by 15 cm water or more. In almost all cases such a pressure rise indicated the start of a hyperreflexic contraction. If the provocation was not successful, a further 60 ml was instilled. Control and neuromodulation provocations were interleaved, and stimulation was always conditional – applied only once the bladder pressure rise of 15 cm water had occurred. At the end of each provocation test, 60 ml was aspirated from the bladder.

As in the tests with Dorsal Penile Nerve stimulation, frequency was set at 15 Hz. The Finetech-Brindley device allows only large variations in the intensity of stimulation, and for neuromodulation this was always set at 1 (the lowest available). The pulse width was varied from 8 to 256 μs to determine the threshold value for successful neuromodulation. This also allowed determination of thresholds for urethral and anal sphincter contraction.

Slow fills After two control cystometrograms, bladder capacity was measured with continuous stimulation via the SPARS. The pulse width was set at between 1.5 and 5 times the threshold level determined using provoked contractions for both channels. This was always several times less than the level necessary to produce a bladder contraction. In addition, in one patient alternating fills were performed using the S2 and S34 channels to confirm the efficacy of neuromodulation with each.

In two patients, the effects of conditional neuromodulation were studied. Here, stimulation was applied for 1 min at the start of a hyperreflexic contraction[9] – defined as a rise in intravesical pressure of greater than 10 cm water. If the contraction was not completely suppressed after 1 min, stimulation was continued for a further minute. These parameters were derived from previous work on conditional neuromodulation via the dorsal penile nerve.[9] The criteria for ending filling were the same as during continuous fills.

Long term neuromodulation In one patient, the transmitter of the Finetech-Brindley device was fixed to the skin using a variety of stoma management materials, and continuous stimulation applied at between three and six times the threshold for suppression of provoked contractions. Two identically programmed transmitter boxes were used alternately, to allow charging. Bladder capacity was measured by self catheterisation, and where incontinence occurred before catheterisation, an attempt was made to estimate its volume. A program of 50 s on, 50 s off stimulation was tried and comparison periods with no stimulation and with oxybutinin were included.

Bladder emptying Conventional interval voiding programs were tried in each patient, and optimised using videourodynamics and the multitip urethral pressure transducer.

Erectile function Patients completed a questionnaire of erectile function before and after the implant. Because reflex erections in spinal cord injury are often variable, we considered this more accurate than testing erectile function in the laboratory.

Criteria for measurement and data analysis
In the preoperative and postoperative tests using slow filling, bladder volume at firing off or sustained detrusor pressure rise >35 cm water was recorded for each fill.

In the postoperative experiments using provoked contractions, the primary measure was the threshold pulse width for successful neuromodulation using each channel. This was derived by plotting the area under 60 s of the bladder pressure-time trace for each provocation, with the data fitted where possible to a Boltzmann sigmoid curve. If the fit was not possible, a best-fit line was drawn manually. The threshold for neuromodulation was defined as the pulse width which gave 50% of maximum suppression. For each patient, the provocation tests were repeated on a separate day and the mean of the two thresholds calculated (a total of 6 days' testing).

dyssynergia preoperatively. After implantation, neither was present, so that the behaviour of his bladder was similar to patients who have undergone posterior rhizotomy.

In three patients (DL, PG and SN), intense stimulation resulted in detrusor pressure >70 cm water. Each had incomplete (less than 50%) bladder emptying, and clear evidence of dyssynergic external urethral sphincter contractions (and periurethral and pelvic floor muscle contraction in PG) in the gaps between bursts of stimulation. Examples are shown in Figure 8.

In one patient (GD) it is not yet possible to achieve significant detrusor pressure with stimulation, in spite of intact hyperreflexia and good bladder pressure rises during intraoperative stimulation. The failure to produce a bladder contraction is probably due to a combination of electrode malposition and neuropraxia.

Discussion

At the start of this study, we tested the response to Dorsal Penile Nerve stimulation to ensure that patients

Figure 4 Bladder capacity with short-term continuous neuromodulation via SPARS

responded to neuromodulation before embarking on a SPARS implant. In our experience, bladder capacity almost always increases[9] with this method of neuromodulation if the intensity of stimulation is set at an optimum level. Testing neuromodulation by percutaneous sacral nerve stimulation (in a similar way to the Peripheral Nerve Evaluation (PNE) test used before implantation of the Medtronic Interstim[11]) is more invasive and in this case may not necessarily be more informative: if a patient responds to dorsal penile nerve stimulation, it is reasonable to suppose that the same afferent fibres can be activated by an implant capable of stimulating sacral roots 2 to 4.

In the four patients tested, dorsal penile nerve stimulation markedly increased bladder capacity. The results of laboratory tests are probably best in patients with significant hyperreflexia who have good bladder capacities with anticholinergics: the capacity falls rapidly on stopping this medication, and is restored with neuromodulation. For this reason, the results with acute neuromodulation using different techniques should be compared with caution: the improvement in bladder capacity is highly dependent on the patient group.

This variability means that any attempt to compare the efficacy of neuromodulation via different sacral roots should either involve large numbers of patients, or a method where different roots may be stimulated in the same patient. Although our series consisted of only three patients, it presented a valuable opportunity for the latter. Provocation of unstable contractions is quick and reproducible, allowing the evaluation of a large number of parameter changes during 1 day of testing.

The stimulation program in the Finetech-Brindley control box allows fine variation in pulse width rather than amplitude. At the settings used here, charge delivered is proportional to pulse width and therefore approximates to intensity, but is not exactly equivalent.[19]

Consistent with previous findings,[10,20] detrusor hyperreflexia could be reliably provoked many times in each patient, with a gap of only 3 min between episodes of neuromodulation. That the residual effect of neuromodulation after several minutes was not sufficient to prevent a hyperreflexic contraction contrasts with the persistent effects seen during
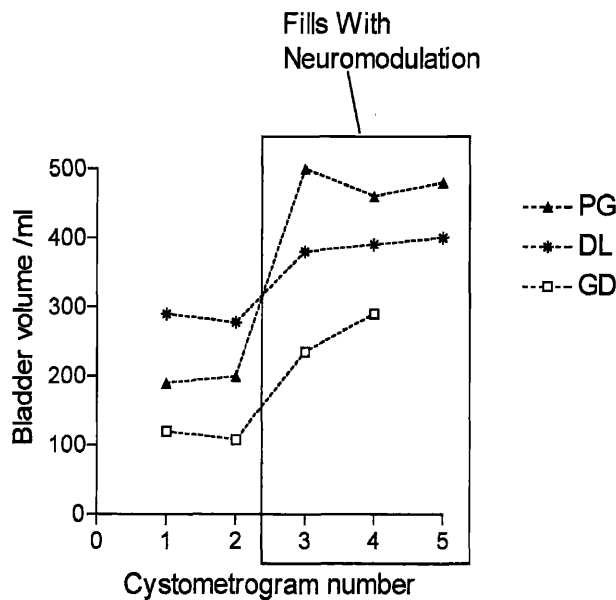

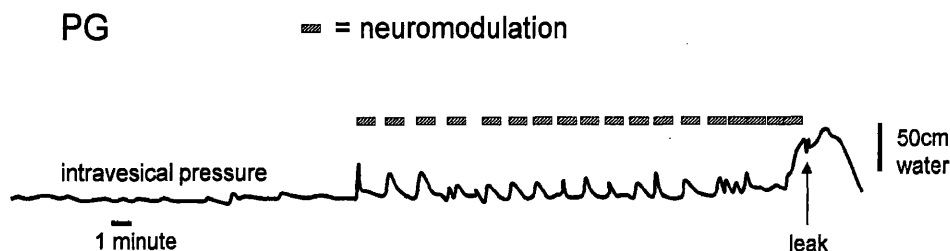**Figure 5** Sample cystometrogram trace in PG during conditional neuromodulation. The bladder was filled from empty at 10 ml/min

Figure 3 Example showing the calculation of threshold for neuromodulation in one patient. For each patient, data similar to this was collected on two separate days

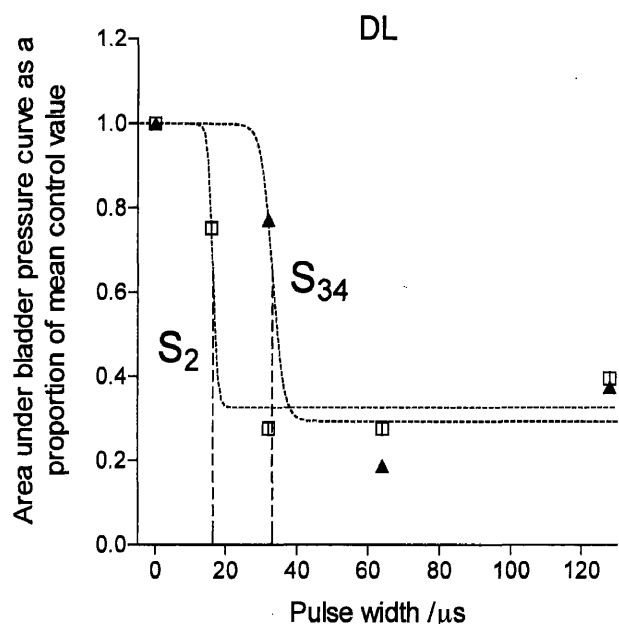neuromodulation via SPARS was also very effective (Figures 5, 6).

Long term neuromodulation
In one subject (PG), neuromodulation was used intermittently at home for a period of 4 months. The volumes at self-catheterisation are shown in Figure 7. The patient found it difficult to wear a sheath, and used an indwelling catheter when urine output was likely to be high or catheterisation inconvenient. This also made accurate estimation of the volume fired off difficult.

The median volume at self-catheterisation (excluding volume fired off) was 100 ml in the control period, and 250 ml in the continuous, on/off and oxybutinin periods. The difference between control and all other periods was highly significant ($P < 0.0001$) in each case. There was not a significant difference between continuous, on/off and oxybutinin periods.

Bladder emptying
In one patient (AS), complete bladder emptying was achieved with intense intermittent stimulation of the S34 channel. However, this patient had mild detrusor hyperreflexia and little evidence of detrusor-sphincter

Table 2 Thresholds for neuromodulation using S2 and S34 channels, and associated urethral and anal sphincter pressure rises

Initials and root	Threshold pulse width for NM/μs day 1/day 2 (mean)	Threshold for urethral sphincter/μs*	Urethral sphincter pressure rise at mean threshold for NM/cm H₂O	Threshold for anal sphincter/μs*	Anal sphincter pressure rise at mean threshold for NM/cm H₂O	Threshold for NM as a multiple of urethral sphincter threshold	Threshold for NM as a multiple of anal sphincter threshold
GD							
S2	8/9.3 (8.6)	7	9	7	8	1.2	1.2
S34	26/30 (28)	7	>170	7	110	4	4
DL							
S2	16.3/124 (70)	14	152	15	92	5	4.7
S34	33/62 (47)	6.5	27	7	95	7.2	6.7
PG							
S2	19/56 (37)	6.5	68	7	170	5.7	5.3
S34	38/54 (46)	7	79	8	195	6.6	5.7

*Figures derived by extrapolation and therefore not precise; NM = neuromodulation

Table 3 Skeletal muscle responses at threshold for neuromodulation using S2 and S34 roots

Initials	S2 skeletal muscle response at mean threshold for NM	Additional S2 response at 3× threshold	S34 skeletal muscle response at mean threshold for NM	Additional S34 response at 3× threshold
GD	none	R>L toe flexion, plantarflexion	R toe flexion	L toe flexion, abdominal spasm
DL	L = R plantarflexion, gluteal contraction	No additional response	L = R toe flexion	No additional response
PG	L = R plantarflexion	R gluteal contraction	R toe flexion	L toe flexion

NM = neuromodulation; L = left; R = right
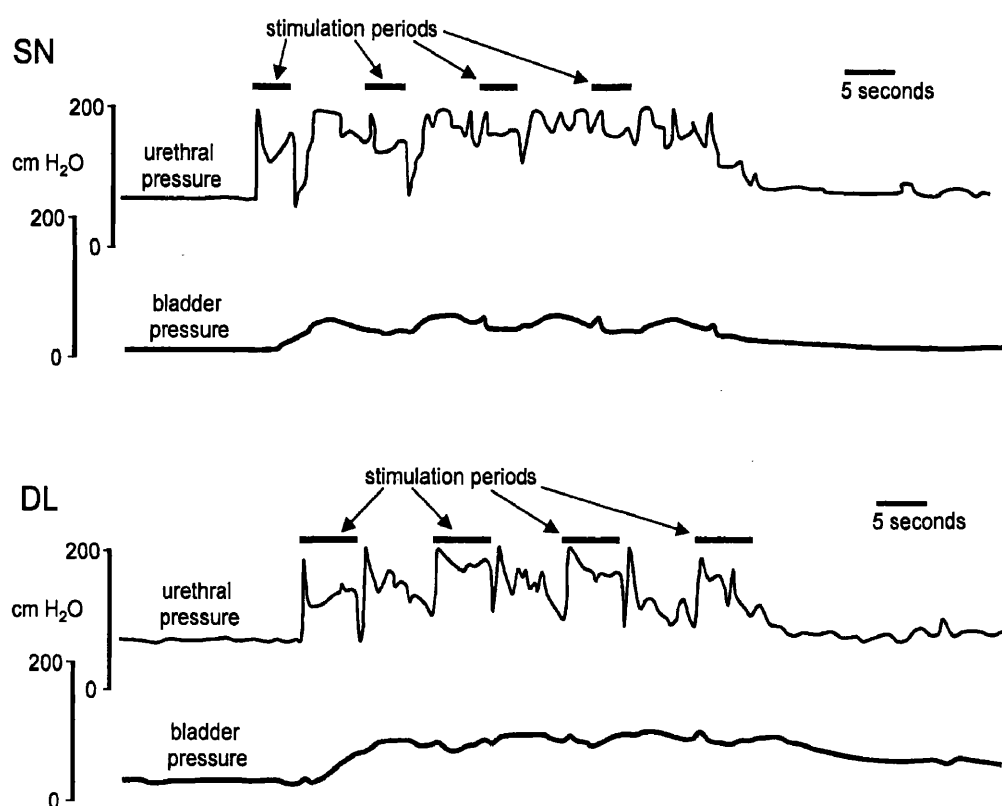
Figure 8 Two examples of intermittent voiding programs for bladder emptying (SN and DL). In each case, detrusor-external urethral sphincter dyssynergia can be seen in the gaps between stimulation

repeated slow fills with continuous neuromodulation, where the effects on bladder volume at first contraction seem to persist for several hours.[9] The likely explanation is that the inhibition of the detrusor reflex gradually diminishes: after 3 min it can be overcome by an intense stimulus (such as the provocation described in this study), but a smaller inhibition can influence the threshold for detrusor hyperreflexia during slow bladder filling. The aim of interleaving of provocations with and without neuromodulation during this study was to minimise the influence of such carry over effects. In all three patients, we found that the area under the detrusor pressure curve for control provocations was not markedly affected by preceding neuromodulation.

Although the results of each day's testing allowed calculation of threshold pulse widths, agreement between the 2 days was poor in DL and only fair in PG. DL has never had marked increases in bladder capacity with neuromodulation, implying that the effect of sacral root stimulation is weak in him, and this may be reflected in the variability of the results with provocation. In PG and GD, S2 stimulation produced neuromodulation at a lower (three out of four tests) or similar (one test) threshold compared to S34, and normalisation of the neuromodulation threshold to the threshold for anal and urethral sphincter contraction did not markedly affect the findings. In GD, however, where the difference is

largest, there is certainly a degree of neuropraxia of the S34 roots, because bladder contractions cannot be achieved. It is therefore likely that there is some neuropraxia of the S34 fibres responsible for neuromodulation, which may account for some of the difference between S2 and S34.

Schmidt has asserted that 'The key to control of the bladder lies in control of the sphincter,[21] and has also observed that stimulation of S2 gives larger external urethral sphincter contractions than S3 or S4,[22] which is consistent with our finding that S2 was in most cases effective at a lower pulse width than S34. However, there is not agreement on this point, and others have found that S3 has the largest contribution.[23] Also, there are several pieces of evidence suggesting that although sphincter contraction may be a marker for an adequate stimulus for neuromodulation, it is not central to the mechanism. Firstly, skeletal muscle paralysis does not abolish bladder suppression in cats,[24] and secondly, stimulation of afferent branches of the pudendal nerve that innervate the region of the external urethral sphincter does not suppress bladder activity in cats, whereas stimulation of afferents from the penis does.[25]

Although our finding of a generally lower threshold for S2 may be due to several causes (some of them artefactual), we have shown that this root certainly can be used for neuromodulation. It is likely that S3 was chosen for the Interstim device
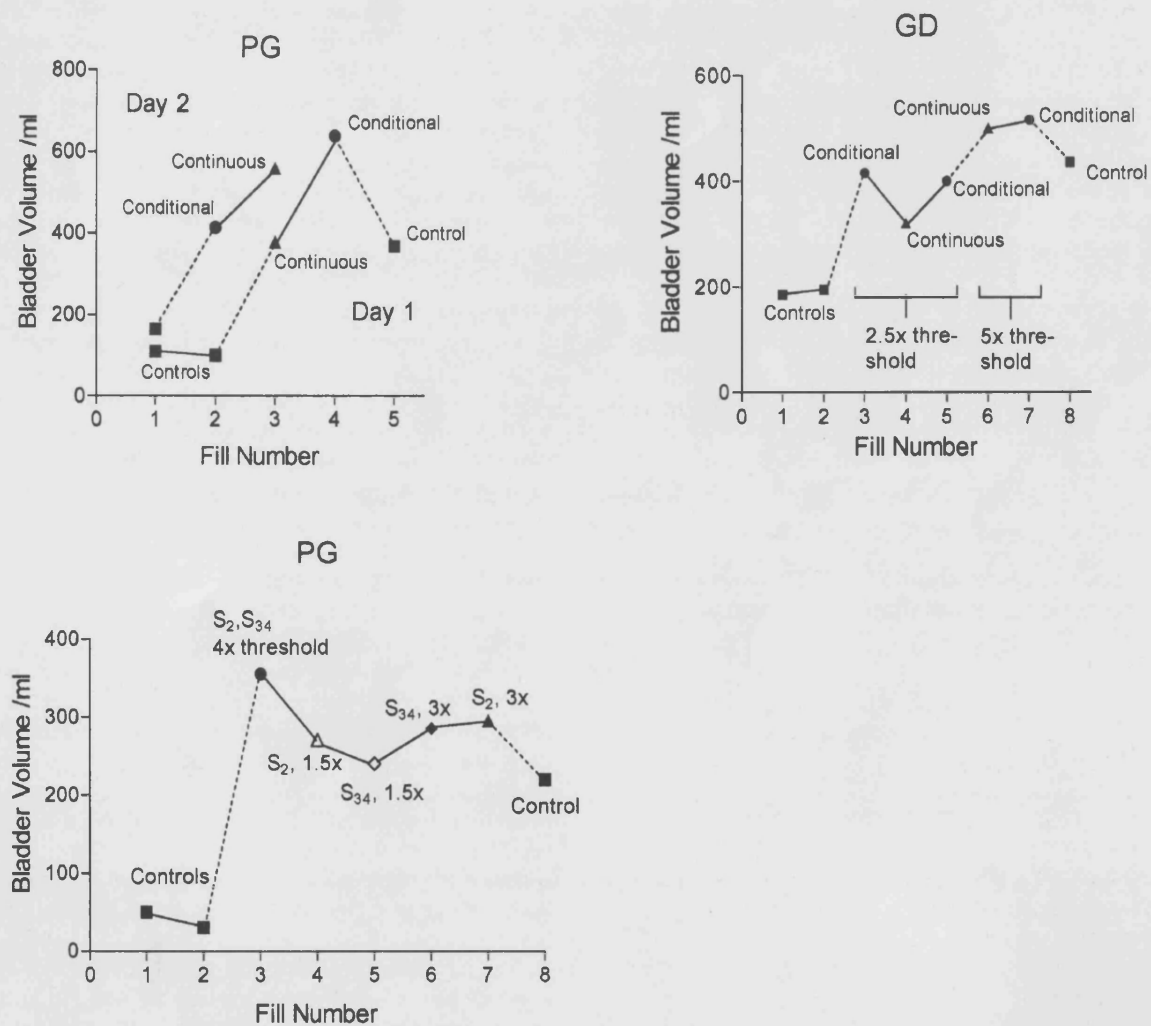
Figure 6 The effect of various parameter changes on the bladder capacity achieved with neuromodulation
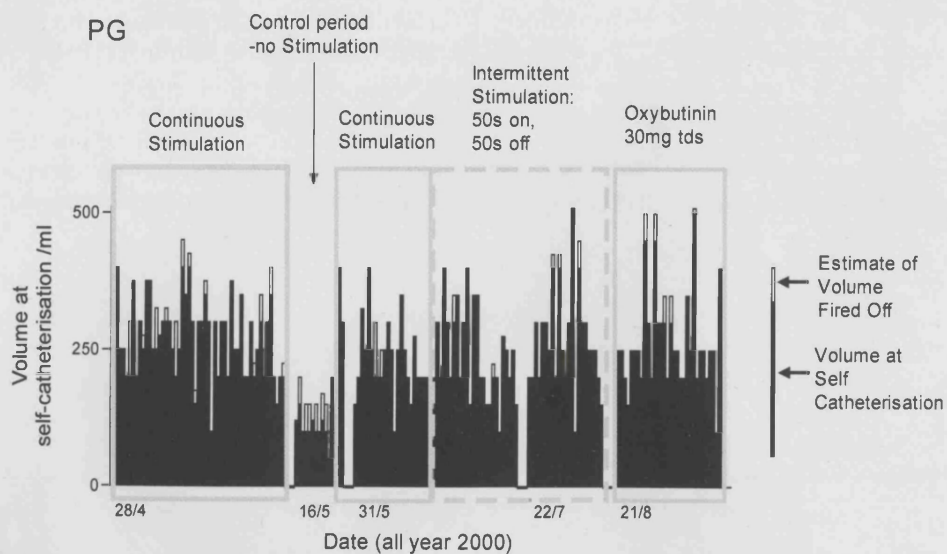

Figure 7 Bladder volume at self-catheterisation: serial measurements during the five marked periods in PG

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(and for previous trials of long-term stimulation in spinal cord injury) because it produces less skeletal muscle contraction than S2.[21] It may be that in neurologically intact patients this does make S3 or S4 preferable, but none of our SCI patients experienced inconvenient skeletal muscle contractions with either S2 or S34 stimulation. Also, one might expect chronic stimulation of the glutei to have a beneficial effect on muscle bulk.

We found that neuromodulation via the SPARS during slow filling can markedly increase bladder capacity: in two patients bladder capacity was more than doubled, and in one it increased by a third. The results were not analyzed statistically because the number of patients was small, bladder capacity is probably not normally distributed and the 'carry over' effect from previous stimulations is considerable.

To study the effect of conditional stimulation, the filling rate should be low (50 ml/min is probably too provocative) and it must be possible to turn the stimulation on and off rapidly. These conditions have not been present in previous studies of sacral root neuromodulation.[11,12] We used conditional stimulation in the two patients who responded well to continuous stimulation, and found it to be highly effective, consistent with a previous finding that conditional stimulation via the dorsal penile nerve is probably at least as effective as continuous.[9] It suggests that current research to develop a device for conditional neuromodulation – capable of detecting bladder pressure rises by recording from the sacral roots, and then suppressing them by stimulation – is justified. The trigger of 10 cm water chosen in this study is similar to the smallest rises in bladder pressure that can be detected by recording from the cat sacral roots.[26]

In previous studies with implanted stimulators for long-term neuromodulation in SCI[12,13] cystometry was performed at predefined intervals after implantation to assess the effect of neuromodulation. Especially with the filling rates used (50 ml/min or greater), this does not necessarily reflect the bladder capacity that the patient experiences at home. It was also not applicable in our case, as the patient used stimulation for variable periods of 4 days to 2 weeks.

Instead, volume at self catheterisation was our primary outcome variable. Recording the volume leaked with a pad and adding this to catheterised volume would have increased the complexity of the measurements and is not necessarily informative: if the patient does not self catheterise immediately after 'firing off', bladder capacity will be overestimated. We considered it more reliable (and easier for the patient) to record bladder volumes at self catheterisation for a long period, and to infer the bladder capacity from the maximum volumes achieved without incontinence. Measuring frequency of self-catheterisation is unreliable as the decision to catheterise is a subjective one, and patients may alter their fluid intake according to their bladder management.

Our current method for long term stimulation is not ideal: it is necessary to fix the transmitter coils to the skin over the subcutaneous receiver for all but the first 30– 60 min after bladder emptying. However, PG used the device intermittently at home over a period of 4 months, and the results show a marked increase in bladder capacity. When stimulation is stopped, this returns in less than 1 day to a much smaller baseline capacity. The effect of neuromodulation was comparable with oxybutinin, although PG stated that incontinence on filling past bladder capacity is generally of larger volume with neuromodulation – when the bladder 'escapes' from electrical suppression, it contracts at close to full force. We did not find that the effect of neuromodulation diminished with time, or that there was a need to increase the stimulation parameters. However, as shown in Figure 8, some incontinence persisted (although stress incontinence was improved with neuromodulation, probably because of persistent urethral sphincter contraction). Volumes with the 50 s on/50 s off program were no worse than with the continuous pattern, and indeed the patient felt strongly that this pattern was more effective than continuous stimulation. He preferred neuromodulation to oxybutinin.

The difficulty in achieving good bladder emptying using the established interval voiding technique is likely to be due to detrusor-external urethral sphincter dyssynergia in DL and SN, and in addition pelvic floor and periurethral muscle spasm in PG. In each case, intact sacral posterior root pathways are likely to be a significant factor. As Brindley suggested,[27] bladder emptying would probably be improved by posterior rhizotomy, and we would not currently implant a SPARS device without rhizotomy in patients with severe detrusor-external sphincter dyssynergia. Brindley's early patients often did not have a rhizotomy, and most achieved good emptying, but the devices were intrathecal and there was posterior root damage in many cases.[28] We are currently investigating different strategies to improve bladder emptying in the patients described here.

In summary, stimulation of the Dorsal Penile Nerve is a simple and non-invasive screening test for the bladder response to neuromodulation. As well as stimulation for bladder emptying, the Finetech-Brindley device can be used to suppress provoked contractions and markedly increase bladder capacity in the laboratory, and we have shown that it is feasible to use long-term stimulation at home as a replacement for oxybutinin. Conditional neuromodulation of the sacral roots was highly effective and is a promising technique for future implanted devices.

Acknowledgements

anticholinergics, drugs which many patients are reluctant to take in high doses and which are not always effective.[16]

In the last 20 years three centres have shown that continuous dorsal penile nerve (DPN) stimulation almost always increases bladder capacity acutely in spinal cord injured patients.[7-9] Shah *et al*[18] have demonstrated that DPN stimulation can reliably suppress provoked hyperreflexic detrusor contractions and have used this technique to define optimum stimulation parameters. Recently, stimulation of the sacral roots has been used successfully to increase bladder capacity in the long term in patients with detrusor hyperreflexia.[19-21]

Neuromodulation can be applied in two fundamentally different ways: (1) conditionally, where it is started as intravesical pressure begins to rise at the beginning of a hyperreflexic contraction, or (2) continuously where it is applied throughout bladder filling. Current systems for long term stimulation use the continuous mode,[19-21] but a conditional system that detects the start of unstable bladder contractions and then suppresses them has theoretical advantages.[22]

Work in animals on a conditional system has shown encouraging early results,[22,23] and it is vital that the technique is evaluated in humans as it becomes technically feasible. DPN stimulation is ideal for these tests because it is simple, effective and non-invasive. For these reasons, it is also a convenient screening test for the response to neuromodulation before considering an implanted device.

The aim of this study was to determine the acute urodynamic effects of both conditional and continuous modes of DPN stimulation in patients with a spinal cord injury, and to compare them where possible.

Materials and methods

Fourteen consecutive male patients were studied. They had complete or incomplete traumatic lesions of the spinal cord, with neurological levels between C6 and L1, and were at least 1 year post injury. Anticholinergic medication was stopped at least 4 days before the tests. Local ethics committee approval and informed consent were obtained.

Urodynamics

Two different types of catheter were used. In the tests with continuous stimulation only, an 8 French bladder filling catheter and a standard water-filled bladder pressure line were used. In other studies a four channel microtip transducer catheter with a central filling channel (Gaeltech, Isle of Skye, UK) was used to allow filling, emptying and measurement of intravesical and urethral pressure simultaneously. Anal sphincter pressure was measured at the same time with a one channel microtip transducer. In some cases, it was not possible to measure bladder volume accurately because the position of the microtip catheter made complete aspiration of urine difficult. In these situations we reverted to a standard 8 French filling catheter and water filled pressure line. Patients were in the supine position.

Two or three control cystometrograms were always performed at the start of each study. Filling was always at 10 ml/min – this was chosen to be as close as possible to natural filling rates whilst enabling the necessary number of cystometrograms (CMGs) to be performed in 1 day. Cystometrograms with neuromodulation were then performed, followed (if time permitted) by final control CMGs. At the end of each CMG, total bladder capacity was calculated by adding the volume voided to the residual volume measured by aspiration.

In each test, filling was stopped when there was a sustained pressure rise of greater then 35 cm water, or voiding – 'firing off'. Compliance was measured as follows: (volume fired off + residual urine volume/ml)/ (intravesical pressure before end-fill unstable contraction – starting intravesical pressure/cm H_2O). This parameter was measured in the continuous fill experiments only.

Neuromodulation was by stimulation of the dorsal penile nerve, using cutaneous self-adhesive siver-silver chloride electrodes and an electrically isolated stimulator (model DS7: Digitimer, Welwyn Garden City, Hertfordshire, UK). The frequency of stimulation was always 15 Hz, with a pulse width of 200 μs. The current was set between 20 and 60 mA, at a level equal to twice the threshold for contraction of the anal sphincter (the level which reliably gave a detectable contraction).

In the tests involving conditional neuromodulation, stimulation was triggered manually after a pressure rise of 10 cm water. Neuromodulation was applied for 1 min, and continued for a further minute if intravesical pressure was not suppressed to within 10 cm H_2O of the baseline.

Simultaneous measurements of anal sphincter and urethral sphincter pressure enabled a comparison of thresholds for the pudendo-anal and pudendo-urethral reflexes.

Protocols

Four protocols were used: (i) Continuous stimulation: Three control fills, followed by three fills with continuous neuromodulation, followed by two final control fills (six patients). (ii) Conditional stimulation: Two control fills, followed by two or three fills with conditional neuromodulation, followed by at least one control fill (six patients). To compare continuous and conditional modes: (iii) Alternating modes on the same day: two control fills, followed by alternating conditional and continuous fills (at least two of each type), followed by at least one final control fill (three patients). (iv) Two days of testing: on each day, two initial controls. Then two or three fills with either continuous or conditional neuromodulation (three patients).

Original Article

The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury

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Study design: Laboratory investigation using serial slow-fill cystometrograms.

Objectives: To examine the acute effects of different modes of dorsal penile nerve stimulation on detrusor hyperreflexia, bladder capacity and bladder compliance in spinal cord injury (SCI).

Setting: Spinal Injuries Unit, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK.

Methods: Fourteen SCI patients were examined. Microtip transducer catheters enabled continuous measurement of anal sphincter, urethral sphincter and intravesical pressures. Control cystometrograms were followed by stimulation of the dorsal penile nerve at 15 Hz, 200 μs pulse width and amplitude equal to twice that which produced a pudendo-anal reflex. Stimulation was either continuous or in bursts of one minute triggered by a rise in detrusor pressure of 10 cm water (conditional). Further control cystometrograms were then performed to examine the residual effects of stimulation.

Results: Bladder capacity increased significantly during three initial control fills. Continuous stimulation ($n = 6$) significantly increased bladder capacity by a mean of 110% ($\pm$ Standard Deviation 85%) or 173 ml ($\pm$ 146 ml), and bladder compliance by a mean of 53% ($\pm$ 31%). Conditional stimulation in a different group of patients ($n = 6$) significantly increased bladder capacity, by 144% ($\pm$ 127%) or 230 ml ($\pm$ 143 ml). In the conditional neuromodulation experiments, the gap between suppressed contractions fell reliably as bladder volume increased, and the time from start of stimulation to peak of intravesical pressure and 50% decline in intravesical pressure rise was 2.8 s ($\pm$ 0.9 s) and 7.6 s ($\pm$ 1.0s) respectively. The two methods of stimulation were compared in six patients; in four out of six conditional neuromodulation resulted in a higher mean bladder capacity than continuous, but the difference was not significant.

Conclusions: Both conditional and continuous stimulation significantly increase bladder capacity. The conditional mode is probably at least as effective as the continuous, suggesting that it could be used in an implanted device for bladder suppression.
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Keywords: male; detrusor hyperreflexia; spinal cord injury; electric stimulation therapy; reflex physiology; penis, innervation

Introduction

Over the last 30 years, the effects on the bladder of stimulating the pudendal afferent nerves have been studied in some detail. Penile squeeze,[1] anal stretch,[2] electrical stimulation by anal or vaginal plug electrodes,[3–5] dorsal penile nerve[6–9] stimulation and magnetic[10] or electrical[11] stimulation of the sacral roots have all been shown to suppress bladder activity. The

effect is seen in normal subjects,[12] spinally injured patients[5,7–11] and those with idiopathic bladder instability.[6,13,14]

Such stimulation can be termed neuromodulation, in which 'activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction'.[15] Neuromodulation in spinally injured patients has the potential to suppress the detrusor hyperreflexia that is the result of lesions of the spinal cord above the cauda equina, and if untreated may contribute to incontinence, vesicoureteric reflux and renal failure. It may be a better tolerated alternative to

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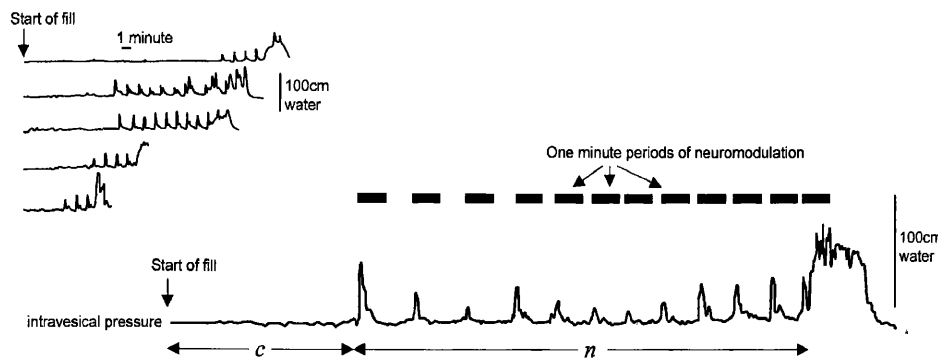
Figure 1 Sample conditional stimulation fill, starting with an empty bladder. n represents the additional bladder capacity from neuromodulation. Complete intravesical pressure traces in a further five patients during the first conditional neuromodulation fill are shown on the top left
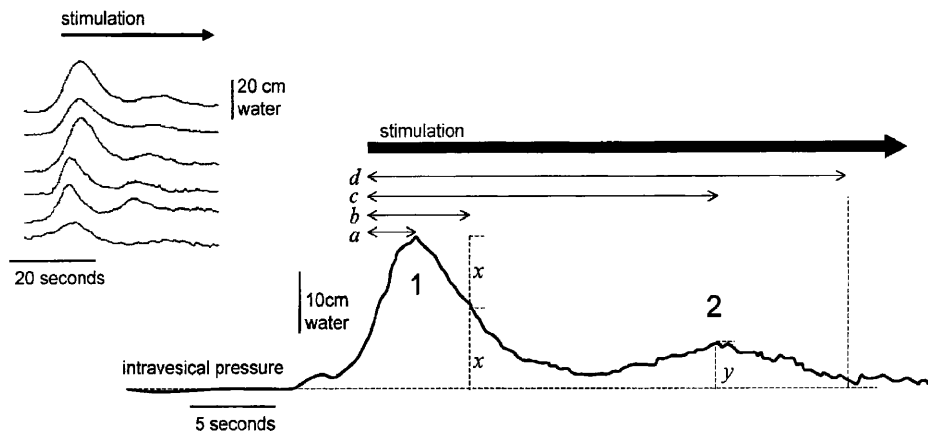
Figure 2 A suppressed contraction during conditional neuromodulation. Curves from the middle of the neuromodulation period in six further patients are shown on the top left
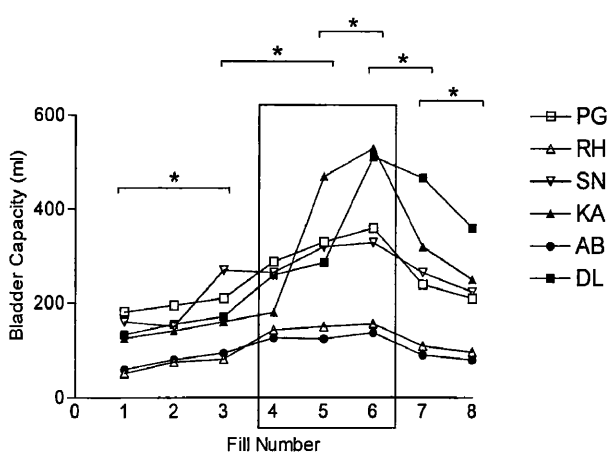
Figure 3 Individual results with continuous neuromodulation. The box encloses the fills with stimulation. Asterisks represent significant differences $(P<0.05)$
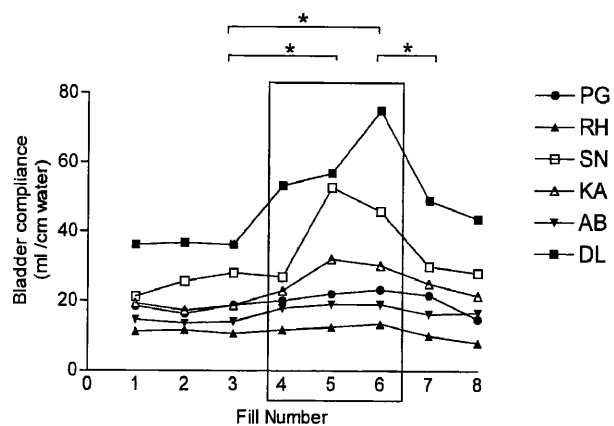
Figure 4 Change in bladder compliance with continuous neuromodulation in six patients. The box encloses the fills with stimulation. Asterisks represent significant differences $(P<0.05)$

The peak of the suppressed contraction ($2x$ in Figure 2) was on average 30 cm H_2O (± 8.7 cm H_2O) above baseline. Several parameters were strikingly similar between patients – the mean time from start

of stimulation to peak of suppressed contraction, and time for the contraction to fall to 50% of peak were 2.8 s (± 0.9 s, range 2.3–3.2 s) and 7.6 s (± 1.0 s, range 6.6–8.7 s) respectively (a and b in Figure 2).

Criteria for analysis
In the experiments with continuous neuromodulation (protocol i), analysis parameters were end fill bladder volume and bladder compliance.

In the experiments with conditional neuromodulation (protocols ii, iii, iv), parameters were end fill bladder volume and time between suppressed contractions. As secondary parameters, we noted time from start of neuromodulation to peak of suppressed contraction, time to 50% decay of suppressed contraction and time to return to within 10% of baseline intravesical pressure. The order of continuous and conditional fills in protocols iii and iv was not formally randomised, and the comparison between the two techniques was a secondary criterion for analysis.

In all experiments, the threshold for the pudendo-anal reflex was recorded, and if possible, the threshold for the pudendo-urethral reflex.

Data analysis
In the results that follow, figures in brackets represent one standard deviation, with ranges (where stated) indicating minimum and maximum values. The statistical test used was a two-tailed Wilcoxon matched pairs test, except when comparing patients with incomplete and complete lesions. Here, a two-tailed Mann-Whitney U-test was used; in both cases a P value of <0.05 was considered significant.

Because the effects of neuromodulation often became larger with successive fills, in most cases we compared greatest (ie maximum) control fill volume (in all cases at least two controls were performed) with greatest neuromodulation fill volume. This gave the best indication of the potential effect of long term neuromodulation. The exception to this was the comparison between continuous and conditional fills in protocols iii and iv. Here, the mean for the conditional and continuous fills was calculated for the comparison (equal numbers of each type of fill were always compared).

Results from the conditional experiments were analysed in two ways: (i) Time method: a constant rate of filling was assumed – justified because the filling rate of 10 ml/min was likely to be much higher than the patient's urine output. The time to first unstable contraction (c in Figure 1) and time of successful conditional suppression (n in Figure 1) were measured. The fraction n/c then represented the proportional increase in bladder capacity with neuromodulation. Because of 'carry over' effects, this measurement was only justified in the first conditional neuromodulation fill of the day, before any continuous neuromodulation had taken place and (ii) Volume method: as in the continuous neuromodulation experiments, volume was measured by aspiration at the end of each fill.

The characteristics of the suppressed contraction (including time to peak, and time to return to within 50% and 10% of baseline – a, b and d in Figure 2) were measured from three suppressed contractions at the

start, middle and end of the conditional neuromodulation period and the mean calculated for each patient.

Results

Pudendo-urethral (PU) and pudendo-anal (PA) reflexes
The catheter configuration enabled direct comparison of the PA and PU reflexes in seven patients. The P-U reflex was usually seen at a lower (but not significantly so) stimulation intensity than the P-A reflex (16.4 *vs* 20.6 mA, $P=0.12$).

Continuous fills (Figures 3 and 4)
The bladder capacity increased significantly during the control fills, with the third control fill higher than the first by a mean of 43% ($\pm 22\%$) ($P=0.03$).

The maximum volume with neuromodulation was greater than the maximum initial control volume by 110% ($\pm 85\%$, range 22–231%) or 173 ml (± 146 ml, range 43–370 ml) ($P=0.03$). The persisting (but diminishing) effect of neuromodulation is demonstrated in Figure 3, with volume falling significantly in each of the final control fills ($P=0.03$ in each case).

The bladder compliance was also significantly ($P=0.03$) increased by neuromodulation, by a mean of 53% ($\pm 31\%$, range 16–104%) in the greatest neuromodulation fill compared to the greatest control.

Conditional fills (Figures 1, 2, 5 and 6)

Time method (six patients: protocol ii) The mean fractional increase in bladder capacity (n/c in Figure 1) was 125% ($\pm 103\%$, range 29 to 300%). In general, percentage increases were higher when the control volume was low. Because this method only measured the first conditional fill, it underestimated the potential increase with conditional neuromodulation: the increase in capacity with subsequent neuromodulation fills is clearly shown in Figures 3 and 5.

Volume method (six patients: protocol ii) The greatest volume with neuromodulation was a mean of 144% ($\pm 127\%$, range 41 to 385%) and 230 ml (± 143 ml, range 97–420 ml) larger than the greatest control volume (Figure 5). In three remaining patients tested with the alternating protocol (iii), the mean increase in the conditional fills was 51% ($\pm 19\%$) or 90 ml (± 6 ml) (Table 2).

The time between suppressed hyperreflexic contractions fell reliably with increasing volume in every patient (Figure 6), although the absolute time varied widely between patients.

Two patients (MC and DS) were excluded from the analysis of conditional neuromodulation in Figure 2 because the tracings were not of sufficient quality, leaving eight patients who were investigated with protocols ii, iii or iv.

Table 1 Patient details

Initials	Age/y	Level	Frankel Grade	Date of injury	Bladder management	Daily dose of oxybutinin	Protocol used
PG	38	T10	D	Jan 1995	ISC, condom	15 mg	i
RH	34	T6	D	Jun 1995	ISC	30 mg	i, ii, iv
KA	37	C6	D	Nov 1996	ISC, condom	30 mg	i
SN	36	T6	D	Oct 1995	ISC	30 mg	i, ii, iv
AB	21	C6	D	Apr 1997	SPC	30 mg	i
DL	34	T4	D	Oct 1995	ISC	30 mg	i
GD	46	T3	D	Jun 1995	ISC	30 mg	ii, iv
MF	20	T6	C	Oct 1998	ISC	30 mg	iii
DS	48	L1	B	1973	ISC, condom	none	iii
SG	29	T2	B	1990	ISC	none	ii
MA	32	T3	D	1994	ISC, condom	15 mg	ii
DQ	29	T4	D	Jul 1998	ISC	7.5 mg	iii
DH	29	T7	D	Apr 1999	ISC	22.5 mg	(ii)*
MC	37	T5	D	Mar 1999	ISC, condom	4 mg Tol.	ii

ISC = intermittent self catheterisation; SPC = suprapubic catheter; Tol = Tolterodine; (ii)* = one conditional fill only

Table 2 Results using protocol iii

Patient, protocol	Control fill volumes/ml	Volumes with continuous/ml	Volumes with conditional/ml	Mean increase with continuous/ml (%)	Mean increase with conditional/ml (%)
MF iii (continuous first)	190, 210, 210	340, 265	310, 285	**99 (49)**	**94 (46)**
DS iii (conditional first)	380, 380	460, 470, 405	470, 500, 450	**65 (17)**	**93 (25)**
DQ iii (continuous first)	160, 170	190, 260	215, 280	**60 (36)**	**83 (50)**

**Table 3** Results using protocol iv

Patient, protocol	Control fills (continuous day)/ml	Volumes with continuous stimulation/ml	Control fills (conditional day)/ml	Volumes with conditional stimulation/ml	Mean increase with continuous/ml (%)	Mean increase with conditional/ml (%)
RH iv	75, 81	143, 150	125, 125	185, 222	**69 (88)**	**79 (63)**
SN iv	160, 150, 270	265, 320, 329	182, 180, 220	380, 370, 385	**111 (58)**	**184 (95)**
GD iv	146, 170	280, 320, 480	105, 100	215, 510, 460	**202 (128)**	**309 (301)**

previously high bladder capacity. As expected, patients who were not previously on anticholinergics had less impressive increases, as there is a limit to the distension that can be achieved in a chronically small bladder during 1 day. However, it is possible that neuromodulation over weeks or months would gradually increase capacity beyond the modest acute rises seen here, in a similar way to the gradual increase in capacity seen after posterior rhizotomy.[30] The smaller bladder capacity in our group of patients with incomplete injuries may be accounted for by differences in medication: two out of three of them were not on anticholinergics, while all of the patients with complete lesions were. It is clear that the selection of patients critically affects the results of neuromodu-

lation studies and means that caution is necessary in comparing results from different centres.

Although continuous neuromodulation is an effective and simple way to increase bladder capacity in spinally injured patients, in many situations it is not ideal. The need for constant current delivery would shorten both battery and electrode life in a completely implanted device, and stimulation of sacral afferents has reflex effects on the anal and urethral sphincters. A device which stimulated the mixed sacral nerves for neuromodulation would cause both reflex and direct activation of the sphincters and skeletal muscles. Conditional stimulation might reduce such unwanted effects, and although it requires a method for detecting intravesical pressure, a major possible benefit of this
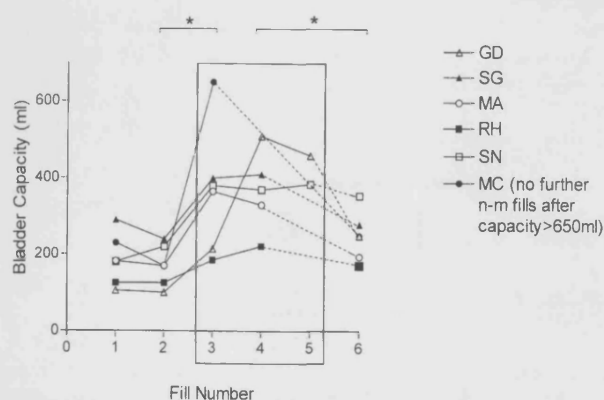
Figure 5 Increase in bladder volume with conditional neuromodulation in six patients. The box encloses the fills with stimulation. Asterisks represent significant differences ($P < 0.05$)
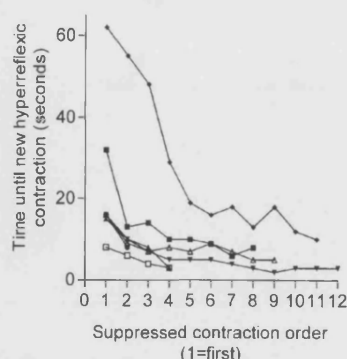
Figure 6 Time between suppressed hyperreflexic contractions during the first conditional neuromodulation fill in seven patients

The initial decay of the suppressed hyperreflexic contraction was approximately fitted by a single exponential function [$y = A + Be^{-t/k}$], with a time constant (k) of 6.9 s (± 0.9 s).

In all cases, the first peak in intravesical pressure was followed by a second, smaller peak after 20.4 s (± 3.0 s) (c in Figure 2). The rise in intravesical pressure over baseline at the height of this second peak (y in Figure 2) was on average 42.5% ($\pm 19.1\%$) of the size of the initial peak.

The mean time taken for the intravesical pressure to decline to within 10% of pre hyperreflexic contraction baseline (d in Figure 2) was 41 s (± 14 s) with only one of 21 measurements longer than 1 min. The mean intravesical pressure during the neuromodulation period was 7.3 cm H_2O (± 1.8 cm H_2O, range 5–10 cm H_2O) higher than the baseline before the onset of hyperreflexia.

Comparison of the two techniques
In the three patients in whom conditional and continuous fills were compared using the alternating protocol (iii), conditional was better than continuous in two out of three cases (Table 2).

In the three patients tested on separate days with each technique (protocol iv), neuromodulation gave greater volume rises in all three patients, and greater percentage rises in two out of three (Table 3).

In five out of the six patients in whom both types of stimulation were compared, the maximum bladder volume achieved with neuromodulation was with the conditional stimulation mode.

Comparison by Frankel grade
The maximum percentage increase in bladder volume using any type of neuromodulation was significantly higher in the group of patients with Frankel D grade lesions compared to the three patients in the incomplete group (mean 143% *vs* 56%, $P = 0.028$).

Discussion

The efficacy of neuromodulation
In every patient examined, continuous stimulation increased bladder capacity. The consistency of these results may reflect the benefits of basing stimulation parameters on values derived from optimisation work using provoked contractions.[18] The continuous stimulation results also demonstrate that the order and number of fills must be taken into account when evaluating the effects of neuromodulation. The rise in bladder volume during the three initial control fills in our six patients was significant – this effect has been noted before.[24,25]

The persisting (but diminishing) effect following neuromodulation in the final control fills has also been found before,[7,8] and was probably due to two main factors. Firstly, an initial mechanical distension is likely to diminish afferent discharge from the bladder at a given volume during subsequent fills; such an effect has been shown directly in cats.[23] Secondly, the effects of neuromodulation at the spinal level may persist, consistent with the observation that the beneficial effects of 'maximal electrical stimulation' of the pelvic floor may last for hours or days.[26] However, such maximal stimulation has mainly been used in patients with intact sensation, and two studies of its use in spinal injury showed that it was of limited efficacy at best,[27,28] suggesting that the residual neuromodulatory effect of penile nerve stimulation diminishes rapidly in the first hour. Experiments with provoked contractions confirm this finding.[29]

The largest rises in bladder capacity during this study occurred in patients who had required a high dose of anticholinergics to maintain a high bladder capacity. On stopping these drugs for the study, they often had hyperreflexia at low bladder volumes during control fills. This was effectively suppressed by neuromodulation, enabling them to return to their

continued during the tests. However, the mean increase in bladder volume at first uninhibited contraction reported by this group was 98% (or 207 ml), which is similar to the results described here.

In both cases, the pudendal afferent nerves are stimulated incompletely: sacral foramen stimulation because only one out of six roots that carry pudendal fibres is stimulated, and DPN stimulation because a fraction of S_2 fibres is stimulated bilaterally.

Both techniques stimulate pudendal afferents, and there are several pieces of evidence indicating that afferent stimulation is central to the mechanism of neuromodulation in spinal cord injury. Skeletal muscle paralysis does not abolish the inhibitory effect of pudendal nerve stimulation in cats,[36] and when pudendal afferents from the cat penis are identified and stimulated, marked inhibition of the bladder occurs, while stimulation of pelvic floor fibres has little effect.[37]

The similarity between the two techniques in mode of action and efficacy suggests that DPN stimulation can be used as a non-invasive screening test for the response to neuromodulation before implantation of a sacral root stimulator. It is also likely that conditional neuromodulation will be effective when applied via the sacral nerve roots.

In conclusion, both continuous and conditional dorsal penile nerve stimulation at twice the threshold for the pudendo-anal reflex reliably increased bladder capacity in spinally injured patients, and continuous neuromodulation significantly increased compliance. Conditional neuromodulation was more effective than continuous in the majority of patients, and never resulted in a rise in mean intravesical pressure of > 10 cm water. During conditional neuromodulation, the time from start of stimulation to intravesical pressure peak and to fall to 50% of peak is similar between patients. The time between suppressed contractions falls as the bladder fills and might be used as a marker of bladder volume. These results suggest that conditional neuromodulation in a fully implanted device will be effective and is a goal worthy of pursuit.

Acknowledgements

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would be the possibility of feedback to the patient about bladder fullness.

Experiments in cats[23] and pigs[22] have shown that it is possible to detect hyperreflexic bladder contractions by recording from the mixed sacral nerve roots, and that these contractions can be suppressed by stimulation of the same roots. Recently, signals have been recorded from a human sacral nerve using a cuff electrode suitable for long term use.[31] This work suggests that an implanted conditional neuromodulation device is feasible, but it will be considerably more complex than a simple stimulator.

Conditional neuromodulation

The combination of slow fill rates and the ability to rapidly switch on stimulation is essential for establishing how effective conditional neuromodulation might be in everyday use; these conditions have not been present in most previous studies, which have used conventional (and more provocative) filling rates of around 50 ml/min.

Filling at 10 ml/min, conditional neuromodulation in this study increased bladder capacity in every patient tested. As with continuous stimulation, the range of increases was wide, so that conditional and continuous modes should ideally be examined in the same patients to compare efficacy. Although the number of patients was too small to answer the question definitively, the results suggest that conditional stimulation is at least as effective as continuous. It was difficult to devise an adequate protocol for comparing the two modes of stimulation: the alternating continuous/conditional strategy for comparison is flawed because it is impossible to eliminate the effects of 'carry over' in a series of CMGs, and comparing results from two different days' testing eliminates the carry over effect but introduces other sources of variation – in particular, varying capacity on the control CMGs, and differing electrode position and stimulation parameters.

The gap between suppressed unstable contractions almost always decreased progressively with increasing bladder volume. This effect resembles the finding that unstable contraction frequency increases with volume in the spinal cat,[32] and may well be useful for the estimation of bladder volume in an implanted system for conditional neuromodulation, because intravesical pressure often rises only a small amount during the stable phase of filling.

Although bladder volume increases with neuromodulation varied widely, the time to peak of suppresssed contractions and time to 50% decline were strikingly similar between patients, suggesting a common mechanism. A mean of 2.8 s from start of stimulation to contraction peak is consistent with a previous observation that the effects of neuromodulation occur after a latency of '1–3 s'.[33] The time constant of 6.9 s (± 0.9 s) for the decay of the suppressed pressure is less than the figure of 9.9 s (± 2.6 s) seen with

magnetic stimulation of the sacral roots in healthy men,[12] but in the latter study stimulation was for 2 s only. The mean rise in intravesical pressure of 7.3 cm water during conditional neuromodulation suggests that this technique will be safe: in no patient was the rise greater than 10 cm water.

The pressure rise of 10 cm water chosen as a trigger for conditional neuromodulation is necessarily somewhat arbitrary but is similar to the smallest intravesical pressure rises that can currently be detected in animals by recording from the sacral roots.[22,23]

The parameters used for neuromodulation via the dorsal penile nerve

The stimulation period of 1 min was sufficient to bring intravesical pressure to within 10% of baseline in almost all cases (the figure of 10% was chosen to allow for any rises due to low compliance or signal noise). This confirms the results of provocation experiments, where 60–70 s was found to be best for minimising the area under the intravesical pressure-time curve,[18] and suggests that 1 min is an appropriate 'on' time for conditional neuromodulation.

We based stimulation current strength on experiments with provoked contractions, and other groups have achieved good results at 2 to 3.5 times the threshold for the bulbocavenosus reflex[7] (which will be similar to the threshold for anal sphincter contraction[34]). One group has specifically examined the influence of current strength on bladder suppression, achieving their best results at twice the threshold and markedly reduced suppression when stimulating at a level equal to the threshold.[24] In the current study, the pudendo-urethral reflex had a lower threshold than the pudendo-anal reflex in a majority of patients, a point which should be borne in mind if using it to set the current level for neuromodulation.

The ideal frequency for bladder suppression is still a matter of debate. Experiments with provoked contractions in humans suggest that 15 Hz is optimal,[18] but in cats this frequency may be too high, with best results at 5 Hz.[35] In one study anal stimulation in humans was equally effective at 5, 10 and 20 Hz,[33] and others have used frequencies between 5 and 20 Hz.[5–9] The numbers of patients in these studies are too small to properly determine the ideal stimulation frequency, so that we relied on findings derived from repeated provocation of unstable contractions.

Dorsal penile nerve vs sacral foramen stimulation

One group has examined the acute increase in bladder capacity that occurs with unilateral sacral foramen stimulation in spinal cord injury.[11] The design of the study was different to the one here in several significant ways – in particular, half the subjects were female, there was a single fill with neuromodulation and it is not clear whether anticholinergic medication was

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