CLOSED-LOOP ELECTRICAL CONTROL OF URINARY CONTINENCE

By

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Dedication

This dissertation is dedicated to my best friend, Anu, for her loving support, encouragement, and for being proud of my accomplishments, and to my parents, Mark and Virginia Wenzel, for inspiring a love of learning within me and being proud of my work.

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Closed-Loop Electrical Control of Urinary Continence

Abstract

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Individuals with spinal cord injury or neurological disorders may develop involuntary bladder contractions at low volumes (bladder hyper-reflexia) that cause incontinence and can lead to significant health problems. Bladder contractions can be suppressed by electrical stimulation of inhibitory pathways, but continuous activation may lead to habituation of the inhibitory reflex and loss of continence. Conditional stimulation, with stimulation of inhibitory pathways applied only at the onset of nascent bladder contractions, should reduce habituation. Conditional stimulation needs methods of detecting the onset of bladder contractions to trigger inhibitory electrical stimulation. The objectives of this study were to determine if the electrical activity of the pudendal nerve could serve as a control signal for conditional stimulation, to determine whether conditional stimulation allowed the bladder to fill to a greater volume before continence was lost than did continuous stimulation, and to determine whether the techniques developed to detect bladder contractions could be transferred to individuals with a spinal cord injury (SCI).

The electrical activity of the pudendal nerve was modulated during bladder contractions and recordings of the pudendal nerve electroneurogram enabled detection of the onset of reflexive bladder contractions within 2 seconds of the start of the bladder contractions in 9 anesthetized male cats. Conditional electrical stimulation based on the electrical activity of the pudendal nerve allowed the bladder to fill to greater capacity

before continence was lost than either continuous stimulation or no stimulation. The techniques developed in preclinical studies were tested on a retrospective clinical data set of 81 subjects with SCI. The activity of the external anal sphincter was modulated in individuals with SCI and enabled detection of the hyper-reflexive bladder contraction. These results indicate that the electrical activity of pudendal nerve can serve as a control signal for conditional inhibitory stimulation, conditional stimulation is more effective at maintaining continence than continuous inhibitory stimulation or no stimulation, and these techniques are transferable to humans with SCI.

Chapter I General Introduction

I.1 Specific Aims

The lower urinary tract has two main functions: the storage of urine (continence) and the voluntary evacuation of the bladder (micturition). Urological complications occur in individuals with spinal cord injury (SCI) or other neurological disorders that lead to significant morbidity, substantial decrease in quality of life, and high medical costs. These individuals experience loss of voluntary control of micturition, bladder hyper-reflexia, and bladder-sphincter dyssynergia. Bladder hyper-reflexia is the involuntarily reflex contraction of the bladder when it contains small fluid volumes, and can result in loss of continence and/or high bladder pressure during bladder-urethral sphincter dyssynergia.

The goal of this project is to test the suitability of using the electrical activity of the pudendal nerve to detect hyper-reflexive bladder contractions. This signal will then be used as a control signal in an event-triggered control system to maintain continence by electrical stimulation of pudendal afferent fibers that inhibit the bladder. The ability to arrest hyper-reflexive bladder contractions is expected to enable treatment of incontinence and to decrease the complications experienced by individuals with SCI or other neurological disorders.

Aim 1. Detecting hyper-reflexive bladder contractions using the electrical activity of the whole pudendal nerve in cats

The hypothesis is that the electrical activity of the pudendal nerve can be recorded and used in an algorithm to detect the onset of a hyper-reflexive bladder contraction. The hypothesis will be tested by recording the pudendal nerve electroneurogram (ENG)

during reflexive contractions in an animal model and analyzing the relationship between bladder pressure and pudendal nerve ENG. Subsequently, a detection algorithm will be developed to detect the onset of hyper-reflexive bladder contractions.

Aim 2. Implement an event-triggered control system for bladder continence

The goal of this aim is to use the detection algorithm to trigger conditional electrical stimulation of the pudendal nerve to maintain continence in an event-triggered control system based on recordings of a bioelectric signal. The hypothesis is that event-triggered control system will allow the bladder to fill to greater volumes before continence is lost than either no stimulation or continuous stimulation. The hypothesis will be tested by comparing in an animal model volumes at which continence is lost in an event-triggered control system to no stimulation and to constant stimulation.

Aim 3. Detecting hyper-reflexive bladder contractions using the activity of the external anal sphincter in cats and humans with spinal cord injury

A non-surgical method of recording the electrical activity of the pudendal nerve is required to test detection of hyper-reflexive bladder contractions in humans. The hypothesis is that the electrical activity of the external anal sphincter (EAS) can be used to detect the onset of hyper-reflexive bladder contractions in both cats and individuals with spinal cord injury. The hypothesis will be tested by recording the EAS EMG during hyper-reflexive bladder contractions in an animal model. An algorithm will be developed to detect the onset of hyper-reflexive bladder contractions using the EAS EMG based. The techniques developed in pre-clinical trials will then be tested in clinical trials by recording EAS EMG from individuals with SCI during hyper-reflexive bladder

contractions, and testing the developed detection algorithm to detect the onset of hyper-reflexive bladder contractions.

At the conclusion of this project, an event-triggered control system to maintain continence will be developed. The electrical activity of the pudendal nerve will be used to detect the onset of hyper-reflexive bladder contractions, and conditional electrical stimulation of the pudendal nerve will be used to inhibit hyper-reflexive bladder contractions. It will also be determined if the activity of the EAS is a proxy for the activity in the pudendal nerve and if EAS EMG can be used to detect hyper-reflexive bladder contractions in humans. Restoration of continence will increase the quality of life for many individuals, and implanting a neural prosthesis on the pudendal nerve will increase the population of persons who could benefit from such a device.

I.2 Background and Significance

I.2.1 Physiology of Lower Urinary Tract

The lower urinary tract has two main functions: the accumulation of urine (continence) and the elimination of urine at an appropriate time (micturition). In able-bodied individuals, continence is maintained by low-pressure urine storage in a highly compliant bladder augmented by tonic activity in the external urethral sphincter. Micturition is achieved by synergic relaxation of the urethral sphincter and contraction of the bladder. The bladder is controlled by a parasympathetic system through the pelvic splanchnic nerve and by a sympathetic system through the hypogastric nerve. The parasympathetic system, from the S_2 - S_4 sacral segments of the spinal cord, terminates on and within the detrusor muscle through cholinergic nerve fibers and contracts the detrusor muscle during micturition. The sympathetic system, from the $T_{10} – L_2$ segments of the spinal cord, terminates on the pelvic plexus and inhibits the detrusor muscle not by

direct effects of noradrenergic neuronal fibers on the detrusor, but by inhibition of the excitatory parasympathetic supply within the ganglia of the pelvic plexus. The urethra and external urethral sphincter are innervated by the pudendal nerve. The pudendal nerve also innervates the bulbocavernosus, the ischiocavernosus, the external anal sphincter, and the genital nerve (dorsal penile nerve in males and clitoral nerve in females, Figure I.1).

Neurological disease or spinal cord injury (SCI) can result in loss of voluntary control of bladder evacuation and bladder hyper-reflexia. Bladder hyper-reflexia can result in loss of continence and/or high bladder pressure during bladder-urethral sphincter dyssynergia (Watanabe, Rivas, & Chancellor, 1996). Under synergic conditions, the bladder contracts while the urethral sphincter relaxes. During bladder-urethral sphincter dyssynergia, the bladder and the urethral sphincter contract at the same time preventing or inhibiting the flow of urine through the urethra while increasing the bladder pressure. Hydronephrosis, the accumulation of urine in the kidneys caused by a pathological increase in bladder pressure, can cause long term damage to the renal system and can eventually lead to renal failure. Loss of voluntary control, hyper-reflexia, and dyssynergia can result in long term renal damage, frequent urinary tract infections, and infections of the kidneys (Shingleton & Bodner, 1993).

I.2.2 Urinary Incontinence and Conventional Treatments to Incontinence

Approximately 6% of the population particularly in women and the elderly has urinary incontinence of such severity as to interfere with their quality of life and represents a significant demand for health care (Hunskaar et al., 2000; Kelleher, 2000). There are several types of incontinence, but fall into two main categories: temporary and chronic incontinence. Temporary incontinence is generally caused by medication,

constipation, urinary infection, restricted mobility, muscle weakness, excitement, and unavailability of restroom. Temporary incontinence can be treated by exercise, change of diet, change of medication, and more frequent urination.

The three main types of chronic incontinence are stress incontinence, urge incontinence, and mixed incontinence, and secondary types of chronic urinary incontinence are reflex incontinence, overflow incontinence, and functional incontinence (Cheater & Castleden, 2000; Keane & O'Sullivan, 2000). Stress incontinence results from when certain activities (laughing, coughing, sneezing, lifting heavy objects, or exercising) increase pressure within the bladder and leakage occurs. Stress incontinence may be caused by weakening of the muscles that support the bladder or the weakening of the external urethral sphincter that controls the outflow of urine. Urge incontinence is the involuntary loss of urine associated with a strong sensation to void (urgency), even when the bladder contains only a small amount of urine. Urge incontinence can either be an overactive detrusor function (motor urgency) or hypersensitivity (sensory urgency). Urge incontinence can be caused by urinary track infection or neuronal damage such as spinal cord injury, stroke, multiple sclerosis, or Parkinson's disease. Mixed incontinence is the combination of stress incontinence and urge incontinence. Reflex incontinence, a subset of urge incontinence, is overactive detrusor function without the urge to void. Reflex contraction is normally caused by neuronal damage such as stroke and spinal cord injury. Overflow incontinence is when the bladder pressure from an over-filled bladder exceeds the strength of the urethra to control the urine flow. Overflow incontinence can be caused by obstructed urethra, prostate enlargement, weakness of the bladder, and neuronal damage such as surgery, diabetes, spinal cord injury, and stroke. Functional incontinence

is a normal urinary tract system, but a mental or physical condition that slows or confines a person such that inappropriate loss of urine occurs.

The treatment of chronic incontinence depends on the mechanisms of loss of urine. Generally, if there is only a small leakage of urine, absorbent pads or undergarments are used to move the urine away from the skin. If the cause of incontinence is urinary tract infections, antibiotics can be prescribe to treat the infection and resolve the incontinence. For mild to moderate stress incontinence, pelvic floor exercises (Kegels) can help support the bladder and relieve incontinence. Sixty percent of individual with mild to moderate stress incontinence improve their stress incontinence with Kegels (Thakar & Stanton, 2000). Stress incontinence is predominantly in postmenopausal woman, especially women with multiple vaginal child deliveries. After menopause, the estrogen levels in the blood drop, and breasts, ovaries, uterus, and vagina begin to age. The anterior wall of the vagina supports the bladder. After menopause, the weakening of the vagina causes the bladder to drop, and the reorientation of the bladder can cause the urethra to drop below the pubococcygeal musculature. Without the support of the pubococcygeal musculature around the superior section of the bladder neck, intra-abdominal pressures are no longer be transmitted to the urethra and stress incontinence occurs. Estrogen is prescribed to rejuvenate the vaginal wall and may cure the leaking. For serious stress incontinence or when exercises and medications have not helped, surgery is usually the final option. The surgeon redevelops the pelvic floor to either strengthen the pelvic floor and/or reposition the bladder and urethral sphincter using slings or other methods. Other procedures include urethral bulking (injective collagen or other materials into the urethral sphincter to increase the size of the sphincter to limit the

flow of urine), artificial sphincter (a pump controlled artificial sphincter implanted around the urethra), and electrical stimulation of the pelvic floor to strengthen the muscles.

When urge incontinence is the result of motor urgency (detrusor instability), the contraction strength of the bladder muscle exceeds the closing strength of the urethral sphincter. Systemic anti-cholinergics are prescribed to weaken and to reduce spasticity of the bladder; however, anti-cholinergics have high incident undesirable side effects (30% to 80%) that limit their use (Enzelsberger, Helmer, & Kurz, 1995). Sometimes alpha-adrenergics are prescribed that strengthen the urethral sphincter instead of weakening the bladder. When urge incontinence is the result of sensory urgency, removal of bladder irritants such as infections and abnormal tissue growth can resolve urge incontinence. If the irritation is caused by hyper-sensitivity of c-fibers, one could infuse agents like resiniferatoxin or capsaicin to reduce activation of c-fibers in the bladder. However, infusions are needed at regular intervals and may produce systemic effects or damage to the bladder (Birder & de Groat, 1992; Fowler, 1999). Another means to reduce the effects of activated c-fibers to perform a dorsal rhizotomy, the transection of the dorsal root, in the sacral segments of the spinal cord. However, the rhizotomy removes all sensation in the pelvic region, removes sexual function (erection in males and lubrication in females), and lose control of fecal defecation. Because of all of the side effects, this procedure is limited to individuals with severe neuronal damage (i.e., spinal cord injury or stroke).

Overflow incontinence is corrected with surgery by removing the obstruction such as a kidney stone or with intermittent self catheterization. To prevent hydronephrosis that can be associate with overflow incontinence, urethral balloon dilation, urethral stenting,

and sphincterotomy are performed (Catz et al., 1997; McFarlane, Foley, & Shah, 1996, 1997). However, these methods make the incontinence worse. Reflex incontinence is treated with self catheterization and anti-cholinergics. Functional incontinence is treated with either behavioral training or by assisting the person with urination.

One of the major bladder impairments in SCI individuals is urinary incontinence. The types of incontinence that individuals with SCI have are urge incontinence, overflow incontinence, stress incontinence, and/or reflex incontinence. Individuals with SCI use a variety of technique to treat incontinence depending on which type of incontinence, the severity of incontinence, and the severity and level of the spinal cord injury. Individuals that cannot void their bladder from either weakened bladder or bladder-urethral sphincter dyssynergia use intermittent self catheterization to empty the bladder to prevent vesicouretral reflux (flow of urine from the bladder to the kidneys), hydronephrosis (accumulation of urine at the kidneys) and leakage of urine as a result of overflow incontinence. However, self catheterization leads to frequent urinary tract infections, and individuals with limited dexterity from the spinal injury have difficult time catheterizing themselves. Individuals with limited dexterity would have an indwelling catheters implanted to empty their bladder (Kuhn, Rist, & Zaech, 1991).

If the person has reflex incontinence, they may take anti-cholinergics to decrease the number of spastic bladder contractions, and empty the bladder using self catheterization. Individuals taking anti-cholinergic tend to stop taking the medication as a result of the side effects (thirst, dry-mouth, lethargy, blurred vision, glaucoma, constipation, dry skin, arrhythmias, and confusion), and anti-cholinergics increase the difficulty of emptying the bladder (Di Stasi et al., 2001). If an individual has

vesicouretral reflux or hydronephrosis from bladder-sphincter dyssynergia and is not responsive to or side effects are too severe from anti-cholinergics, surgery is sometimes performed to reduce bladder pressure. There are two main types surgery that are performed to reduce bladder pressure. The first type reduces the urethra pressure by dilation of the urethra by urethral balloon dilation, urethral stenting, or sphincterotomy such that any increase in bladder pressure will result in urine leakage and maintain a low bladder pressure. The other type of surgery reduces bladder pressure by increasing the size of the bladder by either attaching a patch of bowel to the bladder or cutting through the detrusor to the mucosa. Both of these methods allow the bladder to fill to greater volume before the bladder pressure reaches pathological levels; however, both methods increase the difficulty of the emptying the bladder (Jezernik, Craggs, Grill, Creasey, & Rijkhoff, 2002). With each of these methods, the patients never fully recover to a satisfactory condition.

Another method of restoring bladder function in SCI individuals, the Brindley procedure, has been shown to be successful in restoring bladder control in over 1600 patients implanted since 1982 (Brindley, 1994; Brindley, Polkey, & Rushton, 1982; Creasey, 1993; Schurch, Rodic, & Jeanmonod, 1997). The system consists of a neuroprosthesis that stimulates the sacral anterior roots to achieve micturition. In order to achieve continence, to diminish hyper-reflexia, and to reduce residual volume after micturition, a sacral dorsal rhizotomy, an irreversible transection of the dorsal sacral roots, is performed to remove afferent feedback. A major side effect of the rhizotomy is the loss of all sacral sensory including the loss of reflex sexual functions (loss of reflex erections and ejaculation in males and loss of lubrication in females), loss of perineal

sensation, loss of reflex micturition, and loss of reflex defecation (Creasey, 1993). Because of these side effects and along with a psychological barrier of further injuring an already injured spinal cord, the Brindley procedure has been limited to complete suprasacral SCI individuals who do not retain any sensation or secondary reflexes (Dahms & Tanagho, 1998). However, individuals that received the implanted system have been shown to have a higher quality of life (Vastenholt et al., 2003).

I.2.3 Electrical Stimulation to Treat Incontinence

Electrical stimulation is a potential alternative to other treatments when they fail, when they would results in unacceptable disadvantage (like the loss of reflex bowl emptying and sexual function following dorsal rhizotomy) or when the patients do not tolerate other treatments due to the side effects or for other reasons. Electrical stimulation suppresses bladder contractions through a sensory reflex spinal loop that is nondestructive and nonpharmacological alternative to increase functional bladder capacity and to prevent incontinence. The first forms of long-term electrical stimulation to treat stress and urge incontinence used vaginal or anal plug electrodes to activate the afferents of the pudendal nerve through an external device (Fossberg et al., 1990; Janez, Plevnik, & Suhel, 1979; Jezernik et al., 2002). Typically, 2 to 10 sessions per week of 20 minutes to one hour of stimulation were needed to alleviate incontinence in more than 50% of cases with long-term carry-over effects observed in more than 20% of cases (Fall, 1998). One commercially available product is Empi's Innosense. Innosense is designed to treat either stress or urge incontinence by stimulating through either a vaginal or anal plug. A problem with anal and vaginal electrodes is that they induce skin or mucosa sensations at much lower intensities than pelvic floor contractions. The margin of stimulation intensity between the detection threshold and pain is narrow with maximum

tolerance level at intensity levels about 1.5 to 2 times the detection threshold (Ohlsson, 1988). However, physiologically optimum stimulation is 2 to 3 times the maximum tolerance level which is far above the tolerable stimulation levels (Ohlsson, 1988). Clinically effective stimulation frequency for maintaining continence is between 5 and 10 Hz (Lindstrom, Fall, Carlsson, & Erlandson, 1983). Patients find these lower frequencies unpleasant since the patients can detect every single pulse. Patients tolerate stimulation frequencies about 20 Hz which is above the optimum frequencies to control incontinence (Nakamura, Sakurari, Sugao, & Sonoda, 1987; Primus & Kramer, 1996). Even with these limitations, 60% of patients were still satisfied with the electrical stimulation treatment for stress and urge incontinence after ten years of use (Bratt, Salvesen, Eriksen, & Kulseng-Hanssen, 1998).

Another approach to electrical stimulation to treat urinary incontinence is to stimulate the sacral root. Magnetic stimulation over the sacrum (S_2-S_4) can suppress reflex incontinence in individuals with detrusor hyper-reflexia (Sheriff, Shah, Fowler, Mundy, & Craggs, 1996). Stimulation of the dorsal sacral roots has been further explored and been shown effective in animals (Jezernik, Grill, & Sinkjaer, 2001) and humans (Chartier-Kastler et al., 2001; Craggs et al., 2000; Kirkham, Knight, Craggs, Casey, & Shah, 2002). One commercially available sacral stimulator to treat incontinence is Medtronic's Interstim. The Medtronic Interstim stimulator activates the sacral nerves via wire electrodes inserted into sacral foramina (Siegel, 1992). Results indicate that the Interstim has therapeutic effects (increased volume at first sensation, increased bladder capacity, and reduced pain) in 19 of 36 patients implanted with the device for at least 60 months after implantation in individuals with incontinence in which stimulation was

applied for a few hours to up to 24 hours per day (Weil, Ruiz-Cerda, Eerdmans, Janknegt, & Van Kerrebroeck, 1998). The Interstim is design to treat mostly urge incontinence, but has shown therapeutic effects on stress incontinence (Weil et al., 1998). Besides Medtronic's Interstim, other sacral root stimulator require an invasive laminectomy (removal of spinal column) to expose the sacral roots to implant the neural prosthesis.

The mechanism of continence through sacral stimulation is not well understood, but one theory is that the stimulation activates the pudendal afferent nerve fibers (Lindstrom et al., 1983). The pudendal nerve innervates the urethra, external urethral sphincter, external anal sphincter, and the genital nerve (dorsal penile or clitoral nerve). Stimulation of the genital nerve applied through surface electrodes produces profound and repeatable suppression of bladder contractions with an increase in bladder volume with either continuous or conditional stimulation in individuals with spinal cord injury (Kirkham, Shah, Knight, Shah, & Craggs, 2001; Shah, Edhem, Knight, & Craggs, 1998). Other studies have shown that directly stimulating the pudendal nerve can inhibit the bladder (Craggs, Edhem, Knight, McFarlane, & Shah, 1998; Kondo, Otani, & Takita, 1982; Sundin, Carlsson, & Kock, 1974; Vodusek, Light, & Libby, 1986). A pudendal nerve stimulator to control continence is Advanced Bionic's BION. The BION is a small, RF powered microstimulator that is implanted next to the pudendal nerve to inhibit bladder contractions through activation of pudendal nerve afferents (Grill, Craggs, Foreman, Ludlow, & Buller, 2001).

The last type of type of electrical stimulation to control incontinence is a posterior tibial nerve stimulator (van Balken et al., 2001). Tibial nerve stimulation to treat overactive bladder was originally based on acupuncture. An acupuncture needle was

placed near the posterior tibial nerve to treat pelvic pain (Geirsson, Wang, Lindstrom, & Fall, 1993; van Balken et al., 2003). Stimulation of the tibial nerve was later investigated to treat urinary tract dysfunctions (Vandoninck et al., 2004). The posterior tibial nerve stimulator has shown success (reduction in volume leaked and reduction in total number of leakage episodes) in 63% of the patients (22 of 35) tested (Vandoninck et al., 2003). One product that treats urge incontinence through tibial nerve stimulation is CystoMedix's Urgent PC, however this device is not approved by the FDA.

Although results suggest the previous methods may be effective treating urge and stress incontinence in persons with SCI, the methods were designed primarily to stimulate in an open loop fashion. The implementation of an event-triggered control system and activation of a robust inhibitory neural pathway is expected to increase the performance of such approaches.

I.2.4 Neural Prosthesis

Neural prostheses are used to either record or stimulate the nervous system to regain bodily functions that were lost as a result of a neuropathology. Neural prosthesis can be used to restore sensory sensation (i.e., sight), to restore motor function (i.e., standing and walking), or to augment activity in other areas of the nervous system (i.e., epilepsy suppression) to increase the independence of individuals with a neuropathology. Despite the many progresses over the years, more effective activation of the nervous system needs to be developed by either having a more appropriate command or feedback signal. The conventional means of providing stimulation has either been open-loop stimulation (i.e., preprogrammed stimulation paradigm that runs continuously) or user activated (i.e., the user turns the stimulation on or off). Over time, a variety of external and implanted sensors and command signals to provide feedback have been added to

neural prostheses (Crago, Chizeck, Neuman, & Hambrecht, 1986; Matjacic, Hunt, Gollee, & Sinkjaer, 2003; Popovic, 2003). However, artificial sensors are difficult to build, have insufficient biocompatibility, and are not reliable for extended implantation. More recently, using the body's own natural sensors has been implemented to provide more effective control while being more cosmetic than using artificial sensors.

The peripheral nerves below the lesion remain intact and viable after a spinal cord injury or stroke even though the brain cannot transmit information below the lesion. Somatic sensory information such as proprioception and cutaneous sensors could be used as a feed-back signal for neural stimulation control. Cutaneous sensors such as touch have been used to correct foot-drop in individuals with a stroke (Lyons, Sinkjaer, Burridge, & Wilcox, 2002). After a stroke, paralysis of ankle dorsiflexor muscle prevents the individuals from lifting their toes during the swing phase of gait and causes the individual to stumble. Dorsiflexion in the swing phase can be achieved by electrical stimulation of the peroneal nerve, however, a trigger for turning the stimulation on is needed and has been conventionally a heel-strike senor (Lyons et al., 2002). The external heel-strike sensor limits the device to only be used when shoes are worn. The foot drop system has incorporated the body's natural sensor to detect a heel strike (Haugland & Sinkjaer, 1995; Upshaw & Sinkjaer, 1998). A closed-loop control system was developed by recording the electrical activity of the sural or calcaneal nerve to detect a heel strike and stimulating the peroneal nerve when the electrical activity of the sural or calcaneal nerve increases above a threshold. The results were that 85% of the heel contacts were detected based only on the afferent nerve signal information alone. With stimulation, the gait of the subjects was more stable and more defined.

Natural sensors were also used to control stimulation in hand grasping. The problem using open-loop stimulation or artificial sensors in hand grasp neuroprosthesis led to over stimulation and induced muscle fatigue. There are over 17,000 touch sensing receptors within the skin of a human hand. Bursts of neural activity occur in FAI (fast adapting type I neuron), FAII, and SAI receptors when an objects slips across the skin (Johansson & Westling, 1988). A nerve cuff electrode was implanted around the palmar digital nerve, and the electroneurogram from the palmar digital nerve was used to detect slippage of an object in the hand's grasp (A. Inmann & M Haugland, 2004). When a slippage was detected, the stimulation output to the epimysial electrodes increased to increase the gripping strength to prevent further slippage (A Inmann & M Haugland, 2004). The study showed that during eating, the same force was used to hold the fork for closed-loop control and open-loop control; however, during the break the force to hold the fork was significantly less for closed-loop control than for open-loop control (A. Inmann & M Haugland, 2004). These results showed that a neuroprosthesis incorporating the electrical activity of a nerve as a feedback signal could more closely mimic an able-body's ability to grasp an object.

Another FES system that incorporates natural sensors as a feedback signal to control stimulation is using the electrical activity of the hypoglossal nerve to treat upper airway obstruction. During obstructive sleep apnea, the airway passage is constricted, and stimulating the genioglossus muscles which is innervated by the hypoglossal nerve has been shown to reduce the constriction (Decker, Haaga, Arnold, Atzberger, & Strohl, 4993; Schwartz et al., 1996). When the airway is constricted, the electrical activity of the hypoglossal nerve is modulated with each breath (Sahin, Haxhiu, Durand, & Dreshaj,

1997). A closed-loop FES system was developed that recorded the electrical activity of the hypoglossal nerve to detect each breath and stimulated the hypoglossal nerve to remove the airway obstruction (Sahin, Durand, & Haxhiu, 2000). These results showed that incorporating detection with stimulation in the same nerve cuff allows for restoring function while having fewer electrodes than using multiple nerve cuffs.

I.3 Proposed Approach for Restoration of Bladder Continence

We propose to develop a method to control bladder continence without requiring dorsal rhizotomy while reducing the surgical complications associated with the rhizotomy. The proposed device is a single, multi-electrode nerve cuff placed around the pudendal nerve trunk that will enable event-triggered control of continence by electrical recording the pudendal nerve ENG to detect bladder contraction and triggering the application of inhibitory stimulation. The proposed research is divided into three areas: detection of hyper-reflexive bladder contractions, development of an event-triggered control system to maintain continence, and transfer of the detection techniques to human feasibility tests.

I.3.1 Detection of Hyper-Reflexive Bladder Contractions

Electrical stimulation has been used to treat incontinence through inhibition of hyper-reflexia, but each of the present methods continuously applies stimulation to inhibit the bladder (Chartier-Kastler et al., 2001; Craggs et al., 1998; Grill et al., 2001; Jezernik et al., 2002; Siegel, 1992; van Balken et al., 2001; Vandoninck et al., 2003; Vodusek et al., 1986; Weil et al., 1998). Conditional stimulation, when stimulation is applied only when a hyper-reflexive contraction occurs, may allow the bladder to fill to greater volume before an uncontrollable contraction occurs (Kirkham et al., 2001; Shah et al.,

1998) by minimizing habituation resulting from repetitive activation of spinal reflexes (Cariga, Catley, & Ellay, 2000; Floeter, Gerloff, Kouri, & Hallett, 1998; Granat, Heller, Nicol, Baxendale, & Andrews, 1993; L.M. Harrison, J.A. Norton, & J.A. Stephens, 2000). Further, conditional stimulation at the beginning of the contraction can completely abolish the contraction (Kondo et al., 1982; Shah et al., 1998).

Conditional stimulation to inhibit the bladder requires detection of the onset of nascent hyper-reflexive contractions. We hypothesized that the electrical activity of the pudendal nerve, which innervates somatic skeletal muscles of the pelvic area, could be used to detect the onset of hyper-reflexive bladder contractions. Recent work has demonstrated that recordings of bladder afferent fiber activity in the dorsal S1 root level can be used to detect robustly reflex bladder contractions in cats (Jezernik et al., 2001). While recording from the sacral nerve roots is a feasible approach to electrical detection of the onset of reflex bladder contraction, it requires extensive and complex surgery including a laminectomy and intradural implantation of cuff electrodes on the dorsal roots. In contrast, the pudendal nerve is readily accessible.

It is likely that either urethral motor or urethral sensory activity in the pudendal nerve contains information relating to the onset of bladder activity. Both the urethral sphincter and the external anal sphincter show bursts of activity at or before the onset of micturition (Evans, 1936; Gary, Roberts, & Todd, 1959; Shefchyk & Buss, 1998), and increases in anal sphincter EMG occur during reflex bladder contractions in rats (Thor & Muhlhauser, 1999). In humans, increases in bladder pressure evoked by rapid injections of fluid into the bladder evoke an increase in activity in the muscles of the pelvic floor (Shafik, 1993). These studies suggested that recording from the pudendal nerve would

enable detection of hyper-reflexive bladder contractions, and such a signal could serve as a trigger for conditional stimulation. The objectives of the study (presented in Chapter II) were to characterize the relationship between pudendal nerve trunk electroneurogram (PNT ENG) and bladder pressure during reflex bladder contractions, to determine whether the PNT ENG could be used to detect the onset of bladder contractions, and to compare the performance of three algorithms for detecting bladder contractions from the PNT ENG.

I.3.2 Event-triggered Control System to Maintain Continence

An event-triggered bladder control system requires electrical detection of reflexive bladder contractions and electrical stimulation of the pudendal nerve to abolish nascent bladder contractions. Following detection of the onset of a hyper-reflexive contraction of the bladder, conditional electrical stimulation of the pudendal nerve will inhibit the bladder and arrest the nascent contraction. In unanesthetized chronic spinal cord injured male cats, reflex bladder contractions were inhibited by pudendal nerve stimulation (Walter, Wheeler, Robinson, & Wurster, 1993). Genital nerve (a branch of the pudendal nerve) stimulation has shown to inhibit hyper-reflexive bladder contraction (Jiang & Lindstrom, 1999). Stimulation of other nerves also cause bladder inhibition (Chartier-Kastler et al., 2001; Fall, 1998; Jezernik et al., 2002; Siegel, 1992; van Balken et al., 2001; Weil et al., 1998), however the pudendal nerve will be used since it is robust, effective, and matches the envisioned device. A nerve cuff will be used to record and stimulate the pudendal nerve. However, if stimulation of the pudendal is not effective, the genital nerve branch will be stimulated using either a nerve cuff or percutaneous electrodes in the penis. The hypothesis is that event-triggered control will allow the bladder to fill to greater volumes before continence is lost than either no stimulation or

continuous stimulation. The hypothesis will be tested by comparing the maximal bladder capacity for event-triggered control system, no stimulation, and constant stimulation in an animal model. The results of this study are presented in Chapter III.

I.3.3 Transfer Technique to Human Trials

A non-surgical method for recording the electrical activity of the pudendal nerve needs to be developed to determine if the onset of bladder contractions can be detected from a bioelectric signal in individuals with SCI. By recording the activity of the target muscles innervated by the pudendal nerve using surface or percutaneous EMG electrodes, one could extrapolate some of the electrical activity of the pudendal nerve. It has also been observed that the external anal sphincter neurons depolarize slightly during micturition in cats (Fedirchuk & Shefchyk, 1993), and increases in anal sphincter EMG activity occur during reflex bladder contractions in rats (Thor & Muhlhauser, 1999). Following spinal injury, bladder-urethral sphincter dyssynergia leads to large increases in pelvic floor activity during bladder contractions (Rudy, Awad, & Downie, 1988; Watanabe et al., 1996). These studies suggest that recording from the external anal sphincter will enable the detection of reflexive bladder contraction and the electrical activity of the external anal sphincter will serve as a proxy for the electrical activity of the pudendal nerve. The hypothesis is that the electrical activity of the external anal sphincter (EAS) can be used to detect the onset of hyper-reflexive bladder contractions. The hypothesis will be tested by recording the EAS EMG during hyper-reflexive bladder contractions in an animal model, and to determine whether the EAS EMG could be used to detect the onset of bladder contractions. The detection methodology will then be tested in humans. The hypothesis is that the EAS EMG can be used to detect the onset of hyper-reflexive bladder contractions in individuals with SCI. The hypothesis will be tested by

recording EAS EMG from individuals with SCI during hyper-reflexive bladder contractions, and developing a detection algorithm to detect the onset of hyper-reflexive bladder contractions. At the end of these studies, it will be determined if the EAS EMG is a suitable bioelectric signal to detect hyper-reflexive bladder contraction in individuals with SCI. The results of this study are presented in Chapter IV.

I.4 Conclusion

At the conclusion of this project, an event-triggered control system to maintain continence will be developed. The electrical activity of the pudendal nerve will be used to detect the onset of hyper-reflexive bladder contractions, and conditional electrical stimulation of the pudendal nerve will be used to inhibit hyper-reflexive bladder contractions. It will also be determined if the activity of the EAS is a proxy for the activity in the pudendal nerve and if EAS EMG can be used to detect hyper-reflexive bladder contractions in humans. Restoration of continence will increase the quality of life for many individuals, and implanting a neural prosthesis on the pudendal nerve will increase the population of persons who could benefit from such a device.

I.5 Figure and Tables

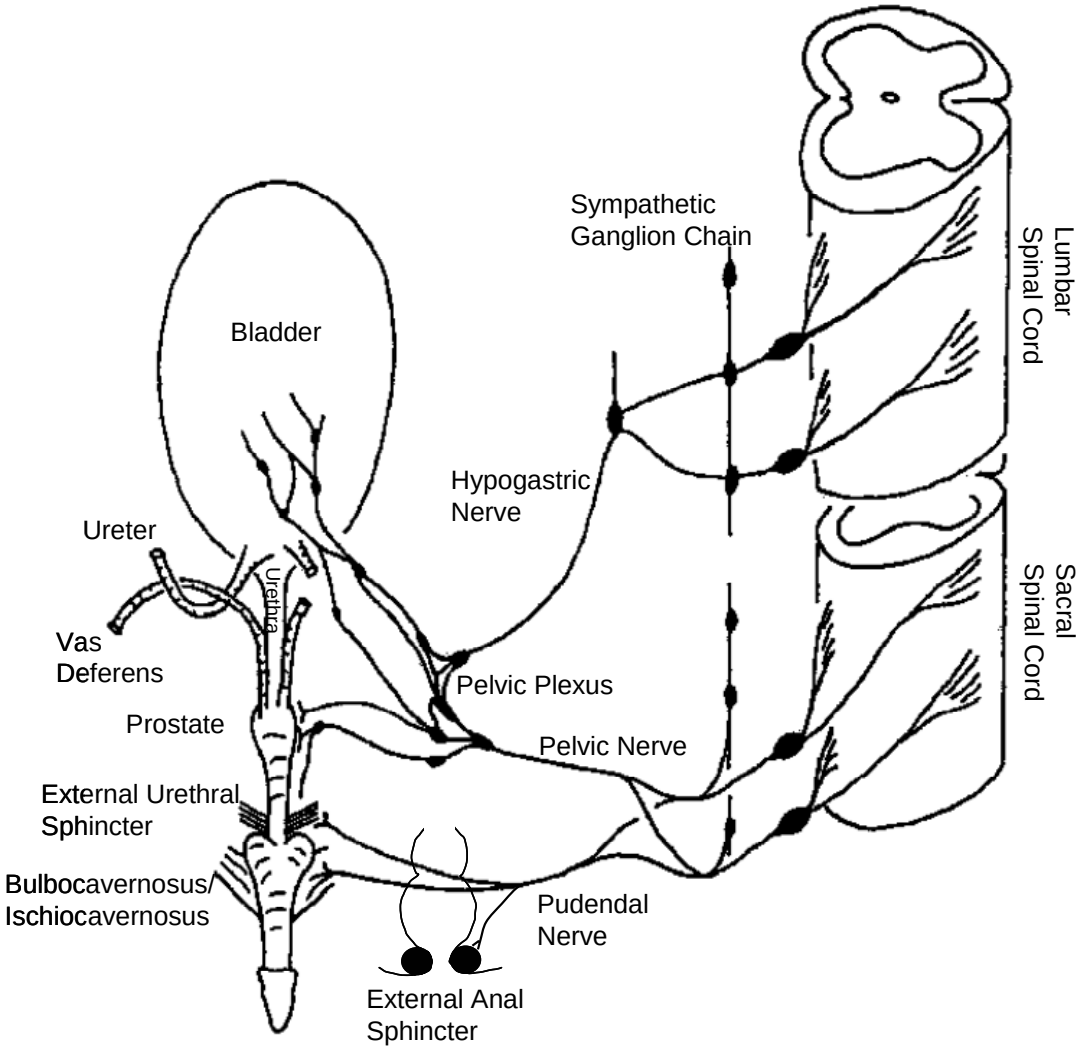

Figure I.1 The lower urinary tract and the innervation of the lower urinary tract. Modified from (de Groat, 1997).

Chapter II Detecting the Onset of Hyper-Reflexive Bladder Contractions from the Electrical Activity of the Pudendal Nerve

II.1 Abstract

Individuals with a spinal cord injury or neurological disorders may develop involuntary bladder contractions at low volumes (bladder hyper-reflexia), which can lead to significant health problems. Present devices can inhibit unwanted contractions through continuous stimulation, but do not enable conditional stimulation only at the onset of bladder contractions. The objectives of this study were to determine the relationship between the electrical activity of the pudendal nerve trunk (PNT) and bladder pressure during hyper-reflexive bladder contractions and to determine whether PNT activity could be used to detect the contractions.

Bladder pressure and PNT electroneurogram (ENG) were recorded in eight adult male cats. The PNT ENG activity increased at the onset of a bladder contraction and the activity during bladder contractions was greater than during the intercontraction interval ($p < 0.001$). Three algorithms were developed to detect the onset of a bladder contraction from the PNT ENG activity. A CUSUM algorithm performed better than either a constant threshold or a dynamic threshold algorithm, and enabled detection of reflex bladder contractions from the PNT ENG an average of 1.2 seconds after the contraction started with an average increase in pressure 7.1 cmH2O when evaluated on data not used to set detection parameters. These data demonstrated that recordings from the PNT could be used to detect hyper-reflexive bladder contractions and provide a signal to control closed-loop inhibitory stimulation.

II.2 Introduction

Our long term goal is to develop a neural prosthesis to detect and abolish hyper-reflexive bladder contractions, and thereby maintain urinary continence in individuals with spinal cord injury or other neurological disorders. The objectives of this study were to characterize the relationship between the electrical activity of the pudendal nerve trunk (PNT) and the presence or absence of reflex bladder contractions and to determine whether PNT activity could be used to detect the occurrence of nascent bladder contractions.

The lower urinary tract has two main functions: the accumulation of urine (continence) and the elimination of urine at an appropriate time (micturition). Neurological disease or spinal cord injury (SCI) can result in loss of voluntary control of bladder evacuation and in bladder hyper-reflexia. Bladder hyper-reflexia is the involuntarily reflex contraction of the bladder at small fluid volumes, and can result in loss of continence and/or high bladder pressure during bladder-urethral sphincter dyssynergia (Watanabe et al., 1996). During bladder-urethral sphincter dyssynergia the bladder and the urethral sphincter co-contract resulting in high pressure or absent micturition. Loss of voluntary control, hyper-reflexia, and dyssynergia can result in long term renal damage, frequent urinary tract infections, and infections of the kidneys (Shingleton & Bodner, 1993).

Electrical stimulation has been used to treat incontinence through inhibition of hyper-reflexia, but each of the present methods continuously applies stimulation to inhibit the bladder (Chartier-Kastler et al., 2001; Craggs et al., 1998; Grill et al., 2001; Jezernik

et al., 2002; Siegel, 1992; van Balken et al., 2001; Vandoninck et al., 2003; Vodusek et al., 1986; Weil et al., 1998). Conditional stimulation, when stimulation is applied only when a hyper-reflexive contraction occurs, may allow the bladder to fill to greater volume before an uncontrollable contraction occurs (Kirkham et al., 2001; Shah et al., 1998) by minimizing habituation resulting from repetitive activation of spinal reflexes (Cariga et al., 2000; Floeter et al., 1998; Granat et al., 1993; L.M. Harrison et al., 2000). Further, conditional stimulation at the beginning of the contraction can completely abolish the contraction (Kondo et al., 1982; Shah et al., 1998).

Conditional stimulation to inhibit the bladder requires detection of the onset of nascent hyper-reflexive contractions. We hypothesized that the electrical activity of the pudendal nerve, which innervates somatic skeletal muscles of the pelvic area, could be used to detect the onset of hyper-reflexive bladder contractions. The external urethral sphincter and external anal sphincter are innervated by the pudendal nerve and exhibit bursts of activity associated with bladder contractions in both cats and rats (Evans, 1936; Fedirchuk & Shefchyk, 1993; Gary et al., 1959; Thor & Muhlhauser, 1999). Following spinal cord injury, bladder-urethral sphincter dyssynergia leads to large increases in activity of the muscles in the pelvic floor during bladder contractions (Rudy et al., 1988; Watanabe et al., 1996). These studies suggested that recording from the pudendal nerve would enable detection of hyper-reflexive bladder contractions, and such a signal could serve as a trigger for conditional stimulation. The objectives of the present study were to characterize the relationship between pudendal nerve trunk electroneurogram (PNT ENG) and bladder pressure during reflex bladder contractions, to determine whether the

PNT ENG could be used to detect the onset of bladder contractions, and to compare the performance of three algorithms for detecting bladder contractions from the PNT ENG.

II.3 Method

II.3.1 Experimental Preparation

All animal care and experimental procedures were performed according to NIH guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee of Case Western Reserve University. Intact male cats (n = 8, 2.9 – 4.3 kg) were anesthetized with ketamine HCl (Ketaset, initial dose 30 mg/kg, supplemental at 15 mg/kg, IM). A catheter was inserted in the cephalic vein, and anesthesia was maintained with alpha-chloralose (Sigma, 60 mg/kg, IV, supplemented at 15 mg/kg). Depth of anesthesia was maintained by monitoring blood pressure, heart rate, and blink and withdraw reflexes. Animals were intubated and respired with continuous monitoring of CO2, body temperature was maintained between 37o and 39o C, 0.9% NaCl saline with 50 grams of dextrose and 8.4 grams of sodium bicarbonate per liter was administered (~15 ml/kg/hr, IV), and heart rate and blood pressure were continuously monitored through a catheter in the carotid artery.

II.3.2 Instrumentation and Signal Conditioning

A ventral midline incision was made to expose the bladder and a 3.5 Fr (1.17 mm) suprapubic catheter was inserted into the bladder through the bladder wall and secured with a purse string suture. The ureters were ligated and transected proximal to the ligation. Drain tubes were placed adjacent to the proximal portion of both transected ureters, and the abdominal incision was closed in layers. A transurethral catheter (3.5 or 5.0 Fr) was inserted into the bladder to occlude the urethra, and allowed the bladder to contract without fluid leakage. The transurethral catheter was connected to a stopcock

and a syringe for filling the bladder with room temperature saline, and the suprapubic catheter was connected to a solid state pressure transducer (Deltran DPT-100, Utah Medical Products).

The pudendal nerve was isolated through a lateral approach, and a cuff electrode was placed on either the whole pudendal nerve trunk (n=3 cats) or the pudendal nerve distal to the urethral sensory branch (n=5 cats). The split silicone tube tripolar nerve cuff had three platinum bands spaced 5 mm apart and an inner diameter between 1.0 and 1.5 mm (Haugland, 1996). The split in the cuff was covered with a piece of silicone sheeting, and the cuff was closed with suture (Appendix A). The nerve signals were preamplified (100X, Stanford SR560, Sunnyvale, CA), filtered (1,000 – 10,000 Hz), and further amplified (1,000X, P511 Grass, Quincy, MA). The high-pass cut-off frequency was set to 1 kHz because the small diameter population and the short nerve cuff electrode cause the characteristic frequency to shift to higher frequencies, and the higher cut-off frequency minimized EMG contamination of the signal (Stein et al., 1975). The ENG and pressure signals were sampled at 24 kHz (CDAT 16, Cygnus Technology, Inc., Delaware Water Gap, PA) and displayed on a strip chart recorder (TA11, Gould Instruments) (Figure II.1). Subsequent processing of the ENG and bladder pressure was performed offline using custom software written in Matlab (Mathworks, Natick, MA).

II.3.3 Experimental Procedure

The bladder was emptied and then slowly filled (0.25 – 1 ml/min) until the onset of distention evoked hyper-reflexive-like bladder contractions, and the bladder volume was then held constant for a series of bladder contractions. The electroneurogram of the pudendal nerve (PNT) was recorded during the slow filling and during the bladder contractions. The PNT ENG was also recorded during different inputs that may interfere

with detection of bladder contractions including rectal distention and bulbocavernosus reflex. A lubricated endotracheal intubation tube was inserted into the rectum and was filled and deflated using a syringe to distend the rectum, and the bulbocavernosus reflex was tested by firmly pinching the base of the penis with a pair of forceps.

II.3.4 Offline Analysis of Bladder Pressure

The onset and duration of a bladder contraction was calculated using a two part process (Figure II.2). The bladder pressure was first linearly detrended to find baseline pressure. The threshold for the first bladder contraction was set 30% above the minimum pressure of the linearly detrended bladder pressure. Once the bladder pressure rose above the 30% threshold, the bladder pressure was traced back until the rate of change in bladder pressure decreased by 50% and this point was defined as the onset of the bladder contraction. The end of a bladder contraction was similarly determined; the bladder pressure had to fall below the threshold pressure (30% above the baseline pressure set at the beginning of the contraction), and the bladder pressure was traced forward until the rate of change in the bladder pressure decreased by 50%. The average contraction pressure was defined as the mean of the bladder pressure during the middle third of the bladder contraction. The baseline pressure was defined as the mean of the bladder pressure between contractions. The next baseline pressure began with the end of the previous bladder contraction, and subsequent bladder contractions were defined using the same procedure as above, but the thresholds were set 30% above each preceding baseline pressure.

II.3.5 Algorithms to Detect Reflex Bladder Contractions

Three different algorithms to detect the onset of bladder contractions from the PNT ENG were implemented and compared: a constant threshold algorithm, a dynamic

threshold algorithm, and a weighted cumulative sum algorithm. The parameters of each algorithm were optimized using a cost function based on four factors weighted with the performance objective of maintaining continence. The relative magnitude of the coefficients in the cost function were 4:2:2:1 for the number of false negatives, the delay from the start of a bladder contraction to the time of detection, the increase in bladder pressure from the start of the bladder contraction to the time of detection, and the number of false positives. The number of false negatives was considered the most important variable in the cost function. As the number of false negatives was minimized, fewer bladder contractions would be uninhibited, thus decreasing the chance of losing continence. The delay before detection and increase in bladder pressure above baseline before detection were the next two important variables. As the delay and increase in bladder pressure were minimized, the bladder pressure would be more likely to remain below pathological levels. The least important variable was the number of false positives. As the number of false positives increased, more inhibitory stimuli would be delivered and the system would approach continuous stimulation. The detection parameters of each algorithm were found using an exhaustive search method such that the cost function was minimized. The parameters were varied from an initially very high value with the next value at each iteration set to 10% less than the previous value. The optimization was performed within each cat, because in practice the device would be optimized for a specific user and a set of parameters optimized for one individual would not be used for another individual. To simulate a functional device, a fifteen second stimulation time was assumed such that detections of bladder contraction had to be at least 15 seconds apart. Any detection that preceded the bladder contraction by 15 seconds or more was classified

as a false positive. Once a bladder contraction started, any subsequent detection of that bladder contraction was classified as a false positive even if the bladder contraction lasted for longer than 15 seconds.

The first detection algorithm used a constant amplitude threshold to detect the onset of bladder contractions (Figure II.5B). The ENG activity was rectified and low pass filtered offline using a 3rd order Butterworth filter. When the activity of the rectified, low pass filtered ENG crossed a constant threshold, the bladder contraction was detected. The parameters that were adjusted in this algorithm to optimize the detection were the time constant of the low pass filter and the value of the threshold.

The second detection algorithm used a dynamic amplitude threshold to detect the onset of bladder contractions (Figure II.5C). When the rectified, low pass filtered ENG activity of the pudendal nerve crossed the threshold, the bladder contraction was detected. However, the value of the amplitude threshold was not constant. The value of the threshold was an offset version of the rectified ENG, low pass filtered with a larger time constant than the signal to create a lag. The parameters of the algorithm that were adjusted were the time constant of the low pass filter for the signal, the time constant of the low pass filter for the threshold, and the offset of the threshold.

The last algorithm was a weighted cumulative sum (CUSUM) (Figure II.5D) (Basseville & Nikiforov, 1993). The CUSUM algorithm is able to detect small increases in a noisy signal by testing the hypothesis that the nerve signal is equal to the baseline activity against the hypothesis that the nerve signal is greater than the baseline activity. The output of the CUSUM algorithm increased when the activity of the ENG increased above baseline, and was compared to a constant threshold to determine the onset of

bladder contractions. The threshold was not adjusted and was the same across all cats. The parameters of the algorithm that were adjusted were the time constant of the low pass filter, the window size for initial mean and standard deviation of the signal, and the number of data points used in the cumulative sum.

II.4 Results

II.4.1 Reflex Bladder Contraction Evoked by Bladder Filling

Slow filling of the bladder led to hyper-reflexive-like bladder contractions at threshold bladder volumes from 11 to 38 ml (22 ± 7.8 ml, n = 8 cats). The baseline bladder pressure between contractions ranged from 10 to 31 cmH20 (16 ± 3.7 cmH20, n = 757 intervals across 8 cats) and the pressure during contraction ranged from 15 to 58 cmH2O (33 ± 8.6 cmH20, n = 781 contractions across 8 cats). The length of contractions ranged from 2.3 to 182.4 seconds (16.7 ± 13.8 seconds), and time between contractions ranged from 0.4 to 170.2 seconds (13.0 ± 13.7 seconds).

II.4.2 Pudendal Nerve Activity during Hyper-Reflexive-Like Bladder Contractions

Pudendal nerve trunk electroneurogram (PNT ENG) was successfully recorded in all eight experiments. The baseline activity (the rectified, low pass filtered ENG averaged over five minutes when the bladder was empty) ranged from 0.42 to 3.52 μV (1.34 ± 0.53 μV, n = 8 cats). The PNT ENG before the first bladder contraction during a fill (averaged over one minute) was 1.57 μV ± 0.68 μV (n = 5 cats) and was not different from the activity when the bladder was empty ($p=0.48$, $\beta=0.14$, 2 sided t-test). Examples of a series of bladder contractions, the PNT ENG activity, and the processed ENG signals are shown in Figure II.3, and a summary of the magnitudes of the PNT ENG during bladder contractions and during the intercontraction intervals are shown in Figure II.4. The PNT ENG activity during a bladder contraction ranged from 0.66 to 13.99 μV (2.06 ± 1.43 μV,

n = 781 bladder contraction across 8 cats) and during intercontraction interval ranged from 0.59 to 8.77 μV (1.59 ± 0.77 μV, n = 757). The PNT ENG activity during the contraction time was greater than PNT ENG activity during the intercontraction intervals (p = 0.01, 2 sided paired t-test, n = 8).

II.4.3 Detection of Hyper-Reflexive-Like Bladder Contractions

The performance of the three algorithms (constant threshold algorithm, dynamic threshold algorithm, and CUSUM algorithm) detecting the onset of the reflexive bladder contractions was quantified, and examples with each algorithm across the same set of contractions are shown in Figure II.5. Summaries of the performance across cats are provided in Table II.1 and Figure II.6 and performance within individual cats is shown in Figure II.7.

The constant threshold algorithm had a delay from the start of the bladder contraction to time of detection of 2.1 ± 2.3 seconds (n = 770 bladder contractions across 8 cats; averaged across cats where parameters were optimized for each cat using all contractions of that cat) with an increase in bladder pressure at detection of 9.5 ± 8.2 cmH2O above baseline (n = 770) (Table II.1). The constant threshold algorithm had a sensitivity of 93%, and a specificity of 54% with 54 false negative and 598 false positives. Sensitivity was the number of detected contractions divided by the total number of contractions, and specificity was the number of detected contractions divided by the number of detected contractions plus the number of false positives. Histograms of the delays and increases in pressure above baseline are shown in Figure II.6. A negative delay implied that the detection of the bladder contraction occurred before the bladder contraction started, and negative delays created negative increases in bladder pressure. A

negative increase in bladder pressure indicated that the bladder pressure at the time of detection was less than the bladder pressure at the time of actual contraction.

To examine the robustness of the detection algorithms, the data sets from 6 cats were divided into two groups, the calibration set and the validation set. The data sets from two of the cats had an insufficient number of contractions (n=8 and n=12) to divide the data into two sets. The parameters for the algorithm were optimized using the calibration set, and the tuned algorithm was subsequently tested on the validation set (i.e., on data not used in parameter tuning). For the constant threshold algorithm, the delay of detection in the calibration set was 1.8 ± 2.2 seconds (n = 424 bladder contractions across 6 cats) whereas the delay in the validation set was 2.8 ± 2.3 seconds (Figure II.7A). The increase in pressure from baseline to time of detection in the calibration set was 9.1 ± 8.5 cmH2O (n = 424) and was 12.1 ± 8.3 cmH2O (n = 318) in the validation set (Figure II.7B). The sensitivity and specificity for the calibration set were 93% and 53%, respectively, and for the validation set were 92% and 46%, respectively.

For the dynamic threshold algorithm, the delay of detection in the calibration set was 1.5 ± 2.6 seconds (n = 431 bladder contractions across 6 cats), and the delay in the validation set was 1.9 ± 2.3 seconds (n = 325, Figure II.7A). The increase in pressure from baseline to time of detection in the calibration set was 5.1 ± 6.9 cmH2O (n = 431) and was 7.5 ± 8.1 cmH2O (n = 325, Figure II.7B) in the validation set.

For the CUSUM algorithm, the delay of detection in the calibration set was 1.4 ± 2.0 seconds (n = 412 bladder contractions across 6 cats), and the delay in the validation set was 1.2 ± 2.3 seconds (n = 294, Figure II.7A). The increase in pressure from baseline

to time of detection in the calibration set was 7.4 ± 8.8 cmH2O (n = 412) and was 7.1 ± 8.0 cmH2O (n = 294, Figure II.7B) in the validation set.

The performance of each algorithm on the validation data sets was compared to determine which algorithm had the best performance (Figure II.7, Table II.1). The delay in detection was significantly lower with the CUSUM algorithm than with either the constant threshold (2 of 5 cats) or dynamic threshold (4 of 5 cats, Figure II.7C). The pressure at detection was significantly lower with the CUSUM algorithm than with either the constant threshold (2 of 5 cats) or dynamic threshold (4 of 5 cats, Figure II.7D).

II.4.4 Origin of Signal

To determine the origin of the ENG signal, nerve transections were conducted in two experiments, and Figure II.8 is an example of the effects of different nerve transections. When the pudendal nerve was cut proximal to the cuff, the ENG was still present (Figure II.8B). The ENG remained after the urethral sensory branch was transected, but had diminished amplitude after the caudal rectal branch distal to the cuff was transected (Figure II.8C). It could not be determined if this change was the result of a loss of activity from the caudal rectal branch or the result of disrupting the position of the cuff during the transection. When the deep perineal nerve was transected distal to the cuff, the ENG was no longer present (Figure II.8D). In a second experiment, the order of transections was reversed. When the deep perineal branch was transected, the signal was lost, and, thus there was no signal to examine following the transection of the remaining branches. These results showed that the major source of the PNT signal during hyper-reflexive contractions was the afferent fibers from the deep perineal branch, and possibly the caudal rectal branch, of the pudendal nerve.

The PNT ENG was recorded with the urethral catheter present and after it was removed from the urethra in four experiments to determine whether movement of the catheter contributed to the recorded signal. There was no difference in the character or amplitude of the signal when the catheter was present or absent.

II.5 Discussion

The objectives of the present study was to characterize the relationship between pudendal nerve activity and bladder pressure during hyper-reflexive bladder contractions, and to determine whether the electroneurogram (PNT ENG) could be used to detect the onset of bladder contractions. The PNT ENG activity increased at the onset of a bladder contraction and the ENG amplitude during a bladder contraction was significantly higher than activity between contractions. This relationship allowed robust detection of the onset of bladder contractions from the pudendal nerve ENG.

The average delay in detection for constant threshold algorithm, dynamic threshold algorithm, and CUSUM algorithm were 2.1, 1.8, and 1.4 seconds, respectively, with an average increase in bladder pressure above baseline of 9.5, 6.6, and 7.3 cmH2O, respectively (Table II.1). The performance of detection of bladder contractions from PNT ENG was comparable to detection using recordings of the electrical activity in the sacral nerve root (Jezernik et al., 2001). Sacral nerve activity enabled detection of the onset of a bladder contraction within 6 seconds (0.2 to 42 seconds, n = 30 bladder contractions across 5 cats) with an average increase in pressure of 9 cmH2O (0.3 to 29.5 cmH2O, n=30). The pudendal nerve approach, however, presents a substantially simpler surgical procedure to implant a recording cuff than required to access the sacral nerve roots.

The PNT ENG activity increased at the onset of a bladder contraction, and the signal originated from afferent fibers in the deep perineal branch of the pudendal nerve. The deep perineal branch innervates the external urethral sphincter (EUS), the bulbus glandis, and the distal urethra (Martin, Fletcher, & Bradley, 1974). Rudy et. al have shown that alpha chloralose anesthesia can induce a dyssynergic response between the urethral sphincter and the bladder of a cat and thus robust pudendal nerve activity is expected during bladder contractions (Rudy, Downie, & McAndrew, 1991). The recorded ENG may be the result of both efferent and afferent fiber activity to and from the EUS, but the deep perineal branch has more afferent fibers (Martin et al., 1974), which may have dominated the signal.

Although the anesthesia-induced dyssynergia may be viewed as an artifact of the experimental preparation, this is representative of what occurs in spinal cord injury (SCI). After SCI, individuals develop dyssynergic responses caused by an increased sensitivity of unmyelinated c-fibers which signal through spinal reflex loops the bladder and the sphincters to contract concurrently (de Groat, 1997; de Groat et al., 1981; Fedirchuk, Hockman, & Shefchyk, 1992). Even though the mechanism of dyssynergia in the animal model and individuals with SCI are different, the resulting co-contraction of the sphincter during bladder contractions will produce similar increases in afferent firing in the deep perineal branch of the pudendal nerve. Thus, the different mechanisms of the dyssynergia should not diminish the ability to detect a bladder contraction from the PNT ENG after SCI.

A potential limitation of this approach is the selectivity of detection from pudendal nerve electrical activity. Different physiological events can increase PNT

activity, for instance, a bowel movement or genital stimulation (Krier, 1984). Interfering inputs [rectal distention (n = 8 trials across 3 cats), bulbocavernosus reflex (n = 24 trials across 5 cats), and perianal stroking (n = 9 trials across 3 cats)] caused transient increases in PNT ENG and resulted in false positives detection with each algorithm (using detection parameters optimized across the entire data set). These interfering inputs, thus reduced the specificity of each algorithm. False positives will, in the limit, cause the system to emulate open-loop stimulation and make the closed-loop system superfluous. However, conditional stimulation has been shown to increase bladder capacity more than continuous stimulation, and thus closed-loop stimulation is worth pursuing (Kirkham et al., 2001; Shah et al., 1998). Failing to detect the occurrence of a bladder contraction (false negative) is more detrimental to maintaining continence than stimulating too often.

The CUSUM algorithm performed the best out of the three algorithms based on its high specificity, short delay, small increase in pressure, and robustness across calibration and validation data sets (Table II.1). The CUSUM algorithm has been implemented in previous work because it exhibits a higher specificity than a constant threshold algorithm (Falou, Khalil, & Duchene, 2001; Jezernik et al., 2001; Jezernik & Sinkjaer, 1998). The CUSUM algorithm had a specificity of 60% in the validation set whereas the constant threshold and dynamic threshold algorithms had a specificity of 45% and 41% in the validation set, respectively. It has been shown that the baseline activity of the urethral sphincter increases as the bladder volume increases (Habler, Janig, & Koltzenburg, 1990). Both the dynamic threshold and CUSUM algorithms had the ability to adjust for changing baselines and this reduced the number of false negatives relative to the constant threshold algorithm. The CUSUM and dynamic threshold

algorithms had a higher sensitivity than the constant threshold algorithm in the calibration set, but the CUSUM and dynamic threshold algorithms had lower sensitivity in the validation set. The CUSUM algorithm was the only algorithm with the delay and increase in pressure in the validation set not statistically different from the calibration set in any of the cats. The CUSUM algorithm provided the best performance with the drawbacks of a requirement for a priori knowledge of the variance of the signal, the longer processing time, and that the algorithm cannot be implemented in an analog circuit.

II.6 Conclusion

Pudendal nerve electrical activity increased during reflexive bladder contractions, and the CUSUM algorithm enabled robust detection of the bladder contractions. Conditional stimulation, when inhibitory stimulation applied only when the bladder is contracting, reduces habituation and allows the bladder to fill to greater volumes before continence is lost than continuous stimulation. Further, if the stimuli are applied early in the contraction, the bladder pressure may not reach pathological levels. The detection of hyper-reflexive bladder contractions from recordings of pudendal nerve electrical activity could be used as a control signal to deliver inhibitory stimuli to arrest nascent bladder contractions and maintain continence.

II.7 Figures and Tables

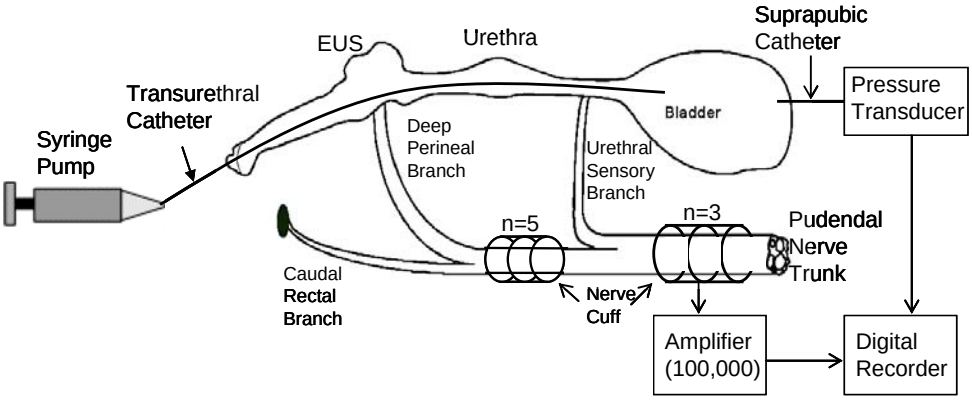

Figure II.1 Experimental instrumentation used to quantify the relationship between pudendal nerve electrical activity and reflex bladder contractions. A tripolar nerve cuff was implanted around the pudendal nerve trunk (PNT), and the PNT electroneurogram (ENG) was amplified and digitally recorded. The bladder volume was maintained with a syringe pump connected to a transurethral catheter, and the bladder pressure was measured through a suprapubic catheter. The bladder was slowly filled (0.25-1.0 ml/min) until reflexive bladder contractions occurred, and the PNT ENG was recorded during filling and during constant volume reflex contractions. Figure adapted from (Wang, Bhadra, & Grill, 1999)

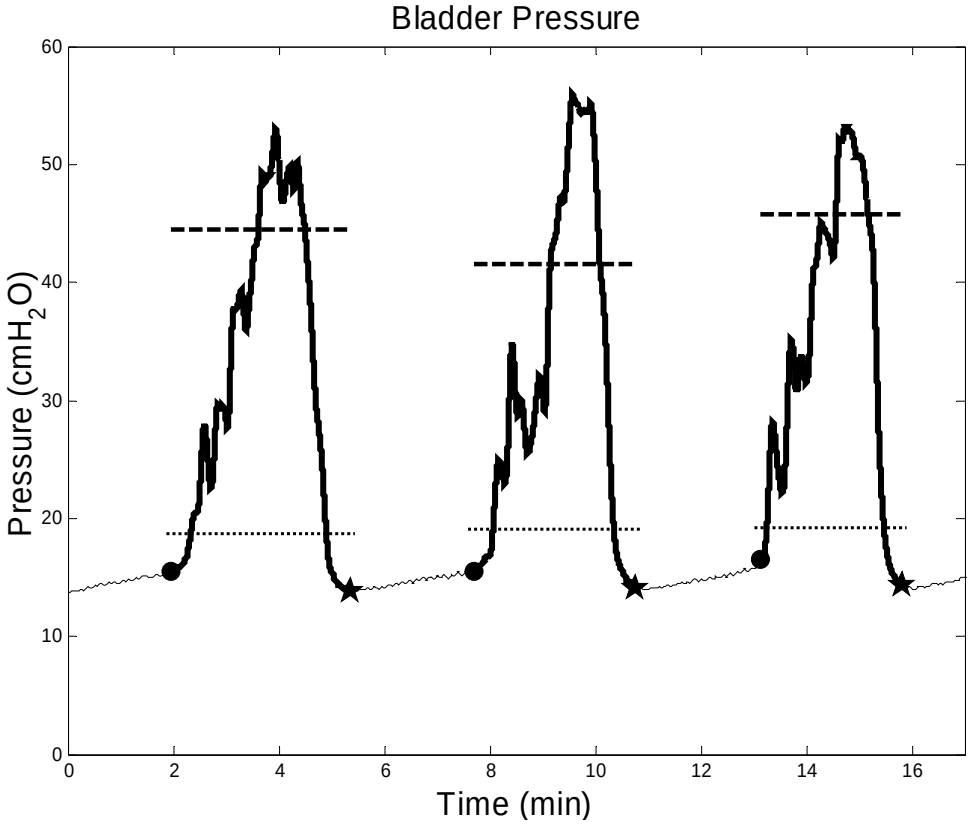

Figure II.2 Determination of the parameters describing distention evoked hyper-reflexive-like bladder contraction. The start (●) and the end (★) of bladder contractions are shown. The bladder contraction (thick line), the intercontraction baseline pressure (thin line), the threshold pressure at 30% above the baseline pressure (…..), and the average pressure of contraction (- -) are indicated by line type. For further details see text.

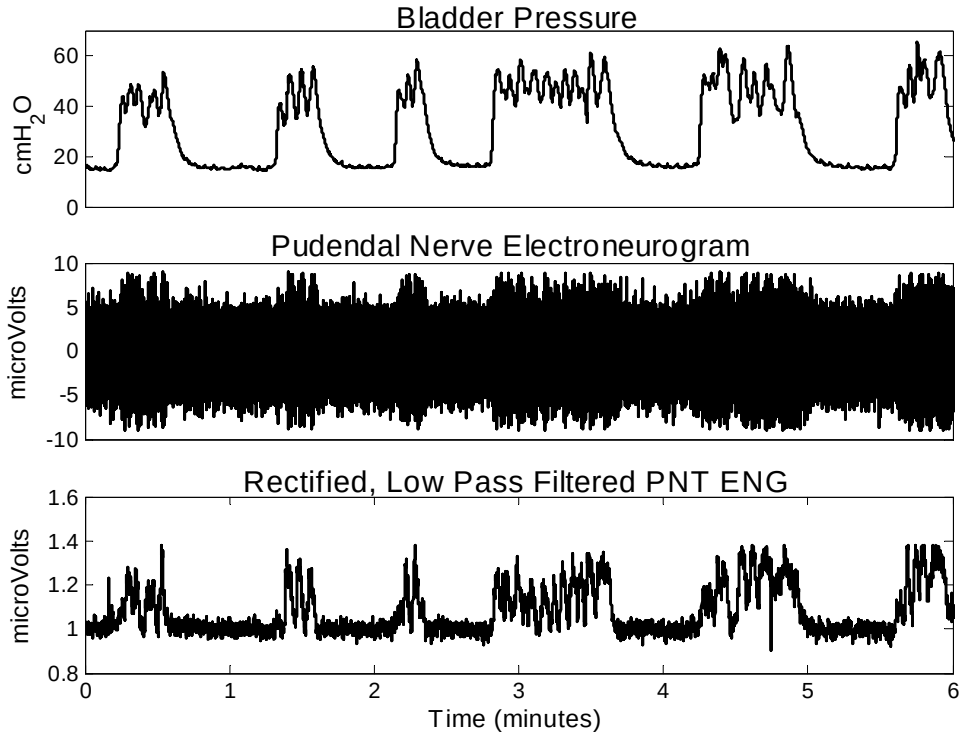

Figure II.3 Pudendal nerve trunk electroneurogram (PNT ENG) during reflex bladder contractions. Series of reflex bladder contractions (top) with corresponding PNT ENG (middle trace). The bottom trace is the PNT ENG after the signal has been rectified and low pass filtered with a 3rd order Butterworth filter. The bursts of ENG activity occurred with each bladder contraction.

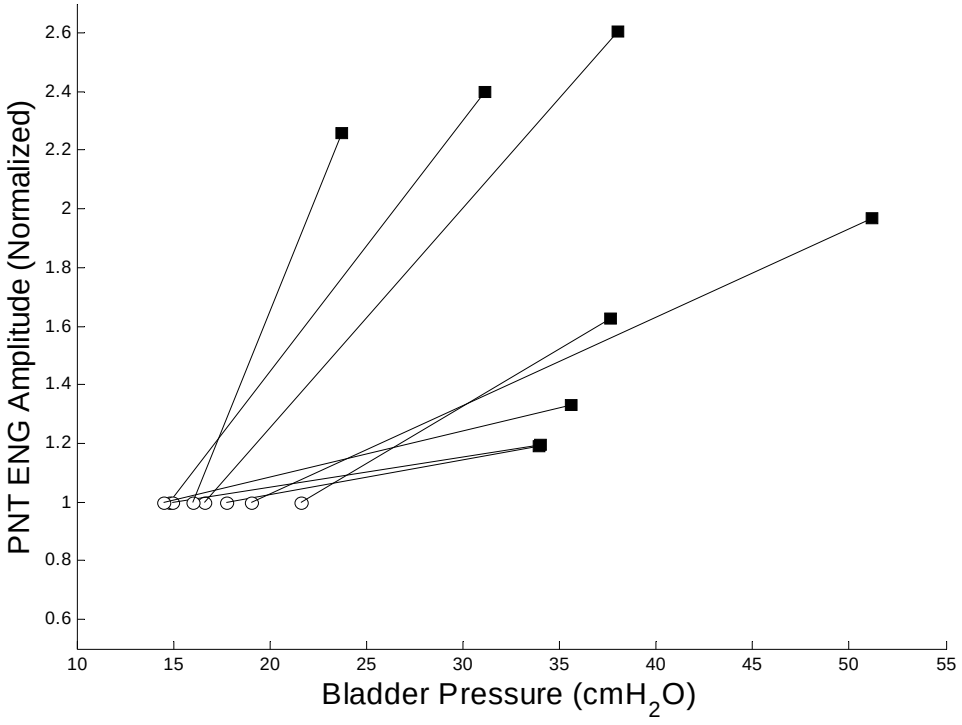

Figure II.4 Average PNT ENG activity during bladder contractions (■) and during the intercontraction intervals (O). The average PNT ENG activity during bladder contractions was normalized to the activity during the intercontraction interval. Different lines represent different experiments.

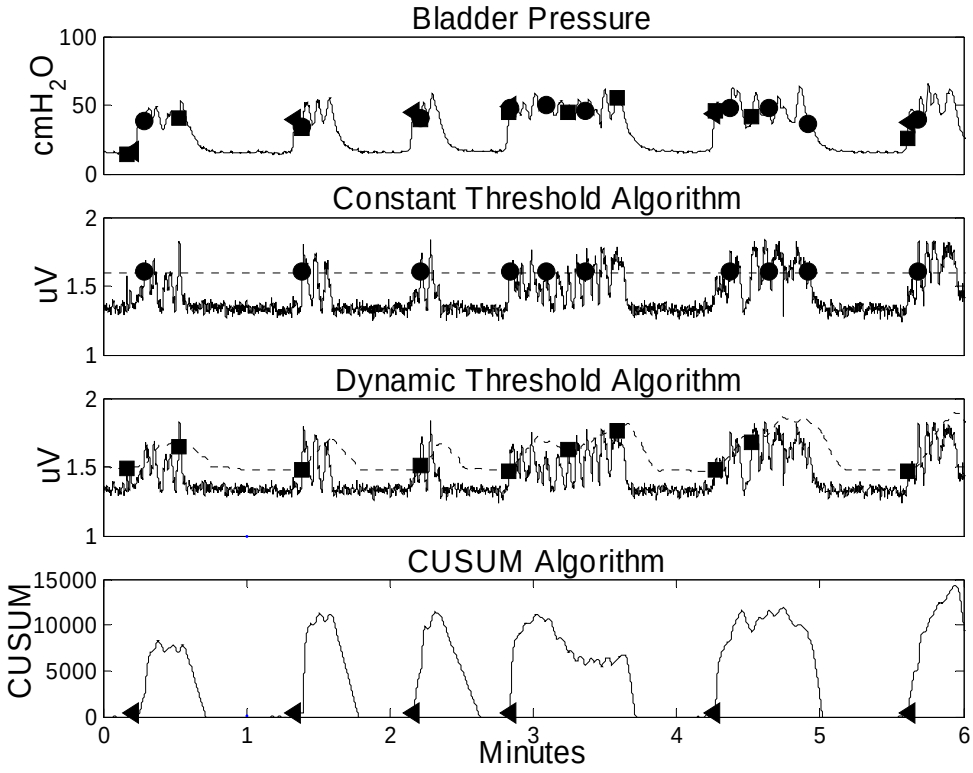

Figure II.5 Detection of reflex bladder contractions from pudendal nerve electroneurogram (PNT ENG). Example of reflexive bladder contraction with corresponding processed PNT ENG. (A) Bladder pressure. (B) Processed PNT ENG and constant detection threshold (dashed line) with detection of bladder contraction detections denoted by ●. (C) Processed PNT ENG and dynamic threshold (dashed line) algorithm (detections denoted by ■). (D) The CUSUM algorithm output (detections denoted by ◄, the threshold was set at 5). The detections from each algorithm are also shown on the pressure trace with their corresponding symbol (the symbols overlay each other).

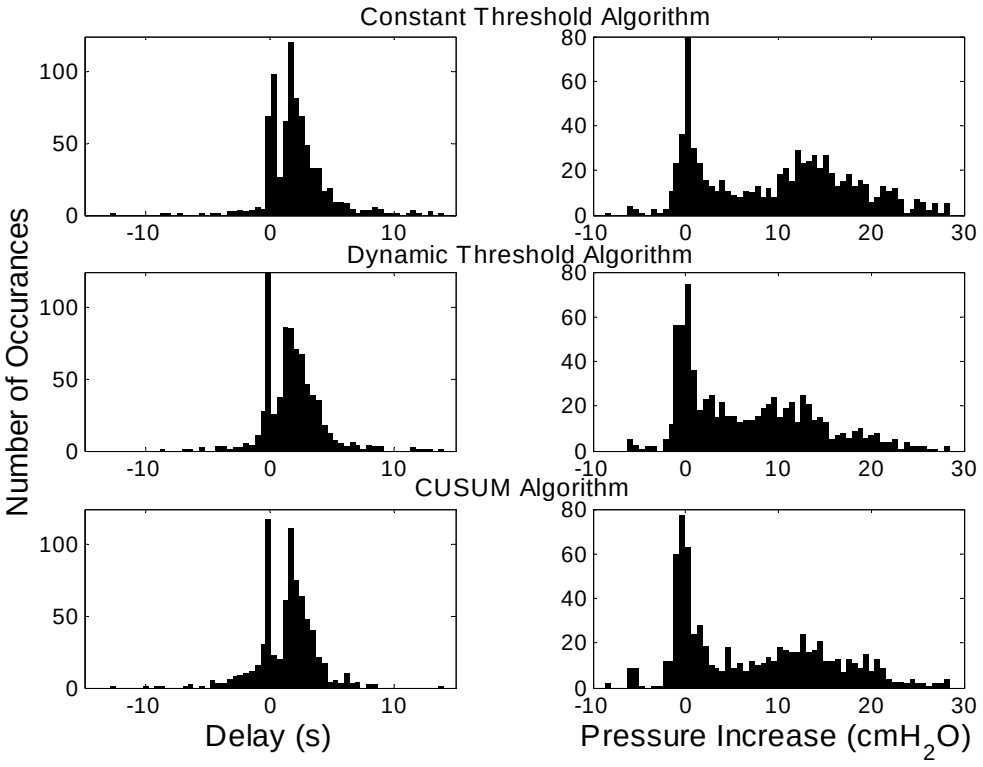

Figure II.6 Performance of three algorithms in detecting reflex bladder contractions from pudendal nerve electroneurogram. Histograms of the delay between the onset of reflex bladder contractions and time of detection (left) and the increase in bladder pressure between baseline and when the contraction was detected (right) for the constant threshold algorithm, dynamic threshold algorithm, and the CUSUM algorithm.

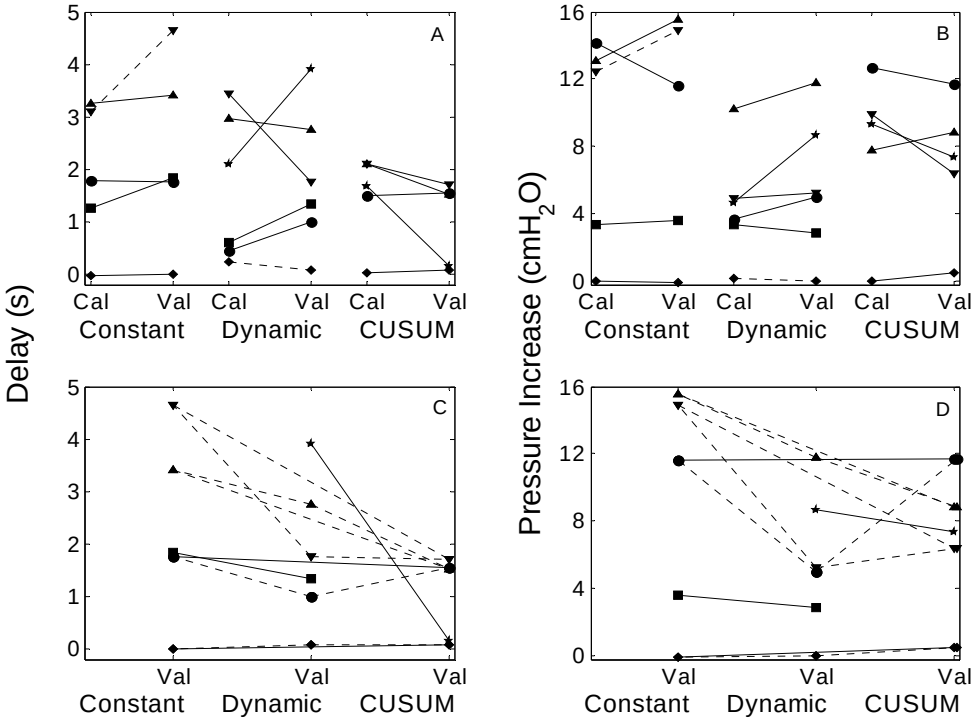

Figure II.7 Performance of three algorithms in detecting reflex bladder contractions from recordings of pudendal nerve electroneurogram. Each algorithm's parameters were optimized using the calibration set (Cal), and the tuned algorithms were subsequently tested on the validation set (Val), and the average delay (A) and increase in bladder pressure (B) for each experiment are shown. The performances of each algorithm were compared with the validation data set to determine which algorithm had the best performance in terms of delay (C) and increase in bladder pressure (D). Each experiment is represented by a different symbol. A broken line represent that the two points are significantly different ($p < 0.05$, Wilcoxon rank sum test).

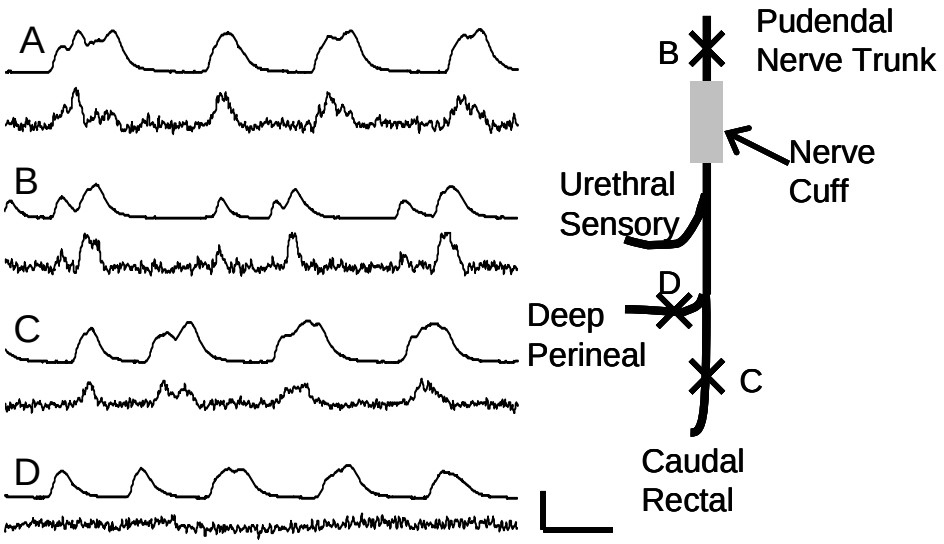

Figure II.8 Nerve transection was used to identify the origin of the increase in pudendal nerve (PNT) activity that occurred during reflex bladder contractions. Each pair of traces shows the bladder pressure (top) and corresponding PNT electroneurogram (bottom). (A) Original signal prior to any transection. (B) Following transection of the PNT rostral to the nerve cuff. (C) Following transection of the caudal rectal and urethral sensory branch distal to the cuff. (D) Following transection of the deep perineal branch caudal to the nerve cuff. The figure on the right shows approximate locations of each transection. Vertical scale: 0.5 μV and 50 cmH2O; horizontal scale: 30 sec.

Table II.1 Performance of three algorithms in detection of hyper-reflexive-like bladder contractions.

	Constant Threshold			Dynamic Threshold			CUSUM		
	All Data	Calibration Set	Validation Set	All Data	Calibration Set	Validation Set	All Data	Calibration Set	Validation Set
Delay (s)	2.1 (2.3)	1.8 (2.2)	2.8 (2.3)	1.8 (2.2)	1.5 (2.6)	1.9 (2.3)	1.4 (2.2)	1.4 (2.0)	1.2 (2.3)
Pressure Increase (cmH2O)	9.5 (8.2)	9.1 (8.5)	12.1 (8.3)	6.6 (7.1)	5.1 (6.9)	7.5 (8.1)	7.3 (8.2)	7.4 (8.8)	7.1 (8.0)
Sensitivity	93%	93%	92%	98%	94%	79%	98%	98%	82%
Specificity	54%	53%	45%	57%	69%	41%	55%	68%	60%

The mean (standard deviation) of the delay between onset of the contraction and its detection, the increase in bladder pressure between baseline and when the contraction was detected, sensitivity (number of detected contractions divided by the total number of contractions), and specificity (the number of detected contractions divided by the number of detected contractions plus the number of false positives) are shown.

Chapter III Closed-Loop Electrical Control of Urinary Continence

III.1 Abstract

Individuals with spinal cord injury or neurological disorders may develop involuntary bladder contractions at low volumes (bladder hyper-reflexia) that cause incontinence and can lead to significant health problems. Bladder contractions can be suppressed by stimulation of inhibitory pathways, but continuous activation may lead to habituation of the inhibitory reflex and loss of continence. The objective of this study was to determine whether conditional stimulation, with stimulation of inhibitory pathways applied only at the onset of nascent bladder contractions, allowed the bladder to fill to a greater volume before continence was lost than did continuous stimulation.

In 6 alpha-chloralose anesthetized cats, cystometries were performed to compare the volumes at which continence was lost under three conditions: no stimulation, continuous stimulation, and conditional stimulation. The pudendal nerve electroneurogram (PNT ENG) was used to detect the onset of bladder contractions and served as the input to an event-triggered control system that regulated conditional inhibitory stimulation to maintain continence. Conditional inhibitory stimulation controlled by the PNT ENG increased the bladder capacity by 36% over no stimulation and by 15% over continuous stimulation ($p<0.001$ and $p=0.027$ for no stimulation and continuous stimulation, respectively). The event-triggered control system had a 67% reduction in stimulation time as compared to continuous stimulation. These results indicate that conditional inhibitory stimulation is more effective than continuous inhibitory stimulation, and support the use of an event-triggered control system to maintain urinary continence.

III.2 Introduction

The goal of this project is to develop a neural prosthesis to treat bladder hyper-reflexia and to restore urinary continence in individuals with spinal cord injury or other neurological disorders. The objective of this study was to determine whether conditional electrical stimulation, with inhibitory stimulation delivered only when the bladder was contracting, enabled the bladder to fill to a larger volume than continuous inhibitory stimulation.

Neurological disease or spinal cord injury (SCI) can result in loss of voluntary control of bladder evacuation and bladder hyper-reflexia. Bladder hyper-reflexia is the involuntarily reflex contraction of the bladder at small fluid volumes, and can result in loss of continence and/or high bladder pressure during bladder-urethral sphincter dyssynergia (Watanabe et al., 1996). During bladder-urethral sphincter dyssynergia the bladder and the urethral sphincter co-contract preventing or inhibiting the flow of urine down the urethra. Loss of voluntary control, hyper-reflexia, and dyssynergia can result in long term renal damage, frequent urinary tract infections, and infections of the kidneys (Shingleton & Bodner, 1993).

Electrical stimulation of inhibitory pathways from the pudendal nerve to the bladder can suppress bladder hyper-reflexia, maintain continence, and increase bladder volume between 60% and 110% (Jiang & Lindstrom, 1998; Kirkham et al., 2002; Kirkham et al., 2001). In each of these previous studies, inhibitory pathways were stimulated continuously, and the effectiveness of bladder inhibition may have been limited by habituation. Conditional stimulation, when stimulation is applied only when a

hyper-reflexive contraction occurs, has several potential advantages over continuous stimulation to inhibit the bladder. First, conditional stimulation at the beginning of the contraction can completely abolish the contraction (Kondo et al., 1982; Shah et al., 1998). Second, conditional stimulation may allow the bladder to fill to greater volume before an uncontrollable contraction occurs (Kirkham et al., 2001; Shah et al., 1998) by minimizing habituation resulting from repetitive activation of spinal reflexes (Cariga et al., 2000; Floeter et al., 1998; Granat et al., 1993; L.M. Harrison et al., 2000). Habituation has been shown in cutaneomuscular reflexes in which the effect of stimulation decreased by 36% within one minute in one study and by between 40% and 70% in 20 to 30 minutes in another study (Floeter et al., 1998; L. M. Harrison, J. A. Norton, & J. A. Stephens, 2000).

Conditional stimulation to inhibit the bladder requires detection of the onset of nascent hyper-reflexive contractions. The activity in the pudendal nerve increases during reflex bladder contractions, and the pudendal electroneurogram can be used as a trigger to control conditional stimulation (Wenzel, Boggs, Gustafson, & Grill, 2005). Conditional stimulation has been shown to increase bladder capacity by 79% to 250% over no stimulation (Dalmose et al., 2003; Kirkham et al., 2002; Kirkham et al., 2001; Lee & Creasey, 2002); however there has been no study to compare directly the effectiveness of continuous stimulation versus the effectiveness of conditional stimulation.

We hypothesized that conditional stimulation, using electrical activity of the pudendal nerve as a control signal, would allow the bladder to fill to a larger volume before continence was lost than continuous stimulation. Experiments were conducted to compare the maximum bladder capacity under three conditions: no stimulation,

unconditional (continuous) inhibitory stimulation, and conditional (event-triggered) inhibitory stimulation delivered only when the bladder was contracting.

III.3 Materials and Methods

All animal care and experimental procedures were performed according to NIH guidelines and were reviewed and approved by the Institutional Animal Care and Use Committees of Case Western Reserve University and Duke University. Intact adult male cats (n=6, 3.0–4.6 kg) were anesthetized with ketamine HCl (Ketaset, initial dose 30 mg/kg, supplemented at 15 mg/kg, IM), and anesthesia was maintained with alpha-chloralose (Sigma, 60 mg/kg, supplemented at 15 mg/kg, IV). Depth of anesthesia was maintained by monitoring blood pressure, heart rate, blink responses, and withdraw reflexes. Animals were intubated and respired to maintain end tidal CO_2 between 3 and 4%, body temperature was maintained between 38^o and 39^o C, 0.9% NaCl saline with 50 grams of dextrose and 8.4 grams of sodium bicarbonate per liter was administered (~15 ml/kg/hr, IV), and heart rate and blood pressure were continuously monitored through a catheter in the carotid artery. The ureters were located, ligated, and cut proximal to the ligation. A 3 French suprapubic catheter was used to fill the bladder and to monitor bladder pressure using a solid state pressure transducer. The bladder was slowly filled (0.9 ml/min) with room saline until continence was lost. The volume at which continence was lost was recorded for each trial, and there were three trial types: no stimulation, continuous stimulation, and event-triggered stimulation (Figure III.1). Incontinence occurred either when 1 ml of fluid was expelled out of the urethra or when an uncontrolled bladder contraction occurred (a bladder contraction lasting longer than 25 seconds with a minimum increase in bladder pressure of 15 cmH_2O). There were a

minimum of three trials of each type of stimulation per cat and the order of the trials was randomized. After each trial, the bladder was slowly emptied at a rate of 0.9 ml/min with no stimulation applied, and there was a minimum of 25 minutes between trials. Electrical stimulation of the contralateral pudendal nerve with a bipolar hook electrode was used to inhibit bladder contractions (5-15 Hz, 400 - 600μA, two to four times the pudendoanal reflex threshold).

Conditional stimulation was controlled using the pudendal nerve trunk electroneurogram (PNT ENG) in 4 cats, and in 2 cats, the bladder pressure was used as the controller input. A tripolar silicone nerve cuff was placed around the pudendal nerve trunk to measure the ENG. The PNT ENG was rectified and low pass filtered (τ = 250 ms), and was the input to an event-triggered control system. The control system was implemented using custom software created using Labview (National Instruments, Inc). A CUSUM algorithm was used by the control system to detect hyper-reflexive bladder contractions from the PNT ENG and had three adjustable parameters: the time constant of the low pass filter cut-off for the ENG signal, the window size for initial mean and standard deviation of the signal, and the number of data points used in the CUSUM (Basseville & Nikiforov, 1993). The detection parameters were set by collecting a trial run at the beginning of the experiment. The duration of stimulation was 15 seconds and the system was allowed to re-trigger if the electrical activity of the pudendal nerve was still higher than baseline at the end of stimulation.

In four cats, the effects of delayed stimulation on the effectiveness of bladder inhibition were measured. Using pressure as a control signal, the sensitivity of the detection algorithm was increased to insure that the bladder contraction would be

detected at its onset. Five different delays between the onset of the initial increase in bladder pressure and the onset of inhibitory stimulation (0, 1, 2, 5, and 10 seconds) were compared to uninhibited bladder contractions (i.e., no electrical stimulation). The area under the bladder contractions was measured to compare the effects of delayed stimulation.

III.4 Results

We compared the maximum bladder volumes achieved with no stimulation, continuous stimulation, and event-triggered inhibitory stimulation delivered only when the bladder was contracting. The volumes at which continence were lost were 28 ± 14 ml (mean ± SD) for no stimulation, 33 ± 14 ml for continuous stimulation, and 38 ± 13 ml for event-triggered stimulation (n = 74 trials across 6 cats with a minimum of 9 trials per cat). The volumes at which continence was lost for continuous and event-triggered stimulation were larger than the volume at which continence was lost for no stimulation ($p=0.029$ and $p<0.001$, respectively, 1 way ANOVA with cats as a random factor and a post-hoc Tukey pairwise comparison to evaluate difference between individual treatments). The volume at which continence was lost for event-triggered stimulation was larger than the volume at which continence was lost for continuous stimulation ($p=0.027$). The event-triggered stimulation reduced stimulation time by 67 ± 21% (Figure III.2).

The reasons for loss of continence were leakage of saline of at least 1 ml (61% of trials) and development of an uncontrolled bladder contraction (39% of trials, Table III.1). For the trials with no stimulation, leakage of saline was the main cause of incontinence (81% of trials), whereas in the trials with either continuous stimulation or

event-triggered stimulation, leakage of saline was responsible for loss of continence in 43% and 54% of the trials, respectively.

The average delay from the start of a bladder contraction as determined from the bladder pressure to the time of detection from the pudendal nerve electroneurogram for the event-triggered control system was 3.0 seconds, and the average increase of bladder pressure above baseline at the time of detection was 9.2 cmH_2O (n = 1364 bladder contractions across 6 cats). The effect of delayed stimulation is shown in Figure III.3. The area under the bladder contractions for delays of 0, 1, 2, and 5 seconds between the onset of the contraction and the onset of stimulation was less than the area under the bladder contractions for no stimulation (0, 1, 2 sec: $p<0.01$, 5 sec: $p<0.05$, N=185 trials across 4 cats with a minimum of 5 trials of each type of stimulation per cat), and the area under the bladder contraction for 10 seconds delay was not different for the area under bladder contraction for no stimulation ($p>0.05$). Post-hoc Tukey paired comparisons across delays showed that there was no significant difference between individual delays ($p>0.3$ for all pair combinations).

III.5 Discussion

We compared the maximum bladder volumes achieved with no stimulation, continuous stimulation, and event-triggered inhibitory stimulation delivered only when the bladder was contracting. The maximum bladder volume achieved by the event-triggered control was greater than continuous stimulation and no stimulation, and the event-triggered control system significantly reduced the stimulation time.

Continuous stimulation increased the bladder volume by 18% over no stimulation and conditional stimulation increased the bladder by 36% over no stimulation. These

results are consistent with work demonstrating that both continuous and conditional stimulation can each increase bladder capacity in animals and humans (Dalmose et al., 2003; Jiang & Lindstrom, 1998; Kirkham et al., 2002; Kirkham et al., 2001; Lee & Creasey, 2002). This study further demonstrates in a direct comparison that conditional stimulation increased bladder capacity more than continuous stimulation, presumably by reducing habituation, and did so while delivering 67% less stimulation during bladder filling.

A smaller increase in bladder capacity was observed in anesthesized cats than has been reported in humans. Previous studies performed in humans showed between 60% and 110% increase in bladder capacity with continuous stimulation over no stimulation and conditional stimulation increased bladder capacity between 124% and 250% over no stimulation (Dalmose et al., 2003; Jiang & Lindstrom, 1998; Kirkham et al., 2002; Kirkham et al., 2001; Lee & Creasey, 2002). The reason for the difference in the magnitude of increases in bladder capacity between the current study and previous studies likely relates to the experimental setup. The subjects used in the previous studies were persons with a spinal cord injury whereas the current study used anesthetized spinal intact cats. Alpha chloralose is known to affect bladder reflex pathways in cats and could possibly diminish the effectiveness of inhibitory stimulation (Rudy et al., 1991). In SCI individuals, hyper-reflexia is caused by a hyper-sensitivity of afferent neurons, and inhibitory stimulation could have a greater effect on suppressing bladder contractions. Also, a catheter was placed in the urethra of the SCI individuals to instill saline and to measure bladder pressure. The catheter partially occluded the urethra and may have limited the amount of leakage from the bladder. Occluding the urethra could inflate the

increased bladder capacity of these studies considering, in the present study, leakage was the reason for incontinence in over 60% of the trials. Nevertheless, conditional stimulation allowed the bladder to fill to greater volume before continence was lost and better performance is expected in humans.

A potential confound in these experiments is carryover effects of prior stimulation. The effects of pudendal genital afferent nerve stimulation are primarily transient and continued inhibition of the bladder required repeated stimulation, but short-term carry-over effects do exist. Continuous stimulation of inhibitory genital afferents for 5 minutes produced protracted inhibition of bladder-to-bladder reflexes for 5-25 min in the cat (Jiang & Lindstrom, 1998), and contractions did not return to prestimulation values until 2 min after termination of 10 min of pudendal nerve stimulation in the spinal cat (Walter et al., 1993). In humans, Kirkham et al. (Kirkham et al., 2001) observed a carryover effect following either continuous or intermittent stimulation of the dorsal nerve of the penis in persons with SCI (~50% increase in threshold volume during post-stimulation control cystometry as compared to last pre-stimulation control cystometry). However, the variability across patients was very large (0-170% carry-over effects). We minimized the potential confounding effects of carry-over by randomizing stimulation condition across trials, and by introducing a delay between trials. The trial number did not significantly affect the maximum bladder volumes achieved in the study ($p > 0.6$, 1 way ANOVA with cats treated as random factor).

The physiological fill rate of a cat is 1 to 15 Hour-Diuresis units (Klevmark, 2002). An Hour-Diuresis unit is 1.1 ml/kg/h for a cat giving a physiological fill rate range from 0.07 to 1.05 ml/min for a 3.8 kg cat. In the current study, the bladder was filled at

0.9 ml/min which is within the physiological range. Assuming a fill rate of 5 Hour-Diuresis units, the current study showed that the additional volume obtained by continuous stimulation would delay voiding by 17 minutes and by 34 minutes for conditional stimulation. Estimates based on the results of previous studies suggest that continuous stimulation will increase the time before voiding from 23 to 68 minutes over no stimulation and conditional stimulation will increase the time before voiding from 25 to 76 minutes over no stimulation assuming a fill rate of 5 Hour Diuresis units for a 75 kg person (Dalmose et al., 2003; Fjorback, Hansen, Dalmose, Rijkhoff, & Sinkjaer, 2003; Kirkham et al., 2002; Kirkham et al., 2001; Lee & Creasey, 2002). However, the literature is inconclusive on the effect of fill rate on the effect size of continuous stimulation versus conditional stimulation (Dalmose et al., 2003; Fjorback et al., 2003; Kirkham et al., 2002; Kirkham et al., 2001).

The performance of continence control with the event-triggered control system may have been limited by the performance of the detection algorithm. The average delay from the start of the bladder contractions to the time of detection was 3.0 seconds and average increase of bladder pressure above baseline at time of detection of 9.2 cmH_20. The detection parameters were not optimized, and previous results with optimized parameters yielded earlier detection (1.4 s) with a smaller increase in bladder pressure above baseline (7.3 cmH_2O) (Wenzel et al., 2005). Detecting bladder contractions closer to their onset increased the ability for the inhibitory stimulation to arrest the bladder contractions (Figure III.3). Thus, modifications to improve the detection algorithm of the event-triggered control system should improve performance.

III.6 Conclusion

Conditional stimulation, regulated by an event-triggered control system using electrical activity of the pudendal nerve as a control signal, allowed the bladder to fill to a larger volume before continence was lost than did continuous stimulation. This study supports using an event-triggered control system to maintain urinary continence.

III.7 Figures and Tables

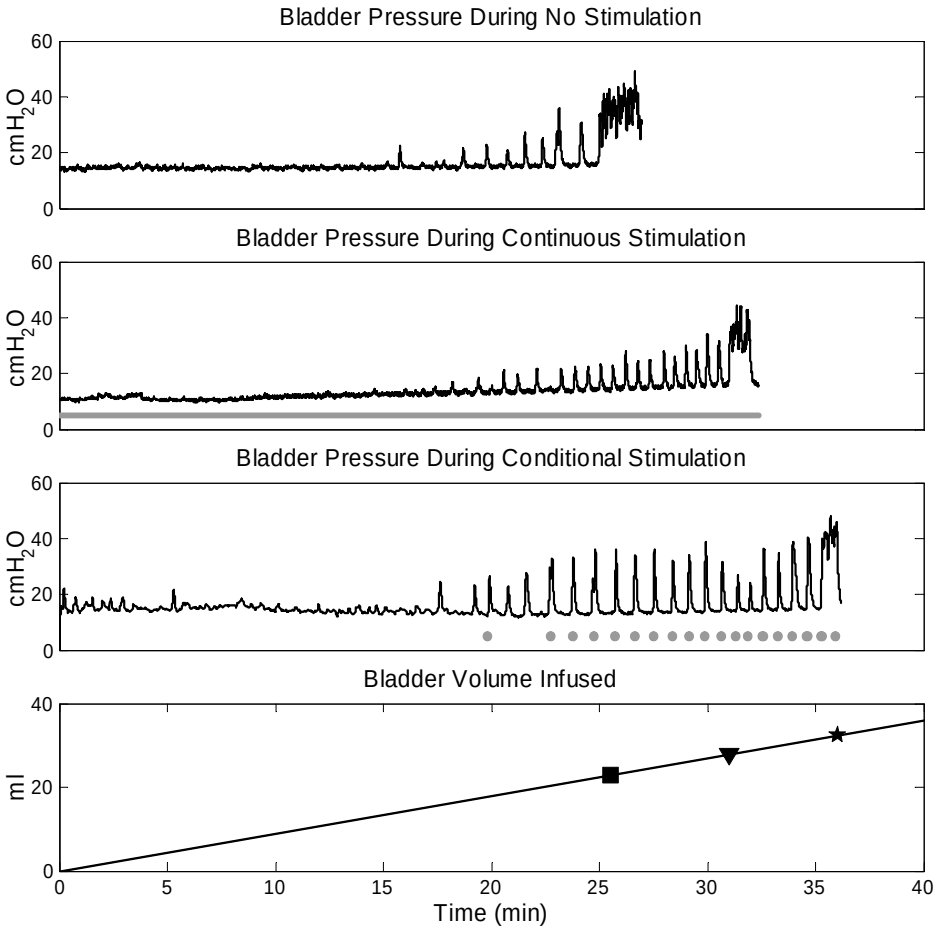

Figure III.1 An example of bladder pressure during filling with no stimulation, continuous inhibitory electrical stimulation of the pudendal nerve, and closed-loop (conditional) inhibitory stimulation applied only at the onset of reflex bladder contractions. The bladder was filled at a constant rate (0.9 ml/min). The bladder volume at which continence was lost for each stimulation type is shown on the volume curve: ■: No Stimulation; ▼: Continuous Stimulation; ★: Condition Stimulation. The grey bars below the continuous and conditional stimulation bladder pressure traces indicate the applied stimulation (400 μA, 10 Hz).

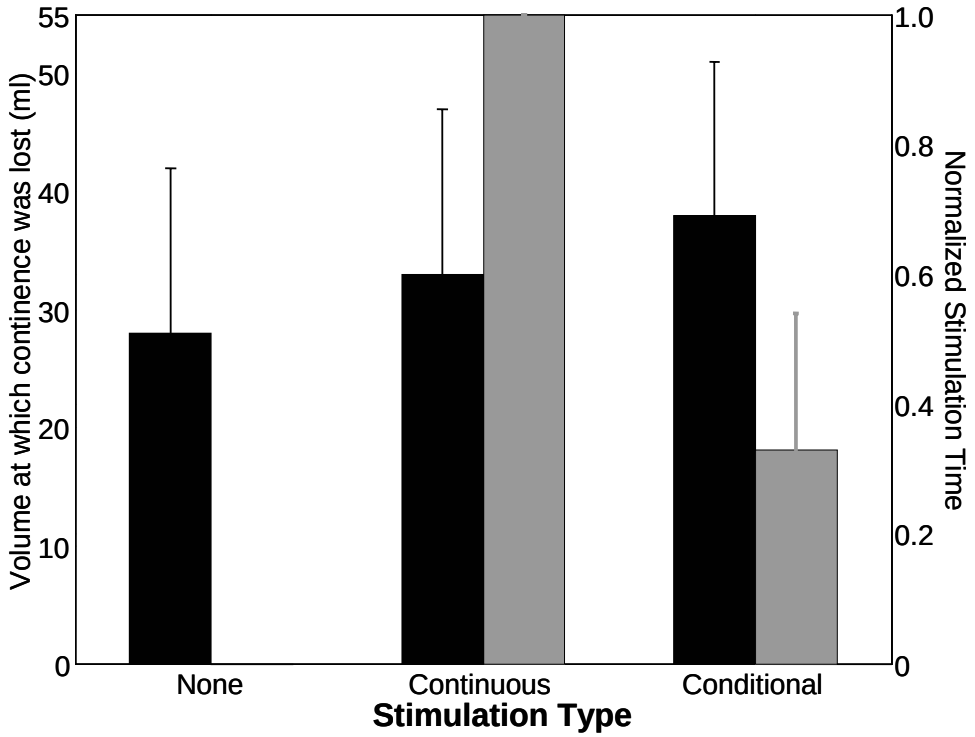

Figure III.2 The volumes (Black bars, left axis) at which continence was lost were compared under three conditions: no stimulation, continuous inhibitory electrical stimulation of the pudendal nerve, and closed-loop (conditional) stimulation with inhibitory stimulation applied only at the onset of bladder contractions. The maximum volume with continuous and conditional stimulation were greater than with no stimulation ($p=0.029$ and $p<0.001$), and the volume with conditional stimulation was greater than with continuous stimulation ($p=0.027$, n = 27, 23, 24 trials across six cats for no stimulation, continuous stimulation, and conditional stimulation, respectively). The stimulation time was normalized such that continuous stimulation was 1 and no stimulation was 0 (Grey bars, right axis). The stimulation amount was decreased by 67% with conditional stimulation when compared to continuous stimulation.

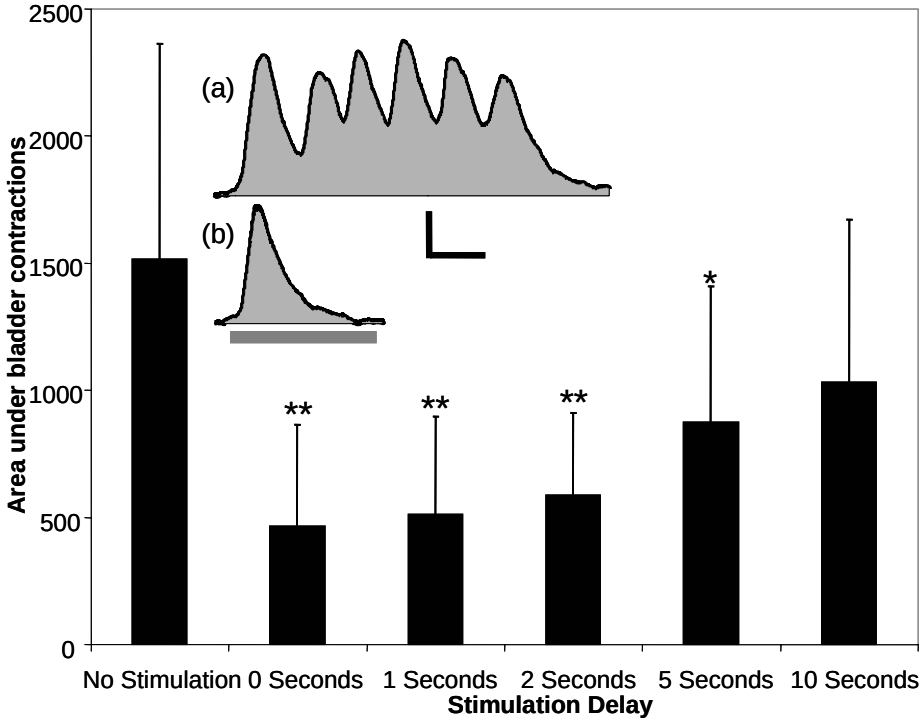

Figure III.3 Effect of a delay between the onset of a reflex bladder contraction and the beginning of inhibitory electrical stimulation. Uninhibited bladder contractions were compared to bladder contractions inhibited by electrical stimulation of the pudendal nerve. The electrical stimulation was applied with 5 different delays: 0, 1, 2, 5, and 10 seconds. The inset shows two bladder contractions: (a) is an uninhibited bladder contraction and (b) was inhibited with a 0 second delay (the grey bar below the bladder contraction indicates the stimulation time, vertical scale bar: 10 cmH_2O, horizontal scale bar: 10 s). The area under the bladder contraction (the grey area in the bladder contractions in the inset) for no stimulation was different than area under the bladder contraction for 0, 1, 2, and 5 second delayed stimulation. However, the area under the bladder contractions for the 10 second delay was not different from the area under the bladder contraction for no stimulation (n = 185 trials across 4 cats with a minimum of 5 trials of each type of stimulation per cat). **: $p<0.01$, *: $p<0.05$.

Table III.1 Reasons why Continence was Lost

Stimulation Type	**Leakage of Saline**	**Uncontrolled Contraction**	**Total**
No Stimulation	22	5	27
Continuous Stimulation	10	13	23
Event-Triggered	13	11	24
Total	45	29	74

Number of trials for each reason of why continence was lost. Continence was lost when at least 1ml of saline leaked out of the urethra or an uncontrolled contraction occurred (at least 15 cmH_2O increase in pressure that lasted longer than 25 seconds).

Chapter IV Detection of Hyper-Reflexive Bladder Contractions from the Activity of the External Anal Sphincter in Cat and Human

IV.1 Abstract

Individuals with spinal cord injury or neurological disorders may develop involuntary bladder contractions at low volumes (bladder hyper-reflexia), which can lead to significant health problems. Present electrical stimulation devices can inhibit unwanted contractions through continuous stimulation, but do not enable conditional stimulation only at the onset of bladder contractions. The objectives of this study were to determine the relationship between the electrical activity of external anal sphincter (EAS) and bladder pressure during hyper-reflexive bladder contractions and to determine whether EAS activity could be used to detect the onset of contractions in both humans and cats.

Bladder pressure and EAS electromyogram (EMG) were recorded in nine adult male cats. Retrospective clinical data consisting of bladder pressure and EAS EMG from 126 spinal cord injured individuals was obtained. A CUSUM algorithm was used to detect the onset of bladder contractions from the EAS EMG. EAS EMG activity increased at the onset of bladder contractions in six cats (dyssynergic), and decreased (synergic) activity in three cats. The onset of bladder contractions was able to be detected within three seconds of the start of the bladder contraction for both the synergic and dyssynergic data sets. The onset of bladder contractions was able to be detected within one second of the start of the bladder contraction for both synergic and dyssynergic subjects. These data demonstrated that recordings from the EAS could be used to detect non-invasively hyper-reflexive bladder contractions and provide a signal to control closed-loop inhibitory stimulation.

IV.2 Introduction

Our long term goal is to develop a closed-loop neural prosthesis to detect and abolish hyper-reflexive bladder contractions in persons with spinal cord injury. This device would maintain urinary continence and reduce the chance of damage to the bladder and upper urinary tract. The objectives of this study were to characterize the relationship between the electrical activity of the external anal sphincter (EAS) and hyper-reflexive bladder contractions, and to determine whether the electromyogram (EMG) of the EAS could be used to detect the occurrence of reflexive contractions in cats and humans.

Neurological disease or spinal cord injury (SCI) can result in bladder hyper-reflexia, the involuntarily reflex contraction of the bladder at small fluid volumes which results in loss of continence and/or high bladder pressures during bladder-urethral sphincter dyssynergia (Watanabe et al., 1996). During bladder-urethral sphincter dyssynergia the bladder and the urethral sphincter co-contract preventing or inhibiting the evacuation of urine while increasing the bladder pressure. Loss of voluntary control, hyper-reflexia, and dyssynergia can result in long term renal damage, frequent urinary tract infections, and kidney damage (Shingleton & Bodner, 1993).

Electrical stimulation has been used to treat incontinence through inhibition of hyper-reflexia, but each of the present methods continuously applies stimulation to inhibit the bladder (Chartier-Kastler et al., 2001; Craggs et al., 1998; Grill et al., 2001; Jezernik et al., 2002; Siegel, 1992; van Balken et al., 2001; Vandoninck et al., 2003; Vodusek et al., 1986; Weil et al., 1998). Conditional stimulation, when stimulation is applied only when a hyper-reflexive contraction occurs, may allow the bladder to fill to greater

volume before an uncontrollable contraction occurs (Dalmose et al., 2003; Kirkham et al., 2001; Shah et al., 1998) by minimizing habituation resulting from repetitive activation of spinal reflexes (Cariga et al., 2000; Floeter et al., 1998; Granat et al., 1993; L.M. Harrison et al., 2000). Further, conditional inhibitory stimulation at the beginning of the bladder contraction can completely arrest the contraction (Kondo et al., 1982; Shah et al., 1998). Conditional stimulation to inhibit the bladder requires detection of the onset of nascent hyper-reflexive contractions.

The onset of hyper-reflexive bladder contractions can be detected from recordings of the electrical activity of the pudendal nerve in cats (Wenzel et al., 2005). However, a less invasive means is required to test in humans the hypothesis that the electrical activity of the pudendal nerve can be used to detect the onset of bladder contractions. The external anal sphincter, which is innervated by the pudendal nerve, exhibits bursts of activity associated with bladder contractions in both cats and rats (Evans, 1936; Fedirchuk & Shefchyk, 1993; Gary et al., 1959; Thor & Muhlhauser, 1999). Following spinal cord injury, bladder-urethral sphincter dyssynergia leads to large increases in activity of the muscles in the pelvic floor during bladder contractions (Rudy et al., 1988; Watanabe et al., 1996). These studies suggested that the external anal sphincter activity is modulated during hyper-reflexive bladder contractions, and such a signal could serve as a proxy for the electrical activity of the pudendal nerve. The objectives of the present study were to characterize the relationship between EAS EMG and bladder pressure during hyper-reflexive bladder contractions and to determine whether the EAS EMG could be used to detect the onset of bladder contractions in both cats and humans. Preliminary

results of this study have been presented in abstract form (Wenzel, Grill, Boggs, & Gustafson, 2003).

IV.3 Materials and Methods

IV.3.1 Animal Experiments

All animal care and experimental procedures were performed according to NIH guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee of Case Western Reserve University. Intact male cats (n = 9, 2.9 – 4.8 kg) were anesthetized with ketamine HCl (Ketaset, initial dose 30 mg/kg, supplemental at 15 mg/kg, IM). A catheter was inserted in the cephalic vein, and anesthesia was maintained with alpha-chloralose (Sigma, 60 mg/kg, IV, supplemented at 15 mg/kg). Depth of anesthesia was maintained by monitoring blood pressure, heart rate, blink responses, and withdraw reflexes. Animals were intubated and respired to maintain end tidal CO_2 between 3 and 4%, body temperature was maintained between 38^o and 39^o C, 0.9% NaCl saline with 50 grams of dextrose and 8.4 grams of sodium bicarbonate per liter was administered (~15 ml/kg/hr, IV), and heart rate and blood pressure were continuously monitored through a catheter in the carotid artery.

A ventral midline incision was made to expose the bladder and ureters. The ureters were ligated and transected proximal to the ligation. A 3.5 Fr (1.17 mm) suprapubic catheter was inserted into the bladder through the bladder wall and secured with a purse string suture. Drain tubes were placed adjacent to the proximal portion of both transected ureters, and the abdominal incision was closed in layers. A transurethral catheter (3.5 or 5.0 Fr) was inserted into the bladder to occlude the urethra and to maintain bladder volume during reflexive contractions. The suprapubic catheter was connected to a solid state pressure transducer (Deltran DPT-100, Utah Medical Products)

and the transurethral catheter was connected to a stopcock and a syringe pump for filling the bladder with room temperature saline. The anal sphincter was located based on anatomical landmarks, and 28 gauge paired EMG wires were inserted 2 mm apart into the EAS. The electromyogram was amplified (10,000X) and filtered (30 Hz – 1 kHz, Universal Amplifier, Gould Instruments). The EMG and pressure signals were sampled at 24 kHz (CDAT 16 Data Recorder, Cygnus Technology, Inc., Delaware Water Gap, PA) and displayed on a strip chart recorder (TA11, Gould Instruments). Subsequent processing of the EMG and bladder pressure was performed offline using custom software written in MATLAB (Mathworks, Inc, Natick, MA).

The bladder was emptied and then slowly filled (0.25 – 1 ml/min) until the onset of distention evoked hyper-reflexive-like bladder contractions. The electromyogram of the external anal sphincter (EAS) was recorded during a series of isovolumetric bladder contractions. The EAS EMG was also recorded during different inputs that may interfere with detection of bladder contractions including rectal distention and bulbocavernosus reflex. A lubricated endotracheal intubation tube was inserted into the rectum and was filled and deflated using a syringe to distend the rectum, and the bulbocavernosus reflex was tested by firmly pinching the base of the penis with a pair of forceps.

IV.3.2 Human Experiments

We retrospectively reviewed urodynamic data from 47 consecutive patients from the Spinal Unit of MetroHealth Medical Center and 79 consecutive patients from the Spinal Unit of Louis Stokes Cleveland Department of Veterans Affairs Medical Center. The protocols were approved by the respective Institutional Review Boards. Of those patients, 81 patients had SCI and were further evaluated in this study. Data consisted of

120 digitized traces of bladder pressure, rectal pressure, and EAS EMG recorded during bladder filling.

The urodynamic methods are briefly described. A three-way Foley catheter was placed into the bladder, the bladder drained, and one of the lumens of the catheter was connected to an external pressure transducer. A balloon catheter was placed in the rectum and detrusor pressure calculated as the difference between bladder pressure and rectal pressure. Surface EMG electrodes were placed on both sides on the anus with a reference electrode over one hip. The bladder was filled at approximately 25 ml/min through the second channel of the Foley catheter until reflex bladder contractions were obtained, the patient became uncomfortable or showed signs or symptoms of autonomic dysreflexia, or a volume of 600 ml was reached. In 24 trials, the recordings terminated before the first bladder contraction ended. The bladder pressure, rectal pressure, EAS EMG, and volume were digitally stored on a clinical urodynamic system (Dantec, Medtronic, Minneapolis, MN). The EMG was sampled at 48 kHz, filtered (30 Hz – 5 kHz), peak-selected, and down sampled to 5-250 Hz. The bladder pressure was sampled at 250 Hz and down sampled to 5-250 Hz. The subsequent processing of the EMG and bladder pressure was performed offline using custom software written in MATLAB.

IV.3.3 Offline Analysis

The onset and duration of a bladder contraction was calculated using a two part process (Wenzel et al., 2005). The bladder pressure was first linearly detrended to find baseline pressure. The threshold to detect the first bladder contraction was set 30% above the minimum pressure of the linearly detrended bladder pressure. Once the bladder pressure rose above the 30% threshold, the bladder pressure was traced back until the rate of change in bladder pressure decreased by 50% and this point was defined as the onset

of the bladder contraction. The end of a bladder contraction was calculated in a similar fashion; the bladder pressure had to fall below the original threshold value set at the beginning of the contraction (30% above baseline bladder pressure). Then, the bladder pressure was traced forward until the rate of change in the bladder pressure decreased by 50%. The average contraction pressure was defined as the mean of the bladder pressure during the middle third of the bladder contraction. The baseline pressure was defined as the mean of the bladder pressure between contractions. The next baseline pressure began with the end of the previous bladder contraction, and subsequent bladder contractions were defined using the same process as above, but the thresholds were set 30% above each preceding baseline pressure.

Conditional stimulation to inhibit the bladder requires detection of the onset of nascent hyper-reflexive contractions, and recordings of the EAS EMG were used to detect the onset of bladder contractions. The EAS EMG signal was rectified and low pass filtered with a third order Butterworth filter and then input into the detection algorithm. The detection algorithm was a weighted cumulative sum (CUSUM) algorithm (Basseville & Nikiforov, 1993). The CUSUM algorithm is able to detect small increases in a noisy signal by testing the hypothesis that the EAS EMG is equal to the baseline activity against the alternative hypothesis that the EAS EMG is greater than the baseline activity. The output of the CUSUM algorithm increased when the activity of the EMG increased above baseline, and was compared to a constant threshold to determine the onset of bladder contractions. The parameters of the algorithm that were adjusted during the optimization were the time constant of the low pass filter for smoothing the EMG, the duration of baseline activity used to set the initial mean and standard deviation of the

EMG, and the number of data points used in the cumulative sum. The parameters of the algorithm were optimized using a cost function based on four factors weighted with the performance objective of maintaining continence (Wenzel et al., 2005). The optimization was performed with each subject, because in practice, the device would be optimized for a specific user and a set of parameters optimized for one individual would not be used for another individual. The threshold to detect an increase in the output of the CUSUM algorithm was not adjusted and was the same across all experiments.

IV.4 Results

The objectives of the present study were to characterize the relationship between external anal sphincter electromyogram (EAS EMG) and bladder pressure during hyper-reflexive bladder contractions and to determine whether the EAS EMG could be used to detect the onset of bladder contractions in both cats and humans.

IV.4.1 Animal Experiments

IV.4.1.a Reflex Bladder Contraction Evoked by Bladder Filling

Slow filling of the bladder led to hyper-reflexive-like bladder contractions in all 9 cats. The baseline bladder pressure between contractions ranged from 9 to 28 cmH_20 (17 $\pm$ 5.7 cmH_20, n = 1594 intervals across 9 cats) and the pressure during contraction ranged from 17 to 54 cmH_2O (30 $\pm$ 8. cmH_20, n = 1650 contractions across 9 cats). The length of contractions ranged from 6.5 to 217.2 seconds (29.5 $\pm$ 37.0 seconds), and time between contractions ranged from 0.4 to 298.5 seconds (10.8 $\pm$ 22.1 seconds).

IV.4.1.b EAS Activity during Hyper-Reflexive-Like Bladder Contractions

EAS EMG was successfully recorded in all nine experiments. The cats were divided into two data sets based on the average ratio of the EMG activity during a bladder

contraction to the EMG activity during the intercontraction interval either being greater than or less than unity. The group of cats that had an EMG ratio greater than unity had a dyssynergic bladder-sphincter response (average ratio = 1.08 ± 0.08, n = 6 cats) and the other group of cats had synergic bladder-sphincter response (average ratio = 0.93 ± 0.10, n = 3 cats). Figure 1 shows a series of bladder contractions with corresponding raw EAS EMG activity and processed EAS EMG. The left set of traces shows the EAS EMG increasing at the offset of bladder contractions (synergic) and the right set of traces shows the EAS EMG increasing at the onset of bladder contractions (dyssynergic). Figure 2 shows a summary of the magnitudes of the EAS EMG during bladder contractions and during the intercontractions intervals for each experiment as well as the average for the dyssynergic and synergic responses.

IV.4.1.c Detection of Hyper-Reflexive-Like Bladder Contractions

The performance detecting the onset of the reflexive bladder contractions in cats was quantified, and summaries of the performance are provided in Table IV.1.

In the dyssynergic data set, the delay between the start of a bladder contraction and when the contraction was detect from the EAS EMG was 2.8 ± 5.8 seconds (n = 1333 bladder contractions across 6 cats; parameters were optimized for each cat using all contractions of that cat) with an increase in bladder pressure at detection of 15.7 ± 13.8 cmH_2O above baseline (n = 1333, Table IV.1). The sensitivity (defined as the number of detected contractions divided by the total number of contractions) was 85%, and the specificity (defined as the number of detected contractions divided by the number of detected contractions plus the number of false positives) was 67% with 202 false negative and 547 false positives.

For the synergic data set, the CUSUM algorithm was modified such that a decrease in EMG activity created an increase in the output of the CUSUM output. The delay of detection in the synergic data set was 1.3 ± 8.4 seconds (n = 293 bladder contractions across 3 cats), and the increase in pressure from baseline to time of detection was 4.4 ± 8.9 cmH_2O (n = 293). The sensitivity was 94% and the specificity was 45% with 17 false negatives and 336 false positives. The detection performance on the dyssynergic data set and the detection performance on the synergic data set were significantly different ($p < 0.001$ for delay and increase in bladder pressure).

IV.4.2 Humans

IV.4.2.a Reflex Bladder Contraction Evoked by Bladder Filling

Of the 81 subjects with SCI, there were 8 female subjects and 73 male subjects ranging in age from 20 to 78 years with an average age of 50 years, and the time since injury ranged from 1 to 25 years. Of the 81 subjects, 41 subjects had reflexive bladder contractions (Table 2). The average baseline bladder pressure (average of bladder pressure when the bladder not contracting) was 11 ± 7 cmH_2O (n=92) and the average bladder pressure during bladder contractions was 66 ± 30 cmH_2O (n=92 bladder contractions across 41 subjects). The average bladder volume when the first bladder contraction occurred was 245 ± 173 ml at an average bladder pressure of 18 ± 14 cmH_2O.

IV.4.2.b EAS Activity during Hyper-Reflexive Bladder Contractions

The subjects with reflexive bladder contractions were divided into three groups: subjects with a ratio of the EMG activity during a bladder contraction to the EMG activity during the intercontraction interval greater than unity (dyssynergic), subjects with an EMG ratio less than unity (synergic), and subjects with an EMG ratio equal to unity

(non-modulating sphincter). The subjects with dyssynergic bladder sphincter response had an average EMG ratio of 2.2 (n=25 subjects), the subjects with synergic bladder sphincter response had an average EMG ratio of 0.6 (n=5), and the subjects whose sphincter did not modulate during bladder contractions (non-modulating) had an average EMG ratio of 1.0 (n=11, Figure 3).

IV.4.2.c Detection of Hyper-Reflexive Bladder Contractions

The performance detecting the onset of the reflexive bladder contractions from EAS EMG in humans was quantified. In subjects with dyssynergia, the delay from the start of the bladder contraction to time of detection was -0.8 ± 3.2 seconds (n = 52 bladder contractions across 25 subjects; averaged across subjects where parameters were optimized for each subject using all contractions of that subject) with an increase in bladder pressure at detection of 3.7 ± 6.1 cmH_2O above baseline (n = 52, Figure 4, Table 1). The sensitivity was 83%, and the specificity was 40% with 9 false negative and 66 false positives.

For the synergic subject data set, the delay in detection was 0.4 ± 6.2 seconds (n = 12 bladder contractions across 5 subjects), and the increase in bladder pressure from baseline to time of detection was 5.0 ± 5.4 cmH_2O (n = 12). The sensitivity was 100% and the specificity was 23% with 0 false negatives and 40 false positives. The detection performance on the dyssynergic subject data set and the performance on the synergic subject data set were equivalent (p = 0.38 for delay, and p=0.51 for increase in bladder pressure). The subjects with a non-modulating sphincter were not used to detection bladder contractions because their EAS activity did not change in response to bladder contractions.

IV.5 Discussion

The objectives of the present study were to characterize the relationship between external anal sphincter electromyogram (EAS EMG) and bladder pressure during hyper-reflexive bladder contractions and to determine whether the EAS EMG could be used to detect the onset of bladder contractions in both cats and humans. In the pre-clinical animal experiments, there were two types of relationships between the bladder contractions and EAS EMG activity: dyssynergic, with the EAS EMG activity increasing at the onset of bladder contractions, and synergic, with the EAS EMG activity decreasing at the onset of bladder contractions. In the human data, there were three types of relationship between bladder contractions and sphincter activity: dyssynergic, synergic, and non-modulating. With the exception of the human population whose EAS EMG activity did not change at the onset of bladder contraction, the onset of bladder contractions was able to be detected in both cats and humans.

In a spinal intact cat, it is expected that, as the bladder contracts, the sphincter relaxes. However, alpha chloralose anesthesia can induce a dyssynergic relationship between the urethral sphincter and the bladder, and thus external anal sphincter activity was expected during bladder contractions (Rudy et al., 1991). Different levels of anesthesia did not produce different types of bladder-sphincter relationships within the same cat, but each cat could have had a different response to the anesthesia which could account for the different types of bladder-sphincter relationships in the animal experiments. Although the anesthesia-induced dyssynergia may be viewed as an artifact of the experimental preparation, this bladder-sphincter relationship is representative of what occurs in chronic spinal cord injury (SCI).

Spinal injury severs the connections between the pontine micturition center of the brainstem and the spinal cord. A complete suprasacral lesion will demonstrate reflex contractions after the individual recovers from the spinal shock (Watanabe et al., 1996). After spinal shock recovery, individuals may develop dyssynergic responses caused by an increased sensitivity of unmyelinated c-fibers which signal, through spinal reflex loops, causes the bladder and the sphincters to contract concurrently (de Groat, 1997; de Groat et al., 1981; Fedirchuk et al., 1992).

Varying degrees and types of detrusor sphincter dyssynergia are seen in most complete suprasacral cord lesions (Blaivas, Sinha, Zated, & Labib, 1981). With each clinical level of injury, subjects could have hyper-reflexia with detrusor-sphincter synergia, hyper-reflexia with detrusor-sphincter dyssynergia, detrusor areflexia, or normal bladder functions (Kaplan, Chancellor, & Blaivas, 1991). Each of the different pathologies was observed in this data set. Subjects with an areflexive bladder, after complete spinal shock recovery, could have a another lesion (subclinical) in the lumbosacral region of the spinal cord involving the sacral visceral reflex arc (Yalla & Fam, 1991). Even though the mechanisms of the changes in the bladder-sphincter relationships are different between cats and humans, the EAS EMG in the cats was representative of what is seen in subjects with a SCI.

The onset of bladder contractions was able to be detected from EAS EMG in both the animal experiments as well as the human data set. The average delays in detection for the synergic and dyssynergic cats and synergic and dyssynergic humans were 1.3, 2.8, 0.4, and -0.8 seconds, respectively, with an average increase in bladder pressure above baseline of 4.4, 15.7, 5.0, and 3.7 cmH_2O, respectively (Table 1). The performance in

detecting the onset of bladder contractions using the EAS EMG signal is comparable to the performance of detecting the onset of bladder contractions using the pudendal nerve electroneurogram (ENG) (Wenzel et al., 2005) and using the sacral nerve root ENG (Jezernik et al., 2001; Jezernik, Wen, Rijkhoff, Djurhuus, & Sinkjaer, 2000) as the input signal. The average delays in detection when using the pudendal nerve ENG and the sacral nerve root ENG as the input signals were 1.4 and 6 seconds, respectively, with an average increase in bladder pressure above baseline of 7.3 and 9 cmH_2O, respectively. These results suggest that EAS activity is a valid proxy for pudendal nerve activity, and that the pudendal electroneurogram is a suitable control signal to regulate conditional inhibitory electrical stimulation to restore of urinary continence.

Closed-loop control of urinary continence was previously implemented using the bladder pressure measured through a transurethral catheter as the control signal to deliver conditional inhibitory electrical stimulation (Fjorback et al., 2003; Kirkham et al., 2001). In these studies, when the bladder pressure increased 10 cmH_2O above baseline, electrical stimulation was applied to the dorsal penile nerve to inhibit the bladder contractions, and average peak bladder pressure of an inhibited bladder contraction was 30 cmH_2O above baseline pressure (Kirkham et al., 2001). In the present study, the bladder contraction was detected with an average increase in bladder pressure above baseline of 5.0 and 3.7 cmH_2O in synergic and dyssynergic subjects, respectively. Detection at a lower pressure enables stimulation earlier in the bladder contraction, and the peak bladder pressure of the inhibited bladder contraction should be less than 30 cmH_2O. By minimizing the peak bladder pressure, the occurrences of bladder pathologies would be decreased (Borden et al., 1981; McGuire & Brady, 1979; McGuire, Woodside, & Borden, 1981).

A potential limitation of implementing this approach clinically is the specificity of detection from EAS EMG activity. Different physiological events can increase EAS activity (e.g., genital stimulation or bowel movement (Krier, 1984)), and interfering inputs (rectal distention and bulbocavernosus reflex) caused transient increases in EAS activity and resulted in false positive detections. The detection threshold of the CUSUM algorithm was held constant in these studies and increasing the threshold for detection could increase the specificity, but at the expense of increasing the delay and increase in bladder pressure at detection. Failing to detect the occurrence of a bladder contraction (false negative) is more detrimental to maintaining continence than stimulating too often. False positives will, in the limit, cause the system to emulate open-loop stimulation and make the closed-loop system superfluous. However, conditional stimulation has been shown to increase bladder capacity more than continuous stimulation, and thus closed-loop stimulation is worth pursuing (Kirkham et al., 2001; Shah et al., 1998).

IV.6 Conclusion

External anal sphincter activity was modulated during reflexive bladder contractions in both humans and cats, and the bladder contractions could be detected robustly from the EAS EMG. The detection of hyper-reflexive bladder contraction from recording of external anal sphincter activity could be used as a control signal to deliver inhibitory stimuli to arrest nascent bladder contractions and maintain continence. These data support pursuing further studies to record the electrical activity of the pudendal nerve during reflexive bladder contractions in humans.

IV.7 Figures and Tables

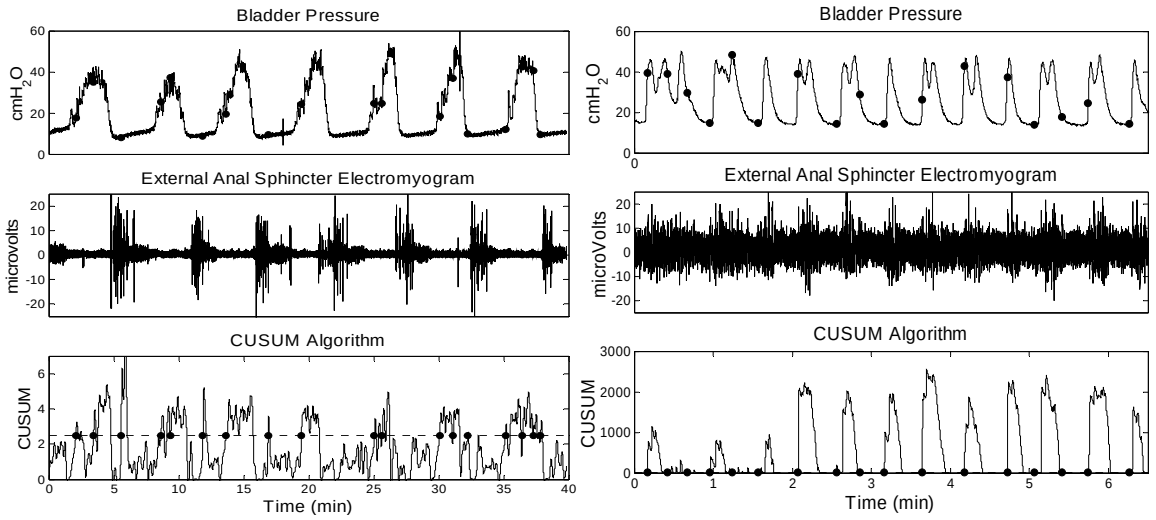

Figure IV.1 External anal sphincter electromyogram (EAS EMG) during reflex contractions in cats. Bladder contraction (top) with corresponding EAS EMG (middle trace). The left set of traces is a synergic response between the bladder and the sphincter. The right set of traces is a dyssynergic response between the bladder and the sphincter. The bottom trace is the output of the CUSUM algorithm. The detection of bladder contraction (●) occurs when the output of the CUSUM algorithm cross threshold (dashed line). The detections are also shown on the pressure trace.

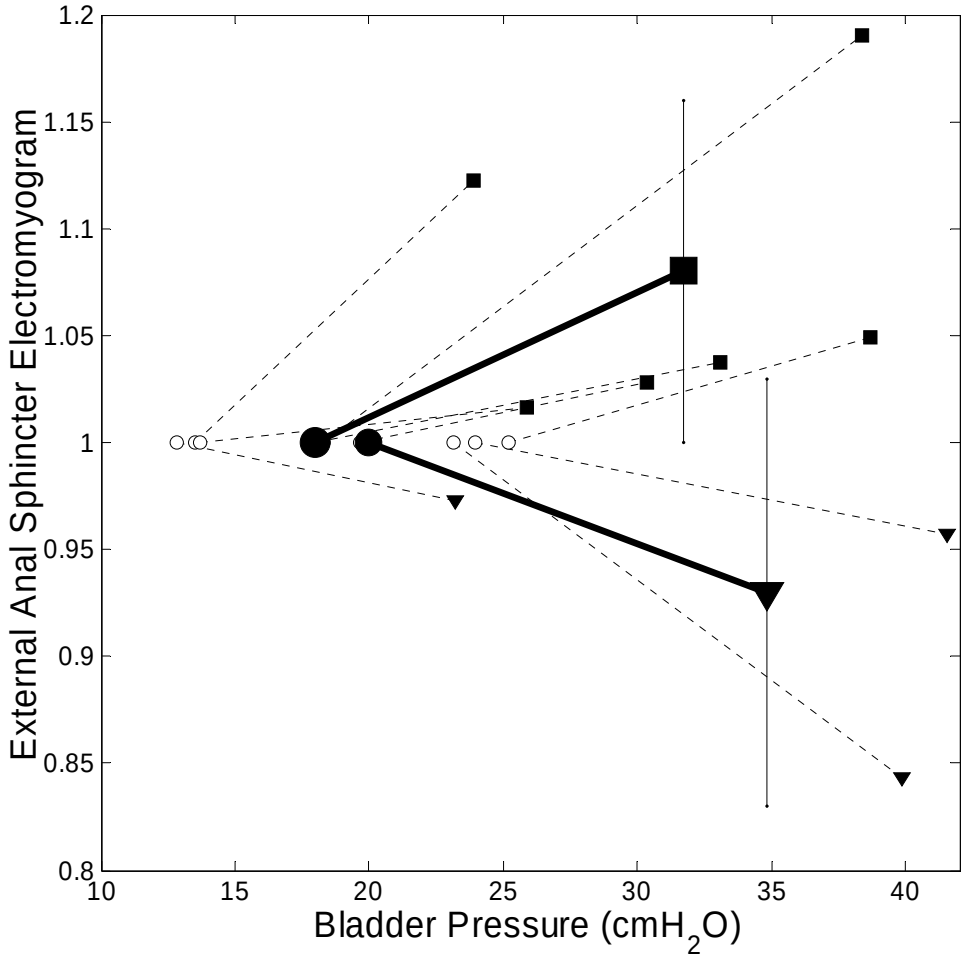

Figure IV.2 Average external anal sphincter electromyogram (EAS EMG) activity of cats during bladder contractions (square and triangle) and during the intercontraction intervals (circles). The average EAS EMG activity during bladder contractions was normalized to the activity during the intercontraction interval. The dyssynergic data set (■) had a normalized ratio of the EMG activity during a bladder contraction to the EMG activity during the intercontraction interval greater than 1, and the synergic data set (▼) had a normalized EMG ratio less than 1. Dashed lines represent individual experiments, and solid lines represent the average for the synergic and dyssynergic data sets.

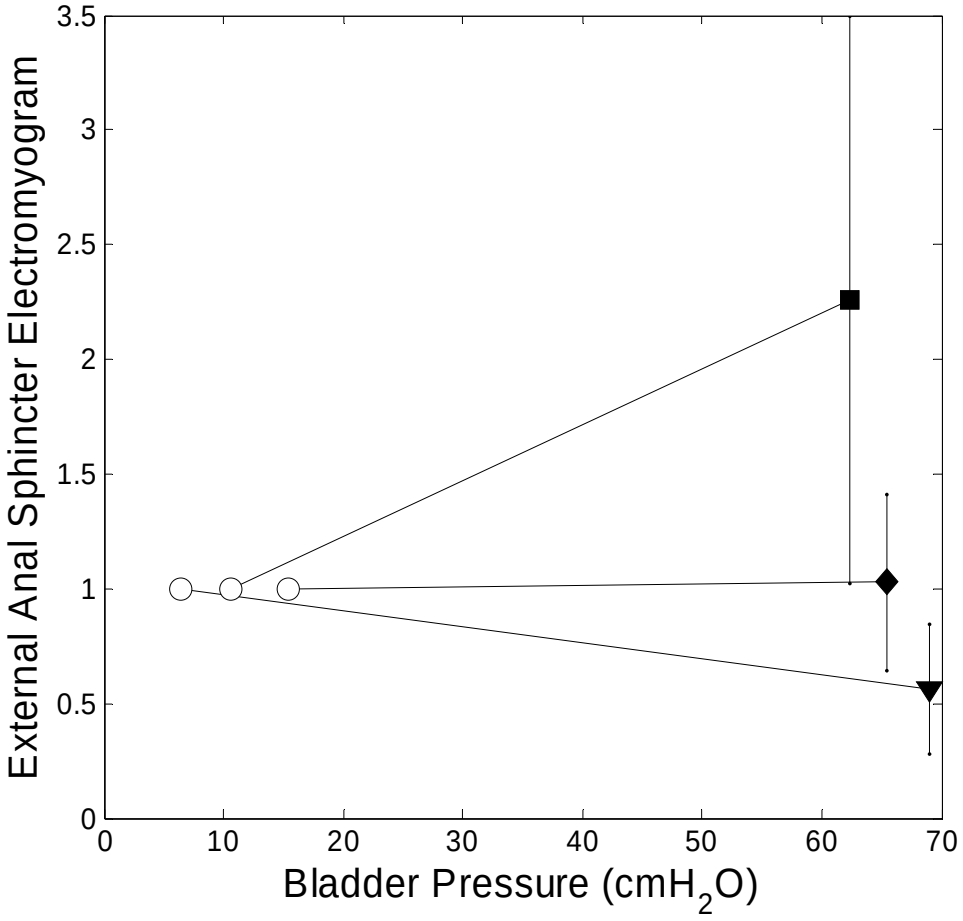

Figure IV.3 Average external anal sphincter electromyogram (EAS EMG) activity of subjects with SCI during bladder contractions (solid symbols) and during the intercontraction intervals (○). The average EAS EMG activity during bladder contractions was normalized to the activity during the intercontraction interval. The dyssynergic data set (■) had a normalized ratio of the EMG activity during a bladder contraction to the EMG activity during the intercontraction interval greater than 1, the synergic data set (▼) had a normalized EMG ratio less than 1, and the non-modulating sphincter data set (♦) had a normalized EMG ratio equal to 1.

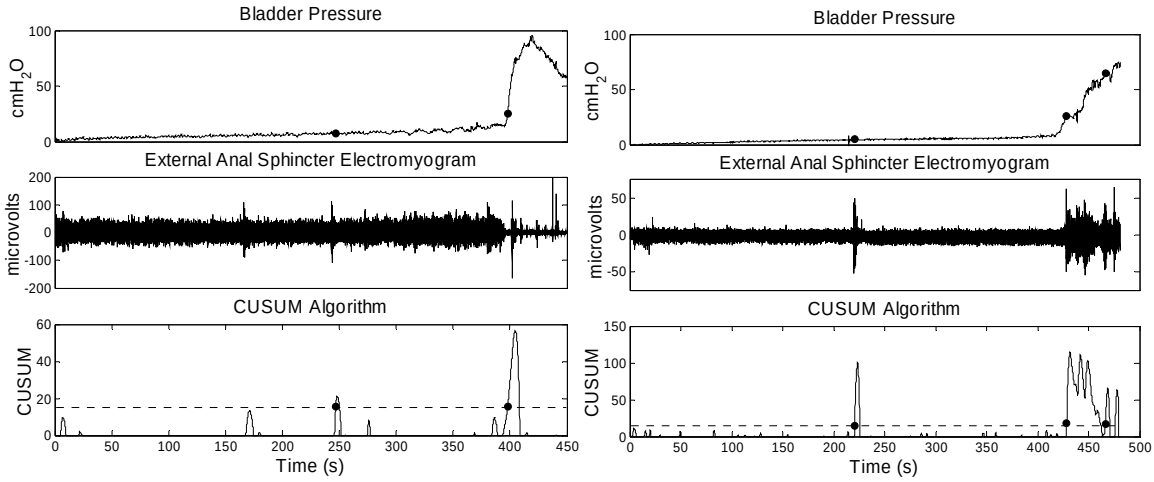

Figure IV.4 External anal sphincter electromyogram (EAS EMG) during reflex contractions of the bladder in subjects with SCI. Bladder contraction (top) with corresponding EAS EMG (middle trace). The bottom trace is the output of the CUSUM algorithm. The left set of traces is a synergic response between the bladder and the sphincter. The right set of traces is a dyssynergic response between the bladder and the sphincter. The detection of bladder contraction (●) occurs when the output of the CUSUM algorithm cross threshold (dashed line). The detections are also shown on the pressure trace.

Table IV.1 Performance of detecting reflex bladder contractions from EAS EMG

	Cats		Humans	
	Synergic	Dyssynergic	Synergic	Dyssynergic
Numbers	3 (293)	6 (1333)	5 (12)	25 (52)
Delay (s)	1.3 (8.4)	2.8 (5.8)	0.4 (6.2)	-0.8 (3.2)
Pressure Increase (cmH2O)	4.4 (8.9)	15.7 (13.8)	5.0 (5.4)	3.7 (6.1)
Sensitivity	94%	85%	100%	83%
Specificity	45%	67%	23%	40%

The total number of subject (total number of bladder contraction) and the mean (standard deviation) of the delay between onset of the contraction and its detection, the increase in bladder pressure between baseline and when the contraction was detected, sensitivity (number of detected contractions divided by the total number of contractions), and specificity (the number of detected contractions divided by the number of detected contractions plus the number of false positives) are shown.

Table IV.2 Distribution of the type of bladder – sphincter relationships by level of spinal injury

	Level of Spinal Injury				
	Cervical	Thoratic	Lumbar	Sacral	Total
Non-Reflexive Bladder	20 (8)	13 (3)	7 (3)	0 (0)	40 (14)
Reflexive Bladder with Synergic Sphincter	1 (0)	1 (1)	2 (0)	1 (0)	5 (1)
Reflexive Bladder with Dyssynergic Sphincter	16 (4)	8 (3)	1 (0)	0 (0)	25 (7)
Reflexive Bladder with Non-Modulating Sphincter	5 (2)	5 (2)	1 (1)	0 (0)	11 (5)
Total	42 (14)	27 (9)	11 (4)	1 (0)	81 (27)

The number of subjects with each level of spinal injury and their corresponding bladder-sphincter relationship present in this study. The number in the parentheses is the number of complete spinal injuries in the group. The areflexive bladder group was not used in the development of the detection algorithm because the subjects' bladders did not reflexively contract. The reflexive bladder with non-modulating sphincter group was not used to detect reflexive contractions because the sphincter activity did not change with bladder contractions.

Chapter V Discussion and Conclusion

V.1 Discussion

There are approximately 250,000 individuals in the U.S.A. with spinal cord injury (SCI). Approximately 81% of individuals with SCI report some degree of impaired bladder function (McKinley, Jackson, Cardenas, & DeVivo, 1999), and, until recently, the leading cause of mortality in individuals with a paraplegic level spinal cord injury was renal failure (Center, 2004; DeVivo, Krause, & Lammertse, 1999; Hackler, 1977). It has been shown that SCI individuals with impaired bladder have a lower quality of life than SCI individuals without bladder impairments (Hicken, Putzke, & Richards, 2001). Over the years, urinary management has increased the length and the quality of life of individuals with bladder impairment; however there is still much more room for improvements. In a recent survey of almost 700 SCI individuals, 40% ranked restoring bladder function as first or second highest priority (Anderson, 2004). Other surveys have shown that restoring bladder function is a major concern among SCI individuals (Estores, 2003; Tate, Zalpakjian, & Forschheimer, 2002; Vastenholt et al., 2003; Widerstrom-Noga, Felipe-Cuervo, Broton, Duncan, & Yezierski, 1999).

One of the major bladder impairments in SCI individuals is urinary incontinence. The types of incontinence that individuals with SCI have are urge incontinence, overflow incontinence, stress incontinence, and/or reflex incontinence. Individuals with SCI use a variety of technique to treat incontinence depending on which type of incontinence, the severity of incontinence, and the severity and level of the spinal cord injury. Individuals that cannot void their bladder from either weakened bladder or bladder-urethral sphincter dyssynergia use intermittent self catheterization to empty the bladder to prevent vesicouretral reflux (flow of urine from the bladder to the kidneys), hydronephrosis

(accumulation of urine at the kidneys) and leakage of urine as a result of overflow incontinence. However, self catheterization leads to frequent urinary tract infections, and individuals with limited dexterity from the spinal injury have difficult time catheterizing themselves. Individuals with limited dexterity would have an indwelling catheters implanted to empty their bladder (Kuhn et al., 1991).

If the person has reflex incontinence, they may take anti-cholinergics to decrease the number of spastic bladder contractions, and empty the bladder using self catheterization. Individuals taking anti-cholinergic tend to stop taking the medication as a result of the side effects (thirst, dry-mouth, lethargy, blurred vision, glaucoma, constipation, dry skin, arrhythmias, and confusion), and anti-cholinergics increase the difficulty of emptying the bladder (Di Stasi et al., 2001). If an individual has vesicouretral reflux or hydronephrosis from bladder-sphincter dyssynergia and is not responsive to or side effects are too severe from anti-cholinergics, surgery is sometimes performed to reduce bladder pressure. There are two main types surgery that are performed to reduce bladder pressure. The first type reduces the urethra pressure by dilation of the urethra by urethral balloon dilation, urethral stenting, or sphincterotomy such that any increase in bladder pressure will result in urine leakage and maintain a low bladder pressure. The other type of surgery reduces bladder pressure by increasing the size of the bladder by either attaching a patch of bowel to the bladder or cutting through the detrusor to the mucosa. Both of these methods allow the bladder to fill to greater volume before the bladder pressure reaches pathological levels; however, both methods increase the difficulty of the emptying the bladder (Jezernik et al., 2002). With each of these methods, the patients never fully recover to a satisfactory condition.

Another method of restoring bladder function in SCI individuals, the Brindley procedure, has been shown to be successful in restoring bladder control in over 1600 patients implanted since 1982 (Brindley, 1994; Brindley et al., 1982; Creasey, 1993; Schurch et al., 1997). The system consists of a neuroprosthesis that stimulates the sacral anterior roots to achieve micturition. In order to achieve continence, to diminish hyper-reflexia, and to reduce residual volume after micturition, a sacral dorsal rhizotomy, an irreversible transection of the dorsal sacral roots, is performed to remove afferent feedback. A major side effect of the rhizotomy is the loss of all sacral sensory including the loss of reflex sexual functions (loss of reflex erections and ejaculation in males and loss of lubrication in females), loss of perineal sensation, loss of reflex micturition, and loss of reflex defecation (Creasey, 1993). Because of these side effects and along with a psychological barrier of further injuring an already injured spinal cord, the Brindley procedure has been limited to complete suprasacral SCI individuals who do not retain any sensation or secondary reflexes (Dahms & Tanagho, 1998). However, individuals that received the implanted system have been shown to have a higher quality of life (Vastenholt et al., 2003).

Even though the numbers of individuals who have received a Brindley stimulator have been limited, the procedure has been shown to cost effective. The yearly cost for a SCI individual without respiratory assistance ranges from $25,000 to $50,000, and, for a SCI individual with respiratory assistance, the average yearly cost jumps to $122,334 (Center, 2004). The average yearly cost to manage bladder and bowel is $8,152 (Cardenas, Haselkorn, McElligott, & Gnatz, 2001; Creasey & Dahlberg, 2001), and, after implantation of the Brindley system, the yearly bladder and bowel costs were reduced by

80% to $948 (Creasey & Dahlberg, 2001). The system was able to pay for itself within 5 years by reducing the yearly expenditures, and cost saving was achieved for every year after that. The life expectancy for a 20 year old SCI individual not on a ventilator is 45 years (Center, 2004), and the cumulative savings using the Brindley system over the lifetime of that same individual is greater than $250,000.

V.2 Summary of Results

Individuals with SCI or neurological disorders experience urological complications that lead to significant morbidity, substantial decrease in quality of life, and high medical costs. The long term goal of this project is to develop a neural prosthesis to restore urinary continence in persons with neurological disorders, particularly spinal cord injury, without requiring a dorsal rhizotomy. The neural prosthesis will abolish unwanted hyper-reflexive bladder contractions to maintain a low bladder pressure and to maintain continence. A hyper-reflexive bladder contraction is an involuntary bladder contraction at a small bladder volume. Electrical stimulation has been used to treat incontinence through inhibition of hyper-reflexia, but each of the present methods continuously applies stimulation to inhibit the bladder (Chartier-Kastler et al., 2001; Craggs et al., 1998; Grill et al., 2001; Jezernik et al., 2002; Siegel, 1992; van Balken et al., 2001; Vandoninck et al., 2003; Vodusek et al., 1986; Weil et al., 1998). Conditional stimulation, when stimulation is applied at the onset of a bladder contraction, will reduce the chance of habituation which would allow the bladder to fill to a greater volume before leakage.

The hypothesis of this project was that the electrical activity of the pudendal nerve can be used to detect the onset of a hyper-reflexive bladder contraction and serve as

a trigger for conditional stimulation to maintain continence. A closed-loop system was developed using the pudendal nerve electroneurogram as the trigger for conditional stimulation to determine if conditional stimulation allows the bladder to fill to greater volume before continence is lost than either continuous stimulation or no stimulation. A non-surgical method of determining the electrical activity of the pudendal nerve is required before testing the device in humans. The hypothesis was that the external anal sphincter electromyogram (EAS EMG) can serve as a proxy for the electrical activity of the pudendal nerve and enable detection of reflex bladder contractions.

V.2.1 Detection of Hyper-Reflexive Bladder Contractions

The aim of Chapter II was to determine if the electrical activity of the pudendal nerve could be used to detect the onset of bladder contractions. The pudendal nerve electroneurogram (PNT ENG) was recorded during reflexive bladder contraction in an animal model. The PNT ENG was modulated during reflexive bladder contractions. The performances of three detection algorithms (constant threshold, dynamic threshold and CUSUM) were compared to determine which algorithm performed the best in detecting the onset of bladder contractions. The CUSUM algorithm outperformed the other two algorithms based on its predictability (performance on data not used to develop the algorithm parameters), sensitivity, specificity, and accuracy (short delay and small increase in bladder pressure at time of detection). Chapter II showed that the onset of reflexive bladder contraction can be detected using the electrical activity of the pudendal nerve, and that the CUSUM algorithm performed the best in detecting the onset of bladder contractions.

V.2.2 Event-triggered Control System to Maintain Continence

The event-triggered bladder control system includes the electrical detection of reflexive bladder contractions and the electrical stimulation of the pudendal nerve to abolish nascent bladder contractions. Following detection of the onset of a hyper-reflexive contraction of the bladder from recordings of the PNT ENG using the CUSUM algorithm, conditional electrical stimulation of the pudendal nerve inhibited the bladder and arrested the nascent contraction. The hypothesis was that event-triggered control will allow the bladder to fill to greater volumes before continence is lost than either no stimulation or continuous stimulation. The hypothesis was tested by filling the bladder until continence was lost (loss of 1 ml of urine or an uncontrolled bladder contraction) for each stimulation method: no stimulation, continuous stimulation, and conditional stimulation. Chapter III showed that conditional stimulation allowed the bladder to fill to greater volume than either continuous stimulation or no stimulation, and that the stimulation time was reduced by 67% compared to continuous stimulation.

V.2.3 Transfer Technique to Human Trials

A non-surgical method for recording the electrical activity of the pudendal nerve needed to be developed to determine if the onset of bladder contractions can be detected from a bioelectric signal in individuals with SCI. By recording the activity of the target muscles innervated by the pudendal nerve using surface or percutaneous EMG electrodes, one could extrapolate some of the electrical activity of the pudendal nerve. The hypothesis was that the electrical activity of the external anal sphincter (EAS) can be used to detect the onset of bladder contractions. The hypothesis was first tested in an animal model by recording the electrical activity of the EAS during reflexive bladder contractions. The EAS was modulated during reflexive bladder contractions, however

some of the cats had a synergic response where as other cats had a dyssynergic response. The onset of bladder contractions was able to be detected using EAS EMG in both bladder-sphincter relationships. The techniques of detecting reflexive bladder contractions from EAS EMG that were developed in cats were demonstrated in humans. A retrospective clinical study was performed on cystometrograms which contained bladder pressure with corresponding EAS EMG during bladder filling in individuals with SCI. Similar to pre-clinical experiments, the onset of reflexive bladder contractions was able to be detected in both synergic and dyssynergic individuals. Chapter IV showed that the onset of reflexive bladder contractions can be detected using the electrical activity of the external anal sphincter in both cats and humans. These data support pursuing further studies to record the electrical activity of the pudendal nerve during reflexive bladder contractions in humans.

V.3 Future Directions

The future direction of this project is to implant a neural prosthesis to restore bladder function in individuals with SCI. There are a series of steps that need to be taken to develop the finished device. The first step will be to continue with animal experiments to refine the control system by improving the performance of the detection algorithm. Another improvement on the control system would be to implement a fully closed-loop control system that gates its stimulation based solely on the electrical activity of the pudendal nerve. The next step will be to determine the effectiveness of the control system in humans. In animals, conditional stimulation increased volume by 15% over continuous stimulation; however, a series of studies in humans need to be conducted to compare the performance of conditional stimulation to the performance of continuous stimulation.

Finally, continence and micturition stimulation methodology need to be combined into one implant to restore all bladder functions in individuals with spinal cord injury.

V.3.1 Closed-Loop Control System to Maintain Continence

The results of the event-triggered control system showed that reducing stimulation time increased the effectiveness of the applied inhibitory stimulation. However, the amount of stimulation per detection in the event-triggered control system was preset and not gated to the electrical activity of the pudendal nerve. The electrical activity of the pudendal nerve was modulated during the stimulation and may provide additional information that could allow for a completely closed-loop system. The potential advantage of a true closed-loop control system is the stimulation time would be sufficient to arrest the bladder contraction without superfluous stimulation.

An analysis was done on some of the data that were collected for Chapter III. The stimulation artifact in the pudendal nerve electroneurogram was removed from the continuous stimulation trials (Figure V.1). These data showed that even though the bladder contractions were being continuously inhibited, the PNT ENG was still modulated during bladder contractions. This modulation in the PNT ENG was also seen in the conditional stimulation trials. By creating a blanking circuit and/or through signal processing, removing the stimulation artifact will allow the analysis of the raw PNT ENG. The PNT ENG could serve as a control signal to turn the stimulation on and off, thus, creating a completely closed-loop system to maintain urinary continence. However, a study would need to be conducted to determine if a closed-loop system would perform better than an event-triggered system in maintaining urinary continence.

V.3.2 Humans Studies of Event-Triggered Control System

Chapter III showed that conditional stimulation in cats allowed the bladder to fill to greater volume before continence was lost than either continuous stimulation or no stimulation. These studies should be repeated in humans with SCI to determine if conditional stimulation performs better than continuous stimulation. The first series of experiments could use the bladder pressure as the control signal to determine if the performance of conditional stimulation is better than continuous stimulation. Even if the performance of conditional stimulation is statistically better than continuous, it will need to be determined if the increased performance is worth the extra power consumption of conditional stimulation (Appendix B). A major question that needs to be answered is: *What percent increase in volume justifies the increase in power consumption of conditional stimulation?*

In later studies, bioelectric signals, such as the external anal sphincter EMG or pudendal nerve ENG, could be used as the control signal. Another question that needs to be answered: *What bioelectric source would have highest performance in detecting the onset of bladder contraction?* Recording the detrusor or EAS EMG would require less amplification and a lower sampling rate than PNT ENG which leads to lower power consumption. Also, recording from the detrusor EMG would allow an earlier detection of the bladder contraction than measuring bladder pressure (Figure V.2). However, a nerve cuff would already be implanted on the pudendal nerve making recording EMGs a more difficult surgery and add additional parts to the implant that would increase the chances of failure. It is expected that recording an EMG would produce better control signal as a result of higher SNR and lower power requirement than recording an ENG. The higher SNR and lower power requirements justify the increase in surgical and device

complexities. The last question that needs to be answered in human studies is: *Is it better to have a completely implantable device or a non-invasive device?* An implanted device would give the individual less concerns because the person would not have to worry donning and doffing the device. However, if a device malfunctions or is upgraded, an external device could be replaced without surgery.

V.3.3 Restoring All Bladder Functions in Individuals with Spinal Cord Injury

The ultimate goal of the research team is to develop a neural prosthesis that restores bladder function of individuals with spinal injury. The scope of the current project was to develop a method to control continence by using the electrical activity of the pudendal nerve. Stimulation of the pudendal nerve has been shown to activate a micturition reflex at a different stimulation frequency than the continence reflex (Boggs, Wenzel, Gustafson, & Grill, 2005). The frequency selectivity lends itself to combining the continence methodology present in this dissertation with the micturition methodology without requiring a multiple contact nerve cuff for specific selective stimulation. Preliminary results showed that continence and micturition methodologies can be combined into one neural prostheses, and provide bladder control (Figure V.1 Figure V.3).

V.4 Conclusion

An event-triggered control system allows the bladder to fill to greater volume than either no stimulation or continuous stimulation. The onset of bladder contractions can be detected by the electrical activity of the pudendal nerve and external anal sphincter. The detection methodologies are transferable to humans. These results support the use of conditional stimulation to restore continence in individuals with spinal cord injury.

Restoration of continence will increase the quality of life for many individuals, and implanting a neural prosthesis on the pudendal nerve will increase the population of persons who could benefit and decrease the yearly expenditures from such a device.

V.5 Figures and Tables

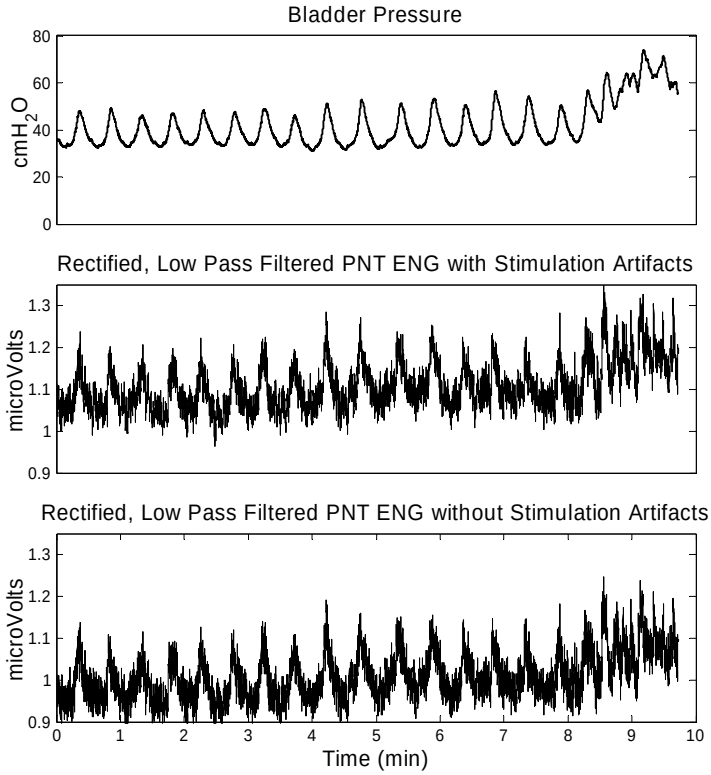

Figure V.1 Bladder pressure (top trace) with corresponding rectified, low pass filter pudendal nerve electroneurogram (PNT ENG) (bottom two traces). The middle traces in the PNT ENG during continuous 10 Hz stimulation of the contralateral pudendal nerve at 400 μA. The bottom trace is the PNT ENG with the stimulation artifacts removed. Notice that the signal amplitude has decreased when the stimulation artifacts were removed. The traces show that the PNT activity was modulated during reflexive bladder contractions even though continuous stimulation was applied. The PNT ENG activity can still be recorded during continuous stimulation, and, with proper blanking of the stimulation artifact, allow for a closed loop system in which the onset and offset of the stimulation is gated to the electrical activity of the pudendal nerve.

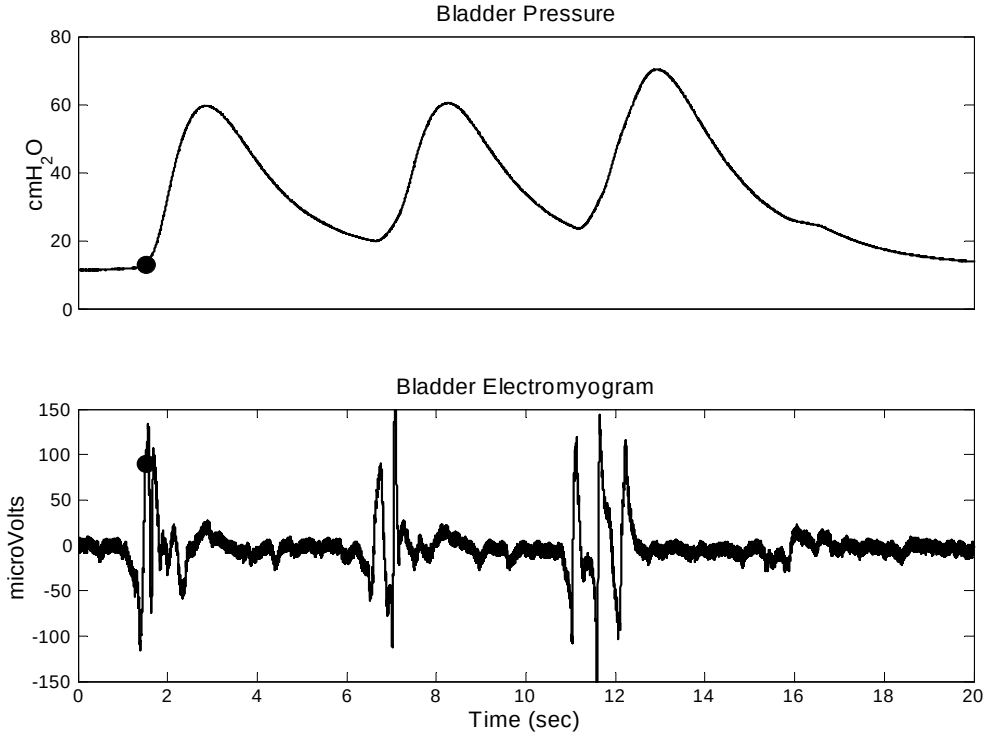

Figure V.2 The bladder pressure (top trace) with corresponding bladder electromyogram (EMG). The action potentials propagating through the bladder causes the bladder to contract and the bladder pressure to rise. The action potentials preceded the initial rise of bladder pressure by approximately 500 miliseconds. The marker (●) represents the start of the bladder contractions that was defined in Chapter II and used throughout the analyses in this dissertation. The action potential propagating through the bladder started 500 milliseconds before the defined start of the bladder contraction. If the bladder EMG was used as the control signal, the delay in detecting the onset of a bladder contraction could be reduced.

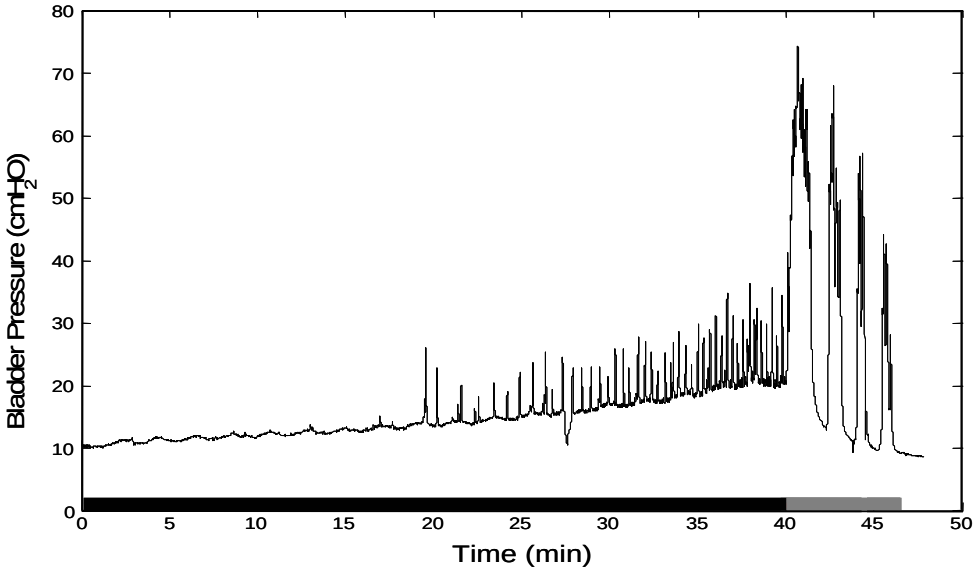

Figure V.3 Bladder pressure during continence and micturition controlled by one neural prosthesis. The black bar represents time in which the bladder controller is in continence mode. In continence mode, the controller conditionally stimulates the pudendal nerve at low frequencies to inhibit bladder contractions (Note: The bladder is continuously being filled at 1.0 ml/min, and the bladder volume at the start of micturition was 40 ml, and the average volume at which continence was lost with no inhibitory stimulation was 34 ml for this cat). The grey bar represents the time in which the bladder controller is in micturition mode. In micturition mode, 68% of urine was expelled from the bladder.

Appendix A

A.1 Silicon split tube nerve cuff electrode fabrication

The process of fabricating the nerve cuff electrodes used through these studies is based on previous design (Haugland, 1996). The reason why this fabrication method was based on its versatility of changing sizes without redesigning molds.

The first step is to determine the sizes of nerve cuffs that are needed. Post mortem dissection where made on four cats, and the diameter and length of the pudendal nerve and its branches were measured. Blunt tip hypodermic needles with an outer diameter equal to the diameter of the pudendal nerve were used as a mandrel for the fabrication.

Platinum foil (25 microns thick) was cut such that the width was 2 mm and the length was the circumference of the hypodermic needle. Along the length of the platinum foil, incisions were made 0.05 mm into the foil at 0.1 mm intervals (Figure A.1). 38 gauge stainless stain multi-stranded wire insulated with Teflon is deinsulated the last 2 mm of the wire. The deinsulated end is spot welded to the center of the platinum foil such that the wire runs perpendicular to the length of the foil.

The platinum foil is wrapped around the mandrel and is held in place by 1 mm long silicon bands. The silicon bands were made from silicon tubing with an inside diameter slightly small than the outside diameter of the mandrel. The flaps on the sides of the contact were folded around the silicon band. The remaining contacts were placed around the mandrel and secured with the silicon bands (Figure A.2). The wires were aligned along one side of the mandrel and the contacts were moved into the desired position (Figure A.3).

Silicon (NuSil MED 1137) was diluted 1:5 by volume with heptane to reduce the viscosity of the silicon. The mandrel, with the electrodes, was dipped in the silicon solution, and allowed to air dry for 20 minutes. The dipping process was repeated until the designed thickness (approximately 1 mm) of the nerve cuff wall was obtained. After the desired thickness was obtained, the silicon was allowed to cure for at least 24 hours. The nerve cuff was slide off the mandrel and excess silicon was removed from the nerve cuff.

An opening was made along the nerve cuff by cutting the silicone and contacts with a pair of scissors. A piece of silicon calendar sheeting was cut the length of the cuff and 3 mm wide. One end of the silicon sheet was glued to nerve cuff 1.5 mm from the cut opening of the nerve cuff such that the other end of the silicon sheet was able to cover the opening. Two sets of 5-0 silk suture (5 cm long) were glued to the outside of the nerve cuff on the opposite side of the cuff as the opening. The suture made the implantation of the cuff easier (Figure A.4).

To implant the nerve cuff, the nerve is first freed from the fascia. The nerve cuff is held open by a pair of forceps while a glass hook guides the nerve into the cuff. The silicon flap is moved such that is covers the opening, and the suture is tied around the cuff to insure good closure of the cuff. To help insure the cuff is well sealed, the cuff is covered in 40^{o}C Vaseline along the flap and at the ends of the cuff.

A.2 Figures and Tables

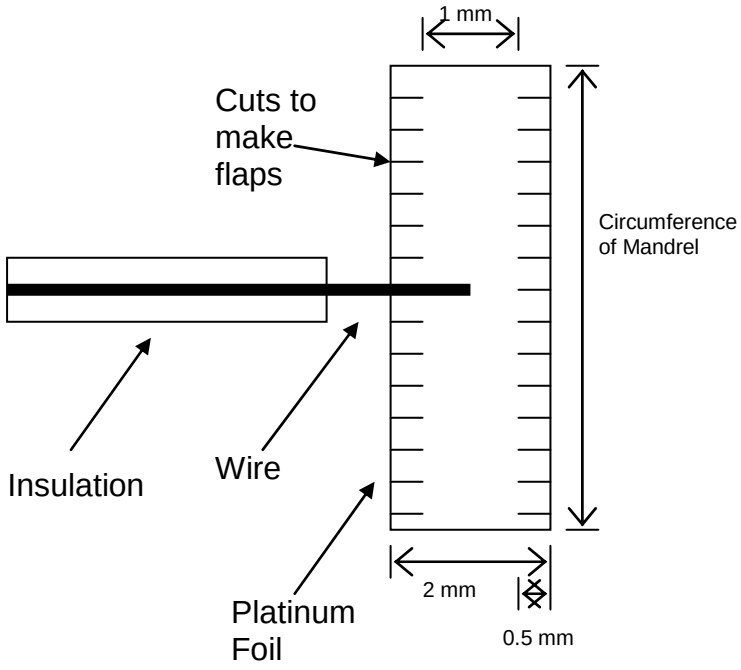

Figure A.1 The platinum foil (25 micron thick) was cut such the width was 2 mm long and the length was the circumference of the mandrel. Slits were cut 0.5 mm into the edge of the foil along the length at 0.1 mm intervals. Stainless stain wire was deinsulated at the tip and spot welded to the center of the foil.

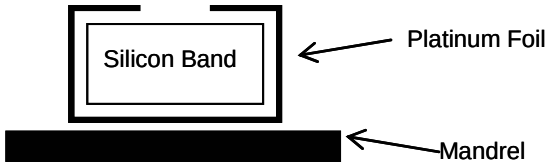

Figure A.2 The foil is wrapped around the mandrel and is secured in place by a silicon band. The flaps made by the slits are bent around the silicon band to help secure the foil in the silicone.

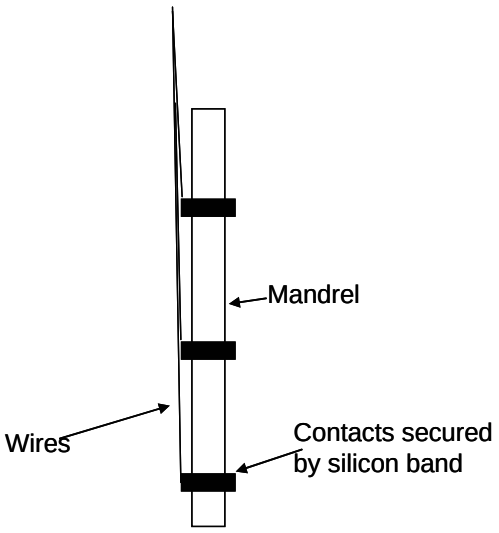

Figure A.3 The contacts are separated to desired positions and wires are aligned along one end of the cuff. The mandrel with contacts is dipped into silicon that has been dilute 1:5 by volume with heptane.

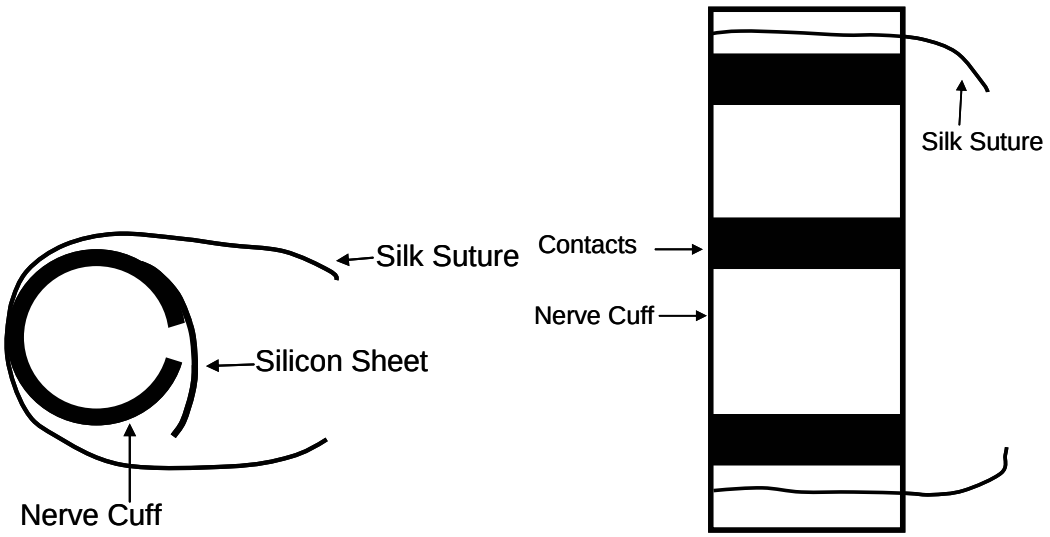

Figure A.4. The top and side view of the silicon nerve cuff. The opening of the nerve cuff is covered by a silicon sheet that been glued along one side of the nerve cuff. Silk sutures are glued to the nerve cuff to allow easier implantation of the nerve cuff.

Appendix B

Comparison of power consumption of a stimulator versus the power consumption of an amplifier with microcontroller

B.1 Stimulator Power Consumption

Assuming the stimulation train will be a 1 mA biphasic pulse with each phase lasting 150 μS at 20Hz with tissue resistance of 1 kOhm, the power consumption will be 6 μW.

Amplifier Power Consumption

An average micropower amplifiers use 3 volt supply and 10 μA supply current for a power consumption of 30 μW per channel. A minimum of two channels are needed to amplify and filter the ENG signal.

B.2 Microcontroller Power Consumption

An open loop microcontroller will spend 95% of its time in sleep mode. In sleep mode, only the counter and clock are still running. In sleep mode, the microcontroller requires 3 μA of current. During active mode, the microcontroller uses 200 μA. Using a 3 volt supply, the microcontroller would use 13 μA of current (95% * 3μA+5% * 200μA) consuming 39 μW.

A closed loop microcontroller will spend 100% of its time in active mode requiring 600 μW of power (200 μA * 3 V).

B.3 Total power consumption

An open loop control will require 45 μW of power (stimulator plus microcontroller). The closed loop control will require 662 μW of power assuming that the stimulation time is 33% of the open loop control (33%* stimulator plus two amplifiers

plus microcontroller). The open loop controller will use approximately 15 times less power than the closed loop controller.

References

Anderson, K. D. (2004). Targeting Recovery: Priorities of the spinal cord injured population. *J Neurotrauma, 21*(10), 1371-1383.

Basseville, M., & Nikiforov, I. V. (1993). *Detection of abrupt changes: theory and application*. Englewood Cliffs, NJ: PTR Prentice-Hall, Inc.

Birder, L. A., & de Groat, W. C. (1992). The effect of glutamate antagonists on c-fos expression induced in spinal neurons by irritation of the lower urinary tract. *Brain Res, 580*(1-2), 115-120.

Blaivas, J. G., Sinha, H. P., Zated, A. A. H., & Labib, K. B. (1981). Detrusor-External Sphincter Dyssynergia - A detailed electromyographic study. *Urology, 125*(4), 545-548.

Boggs, J. W., Wenzel, B. J., Gustafson, K. J., & Grill, W. M. (2005). A spinal micturition reflex mediated by afferents in the deep perineal nerve. *Journal of Neurophysiology, In Press*.

Borden, T. A., McGuire, E. J., Woodside, J. R., Allen, T. D., Bauer, S. B., Firlit, C. F., Gonzales, E. T., Kaplan, W. E., King, W. E., Klauber, G. T., Perlumtter, A. D., Thornbury, J. R., & Weiss, R. M. (1981). Urinary undiversion in patients with myelodysplasia and neurogenic bladder function. *Urology, 18*(3), 223-228.

Bratt, H., Salvesen, K. A., Eriksen, B. C., & Kulseng-Hanssen, S. (1998). Long-term effects ten years after maximal electrostimulation of the pelvic floor in women with unstable detrusor and urge incontinence. *Acta Obstet Gynecol Scand, Suppl 168*(77), 22-24.

Brindley, G. S. (1994). The first 500 patients with sacral anterior root stimulator implants: general description. *Paraplegia, 32*(12), 795-805.

Brindley, G. S., Polkey, C. E., & Rushton, D. N. (1982). Sacral anterior root stimulators for bladder control in paraplegia. *Paraplegia, 20*(6), 365-381.

Cardenas, D. D., Haselkorn, J. K., McElligott, J. M., & Gnatz, S. M. (2001). Bibliography of cost-effectiveness practices in physical medicine and rehabilitation: AAPM&R white paper. *Arch Phys Med Rehabil, 82*(5), 711-719.

Cariga, P., Catley, M., & Ellay, P. H. (2000). Habituation of the sympathetic skin response in normal human subjects: the effect of repeated electrical stimulation of peripheral nerves. *J Physiology - London, 523*, 221P.

Catz, A., Luttwak, Z. P., Agranov, E., Ronen, J., Shpaser, R., Paz, A., Lask, D., Tamir, A., & Mukamel, E. (1997). The role of external sphincterotomy for patients with a spinal cord lesion. *Spinal Cord, 35*(1), 48-52.

Center, N. S. C. I. S. (2004). *Annual report for the Model Spinal Cord Injury System for Care*. Birmingham, AL: University of Alabama.

Chartier-Kastler, E. J., Denys, P., Chancellor, M. B., Haertig, A., Bussel, B., & Richard, F. (2001). Urodynamic monitoring during percutaneous sacral nerve neurostimulation in patients with neurogenic detrusor hyper-reflexia. *Neurourology and Urodynamics, 20*, 61-71.

Cheater, F. M., & Castleden, C. M. (2000). Epidemiology and classification of urinary incontinence. *Clinical Obstetrics & Gynaecology, 14*(2), 183-205.

Craggs, M. D., Casey, A., Shah, P. J. R., Creasey, G., Kirkham, A., Khastgir, J., & Knight, S. L. (2000). SPARSI: an implant to empty the bladder and control

incontinence without posterior rhizotomy in spinal cord injury. *British Journal of Urology International, 85*(Suppl 5), 2.

Craggs, M. D., Edhem, I., Knight, S. L., McFarlane, J. P., & Shah, N. (1998). Suppression of normal human voiding relfexes by electrical stimulation of the dorsal penile nerve. *Journal of Physiology (London), 507P*, 19P-20P.

Crago, P., Chizeck, H. J., Neuman, M. R., & Hambrecht, F. T. (1986). Sensors for use with functional neuromuscular stimulation. *IEEE Trans Biomed Eng, 33*, 256-268.

Creasey, G. H. (1993). Electrical stimulation of sacral roots for micturition after spinal cord injury. *Urol Clin North Am, 20*(3), 505-515.

Creasey, G. H., & Dahlberg, J. E. (2001). Economic consequences of an implanted neuroprosthesis for bladder and bowel management. *Arch Phys Med Rehab, 82*(11), 1520-1525.

Dahms, S. E., & Tanagho, E. A. (1998). The impact of sacral root anatomy on selective electrical stimulation for bladder evacuation. *World J Urology, 16*, 322-328.

Dalmose, A. L., Rijkhoff, N. J. M., Kirkeby, H. J., Nohr, M., Sinkjaer, T., & Djurhuss, J. C. (2003). Conditional Stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in patients with spinal cord injury. *Neurourology and Urodynamics, 22*(2), 130-137.

de Groat, W. C. (1997). A neurologic basis for the overactive bladder. *Urology, 50*(6A Suppl), 36-52; discussion 53-36.

de Groat, W. C., Nadelhaft, I., Milne, R. J., Booth, A. M., Morgan, C., & Thor, K. (1981). Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine. *J Auton Nerv Syst, 3*(2-4), 135-160.

Decker, M. J., Haaga, J., Arnold, J. L., Atzberger, D., & Strohl, K. P. (4993). Funcitonal electrical stimulation and respiration during sleep. *Journal of Applied Physiology, 75*, 1053-1061.

DeVivo, M. J., Krause, J. S., & Lammertse, D. P. (1999). Recent trends in mortality and causes of death among person with spinal cord injury. *Arch Phys Med Rehabil, 80*, 1411-1419.

Di Stasi, S. M., Giannantoni, A., Vespasiani, G., Navarra, P., Capelli, G., Massoud, R., & Stephen, R. L. (2001). Intravesical electromotive administration of oxybutynin in patients with detrusor hyper-reflexia unresponsive to standard anti-cholinergic regimens. *Journal of Urology, 165*, 491-498.

Enzelsberger, H., Helmer, H., & Kurz, C. (1995). Intravesical installation of oxybutynin in women with idopathic detrusor instability - a randomized trial. *British Journal of Obstetrics and Gynaeology, 102*(11), 929-930.

Estores, I. M. (2003). The consumer's perspective and the professional literature: What do persons with spinal cord injury want? *J Rehabil Res Dev, 40*(Suppl 4), 93-98.

Evans, J. P. (1936). Observations in the nerves of supply to the bladder and urethra of the cat with a study of their action potentials. *Journal of Physiology, 86*, 396-414.

Fall, M. (1998). Advantanges and pitfalls of functional electrical stimulation. *Acta Obstetition and Gynecology of Scand, 168*(Suppl), 16-21.

Falou, W. E. l., Khalil, M., & Duchene, J. (2001). Adaptive approach for change detection in EMG recordings. *Proc 23rd Annu IEEE Engineering in Medicine Biological Sciences Conf, Istanbul, 23*, 1875-1878.

Fedirchuk, B., Hockman, S., & Shefchyk, S. J. (1992). An intracellular study of perianal and hindlimb afferent inputs onto sphincter motoneurons in the decerebrate cat. *Experimental Brian Research, 89*, 511-516.

Fedirchuk, B., & Shefchyk, S. J. (1993). Membrane potential changes in sphincter motor neurons during micturition in the decerebrate cat. *Journal of Neuroscience, 13*(7), 3090-3094.

Fjorback, M. V., Hansen, J., Dalmose, A. L., Rijkhoff, N. J. M., & Sinkjaer, T. (2003). A portable device for experimental treatment of neurogenic detrusor overactivity. *Neuromodulation, 6*(3), 158-165.

Floeter, M. K., Gerloff, C., Kouri, J., & Hallett, M. (1998). Cutaneous withdrawal reflexes of the upper extremity. *Muscle & Nerve, 21*, 591-598.

Fossberg, E., Sorensen, S., Ruutu, M., Bakke, A., Stien, R., Henriksson, L., & Kinn, A. C. (1990). Maximal electrical stimulation in the treatment of unstable detrsuor and urge incontinence. *European Urology, 18*, 120-123.

Fowler, C. J. (1999). Neurological disorders of micturition and their treatment. *Brain, 122*(Pt 7), 1213-1231.

Gary, R. C., Roberts, T. D. M., & Todd, J. K. (1959). Reflexes involving the external urethral sphincter in the cat. *Journal of Physiology (London), 149*, 653-665.

Geirsson, G., Wang, Y. H., Lindstrom, S., & Fall, M. (1993). Traditional acupuncture and electrical stimulation of the posterior tibial nerve - A trial in chronic interstitial cystitis. *Scandinavian Journal of Uorlogy & Nephrology, 27*(1), 67-70.

Granat, M. H., Heller, B. W., Nicol, D. J., Baxendale, R. H., & Andrews, B. J. (1993). Improving limb flexion in FES gait using the flexion withdrawal response for the spinal-cord injured person. *J Biomedical Engineering, 15*(1), 51-56.

Grill, W. M., Craggs, M. D., Foreman, R. D., Ludlow, C. L., & Buller, J. L. (2001). Emerging clinical applications of electrical stimulation: Opportunities for restoration of function. *Journal of Rehabilitation Research and Development, 38*(6), 641-653.

Habler, H. J., Janig, W., & Koltzenburg, M. (1990). Activation of unmyelinated afferent fibers by mechanical stimuli and inflammation of the urinary bladder in the cat. *Journal of Physiology (London), 425*, 545-562.

Hackler, R. H. (1977). A 25 year prospective mortality study in the spinal cord injured patient: Comparison with the long-term living paraplegic. *J Urology, 117*, 486-488.

Harrison, L. M., Norton, J. A., & Stephens, J. A. (2000). Habituation of cutaneomuscluar reflexes recorded from the first dorsal interosseous and tricep muscle in man. *J Neurological Sciences, 177*, 32-40.

Harrison, L. M., Norton, J. A., & Stephens, J. A. (2000). Habituation of cutaneomuscular reflexes recorded from the first dorsal interocceous and tricep muscle in man. *J Neurological Sciences, 177*, 32-40.

Haugland, M. (1996). A flexible method for fabrication of nerve cuff electrodes. *18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 359-360.

Haugland, M. K., & Sinkjaer, T. (1995). Cutaneous whole nerve recordings used for correction of footdrop in humiplegic man. *IEEE Trans Rehabilitation Engr, 3*(4), 307-317.

Hicken, B. K., Putzke, J. D., & Richards, J. S. (2001). Bladder management and quality of life after spinal cord injury. *Am J Phys Med Rehabil, 80*(12), 916-922.

Hunskaar, S., Arnold, E. P., Burgio, K., Diokno, A. C., Herzog, A. R., & Mallett, V. T. (2000). Epidemiology and natural history of urinary incontinence. *International Urogynaecology Journal, 11*, 301-319.

Inmann, A., & Haugland, M. (2004). Functional evaluation of natural sensory feedback incorporated in a hand grasp neuroprosthesis. *Medical Engineering & Physics, 26*, 439-447.

Inmann, A., & Haugland, M. (2004). Implementation of natural sensory feedback in a portable control system for a hand grasp neuroprosthesis. *Medical Engineering & Physics, 26*, 449-458.

Janez, J., Plevnik, S., & Suhel, P. (1979). Urethral and bladder responses to anal electrical stimulation. *Journal of Urology, 122*, 192-194.

Jezernik, S., Craggs, M. D., Grill, W. M., Creasey, G. H., & Rijkhoff, N. J. M. (2002). Electrical stimulation for the treatment of bladder dysfunction: Current status and future possibilities. *Neurological Research, 24*, 413-430.

Jezernik, S., Grill, W. M., & Sinkjaer, T. (2001). Detection and inhibition of hyper-reflexive-like bladder contractions in the cat by sacral nerve root recording and electrical stimulation. *Neurourology and Urodynamics, 20*, 215-230.

Jezernik, S., & Sinkjaer, T. (1998). On statistical properties of whole nerve cuff recordings. *IEEE Trans Biomedical Engineering, 46*, 1240-1245.

Jezernik, S., Wen, J. G., Rijkhoff, N. J. M., Djurhuus, J. C., & Sinkjaer, T. (2000). Analysis of bladder related nerve cuff electrode recordings from preganglionic pelvic nerve and sacral roots in pigs. *J Urology, 163*, 1309-1314.

Jiang, C. H., & Lindstrom, S. (1998). Prolonged increase in micturition threshold volume by anogenital afferent stimulation in rat. *BJU, 82*, 398-403.

Jiang, C. H., & Lindstrom, S. (1999). Prolonged enhancement of the micturition reflex in the cat by repetitive stimulation of bladder afferents. *J Physiol (Lond), 517*(Pt 2), 599-605.

Johansson, R. S., & Westling, G. (1988). Programmed and triggered actions to rapid load changes during precision grip. *Experimental Brain Research, 71*, 72-86.

Kaplan, S. A., Chancellor, M. B., & Blaivas, J. G. (1991). Bladder and sphincter behavior in patients with spinal cord lesions. *J Urology, 146*, 113-117.

Keane, D. P., & O'Sullivan, S. (2000). Urinary incontinence: anatomy, physiology, and pathophysiology. *Clinical Obstetrics & Gynaecology, 14*(2), 207-226.

Kelleher, C. (2000). Quality of life and urinary incontinence. *Clinical Obstetrics & Gynaecology, 14*(2), 363-379.

Kirkham, A. P. S., Knight, S. L., Craggs, M. D., Casey, A. T. M., & Shah, P. J. R. (2002). Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator. *Spinal Cord, 40*, 272-281.

Kirkham, A. P. S., Shah, N. C., Knight, S. L., Shah, P. J. R., & Craggs, M. D. (2001). The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. *Spinal Cord, 39*, 420-428.

Klevmark, B. (2002). Volume threshold for micturition. Influence of filling rate on sensory and motor bladder function. *Scand J Urol Nephrol, Suppl 210*, 6-10.

Kondo, A., Otani, T., & Takita, T. (1982). Suppression of bladder instability by penile squeeze. *British J Urology, 54*(4), 360-362.

Krier, J. (1984). Discharge patterns of pudendal efferent fibers innervating the external anal sphincter of the cat. *Journal of Physiology (London), 368*, 471-480.

Kuhn, W., Rist, M., & Zaech, G. A. (1991). Intermittent urethral self-catheterization - Long-term results (bacteriological evolution, continence, acceptance, complications). *Paraplegia, 29*(4), 222-232.

Lee, Y. H., & Creasey, G. H. (2002). Self-controlled dorsal penile nerve stimulation to inhibit bladder hypperreflexia in incomplete spinal injury: A case report. *Arch Phys Med Rehabil, 83*(2), 273-277.

Lindstrom, S., Fall, M., Carlsson, C. A., & Erlandson, B. E. (1983). The neurophysiological basis of bladder inhibition in response to intravaginal electrical stimulation. *J Urol, 129*(2), 405-410.

Lyons, G. M., Sinkjaer, T., Burridge, J., & Wilcox, D. J. (2002). A review of portable FES-based neural orthoses for the correction of drop foot. *IEEE Trans Neural Systems Rehab Eng, 10*(4), 260-279.

Martin, W. D., Fletcher, T. F., & Bradley, W. E. (1974). Innervation of feline perineal musculature. *Anat Rec, 180*(1), 15-29.

Matjacic, Z., Hunt, K., Gollee, H., & Sinkjaer, T. (2003). Control of posture with FES systems. *Medical Engineering and Physics, 25*, 51-62.

McFarlane, J. P., Foley, S. J., & Shah, P. J. (1996). Long-term outcome of permanent urethral stents in the treatment of detrusor-sphincter dyssynergia. *Br J Urol, 78*(5), 729-732.

McFarlane, J. P., Foley, S. J., & Shah, P. J. (1997). Balloon dilatation of the external urethral sphincter in the treatment of detrusor-sphincter dyssynergia. *Spinal Cord, 35*(2), 96-98.

McGuire, E. J., & Brady, S. (1979). Detrusor-sphincter dyssynergia. *J Urology, 121*(6), 774-777.

McGuire, E. J., Woodside, J. R., & Borden, T. A. (1981). Prognostic value of urodynamic testing in myelodysplastic patients. *J Urology, 126*, 205-209.

McKinley, W. O., Jackson, A. B., Cardenas, D. D., & DeVivo, M. J. (1999). Long-term medical complications after traumatic spinal cord injury: A regional model systems analysis. *Arch Phys Med Rehabil, 80*, 1402-1410.

Nakamura, M., Sakurari, T., Sugao, H., & Sonoda, T. (1987). Maximal electrical stimulation for urgency incontinence. *Urology International, 42*, 285-287.

Ohlsson, B. L. (1988). Effects of some diffferet pulse parameters on the perception of intravaginal and intraanal electrical stimulation. *Medical & Biological Engineering & Computing, 26*(5), 503-508.

Popovic, M. B. (2003). Control of neural prostheses for grasping and reaching. *Medical Engineering and Physics, 25*, 41-50.

Primus, G., & Kramer, G. (1996). Maximal external electrical stimulation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence. *Neurourology & Urodynamics, 15*, 187-194.

Rudy, D. C., Awad, S. A., & Downie, J. W. (1988). External sphincter dyssynergia: an abnormal continence reflex. *Journal of Urology, 140*, 105-110.

Rudy, D. C., Downie, J. D., & McAndrew, J. D. (1991). Alpha-Chloralose alters autonomic reflex function of the lower urinary tract. *American Journal of Physiology, 261*, R1560-R1567.

Sahin, M., Durand, D. M., & Haxhiu, M. A. (2000). Closed-loop stimulation of hypoglossal nerve in a dog model of upper airway obstruction. *IEEE Trans Biomedical Engineering, 47*(7), 919-925.

Sahin, M., Haxhiu, M. A., Durand, D. M., & Dreshaj, I. A. (1997). Spiral nerve cuff electrode for recordings of respiratory output. *Journal of Applied Physiology, 83*(1), 317-322.

Schurch, B., Rodic, B., & Jeanmonod, D. (1997). Posterior sacral rhizotomy and intradural anterior sacral root stimulation for treatment of the spastic bladder in spinal cord injured patients. *J Urology, 157*, 610-614.

Schwartz, A. R., Eisele, D. W., Hari, A., Testerman, R., Erickson, D., & Smith, P. L. (1996). Electrical stimulation of the lingual musculature in obstructive sleep apnea. *Journal of Applied Physiology, 81*, 643-652.

Shafik, A. (1993). Vesicolevator. *Urology, 41*, 96-100.

Shah, N., Edhem, I., Knight, S. L., & Craggs, M. D. (1998). Acute Suppression of Detrusor Hyper-reflexia with Detrusor-Sphincter Dyssynergia by Electrical Stimulation of the Dorsal Penile Nerve in Patients with a Spinal Injury. *European Urology, 33*(Suppl 1), 60.

Shefchyk, S. J., & Buss, R. R. (1998). Urethral pudendal afferent-evoked bladder and sphincter reflexes in decerebrate and acute spinal cats. *Neurosicence Letters, 244*(3), 137-140.

Sheriff, M. K. M., Shah, P. J. R., Fowler, C., Mundy, A. R., & Craggs, M. D. (1996). Neuromodulation of detrusor hyper-reflexia by functional magnetic stimulation of the sacral roots. *British Journal of Urology International, 78*, 39-46.

Shingleton, W. B., & Bodner, D. R. (1993). The development of urologic complications in relationship to bladder pressure in spinal cord injured patients. *Journal of American Paraplegia Society, 16*(1), 14-17.

Siegel, S. W. (1992). Management of voiding dysfunction with an implantable neuroprosthesis. *Urologic Clinic of North America, 19*, 163-170.

Stein, R. B., Charles, D., Davis, L., Jhamandas, J., Mannard, A., & Nichols, T. R. (1975). Principles Underlying New Methods for Chronic Neural Recording. *Le Journal Canadien Des Sciences Neurologiques, 2*(3), 235-244.

Sundin, T., Carlsson, C. A., & Kock, N. G. (1974). Detrusor inhibition induced from mechanical stimulation of the anal region and from electrical stimulation of pudendal nerve afferents: An experimental study in cats. *Investigative Urology, 11*, 374-378.

Tate, D. G., Zalpakjian, C. Z., & Forschheimer, M. B. (2002). Quality of life issues in individuals with spinal cord injury. *Arch Phys Med Rehabil, 83*(Suppl 2), S18-S25.

Thakar, R., & Stanton, S. (2000). Management of urinary incontinence in women. *BMJ, 321*, 1326-1331.

Thor, K. B., & Muhlhauser, M. A. (1999). Vesicoanal, urethroanal, and urethrovesical reflexes initiated by lower urinary tract irritation in the rat. *American Journal of Physiology, 277*(4 Pt 2), R1002-1012.

Upshaw, B., & Sinkjaer, T. (1998). Digital signal processing algorithms for the detection of afferent activity recorded from cuff electrodes. *IEEE Trans Rehabilitation Engr, 6*(2), 172-181.

van Balken, M. R., Vandoninck, V., Gisolf, K. W. H., Vergunst, H., Kiemeney, L. A. L. M., Debruyne, F. M. J., & Bemelmans, B. L. H. (2001). Posterior tibial nerve stimulation as neuromodulative treatment of lower urinary tract dysfunction. *Journal of Urology, 166*(3), 914-918.

van Balken, M. R., Vandoninck, V., Messelink, B. J., Vergunst, H., Heesakkers, J. P. F. A., Debruyne, F. M. J., & Bemelmans, B. L. H. (2003). Percutaneous tibial nerve stimulation as neuromodulative treatment of chronic pelvic pain. *European Urology, 43*(2), 158-163.

Vandoninck, V., van Balken, M. R., Agro, E. F., Heesakkers, J. P. F. A., Debruyne, F. M. J., Kiemeney, L. A. L. M., & Bemelmans, B. L. H. (2004). Posterior tibial nerve stimulation in the treatment of voiding dysfunction: Urodynamic data. *Neurourology & Urodynamics, 23*(3), 246-251.

Vandoninck, V., van Balken, M. R., Agro, E. F., Petta, F., Caltogirone, C., Heesakkers, J. P. F. A., Kiemeney, L. A. L. M., Debruyne, F. M. J., & Bemelmans, B. L. H. (2003). Posterior tibial nerve stimulation in the treatment of urge incontinence. *Neurourology and Urodynamics, 22*(1), 17-23.

Vastenholt, J. M., Snoek, G. J., Buschman, H. P. J., van der Aa, H. E., Alleman, E. R. J., & Ijzerman, M. J. (2003). A 7-year follow-up of sacral anterior root stimulation for bladder control in patients with a spinal cord injury: quality of life and users' experiences. *Spinal Cord, 41*, 397-402.

Vodusek, D. B., Light, J. K., & Libby, J. M. (1986). Destrusor inhibition induced by stimulation of pudendal nerve afferents. *Neurourology and Urodynamics, 5*, 2381-2389.

Walter, J. S., Wheeler, J. S., Robinson, C. J., & Wurster, R. D. (1993). Inhibiting the hyper-reflexic bladder with electrical stimulation in a spinal animal model. *Neurourol Urodyn, 12*(3), 241-252.

Wang, B., Bhadra, N., & Grill, W. M. (1999). Functional anatomy of the male feline urethra: morphological and physiological correlations. *J Urol, 161*(2), 654-659.

Watanabe, T., Rivas, D. A., & Chancellor, M. B. (1996). Urodynamics of Spinal Cord Injury. *Urologic Clinics North America, 23*, 459-473.

Weil, E. H., Ruiz-Cerda, J. L., Eerdmans, P. H. A., Janknegt, R. A., & Van Kerrebroeck, P. E. V. A. (1998). Clinical results of sacral neuromodulation for chronic voiding dysfunction using unilateral sacral foramen electrodes. *World Journal of Urology, 16*, 313-321.

Wenzel, B. J., Boggs, J. W., Gustafson, K. J., & Grill, W. M. (2005). Detecting the Onset of Hyper-Reflexive Bladder Contractions from the Electrical Activity of the Pudendal Nerve. *IEEE Trans Neural Systems Rehabilitation Engineering, In Press*.

Wenzel, B. J., Grill, W. M., Boggs, J. W., & Gustafson, K. J. (2003). *Using external anal sphincter to detect the onset of hyper-reflexive bladder contractions.* Paper presented at the Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico.

Widerstrom-Noga, E. G., Felipe-Cuervo, E., Broton, J. G., Duncan, R. C., & Yezierski, R. P. (1999). Perceived difficulty in dealing with consequences of spinal cord injury. *Arch Phys Med Rehabil, 80*, 580-586.

Yalla, S. V., & Fam, B. A. (1991). Spinal Cord Injury. In E. Bors & A. E. Comarr (Eds.), *Neurological Bladder, Second Edition* (2nd ed., pp. 319-331). Baltimore: University Park Press.