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NEUROSTIMULATION OF THE SACRAL ROOTS IN NEUROGENIC BLADDER: THE EFFECT OF SELECTIVE HIGH-FREQUENCY BLOCKADE ON EXTERNAL URETHRAL SPHINCTER ACTIVITY

by

Le Mai Tu

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

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March 1997

To my husband, parents, family and friends for their faithful and continual encouragement, understanding and love.

Abstract

Bladder dysfunction secondary to neurologic impairment can be caused by any pathologic condition affecting the central or peripheral nervous system or both (brain lesions, cerebrovascular accidents, multiple sclerosis, Parkinson's disease, spinal cord injury, myelodysplasia, etc.). Among those pathologies, the spinal cord injury (SCI) at the suprasacral level leads to the development of detrusor hyperreflexia associated with detrusor-external sphincter dyssynergia. The dyssynergic voiding results in a high voiding pressure which is the origin of upper urinary tract damage observed in spinal cord injured patients.

The ultimate goals of the management of neurogenic bladder in suprasacral SCI are to achieve low-pressure urine storage, low-pressure and adequate urine emptying, control of detrusor hyperreflexia and catheter-free state. Different attempts varying from medication to sphincteric surgery or denervation have been tried in the past few decades to achieve these goals. The use of neurostimulation to achieve some of these outcomes in neurogenic bladder had also been attempted in the past with variable results.

Electrical stimulation of selective sacral roots has been used in the management of neurogenic bladder secondary to SCI. However, since the ventral S_2 root contains mixed somatic fibers innervating the external sphincter and autonomic fibers innervating the bladder, electrostimulation of this root could even worsen the dyssynergia. In this acute canine work, we evaluated the feasibility of the principle of selective high frequency blockade of the somatic component of the sacral root. A stimulus was delivered by a new functional stimulator via a single bipolar electrode. This stimulus is composed of two independent current waveforms. The selectivity is caused by the inhibition of the somatic fibers by the high frequency component while

the autonomic fibers are stimulated by low frequency stimuli. Using this technique of high-frequency blockade, we evaluated and showed the possibility of reduction of bladder outlet resistance during simultaneous detrusor contraction thus achieving a normal physiologic pattern of micturition.

Résumé

La dysfonction vésicale secondaire à l'atteinte neurologique peut être causée par toute pathologie atteignant le système nerveux central et/ou périphérique telle: les lésions cérébrales, les accidents cérébrovasculaires, la sclérose en plaques, la maladie de Parkinson, les traumatismes médullaires ou la myélodysplasie. Parmi ces pathologies, le traumatisme médullaire suprasacré entraîne fréquemment le développement d'une hyperréflexie vésicale associée à une dyssynergie vésico-sphinctérienne. Cette perte de coordination entre le détrusor et le sphincter externe a comme conséquence clinique une vidange vésicale sous haute pression qui peut être à l'origine de dommages à l'arbre urinaire supérieur observés chez ces patients.

Le traitement prodigué aux patients ayant une vessie neurogène seçondaire au traumatisme médullaire suprasacré a pour but d'obtenir un remplissage vésical à basse-pression, une vidange adéquate, un contrôle de l'hyperréflexie vésicale sans avoir recours à une cathéterisation chronique. Différentes alternatives, variant du traitement pharmacologique jusqu'à la sphinctérotomie externe, ont été essayées y compris l'application de l'électrostimulation.

L'électrostimulation des racines nerveuses sacrées dans le but de contrôler la vessie neurogène post traumatisme suprasacré a été étudiée depuis quelques décades. Du au fait que la racine sacrée ventrale est composée de fibres nerveuses mixtes qui innervent le sphincter strié externe et le détrusor, l'application du courant électrique à ce niveau stimule ces deux types de fibres simultanément, aggravant ainsi la dyssynergie vésico-sphinctérienne préexistante. Dans cette étude animale aiguë, nous avons évalué la faisabilité du principe de blocage sélectif à haute-fréquence de la composante somatique de la racine sacrée. Un stimulus est généré par un stimulateur nouvellement conçu et est libéré via une électrode bipolaire. Ce stimulus est composé de deux ondes

électriques indépendantes. La sélectivité est obtenue via une inhibition des fibres somatiques par le courant à haute-fréquence tandis que le détrusor est stimulé par celui à basse-fréquence. Cette technique nous a permis d'évaluer et de démontrer la possibilité de réduire la résistance infravésicale durant la contraction vésicale accomplissant ainsi une vidange vésicale physiologique et adéquate.

Acknowledgements

I would like to express my sincere gratefulness to my research supervisors, Dr. M.M. Elhilali and Dr. Stephane B. Dion, for their constant and excellent support and guidance.

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I would like to thank Dr. H.S. Shaker, Mr. S. Robin, Eng., Dr. M. Sawan, and other co-workers for their appreciated contribution in this project.

I am also thankful to Dr. Gerald B. Brock for his encouragement and listening.

Preface

In accordance with the guidelines concerning thesis preparation, I have exercised the option of writing the experimental part of this thesis (chapter 4) in the form of an original paper. The manuscript entitled Reduction of bladder outlet resistance by selective sacral root stimulation using high-frequency blockade in dogs: An acute study, by L.M. Tu, H.S. Shaker, S. Robin, K. Arabi, M. Sawan, M. Hassouna and M.M. Elhilali, has been submitted by the Department of Urology of the McGill University for publication.

The new electrical stimulator was built by Department of Electrical and Computer Engineering, École Polytechnique de Montréal, Montreal, Quebec, Canada.

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List of abbreviations

Ach:	Acetylcholine
CGRP:	Calcitonin gene-related peptide
DESD:	Detrusor-external sphincter dyssynergia
DH:	Detrusor hyperreflexia
IC:	Intermittent catheterization
NANC:	Non-adrenergic non-cholinergic
NE:	Norepinephrine
NGF:	Nerve growth factors
NT(s):	Neurotransmitter(s)
SCI:	Spinal cord injury
VIP:	Vasoactive intestinal polypeptide

CHAPTER 1

GENERAL INTRODUCTION

1.1 Anatomy of the lower urinary tract

1.1.1 Anatomy of the bladder

The bladder is an extraperitoneal organ. It serves as a reservoir for urine storage.[1] In a distended state, the bladder is a hollow muscular organ. In the empty state, the bladder has a form of a tetrahedron with the internal surface covered by meshlike mucosal folds. The contracted bladder has four distinct surfaces: a superior surface, two inferolateral surfaces and a base or posterior surface.[2] The bladder is made up of epithelial and connective tissues, smooth muscle, blood vessels and lymphatics. All of these components are able to stretch together as the bladder fills and to collapse as the bladder contracts. This viscoelastic property of the bladder allows for maximal storage capacity with little rise in the intravesical pressure. The anatomy of the musculature of bladder is quite complex. It is usually described as having three muscular layers: an inner longitudinal, a middle circular, and an outer longitudinal coat, but in reality it is not possible to separate them into the three layers in most of the bladder. Classically, the bladder is divided into the body and trigone. The muscle of the bladder wall or detrusor is made up of criss-crossing fascicles of smooth muscle, which have no specific direction (Figure I). However, near the bladder neck, these fibers do become arranged in more distinct layers as described above. At this level, the inner longitudinal layer, which is located beneath the vesical mucosa, runs through the bladder neck and into the urethra as its inner longitudinal layer (Figure II).

The trigone is made up of two distinct smooth muscle layers termed the superficial and deep trigones. The superficial trigone is a direct continuation of the ureteral muscle. Fibers from this superficial layer continue down toward the bladder neck and stop near the external sphincter in the male but continue almost the entire length of the urethra in the female. The deep trigone is formed by the continuation of

Waldeyer's sheath. It is a thick muscular layer at the base of the bladder near the bladder neck. There is no muscular communication between the superficial and deep trigones. However, the muscle cells of the deep layer are indistinguishable from those of the detrusor (Figure III).

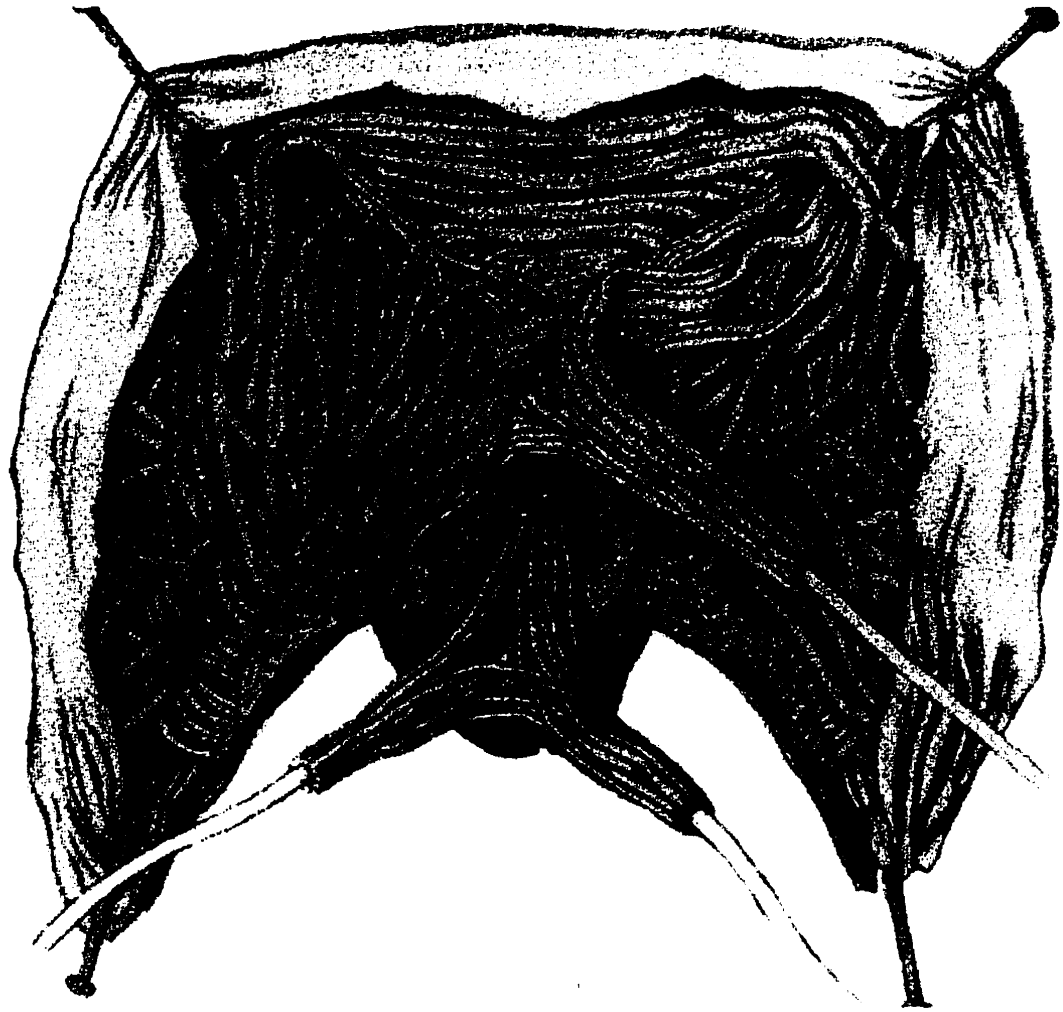


Figure I. Musculature arrangement of the bladder wall (From Tanagho, 1966).

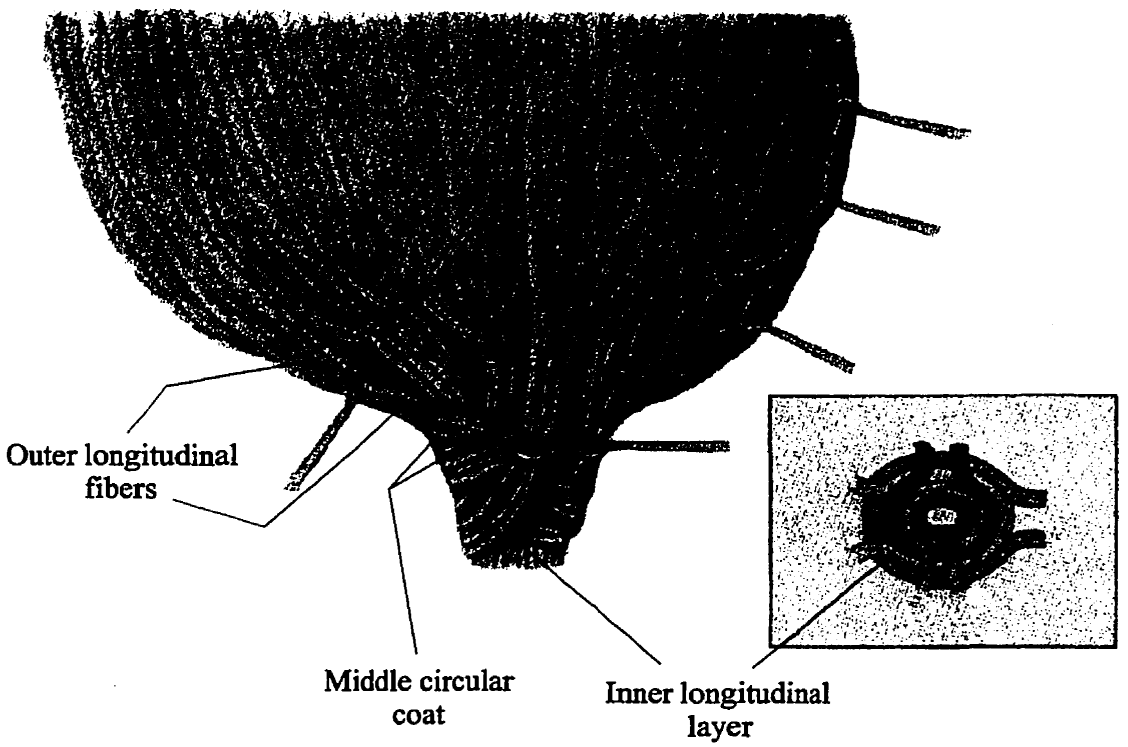


Figure II. Muscle layers at the bladder neck (From Tanagho, 1966).

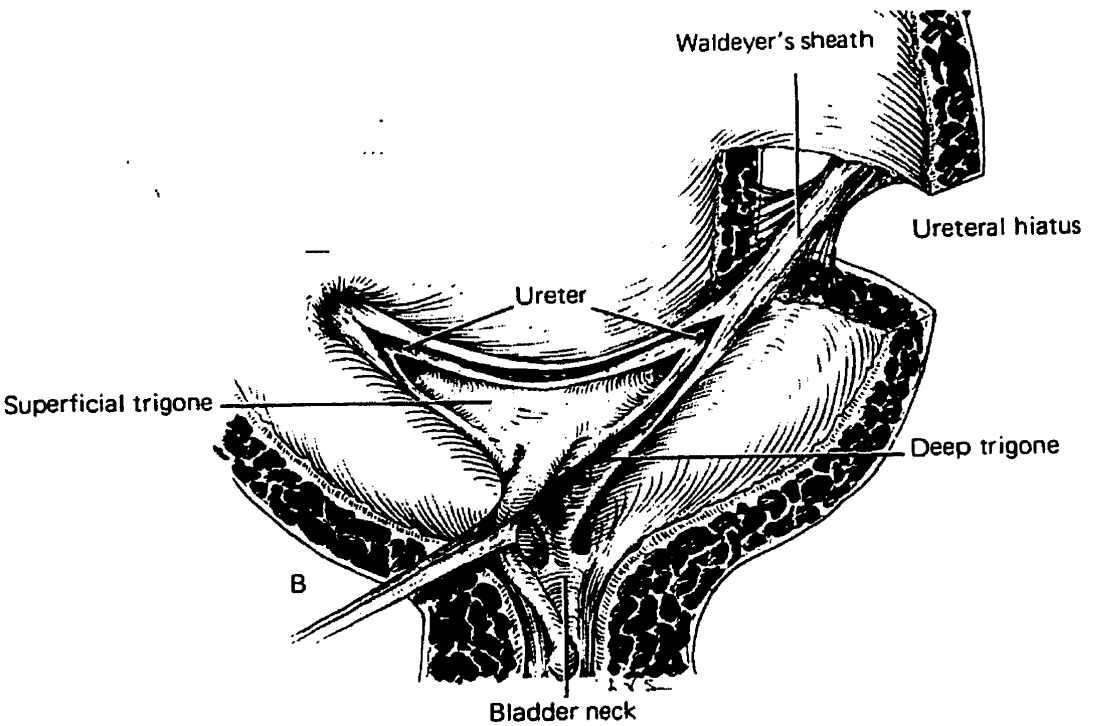


Figure III. Normal ureterovesico-trigonal complex (From Tanagho, 1963).

1.1.2 Anatomy of urethral sphincter

1.1.2.1 Internal smooth muscle component

The smooth muscle internal sphincter consists of the bladder neck and the short segment of the proximal urethra. However, there is no distinct anatomic sphincter but rather a physiologic internal sphincter in this area. The sphinteric effect of the latter is mainly dependent on the abundant amount of elastic fibers between the smooth muscle cells which arise the tone of the smooth musculature. With the progressive filling of the bladder, there is increasing tone of the smooth muscle to keep the urethral pressure higher than intravesical pressure. With voiding, this tone dramatically decreases, resulting in opening and funneling of the bladder neck.[3]

1.1.2.2 External striated sphincter

The striated sphincter has a horseshoe configuration with incomplet posterior development. It consists of intrinsic and extrinsic components. The intrinsic portion, which is also called the rhabdosphincter, is located around the membranous urethra in the male and the mid urethral segment in the female. The extrinsic component or periurethral muscle is structurally separate from the urethra and consists of a part of the levator ani muscles. This periurethral portion encircles the membranous urethra and is within the urogenital triangle of the pelvic diaphragm (Figure IV).[4]

The external striated sphincter has two types of fibers: slow-twitch and fast-twitch. Slow-twitch fibers are known as fatigue-resistant, and fast-twitch which are subdivided into fatiguable or fatigue-resistant. Despite discrepancy between authors concerning the location and exact distribution of fiber types,[5-7] it is agreed upon however that slow-twitch fibers contribute to maintaining the urethral tone and thus continence at rest. These fibers are thought to contribute to the background electromyographic activity of the urethral sphincter. The fast-twitch fibers, which are

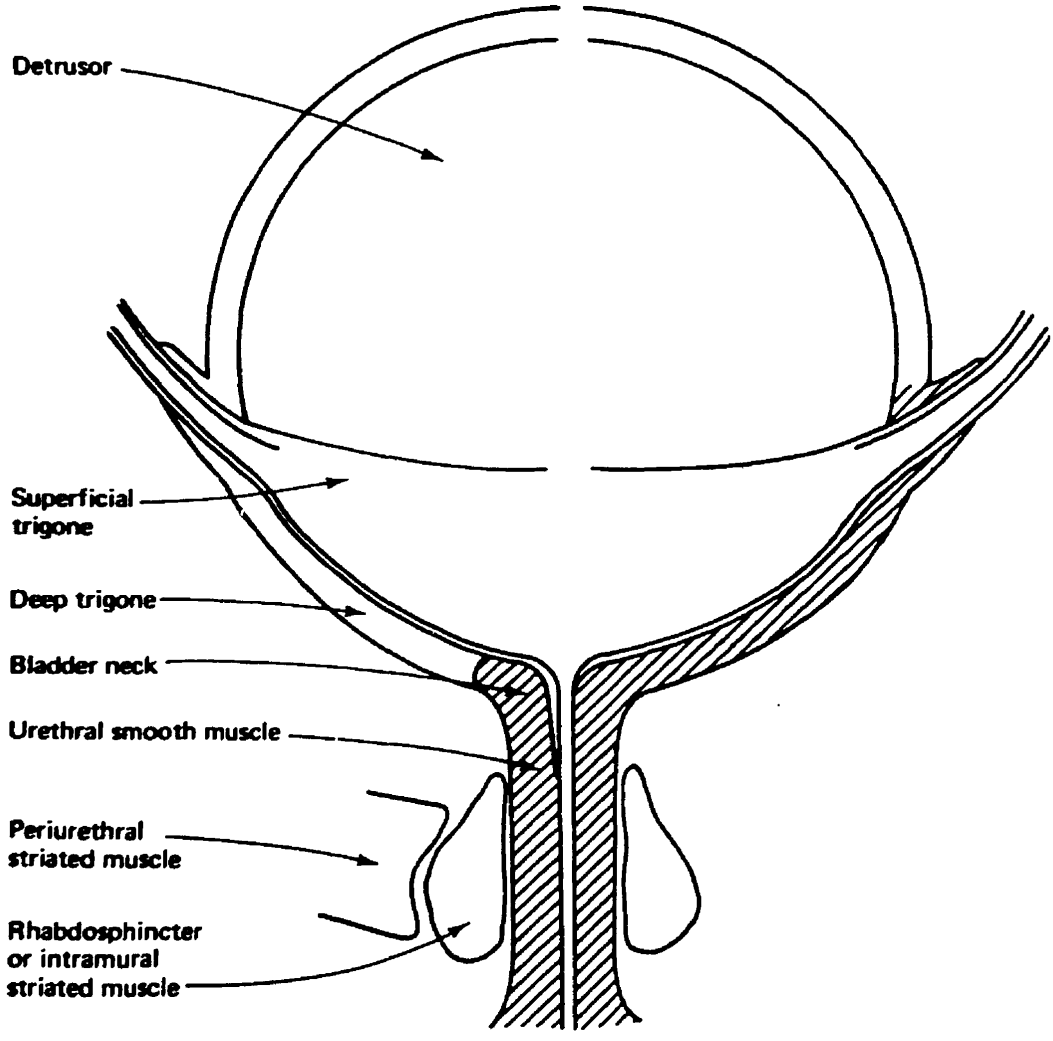


Figure IV. A view of anatomy of external urethral sphincter (From Torrens, 1987).

abundantly distributed in the periurethral muscle, are able to cause rapid contraction of the external sphincter, both to interrupt the urinary stream and to maintain continence when there is sudden rise in intra-abdominal pressure.[3,4]

Recent studies suggest that the internal and external sphincters are not working as separate entities but rather as a sphincteric unit extending from the membranous urethra to the base of the bladder.[8,9] Traditionally, the external striated sphincter is thought to be primarily responsible for maintaining continence; however, curarization of this structure does not result in incontinence except if the internal smooth muscle component has been destroyed. This evidence emphasizes the importance of the smooth muscle of the proximal urethra. Urodynamically, for continence to be maintained, the urethral pressure must exceed the intravesical pressure. There is no specific anatomic location of this critical pressure; rather, it may be anywhere along the length of the proximal urethra.

1.2 Innervation of the lower urinary tract

Voiding cycle, which includes urinary bladder storage and voluntary periodic expulsion of urine, requires integrity and coordination of the autonomic, sensory and somatic as well as central nervous systems. The neural regulation of the lower urinary tract is quite complex. Injury occurring at any level of this neuraxis leads to various types of neurogenic bladder.

1.2.1 Peripheral nervous supply

1.2.1.1 Sacral parasympathetic pathways

The micturition center in the spinal cord is primarily localized at the second to fourth sacral spinal segments in human which corresponds to the T_{12}-L_1 vertebral level. The parasympathetic efferent input to the bladder originates from the

parasympathetic nucleus, which is also called parasympathetic detrusor nucleus, and is located in the intermediolateral gray column of the S_2 to S_4 segments of the spinal cord in human and the first to third sacral segments in dog.[10] The preganglionic fibers are transported by the pelvic nerve to ganglionic cells within the pelvic plexus or detrusor muscle. Short cholinergic postganglionic fibers end at the smooth muscle receptor.

1.2.1.2 Thoracolumbar sympathetic pathways

The sympathetic efferent supply arises from the intermediolateral gray matter of the T_{11} to L_2 segments of the spinal cord in human and the first to fourth lumbar segments in dog.[10] The short preganglionic fibers pass through lumbar sympathetic paravertebral ganglia to the sympathetic prevertebral ganglia which may be located anywhere between the paravertebral ganglia and the urogenital organs. The long adrenergic postganglionic fibers are then conveyed by the hypogastric nerves or by the pelvic nerve to the pelvic plexus or the target organ of the lower urinary tract. There is compelling evidence that the pelvic nerve carries both parasympathetic and sympathetic supply.

The neural organization of the pelvic plexus is quite complex. Within the ganglia, there is interganglionic interaction between the cholinergic and adrenergic neurons. This interganglionic transmission is modulated by another cell type, also located within the ganglia, called small intensely fluorescent cells (SIF).[7,11]

1.2.1.3 Sacral somatic pathways

The external striated sphincter has somatic motor innervation. This efferent supply arises from the pudendal nucleus, which is also termed Onuf's nucleus. These motor neurons are located in the anterior horn cells of the second to fourth sacral spinal segments and are separate from the parasympathetic detrusor nucleus. The somatic impulses are then carried to the external urethral sphincter via the pudendal nerve.

Despite the anatomic difference between the somatic and parasympathetic nuclei at the sacral level, there are considerable synaptic connections between them through interneurons, such that the coordination of different components of the lower urinary tract is possible, through the interaction between autonomic and somatic afferent and efferent activity.

1.2.2 Vesicourethral sensory afferents

Afferent impulses originating from the urinary bladder and urethra are essential to activate the appropriate efferent pathways hence resulting in urine continence and voiding. There are several afferent pathways which are transmitted to the central nervous system by both autonomic and somatic nerves. In the bladder and urethra, these sensory terminals are found mainly in the submucosal and the muscularis layers. The main afferent nerves triggering the micturition in response to mechanoreceptors, tension receptors and nociceptors within the bladder wall travel via the pelvic nerve to the sacral spinal cord.[12] The sensory inputs from the posterior urethra travel to the sacral cord via the pudendal nerves. The nociceptive afferents from the bladder especially in the trigone and bladder neck are also carried by hypogastric nerves.[12] Anatomic and neurophysiological studies shown that the sacral afferents consist of small myelinated (A-delta) and unmyelinated (C) fibers. The relative contribution of A-delta and C fibers in the regulation of micturition reflex varies considerably between species,[13] however, electrophysiologic studies clearly demonstrated that only A-delta afferents did respond to bladder distension under normal physiological conditions.[14]

The small myelinated A-delta fibers have a low activation threshold and a low conduction velocity (0.3 meters/second). Their activity is initiated by the progressive bladder filling and the intravesical pressure threshold for their activation ranges from 5 to 15 mm Hg which corresponds to the pressure triggering normal, non-painful voiding in human. In contrast, the unmyelinated C-fibers possesses a fast conduction velocity

(up to 30 meters/second) and a high activation threshold.[13] Under physiologic voiding, these C- fibers afferents are silent. However, they are activated under pathological conditions such as chemical irritation of the bladder mucosa, cystitis, cold temparature or functional bladder outlet obstruction (e.g. benign prostatic hyperplasia, detrusor-sphincter dyssynergia).[13,15]

During the past decade, understanding of bladder sensory afferents has dramatically advanced with utilization of capsaicin which is a pungent ingredient from red pepper, which has the selective neurotoxin activity on C-fibers.[13] Systemic administration of capsaicin has a biphasic action on the C-fibers sensory nerves with a transient initial excitation, followed by a long-lasting inactive state. This phenomenon is called desensitization which renders the C-fibers unexcitable by physiological stimuli. These primary afferents, whose cell bodies are located in dorsal root ganglia, project their axons both to the central (spinal cord) dorsal horn and peripheral (target organ) direction. These sensory nerves have an efferent function through release of transmitters from their peripheral endings.[13]

The pelvic afferent pathways from the urinary bladder end in the sacral parasympathetic nucleus. The pudendal nerve afferent pathways from the external urethral sphincter terminate in the Onuf's nucleus. There is considerable overlapping projections between these nuclei at the spinal level. It has also been demonstrated, by physiologic and anatomic tracing techniques, that interneurons found in the spinal cord are involved in the coordination of different afferent inputs from the lower urinary tract.[15]

1.2.3 Neurotransmitters and receptors in the lower urinary tract

The traditional autonomic neurotransmitters (NTs) of the lower urinary tract are norepinephrine (NE) and acetylcholine (ACh). The preganglionic parasympathetic neurons release ACh which activates nicotinic receptors on peripheral ganglion cells. The post ganglionic parasympathetic neurotransmitters is also ACh. This latter has its main action on cholinergic muscarinic receptors which are located especially in the bladder body and to a lesser extend in the bladder base. Currently, five types of muscarinic receptors have been identified pharmacologically: $M_1$to M_5. [16] The distribution of these subtypes of muscarinic receptors varies according to the target organ. In general, cholinergic transmission in the human bladder is predominantly mediated by M_2, while M_1 receptors prevail at the ganglia and secretory glands.

The postganglionic sympathetic NT is NE. Adrenergic receptors where NE exert its action are subdivided into two categories: α or ß. Classically, α-adrenergic effects consist of vasoconstriction and contraction of the smooth muscle. ß-adrenergic effects include cardiac stimulation, vasodilation, bronchodilation, and other types of smooth muscle relaxation. The α-adrenergic receptors are further classified as α_1 and α_2. The relative distribution and density of α_1 and α_2 receptors varies between species. Levin et al[17] demonstrated that human bladders contain 80% α_1 and 20% α_2 receptors. The majority of α_1-adrenergic receptors in the lower urinary tract is concentrated at the bladder base and urethra.

The ß-adrenergic receptors have been characterized $ß_1$, $ß_2$ and $ß_3$. Bladder detrusor contained primarily $ß_2$-receptors with a minor $ß_1$ component.[18] The $ß_2$ adrenoceptors are responsible for bladder smooth muscle relaxation.

For many years, acetylcholine and norepinephrine were recognized as the only excitatory and inhibitory NT_s of the lower urinary tract. However, it has become

obvious that other transmitters termed non-adrenergique non-cholinergique (NANC) might also be present in the autonomic nervous system. These NT_s, which can be co-transmitters released along with a classical NT, can act as a NT or a neuromodulator.[19] The co-transmitter may have a direct action on post junctional cells or may facilitate the action of the classical NT and/or act as an inhibitor of its release. This concept of co-transmitter may explain the inability of traditional cholinergic and adrenergic antagonists such as atropine and prazosin to completely abolish the contractility of bladder and urethral smooth muscle evoked by neural stimulation.

Among these NANC neurotransmitters, adenosine triphosphate, a purinergic nucleotide, has been demonstrated as an excitatory NT involved in the bladder response to pelvic nerve stimulation in experimental models.[19] There is convincing evidence that several neuropeptides affect the lower urinary tract function. Of the peptide-containing nerves, vasoactive intestinal polypeptide (VIP) is widely distributed within the detrusor muscle, especially in the submucosa and muscularis layers. The inhibitory effect of VIP on bladder smooth muscle contractility is variable according to species and controversial. It seems to play a role in the modulation of cholinergic transmission.[20]

Neuropeptide Y is frequently co-localized with norepinephrine in sympathetic nerves. Its bladder distribution is similar to that of VIP and it acts as potent stimulant of smooth muscle.[21] There is considerable evidence that tachykinins such as substance P and neurokinin A and calcitonin gene-related peptide (CGRP) are transmitters in sensory nerves and it is likely that these nerve fibers existing in the subepithelial layer of the bladder represent the terminal endings of the bladder sensory afferents.[19] Tachykinins and CGRP released from the peripheral terminals of these C-afferent fibers are responsible not only of sensory afferent function mediation in the spinal cord but also of a local efferent effects such as changes in smooth muscle activity, vasodilation, and increase in vascular permeability in the bladder and urethra.[13]

The above mentioned NT_S and other neuropeptides identified within bladder detrusor and urethra innervation include as well as enkephalin and somatostatin. Recently, nitric oxide synthase has been localized in the smooth muscle of the urethra and parasympathetic post ganglionic neurons from a variety of species .[22] Pharmacological studies provided evidence that nitric oxide is implicated as a NT or neuromodulator mediating relaxation of the urethral smooth muscle. [23-26]

In summary, the integration of the nervous control of the urethra and bladder occurs not only by the anatomical overlap of the neural pathways but also by the functional interactions of a variety of NT_S, classical or non classical, and/or neuromodulators which have been identified in neuronal cell bodies and peripheral axonal endings.

1.2.4 Central nervous system influence on micturition

It is well recognized that normal micturition is not only a spinal reflex mediated by the parasympathetic nervous system. It is clear that the sympathetic and the parasympathetic pathways of the autonomic nervous system act in harmony with the somatic motor nervous system through the coordination by higher centers in the brain. These latter have both inhibitory and facilitatory influences on the reflexes involved in the micturition.

The ascending sensory routes responsible for transmitting bladder sensation and triggering micturition travel in the lateral spinothalamic tract and posterior column of the spinal cord.[27] These axons are known to synapse in different areas of the brain. The descending central control of the lower urinary tract starts at the pontine-mesencephalic reticular formation. This micturition center, which has also been called Barrington's center [28], initiates the voiding by sending facilitatory impulses to the sacral parasympathetic motoneurons. In animal models with an intact neural axis, this

supraspinal reflex pathway is the most prominent to induce bladder emptying. This area plays also a role in sphincter-detrusor coordination because in addition to causing a bladder contraction, when it is stimulated, there is likewise a decrease of electromyographic activity in the external urethral sphincter thence complete expulsion of bladder content. This is achieved by simultaneous inhibition of the somatic pathway to the urethral sphincter through sacral Onuf's nucleus (Figure V). [27]

There is evidence that other areas of the central nervous system also have an influence on micturition. Animal studies have revealed that stimulation of specific areas of the cerebral cortex may facilitate or inhibit detrusor muscle contraction. The overall effect of the frontal lobe on bladder activity is inhibitory since lesions of these areas of whatever nature may increase the bladder activity hence reducing the bladder capacity.[29]

The cerebellum is involved in maintaining the tone of pelvic floor musculature and external urethral sphincter. It also influences detrusor activity by primarily modulating the activity of Barrington's center. Ablation of the anterior vermis in experimental animals produced detrusor hyperactivity. [30]

The midbrain comprising various ganglia such as caudate nucleus, putamen, globus pallidus and substantia nigra has also been found to be involved in modulating the central inhibitory effect on detrusor contraction. [31] This finding may be a possible explanation for the development of detrusor hyperactivity often seen in patients with Parkinson's disease with basal ganglia dysfunction.

Thus far, the voluntary and physiological micturition, in the presence of normal intact neuraxis, involves the spinobulbospinal pathways which is mediated by myelinated A-delta fibers. Any condition that causes interruption of the central nervous system coordination, such as suprasacral spinal cord injury, will result in a spinal voi-

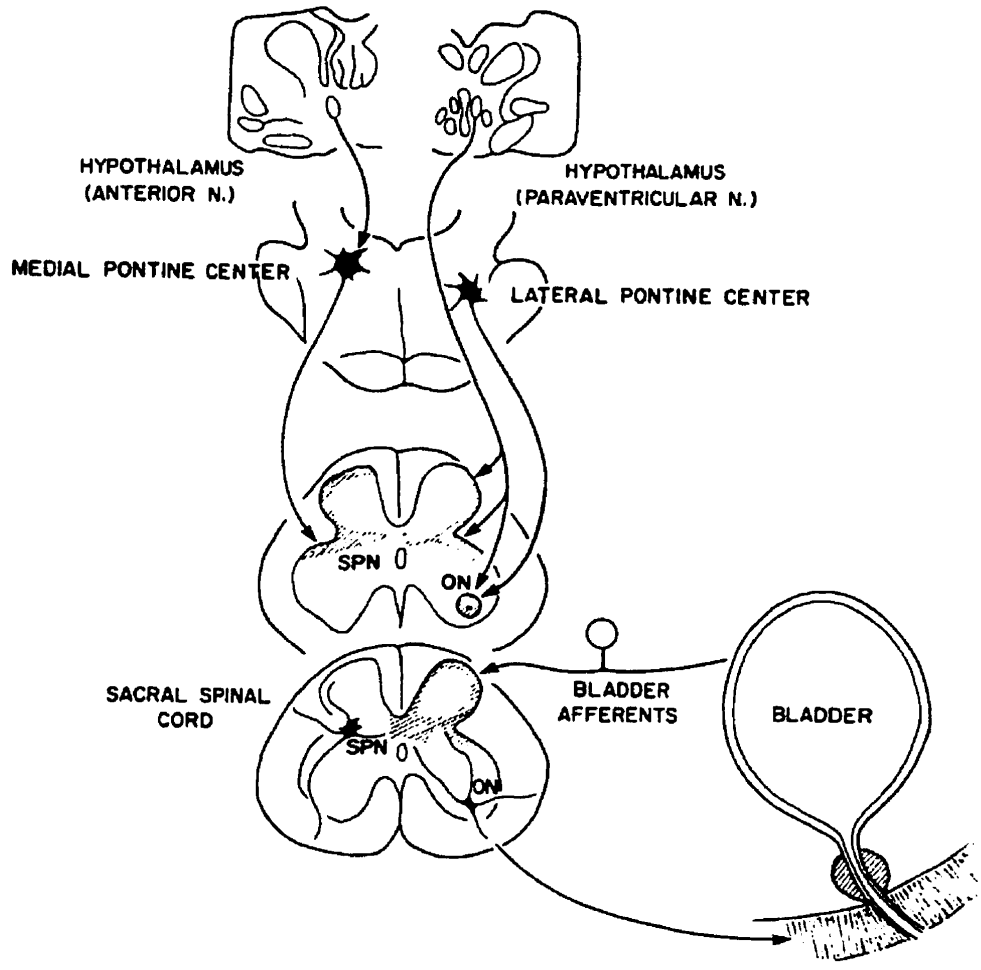


Figure V. Neural connections between the brain and the sacral spinal cord: the medial pontine center is postulated to regulate the voiding through sacral parasympathetic nucleus (SPN). The latteral pontine center is involved in urethral and pelvic floor striated muscle activity through Onuf's nucleus (ON) (From de Groat, 1990).

ding reflex triggered by C-unmyelinated bladder afferents. This spinal reflex will result in an involuntary or automatic voiding.

1.3 Neurophysiology of urinary bladder

The urinary bladder acts as a reservoir whose function is to store urine at low intravesical pressure and periodic emptying of its content by coordinated bladder contraction and urethral relaxation which results in a low voiding pressure.

During the initial bladder filling, there is little change in intravesical pressure because of the passive accommodation due to the intrinsic viscoelastic property of the bladder. With further filling, the sympathetic efferents are active and these produce an increase contraction of the bladder neck and urethra via activation of α-adrenergic receptors and relaxation of bladder body via activation of ß-adrenergic receptors. There is also evidence that the sympathetic stimulation inhibits excitatory parasympathetic ganglionic transmission thus keeping the parasympathetic efferent quiescent. [15] As the filling continues, the electromyographic activity of external urethral sphincter rises progressively due to increased somatic discharges via the pudendal nerve (Table I). [32] This phenomenon has been called the "continence reflex". There is also evidence that suggests that the somatic activity inhibits the parasympathetic detrusor nucleus. When there is a sudden rise in intra-abdominal pressure during the filling phase, continence is still maintained by a transient increase in firing to the external urethral sphincter thus promoting the guarding reflex which keeps the urethral pressure higher than that of the bladder.

Voiding is initiated by a fall in urethral pressure through inhibition of the sympathetic and somatic efferents which is immediately followed by activation of parasympathetic outflow resulting in sustained bladder contraction with a rise of intravesical pressure (Figure VI).

Table I Reflexes to the Lower Urinary Tract

Afferent Pathway	Efferent Pathway	Central Pathway
Urine storage, low-level vesical afferent activity (pelvic nerve)	1. External sphincter contraction (somatic nerves) 2. Internal sphincter contraction (sympathetic nerves) 3. Detrusor inhibition (sympathetic nerves) 4. Ganglionic inhibition (sympathetic nerves) 5. Sacral parasympathetic outflow inactive	Spinal reflexes
Micturition, high level vesical activity (pelvic nerve)	1. Inhibition of external sphincter activity 2. Inhibition of sympathetic outflow 3. Activation of parasympathetic outflow	Spinobulbospinal reflexes

From de Groat, 1993

In summary, urinary bladder storage or emptying is a coordinated event which requires the integration of parasympathetic, sympathetic and somatic nervous systems at the level of spinal cord, which is under the control of higher centers in the brain.

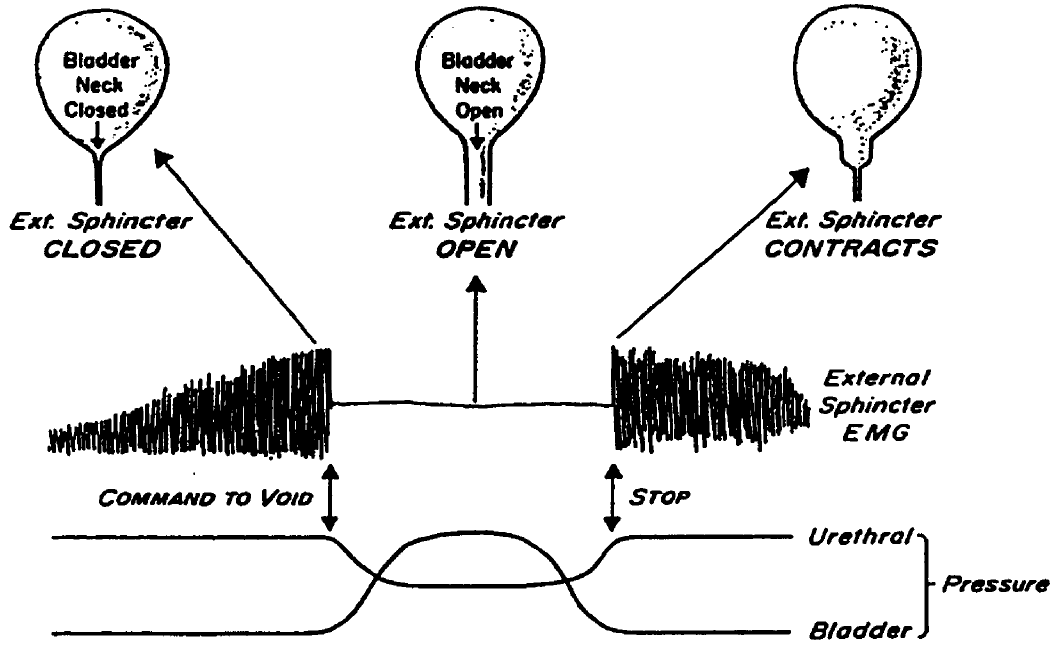


Figure VI. Physiology of micturition (From Blaivas, 1980).

CHAPTER 2

SPINAL CORD INJURY

2.1 General considerations of spinal cord injury

Spinal cord injury (SCI) is one of the most challenging clinical problems in urologic practice. The incidence of SCI has significantly decreased during peacetime. In the United States, the annual incidence of SCI is estimated at 30 per one million of population. [33] The prevalence of SCI is approximately 900 per million population. The majority of SCI occurs in young male patients. There is as many as 85% of injuries occuring in men with the peak incidence being in the 16 to 30 age group. Most spine injuries occur at the cervical region and the thoracolumbar junction. Approximately 55% of patients with SCI are quadriplegic while the remainder develop paraplegia. [34] The incidence of neurologically incomplete injuries is estimated at about 54%. Nevertheless, recent evidence shows that the incidence of incomplete injuries is steadily increasing which is likely related to the improved quality of emergency care in transport and improved early care in SCI. Currently, the most common cause of SCI are motor vehicle accidents accounting for 50%, falls (20%), sports such as diving (15%) and acts of violence (15%). [33]

2.2 Bladder dysfunction in spinal cord injury

SCI can result in varying degrees of dysfunction of the lower urinary tract due to the numerous type of possible lesions. The complete injuries provide the clearest urological picture. A complete lesion is considered when there is complete loss of voluntary motor and sensory function below the level of the lesion. While incomplete injuries imply either that some sensation and/or voluntary motor activity is present. The recognition of the segmental level of the spinal cord lesion is also important because it can predict the long-term behaviour of the urinary bladder dysfunction. If the injury occurs to the spinal cord above the conus medullaris, which is also termed upper motor

neuron or suprasacral lesion, it usually results in reflex bladder meaning detrusor hyperreflexia (DH) with various degrees of detrusor-external sphincter dyssynergia (DESD). If the injury occurs through the conus medullaris or cauda equina, it generally results in an areflexic bladder.

Immediately following the SCI, whatever the level of the lesion, there is a period of bladder areflexia termed spinal shock phase. During this period, there is an areflexia accompanied by atonic paralysis of the bladder, and bowel as well as complete loss of sensory and motor control below the level of injury. However, both rectal and urethral sphincter intrinsic activity persist.[35] The urinary incontinence encountered in this period is by overflow as the pressure in the overdistended bladder overcomes urethral resistance. The duration of the spinal shock varies widely from few days to several weeks. Although the pathophysiology of spinal shock is not completely understood, most investigators agree that its occurrence after SCI is due to suppression of autonomic activity.[35]

Following recovery from spinal shock, the neurogenic bladder pattern progressively appears. In patients with lower motor neuron lesion, detrusor areflexia is generally persistent and the patient can be managed by clean intermittent catheterization (IC). Nevertheless, some of these patients will eventually develop poor bladder compliance which can jeopardize the upper urinary tract because of the elevated intravesical pressure during bladder filling. Thence, periodic and long-term follow-up of all patients with SCI is mandatory.

In patients with suprasacral spinal cord lesions, the development of detrusor hyperreflexia is almost invariably a rule. These uninhibited reflex bladder contractions can be associated with or without DESD. Classical DESD is seen between 70-100% of patients with suprasacral SCI especially in complete thoracic and cervical lesions. Blaivas et al [35] reported that DESD was found in 96% of their series of patients with

suprasacral SCI. It refers to the loss of synergistic coordination between the detrusor and external urethral sphincter characteried by an inappropriate increase in external urethral sphincter activity which take place during an involuntary detrusor contraction (Figure VII). [34] In other words, DESD leads to a functional outlet obstruction state thence inducing a high intravesical pressure during bladder contraction which can potentially put the upper urinary tract at risk for damage. Moreover, DESD results in incomplete bladder emptying leading to high residual urine volume.

2.3 Pathophysiology of the neurogenic bladder associated with suprasacral Spinal cord injury

Following the complete suprasacral spinal cord transection, the normal spinobulbospinal micturition reflex pathways that go through the pontine micturition center are lost. After the initial acute spinal shock phase as described previously, reflex voiding ensues by DH resulting from a reorganization of the micturition reflex pathways in the sacral spinal cord. These spinal reflexes are not efficient enough to empty the bladder owing to the DESD.

Great strides have been achieved in the field of SCI bringing new information on the pathophysiology of the urinary bladder dysfunction in suprasacral SCI. As discussed earlier, in animal experiments with an intact spinal cord, the main afferent inputs to the micturition reflex consist of myelinated A-delta fibers. Whereas in chronic spinalized cat, electrophysiologic studies have shown that the afferent limb is mediated by unmyelinated C-fibers which form the short latency spinal reflex. [36] This neural pathway has, once again, been confirmed by de Groat et al which used the C-fiber neurotoxin, capsaicin. In normal animals, capsaicin did not block the A-delta fibers evoked bladder contraction. However, in chronic spinalized animals, systemic administration of capsaicin abolished the detrusor contractions induced either by the

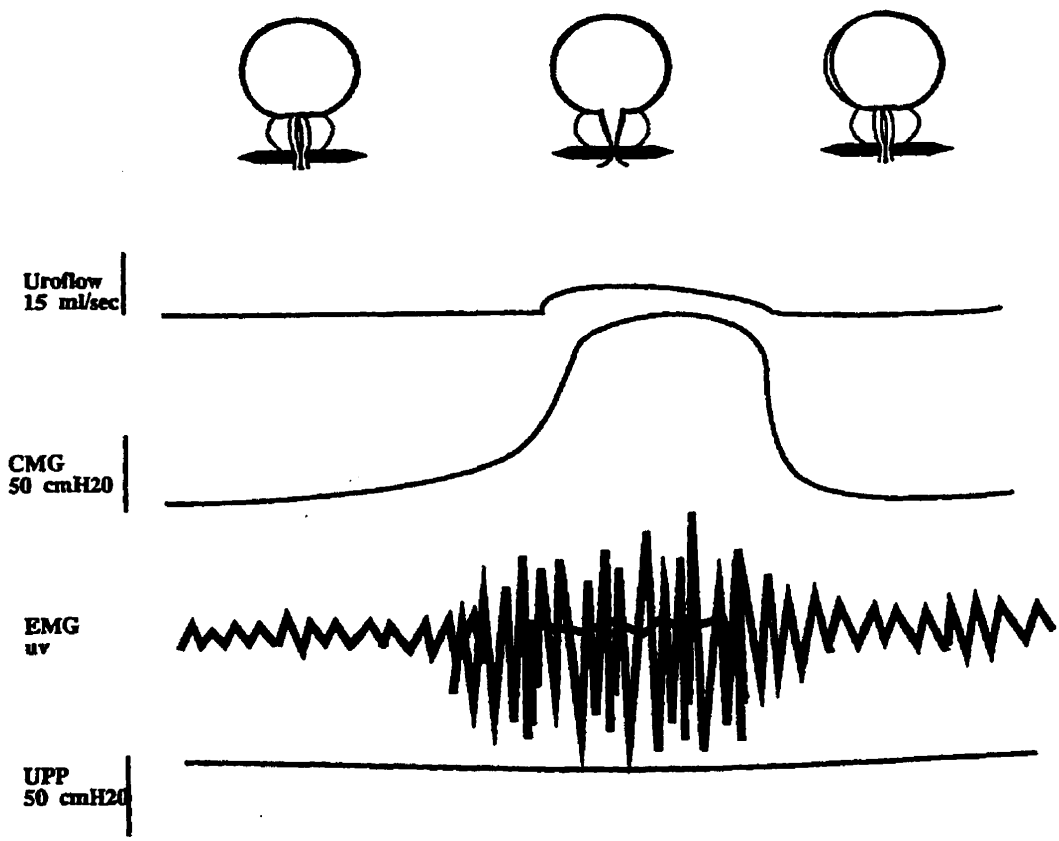


Figure VII. Detrusor-external sphincter dyssynergia (From Chancellor, 1993).

bladder filling or the C-fibers evoked reflex (Figure VIII).

Several mechanisms have been proposed to explain the appearance of reflex bladder contractions and C-fiber evoked spinal micturition reflexes in SCI. [15] First, the disruption of central inhibitory descending pathways has given opportunity to the emergence of other types of reflexes. Secondly, there is an increase in preexisting synaptic connections or formation of new synapses resulting from axonal sprouting following the SCI. An increase in the C-fiber afferents marker have been shown, as an increased VIP immunoreactivity, in the spinal cord.[36] Moreover, there is alteration of several putative NT_S not only in their synthesis or release in SCI but also in their function. Intrathecal administration of small doses of VIP, which normally reduce bladder activity, produce bladder contraction in chronic spinalized cat . [36] Other authors have suggested the involvement of neurotrophic factors such as nerve growth factors (NGF) in the urinary bladder, after spinal cord transection, responsible for the re-adjustment of neural reflexes. In fact, the functional outlet obstruction due to DESD can, to some extent, cause morphological and neuronal changes in the urinary bladder and spinal cord similar to that of obstruction following partial urethral ligation. Steers et al [37-40] have demonstrated that the bladder hypertrophy observed in animals having partial outlet obstruction is associated with neuronal hypertrophy, afferent axonal sprouting at the spinal level and development of peripheral reflexes. These changes are accompanied by an augmentation of the levels of NGF either in the bladder or in the spinal cord. Furthermore, the neuroplasticity of the afferent neurons has been confirmed in spinal cord transected animals. [41-43]

Other convincing evidence of the reorganization of sacral spinal center has been demonstrated by the re-emergence of the primitive or neonatal excitatory somatovesical reflex. These reflexes ensure the bladder evacuation in neonates by stimulating

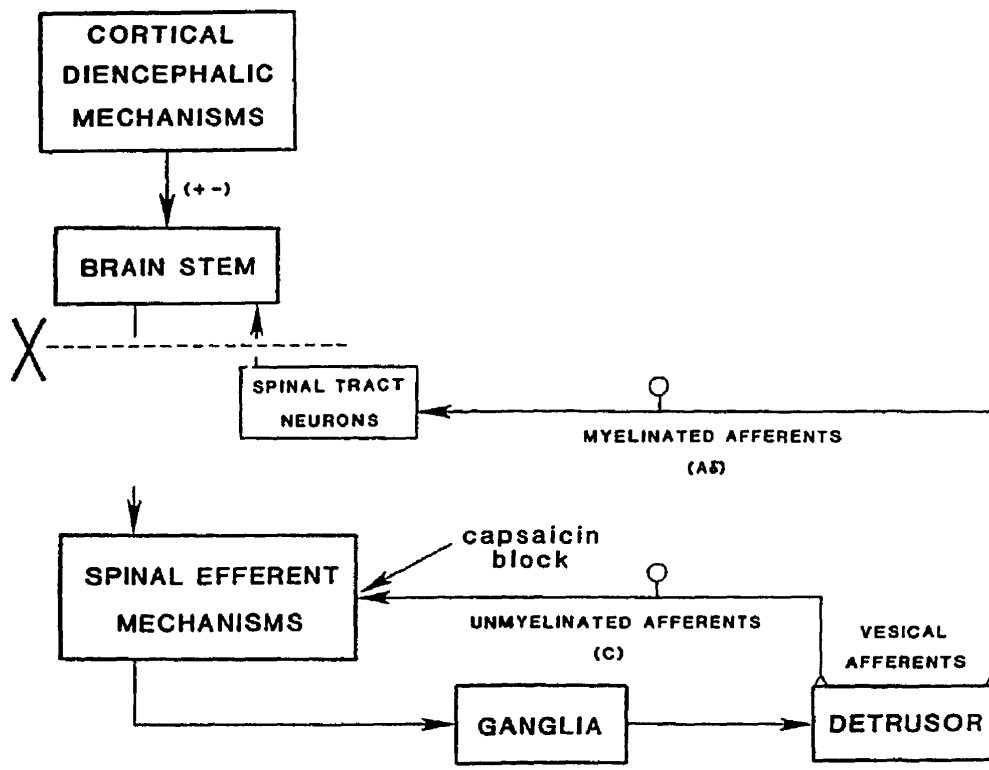


Figure VIII. Diagram of the central reflex pathways regulating micturition in the cat (From de Groat, 1990).

cutaneous regions which correspond to sacral dermatomes which have disappeared during the maturation of the central nervous system. In spinal cord injured patients, this excitatory somato-bladder reflex reappears and possibly caused by expansion of afferent terminals at the spinal level.

In conclusion, the reorganization of sacral spinal micturition reflexes is essential to facilitate the automatic voiding resulting from uninhibited bladder contractions in suprasacral SCI. This condition involves multiple mechanisms including alteration of NTs synthesis and function, neuroplasticity, and the loss of the central micturition control.

2.4 Management of suprasacral spinal cord injury

The primary urological management of spinal shock phase is directed at bladder emptying. The quantity of urine output varies widely in this acute phase. Most patients have an initial period of low urine output secondary to trauma-induced antidiuresis which is then followed by a period of brisk diuresis. To adequately monitor fluid balance and to prevent bladder overdistention, indwelling Foley catheter is recommended as the standard choice for the initial continous bladder drainage. Suprapubic catheterization is a substitution of choice when urethral manipulation is contraindicated. Some authors have advocated that the method of treatment chosen during the early phase (indwelling Foley catheter, IC or suprapubic catheterization) can influence the long-term urological outcome. However, Lloyd et al [44] have demonstrated in their prospective study at one year of follow-up post injury that there was no difference in the morbidity associated (urinary tract infection rate, renal function, urological complication, etc.) whatever the option employed. Previous work in our laboratory have evaluated the role of sacral root stimulation compared to the IC in

the canine model during the spinal shock phase. Electrical stimulation shortened the time required for the recovery of detrusor activity and significantly decreased the rate of urinary tract infection rate. [45]

Once the patient is stabilized, IC can be instituted during the spinal shock period prior to the return of reflex voiding activity. The long-term major goal of urologic management is preservation of upper urinary tract integrity. In suprasacral spinal cord injured patients, reflex bladder contractions return generally after several weeks (2-8 weeks).[34] These contractions may be brief, low-level contraction initially, replaced by prolonged, forceful contraction and eventually DH may progressively appear. Moreover, the progressive development of DESD will eventually lead to incomplete bladder emptying with high storage pressure and high voiding pressure and elevated residual volume.

The aims of DH and DESD management are to ensure a low pressure urine storage, a low pressure and efficient urine emptying with minimal residual urine volume, control of DH and catheter-free state. The DH can be usually controlled by pharmacologic agents such as musculotropic relaxants or anticholinergic agents inhibiting the bladder contraction. In few resistant cases, peripheral denervation to decrease sensory afferent input can be considered and occasionally surgical augmentation cystoplasty should be comtemplated for patients with DH associated with poor detrusor compliance in whom conservative treatments failed. [46] Recently, intravesical administration of capsaicin in these patients has been reported and seemed to be promising [47], however, controlled and prospective study is needed to confirm its clinical application.

Multiple treatment modalities have been attempted to overcome the high bladder outlet resistance due to DESD in order to obtain adequate bladder evacuation. Clean intermittent catheterization is frequently used in paraplegics. In quadriplegic patients,

this may be difficult. Therapy can be targeted at different levels. [46] Alpha-adrenergic antagonists have been used by some authors to reduce the internal smooth muscle tone of the urethra, but a beneficial effect on DESD has not been demonstrated. [48] At the striated external sphincter level, surgical sphincterotomy with an external collecting device is still a frequent treatment for DESD. This procedure has been shown to be effective for improving bladder emptying, however, it has been criticized for its irreversibility and high reoperation rate. Pharmacologic therapy has also been tried in order to reduce the activity of striated external sphincter by skeletal muscle relaxant, though the results are not satisfactory.

Pudendal neurectomy has been condemned because of its major adverse effects on erectile and anal function. Attempts have been made to establish non-invasive and reversible alternatives dealing with DESD. Botulinum-A toxin which is an inhibitor of presynaptic Ach released at the neuromuscular junction produces a paralytic action at the external urethral sphincter when it is injected transurethrally or transperineally. Preliminary results of this "pharmacological sphincterotomy" seemed promising [49] but its future role remains to be clarified. Another option is the use of implantable urolume sphincter stent prosthesis. Chancellor et al have recently reported promising data comparing its use versus classical sphincterotomy. Although urethral stent appears to be attractive, the major drawbacks of this alternative are the potential early migration, the unknown long-term effect of implanted foreign materials and urethral mucosal hyperplasia. [34,50,51]

As a last resort an indwelling urethral or suprapubic catheter may be used. This option should be considered only in rare selected cases where other modalities of treatment have all been attempted unsuccessfully. One should keep in mind that this option is associated with significant complications including infection, stones, urethral stricture and fistula, pyelonephritis, and even bladder carcinoma.

Finally, neuromodulation of the lower urinary tract using electrical stimulation has been studied in the last few decades in an attempt to achieve functional, near physiologic and controlled micturition in suprasacral SCI. Chapter 3 will discuss all aspects of neurostimulation that have been reported in the litterature.

CHAPTER 3

NEUROSTIMULATION IN SUPRASACRAL CORD INJURY INDUCED NEUROGENIC BLADDER

3.1 Introduction

The management of neurogenic bladder secondary to suprasacral SCI has evoked great concern and challenges since the urinary tract complications have been the major source of morbidity and mortality in these patients. Interest in the electrical control of neurogenic bladder dysfunction began since the middle of the nineteenth century. Many attempts have been described, both in animal and human research, to induce bladder evacuation through implantable electrodes. There are several potential sites where application of implantable devices have been reported to induce bladder emptying. Initially, most reports related to the direct stimulation of the detrusor or pelvic nerve or sacral spinal cord. Sacral nerve root stimulation was then attempted since it offers an easy access for the implantation of electrodes because of its relatively long course within the spinal canal.

3.2 Direct detrusor stimulation

Direct application of electric stimuli to the detrusor muscle have been explored in the 1960s. [52-58] Among the advantages, ease of electrode placement and high specificity of the target organ have been reported. Electrodes were implanted into the bladder wall on the anterior and posterior surfaces (Figure IX). Electrical stimuli were applied to each electrode to obtain adequate detrusor contractile responses with subsequent rise of intravesical pressure to overcome urethral resistance. The voltage of stimulation ranged between 5-25V, frequency was 20-25 cycles per second and pulse width was 1-8 msec. [57,60] Early results were encouraging but long-term stimulation revealed several problems inherent in this technique of electrostimulation of the bladder. Electrode malfunction and displacement have been reported. There were also

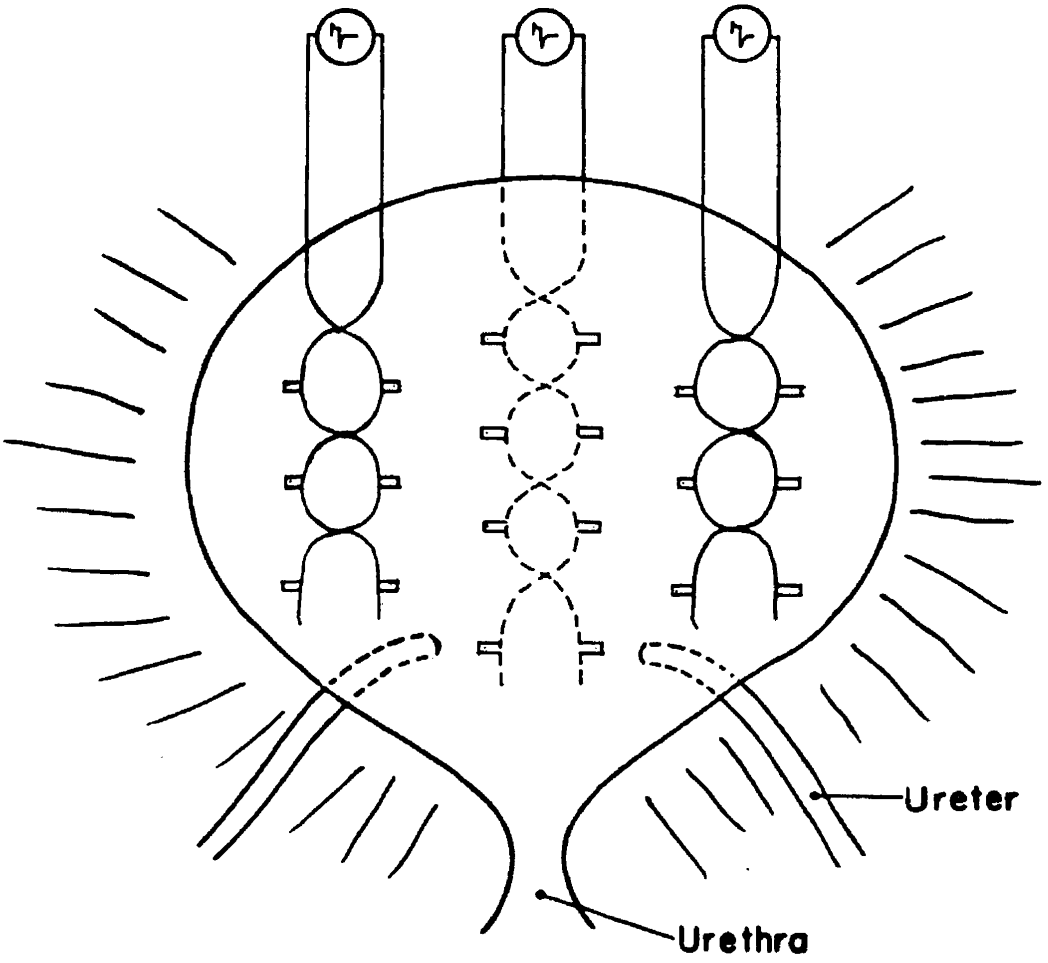


Figure IX. Diagram of electrodes placement in direct detrusor stimulation (From Timm, 1969).

increased production of bladder fibrosis and occasionally, electrode migration into the bladder. Furthermore, electrophysiologic studies showed that urethral resistance increased steadily while contraction of the detrusor became weaker thus compromising the bladder emptying. Another drawback was that the detrusor muscles became progressively refractory to prolonged stimulation in spite of increased current density. Finally, the stimulation resulted in abdominal and perineal pain and spasm of the pelvic diaphragm and adductor muscles of the lower extremities in incomplete paraplegic patients due to the spread of electrical stimulus to the surrounding pelvic structures. These drawbacks have lead to the abandonment of direct detrusor stimulation techniques.

3.3 Spinal cord stimulation

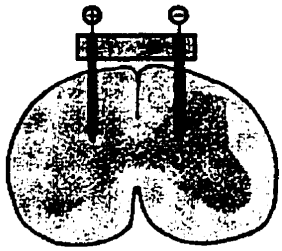
Since direct detrusor stimulation had limited clinical success in an attempt to achieve bladder emptying other alternatives were considered. Some researchers focused on electrical stimulation of the spinal cord or conus medullaris to induce micturition. [59-63] The principle of this method was based on the fact that micturition center is located in the sacral spinal cord, thence stimulation at this level would theoretically initiate voiding. Initial trials using surface electrodes applied on the spinal cord, did not seem to produce the expected results. Different types of electrodes were then designed including implantable electrodes with many variations: bipolar, coaxial, tripolar, etc. (Figure X), to optimize the stimulation by reducing the current spread and activating mainly the parasympathetic neurons located in the area of the intermediolateral gray matter. The parameters of stimulation giving the highest detrusor response varied between 2 to 5 volts amplitude, 10 to 15 cycles per seccond frequency and pulse duration of 1 msec.[62]

The data from these attempts to achieve bladder emptying with spinal cord stimulation were somewhat disappointing. First, the detrusor responses to stimulation were similar regardless of the type of electrode employed. It was then soon observed that the strong detrusor contraction generated by electrical stimuli was associated with simultaneous high sphincteric contraction thus preventing adequate voiding. However, Jonas et al [63] showed that a small amount of urine was expelled at the end of each stimulation in animals with high spinal cord transection. This phenomenon of post-stimulus voiding was explained by the fact that the striated urethral musculature reacts differently to stimulation when compared to detrusor smooth muscle. Stimulation of the former arises as well as drops the pressure at a sharp and abrupt rate, whereas stimulation of the latter produces more prolonged response. Thus, when the stimulus was turned off, there was a brief period of time where the intravesical pressure was higher than the outlet resistance resulting in a spurt of urine. Based on this observation, the investigators proposed the use of a train of short stimuli to achieve bladder emptying avoiding the need for pudendal neurectomy or sphincterotomy or drug blockade (Figure XI). But soon after its application, this attractive form of electrically induced micturition has been found to be unsatisfactory because of the elevated unphysiological voiding pressure.

3.4 Pelvic nerve stimulation

Direct pelvic nerve stimulation has been attempted to initiate voiding. [64-66] However, shortly after its introduction, several investigators have reported the disadvantages of this method. The electromicturition induced by the stimulation was again an unphysiological event since there was no relaxation of urethral musculature preceding or during the detrusor contraction. This was due to an antidromic stimulation from the pelvic nerves to the pudendal nerves which innervate the external urethral

A



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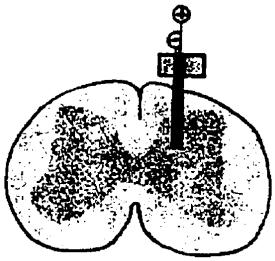

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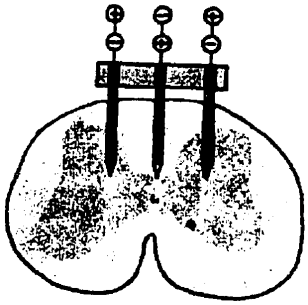

Figure X. Various types of depth electrodes used in spinal cord stimulation: A: Bipolar horizontal electrode, B: Coaxial unilateral electrode, C: Tripolar electrode (From Jonas, 1975).

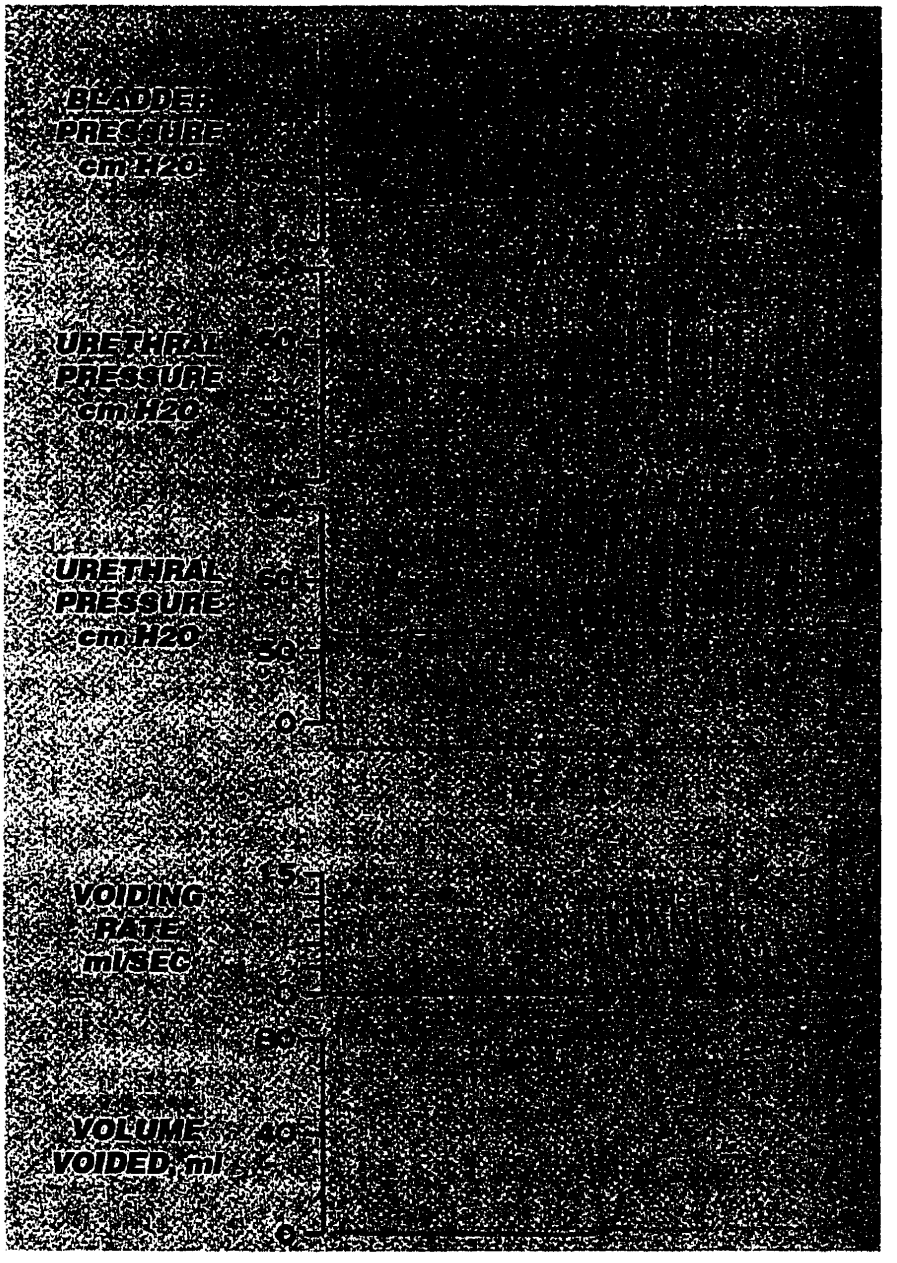

Figure XI. Diagram of poststimulus voiding (From Jonas, 1975).

sphincter. To overcome this high outlet resistance and obtain bladder emptying, Holmquist et al [66] proposed bilateral pudendal neurectomy. Moreover, it has been shown that the use of pelvic nerves were not appropriate for long-term stimulation and nerve damage can occur owing to the too close contact between the nerve and the electrode. Finally, few publications in human reported pain secondary to simultaneous activation of sympathetic hypogastric nerve.

3.5 Sacral nerve root stimulation

Data obtained by direct spinal cord stimulation showed an overlap between the sacral spinal cord detrusor parasympathetic nucleus and pudendal somatic center. It was impossible to stimulate them individually, leading to failure to initiate physiologic micturition pattern. Investigators have then focused their research on sacral root stimulation in an attempt to identify a specific sacral nerve root which innervates mainly the detrusor muscle without activation of sphincteric mechanism. This procedure can be performed either intradurally or extradurally within the spinal canal after an extensive sacral laminectomy from L7 to S3 in the dog. The intradural technique was first developed by Brindley [67-72] to facilitate the separation of anterior or ventral from posterior or dorsal roots. An extradural approach was subsequently proposed by Tanagho and Schmidt where sacral spinal nerves were stimulated extradurally via a cuff or helical electrode. [73-77]

Root identification was obtained by electrical stimulation and urodynamic measurement of bladder and urethral pressure. Occasionally, electromyogram of external urethral sphincter and/or evoked potential were recorded. The neuroanatomy of the sacral root in canine model differs from the human. In dog, stimulation of S1 root induces an increase in intraurethral pressure with minimal change in the intravesical pressure. Stimulation of S2 elicits generally strong bladder contraction associated with

various degrees of sphincteric contraction. Whereas S3 root stimulation produces usually weak detrusor response and minimal striated muscle activation. In human, S2 root innervates a variety of muscles in the lower limb and provides sensation to the perineum, its stimulation elicits especially motor response of the lower extremity with little perineal activity but no bladder response. S3 root carries mainly the innervation of the detrusor and also of muscles of the pelvic floor, its stimulation usually produces detrusor and urethral activity as well as anal sphincteric contraction. S4 stimulation generally elicits contraction of levator ani and occasionally a detrusor response. Thus, third sacral root is the main component involved in human neurostimulation application while second sacral is chosen in dog experiments.

The intradural and extradural techniques are two parallel approaches to bladder stimulation. The strength of one constitute the weakness of the other. The main advantage of the intradural implantation of electrode approach is the ease of separation of the ventral and dorsal root components. However, it involves violation of the dural sac which might be complicated by cerebrospinal fluid leakage, myelomeningitis and risk of anterior root damage due to manipulation. In contrast, the extradural method facilitates the access to the sacral root without opening of the dura or the epineurium thus lessening the risk of nerve damage. Nevertheless, its principal disadvantage is the mixed parasympathetic and somatic composition of the nerve root (Figure XII).

The sacral root stimulation either intradural or extradural have to face up to a major difficulty. The induced electromicturition did not have a physiologic pattern due to simultaneous activation of the detrusor and the external urethral sphincter owing to the lower activation threshold of the latter in response to electric stimulation. Moreover, human applications showed that sacral root stimulation could not control the detrusor hyperreflexia responsible for clinical incontinence. In an effort to overcome

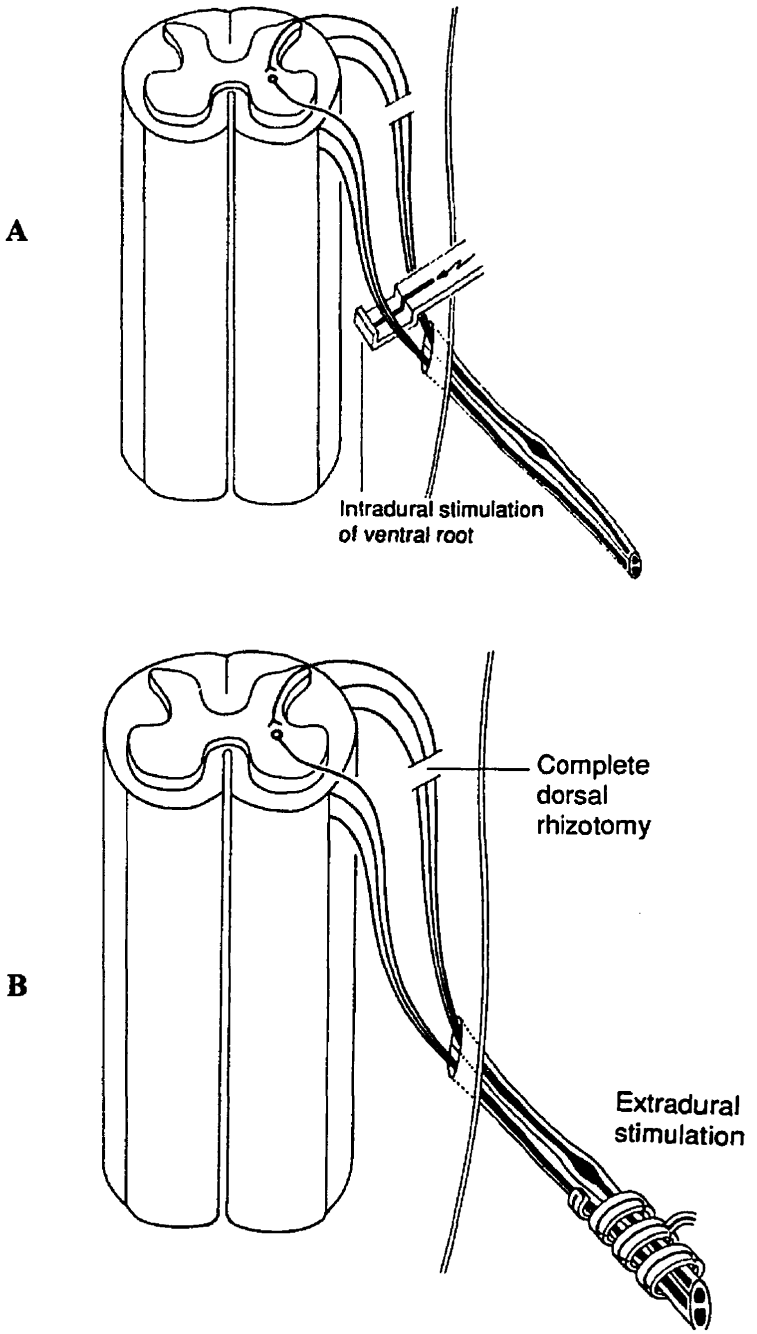

Figure XII. Sacral root stimulation technique: A: Intradural stimulation of ventral root with dorsal rhizotomy, B: Extradural stimulation of sacral root with dorsal rhizotomy (From Hohenfellner, 1992).

these detrimental effects, deafferentation by dorsal root rhizotomy has been suggested by both pioneer teams of sacral root stimulation.[67-77]

Dorsal root rhizotomy extending from S2 to S5 has been performed by different investigators. Most of them have agreed that the intradural approach provides an easier and more complete dissection. The deafferentation has a role to play in the success of neurostimulation. It reduces DH increasing bladder capacity and compliance, improves detrusor response to neurostimulation and decreases the spasticity of the pelvic floor and external urethral sphincter. The main advantage of dorsal root rhizotomy is to avoid DESD. Inspite of these advantages, the dorsal root rhizotomy is not without complication. Apart from its irreversibility, the deafferentation interferes with erectile and bowel function as well as lower extremities functions.

Other strategies to attenuate the elevated urethral resistance include irreversible surgical procedures such as levatorotomy, external sphincterotomy or pudendal neurectomy. [76,78-80] Hohenfellner et al [77] have proposed, in addition to dorsal rhizotomy, that intradural selective transection of ventral rootlets innervating the pelvic floor and striated urethral muscle should be performed. It would reduce the electrostimulation induced DESD. Conservative techniques such as fatigue of the external urethral sphincter either by high frequency stimulus applied directly to the urethral sphincteric muscle [81-83] , on the ventral S2 root [84] or on the pudendal nerve [85,86] have been evaluated.

3.5.1 External urethral sphincter fatigue

The principle of using high frequency current to induce sphincteric fatigue is based on the different properties of the detrusor smooth and sphincteric striated muscles. It has been shown by Thrüroff et al [84] that detrusor muscle is more fatigue

resistant to high frequency stimulation while the urethral striated muscle is easily fatiguable. Reports in the litterature using this technique in animal models [84-86] have achieved satisfactory bladder emptying obviating the need of pudendal neurectomy or external sphincterotomy. Nevertheless, the resultant voiding pattern has been considered as non-physiologic. High frequency stimulus produced fatigue of the fast twitch striated fibers, while the low twitch component responsible for the urethral resting tone is not affected since they are very resistant to stimulation fatigue. [84,87] The intravesical pressure generated by electrostimulation should be higher than the one observed under physiologic conditions when detrusor contraction is induced by sphincteric relaxation to produce bladder evacuation. Moreover, chronic use of electrostimulation leads to histochemical alterations of the muscle fibers. The fatiguable fast twitch glycolytic fibers are converted into oxidative state. There is also an increased oxidative enzymatic activity with hypertrophy of the stimulated fibers. The end result of these changes is that the striated musculature of the urethra will become increasingly resistant to fatigue. [87]

3.5.2 Principle of selectivity

Other authors have explored different techniques based on the intrinsic property of the sacral ventral root to reduce bladder outlet resistance.[88-90] The ventral root is known to be composed of mixed population of large somatic (A-alpha) fibers innervating the pelvic floor, urethral and anal sphincters, and small parasympathetic (A-delta) fibers innervating the detrusor muscle. Since these fibers respond differently to the electrostimulation, one would expect that, using two different current stimulus characteristics, we can on the one hand selectively activate the small fibers innervating the bladder, while blocking the sphincteric activity, allowing for better bladder evacuation.

The collision block through pudendal nerve has been studied by Sweeney et al.[88] This procedure required the application of two electrodes. One proximal provided the orthodromic flow of the excitatory action current, while the distal one induced an antidromic unidirectional signal. The propagation of the orthodromic action potential is blocked if the action current is reduced to a subthreshold level by the collision with the antidromic signal. Thus, resulting in selective somatic fibers blockage (Figure XIII). This technique has been criticized due to the need of an extensive surgery. Furthermore, it required the placement of several electrodes, both centrally and peripherally, which enhanced the risk of electrode inherent complications.

Other authors have investigated the technique of anodal block of the large A-alpha fibers resulting in selective stimulation of the detrusor without activation of the urethral striated muscles. Electrical stimulation of the sacral ventral root is done using an asymetrical tripolar cuff electrode. [89,90] Excitatory action potential propagates bidirectionally from the central cathode (Figure XIV). The cell membrane of the distal anode which has been hyperpolarized becomes unable to be depolarized. Thus selectively arrest the propagation of the action potential in large fibers while action potential propagation in small A-delta fibers remains unaffected.

High-frequency blockade has also been explored at the pudendal nerve. [91] The knowledge of the mixed nature of the ventral root has lead us to hypothesize that using a stimulator which delivers simultaneously low and high frequency currents, we might selectively block the large nerve fibers. This could subsequently attenuate the bladder outlet resistance and allow an adequate bladder emptying. Chapter 4 will describe the acute experiment which was done in our laboratory to study the principle of selective high-frequency blockade by sacral root stimulation.

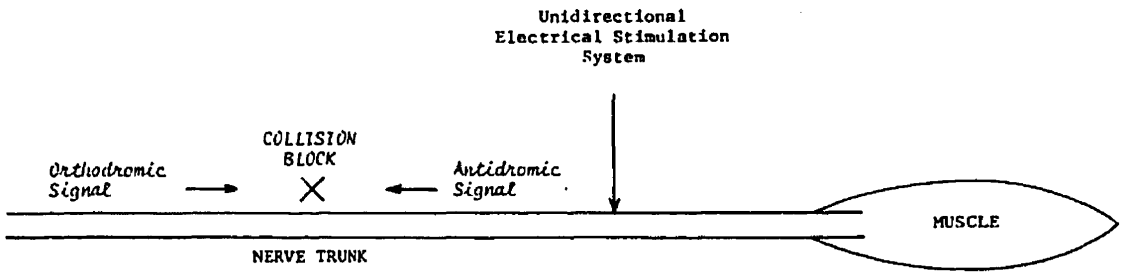

Figure XIII. Diagram of collision block (From Sweeney, 1989).

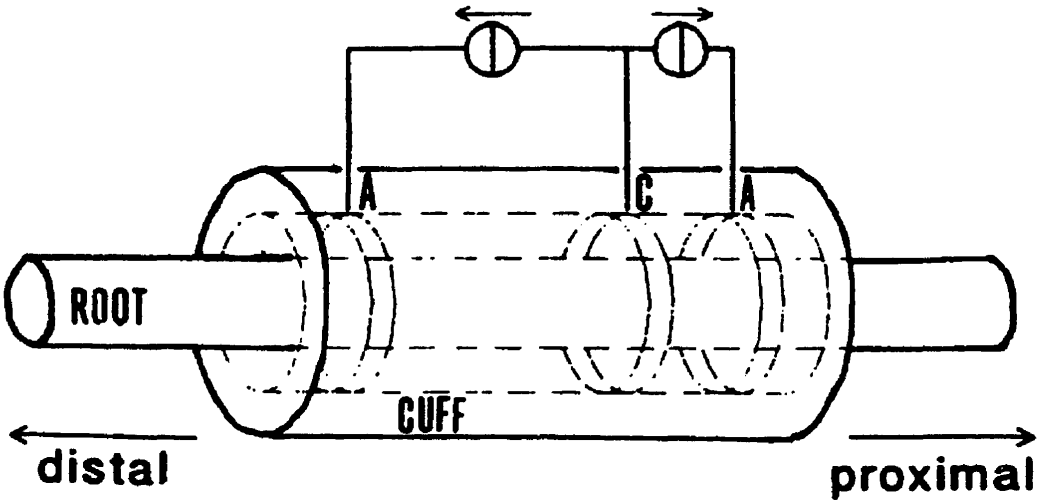

Figure XIV. Tripolar cuff electrode used in anodal block. A: Anode, C: Cathode (From Koldewijn, 1994).

CHAPTER 4

REDUCTION OF BLADDER OUTLET RESISTANCE BY SELECTIVE SACRAL ROOT STIMULATION USING HIGH-FREQUENCY BLOCKADE IN DOGS: AN ACUTE STUDY

4.1 Abstract

Detrusor-sphincter dyssynergia is a main problem in supra-sacral spinal cord injured patients. This problem of high pressure voiding is also encountered in most of electrically induced micturition because of the mixed somatic and autonomic fibers components of the ventral sacral root. We studied the effect of selective high-frequency blockade at the sacral nerve root in an acute spinalized canine model in order to prevent the deleterious consequences associated with the elevated bladder outlet resistance. A new functional electrical stimulation system which can generate one signal composed of two independent adjustable current waveforms delivered via a single bipolar electrode was used in 11 dogs. The selectivity was performed by the inhibition of the sphincteric somatic innervation by high frequency pulse whereas the low frequency stimuli is dedicated to activate the bladder autonomic fibers. Bladder and urethral pressure as well as electromyogram of external urethral sphincter were recorded to determine whether selective high-frequency blockade occurred.

Using this concept, our experiment shown that we were able to achieve selective blockade of the external urethral sphincter during the simultaneous detrusor stimulation thus obtaining a more physiologic voiding.

4.2 Introduction

During the last 4 decades, researchers in the field of electrical stimulation have been working to achieve a normal physiologic pattern of bladder evacuation with minimal residual urine volume in patient with neurogenic bladder dysfunction especially secondary to spinal cord injury. Various possible sites for electrical stimulation have been tried including spinal cord, spinal sacral nerves, peripheral pelvic nerves and bladder wall itself. [91,92] After having been thoroughly studied in different animal models, neurostimulation of the anterior sacral roots seemed to be the only potential technique which can fulfill the ultimate goal in controlled micturition in these patients. However, soon after its early application, a major associated problem has been described. Electrical-induced bladder emptying by sacral root stimulation did not achieve a coordinated micturition but rather a dyssynergic voiding pattern because of the concomitant contraction of detrusor muscle and the external urethral sphincter. [62] This limitation has been explained by advanced knowledge in neuroanatomy. It has been shown by histochemical techniques that the sacral parasympathetic nuclei is located close to somatic pudendal nuclei in the sacral spinal cord. [93] This intimate relationship made it practically impossible to stimulate urinary bladder without activation of external urethral sphincter. Furthermore, the ventral sacral roots were composed of both large somatic fibers (A-alpha) which innervate the pelvic floor and external urethral sphincter through pundendal nerves and small preganglionic parasympathetic fibers (A-delta) innervating the detrusor muscle via pelvic nerves. Since large nerve fibers have a lower stimulation threshold compared to the one of small nerve fibers, the activation of the latter, which require a higher current, involves necessarily simultaneous excitation of the former. Therefore, attempts to empty the bladder by ventral sacral root stimulation do not result in a satisfactory micturition pattern owing to the elevated urethral resistance associated with high bladder pressure.

Efforts have been made to refine the technique of sacral root stimulation thence preventing co-contraction of urethral sphincter during bladder stimulation. In 1975, Jonas and Tanagho [62] described the post stimulus voiding technique based on differential relaxation times existing between detrusor smooth muscle and urethral striated fibers. However, the major drawback of this method was that the induced voiding pattern was intermittent instead of continuous with a high voiding pressure which can potentially jeopardize the upper urinary tract. To overcome the abnormal urethral resistance, Schmidt and Tanagho's team [75,76,78] introduced pudendal neurectomy with or without dorsal root rhizotomy. These surgical techniques have been criticized for their irreversibility and interferences with the anal and sexual function. More conservative methods have since been proposed to fatigue the external urethral sphincter via the second sacral root [84] or the pudendal nerve [85,86] using high frequency current. However, these techniques could not produce a real sphincteric relaxation, since the striated low twitch fibers responsible for the urethral resting tone are very resistant to stimulation fatigue. Other reversible techniques, described as selective blocks, were based on the different internal conductance or on the different conduction velocity of the A-delta and A-alpha fibers. Several authors reported the collision block of the pudendal nerve [88], anodal block through sacral root stimulation [89,90] and high-frequency block of the pudendal nerve [91].

The principle of high-frequency blockade has been studied in the peripheral nerves [94,95]. Because of the mixed nature of ventral sacral root, we expect that blockage of large somatic fibers, using high frequency stimulation, is theorically possible while leaving the bladder muscle free to be selectively activated by low frequency current. Hence, we undertook an acute study to investigate the feasibility of selective high-frequency blockade at the sacral level.

4.3 Materials and methods

Eleven male mongrel dogs weighing 20-25 kg were used. After induction using diazepam (0.02mg/kg) and fentanyl-droperidol (1ml/25kg) IV, dogs were then intubated and ventilated. Anesthesia was maintained with isoflurane and oxygen. Body temperature was controlled and maintained by heating pad. Monitoring of cardiorespiratory system was performed. Cystostomy was done. Bladder pressure was recorded through a suprapubic 8F double lumen catheter or through an 8F double microtip pressure tranducer (16CT/S2L, Medical Measurement Inc., Hackensack, New Jersey) inserted transurethrally. The area of maximum urethal pressure was identified by pulling the urethral catheter while maintaining perfusion rate through the proximal hole at 2 ml/min. The catheter was then secured on the foreskin to prevent accidental displacement. Bladder was emptied periodically and filled with 50ml of sterile saline for each serie of stimulations. Bladder pressure and urethral pressure were recorded by a Grass polygraph, model 7D. This method of recording was done for the first few dogs. We then improved our urodynamic study using computerized urodynamic machine (UDS 120 software, Laborie Medical Technologies Inc.). Electromyogram (EMG) of external urethral sphincter using needle electrodes was also evaluated with EMG unit (UDS-110, Laborie Medical Technologies Inc.). Subsequently, we measured the bladder pressure separately using a suprapubic catheter which was pre-calibrated with 50ml of saline in an attached latex balloon. The prefilled balloon together with the catheter were then inserted in the bladder. Another 10F polyethylene feeding tube was simply introduced at the bladder base to allow continuous drainage of the urine output during the experiment. This technique of recording allows a more accurate correlation between bladder pressure and bladder volumes. Moreover, it precludes the transmission of bladder pressure to urethral pressure measurement.

All animals underwent a suprasacral spinal cord section at the T_{10} vertebra level. In the same prone position, sacral laminectomy was performed at the level of L_7-S_1. Sacral nerves were exposed extradurally, the first and second sacral roots were identified using a bipolar nerve probe connected to a Grass stimulator SD9 (Grass Instruments Co., Quincy, Massachusetts). The parameters of stimulation were 2-5V, 30Hz, 10msec for a period of 5 to 10 seconds. Once the sacral nerves giving the best urethral and/or bladder pressure were chosen, we wrapped the selected root with a stainless steel bipolar cuff electrode (length of electrode 10mm, distance between two wires 4mm, inner cuff diameter 1.5mm, from Micro Probe Inc., Clarksburg, Maryland). The stimulator consisting of a self-built external test-bench type analog stimulator. It was composed of two independent waveform generators whose signal outputs (low and high frequency) were mixed into a single channel to produce the selective stimuli (Figure XV). The produced pulses were biphasic rectangular with active charge balancing. The device allowed also a wide range adjustment of stimulus parameters of each waveform independently (Table II).

We first determined the bladder and sphinteric contraction threshold by unilateral stimulation of S_2 with an increasing current. the best low frequency pulse giving the highest detrusor contraction was also evaluated. The parameters of the blocking stimulation were adjusted separately to obtain the optimal urethral blocking. Then combination of both low and high frequency pulses was used to define the selective blockade of the urethral sphincter. Every stimulation lasted 10sec with 60sec of rest to prevent the fatigue of the detrusor muscle and urethral sphincter. The efficacy of sphincteric blocking was evaluated either by the percentage of differential pressure between the maximal urethral pressure and the baseline measurement over the maximal pressure and by the EMG activity with similar calculation [91] (blocking effectiveness= ($P_{ure\ max}$-$P_{ure\ BL}$/ $P_{ure\ max}$)x 100%; or (EMG_{max}-EMG_{BL}/ EMG_{max})x 100%). At

the end of the experiment, the animal was sacrified with a large dose of intravenous nembutal.

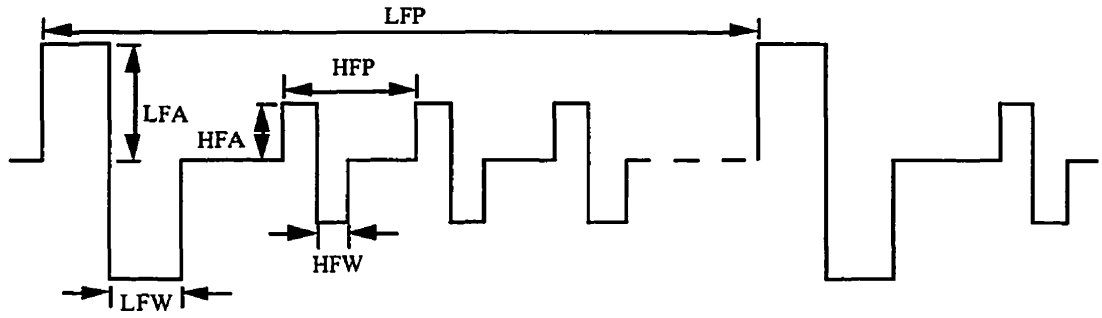

Figure XV. Typical waveform generated by the stimulator. LFA: low frequency amplitude, LFW: low frequency pulse width, LFP: low frequency period, HFA: high frequency amplitude, HFW: high frequency pulse width, HFP: high frequency period.

Table II: Main available parameters and range

	Low frequency			High frequency		
Parameter	Period	Pulse width	Amplitude	Period	Pulse width	Amplitude
Mnemonic	LFP	LFW	LFA	HFP	HFW	HFA
Units	1/Hz	micro-sec.	mA	1/Hz	micro-sec.	mA
Range	1/100-1/10	0-300	0-2.5	1/1000-1/100	0-1000	0-2.5

4.4 Results

The excitation threshold of bladder and urethra have first been evaluated with unilateral S_2 stimulation. The frequency and pulse duration were initially fixed at 30Hz and 150μs. These parameters have been recommended by Thüroff et al [96] in order to avoid muscle fatigue and get good sphincteric contraction. Figure XVI shows the typical response of bladder and urethra to stimulation with increasing current. The discrepancy between diameter and conduction velocity of the small A-delta and large A-alpha fibers results in contraction of urethral sphincter at a lower current than the bladder. Thus the excitation threshold of urethral sphincter is below bladder threshold ranging from 0.075 to 0.3mA and 0.12 to 0.9mA, respectively. The best low frequency stimulation parameters have been determined so that we could apply them subsequently in combination with high frequency current to demonstrate the blocking and evaluate the bladder activity during the block. With the stimulus frequency of 30Hz, the maximal contraction of bladder occurred at a pulse duration about 150-180μs and a stimulation amplitude ranged from 0.45 to 1.8mA. The majority of animals had the best bladder pressure response at 0.9-1.1mA (7 of 11 animals).

Figure XVII illustrates the pressure response of bladder and urethral sphincter during the first five animals when we combined the low and high frequence current. We were not able to demonstrate the blocking due to the transmission of the bladder pressure to the urethra during the stimulation. This was demonstrated by comparing the pressure recordings and showing the striking similarities between bladder and urethra. The external urethral sphincter, which is a striated muscle, contracts as well as relaxes at a faster rate than does smooth bladder muscle. When we examinated the curves closely figure XVII, we initially saw a steep rise of urethral pressure response to the stimulation which has been followed by a more smooth increase of pressure

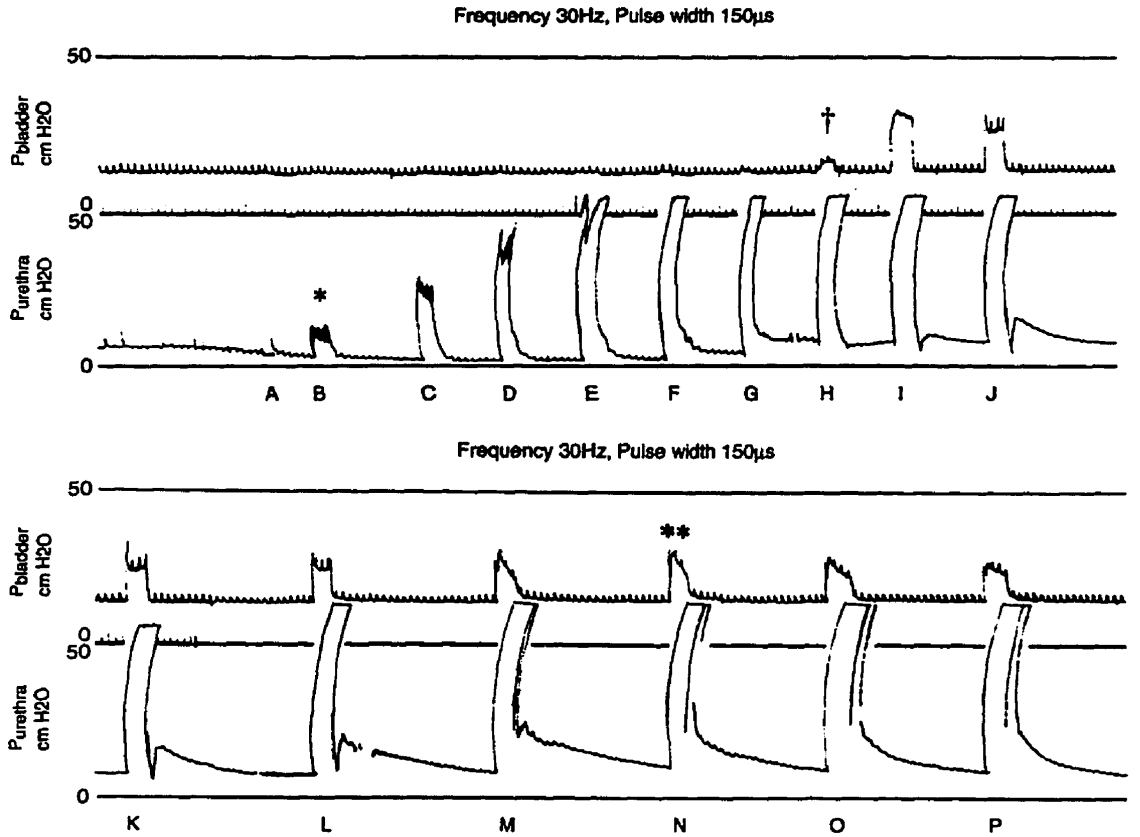

Figure XVI. Contraction threshold of bladder and urethra according to bladder pressure ($P_{bladder}$) and urethral pressure ($P_{urethra}$) response to stimulation of S_2 left with increasing amplitude from 0.055 to 0.9mA in animal 3: A: 0.055, B: 0.075, C: 0.095, D: 0.11, E: 0.13, F: 0.15, G: 0.17, H: 0.19, I: 0.20, J: 0.22, K: 0.24, L: 0.30, M: 0.45, N: 0.6, O: 0.75, P: 0.9.

† Excitation threshold of the bladder

* Excitation threshold of the urethral sphincter

** Best bladder contraction.

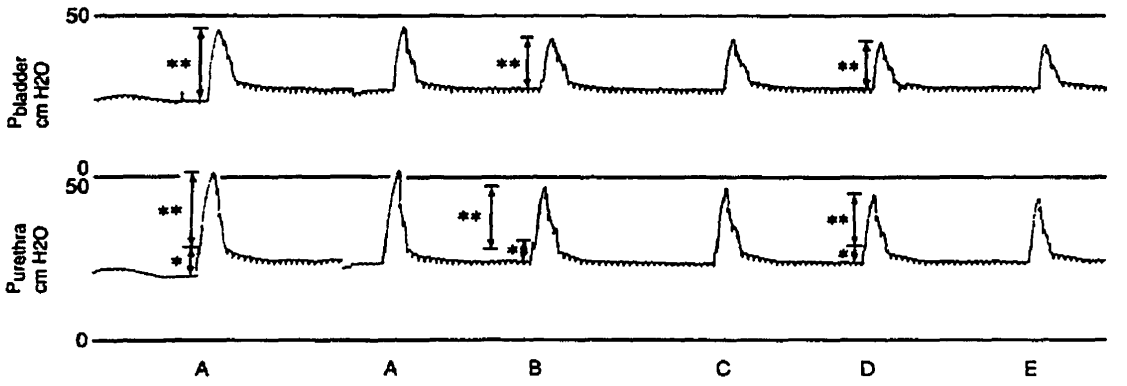

Figure XVII. Bladder and sphincteric pressure responses to combination of high and low frequency stimulation of S_2 left in animal 5. Low frequency stimulus parameters: 30Hz, 180μs, 1.8mA. Blocking stimulus parameters: 600Hz, 150μs with increasing current (mA): A: 0.3, B: 0.45, C: 0.6, D: 0.9, E: 1.2.

* Urethral pressure response

** Bladder pressure response

response. The first part corresponded to the proper urethral sphincter response and the latter being the bladder pressure which have been transmitted to the sphincteric area (same shape of peak when compared to bladder pressure recording). Subsequently, we have modified our technique of bladder filling using a balloon as mentioned previously. By this ameliorated method, the high-frequency blockade have been demonstrated by reduction of urethral pressure or EMG activity (Figure XVIII). The intermittent stimulation with low frequency alone allowed us to confirm the existence of urethral blocking and its reproducibility. The high-frequency blockade was mainly dependent of the current amplitude. The range of the current giving an optimal blocking varied from 1.1 to 1.5mA while the majority of animals required 1.3mA. In animal 9, the optimal blocking amplitude was 1.3mA (pulse C, Figure XVIII). Current higher than 1.3mA did not result in a better block. Pulse duration has also been shown to be important to differentiate the small and large fibers thus enhancing the selectivity of the blocking [90]. In order to evaluate the role of pulse duration in the selective high-frequency blocking, we have progressively increased the pulse duration of high frequency stimulus (range from 20-500μs) with the fixed frequency and current amplitude. Figure XIX showed the sphincteric blocking pattern of stimulating left first sacral root, with increasing pulse duration. The selective blocking was optimal at pulse duration of 60μs. Pulse width above this level did not produce a better blockade. Pulse width smaller than 20μs required nearly double current amplitude to produce even a lesser block. Theorically, stimulation of both sacral nerves should produce a better blockade since we recruit more motor units. Nevertheless, bilateral second sacral root stimulation in this experiment has not been shown to induce a more effective blocking even if we have used the optimal blocking parameters obtained from the unilateral stimulation. Although high-frequency blockade at the sacral root has been demonstrated, several issues should have been addressed. First, the degree of blocking is variable between animals and is not complete. The reduction of sphincteric pressure

and EMG activity ranged from 31.1-75.6% and 65.7-90.3%, respectively (Table III). Moreover, the blocking stimulation has reduced the bladder pressure but to a lesser extent (range 3.5-36.7%). The optimal high-frequency blockade parameters on the last five dogs are summarized in Table III.

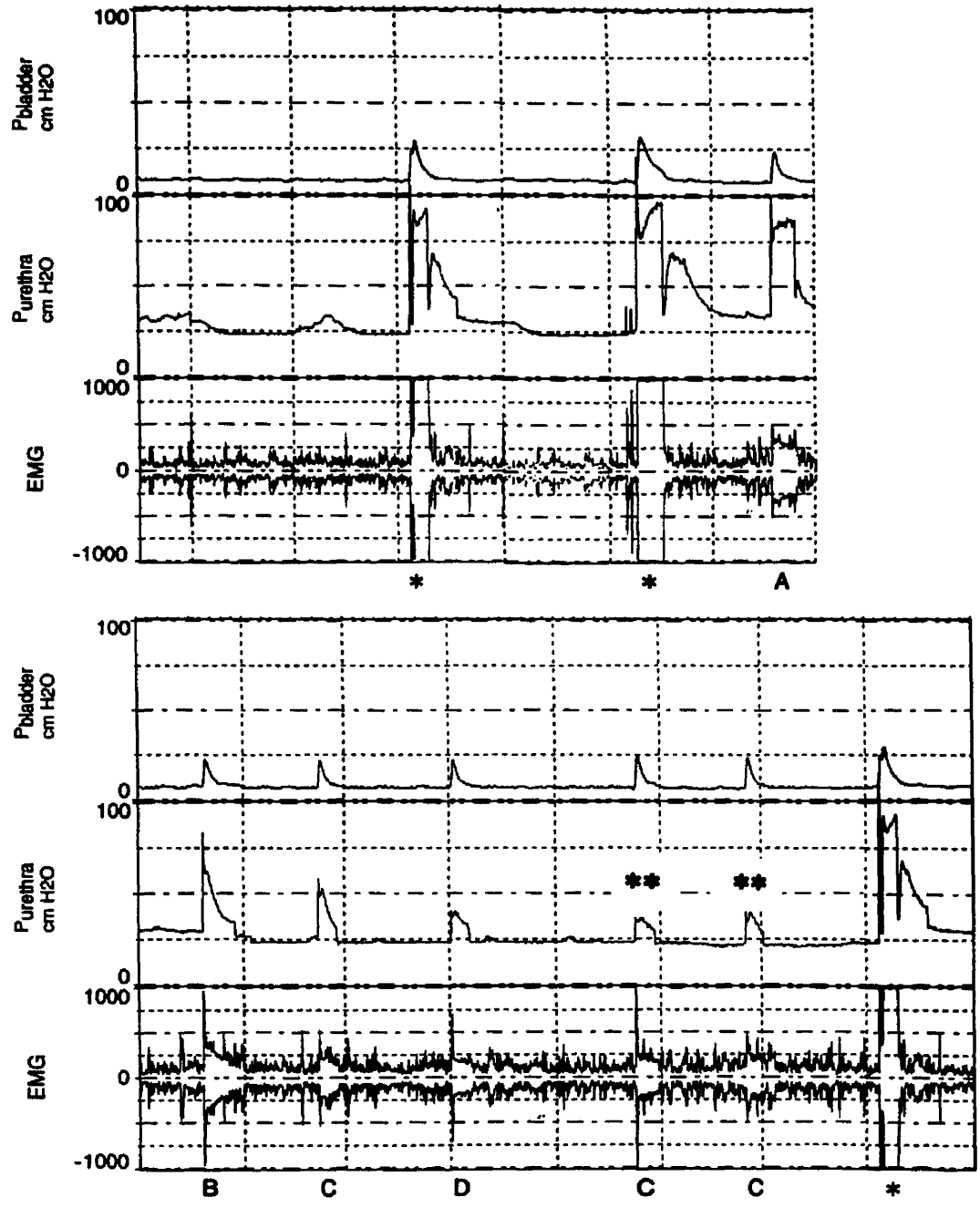

Figure XVIII. Sphincteric and bladder pressure response and EMG activity of urethral sphincter to high-frequency blockade through S_2 right stimulation in animals 9. Low frequency stimulus parameters: 30Hz, 60μs, 0.9mA. Blocking stimulus parameters: 600Hz, 60μs and increased current (mA): A: 0.7, B: 1.1, C: 1.3, D: 1.5.

* Low frequency alone

** Optimal sphincteric blocking

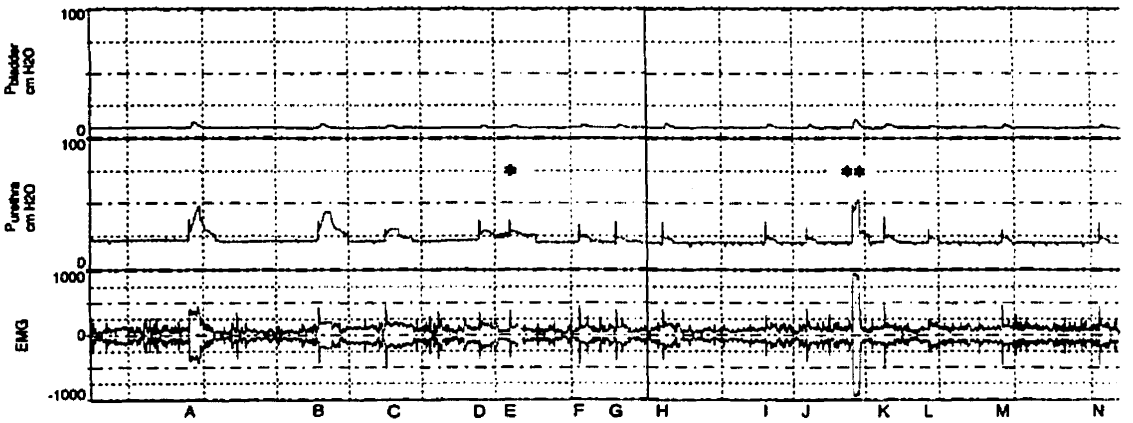

Figure XIX. Sphincteric and bladder pressure response and EMG of urethral sphincter to high-frequency blockade through S_1 left stimulation in animals 9. Low frequency stimulus parameters: 30Hz, 175μs, 0.9mA. Blocking stimulus parameters: 600Hz, 0.7mA and increased pulse duration (μs): A: 20, B: 30, C: 40, D: 50, E: 60, F: 70, G: 80, H: 100, I: 150, J: 200, K: 250, L: 300, M: 400, N: 500).

* Optimal blocking at 60μs pulse duration

** Low frequency alone

Table III: Effectiveness of the high-frequency blockade of urethral sphincter with optimal parameters of stimulation in five dogs

Dog No.	Parameters of stimulation		% of reduction		
	Low frequency Hz, μs, mA	High frequency Hz, μs, mA	$P_{bladder}$	$P_{urethra}$	EMG
7	30, 180, 1.3	600, 50, 1.1	20.0	N/A	90.0
8	30, 180, 1.3	600, 50, 1.3	32.0	31.1	65.7
9	30, 180, 0.9	600, 60, 1.3	36.7	75.6	90.3
10	30, 180, 0.9	600, 60, 1.1	28.9	70.4	N/A
11	30, 180, 0.9	600, 150, 1.3	3.5	65.8	70.4

N/A: Not available.

4.5 Discussion

Detrusor-external sphincter dyssynergia is a challenging problem in urological practice where one would like to avoid the irreversible surgical techniques such as sphincterotomy or pudendal neurectomy. Selective blocking via anterior sacral root stimulation seems to be promising to induce a coordinated, low pressure voiding. Several techniques have been described. This study is the first to demonstrate the effect of high-frequency blockade on the external urethral sphincter through sacral root stimulation. Our results showed that this concept of blocking, although not "optimally" selective and complete, is possible and reproducible. Several hypothesis have been proposed trying to explain why the blocking is not complete. The transmission of intravesical pressure to sphincteric pressure encountered initially has been resolved during the study. Thus the recording technique could not be reason of the incomplete blocking. We subsequently evaluated the parameters of blocking stimulation determining whether they can influence our outcome. In fact, the flexibility of our stimulator allows us to adjust each parameter independently and in a wide range. With the established optimal parameters, most of our animals can consistently get a reduction of urethral pressure about 70% and EMG activity about 70-90% except for animal 8. The urethral pressure in this animal has only decreased 31% which was similar to the value of intravesical pressure reduction. Retrospectively, this result could be improved by increasing the pulse duration of the high frequency stimulus above 50μs as seen in the last animal in order to get a better block (Figure XX). Another possible reason might be ascribed to the current spread. This abnormal outflow current can stimulate surrounding nerves which can have fibers innervating the urethral sphincter hence decreasing the blocking effect. Moreover, the virtual cathode established by this leakage current, when high enough, will have an excitation effect on large nerve fibers and consequently counterbalance the blockade [97]. To avoid this event, the insulator

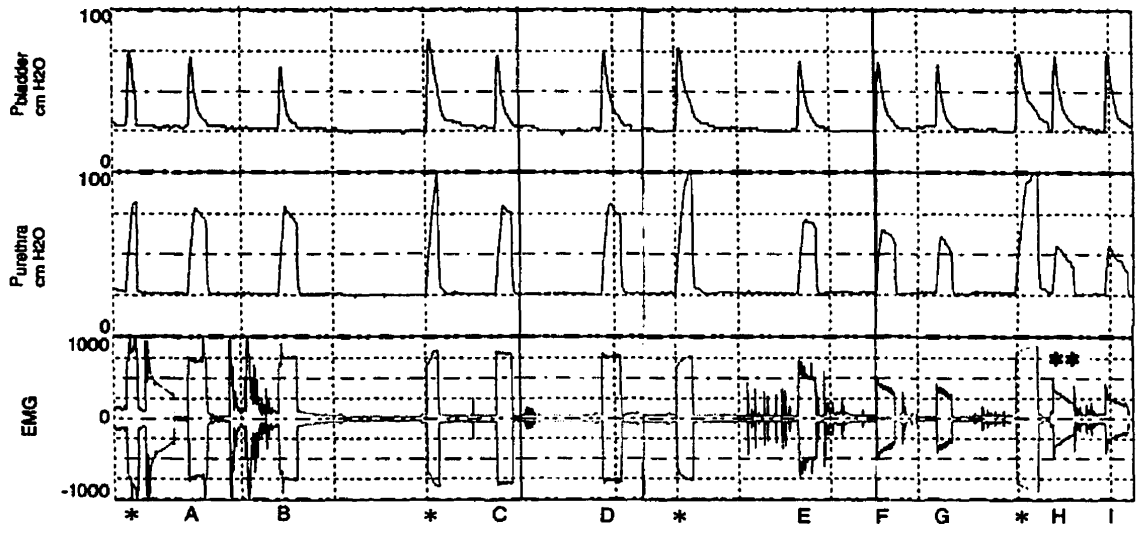

Figure XX. Sphincteric and bladder pressure response and EMG of urethral sphincter to high-frequency blockade through S_2 left stimulation in animals 11. Low frequency stimulus parameters: 30Hz, 175μs, 0.9mA. Blocking stimulus parameters: Pulses A to D being 600Hz, 60μs and increased current (mA): A: 1.1, B: 1.3, C: 1.3, D: 1.5; pulses E to G being 600Hz, 100μs and increased current (mA): E: 1.1, F: 1.3, G: 1.5; pulses H and I being 600Hz, 150μs and increased current (mA): H: 1.3, I: 1.5.

* Low frequency alone

** Optimal blocking at 150μs pulse duration and 1.3 mA current amplitude

length in each extremity of the bipolar electrode should be maximal (can be optimized by having a minimum distance between two electrodes). Otherwise, an asymetrical tripolar electrode with the cathode surrounded by two anodes has been proposed to circumvent this problem.

The parameters of excitation threshold and blocking stimulation in our experiments were variable between animals. This can be explained by individual variation, contact of nerve fibers with the inner surface of the electrode and possibly some degree of nerve damage due to manipulation. In spite of this later potential injury, we have got good blocking response to stimulation during the first hours in contrast to what was described by Koldewijn et al [90].

Ishigooka et al [91] have reported an average blocking efficacy ranging from 30 to 45%. This result is nearly half of ours. This is probably because they applied the blocking stimulus at the pudendal nerve after a tetanic drive stimulation. This tetanic contraction of striated urethral sphincter may be more resistant to the subsequent blocking procedure. Finally, their best blocking frequency was similar to ours (600Hz).

Because our sacral root stimulation was extradural, one would expect that the excitation threshold of the bladder and urethral sphincter in our experiments should be higher since the nerve is covered by the epineurium and connective tissue which produce a higher impedance. However, our data showed low sphincteric and bladder threshold of contraction (ranged from 0.075 to 0.3mA and 0.12 to 0.9mA, respectively). These results are only slightly higher than Koldewijn et al [90] using intradural anodal blocking. Moreover, the self-built stimulator allowed us to use a biphasic with active charge balancing current waveforms in order to prevent nerve damage due to longterm stimulation.

In conclusion, despite the incomplete blocking of the urethral sphincter and some degree of simultaneous reduction of intravesical pressure, the technique of high-frequency blockade can reduce the urethral resistance sufficiently to acheive an efficient and physiologic bladder emptying. A newly developed programmable implantable stimulator using this technique is currently being evaluated in a chronic phase in order to assess its feasibility for future human application.

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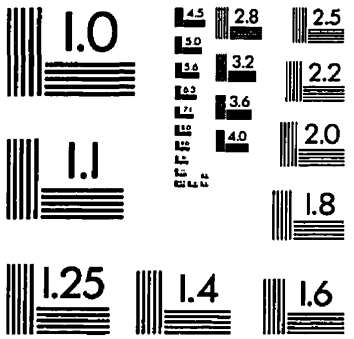

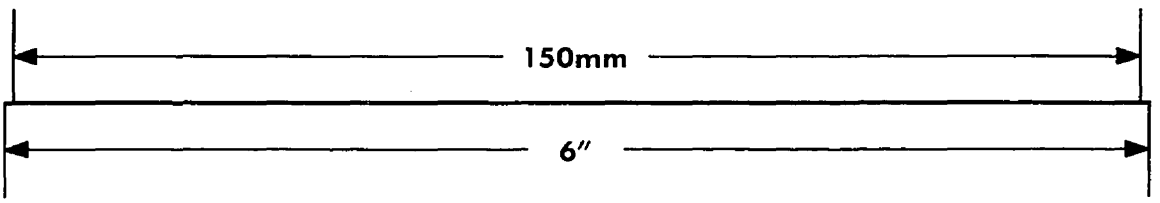

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