NEW STIMULATION STRATEGY TO IMPROVE THE BLADDER FUNCTION IN PARAPLEGICS: CHRONIC EXPERIMENTS IN DOGS

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***Abstract* – New neural electrical stimulation strategy, intended to recover the bladder functions, is proposed. Restoring urinary functions allows voluntary bladder voiding, and reduces or even suppresses hyperreflexia. The preliminary stimulation system is composed of subcutaneous implantable stimulators (an implant) and an external device. The implant includes the selective stimulation for bladder voiding, in addition to a new permanent stimulation technique to reduce (or cancel) the bladder hyperreflexia and so cures other related diseases. Permanent stimulation is a low frequency, low amplitude and all day long stimulation that needs to be battery powered. On the other hand, selective stimulation is a bi-frequency, punctual, precise and at a higher amplitude stimulation that is well controlled and powered from the outside. Eight prototypes of the stimulator have been used in an experimental evaluation in dogs to characterize the reliability and functionality of the new implant in a real application environment. Preliminary results of the study show that the proposed stimulation system and the stimulation strategy provide significant improvement for bladder hyperreflexia curing while it confirmed the efficiency of the selective stimulation by means of high frequency blockage.**

***Keywords*– Microstimulator, Selective stimulation, Hyperreflexia, Bladder, Sacral nerve, Chronic experiments.**

I. INTRODUCTION

Electrical neural stimulation is widely used to recover partial functionality of failed organs after spinal cord injury. Among the affected organs, the urinary bladder, where the patient is unable to voluntarily evacuate the urine from his filling bladder, and he often suffers from many urinary bladder complications related to the detrusor hyperreflexia [1]-[3]. Many attempts have been made to recover voluntary control of the micturtion reflex by means of electrical stimulation at different sites of the urinary system [4]. More recently, neurostimulation and neuromodulation of the sacral nerve root seems to be one of the most promising options to enhance voiding and suppress detrusor hyperreflexia. Unfortunately, conventional stimulation of sacral nerves induce simultaneous contraction of the sphincter and the bladder muscle, called dyssynergia, which induce high detrusor pressure that can eventually leads to incontinence or kidney failure [5]-[7]. Among existing techniques that perform good bladder voiding, the selective stimulation using high frequency blockage to avoid dyssynergie [8]-[9] appear to have less draw back than others solutions that use neurotomy or rhizotomie [10]-[11].

Most research in bladder rehabilitation have only focus on the voiding, but few studies have been made on the detrusor hyperreflexia problem. Hyperreflexia consists of a hyperactivity of the autonomic nervous system (ANS). It occurs when the overfull bladder sends impulses to the spinal cord, where they travel upward until they are blocked by the lesion of the level of injury. Since the impulses cannot reach the brain, the reflex arc stays activated, which increases activity of the sympathetic portion of the ANS and causes spasms.

This paper presents a new stimulation strategy together with a system designed to perform selective electrical stimulation (SES) for bladder voiding and permanent electrical stimulation (PES) for hyperreflexia regulation. Eight prototypes, made with commercially available electronic devices on a printed circuit board, have been tested on dogs for 1 year to characterize the new permanent stimulation technique. The remaining sections of this paper are a system description in section II. Section III concerns the experimental protocol. Results are shown in section IV. Finaly, discussion and conclusion are the subject of sections V and VI respectively.

II. SYSTEM DESCRIPTION

The stimulation system is composed of an external controller and two implanted stimulators connected to the nerve via one bipolar cuff electrode (

Fig. 1). The external part of the system is used to select stimulation parameters and send them with needed energy using inductive link to power up and program the subcutaneously implanted stimulators (implant).

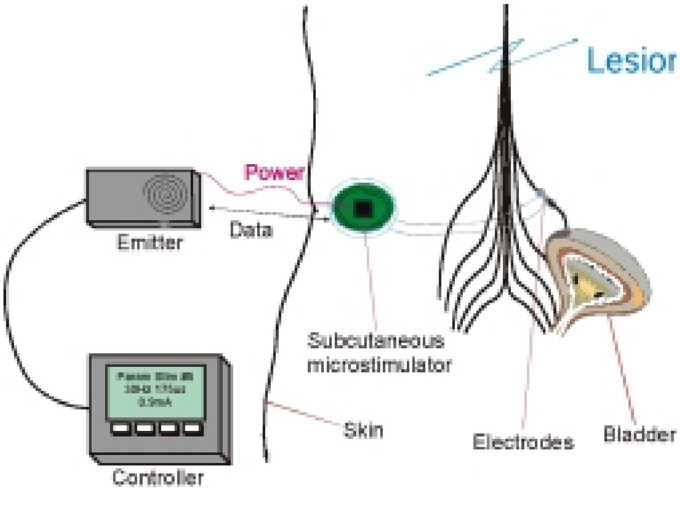

Fig. 1. The complete subcutaneous stimulation system

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Abstract

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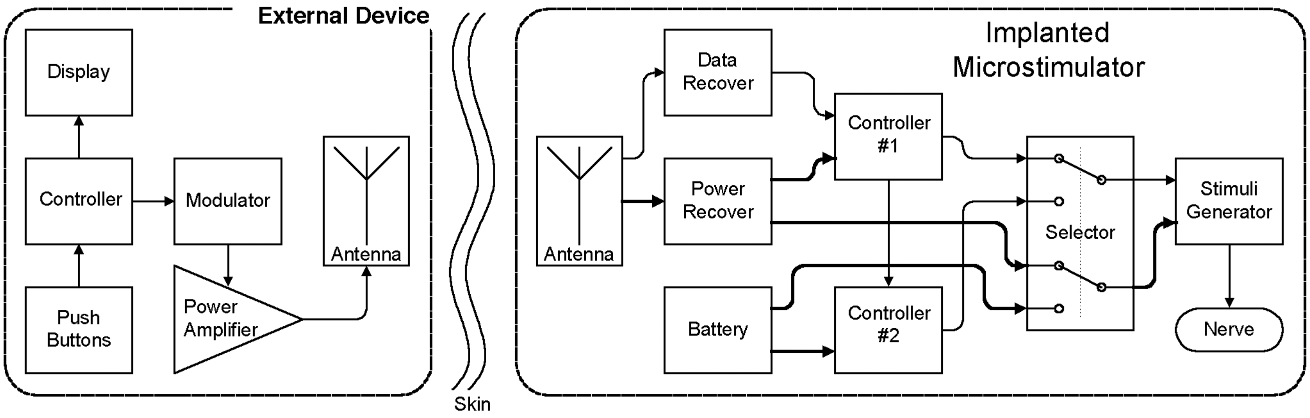

Fig. 2. Simplified block diagram of the stimulation system.

The External Controller

A single microcontroller chip is use to handle the whole user interface, including LCD (Liquid Crystal Display), keyboard and data encoding. Encoded digital data are fed to an amplitude modulator (AM) which uses a central frequency of 20 MHz. Modulated signal is then amplified, by a power amplifier, to enable power and data transfer to the subcutaneous microstimulators. Push buttons can be used to select among stimulation modes and stimulations parameters (amplitudes, frequencies and pulses width) and then push on the stimulation switch to start data and power transfer. As long as the user keeps the stimulation switch on, data remains transfered to one of the subcutaneous micro-stimulators and the corresponding output stage is delivering the stimuli. But as soon as the stimulation switch is released the stimuli generators stop.

The Implant

The implant regroups two stimulators. One of them operates as a selective stimulation generator and the other is used as a permanent stimulator. Either of these stimulators recovers power and data from the RF (Radio Frequency) signal send by the external controller. Then decodes the data stream and check its integrity with classical communication CRC checksum. Depending on the stimulation mode, one of both implants receives parameters and starts to generate stimuli for selective stimulation or the other reprograms the dedicated internal memory for new permanent stimulation.

The selective stimulator gets its power from the RF signal send by the external controller. But the permanent stimulator is self powered by an embedded battery. Figure 2 shows a simplified scheme to illustrate the implant. Two different controllers are used to synchronously run all functions of the implant. Controller #1 is always powered by the external RF signal. controller #2 is powered by the embedded battery. Using such dual power supply allow a longer battery life, because permanent stimulation is not that power demanding than selective stimulation which would empty the battery in few weeks.

The implanted microstimulator, as mentioned early, is based on two main controllers that share the same output stage via a double bipolar electrode to generate stimuli. The controller #1, based on a FPGA (Field Programmable Gates Array), is powered by the external RF power and is used to decode and detect error and then correct data send by the external controller. It also allows to generate stimuli for the selective stimulation.

The controller #2 is based in a microcontroller which is responsible of the generation of the low power stimuli for the permanent stimulation. This controller #2 is battery powered and also supervises the power switching between the RF received and regulated voltage and the battery to power up the stimuli generator. This combination of two controllers and two power supplies allows the implant to be either a high amplitude bi-frequency selective stimulator or a low power and low amplitude permanent stimulator.

The Electrodes

Two categories of electrode were built by our research team. The first uses a shape memory alloy, while the other is based on a super elastic memory alloy. These new types of electrodes allow to facilitate surgery and optimize contacts with nerves [12]. Memory shape alloy electrodes are easy to wrap and manipulate when kept at low temperature, but they automatically remember and recover their original shape (cylindrical around the nerve) when heated at body temperature. Super elastic electrodes are naturally closed and strong enough to stay wrapped around the nerve if low stretching forces are applied. But over a given tension (apply by the surgeon) electrodes could be open and placed easily around the nerve.

III. EXPERIMENTAL PROTOCOL

The chronic study was conducted on 6 adult male mongrel dogs. Animals were subjected to laminectomy at the level of T10 vertebra and the spinal cord was sectioned under direct vision. The procedure was carried out under general anesthesia and aseptic techniques. At the same setting, a limited sacral laminectomy was performed and the sacral roots were identified. The extradural ventral sacral nerves supplying the urinary bladder and external sphincter were hooked and stimulated with an external pulse generator (SD9 Stimulator, Grass Medical Instruments). The intravesical pressure was measured through a tri-way 7F catheter connected to a portable urodynamic analyzer (UDS-120, Laborie Medical Tech. Inc.) and a computer. After identification of the proper sacral root (S2 in dogs), SMA electrode was wrapped around the nerve and the stimulator was implanted subcutaneously in the flank of the animal.

Following the surgery, the dogs were kept on the following stimulation protocol:

No Stimulation Phase

This phase includes the first two months of the study, where the dogs were kept on intermittent catheterization only without any stimulation.

Low-frequency only stimulation (standard stimulation)

During the third month, the animals were stimulated with low-frequency current pulses only. After the spinal-cord shock phase, the animals usually developed bladder hyperreflexic contractions with reduction of the bladder capacity. Cystometric evaluations of the intravesical and intraurethral pressure measurements with electromyographic (EMG) recording of the pelvic floor muscles were performed to determine the most suitable set of stimulation parameters for each dog. During the procedure, the bladder of each animal was filled with sterile saline solution until it leaks and then evacuated of half its capacity.

Selective and continuous stimulation

Two weeks after the development of detrusor hyperreflexia, the continuous low frequency / low amplitude neuromdulation current was turned on, in order to suppress detrusor hyperreflexia, together with the application of selective stimulation, in order to induce micturition in these dogs. Different sets of selective stimulation parameters for high-frequency blockage were applied in order to select the one that could give maximum bladder evacuation with high intravesical pressure and low intraurethral pressure (Fig. 3).

The dogs were stimulated with the programmed set of parameters twice a day. Expelled and residual urine volumes were measured. Also the applied parameters for the continuous low frequency / low amplitude neuromodulation current stimuli were selected on urodynamic basis; the parameters that gave the least effective change in the vesical and urethral pressures with an associated EMG activity of the external urethral sphincter, were selected.

Weekly cystometric study to monitor intravesical and intraurethral pressures and monthly intravenous urography (IVU) to visualize both kidneys, ureters and the bladder were performed for each animal. Voiding cystourethrogram (VCUG) with neurostimulation was carried out after IVU study.

Low-frequency only stimulation

During the 7th month, daily stimulations were performed with low-frequency only current pulses to compare selective high-frequency blockage with low-frequency only stimulation. In the same time, the continuous low frequency / low amplitude neuromodulation current was stopped till the end of the study.

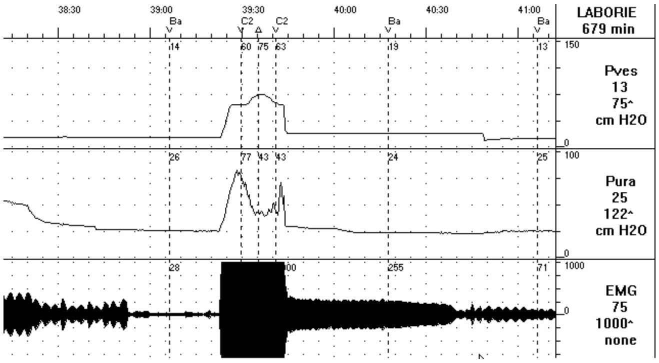

Fig. 3. Typical CMG during a selective stimulation

No stimulation phase

This included the last month of the study where all forms of stimulation were stopped and the dogs were kept again on intermittent catheterization only.

IV. RESULTS

All the dogs completed the study. Only one dog spontaneously developed detrusor hyperreflexia (DH), 6 weeks after the surgery and before the application of neurostimulation. The other 5 dogs developed DH 1-4 weeks after the start of low frequency stimulation only. With the application of continuous low frequency / low amplitude neuromodulation current, DH disappeared from all the animals within 2-4 weeks.

During the period of the initial intermittent catheterization and before the development of the detrusor hyperreflexia the average functional bladder capacity was 256.5 ± 32.5 ml (Fig. 4). During the period of detrusor hyperreflexia (spontaneously developed in one dog or after the application of low frequency stimulation in the other 5 dogs), the average functional bladder capacity was significantly reduced to 127.1 ± 17.3 ml ***($P < 0.05$)***. The average voided urine volume was 39.5 ± 5.3 ml and this represents 31.1 % of the mean total functional bladder capacity during that stage. The average residual urine volume was 87.6 ± 13.6 ml and this represents 68.9 % of the total functional bladder capacity.

When the continuous low frequency and low amplitude neuromodulation current was turned on in order to suppress the detrusor hyperreflexia together with the application of the selective stimulation to induce bladder voiding, the average functional bladder capacity was significantly increased to 279.9 ± 39.4 ml, compared with the functional bladder capacity during the stage of detrusor hyperreflexia (**$P < 0.05$**). With the application of the selective stimulation the mean voided urine volume was 247.1 ± 24.1 ml and this represents 88.3 % of the mean total functional bladder volume. The average residual urine volume was 32.8 ± 17.6 ml and this represents 11.7 % of the mean total functional capacity**.** The dogs were kept on that form of stimulation until the 7th month. During the 7th month the dogs were kept on low frequency only stimulation for one month and the permanent stimulation was turned off. During that period the mean functional bladder capacity was 262.9 ± 30.7 ml. The mean voided urine volume was 89.8 ± 13.1 ml and this represents 34.2 % of the mean total functional bladder capacity. The mean residual urine volume was 173.1 ± 31.8 ml and this represents 65.8 % of the mean total functional capacity**.** Over the last month, when the dogs were kept on intermittent catheterization only, the mean functional bladder capacity was 253.4 ± 32.5 ml.

None of the animals showed backpressure on the ureters or kidneys as evidenced by monthly radiological investigation (IVU, VCUG).

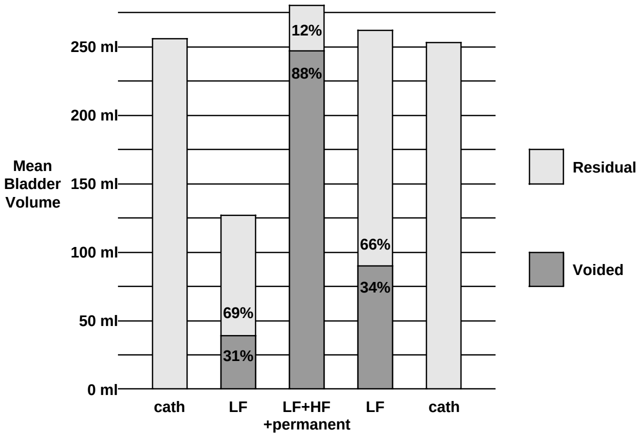

Fig. 4. Average bladder volume and voided urine for three stimulation steps

V. DISCUSSION

Preliminary results of this new stimulation strategy and dedicated implantable stimulators confirmed that the reliability of the selective high frequency blockage stimulation has a valuable solution for long term bladder voiding in paraplegics. Furthermore, our new neuromodulation technique to cure hyperreflexia within few weeks by means of permanent low frequency and low amplitude current stimulation, seems to be one promising solution for a complete rehabilitation of the urinary bladder with no drawback.

VI. CONCLUSION

The experimental validation on animals confirmed that combining both selective and permanent stimulations have great promises for bladder rehabilitation. Furthermore, such stimulation system can be reprogrammed for other electrical stimulation applications that need both neural selective and permanent electrical stimulation.

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