Restoring Urinary Function by Surface Electrical Stimulation

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Abstract— **The recovery of urinary function is recognized as a high priority among persons with chronic spinal cord injury (SCI). Although drugs can be very effective in maintaining continence for these individuals, this treatment can also cause significant side effects (e.g., dry mouth and constipation). As an alternative, tibial nerve (TN) stimulation has been shown in both preclinical and clinical studies to effectively evoke bladder-inhibitory reflexes. However, the clinical development of this therapeutic approach in SCI patients has been limited. In this study, we investigated a novel bladder-inhibitory reflex that is evoked by saphenous nerve (SAFN) stimulation. In anesthetized rats, we showed that SAFN stimulation can achieve bladder inhibition in a frequency dependent manner, where 20 Hz stimulation was most effective at suppressing bladder activity. We further showed that SAFN stimulation can achieve robust inhibition of bladder function in a hyperactive bladder model (0.5% acetic acid infusion). The results of this study suggest further work in applying SAFN stimulation to treat detrusor overactivity in chronic SCI patients.**

I. INTRODUCTION

The loss of lower urinary tract function remains a significant problem for individuals with chronic spinal cord injury (SCI). Similar to patients with overactive bladder (OAB), the inability to maintain proper storage of urine can result in profound quality of life issues, such as increased morbidity and decreased social relationships [1, 2]. Drug therapies (e.g., anti-cholinergic medication) can offer an effective solution for persons with SCI, but long-term compliance is a significant challenge due to the myriad of side-effects [3, 4].

Electrical nerve stimulation is a promising technology that could potentially offer SCI patients with an alternative means of restoring urinary function (i.e., continence). Pudendal nerve stimulation, in particular electrical activation of the dorsal genital nerve, is known to evoke very strong bladder-inhibitory reflexes. Studies in both spinalized animals [5] and persons with SCI [6], show robust decreases in ongoing bladder activity and also corresponding increases in bladder capacity. This reflex is characterized as an acute response, which is rapidly 'turned ON' by electrical stimulation and rapidly 'turned OFF' when electrical stimulation has ceased. As a consequence, a permanently implanted neurostimulation device is required to provide continuous electrical activation of this bladder-inhibitory mechanism. The long-term feasibility of such an implant in persons with SCI remains unresolved [7].

Tibial nerve (TN) stimulation offers another potential solution for restoring continence in persons with chronic SCI.

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As originally described by McGuire et al [8, 9], effective inhibition of detrusor activity can be achieved by electrically activating the TN with transcutaneous (surface) electrodes placed on the lower leg. In both animal and human subjects, the authors reported significant changes in urodynamic behavior that were achieved by electrical stimulation. It is important to note that the bladder-inhibitory effects of TN stimulation were demonstrated in spinalized animals as well as in chronic SCI subjects [8, 9].

Since this published work, this therapeutic approach has evolved into a U.S. Food and Drug Administration (FDA) approved treatment for overactive bladder (OAB) (Urgent PC, Cogentix Medical Inc.). Also known as percutaneous tibial nerve stimulation (PTNS) therapy, electrical stimulation of the TN is achieved by a needle electrode inserted just above the medial malleolus. Once a stimulation-evoked foot motor response is confirmed (i.e., activation of the TN), the amplitude is then reduced below the motor threshold and electrical pulses are applied continuously at 20 Hz for a duration of 30 minutes. Significant improvements in OAB symptoms are achieved after this procedure has been repeated weekly, over a period of 3 months. Randomized, double-blinded trials confirm long-term therapeutic effectiveness with treatment outcomes that are comparable to drugs [10-12]. However, widespread acceptance of PTNS therapy among clinicians is limited, due in part to the fact that the clinical outcomes among patients can vary between 49 % and 75 % [13]. This unpredictability of PTNS underscores a major gap in our physiological understanding of TN stimulation.

Recent work in our lab has begun to investigate the potential therapeutic effects of saphenous nerve (SAFN) fibers that can be electrically activated during PTNS therapy. Given the close proximity of the TN and SAFN fibers at the site of needle insertion, the relatively large stimulation amplitudes (~order of several mA), and the use of an uninsulated needle electrode, we hypothesized that any spillover (or concomitant) activation of SAFN fibers can contribute to the bladder-inhibitory effects evoked by TN stimulation, whether delivered by percutaneous or transcutaneous electrodes.

In this paper, we describe a novel bladder-inhibitory reflex that is evoked by electrically activating the SAFN in anesthetized rats. We characterized the effects of different stimulation parameters on bladder function and also confirmed the effectiveness of this bladder-inhibitory reflex in a hyperactive bladder model.

II. METHODS

A. Acute experimental set-up

All experimental protocols were approved by the Animal Use Committee (AUC) at the University of Toronto. Ten adult female Sprague-Dawley rats (250 g - 300 g, Charles River Inc.) were initially anesthetized with isoflurane (3-5%, O_2 flow rate: 0.1 L/min) and later transitioned to urethane (1.2 mg/kg, 2IP injections) following completion of all surgical procedures. Vitals including the core body temperature (37°C-40°C) and the blood O_2 level (97%-100%) were monitored throughout the experiment. The experiment was

terminated by euthanizing the animal with a dose of T-61 (0.3 mL/kg, intra-cardiac, Merck Animal Health).

The bladder was exposed following a midline abdominal incision. The dome of the bladder was catheterized using PE-50 tubing and secured via 6-0 sutures. The catheter was connected in series with a pressure transducer (Deltran, Utah Med, Midvale, USA) and an infusion pump (Harvard Apparatus, Holliston, USA). An incision along the medial aspect of the knee joint provided access to the SAFN trunk where a bipolar nerve cuff electrode (Platinum contacts) was implanted. Electrical stimuli were provided by an external pulse generator (A-M Systems, Carlsborg, USA). A pair of de-insulated stainless steel wire electrodes was inserted into the external urethra sphincter (EUS) muscle using a perineal approach. The EUS EMG signal was filtered and amplified (Bandwidth: 100-3kHz, Gain: 1000). A subcutaneous needle in the thoracic region served as the electrical ground.

B. Stimulation Protocol

A urodynamic model of bladder function was established by constantly infusing physiological saline (infusion rate: 0.08-0.1 mL/min) via the suprapubic catheter. The bladder was allowed to contract repeatedly, as indicated by the peak bladder pressure and corresponding burst in EUS activity. The stimulation amplitude was set at 25 µA and the stimulation frequency was varied between 2 Hz and 50 Hz. The pulse width was set at 200 µs. The stimulation protocol involved an initial 10-minute baseline period (no stimulation) that was followed by alternating 10-minute periods of stimulation (intra-stimulation phase) and no stimulation (post-stimulation phase).

The stimulation trials were delivered in a randomized order, so as to minimize any carry-over effects. All data was collected digitally at a sampling rate of 10 kHz using PowerLab (AD Instruments Inc., Colorado Springs, CO) and analyzed post-hoc using MATLAB (MathWorks Inc., Torrance, CA, USA) and LabChart (AD Instruments Inc., Colorado Springs, CO) software.

C. Hyperactive Bladder Model

In lieu of physiological saline, the urinary bladder was infused with 0.5% acetic acid to induce C-fiber mediated increase in bladder activity.

D. Data Analysis

In accordance with previous studies [14], the bladder contraction rate (BCR) was calculated during each phase: baseline (no-stimulation), intra-stimulation, and post-stimulation. Wilcoxon paired test (non-parametric) was applied to conduct statistical comparisons for each stimulation parameter during intra- and post-stimulation phases with a CI of 95% using JMP 12 (SAS Institute Inc., Cary, NC). All data presented is summarized as mean ± SE.
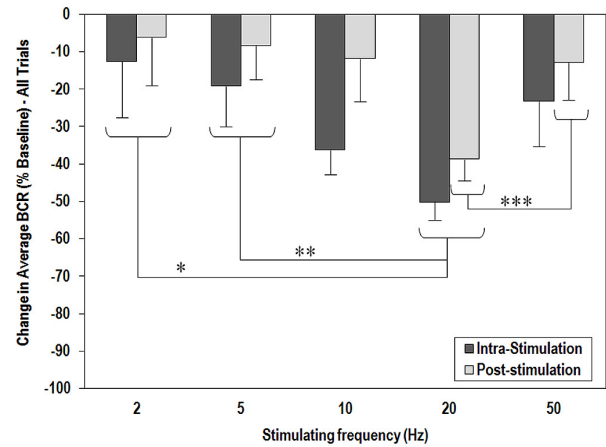

Figure 1. Frequency-dependent change in the averaged bladder contraction rate (BCR) across 41 SAFN stimulation trials (n=10 rats). Changes in BCR during the intra-stimulation periods were significant between 2 & 5 Hz and 20 Hz (*p=0.04, **p=0.03). The post-stimulus inhibitory effects at 20 Hz were significantly different from 2 Hz, 5 Hz and 50 Hz (*p=0.04, **p=0.02, ***p=0.04).

III. RESULTS

A total of 41 stimulation trials were performed in 10 rats, where the average BCR across all baseline periods was 0.7 ± 0.13 contractions/min (range: 0.3 – 1.5 contractions/min, n = 10). Due to long-lasting post-stimulation responses (> 1 hour) observed in some experiments, not all parameters were tested in each experiment.

A. Frequency-Dependent changes in the Bladder Function

During the intra-stimulation phase, SAFN stimulation resulted in an overall 28.3 ± 5.5 % (range: 12.6 % - 50.2 %) decrease in average BCR across all five frequencies (Figure 1). Compared to low-frequency stimulation trials (2 Hz and 5 Hz), 20 Hz stimulation (50.2 ± 4.8%; range: 33.8 % - 78.1%, n=9) resulted in significant bladder inhibition.

The average inhibitory effects during the post-stimulation phase resulted in a 15.6 ± 5.3 % decrease in bladder activity across the range of tested frequencies. Strong inhibitory effects were observed following 20 Hz stimulation (38.7 ± 5.9 %; range: 10.5 % - 62.2 %, n=9), which was significantly different from post-stimulus effects at 2 Hz, 5 Hz and 50 Hz (Figure 1).

B. Effects of SAFN Stimulation in a Hyperactive Bladder

Electrical stimulation of the SAFN during bladder infusion with 0.5% acetic acid also resulted in robust inhibition of bladder function. As shown in Figure 2, the rhythmic bladder activity during the pre-stimulation phase is abolished within 5 minutes of stimulation (25 µA, 20 Hz). The complete loss of bladder activity (absence of both bladder pressure spikes
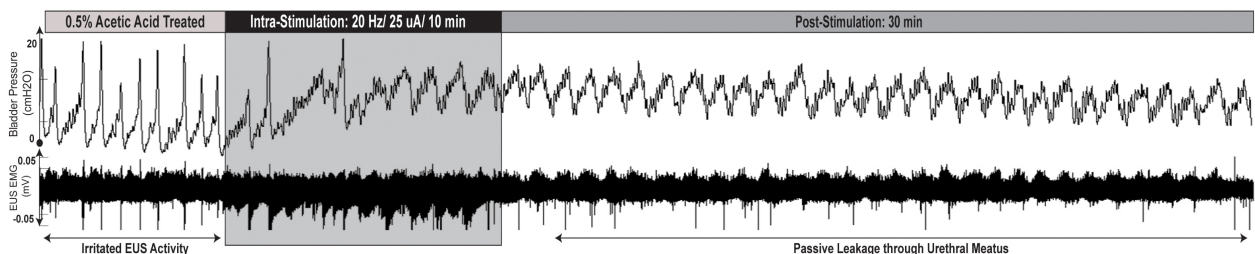

Figure 2. Inhibition of bladder activity evoked by SAFN stimulation in a hyperactive bladder model (continuous infusion of 0.5% acetic acid). Following a brief (10-minutes) duration of low-amplitude (25 µA) SAFN stimulation applied at 20 Hz, complete inhibition of bladder function was achieved within the intra-stimulation period. This loss of bladder function persisted for more than 30 minutes after the end of the stimulation trial.

and concomitant bursting EUS EMG) persists well beyond the 10-minute duration of continuous SAFN stimulation. This state of 'bladder inactivity' is characterized by passive distention of the urinary bladder and random leakage (drops) of fluid through the urethral meatus.

IV. DISCUSSION

Our results show that low-amplitude (25 µA) electrical stimulation of the SAFN elicits robust bladder-inhibitory responses that suggest a highly sensitive reflex pathway. The stimulation amplitude used in this animal study were approximately four times lower than what was used in our previous rat TN stimulation study [14]. Compared to the bladder-inhibitory reflexes evoked by TN stimulation, the results of this study suggest that the SAFN-mediated inhibitory reflex is mediated by significantly larger diameter myelinated fibers. Our findings also point to a reflex that is highly-tuned to stimulus pulses applied between 10 Hz and 20 Hz. This frequency-dependent behavior is consistent with other bladder-inhibitory reflexes evoked by TN stimulation (5 Hz or 30 Hz) [14-16], sacral nerve stimulation (10 Hz- 20 Hz) [17], as well as pudendal nerve stimulation (7 Hz- 15 Hz) [18].

In this study, the effectiveness of SAFN stimulation in suppressing bladder activity during 0.5% acetic acid infusion was shown as an elevated bladder pressure accompanied by random fluid leakage through the urethral meatus (post-stimulation period, Figure 2). Despite the continuous infusion of saline through the suprapubic catheter, the bladder remained in a state of passive distension. And instead of bursts of EUS EMG activity, only random EMG spikes corresponding to leaks (i.e., drops) were observed. The inhibitory effects of SAFN stimulation suggests that this bladder-inhibitory reflex may be effective in treating the various forms of neurogenic bladder (e.g., detrusor overactivity in chronic SCI individuals). These results also support our hypothesis that 'unintended' electrical activation of SAFN fibers could have contributed to the effects of transcutaneous TN stimulation in chronic SCI patients [9, 19], and also in OAB patients receiving PTNS treatment [11].

The cutaneous innervation of the SAFN along the medial aspect of the lower leg suggests that transcutaneous electrical stimulation may be conducive for activating these sensory afferents, and thereby provide an effective means of helping to restore urinary function in persons with SCI. Further translational work is needed to confirm our hypothesis.

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