33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Selective Co-stimulation of Pudendal Afferents Enhances Reflex Bladder Activation

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Abstract—**The loss of normal bladder function is common in persons with spinal cord injury (SCI) and negatively impacts their quality of life. Electrical stimulation of pudendal nerve afferents is a promising approach to restore control of bladder function. Pudendal afferent stimulation can generate reflex contraction of the bladder, but the resulting bladder voiding efficiency remains low. The objective of this work was to evaluate selective co-stimulation of two branches of the pudendal nerve – the cranial urethral sensory nerve (CSN) and the dorsal nerve of the penis (DNP) – as a means to enhance reflex bladder activation and bladder voiding efficiency. In preclinical studies in anesthetized adult cats, co-stimulation of CSN and DNP evoked larger bladder contractions than individual stimulation of either CSN or DNP. In a parallel clinical experiment involving a participant with chronic SCI, co-stimulation of the proximal and distal urethra also produced synergistic augmentation of reflex bladder activity, and thus improved voiding efficiency when compared to reflex distension-evoked voiding. Selective co-stimulation of pudendal afferents is efficacious and should be considered in the development of neural prosthetics for restoration of bladder function in persons with SCI.**

I. Introduction

SPINAL cord injury (SCI) can cause neurogenic bladder dysfunction, including overactive bladder and detrusor-sphincter dyssynergia, leading to urinary incontinence and impaired micturition [1]-[3]. Management of bladder dysfunction in persons with SCI usually consists of the use of anticholinergic medications and intermittent bladder catheterization. However, drug side effects and frequent urinary tract infections negatively impact quality of life [2].

Bladder activation through electrical stimulation is a potential alternative to intermittent catheterization, and recent work has evaluated the effects of stimulation of pudendal nerve (PN) afferents for restoration of bladder emptying [4]-[6]. Electrical stimulation of PN afferents generates reflex bladder contractions and voiding in cats [5],[7]. Similarly, PN stimulation evokes bladder contractions in persons with chronic spinal cord injury [6],[8].

Selective stimulation of secondary branches of the PN, the cranial urethral sensory nerve (CSN) and dorsal genital nerve (dorsal nerve of the penis, DNP), evokes sustained bladder contractions in cats [5]. Additionally, these sensory branches have been shown to innervate the proximal (CSN) and distal (DNP) urethra in cats [9]. Although the PN innervation of the human urethra is not fully known, a recent study in SCI patients showed selective bladder activation through selective stimulation of the proximal and distal urethra [8]. Importantly, selective electrical stimulation of the CSN and DNP in cats showed that reflex bladder activation required different frequencies of stimulation for each branch [5] and in another study, different frequencies of stimulation were needed for excitation at different locations along the urethra [10], suggesting that non-selective co-stimulation is unlikely to be effective.

The purpose of the present study was to test the hypothesis that selective co-stimulation of the CSN and DNP, each at the respective optimal frequency, will enhance reflex bladder activation and improve the efficiency of bladder emptying. The effects of co-stimulation of the CSN and DNP on bladder pressure were measured first in anesthetized cats and subsequently in translational experiments in persons with SCI. The results demonstrate that co-stimulation of CSN and DNP branches at selected frequencies is more effective than individual branch stimulation in cats and dependent on electrode location, stimulation frequency, and stimulation amplitude in persons with SCI.

II. Methods

A. Pre-clinical Experiments

All animal care and experimental procedures were approved by the Duke University Institutional Animal Care and Use Committee. Three sexually intact, adult male cats weighing 4-4.1 kg were anesthetized with ketamine-HCl (35 mg/kg im) and anesthesia was maintained with α-chloralose (65 mg/kg iv, supplemented at 15 mg/kg). The end-tidal CO_2 was maintained between 3.0 and 4.5% with artificial respiration. A catheter in the carotid artery was used to monitor the blood pressure, core body temperature was maintained at 38°C using a thermostatic heating pad, and intravenous fluids were administered (saline or lactated Ringer's solution at 15 $ml \cdot kg^{-1} \cdot h^{-1}$).

The bladder was exposed through a midline abdominal incision, a suprapubic catheter (3.5 Fr) was inserted into the bladder dome, secured with a purse string suture, and the incision was closed in layers. A solid-state pressure transducer (Deltran, Utah Medical) connected in series with the catheter was used to measure bladder pressure and recorded (Astromed8Xe, Astro-Med). The urethra was

Manuscript received March 24, 2011. This work was supported by NIH R01 NS050514.

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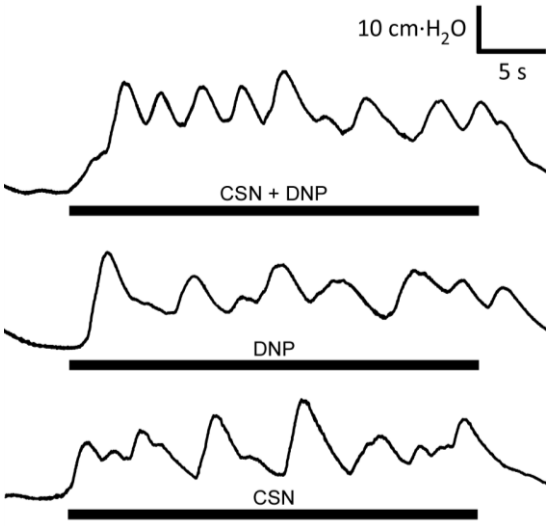

Fig. 1. Representative bladder pressure recordings from one cat in response to stimulation (thick bar). Co-stimulation of CSN and DNP results in larger magnitude bladder contractions than individual DNP or CSN stimulation.

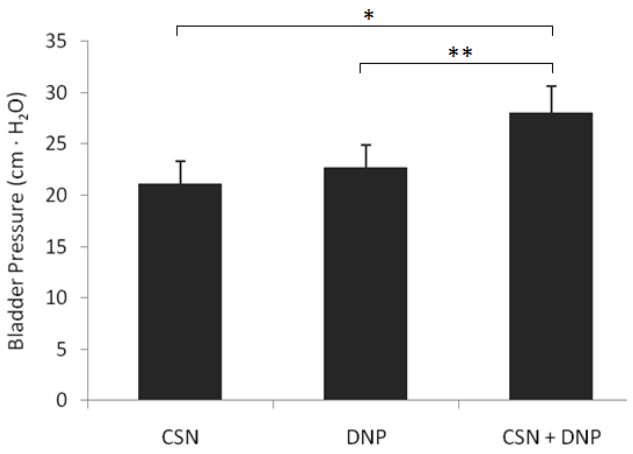

Fig. 2. Co-stimulation of CSN and DNP evokes larger bladder contractions than individual stimulation of CSN or DNP. Mean bladder contractions were significantly different ($p = 0.0073$, ANOVA, $n = 3$ cats). *Post hoc* comparisons indicate that CSN+DNP was significantly different than CSN and DNP alone (* $p = 0.0028$, ** $p = 0.0168$, Fisher's PLSD). Error bars indicate standard errors.

occluded with a 3.5 Fr catheter for isovolumetric experiments. Electromyographic (EMG) activity was recorded from wire electrodes inserted into the external anal sphincter.

The CSN and DNP branches of the PN were stimulated unilaterally by placing cuff electrodes directly around each branch [9]. Monopolar electrodes were composed of platinum contacts embedded within silicone elastomeric cuffs, and a current pulse generator (Pulsar 6bp, FHC Inc.) was used to deliver electrical stimulation to each nerve branch. Two 20-gauge needles placed in the skin served as the counter returns.

Isovolumetric bladder contraction trials were performed at approximately 80% of the volume at which distension-evoked reflex contractions (DECs) began to occur. Trains of monophasic, cathodic stimulus pulses (pulse width=0.1 ms, duration=30 s) were delivered through the nerve cuff electrodes around the CSN and DNP at 2 Hz and 33 Hz, respectively, the optimal frequencies identified in previous studies [5]. Stimulation amplitude was fixed at 3 times that of the threshold to produce a reflex EMG response in the external anal sphincter at 1 Hz for each electrode.

B. Clinical Experiments

Experimental protocols were approved by the Institutional Review Board of Duke University Medical Center and written informed consent was obtained from each volunteer. The subjects were instrumented by intraurethral insertion of a custom stimulating catheter that was also used to adjust bladder volume and rectal insertion of a 9 Fr balloon catheter. The stimulating catheter was a custom Foley catheter made of silicone (0.4 cm diameter) with 15 platinum electrode contacts. The electrode locations were based on the typical anatomical landmarks that are associated with proximal and distal innervation of pudendal nerve afferents: the prostate and urethral meatus. Given the significant inter-individual variability of these landmarks and the total length of the urethra, the electrodes were positioned with 6 targeting the proximal urethra (0.3 cm width, 0.5 cm spacing) and 9 targeting the distal urethra (0.3 cm width, 1.4 cm spacing). Pressure transducers were connected in series to each of the catheters and used to record vesical pressure (P_{ves}) and abdominal pressure (P_{abd}), respectively. Perineal and anal sphincter EMG activity was recorded from percutaneous stainless steel wires. Bladder pressure ($P_{bla} = P_{ves} - P_{abd}$) and EMG responses were recorded throughout the stimulation trials and voiding efficiency trials.

Stimulating catheter electrode contacts were selected to target the proximal (CSN) and distal (DNP) urethra and minimize the threshold (T) to evoke reflex EMG activity. A control bladder fill was performed at the beginning of the experiment to determine the volume threshold for distension evoked bladder contractions.

Stimulation evoked bladder contraction trials were conducted under isovolumetric conditions at 80% of the volume for DECs. Battery powered Empi 300PV electrical stimulators were used to deliver trains of charge balanced, asymmetric biphasic current pulses (pulse width=0.2 ms, duration= 20 s). Blocks of sixteen randomized combinations of stimulation frequencies (2, 10, 20, and 40 Hz each, for proximal and distal electrodes) were presented at stimulation amplitudes of 2 and 4 times the thresholds to evoke reflex EMG responses (2T and 4T, respectively).

Trials to measure voiding (bladder emptying) were then conducted with two pairs of effective stimulation frequency combinations. Control voiding efficiency was determined by filling the bladder without stimulation, and was compared to the voiding efficiency from stimulation at 100% of the DEC bladder volume.

C. Data Analysis

For the pre-clinical experiments mean bladder pressure

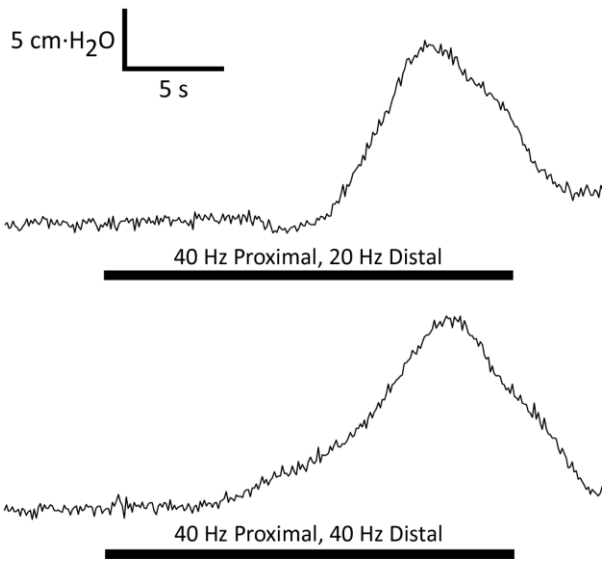

Fig. 3. Bladder pressure recordings from the human in response to co-stimulation (thick bar) for successful proximal and distal frequency combinations.

was calculated as the average of the bladder pressure when stimulation was on, minus the average of the baseline pressure during the 3 seconds before stimulation began. The contraction maximum was the maximum pressure that the bladder contraction generated during the contraction, minus the baseline average. The mean and maximum bladder contraction pressures were averaged for each cat and compared in an ANOVA with *post hoc* comparisons using Fisher's Protected Least Significant Difference (PLSD) test.

Mean bladder pressure and maximum contraction values were calculated similarly for the clinical experiments. Mean bladder pressure was the average P_{bla} during stimulation minus the baseline pressure averaged during the 5 seconds before stimulation. The contraction maximum was the maximum pressure that P_{bla} reached during stimulation, minus the baseline pressure.

Voiding efficiency was calculated by dividing the difference between initial bladder volume and residual volume by the initial bladder volume:

Voiding efficiency (%) = $((V_{initial}-V_{residual})/V_{initial}) \times 100$.

III. Results

A. Isovolumetric Bladder Contractions in Cats

Bladder contractions were evoked in 3 of 3 cats with both 2 Hz CSN stimulation and 33 Hz DNP stimulation (Fig. 1). Mean and maximum stimulation-evoked contraction magnitudes were calculated for each stimulation configuration: CSN alone, DNP alone, and co-stimulation of CSN and DNP. Fig. 2 shows the mean bladder pressures from trials of stimulation-evoked contractions. Mean stimulation-evoked contraction magnitudes were larger for co-stimulation of CSN and DNP (mean ± SE: 28 ± 3 cm·H_2O) than CSN (21 ± 2 cm·H_2O) or DNP (23 ± 2 cm·H_2O) individually. Maximum stimulation-evoked contraction magnitudes were also larger for co-stimulation of CSN and DNP (35 ± 3 cm·H_2O) than CSN (29 ± 2 cm·H_2O) or DNP (30 ± 3 cm·H_2O) individually.

B. Isovolumetric Bladder Contractions in Human

Bladder contractions were evoked in response to stimulation of the proximal and distal urethra at approximately 80% of the DEC volume in a single trial with a male participant with chronic SCI (Fig. 3). The electrode contacts selected to minimize T for distal and proximal stimulation were located 7 cm and 19 cm from the urethral meatus, respectively. Both the mean and maximum stimulation-evoked bladder pressures were dependent on the

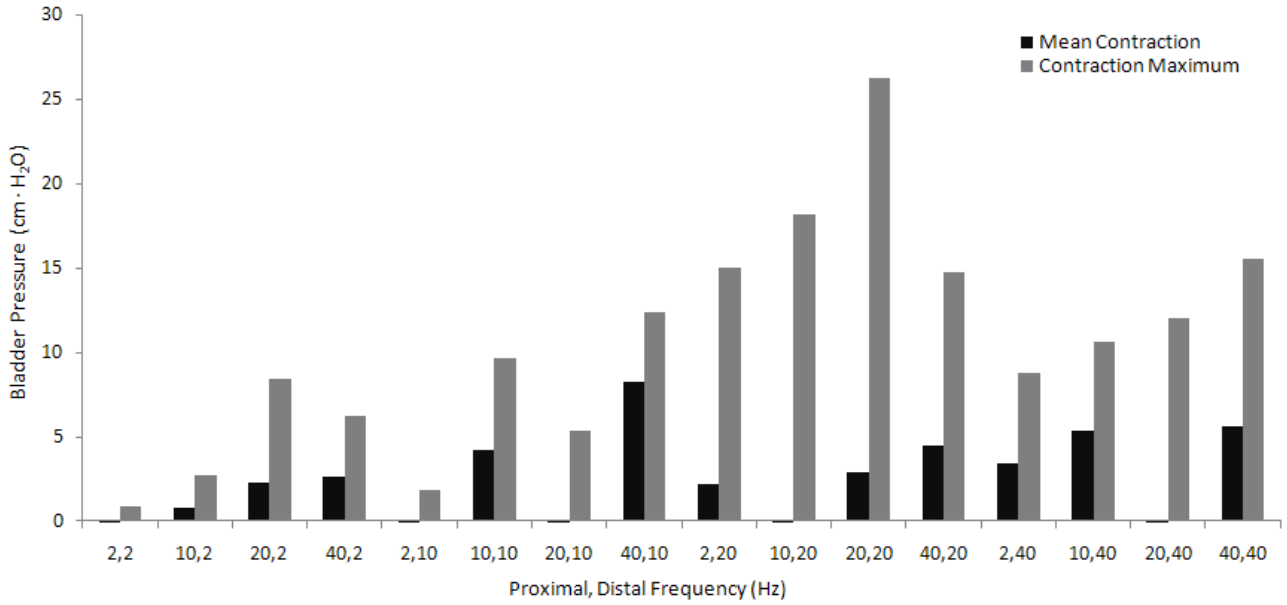

Fig. 4. Bladder contractions evoked from one trial of co-stimulation of the proximal and distal urethra with amplitude of 4T. Bladder pressure for mean bladder contractions and maximum contractions varied for different combinations of proximal and distal frequencies.

stimulation amplitude. Electrical stimulation at 4T evoked bladder contractions that were larger (% change= 542% ± 178%) than those at lower stimulation amplitudes (2T). In addition, both measures of bladder activity varied across the different combinations of stimulation frequencies (Fig. 4) applied to the proximal and distal segments of the urethra.

C. *Voiding Efficiency in Human*

In the same subject, two sets of proximal and distal stimulation frequencies that were effective in evoking bladder contractions were selected for voiding efficiency trials. Stimulation pairs of 40 Hz proximal, 20 Hz distal and 20 Hz proximal, 20 Hz distal were selected as they produced robust contractions in the isovolumetric bladder contraction trials. Co-stimulation with these stimulation frequencies led to successful voiding of volume from the bladder. Voiding efficiency was improved over control (17%) with co-stimulation of 40 Hz proximal, 20 Hz distal (56%) and 20 Hz proximal, 20 Hz distal (36%).

IV. Discussion

Spinal cord injury and other neurological disorders result in the loss of ability to empty the bladder efficiently, leading to serious medical complications including urinary tract infections, incontinence, and damage to the bladder and kidneys. Electrical stimulation of the nervous system is a promising approach to restore control of bladder function. In particular, electrical stimulation of pudendal nerve afferents has been shown to generate reflex contractions of the bladder and bladder emptying, but the voiding efficiency is less than required for clinical application. The purpose of the present study was to test the hypothesis that selective co-stimulation of two discrete sensory branches of the pudendal nerve, the CSN and DNP, each at the respective optimal frequency, would enhance reflex bladder activity and thus lead to improved voiding efficiency.

The effects of co-stimulation of the CSN and DNP on bladder pressures were measured in anesthetized cats and subsequently in translational experiments in persons with SCI. Co-stimulation of CSN and DNP evoked larger bladder contractions than individual stimulation of CSN or DNP alone. The results demonstrate that co-stimulation of CSN and DNP branches at selected frequencies is more effective than individual branch stimulation.

The effects of selective stimulation of the proximal and distal urethra, corresponding to the CSN and DNP, respectively, were measured in a person with chronic SCI. The evoked bladder contraction pressures were dependent on the electrode location, the stimulation frequency, and the stimulation amplitude. This corroborated previous work suggesting the importance of stimulation frequency in intraurethral stimulation in the human for reflex control of bladder function [8]. A similar synergistic effect of co-stimulation may also exist in humans, as the magnitude of bladder contractions varied with different combinations of frequency and amplitude of stimulation. Most importantly, co-stimulation of the proximal (CSN) and distal (DNP) urethra at effective combinations of frequencies improved voiding efficiency over control, distension-evoked voiding.

V. Conclusion

Co-stimulation of specific pudendal afferent branches, CSN and DNP, was effective and evoked robust bladder contractions. Simultaneous electrical stimulation of CSN and DNP at optimal frequencies for each revealed a synergistic effect on bladder contraction magnitude and voiding efficiency. The results support that bladder contractions can be generated by stimulation of pudendal afferents, and that the reflex circuitry mediating these effects is present in the spinal cord [4], as comparable effects were evoked in a human volunteer with chronic spinal cord injury. This work demonstrates that co-stimulation of CSN and DNP is a viable approach to produce larger bladder contractions and increased voiding efficiency and suggests that spatial patterning of stimulation may be effective in both the cat and human. Future development of neural prosthetics for restoration of bladder function should include these techniques of pudendal afferent stimulation to improve micturition for persons with SCI.

Acknowledgment

The authors thank B. Swan, J. Maynor, J. Beaudry, and B. O'Neal for their assistance with the clinical experiments. The authors thank G. Mills for her technical assistance with the animal experiments.

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