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Pudendal Neuromodulation with a Closed-Loop Control Strategy to Improve Bladder Functions in the Animal Study

Chih-Wei Peng *, Yin-Tsong Lin, Shih-Ching Chen, Te-Son Kuo

Abstract—**The aim of this study was to develop a new closed-loop control strategy for improving bladder emptying and verify its performance in animal experiments. Two channel outputs of electrical currents triggered by intravesical pressure (IVP)-feedback signals were set to automatically regulate the rat's pudendal nerve for selective nerve stimulation and blocking. Under this experimental design, a series of *in-vivo* animal experiments were conducted on anesthetized rats. Our results showed that the IVP-feedback control strategy for dual-channel pudendal neuromodulation performed well in animal experiments and could be utilized to selectively stimulate and block the pudendal nerve to augment bladder contraction and restore external urethral sphincter (EUS) bursting activity to simultaneously improve bladder emptying. This study demonstrates the feasibility of the IVP-based feedback-control strategy with animal experiments, and the results could provide a basis for developing a sophisticated neural prosthesis for restoring bladder function in clinical use or the relative neurophysiological study.**

I. INTRODUCTION

Currently, electrical neuromodulations have been developed to treat patients with neurogenic bladder [1]. For example, sacral anterior root neuromodulation (SARN) was successfully introduced in SCI patients with voiding dysfunction [2]. Despite its clinical efficacy, the surgical procedure required to implant the electrodes on the sacral roots is invasive and time consuming [3]. In addition, for certain groups of patients such as neurogenic patients, SARN is not widely accepted due to the need to conduct a dorsal rhizotomy to minimize dyssynergic contractions of the sphincter. However, transection of the dorsal nerve roots can eliminate residual sensation and reflexes including defecation, erection, ejaculation, and lubrication [4, 5]. Thus, there is a need for a more-effective prosthesis to restore the bladder's voiding function.

The aims of the present study were to develop a reliable closed-loop control strategy by electrically modulating pudendal nerve activity to improve bladder emptying in animal experiments. We initially characterized the intravesical pressure (IVP) and EUS-electromyogram (EUS-EMG) signals to determine whether these bio-signals could be used for the closed-loop control of pudendal neuromodulation. On the basis of those characterization results, a dual-channel feedback control strategy and an intermittent an intermittent high-frequency blocking current (HFBC) pattern were designed. Finally, the control strategy combined with the designed electrical current pattern was applied to pudendal nerve in acute animal experiments to assess its performance on bladder function, and the results could provide a basis for developing a new type of bladder controller for clinical use.

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C. W. Peng is with the Department of Physical Medicine and Rehabilitation, Taipei Medical University and Taipei Medical University Hospital, Taipei, Taiwan (corresponding author: 886-9-22550265; e-mail: cwpeng@ tmu.edu.tw).

Y.T Lin is with Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan

T. S. Kuo is with Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan

S. C. Chen is with the Department of Physical Medicine and Rehabilitation, Taipei Medical University, Taipei, Taiwan

II. MATERIALS AND METHODS

A. Computationally characterized physiological signals

The Institutional Animal Care and Use Committee of Taipei Medical University and Hospital approved the experimental protocols involving the use of animals in this study. In total, 16 female Sprague-Dawley rats weighing 290~360 g were used in this study. Initially, ten normal rats were used in the experiment of computational characterization of IVP and EUS-EMG signals. Rats were anesthetized with urethane (1.2 g/kg, s.c.). The urinary bladder was exposed via a midline abdominal incision, and a PE-50 tube was inserted into the bladder lumen for bladder-pressure measurements. Two insulated silver wire electrodes with exposed tips were inserted into the lateral aspects of the mid-urethra to record the EMG from the EUS. Finally, the abdominal wall was closed with nylon sutures.

The IVP and EUS-EMG were simultaneously recorded during continuous-infusion cystometry with an open urethra. The bladder was filled at 0.2 ml/min with physiological saline via the superpubic catheter until voiding occurred and continued such that each trial included at least three voiding contractions. The recorded signals were used for computational characterization.

B. Setup of the experimental systems

The flowchart of the entire experimental system is shown in Fig. 1. There are several operating procedures in this flowchart. The IVP and EUS-EMG signals were simultaneously recorded (sampling rate at 5 kHz) during continuous- infusion cystometry, and the recorded signals were delivered to an analog input of the LabVIEW program written by our lab (National Instruments, Austin, TX, USA) via an analog-to-digital (A/D) converter (Biopac MP 36, BIOPAC Systems, Santa Barbara, CA, USA). The IVP signal was amplified by the A/D converter at 100 folds with 1 kHz of low-pass filter, whereas EUS-EMG signal was at 1000 folds with 10-3k Hz of band-pass filter. The program sampled and analyzed the bladder pressure signal and generated a voltage signal to each of the stimulators via a digital-to-analog converter (USB-6212, National Instruments, Austin, TX, USA). The stimulator was triggered when the IVP reached a preset threshold and stopped when the real-time IVP feedback signal returned to below this threshold.

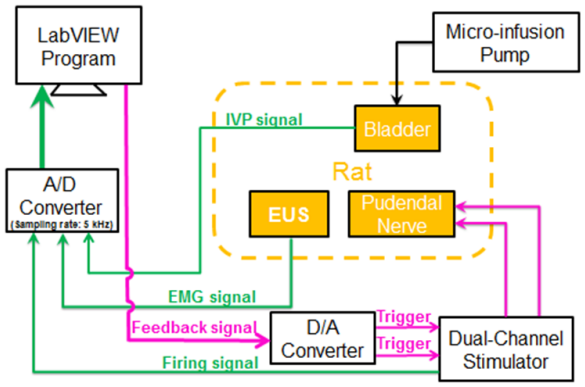

Figure 1. The flowchart of the entire experimental system. The feedback control for dual-channel neuromodulation of the pudendal nerve in the rat was determined by the amplitude of the intravesical pressure (IVP) signals.

C. *Verification of the closed-loop control strategy in the animal experiments*

Several anesthetized rats (n=6) were used in this experiment to verify the performance of our developed device in rats with acute SCI. Acute spinal cord transection was initially carried out in rats at the T_9~T_{10} vertebral level under anesthetized condition. After the T_9~T_{10} laminectomy, the dura matter and spinal cord were transected with fine scissors. The severed ends of the spinal cord typically retracted 1~2 mm and were inspected under a surgical microscope to ensure complete transection. The overlying muscle and skin were sutured closed after spinal transection. Rats further underwent midline abdominal surgery to insert a PE-50 tube into the bladder lumen and two insulated silver wire electrodes into the mid-urethra for IVP and EUS-EMG measurements. The IVP and EUS-EMG measurements in acute-SCI rats usually began 8-24 hr after the conduction of spinal transection, which was determined by the re-emergence of micturition reflex.

Subsequently, the sensory and motor branches of the pudendal nerve were unilaterally exposed via a posterior approach by incising the distal portions of the gluteus major muscles. The pudendal nerve was mounted with a bipolar cuff electrode on the sensory branch to augment reflex bladder contractions and a tripolar cuff electrode on motor branch to block intermittent EUS. Selective stimulation and blocking of the pudendal nerve were performed under continuous-infusion cystometry to quantify its effects on bladder emptying. The bladder was filled via the superpubic catheter until voiding occurred and continued until each trial included at least three voiding contractions. The trigger and stop of the dual-channel neuromodulation were determined by the real-time IVP feedback signal.

D. *Data and Statistical Analyses*

The following cystometric parameters were measured to quantify the effects of pudendal afferent stimulation on voiding: (1) the micturition volume threshold (VT), defined as the infused volume of saline sufficient to induce the first voiding contraction; (2) the contraction amplitude (CA), defined as the maximum pressure during voiding; (3) the bladder contraction duration (CD) during voiding; (4) the inter-contraction interval (ICI), which was the interval between two consecutive voiding contractions. The voiding efficiency (VE) was the ratio between the voided volume (VV) and the VT. The VV was obtained from the value of VT minus the residual volume (RV) of saline withdrawn through the intravesical catheter after the final voiding contraction.

All data are presented as the mean ± standard deviation. One-way analysis of variance (ANOVA) was used for overall comparisons between groups and was followed by the Student-Newman Keuls post hoc test using SigmaStat (SPSS, Chicago, IL). Individual comparisons in a group were made using Student's t test. For all tests, a value of $P < 0.05$ was considered statistically significant.

III. RESULTS

A. *Characteristics of IVP and EUS-EMG in NC and SCI rats*

The typical pattern of IVP and EUS-EMG measurements in both NC and SCI rats are depicted in Fig. 2, and cystometric parameters are summarized in Table I.

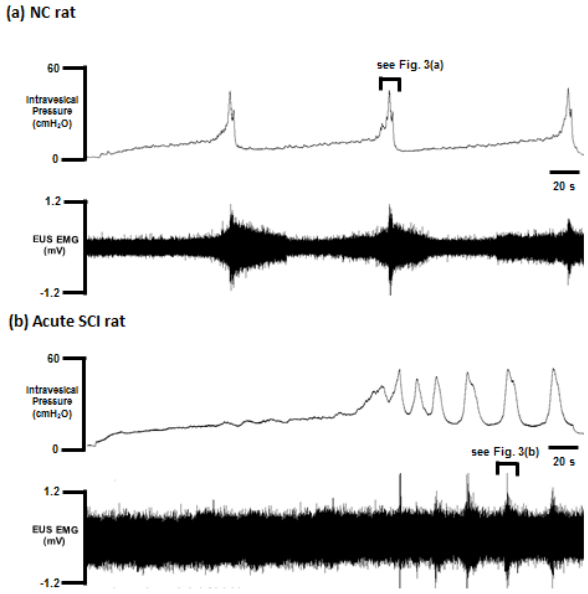

Figure 2. Comparison of IVP and EUS-EMG activity under transvesical infusion beween (a) normal control (NC) and (b) spinal cord-injured (SCI) rats.

Patterns of the IVP during the continuous intravesical infusion of saline did not significantly differ between NC and SCI rats. After the acute SCI intervention, the volume threshold and bladder contraction amplitude increased and the inter-contraction interval and voiding efficiency decreased compared to values in NC rats (Table I). The lower voiding efficiency appeared to decrease the intercontraction interval (Fig. 2), since there was a larger residual volume after the impaired contractions and at a constant filling rate, the bladder again reached the threshold volume in less time.

Table I. Parameters of intravesical pressure (IVP) in normal control (NC) and spinal cord injured (SCI) rats.

Groups	NC rat	SCI rat
VT (ml)	0.41 ± 0.05	0.83 ± 0.04*
CA (cmH_2O)	29.64 ±1.05	38.46 ± 1.24*
CD (s)	27.92 ± 0.99	17.91 ± 1.56*
ICI (s)	158 ± 11	16 ± 2*
VV (ml)	0.32 ± 0.05	0.11 ± 0.03*
RV (ml)	0.09 ±0.02	0.72 ± 0.06*
VE (%)	77.18 ± 5.32	12.77 ± 3.99*

VT: volume threshold ; CA: contraction amplitude; CD: contraction duration; ICI: inter-contraction interval; VV: void volume; RV: residual voulme; VE: void efficiency=VV/VT. Values are Mean±SD, n=10 rats. * $p < 0.05$ indicates a statistically significant difference compared with NC values.

B. Computational characterization of IVP and EUS-EMG

A single micturition contraction of the bladder can be divided into thre phases of IVP: phase 1, rising phase, from point A to B; phase 2, high-frequency oscillation (HFO) and rebound phase, from point B to C; and phase 3, falling phase, from point C to D, as shown in Fig. 3a. During a single micturition contraction, the EUS-EMG clearly showed a long bursting period (BP), which lasted from the end of phase 1 throughout the entire duration of phase 2 (Fig. 3a), which was characterized by clusters of high-frequency spikes (in the active period; AP) separated by periods of quiescence (in the silent period; SP) (Fig. 3c).

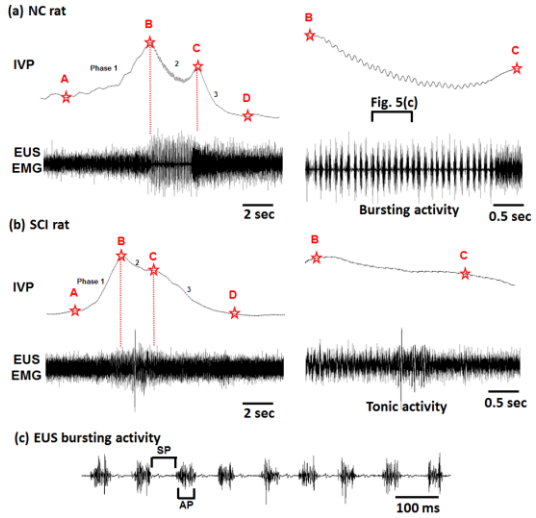

Figure 3. Computational characterization of a micturition contraction in normal control (NC) (a) and spinal cord-injured (SCI) (b) rats.

In contrast, in SCI rats, EUS bursting activity was disapeared and was transformed into tonic activity, and thereby long-lasting EUS tonic activity was observed throughout 3 phases of IVP (Fig. 3b). Note that no rebound wave was detected in phase 2 of IVP (n=10 out of 10 rats). Loss of EUS bursting activity and the rebound wave of the IVP was attributed to acute SCI which induced detrusor-sphincter dyssynergia. Therefore, the EUS tonic activity, represented by the closing of the urethra, appeared during phase 2 of the micturition contraction, which prevented evacation of urine from the urinary bladder.

The IVP and EUS signals were computationally characterized by measuring four critical IVP points that divide the micturition contraction into three IVP phases (Fig. 3). Since urine evacuation and EUS bursting activity simultaneously occurred during phase 2 of IVP (IVP points B to C), the characterization results could feasibly be used to exactly predict the voiding phase of IVP for pudendal neuromodulation. Our results showed that the four caculated pressure points of a micturition contraction in acute-SCI rats were all significantly higher than those values in NC rats (Table II). On the other hand, EUS-EMG measurements in NC rats showed that the SP was 99.2 ± 2.2 ms, which was much longer than the 59.8 ± 2.8 ms of the AP. No EUS bursting activity was observed in acute SCI rats (Table II).

Table II. Computational caculation of IVP and EUS-EMG signals

Points	NC rat	SCI rat
IVP Point A	**9.22 ± 1.33**	**16.25 ± 0.68 ***
IVP Point B	**29.64 ± 1.05**	**38.46 ± 1.24**
IVP Point C	**25.97 ± 1.47**	**34.73 ± 1.68**
IVP Point D	**4.78 ± 1.07**	**15.69 ± 0.60**
EUS AP	**59.8 ± 2.8**	**NA**
EUS SP	**99.2 ± 2.2**	**NA**

Values are mean ± SD, n=10 contractions across 3 rats. * $p < 0.05$ indicates a statistically significant difference compared with NC value.

C. Design of intermittent HFBC pattern

In the present study, EUS bursting activity was replaced by tonic activity in acute-SCI rats, which prevented urine evacuation. EUS bursting activity represents the relaxation and opening of the outlet, which is essential to achieving efficient voiding [6]. Therefore, we applied LFSC and HFBC respectively to the sensory and motor branches of the pudendal nerve to modulate bladder and EUS activities during micturition contractions.

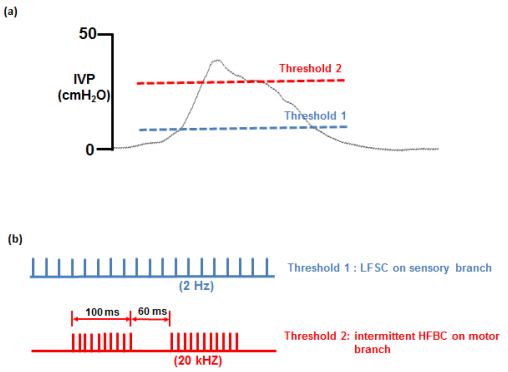

Figure 4. The intravesical pressure (IVP)-feedback control strategy for dual-channel neuromodulation of the pudendal nerve. LFSC: low frequency stimulation current; HFBC: high frequency blocking current.

According to the results of computational characterization of IVP (Table II), two pressure thresholds of IVP were set to trigger and stop the stimulators via a LabVIEW GUI for dual-channel pudendal neuromodulation (LFSC and HFBC outputs), as shown in Fig. 4a. Low frequency stimulation current (LFSC), a monophasic waveform fixed the frequency, amplitude, and pulse width, at

2 Hz, 0.05 mA and 0.1 ms, respectively, was applied to the sensory branch of the pudendal nerve [7] to augment bladder contractions, and the current was delivered when the bladder pressure exceeded 20 cmH_2O and stopped when the pressure dropped below this threshold. An intermittent HFBC, a monophasic waveform fixed the frequency, amplitude, and pulse width, at 20 kHz, 2 mA and 0.01 ms, respectively, was applied to the motor branch of pudendal nerve to restore EUS bursting activity with 25 cmH_2O pressure threshold. The pattern of the intermittent HFBC was characterized by clusters of a 100/60-ms stimulation-on/off ratio, as shown in Fig. 4b. These selected nerve stimulation and blocking parameters were further verified in animal experiments to assess their effects on bladder emptying.

D. Verification in acute animal experiments

In animal experiments, we first accessed whether the LFSC and intermittent HFBC were delivered in the correct IVP phase. Our results showed that the LFSC and the intermittent HFBC were delivered and stopped with correct timing (Fig. 5), in which the LFSC output began from phase 1 and stopped before the end of phase 3 and the HFBC was delivered during phase 3. Our statistical data showed that both LFBC and HFBC were exactly delivered in correct timing for 49 times out of 50 experimental trials. The results demonstrated that the control feedback strategy provided a satisfactory performance for pudendal neuromodulation since the accuracy of current output timing was approximately 100%.

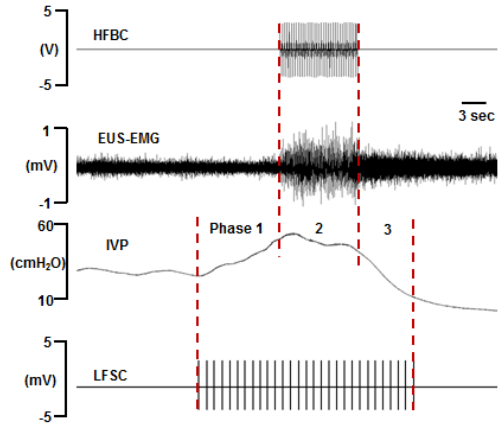

Figure 5. An example of the timing of LFSC and HFBC delivery for pudendal neuromodulation during a micturition contraction. The LFSC was output throughout the IVP phases from 1 to 3, while the output of HFBC was exactly located to phase 2.

After evaluating the timing of the current outputs, the independent application of LFSC and the simultaneous application of LFSC and HFBC on pudendal nerve were separately performed under continuous-infusion cystometry to quantify their effects on bladder emptying in acute-SCI rats (n=6). Results showed that after acute SCI, rats exhibited impaired coordination of the detrusor and EUS during micturition, and thereby SCI rats before neuromodulation exhibited a significant increase in the bladder contraction amplitude and residual volume and a significant decrease in the contraction bladder, inter-contraction interval and voided volume. Thus, the voiding efficiency was significantly reduced from 77% to 12% (Table 1).

Subsequently, the acute SCI rat applied independently with LFSC on the pudendal nerve, the voiding efficiency was significantly increased to 19.8 ± 1.9%; and this was further increased to 24.9 ± 7.0% by the simultaneous application of LFSC and intermittent HFBC. In addition, the voided volume and voiding efficiency were also further increased by the simultaneous application of LFSC and HFBC when compared to the values of the independent application of LFSC. Note that the bladder contraction duration, inter-contraction interval, and voided volume were all increased by either the independent application of LFSC or the simultaneous application of LFSC and HFBC but no significant difference was found in these cystometric parameters between the two neuromodulation schemes.

IV. Discussion and Conclusion

We successfully implemented a closed-loop strategy to control pudendal neuromodulation via IVP feedback signals. Our results showed that pudendal neuromodulation performed well under the control strategy. Pudendal nerve stimulation and blocking were accurately timed using IVP feedback signals in all trials, and the voiding efficiency in acute-SCI rats significantly increased using the sophisticated control strategy. The IVP feedback control strategy can provide a basis for the design of novel neural prostheses to improve bladder emptying in patients with voiding dysfunction. Although the experimental system was temporarily built on commercial equipment, the design principles and animal experience gathered from in this research can also serve as a basis for developing an implantable dual-channel microcontroller-based microstimulator in the future.

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