Aims: To investigate pudendal-to-bladder spinal reflexes in chronic spinal cord injured (SCI) cats induced by electrical stimulation of the pudendal nerve. Methods: Bladder inhibition or voiding induced by pudendal nerve stimulation at different frequencies (3 or 20 Hz) was studied in three female, chronic SCI cats under α-chloralose anesthesia. Results: Voiding induced by a slow infusion (2–4 ml/min) of saline into the bladder was very inefficient (voiding efficiency = 7.3% ± 0.9%). Pudendal nerve stimulation at 3 Hz applied during the slow infusion inhibited reflex bladder activity, and significantly increased bladder capacity to 147.2 ± 6.1% of its control capacity. When the stimulation was terminated, voiding rapidly occurred and the voiding efficiency was increased to 25.4 ± 6.1%, but residual bladder volume was not reduced. Pudendal nerve stimulation at 20 Hz induced large bladder contractions, but failed to induce voiding during the stimulation due to the direct activation of the motor pathway to the external urethral sphincter. However, intermittent pudendal nerve stimulation at 20 Hz induced post-stimulus voiding with 78.3 ± 12.1% voiding efficiency. The voiding pressures (39.3 ± 6.2 cmH2O) induced by the intermittent pudendal nerve stimulation were higher than the voiding pressures (23.1 ± 1.7 cmH2O) induced by bladder distension. The flow rate during post-stimulus voiding induced by the intermittent pudendal nerve stimulation was significantly higher (0.93 ± 0.04 ml/sec) than during voiding induced by bladder distension (0.23 ± 0.07 ml/sec). Conclusions: This study indicates that a neural prosthetic device based on pudendal nerve stimulation might be developed to restore micturition function for people with SCI.


**Bladder Inhibition or Voiding Induced by Pudendal Nerve Stimulation in Chronic Spinal Cord Injured Cats**

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**Key words:** cat; electrical stimulation; micturition; pudendal nerve; spinal cord injury

**INTRODUCTION**

After SCI above lumbosacral level the coordinated activity of the detrusor and urethral sphincter is reduced or eliminated. The detrusor and urethral sphincter contract simultaneously (detrusor sphincter dyssynergia), and the detrusor also contracts frequently even at a relatively small bladder volume (detrusor overactivity). Detrusor sphincter dyssynergia prevents elimination of urine and requires daily urethral catheterization to empty the bladder. Large residual urine volumes and urethral catheterization can cause bladder infections. In addition, detrusor overactivity causes a small bladder storage capacity and frequent incontinence. Currently no single medication can treat both detrusor overactivity and detrusor sphincter dyssynergia.

In the 1970s, Brindley and co-workers developed an implantable sacral anterior root stimulator to restore functions of the lower urinary tract after SCI. This stimulator is commercially available (Finetech Medical Limited, Wellyn Garden City, UK) and has been implanted in over 2000 individuals around the world. It requires sacral posterior root rhizotomy to prevent detrusor overactivity and detrusor sphincter dyssynergia in order to achieve optimal results. The sacral posterior root rhizotomy interrupts the afferent pathways of the lower urinary tract resulting in bladder areflexia—loss of spinal reflex bladder contractions. Thus, the sacral anterior root stimulator is needed to activate the efferent pathways to the bladder to induce voiding. However, the efferent nerve fibers in sacral anterior roots that innervate the external urethral sphincter are larger and have a lower threshold than those that innervate the bladder. Thus, stimulation that activates the small bladder efferent axons also activates the large sphincter efferent axons. In order to solve this problem, a post-stimulus method was developed to induce voiding, which makes use of the fact that the striated muscles of the sphincter contract and relax more rapidly than the smooth muscles of the detrusor. Intermittent bursts of stimulation can be timed so that at the end of each burst the pressure in bladder is maintained high enough to overcome the rapidly reduced sphincter pressure. Although Brindley’s technique is the most successful treatment currently available for both detrusor overactivity and detrusor sphincter dyssynergia, the sacral posterior root rhizotomy is destructive and irreversible which also results in the loss of reflex sexual functions and reflex defection. In order to improve on Brindley’s technique, in this study we investigated the voiding reflex induced by electrical stimulation of the pudendal nerve in chronic SCI cats. Our study aimed at developing a new method to treat both detrusor overactivity and detrusor sphincter dyssynergia without rhizotomy, thereby preserving the reflex sexual and defecation functions that remain after SCI.

Bladder inhibition can be elicited in humans with an intact spinal cord and in chronic SCI cats by stimulating the pudendal nerve with needle electrodes inserted through the perineum or by stimulation of dorsal penile/clitoris nerve in people with SCI. Stimulation of pudendal afferent nerves by intravaginal electrical stimulation also inhibits bladder activity in both normal and acute SCI cats. Pudendal nerve stimulation via electrodes placed directly on the nerve also inhibited pelvic nerve efferent activity in normal cats when bladder volume was low. Previous studies showed that the effective pudendal nerve stimulation frequency to induce bladder inhibition was below 10 Hz. On the other hand, stimulation of the sacral roots in people with SCI using relatively low intensities at 10–15 Hz inhibited detrusor overactivity. It is assumed that the excitatory effect of sacral spinal root stimulation on detrusor activity is due partially to activation of the large diameter pudendal afferents in the sacral posterior roots. Our previous study in chronic SCI cats has shown that pudendal nerve stimulation
could inhibit bladder activity at frequencies below 10 Hz while a maximal inhibition can be achieved at 3 Hz.

Bladder excitation by stimulation of pudendal afferent axons should also be possible because mechanical stimulation of the perigenital area in chronic SCI cats can induce bladder contractions. Our previous study has shown that excitatory perineal-to-bladder reflex, which is also present in neonatal kittens but suppressed during development, reappears after spinal injury. The response to mechanical stimulation of the perigenital region must be due in part to activation of pudendal afferent pathway since the pudendal nerve provides innervation to this skin area. Direct pudendal nerve stimulation in normal cats elicited reflex efferent firing in the pelvic nerve when the bladder is full. It also induced small bladder contractions in acute SCI cats. Our previous study has shown that pudendal nerve stimulation at 20 Hz could induce large bladder contractions in chronic SCI cats. More recently, bladder excitation was demonstrated by intraurethral electrical stimulation in humans with complete SCI, in which bladder excitation was demonstrated by intraurethral electrical stimulation in humans with complete SCI, in which urethral sensory nerve fibers (one branch of pudendal afferents) were assumed to be activated.

Our previous study in chronic SCI cats indicated that the pudendal-to-bladder reflex could be either inhibitory or excitatory depending on the frequency of pudendal nerve stimulation. At a stimulation frequency of 3 Hz, bladder activity could be maximally suppressed, but at 20 Hz bladder excitation could be induced. However, our previous study was conducted under isovolumetric bladder conditions (i.e., the urethra was closed). Therefore, voiding could not occur, and the effectiveness of 3- or 20-Hz stimulation to induce voiding could not be determined. The aim of this study was to further investigate the voiding reflex induced by pudendal nerve stimulation in chronic SCI cats in an effort to improve on Brindley’s technique and develop a new neural prosthetic device to modulate micturition after SCI.

MATERIALS AND METHODS

All protocols involving the use of animals in this study were approved by the Animal Care and Use Committee at the University of Pittsburgh.

Voiding reflexes induced by electrical stimulation of the pudendal nerve were evaluated in three female, chronic SCI cats (3.7–4.3 kg). Spinal cord transection was performed (5–11 months prior to the experiment) at T9-T10 vertebra level by a dorsal laminectomy under isoflurane anesthesia and aseptic conditions. After injection of a local anesthetic (lidocaine, 1%) first on the spinal cord surface and then into the cord through the dura, the spinal cord was cut completely. A piece of gel foam was placed between the cut ends (usually a separation of 2–3 mm). The muscle and skin were then sutured and after full recovery from anesthesia the animal was returned to its cage. Antibiotic (Amoxicillin Trihydrate/Clovanulate Potassium, 15–20 mg/kg) was administered at the time of surgery and again the day following surgery. The bladder was manually expressed twice a day to prevent bladder over-distension and infection. Approximately 3–4 weeks after spinal cord transection, spinal micturition reflexes in response to bladder distension or tactile stimulation of the perigenital region were prominent. At the time of experiments 5–11 months after spinal cord transection, the bladder function had been stabilized in all of the animals.

During the experiments animals were anesthetized with α-chloralose (60 mg/kg i.v., supplemented as needed). A double lumen catheter (5 French) was inserted into the bladder via the dome and secured by a ligature. One lumen of the catheter was attached to a pump to infuse the bladder with saline, and the other lumen was connected to a pressure transducer to monitor the bladder activity. A funnel was used to collect the voided volume into a beaker that was attached to a force transducer to record the volume. The pudendal nerve (usually on the left side) was accessed posteriorly between the sciatic notch and the tail. A tripolar cuff electrode was placed around the pudendal nerve at a location central to the deep perineal branch. The electrode leads were made of platinum wires (diameter 0.25 mm) with a 2 mm distance between the leads. After implanting the pudendal nerve electrode, the muscle and skin were closed by sutures. The temperature of the animal was maintained at 35–37 °C using a heating pad.

Uniphasic pulses (pulse width 0.2 msec) of 2–10 V intensity were used to stimulate the pudendal nerve at frequency of 3 or 20 Hz. The stimulation intensity was determined at the beginning of each experiment by a preliminary test of its effectiveness to induce voiding at the frequency of 20 Hz. Stimulation intensity was gradually increased during the preliminary test until it could generate peak bladder pressure above 40 cmH2O. At this intensity post-stimulus voiding could be induced. Once the intensity was determined, it was used for both 3- and 20-Hz stimulation throughout the same experiment. Anal sphincter contractions were clearly observable at the stimulation intensities used. A Grass S88 stimulator (Grass Medical Instruments) with stimulus isolator (Grass Medical Instruments, SU15) was used to generate stimulus pulses. In order to instill saline into the bladder and induce voiding reflexes, slow infusion (2–4 ml/min) of the bladder was always started with the bladder empty (i.e., a cystometrogram—CMG). Multiple CMGs were performed in each animal. During some of the CMGs when the bladder was filled to half of its control capacity, continuous stimulation of the pudendal nerve at 3 Hz was applied in order to suppress reflex bladder activity and increase bladder capacity. Bladder capacity was defined as the infused volume at which a bladder contraction was induced and fluid was released from the bladder, or when fluid leaked from the bladder in the absence of bladder contraction. When fluid was released from bladder, the infusion was stopped immediately. Then, the bladder was either allowed to contract spontaneously several times to evaluate voiding efficiency, or 20-Hz stimulation was applied to the pudendal nerve to induce a voiding reflex and bladder emptying. Bladder capacities and number of non-voiding contractions were measured during CMGs with or without 3-Hz pudendal nerve stimulation to determine the inhibitory effect on bladder induced by pudendal nerve stimulation. Voiding efficiency, residual bladder volume, peak bladder pressure, and average flow rate were also measured in order to evaluate the effectiveness of 20-Hz pudendal nerve stimulation to induce voiding. Voiding efficiency is defined as the total voided volume divided by the total infused volume. Parameters measured from multiple trials in the same animal were averaged, and the final data are presented as mean ± standard error (SE) for three animals. Paired T-test was used to determine statistical significance (P < 0.05).

RESULTS

Voiding Induced by Bladder Distension

In chronic SCI cats, voiding induced by bladder distension was very inefficient. As shown in Figure 1A, when the bladder was slowly filled at the rate of 4 ml/min, several reflex bladder
contractions appeared first, but no voiding occurred. These initial reflex bladder contractions were defined as non-voiding contractions. When bladder volume increased, a reflex bladder contraction defined as a voiding contraction could elicit the release of saline from bladder. As shown in Figure 1A the voiding contraction occurred just before stopping the infusion after a total of 86 ml was infused. Although several additional reflex bladder contractions occurred after the infusion was stopped, no further release of saline from the bladder was observed. The voided volume was only 3 ml and the residual volume remaining in the bladder was 83 ml (voiding efficiency = 3.5%). Repeated tests in three cats

(Received Manuscript Date: 92.7%, Fig. 2D).

pressure trace indicates stimulation duration. Stimulation: 3 Hz frequency, 8 V intensity, 0.2 msec pulse width. Infusion rate: 4 ml/min.

Contractions. Bladder pressure and flow rate were measured from individual voiding contractions, but the voiding peak pressure during voiding contractions. At the end of each CMG, voiding occurred with several voiding contractions, and increased bladder capacity to 116 ml at which point fluid leaked from the bladder due to the relatively high baseline pressure. When the nerve stimulation was stopped, several reflex bladder contractions occurred accompanied by voiding of small volumes. A total of 26 ml was voided leaving a residual volume of 90 ml in the bladder. Although a larger volume (26 vs. 3 ml) was voided after termination of the 3 Hz inhibitory pudendal nerve stimulation and voiding efficiency was increased (22.4% vs. 3.5%), the 3 Hz stimulation did not reduce the residual bladder volume (90 vs. 83 ml) due to a larger bladder capacity.

voiding after the 3 Hz stimulation (8 V, 0.2 msec) was applied to the pudendal nerve when the infused volume was about half of the control capacity. At the start of the stimulation, it induced a small bladder contraction without voiding. The 3-Hz stimulation completely inhibited non-voiding bladder contractions, and increased bladder capacity to 116 ml at which point fluid leaked from the bladder due to the relatively high baseline pressure. When the nerve stimulation was stopped, several reflex bladder contractions occurred accompanied by voiding of small volumes. A total of 26 ml was voided leaving a residual volume of 90 ml in the bladder. Although a larger volume (26 vs. 3 ml) was voided after termination of the 3 Hz inhibitory pudendal nerve stimulation and voiding efficiency was increased (22.4% vs. 3.5%), the 3 Hz stimulation did not reduce the residual bladder volume (90 vs. 83 ml) due to a larger bladder capacity.

Table I and Figure 2A summarize the increase in bladder capacity in three animals induced by 3 Hz stimulation of the pudendal nerve. In each animal bladder capacities were normalized to the averaged capacity measured during the control period (i.e., without 3 Hz stimulation). The 3 Hz stimulation significantly (P < 0.05) increased bladder capacity to 147.2% ± 6.1% of the control capacity. Meanwhile, it also inhibited reflex bladder activity and significantly (P < 0.05) reduced the total number of non-voiding bladder contractions from 5.6 ± 1.3 to 1.2 ± 0.7 (see Fig. 2B). Figure 2C summarizes the efficiency of voiding induced by bladder distension in three animals. CMGs in the absence of 3 Hz pudendal nerve stimulation induced a low voiding efficiency (7.3% ± 0.9%). The 3 Hz stimulation not only increased the bladder capacity (see Fig. 2A) but also slightly increased voiding efficiency to 25.4% ± 6.1% (not significant, P > 0.05). Residual bladder volumes after reflex bladder contractions with or without 3 Hz pudendal nerve stimulation are shown in Figure 2D. The residual volumes were normalized to the averaged control capacity in each animal. Under control conditions, 92.7% ± 0.9% of the infused volume remained in the bladder after the voiding. Although 3 Hz stimulation of the pudendal

### Table I. Measurements From Each Cat Under Different Experimental Conditions

<table>
<thead>
<tr>
<th></th>
<th>Cat #1</th>
<th>Cat #2</th>
<th>Cat #3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder capacity</td>
<td>79.3 ± 2.4 (6)</td>
<td>22.6 ± 0.6 (11)</td>
<td>25.0 ± 1.3 (6)</td>
</tr>
<tr>
<td>Voiding efficiency</td>
<td>5.7 ± 0.7 (6)</td>
<td>7.6 ± 0.9 (8)</td>
<td>8.7 ± 2.4 (3)</td>
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<tr>
<td>Bladder pressure</td>
<td>26.1 ± 2.0 (18)</td>
<td>23.0 ± 1.0 (18)</td>
<td>20.2 ± 1.9 (12)</td>
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<tr>
<td>Flow rate (ml/sec)</td>
<td>0.29 ± 0.05 (18)</td>
<td>0.30 ± 0.03 (18)</td>
<td>0.09 ± 0.04 (12)</td>
</tr>
<tr>
<td>Number of non-voiding contractions</td>
<td>6.0 ± 0.6 (6)</td>
<td>3.1 ± 0.4 (8)</td>
<td>7.7 ± 0.6 (6)</td>
</tr>
<tr>
<td>Normalized capacity</td>
<td>150.5 ± 3.0 (3)</td>
<td>155.7 ± 2.2 (6)</td>
<td>135.3 ± 11.2 (6)</td>
</tr>
<tr>
<td>Voiding efficiency</td>
<td>22.6 ± 1.4 (3)</td>
<td>37.1 ± 0.0 (1)</td>
<td>16.5 ± 1.5 (3)</td>
</tr>
<tr>
<td>Number of non-voiding contractions</td>
<td>0.3 ± 0.3 (3)</td>
<td>0.7 ± 0.3 (6)</td>
<td>2.5 ± 0.8 (6)</td>
</tr>
<tr>
<td><strong>3 Hz</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normalized capacity</td>
<td>150.5 ± 3.0 (3)</td>
<td>155.7 ± 2.2 (6)</td>
<td>135.3 ± 11.2 (6)</td>
</tr>
<tr>
<td>Voiding efficiency</td>
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</tr>
<tr>
<td>Number of non-voiding contractions</td>
<td>0.3 ± 0.3 (3)</td>
<td>0.7 ± 0.3 (6)</td>
<td>2.5 ± 0.8 (6)</td>
</tr>
<tr>
<td>20 Hz</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bladder pressure</td>
<td>36.0 ± 2.3 (22)</td>
<td>30.6 ± 1.0 (30)</td>
<td>51.4 ± 1.9 (36)</td>
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<tr>
<td>Flow rate (ml/sec)</td>
<td>0.96 ± 0.04 (12)</td>
<td>0.98 ± 0.03 (30)</td>
<td>0.85 ± 0.03 (36)</td>
</tr>
<tr>
<td><strong>3 + 20 Hz</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voiding efficiency</td>
<td>78.4 ± 2.6 (2)</td>
<td>88.9 ± 3.4 (6)</td>
<td>91.1 ± 1.6 (6)</td>
</tr>
</tbody>
</table>

*Control—Voiding induced by bladder distension alone without any stimulation. 3 Hz—3-Hz pudendal nerve stimulation applied during a slow bladder filling. 20 Hz—20-Hz pudendal nerve stimulation applied at the end of bladder filling. 3 + 20 Hz—Voiding induced by 20-Hz stimulation with prior 3-Hz stimulation. Bladder pressure—peak pressure during voiding contractions. At the end of each CMG, voiding occurred with several voiding contractions. Bladder pressure and flow rate were measured from individual voiding contractions, but the voiding efficiency was calculated from the total voided volume for each CMG. The numbers in parentheses indicate the number of measurements in each animal.*
nerve significantly increased bladder capacity (see Fig. 2A), it did not reduce the absolute residual volume, but rather slightly increased it by approximately 10% (see Fig. 2D).

**Voiding Induced by 20-Hz Stimulation of Pudendal Nerve**

Electrical stimulation of the pudendal nerve at 20 Hz applied at the end of the CMG induced a large amplitude, long-lasting bladder contraction (Fig. 3). However, voiding only occurred after the stimulation was terminated (i.e., post-stimulus voiding, see Fig. 3 lower trace) because the external urethral sphincter, which is innervated by the pudendal nerve, was also activated during the 20-Hz stimulation. When the stimulation was stopped, the external urethral sphincter (striated muscle) relaxed faster than the detrusor (smooth muscle) allowing bladder pressure to exceed urethral pressure, and thereby inducing post-stimulus voiding.

As shown in Figure 3, intermittent, short burst, pudendal nerve stimulation at 20 Hz could induce a series of post-stimulus voiding responses, which resulted in a total of 18 ml

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**Fig. 2.** Bladder capacity (A), number of non-voiding contractions (B), voiding efficiency (C), and residual volume (D) with or without 3-Hz pudendal nerve stimulation in three chronic SCI cats (N = 3). Control—with without 3 Hz nerve stimulation. 3 Hz—with 3-Hz nerve stimulation. Stimulation: 2–10 V intensity, 0.2 msec pulse width. Infusion rate: 2–4 ml/min. * indicates statistical significance (P < 0.05).

**Fig. 3.** Voiding induced by 20-Hz stimulation of the pudendal nerve in a chronic SCI cat (9 months). Total 23 ml was infused into the bladder and 18 ml was voided. The black bars under the bladder pressure trace indicate stimulation durations. Stimulation: 20-Hz frequency, 2 V intensity, 0.2 msec pulse width. Infusion rate: 2 ml/min.
voided out of the 23 ml infused (voiding efficiency = 78.3%). In this study, the intermittent stimulation was generated manually by switching on/off the stimulator while visually monitoring the bladder pressure. With the bladder gradually emptying, the intermittent 20 Hz stimulation generated a series of gradually decreasing bladder pressures, and voiding eventually stopped.

The post-stimulus voiding induced by intermittent, short burst, 20-Hz stimulation was also evaluated after the bladder capacity was significantly increased by 3 Hz stimulation. As shown in Figure 4, the 3-Hz stimulation increased the bladder capacity from 23 to 34 ml (Figs. 3 and 4 show results from the same animal). The intermittent 20-Hz stimulation produced a total voided volume of 32 ml resulting in a voiding efficiency of 94.1%.

Table I and Figure 5A summarize the voiding efficiencies induced by intermittent 20 Hz stimulation of the pudendal nerve in all animals. Compared to the efficiency of voiding induced by bladder distension alone, intermittent 20 Hz stimulation of the pudendal nerve significantly \((P < 0.05)\) increased the voiding efficiency from \(7.3\% \pm 0.9\%\) to \(78.3\% \pm 12.1\%\). When 3 Hz stimulation was applied during bladder filling to increase bladder capacity, the intermittent 20-Hz stimulation produced a voiding efficiency of \(86.1\% \pm 3.9\%\) (see Fig. 5A), which was not significantly different from 20-Hz stimulation alone \((P > 0.05)\). Figure 5B summarizes the residual bladder volumes in all animals after voiding induced by the intermittent 20-Hz stimulation with or without the prior 3-Hz stimulation. The residual volume was normalized to the averaged control capacity in each animal. Compared to the residual volumes after the voiding induced by bladder distension alone, the intermittent 20-Hz stimulation significantly \((P < 0.05)\) reduced the bladder residual volumes from \(92.7\% \pm 0.9\%\) to \(21.7\% \pm 12.1\%\). However, the 3-Hz stimulation applied prior to the intermittent 20-Hz stimulation did not further reduce the residual volumes \((21.0\% \pm 6.8\%, \text{see Fig. 5B})\).

Figure 6A compares the peak bladder pressures during voiding induced by bladder distension (see Fig. 1) with the averaged peak bladder pressures during the first three voidings induced by the intermittent 20-Hz stimulation (see Fig. 4). The average peak bladder pressure \((39.3 \pm 6.3 \text{ cmH}_2\text{O})\) induced by intermittent 20-Hz stimulation of the pudendal nerve was not significantly higher than the average peak bladder pressure \((23.1 \pm 1.7 \text{ cmH}_2\text{O})\) induced by bladder distension \((6.1%, P > 0.05)\). Figure 6B compares the average flow rates during the voidings induced by bladder distension and by intermittent 20-Hz stimulation of the pudendal nerve. The average flow rates during intermittent 20-Hz stimulation were also measured during the first three short bursts of

![Fig. 4. Voiding induced by intermittent 20-Hz pudendal nerve stimulation following 3-Hz continuous stimulation in a chronic SCI cat (9 months). Thirty-four milliliter was infused into the bladder and 32 ml was voided. The black bars under the bladder pressure trace indicate stimulation durations. Stimulation: 2 V intensity, 0.2 msec pulse width. Infusion rate: 2 ml/min.](image-url)

![Fig. 5. Voiding efficiency (A) and residual bladder volume (B) induced by intermittent 20-Hz pudendal nerve stimulation in three chronic SCI cats \((N = 3)\). Control—Voiding induced by bladder distension alone. 20 Hz—Voiding induced by intermittent 20-Hz stimulation without prior 3-Hz continuous stimulation. 3 Hz + 20 Hz—Voiding induced by intermittent 20-Hz stimulation with prior 3-Hz continuous stimulation. Stimulation: 2–10 V intensity, 0.2 msec pulse width. Infusion rate: 2–4 ml/min. * indicates statistical significance \((P < 0.05)\).](image-url)
stimulation (see Fig. 4) when the bladder volume was still large and comparable to the bladder volume during the voiding induced by bladder distension (see Fig. 1). The intermittent 20-Hz stimulation of the pudendal nerve increased the voiding flow rate significantly ($P < 0.05$) from 0.23 ± 0.07 to 0.93 ± 0.04 ml/sec (Fig. 6B).

**DISCUSSION**

This study in anesthetized chronic SCI cats has shown that storage and voiding functions of the lower urinary tract, which are impaired after SCI, could be improved by activation of the somatic afferent pathways in the pudendal nerve. Electrical stimulation of the pudendal nerve at 3 Hz inhibited non-voiding contractions during bladder filling, suppressed reflex voiding, and increased bladder capacity (Figs. 1 and 2). Thus the 3 Hz pudendal nerve stimulation converted the overactive bladder (small capacity with many non-voiding contractions during storage phase, see Fig. 1A) to a quiescent larger capacity bladder (see Fig. 1B). Furthermore, voiding efficiency which is very low in chronic SCI cats was significantly increased by intermittent 20-Hz stimulation of the pudendal nerve (see Fig. 5A). Although the peak bladder pressures induced by intermittent 20-Hz stimulation of the pudendal nerve were not significantly higher than those induced by bladder distension alone (Fig. 6A), the average flow rates were significantly faster with the stimulation (Fig. 6C). This study shows that after SCI the spinal voiding reflex in cats can be either inhibited or activated depending on the frequency of pudendal nerve stimulation (i.e., 3 or 20 Hz).

In anesthetized cats with an intact spinal cord, reflex micturition is mediated by a spinobulbospinal reflex involving a control center located in the rostral pons—pontine micturition center (PMC). The PMC coordinates the activity of bladder and urethra, so that during storage the bladder is quiescent and the urethra is closed, whereas during voiding the bladder contracts and the urethra relaxes. After SCI, this coordination is lost due to the absence of supraspinal control. However, a few weeks after SCI, a spinal micturition reflex emerges. This spinal reflex results in frequent bladder contractions during storage (i.e., neurogenic detrusor overactivity), inefficient voiding, and a large residual bladder volume (see Figs. 1 and 2).

A recent study showed that intermittent pudendal nerve stimulation at 33 Hz induced a voiding reflex in cats with an intact spinal cord. However, it is very difficult to attribute this voiding effect solely to a spinal reflex in normal cats, since the spinobulbospinal micturition reflex is intact and the PMC coordinates voiding once the bladder contraction is initiated by pudendal nerve stimulation. After SCI the spinal reflexes of the lower urinary tract undergo significant plasticity. Our previous study using chronic SCI cats showed that the property of pudendal-to-bladder spinal reflex was frequency dependent (inhibitory at 3 Hz, but excitatory at 20 Hz). In the present study we further showed that although the parasympathetic bladder-to-bladder spinal reflex after SCI could not induce efficient voiding, the pudendal-to-bladder spinal reflex could either increase bladder capacity or induce efficient voiding when the pudendal nerve (somatic pathway) was stimulated at frequency of 3 or 20 Hz.

In our previous study of chronic SCI cats, a large amplitude, long-lasting, rebound bladder contraction was observed at the termination of the inhibitory 3-Hz pudendal nerve stimulation when the urethral outlet was closed. Therefore, it was expected that this large rebound bladder contraction might be able to induce efficient voiding if the urethral outlet was open. However, in this study we failed to induce this large rebound bladder contraction with an open urethra. Instead, several small, short-lasting bladder contractions followed the termination of the inhibitory 3-Hz pudendal nerve stimulation (Fig. 1B), which slightly increased the voiding efficiency (Fig. 2C), but the absolute residual volume was still large (Fig. 2D). Similar short-lasting bladder contractions were also observed in awake, chronic SCI cats.

This very different bladder response might be related to the condition of the urethra, that is, either open or closed. The bladder volume was much larger than its control capacity at the end of inhibitory pudendal nerve stimulation (see Fig. 1). Once the inhibition was removed, the excitatory parasympathetic bladder-to-bladder spinal reflex would induce a bladder contraction. If the urethra was closed at this moment, no bladder volume could be released and the increased tension on the bladder wall would further enhance the bladder-to-bladder spinal reflex, which would result in a large amplitude, long-lasting, rebound bladder contraction. However, if the urethra was open as in this study, the bladder contraction induced by the removal of inhibitory pudendal nerve stimulation would cause a release of bladder content. This

**Fig. 6.** Peak bladder pressure (A) and average flow rate (B) induced by bladder distension or by intermittent 20-Hz stimulation in three chronic SCI cats (N = 3). Control—Voiding induced by bladder distension. 20 Hz—Voiding induced by intermittent 20-Hz stimulation. Only the peak bladder pressures and the average flow rates of the first three voids during a series of voids induced by intermittent 20-Hz stimulation were measured. Stimulation: 2–10 V intensity, 0.2 msec pulse width. Infusion rate: 2–4 ml/min. * indicates statistical significance ($P < 0.05$).
would reduce tension in the bladder wall, and in turn reduce mechano-sensitive afferent firing and excitatory input to the bladder-to-bladder spinal reflex pathway. Therefore, only small, short-lasting bladder contractions and release of saline from the bladder occurred (see Fig. 1B). The different results due to open or closed urethral conditions indicates that the spinal micturition reflex emerging after SCI is very different from the spinobulbospinal micturition reflex that is under the control of the PMC. Prolonged activation of the spinal micturition reflex that would be necessary for complete bladder emptying seems to require a persistent afferent excitatory input driven by a maintained bladder wall tension. On the other hand, the spinobulbospinal micturition reflex, once it is activated, can be kept active by the PMC even when the bladder is emptying and its volume becomes progressively smaller.

Intermittent 20-Hz stimulation induced post-stimulus voiding and increased voiding efficiency dramatically (Fig. 5A). During the intermittent pudendal nerve stimulation the bladder pressure induced by each burst of stimulation gradually decreased with time (Figs. 3 and 4) indicating that the effect of pudendal nerve stimulation was gradually attenuated by the progressive decrease of bladder volume. The post-stimulus voiding is attributable to the persistence of the bladder contractions after termination of the stimulation in contrast to the rapid relaxation of the urethral sphincter striated muscles. However, as the bladder pressure induced by each stimulus burst progressively decreased (see Figs. 3 and 4), it eventually failed to overcome the urethral outlet resistance resulting in a residual volume. The residual volumes were almost same (Fig. 5B) even when the initial bladder volumes were different (see Fig. 2A) indicating that the ability of pudendal nerve stimulation to empty the bladder was determined by urethral outlet resistance rather than the initial tension in the bladder wall. This also explains why 3-Hz stimulation increased bladder capacity, but did not reduce the absolute residual volume (see Fig. 2D and Fig. 5B).

The peak bladder pressures induced by intermittent 20-Hz stimulation were not significantly higher than those induced by the bladder distension (Fig. 6A). However, the average flow rate induced by the intermittent 20-Hz stimulation was significantly greater than that induced by bladder distension (see Fig. 6B). This indicated that the urethral outlet resistance was significantly lower during the post-stimulus voidings than during the voidings induced by bladder distension alone. One of the possible explanations is that the 20-Hz pudendal nerve stimulation inhibited the bladder-to-sphincter spinal reflex while it was activating the pudendal-to-bladder spinal reflex. This possibility warrants a further investigation into the interactions between pudendal nerve stimulation and other spinal reflexes to the sphincter, such as bladder-to-sphincter reflex, or sphincter-to-sphincter reflex, etc. Currently, little is known about how the pudendal afferents interact with these spinal reflexes after chronic SCI.

In this study the intermittent pudendal nerve stimulation was timed by manually switching on/off the stimulator while visually monitoring the induced bladder pressure. The duration of and the interval between the short burst stimulations could influence voiding efficiency (see Figs. 3 and 4). Meanwhile, the stimulation intensity could also influence the result, because higher intensities could induce stronger contractions of the external urethral sphincter resulting in higher urethral resistance. However, a higher stimulation intensity might also cause the bladder pressure to rise faster and require a shorter burst duration to reach the bladder pressure effective for voiding. The influence of stimulation parameters (stimulation duration, interval, and intensity) on voiding efficiency needs to be studied in the future.

The effectiveness of 3-Hz (inhibitory) or 20-Hz (excitatory) chronic pudendal nerve stimulation needs to be tested in humans to evaluate the potential clinical benefits of this therapy. In people with SCI electrical stimulation of dorsal penis/clitoris nerve using surface electrodes at frequencies ranging from 5 to 10 Hz can inhibit the hyperreflexic bladder activity.11 34 Since these nerves are branches of the pudendal nerve, the results with surface stimulation indicate that pudendal nerve stimulation at a frequency between 5 and 10 Hz might have to be employed in humans instead of 3 Hz. In complete SCI subjects, intra-urethral electrical stimulation at a frequency of 20 Hz excited the bladder.28 29 Since the urethra is innervated by pudendal nerve, the 20-Hz pudendal nerve stimulation might be also effective in humans to activate bladder reflexes.

CONCLUSIONS

This study using chronic SCI cats has shown that a neural prosthetic device based on pudendal nerve stimulation might be developed to restore micturition function after SCI. This neural prosthetic device will not require a sacral posterior root rhizotomy which is needed in Brindley’s method.5 7 Therefore, it will preserve the remaining spinal reflexes for defection and sexual functions after SCI. The surgery needed to access the pudendal nerve is also less invasive8 9 than Brindley’s method that requires a spinal laminectomy to access the sacral anterior and posterior roots. Although considerable study is still needed to fully implement the design of a pudendal nerve-stimulating device, further analysis of the pudendal-to-bladder spinal reflexes could provide substantial benefits for people with lower urinary tract dysfunctions after SCI.

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