Comparison of direct bladder and sacral nerve stimulation in spinal cats

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Abstract—Neuroprosthetic techniques have been used to facilitate voiding via electrical stimulation for bladder management following spinal cord injury (SCI), but high urethral resistance has been a problem. This problem was investigated here in the chronic, spinal, male cat (C6-T1) using direct bladder and sacral nerve stimulation. Direct bladder stimulation was only conducted during terminal procedures with an open abdomen and with four hook electrodes inserted into the bladder wall. Sacral stimulation was conducted daily during the 10 weeks post-SCI and during terminal procedures. Stimulation was conducted with both implanted epidural electrode and surface electrodes over the sacral bone. Both of these sacral methods stimulated anterior and posterior roots. However, these sacral methods were generally ineffective for inducing voiding during the study. In three of the five animals investigated, stimulation did not empty the bladder. In the remaining two animals, the bladder was emptied with sacral stimulation, but only after return of bladder reflex activity, 2 to 4 weeks post-injury. When poor voiding occurred in spite of high bladder pressures, it indicates high urethral resistance. This was confirmed using video cystourethrography where the membranous urethra was observed to remain closed following stimulation.

Direct bladder stimulation was then compared to sacral nerve stimulation during terminal procedures. Direct bladder stimulation induced voiding at a high rate both during and after stimulation, whereas sacral nerve stimulation with implanted electrodes induced voiding at a lower rate and only after stimulation. A simple urethral resistance measure, the ratio of bladder pressure to voiding rate, was lower with direct bladder stimulation than sacral nerve stimulation.

Stimulation-facilitated voiding has also been associated with the development of bladder wall hypertrophy. This problem was investigated by evaluating bladder wall thickness postmortem in three groups of animals: the first group was the spinal-stimulated animals detailed above; the additional two groups were a spinal-nonstimulated but instrumented group maintained for 10 weeks following injury, and an intact group of animals. The stimulated spinal cats tended to have the thickest bladder wall followed by the nonstimulated spinal cats. The wall thickness of intact animals served as a control.

Key words: bladder wall hypertrophy, neuroprosthetics, spinal cat, spinal cord injury, urethral function, urodynamics.

INTRODUCTION

Bladder activity after suprasacral spinal cord injury (SCI) is characterized by loss of control and contractions that do not completely empty the bladder. Bladder activity is also associated with an increased urethral resistance that further reduces voiding in the majority of SCI patients (1,2,3,4). Current management techniques for these problems involve some form of catheterization (i.e., intermittent, external collection, continuous or suprapubic). In addition, drugs and surgery are often used to reduce outlet resistance. However, the drawbacks with these management techniques include urinary tract infections, incontinence, and poor control over bladder function (3,4).
Neuroprosthetic techniques have been introduced as alternative methods to manage the problems of micturition control and complete bladder emptying (5,6,7,8,9,10). Two methods of inducing bladder contractions and voiding have primarily been investigated are sacral, ventral-root nerve stimulation and direct bladder stimulation. Excellent results have been reported in 57 patients worldwide (6) using ventral-root stimulation with the Brindley method (1,6,11). This method, however, requires that sacral afferent roots be cut to reduce high urethral resistance or incontinence. Also, electrodes are implanted within the dura, a difficult surgical procedure. Tanagho and Schmidt (9,12) have reported similar problems with high urethral resistance while stimulating the sacral ventral root extradurally within the sacral canal. Alternatively, direct bladder stimulation has also shown success in clinical trials. Magasi and Simon (13) induced daily micturition with eight electrodes implanted in the bladder wall in patients with various neurological problems, including SCI. They indicate that high outlet resistance can be managed by bladder neck resection. These encouraging clinical results with sacral and direct bladder stimulation suggest that further investigation is warranted comparing and optimizing stimulating techniques.

We have previously investigated sacral nerve stimulation using small needle-type electrodes in the sacral canal in a dog model. We found that: 1) a single electrode in the canal was effective for stimulation to obtain maximum bladder contractions (14); 2) daily voiding of the bladder could be induced with complete bladder emptying (10,15,16); 3) voiding improved with time following the recovery of bladder reflex activity (10,15,17); and, 4) that surface electrodes over the sacrum were effective for inducing bladder contractions (16). However, there is a concern that our dog model does not represent SCI patients because of low urethral resistance. Alternatively, Galiano et al. (2) have argued that the high-level lesioned cat has lower urinary tract characteristics similar to SCI patients. Therefore, we have reevaluated our stimulation studies using T1-lesioned cats. We also compared direct bladder and sacral nerve stimulation to further evaluate the high urethral resistance problem often associated with neuroprosthetic techniques (18). Urodynamic parameters of pressure, flow, and urethral resistance were used for this comparison along with cystourethrography. Our findings support the role of the membranous urethra in high urethral resistance problems (2,3,4,17).

An additional problem associated with stimulation-driven voiding has been the possible development of bladder wall hypertrophy (3,19). This problem was assessed by comparing the bladder wall thickness of intact, spinal-injured, and spinal-injured and stimulated cats.

**METHODS**

**Preparation**

Nine vendor-supplied male cats weighing 2 to 4 kg were spinalized and instrumented with sacral electrodes. The animals were anesthetized with IM ketamine hydrochloride (27 mg/kg) and xylazine (1 mg/kg) and placed on a respirator. Periodic doses of anesthesia were given intravenously (IV) to maintain a deep plane of anesthesia. The spinal cord was exposed and a complete C6-T1 transection was made by slowly separating the cord with dissecting forceps over a period of 20 minutes to prevent a precipitous fall in blood pressure. Following spinalization, epidural-type electrodes were implanted in the sacral canal along the midline via a burr hole drilled into the canal at the L5-6 level. A quadripolar electrode (Pisces Quad, Medtronic, Minneapolis, MN) was inserted to lie along the length of the canal as shown in Figure 1. A bone screw and dental acrylic were used to secure the electrode. Muscle and skin layers were closed and the electrode lead was brought out through a separate trocar hole and left under an animal jacket (Alice King Chatham Med., Hawthorne, CA). Antibiotic (0.25 ml/kg, Floxicillin) was administered regularly for 4 days, and analgesics (buprenorphine hydrochloride 0.05 mg/kg) for 2 days. The cats were kept in an environmental chamber for one week. They were placed between thick pads (Pressure Relief Pad, American Hospital Supplies, Wheeling, IL) to help the animal maintain a temperature between 101 and 103 degrees Fahrenheit. The spinal animals were given food and water ad libitum. Sulfadiazine 100 mg and trimethoprim 20 mg (Di-Trim, Synthex, West Des Moines, IA) was given daily to prevent urinary tract infection. Urethral catheterization (3 Fr ureteral catheter, Porges) was done as needed for emptying the bladder and for animal instrumentation.

**Experimental procedure**

The nine spinal-instrumented cats were divided into two groups to evaluate the effects of electrical stimulation. The first group of 5 animals were stimulated 5 days/week to induce voiding with sacral electrodes. They were also stimulated with bladder wall electrodes during terminal procedures at the end of the 10-week study. The second group of 4 spinal cats was not stimulated. The bladder in each of these animals was catheterized twice daily with a 4 Fr ureteral catheter (Porges). These animals were main-
tained for 10 weeks post-injury with the exception of two animals that were sacrificed after 8 weeks after protracted urinary tract infections. This second group was only used as a control to assess bladder wall thickness in stimulated versus nonstimulated spinal cats as discussed below.

All forms of stimulation were performed using isolated, constant current pulses from a Grass S48 stimulator and Grass constant current units (SIU and CCU model 1A) (14). The pulses were capacitor-coupled to the electrodes with a 2.5 μF series capacitor, and a 5 K ohm parallel resistor across the output of the stimulator (discharge time constant of 13 ms). Stimulation current was monitored using an isolated oscilloscope by measuring the voltage drop across a 100 ohm resistor placed in series with the electrodes. Sacral stimulation with implanted electrodes used monopolar electrodes with the implanted electrode as the cathode (negative) and a surface carbon rubber electrode (2-inch by 4-inch carbon rubber, Medtronic) placed on the animal’s back as an anode (positive) (9). Sacral surface stimulation was also occasionally used, but not direct bladder stimulation. Stimulation parameters for epidural electrodes were typically 20 pps, 150 μs, and 6 mA (20). Stimulating parameters for surface electrodes were similar, but high stimulating currents were needed (20 to 40 mA). Stimulation was applied for 2 to 4 sec periods and voiding was collected in cups to determine the volume voided (15). Following the end of voiding, the stimulation period was repeated 4 to 8 times until a small stream of urine was seen or no voiding occurred. Following a 5-minute rest, this series was again repeated 1 to 3 times. Whether or not the bladder was emptied following stimulation with less than 5 ml of residual volume was determined with suprapubic palpation. The bladder in the cat lies low in the abdomen and can be palpated between the fingers and thumb. Initially, it was determined that if the bladder felt small upon palpation, then the residual volume measured with catheterization was less than 5 ml. In this way, daily catheterization was avoided. If the bladder felt distended (<5 ml residual volume) upon palpation following the end of stimulation, it was emptied with suprapubic pressure (Crede) or with catheterization.

To further evaluate effects of stimulation on voiding, the cats were instrumented. The bladder was catheterized to monitor pressure using a 3 Fr ureteral catheter (Porges). However, even these small catheters reduced urine flow. Colon pressure was monitored with a latex balloon-tipped catheter. Voided urine was measured in a 10 cc syringe under a collecting tray. A pressure transducer connected to the bottom of the syringe registered volume. Full-wave rectified and integrated (0.2 sec decay time) electromyography (EMG) of the periurethral striated muscle was monitored adjacent to the pubic bone and bulbous urethra using two fine-wire hook electrodes (Life Tech, Houston, TX) inserted 1 cm into the perineum with a 27-gauge needle (17). A needle ground was also inserted subcutaneously in the tail. Additional EMG recordings were made from the external anal sphincter and abdominal muscles. In urethral pressure recording studies, a second 3 Fr catheter with one of the two side holes plugged was placed in the urethra. Pressures were recorded at the level of the membranous urethra, 45 to 55 mm from the urethral meatus. All parameters were recorded on an 8-channel recorder (Grass, model 7).

Following instrumentation, bladder responses to sacral epidural and occasionally sacral surface stimulation was determined (16). The sacral epidural electrodes and surface electrodes were evaluated in early (1 to 3 weeks) and late (4 to 10 weeks) postspinal periods. Recorded bladder contractions were usually isometric, as the urethral catheter prevented voiding, and initial bladder volume was 30 to
40 ml. Five minutes were generally allowed between each stimulation sequence to avoid fatigue. Stimulating parameters that were investigated included current, frequency, period, and pulse duration. Stimulation techniques to inhibit the hyperreflexic bladder were also investigated, but are to be reported elsewhere. These studies consisted of low frequency stimulation of sacral nerves with the implanted electrodes, and pudendal nerves and tibial nerves with electrodes inserted percutaneously (Life Tech, Houston, TX). Stimulation was conducted during spontaneous bladder activity, and pudendal nerve stimulation was most effective. The methods and stimulation were not expected to interfere with the results presented here.

Voiding cystourethography was conducted after filling the bladder with 25 percent radiopaque medium (Hypaque, Winthrop Pharmaceuticals, New York, NY). To view the voiding responses on the fluoroscope, sacral stimulation was used alone or in conjunction with Crede (suprapubic pressure). Crede was conducted along with stimulation to show the effects of stimulation on the open urethra (17).

Comparison of sacral nerve and direct bladder stimulation
During terminal procedures at 10 weeks post-injury, the animals were sedated with ketamine hydrochloride (10 mg/kg IM) and then anesthetized with alpha-chloralose (30-50 mg/kg IV) dissolved in 30 percent borax. The bladder was exposed with a midline incision. Four multistranded stainless steel wires (A5633, Cooner, Chatsworth, CA) had the last cm of Teflon™ insulation stripped for the electrode. The electrode was bent back to make a barb for insertion into the bladder wall with a 21-gauge needle. Two electrodes were inserted adjacent to and above each ureter bilaterally. Two electrodes were connected to the positive pole (one by each ureter), and two to the negative pole of a single stimulator. Stimulation was conducted with and without a catheter in the urethra—first to determine isometric pressure responses, and then to determine voiding responses, respectively.

Assessment of bladder wall thickness
At autopsy, the bladders were removed to evaluate the effects of SCI and stimulation on the development of bladder wall hypertrophy. There were three groups of animals for this analysis. The first two groups are detailed above and are the spinal-stimulated (5 animals), and spinal but not stimulated (4 animals) groups. The third group of cats consisted of intact animals obtained postmortem from other investigators (7 animals). Their bladders were harvested to obtain normal bladder wall thickness. The bladders were removed and filled with 20 ml of formalin solution (HT50, Sigma, St. Louis, MO). Following fixation, small sections of the bladder were removed from the wall and dome. As the sections were several mm thick, they were easily measured with a ruler. Urological responses to stimulation were analyzed using paired Student’s t-test. A significance level of $P \leq 0.05$ was adopted for single tests, and a $P \leq 0.01$ was adopted for multiple tests.

RESULTS

Daily voiding with sacral stimulation
Sacral nerve stimulation with the implanted epidural electrodes was conducted 5 days per week in SCI cats (spinal-stimulated group). Regularly repeated stimulation was used at 4 mA, 20 pps, 0.15 ms duration pulses, and 3 to 5 sec stimulation periods. Higher and lower stimulating currents were also tested. In 3 of the 5 cats tested, stimulation did not empty the bladder. The maximum volume voided following a single stimulation period (2 to 4 sec) was 0 to 0.5 ml during the early period post-spinal (1-3 weeks). This volume increased to 0.5 to 2 ml during the late post-injury period (4-10 weeks). Repeated stimulation did not empty the bladder and Crede or catheterization procedure was needed to drain more than half of the urine (15 to 30 ml). Two of the 5 cats in this group did empty their bladders (<5 ml residual) with stimulation during the late post-injury period. At that time, 6 ml or more (12 ml in one cat), of voiding was observed after a single stimulation period of 3 to 5 sec. However, during the early period, the bladders of this group were incompletely emptied (>5 ml residual), and the maximum volume voided following a single stimulation was only 1 ml. Possible causes of poor voiding as well as optimum electrode arrangements were further investigated with pressure/flow studies, and voiding cystourethography (17).

Urodynamic evaluation with sacral stimulation
The cats were instrumented as detailed above, and responses to stimulation with the four electrodes implanted in the sacral canal from L-7 to S3 foramina level were evaluated (Figure 1) (14). Voiding usually was not observed in the instrumented animal as the urethral catheter caused obstruction. The rostral electrodes (L7-S1) tended (not statistically significant) to induce higher bladder pressure than the more caudal electrode at S2. However, this trend was only apparent at stimulating currents of 2 and
Effects of implanted sacral electrodes on bladder responses to stimulation. 

<table>
<thead>
<tr>
<th>Electrode Location</th>
<th>N</th>
<th>2 mA</th>
<th>4 mA</th>
<th>6-10 mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>L7</td>
<td>5</td>
<td>48 ± 3.7</td>
<td>63 ± 7.1</td>
<td>81 ± 11</td>
</tr>
<tr>
<td>S1</td>
<td>5</td>
<td>43 ± 8.5</td>
<td>56 ± 9.4</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>S2</td>
<td>5</td>
<td>23 ± 11</td>
<td>26 ± 9.7</td>
<td>75 ± 5.9</td>
</tr>
</tbody>
</table>

a Studies were conducted in spinalized awake animals, 6-10 weeks post-injury. A comparison of the peak detrusor pressure at each of the three stimulating currents indicated that there was not a significant effect of electrode location. Electrode location had no significant effect on peak bladder pressure responses at the three stimulating currents.

b Peak detrusor pressure values are maximum responses and are subtracted values (recorded bladder pressures — recorded colon pressures). Initial bladder volume was held constant in each animal so as not to affect comparisons. However, between animals this volume varied between 20 and 50 ml.

c Electrode location is in relation to the sacral foramina indicated. Monopolar implanted electrodes at the level of L7, S1 and S2 foramina were connected to the negative pole of the stimulator, while a surface electrode on the back of the animals was connected to the positive pole of the stimulator. Sacral stimulation parameters were 20 pps, 150 μs, 2-10 mA applied for 5 sec.

d N represents the number of animals investigated.

4 mA, not at the higher stimulating current of 6 to 10 mA where all of the electrodes induced similar responses (Table 1). Considerable leg flexion was observed when stimulation induced bladder pressure over 30 cm H$_2$O for all of the electrodes. Stimulating currents from 2 to 5 mA were generally effective in inducing bladder contractions with pressures between 20 and 70 cm H$_2$O; 10 mA induced excessive leg movement. Bladder pressures in the range of 40 to 90 cm H$_2$O could be induced with stimulating frequencies from 6 to 35 pps, stimulating periods from 3 to 5 sec, and pulse durations from 0.1 to 0.5 ms.

Surface stimulation over the sacrum was also evaluated. This method induced peak bladder pressures equivalent to implanted sacral electrodes. However, stimulation with surface electrodes required approximately 20 times higher stimulating currents (20 mA to 40 mA) than implanted sacral electrodes. Leg flexion and pelvic floor EMG recordings with sacral surface electrodes were similar to those with implanted electrodes.

The bladder was more responsive to stimulation after recovery from spinal shock (late period) than immediately after spinalization (early period). As shown in Figure 2, stimulation with implanted sacral electrodes at 4 and 6 mA on day 20 induced peak bladder pressures of 38 cm H$_2$O and 48 cm H$_2$O, respectively, and higher pressures of 74 and 90 cm on day 55. Stimulation in the early and late periods also induced transient changes in leg movement and colon pressure. Pelvic floor EMG

Figure 2.
Comparison of urodynamic responses to sacral stimulation during early and late periods post-injury. A. 20 days post-injury. B. 55 days post-injury. Note increased bladder Pr response in the late post-injury period. Stimulation in each recording was applied with 20 pps and with a monopolar electrode located between sacral foramina L7 and S1. Initial bladder volume was 40 ml in each record, and no voiding occurred in any of the recordings. The large EMG response during stimulation is an artifact from the stimulus.
The lack of voiding often observed with sacral stimulation appears to be due to high urethral resistance. Urethral pressure recordings showing prolonged spasms with high pressure following sacral stimulation are shown in Figure 3. Recording of the pelvic floor and anal EMG showed a similar pattern to the urethral pressure recording, but abdominal EMG increases indicating abdominal muscle contraction only occurred during the largest pelvic floor spasms.

The high urethral resistance problem was further investigated with voiding cystourethrography. Urethral opening and voiding was induced by Crede maneuver which maintained bladder pressure at 50 to 100 cm H2O Pr (Figure 4A). As the pressure was continued, stimulation was initiated, and closure of the membranous urethra, but not the bladder neck, occurred (Figure 4B). Bladder neck closure during sacral stimulation was noted in only one of the five animals investigated, and only during the early period post-injury. In contrast, the membranous urethra was always closed during, and for varying periods after, stimulation. These results show a principal role of the membranous urethra closure on urethral resistance.

Comparison of sacral and direct bladder stimulation

Direct bladder stimulation was compared to sacral nerve stimulation because of the urethral resistance problem. The two methods were compared during terminal procedures with the cats anesthetized. Stimulation was conducted with and without the urethral catheter for recording bladder pressure because of the obstruction due to this catheter. As shown in Figure 5, direct bladder stimulation induced voiding both during and after stimulation, whereas epidural sacral nerve stimulation induced only post-stimulation voiding with less volume.

Table 2 shows that for the four cats investigated, voiding rates were significantly higher with direct bladder stimulation than sacral nerve stimulation at similarly induced peak bladder pressure. A simple urethral resistance measure was calculated as the ratio of peak bladder pressure to peak flow rate. This ratio tended to be smaller with direct bladder than sacral nerve stimulation, but not statistically significant.

Bladder wall hypertrophy

The bladder wall was fixed postmortem (as detailed above), and the thickness of the mid-bladder wall and dome were measured. Both the walls from the stimulated and nonstimulated spinal cats showed significant thickening responses following the end of stimulation were high, indicating high urethral resistance. The end of the bladder contraction was associated with high voltage EMG phasic response (200 to 600 μV) for 3 to 10 sec.
Cystofluoroscopic observations showing closure of the membranous urethra but not the proximal urethra during sacral stimulation. A. Open urethra during Crede-induced voiding. B. During continued Crede, sacral stimulation causes the membranous urethra to close. Stimulation was with a monopolar electrode located between sacral foramina L7 and S1; initial bladder volume was 40 ml. Stimulation parameters were: 20 pps, 6 mA, 150 µs pulse duration. Cat 55 days post-injury.

Figure 4

Compared to the bladder walls from intact animals (Table 3). For example, the average thickness of the midwall was only 1 mm in the intact cat, whereas it was 2.6 and 3.9 mm in the spinal nonstimulated and stimulated groups respectively. This difference is not due to tissue preparation; the bladders were all filled to the same volume during fixation. However, the lower average animal weight in the nonspinal 2.6 kg versus the two spinal groups (4.3 and 3.6 kg) was a factor in this difference.

A final comparison can be made between the two spinal groups to evaluate the effects of stimulation on bladder wall thickness. The bladder of the spinal-stimulated cats tended (not significant) to have increased wall thickness in both the dome (p=0.2) and midwall (p=0.1) compared to the nonstimulated spinal cats. This occurred in spite of the fact that the average weight of the stimulated spinal animals was less than the nonstimulated animals. Thus, this indicates an adverse effect in injured animals of stimulation on bladder wall structure.

DISCUSSION

Improved voiding was noted in response to sacral stimulation with implanted or surface electrodes over the first 3 weeks following spinalization. These improvements were modest (0.5 to 2 ml) in three of the animals following a single stimulation period, whereas in two of the animals the improvements were dramatic (5 to 11 ml). This improvement over 3 weeks probably indicates the return of bladder reflex activity (Figure 2) (2,3,10,15,21), although decreased urethral resistance may also be involved (17). In spite of this improvement, sacral nerve stimulation remained ineffective in emptying the bladder in over half of the SCI cats evaluated. This was because of the high

Figure 5

Comparison of urodynamic responses between sacral nerve stimulation and direct bladder stimulation. 1A,B. Voiding with and without a catheter in response to direct bladder stimulation. 2A,B. Voiding with and without a catheter in response to sacral nerve stimulation. Note, direct bladder stimulation induced better voiding with less abdominal Pr changes than sacral nerve stimulation. Direct bladder stimulation was conducted with four electrodes implanted in the bladder wall adjacent to the ureters. Two of the electrodes were connected to positive and two to negative poles of the stimulator. Sacral nerve stimulation was conducted with a monopolar electrode implanted in the sacrum at the level of S2 foramina. Initial bladder volume in each recording was 40 ml. Recordings conducted during terminal procedures with the animal anesthetized.
Table 2.
Comparison of voiding responses between direct bladder and sacral nerve stimulation in the anesthetized, chronic, spinal injured cat. 

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>N</th>
<th>Max. Detrusor Pr$^{b}$(cm H$_2$O)</th>
<th>Max. Voiding Rate$^{c}$(ml/sec)</th>
<th>Urethral Resistance$^d$(cm H$_2$O/(ml/sec))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Bladder</td>
<td>4</td>
<td>120 ± 32</td>
<td>0.92 ± 0.04*</td>
<td>130 ± 33*</td>
</tr>
<tr>
<td>Sacral Nerve</td>
<td>4</td>
<td>120 ± 25</td>
<td>0.56 ± 0.11</td>
<td>260 ± 100</td>
</tr>
</tbody>
</table>

$^a$ Studies conducted in anesthetized animal during terminal procedure, 10 weeks post-injury. Direct bladder stimulation conducted with four electrodes adjacent to the ureters, and stimulation parameters were: 20 pps, 350 μs, and 20 to 30 mA applied for 3 to 5 seconds. Sacral nerve stimulation was conducted with 150 μs and the stimulus current was adjusted to give a similar peak bladder pressure.

$^b$ Peak bladder pressure was recorded with the bladder catheterized via the urethra.

$^c$ Peak voiding rate was recorded with the same stimulation parameters as peak pressure but without the urethral catheter.

$^d$ A simple urethral resistance measure was obtained as the ratio of detrusor pressure to flow rate. The value is the average of individual animals.

* Statistically significant difference between direct bladder and sacral nerve stimulation, $P \leq 0.05$.

urethral resistance shown in Figure 3 and Figure 4. These responses are in contrast to the effective voiding induced with sacral nerve stimulation in the dog (8,9,10,12,14,15, 16,17). This species difference is probably due to a lower urethral resistance following spinal cord injury in the dog than in the cat (2,8,21). In SCI patients, stimulation of the sacral nerves (dorsal and ventral roots) was found to be effective in an initial patient, but was not confirmed in subsequent studies (8,9). However, selective stimulation of the ventral sacral roots has been effective with electrodes implanted both within the spinal dura (1,6,11) and outside the spinal dura (9,12). In this study, because we observed poor voiding with sacral nerve stimulation, we have begun to evaluate the alternative technique of direct bladder stimulation.

Direct bladder stimulation was more effective than sacral nerve stimulation (dorsal and ventral sacral roots) in inducing voiding, although high urethral resistance was still a problem (Table 2 and Figure 5). For example, voiding pressures were high at 120 cm H$_2$O with direct bladder stimulation indicating high urethral resistance. This is further indicated by the observations of spontaneous voiding at lower pressures of 40 to 60 cm H$_2$O in intact male cats instrumented with suprapubic catheters (22). These results, however, support the efficacy of direct bladder stimulation for inducing voiding. Previous studies have shown effective bladder emptying with direct bladder stimulation in paraplegic dogs, although high urethral resistance was reported (9,21,23,24,25,26). Early studies with direct bladder stimulation in SCI patients reported high pressure voiding. Problems encountered included high stimulating currents, high urethral resistance associated with stimulation, and coactivation of the bladder and striated sphincter mechanisms and lower limb muscles, as reviewed by Talalla, et al. (8). Improved results, however, have been shown in clinical trials of direct bladder stimulation by Magasi and Simon (13). Thirty-two patients were implanted with an 8-channel stimulator using refined electrode design and stimulating protocols. Bladder paralysis was due to peripheral injury in 21 patients and central neural lesions in 11 patients. Small round platinum disks were implanted in the bladder wall after making small longitudinal cuts in the wall adventitia, inserting the electrodes, and closing the adventitia over the electrodes with sutures. Electrodes adjacent to the ureterovesical junctions were most effective for inducing voiding, and 29 of the 32 patients voided without residual urine after the operation. In three patients with central upper motor neuron lesions, voiding was difficult due to rigidity and fibrosis of the inner sphincter, but transurethral bladder neck resection was sufficient to allow for effective voiding. Also, regular use of the stimulator led to the elimination of ureteral reflux in patients with this problem. These encouraging results by Magasi and Simon support the continued development of this approach for bladder management. Because our study shows that the cat model correlates well with Magasi's clinical study, further refinement of direct bladder stimulation using this model is planned.

Several neuroprosthetic approaches are currently under investigation for bladder management. However, improvements are needed for this application. In clinical trials with SCI patients using sacral ventral root stimulation, a sacral afferent neurectomy is usually conducted (1,9,11,12,26). Benefits from these lesions could include decreased incontinence and decreased urethral resistance. However, the beneficial effects of neurectomies may be
Table 3.
Effects of spinal cord injury and electrical stimulation on bladder wall hypertrophy.

<table>
<thead>
<tr>
<th>Cat Type</th>
<th>N</th>
<th>Cat wt. (kg)</th>
<th>Midwall thick (mm)</th>
<th>Dome thick (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspinal</td>
<td>7</td>
<td>2.6 ± 0.3</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Spinal nonstimulated</td>
<td>4</td>
<td>4.3 ± 0.5</td>
<td>2.6 ± 0.2*</td>
<td>2.8 ± 0.2*</td>
</tr>
<tr>
<td>Spinal stimulated</td>
<td>5</td>
<td>3.6 ± 0.4</td>
<td>3.9 ± 0.6*</td>
<td>4.2 ± 0.6*</td>
</tr>
</tbody>
</table>

*Significantly different from nonspinal cat.

limited because of inhibited reflex bladder activity. For example, early after spinal injury, in this study, bladder reflexes were reduced and high stimulating currents were needed to induce bladder contractions (Figure 2). Clearly, high urethral resistance needs to be managed for neuroprosthetics to be effective. Magasi and Simon (13) reported that a simple bladder neck resection may be sufficient in some patients. However, pelvic floor and membranous urethral contractions are often encountered in SCI patients, and resection of this part of the urethra will result in incontinence (3,19). Other methods of lowering urethral resistance, therefore, must be sought.

Spinal cats receiving stimulation in this study tended (not significantly) to have thicker bladder walls (3.9 ± 0.6 mm midwall) than nonstimulated spinal cats (2.6 ± 0.2 mm midwall). This further substantiates reports that higher urethral resistance and stimulation-induced high bladder pressure results in a thick hypertrophied bladder wall (3,19). These histological changes could cause deleterious upper urinary tract changes and will have to be carefully monitored in future bladder neuroprosthetic investigations.

The SCI cat appears to be a better model than the SCI dog for the lower urinary tract problems seen in patients. Hyperreflexia and underactive bladder activity can be shown in the high-level lesioned cat (2). Spastic pelvic floor activity can also be shown in this model representative of increased urethral resistance. The adverse urethral response is shown to be at the level of the membranous urethra similar to SCI patients (3,4) (Figure 3 and Figure 4). Galeano et al. (2) proposed that the high level lesion, C5-C6, is a better model than lower thoracic level lesions because of demonstrated urethral responses. Our T-1 level lesion should be equivalent to the higher level lesion cat.* The T-1 level lesion does have the advantage over the C5-C6 level lesion in that there is less paralysis in the upper extremities. Therefore, we expect this animal model to become more widely used for evaluating the lower urinary tract problems of SCI patients.

Further improvement in electrode design and implantable stimulators may also increase the efficacy of direct bladder stimulation techniques. Multichannel implantable stimulators as developed at Case Western Reserve University (27), Rancho Los Amigos Rehabilitation Hospital (MinimMed Technologies), University of Sherbrooke, Canada (28), and at Nucleus, Australia (5), have raised the potential of applying neuroprosthetics for controlling the lower urinary tract. These new stimulators also provide stimulating alternatives such as bipolar electrodes and biphasic stimulating wave forms. These alternatives may help to limit the stimulating field to the bladder wall. Finally, electrode design for the bladder wall may be improved. Such improvements are currently underway with continuous filament carbon fiber electrodes (29). Also, electrodes with a larger stimulating surface area may be effective in activating the ramified innervation of the urinary bladder.

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