Evaluation of Bipolar Permaloc™ Electrodes for Direct Bladder Stimulation

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Abstract: *Purpose*: A bladder control system for spinal cord injured (SCI) patients is needed that can be implanted with minimally invasive methods. New Permaloc bipolar electrodes consisting of 6 mm helical, wire, stimulating surfaces separated by 3 mm and a polypropylene securing barb (Synapse Biomedical Inc) were developed for this application. They are implanted on the bladder wall with a 16 gauge needle, a minimally invasive method.

Methods: Seven swines were anesthetized, the lower urinary tract exposed and instrumented with pressure transducers. Four Permaloc™ electrodes were implanted following identification of effective bladder wall stimulation sites next to the ureters and dorsal neurovascular bundle. Bladder stimulation to induce high pressures was conducted at 40 Hz, 400 μs pulses, 5 s stimulation periods and a high stimulating current of 40 mA.

Results: At the high stimulating current peak bladder pressures were low, ranging from 12±2 to15±3 cm H_20, insufficient to induce urination. Urethral sphincter contractions occurred during high bladder pressure. A spinal reflex role for high sphincter pressures during stimulation was shown by similar high pressures recorded during a bladder squeeze test without stimulation.

Conclusions: Stimulation with Permaloc™ bipolar electrodes at high currents produced insufficient bladder pressures for urination. Further modifications of the electrode such as greater separation of the bipolar stimulating surfaces or changes in the testing methods such as alternative animal models are needed to induce high bladder pressures without side effects.

Keywords: Electrical stimulation, electrodes, neuroprosthetics, spinal cord injury, urinary, urinary incontinence, paralysis, urinary dysfunction, implantable stimulator, minimally invasive implants.

INTRODUCTION

The Finetech-Brindley, Bladder Control System (Branded as VOCARE in the US) is the only implantable stimulator available for urinary management following spinal cord injury (SCI) [1]. A report of world-wide use of this device has demonstrated that nearly all individuals obtained daily bladder emptying that is also catheter, incontinence, and infection free [2, 3]. The system, however, has limitations including invasive surgery with one or two spinal lamenectomies, transection of the sacral sensory nerves, and implantation of electrodes within the sacral canal [2, 4, 5].

Another approach for bladder control is direct bladder stimulation. Early clinical experience using long wire electrodes reported problems such as high urethral resistance, low bladder pressures, pain, electrode migration and other slide effects [6-11]. In a more recent study, however, Magasi *et al.* [12, 13] reported success with eight, small, platinum-iridium, disk electrodes implanted on the surface of the bladder wall as four bipolar pairs. Separation of the electrodes in the bipolar sets was one-fourth the distance around the bladder, and the most important implant locations were on the ventral side of the bladder near the ureters. Results for 32 patients (21 peripheral injuries, 11 with central injuries including SCI) included daily bladder stimulated emptying and subjects were followed for one to two years. Three patients, however, required a bladder neck incision to reduce urethral resistance.

We have been investigating optimal methods of bladder wall stimulation [14-19]. Recently we reported that bipolar barb electrodes with little separation between the two stimulating surfaces were effective for inducing high bladder pressures in anesthetized dogs [14]. In this study, we purchased Permaloc™ bipolar electrodes (Synapse Biomedical Inc, Oberlin OH) that also had little separation

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1874-9437/12

between the stimulating surfaces, in contrast to the wide seperation used by Magasi *et al.* [12, 13], and tests were conducted with bladder wall stimulation in swine.

METHODS

Anesthesia

The Institutional Animal Studies Committee at Hines VA Hospital approved these protocols. Seven female York-Landrace swine (30±3 Kg) underwent terminal surgeries. Anesthesia was initiated with a pre-anesthetic intramuscular injection of ketamine (25 mg/kg) and xylazine (1-2 mg/kg). After placement of an intravenous catheter Propofol (3-6 mg/kg) was administered. After tracheal intubation the swine were maintained at a surgical plane of anesthesia using inhaled isoflurane (0.5-2.0%) and intravenous fentanyl (5-10 µg/kg/hr) [20, 21]. Body temperature was maintained at 38°C with an air-blanket heater. Isotonic fluids were administered intravenously at a rate of 10 mg/kg/hr.

Electrodes

Three different types of bipolar electrodes were used (Fig. **1**). Surface wire electrodes were used first to identify effective stimulation sites. These electrodes were made from insulated tinned wire leads (PVC paired wire speaker cable, C1360-1000, www.Digikey.com). The electrode surface was constructed by stripping the insulation from the last 5 mm of the lead and bending the electrodes back to produce a flat stimulating area.

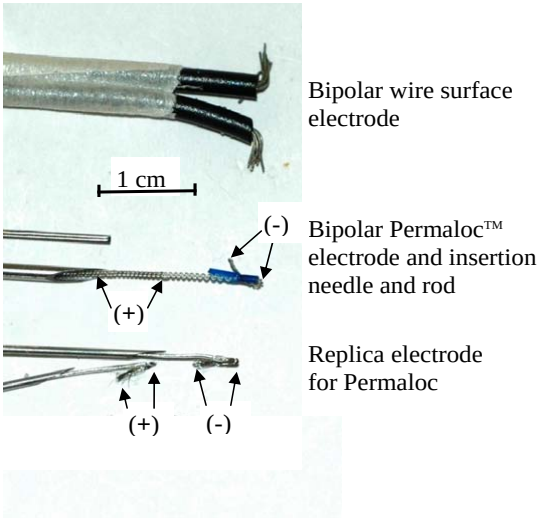

Fig. (1). Electrodes used in this study: one, bipolar wire surface, two, bipolar Permaloc™ (Synapse Biomedical Inc) with insertion rod and 16 gauge insertion needle and, three, replica bipolar Permaloc™ electrodes with 21 gauge insertion needles.

Either bipolar Permaloc™ (Synapse Biomedical Inc., Oberlin OH) or replica electrodes were implanted on the bladder wall. The bipolar Permaloc™ electrodes consisted of two helical-wound, multi-stranded stainless-steel wires insulated with Teflon®. The electrodes were formed by stripping the insulation from the end of the leads and wrapping them into a helix. One wire was used for the positive electrode and the second wire for the negative electrode and there was 5 mm separation between them. A polypropylene barb located near the tip was used for securing; a 16 gauge needle and a discharge rod were used to insert the electrode (Fig. **1**). The discharge rod is thin and flattened and placed inside the needle with the electrode. During withdrawal of the needle the rod was pushed against the electrode to insure electrode discharge and accurate placement [22]. These bipolar Permaloc™ electrodes could only be used once because the leads were stretched upon explantation. Thus, the twelve electrodes provided courtesy of Synapse Biomedical were limited to just three animals. For the remaining four animals, we made replica bipolar electrodes (Fig. **1**) modeled after the bipolar Permaloc™ electrodes [14]. The replica electrodes consisted of multi-stranded, stainless-steel wires insulated with Teflon® (Model X, Cooner wire Inc, Chatworth, CA) in which five mm of Teflon® insulation was stripped from the end of the lead and then was bent back over a 20 G needle to create a barb electrode. Two such electrodes were inserted close together to replicate the bipolar Permaloc™ electrode.

Stimulator

Stimulators for these studies were electrically isolated and produced monophasic pulses (Grass Model S48, S88, SD9, Astromed, Houston, TX). For charge balanced stimulation a 1.2 µF capacitor (www.Digikey.com) was placed in series with the stimulating electrodes and a 4.2 KΩ resistor was placed across the output of the stimulator. All stimulating voltages and currents were monitored on an oscilloscope (battery powered TEKScope, Tektronix Inc., Beaverton OR). Current was calculated from the voltage drop across a 100 ohm resistor in series with the stimulating electrodes and by applying Ohm's law (V = IR).

Animal Instrumentation

Following anesthesia and prior to stimulation tests, the urethra was catheterized with a three lumen catheter (Model G15540, Urodynamic triple-lumen catheter, 7.4 French, Cook Urological Co. Spencer, IN; Fig. **2**). One lumen was used for bladder filling and pressure recording; this lumen was extended by 6 cm so it would insert into the bladder. The extention consisted of a silastic tube with a short insert of steel tubing. The steel insert extended out of the plastic tubing and was pushed into the lumen of the catheter; the whole extension was secured with Epoxy. Holes were cut in the bladder end of the plastic extension. The second lumen of the catheter included a balloon near the tip that was used for urethral pressure recording. Techiques for filling the balloon with water and connecting it to a pressure transducer have been detailed elsewhere [23]. The third lumen was capped to prevent leakage and not used.

The urethral meatus in the female swine is recessed 3 to 4 cm within the vaginal opening and catheterization was facilitated by antegrade maneuvers. These maneuvers consisted of: one, inserting an 18 guage needle into the bladder wall, two, advancing a stylet through the needle and through the urethral meatus, three, attaching the catheter to the stylet and pulling it into the bladder, four, removing the stylet and needle, and five closing the bladder wall with a single stitch. The balloon was positioned just inside of the urethal meatus to record urethra skeletal sphincter pressures.

An anal balloon for pressure recording was fashioned from silastic tubing (15 mm outside diameter). The ends of the tube were sealed with silicone (Med-1037, NuSil Inc,

Carpinteria, CA), and the ends were further enlarged to maintain the tube in the sphincter. Pressure transducers (World Precision Instruments Inc, Sarasota, FL) were used for urodynamic measures and data recorded with a digital system (PowerLab, AD Instruments Inc, Colorado Springs, CO).

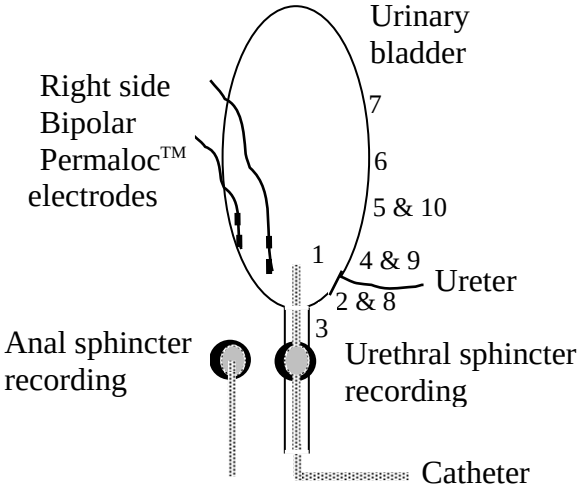

Fig. (2). Urodynamic instrumentation and electrode test sites. The catheter (three-way urodynamic, Cook Urological Inc) includes a balloon for urethral sphincter pressure recording. Bipolar Permaloc™ electrodes are shown on the right, ventral side of the bladder wall. Bipolar wire surface electrodes were tested first on the bladder wall at ten different sites. Seven bilateral sites on the ventral side (1 - 7) of the DNVB and three on the dorsal side of the DNVB (8 - 10) are depicted in figure on the left side of the bladder.

Surgery and Bladder Wall Stimulation

A six inch midline incision was made from the lower mid-abdomen to the superior border of the pubic bone; hemostasis was maintained with electrocautery. Blunt dissection exposed the perivesical fascia, bilateral ureters, and dorsal neurovascular bundles (DNVB) along the bladder neck.

The urodynamic catheter was placed in the urethra to measure the skeletal urethral sphincter just inside the urethral meatus and to measure bladder pressure and for bladder filling. Bladder volumes of 60 or 100 ml were used during testing; 100 mls was used in two larger animals (41 and 42 Kg) that had larger bladders with over 200 ml internal volume upon first measurement. In the remaining five smaller swine (26±2 Kg) with smaller bladders wand maximal 125 ml volumes upon first measurement, 60 ml was used. As peak bladder pressure responses to electrical stimulation were similar for these two different filling volumes, all results were combined.

Effective bilateral stimulation sites on the bladder wall were determined using the bipolar, wire-surface electrodes (Fig. **1**). Tests were conducted at 10 locations next to the bladder wall, seven ventral and three dorsal to the DNVB that includes the bladder innervation, vasculature, and origin of the ureters (Fig. **2**). Site 1 was 1 cm medial and 1 cm rostral to the ureter; sites 2 & 3 were 0.5 and 2 cm caudal to the ureter along the DNVB, respectively. Sites 4, 5, 6, and 7 were 1, 2, 3 and 5 cm rostral to the ureter along the DNVB. On the dorsal side of the DNVB site 8 was 0.5 caudal and site 9 and 10 were 1 and 2 cm rostral to the ureter and just dorsal to locations 2, 4, and 5; (Fig. **2**). Currents of 20 and 40 mA were used in tests because lower currents had little effect on bladder pressure; 40 mA was the highest available current from the stimulator. In a few initial tests, a lower current of 10 mA was tested first when there was a concern about possible leg muscle contractions. Other stimulation parameters were set to levels reported to induce maximal bladder pressures including 400 μs pulses, 40 Hz stimulating frequency and 5 s stimulation periods [14, 16-19].

After determining the two most effective bilateral stimulation sites, four bipolar Permaloc™ or replica electrodes were implanted at these locations superficial to the detrusor muscle. Testing with 20 mA and 40 mA was conducted with individual bilateral pairs of electrodes followed by stimulation with combined pairs. The stimulation protocol with the four implanted bipolar electrodes was repeated after abdominal closure. As stimulation results for the bipolar Permaloc™ (Synapse Biomedical Inc) and replica electrodes were not significantly different only combined results are reported.

Autopsy

Animals were sacrificed by administering 50 ml of saturated KCl intravenously while under surgical anesthesia. During autopsy the location of the implanted electrodes were photographed. Summary results are presented as mean±SEM. Student's t-tests for paired data were used for all statistical analyses with a significance set at $P \leq 0.05$.

RESULTS

Bladder Wall Testing

Urodynamic responses to bladder wall stimulation with the bilateral, wire, bipolar, surface electrodes are shown in Fig. (**3**) (40 mA, left panel); location 1, 1 cm medial and 1 cm rostral to the ureters. An increase in bladder pressure occurs during the first second of stimulation and reaches a peak of 10 cm H_2O at the end of 5 seconds of stimulation. In addition to the desired increase in bladder pressure there was an unwanted increase in urethral pressure starting 2.5 s after the start of stimulation. This increased urethral pressure is probably not due to direct pudendal nerve stimulation because the pressure is small and is delayed. In contrast, an example of direct pudendal nerve stimulation is shown in Fig. (**3**) (10 mA, right panel) at location 3, 2 cm caudal to the ureter along the DNVB; this direct urethral contraction is very strong and occurs immediately at the start of stimulation. Stimulation was stopped at 0.2 s because of leg muscle contractions.

Location 1 was associated with the highest peak bladder pressures (10±2 cm H_20, 40 mA, Table **1**); this location was also associated with little leg or pelvic floor contractions as determined by palpation (Table **1**). Peak bladder pressures from 1±1 to 9±3 cm H_2O at 40 mA were recorded at the remaining nine test sites. In general, locations next to the DNVB and near the ureter were most effective. These locations on the ventral side of the DNVB included 2, 4, 5, that were 0.5 cm caudal and 1 and 2 cm rostral to the ureter respectively. These locations on the dorsal side of the DNVB were limited to one site which was 1 cm rostral to the ureter. Bladder locations more rostral or caudal along the DNVB than the effective sites just described were less effective (Table **1**). Tests at 20 mA induced peak bladder pressures only 44% of the response induced at 40 mA.

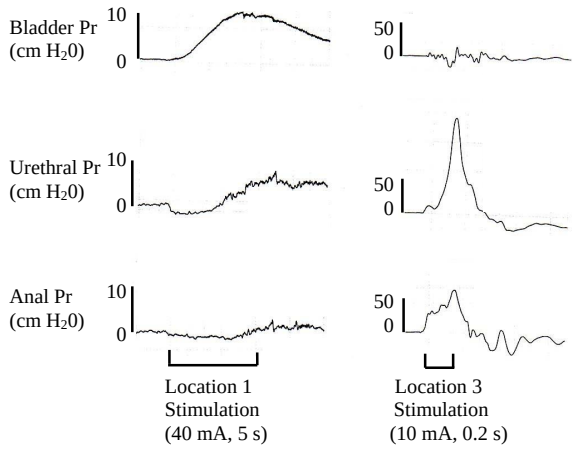

Fig. (3). Urodynamic responses to bladder wall stimulation with surface wire electrodes at location 1 (1 cm ventral and 1 cm medial to the ureter) and location 3 (1.5 cm caudal to the ureter on the ventral side of the DNVB). Location 1 stimulation was 40 mA applied for 5 s. Location 3 stimulation was 10 mA for 0.2 s; the stimulation was stopped early at 0.2 s because of leg kicking. Bladder wall stimulation with two surface electrodes was at 40 Hz 400 μs pulses; currents and times are noted.

Side effects of stimulation with the wire surface electrodes included urethral skeletal sphincter, leg and abdominal rectus muscle. Sphincter and leg contractions were greatest at distances 0.5 and 2 cm caudal to the ureters (sites 2, 3 and 8). Several stimulations had to be stopped early because of strong leg contractions, and urethral skeletal sphincter pressures at these locations were 20 cm H_20 or greater. Slight abdominal rectus muscle contractions were also observed in five cases. Tests at 20 mA had reduced all side effects to stimulation.

Bipolar Permaloc™ Electrodes

Based on the induction of high bladder pressures and limited side effects with the wire surface electrodes, two bilateral sites were determined in each animal for implanting the four bipolar Permaloc™ (3 animals) or replica (4 animals) electrodes. Location 1 was the first implant site in all animals. The second implant site varied and was location 4 in 3 animals (ventral side of DNVB and 1 cm rostral to ureter) location 5 in 2 animals, (ventral side DNVB and 2 cm rostral to ureters), and location 9 in 2 animals (dorsal side of the DNVB and 1 cm rostral to the ureter).

A photograph of four bipolar Permaloc™ electrodes implanted at the identified bladder wall sites is shown in Fig. (**4**). The electrodes were easily placed with the insertion needle at the desired locations by using the discharge rod; they were secured just under the bladder wall adventitia with the polypropylene barb (Fig. **1**). A typical urodynamic response to stimulation with the four electrodes is shown in Fig. (**5**) (40 mA, left panel). The bladder pressure increased slowly during the 5 s of stimulation reaching a peak of 17 cm H_20. No skeletal muscle contractions occurred in the perineum, abdomen, or in the legs. Higher urethral pressures reaching 30 cm H_20, however, were also observed. To

Table 1. Peak Urodynamic Pressure and Palpation Responses to Stimulations at the 10 Bladder Wall Sites with Bilateral and Bipolar Wire Surface Electrodes Stimulated at 40 mA.[a]

Location Number	Bladder Pr (cm H_20)	Urethral Pr (cm H_20)	Anal Pr (cm H_20)	Palpation[b,c] (Rating Scale)
A. 1 cm Ventral and 1 cm Rostral to the Urethrovesical Junction				
1: (see heading)	10±2	14±4	2±1	none 6, slight rectus 1
B. Ventral and Along the DNVB				
a. Caudal to the Ureter				
2: 0.5 cm	7±2	22±7	6±4	none 3, moderate 2, strong 1, stop 1[c]
3: 2 cm	1±1	26±11	7±6	none 1, slight 1; moderate 1; stop 4
b. Rostral to the Ureter				
4: 1 cm	8±2	13±4	3±2	none 4, slight 1, moderate 1, strong 1
5: 2 cm 1	7±2	8±5	0±0	none 5, slight 1, slight rectus
6: 3 cm	6±2	0±0	0±0	none 5, slight rectus 1, not tested 1
7: 5 cm	3±1	0±0	0±0	none 5, slight rectus 1, not tested 1
C. Dorsal and Along the DNVB				
a. Caudal to the Ureter				
8: 0.5 cm	4±2	20±9	3±2	none 3, moderate 2, stop 2
b. Rostral to the Ureter				
9: 1 cm	9±3	17±9	2±1	none 3, slight rectus 1, moderate 1, stop 2
10: 2 cm	5±2	1±1	1±1	none 6, not tested 1

[a]Stimulation with bipolar wire surface electrodes (40 Hz, 400 μs pulses for 5 s); test sites at ventral and dorsal locations to the DNVB.
[b]Palpation of legs, pelvic floor, and abdominal rectus muscles.
[c]Stop indicates that stimulation was stopped early due to excessive leg contractions; no pressures was included in the table for stopped tests.

determine if bladder-urethral spinal reflexes were involved in generating these high urethral pressures, we conducted a bladder squeeze test which elicits bladder-spinal reflexes (Fig. **5**, right panel). The manually induced bladder pressures also induced high urethral sphincter pressures showing the role of spinal reflexes in the observed response. The lack of significant responses from the anal sphincter during both maneuvers also supports the notion that the bladder-urethral, sphincter reflex arc is involved in the observed response.

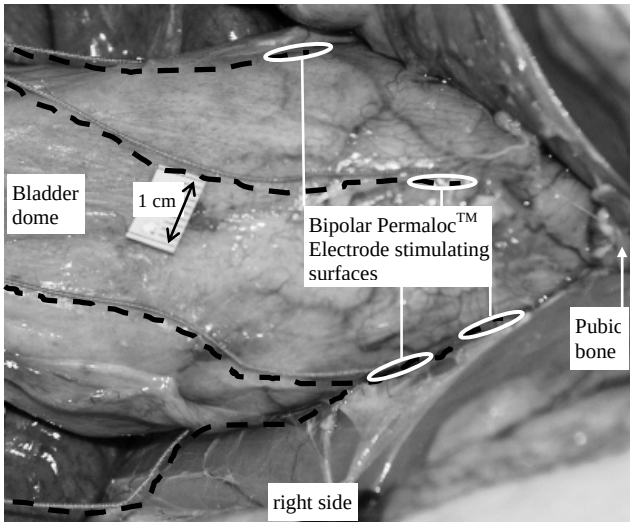

Fig. (4). Ventral side of the urinary bladder with four bipolar Peterson electrodes implanted. Bilateral implants were at location 1 (1 cm rostral and medial to the ureter) and location 5 (2 cm rostral to the ureter along the DNVB). The electrode lead is shown adjacent to the black dashed line. The approximate location of the bipolar electrode stimulating surface areas are shown by the white circles.

Peak bladder, urethral and skeletal muscle responses to stimulation with the two individual bilateral pairs of bipolar Permaloc™ electrodes and combined pairs are shown in Table **2**. With abdomen open, peak bladder pressures were significantly increased during testing of the two combined pairs of bilateral electrodes compared to individual pairs

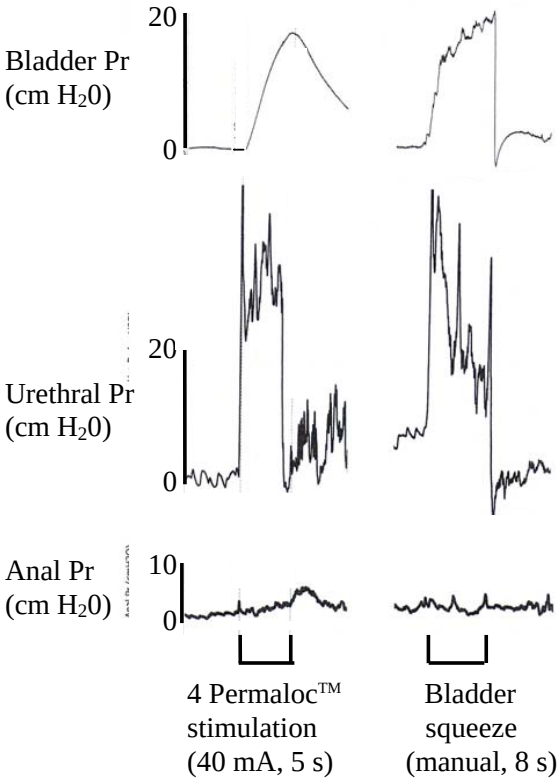

Fig. (5). Urodynamic responses to bladder stimulation and manually squeezing the bladder. Bladder and urethral sphincter pressure responses are similar for the two methods indicating a role of bladder-urethral, spinal reflexes in the urethral sphincter contractions. Bladder stimulation with two bilateral pairs of bipolar Permaloc™ electrodes at 40 mA, 40 Hz, 400 µs pulses for 5 s. Bladder squeezed by the investigator with four fingers around the bladder.

(12±2 versus 7±2 and 6±2 cm H_20; $P \leq 0.05$). There were no significant differences in urethral or anal pressures comparing combined Permaloc™ pairs to single pairs or

Table 2. Peak Urodynamic Pressure and Palpation Responses to Stimulation with Different Combinations of Permaloc™ Bipolar or Replica Electrodes Stimulated at 40 mA and to the Bladder Squeeze Test

Method	Peak Bladder Pr (cm H_20)	Urethral Pr (cm H_20)	Anal Pr (cm H_20)	Palpation (Rating Scale)
A. Permaloc™ Bilateral Electrodes, Open Abdomen				
Pair 1[b]	7±2	17±7	0±0	none 6; slight 1
Pair 2[b]	6±2	5±3	0±0	none 4; slight 2; strong 1
Combined Pairs	12±2[t]	17±8	2±1	none 4; slight 2; strong 1
B. Combined pairs, Closed Abdomen				
	15+3	24±10 16±13	none 3; moderate 2; strong 1; not tested 1	
C. Bladder Squeeze Test, Open Abdomen				
	25±5	14±7	1±1	none 4, not tested 3

[a]Stimulation with bilateral and bipolar Permaloc™ electrodes (40 mA, 40 Hz, 400 us pulses for 5 s).
[b]See text for detailed description for locations for the bipolar Permaloc™ electrodes were implanted as bilateral pairs 1 and 2.
[t]Significantly different peak bladder pressures compared to Permaloc™ electrode pair 1 and pair 2.

tests with the abdomen closed. Urethral pressures, however, were proportionally high when higher bladder pressures were present. For example, with the combined Permaloc™ electrodes and the abdomen open, the peak bladder pressure was 12±2 cm H_20 and the peak urethral pressure was 17±8 cm H_20. Palpation of the perineal region revealed greater unwanted pelvic floor, leg, and anal contractile activity following closure of the abdominal cavity. Abdominal closure was complicated by gas in intestines that expanded and pushed against the bladder; impingement of the bladder may have brought the electrodes closer to the sciatic nerve coursing through the pelvis to the legs causing unwanted contractions.

Testing for each of the Permaloc™ electrode configurations was also conducted at 20 mA and the pressure response averaged 44 % of the response seen at 40 mA (a similar percentage to the wire electrode results above). In addition, bladder squeeze test results are shown in Table **2**; both the peak bladder and urethral pressures for the bladder squeeze test were not significantly different from those pressures for stimulation with the four combined Permaloc™ electrodes; the squeeze test was only conducted in four animals.

DISCUSSION

We identified two bilateral stimulation sites that were implanted with bipolar Permaloc™ electrode on the bladder wall of swine. When increasing the stimulating current to 40 mA, it induced higher peak bladder pressures, but didn't produce urination. Possible reasons for these low pressures are:

Problem with the Animal Model

The swine didn't have high bladder pressure contractions. In our prior of cats and dogs studies we observed higher bladder pressures to stimulation [14-19]. In our most recent study of dogs, we used similar but fewer bipolar barb electrodes on the bladder wall than were used in this study. Peak bladder pressures over 30 cm H_20 were induced with 20 mA stimulating current. Other study differences between the current study and our prior studies were the type of anesthetic and presence of spontaneous bladder activity. The anesthetic differences were small. The spontaneous bladder activity was a major difference. The dog model regularly demonstrated spontaneous bladder contractions whereas no such activity was observed in the swine. Thus, we conclude that the use of swine should be limited for direct bladder stimulation studies, and we plan to use the dog model in the future. Peak bladder pressures of 30 cm H_20 or greater, however, were reported in two experimental studies using electrical stimulation in female minipigs or swine of similar size, suggesting that other deficiencies may be present with our protocol [24, 25]. There methods of stimulating pelvic plexus nerves close to the spinal cord, cuff electrodes and 10 s stimulation periods may have been superior to our direct bladder wall stimulation methods.

Problem with Stimulation Methods

Current stimulation methods were not optimal as compared to the clinical study by Magassi *et al.* [12, 13] in areas of electrode characteristics and electrode geometry.

The first area of concern is electrode characteristics; Magasi *et al.* successfully implanted a stimulator with eight stimulating surfaces on eight electrode leads in patients. Daily bladder-stimulated emptying was obtained in all 32 patients; however, three patients required a bladder neck incision to reduce urethral resistance. There stimulation parameters included 1 ms pulse duration and increased the stimulating current until urination was obtained. There pulse duration is similar to the 400 μs pulse duration used here. Our prior study using current-response tests demonstrated no improvement in the peak bladder pressure that was induced with pulse duration longer than 400 μs [15,19]. ' Magasi *et al.* [12, 13] did not state their stimulating frequency; based on their extensive review of the literature they may have been using a frequency in the range of the 40 Hz tested here. A major difference in the stimulation methods between their study and ours was that Magasi *et al.* used a much greater separation of the two stimulating surfaces within a bipolar set; one-fourth the distance around the bladder (horizontal plane of orientation) rather than the 5 mm separation used in this study.

Another comparison between their study and ours was the emphasis placed on electrodes close to the ureterovesical junctions: Magasi *et al*, stated:

> "Of the 8 electrodes, 2 have the most important function: those which are implanted next to the ureterovesical junctions. The contraction of the detrusor muscle and the perfect emptying of the bladder are only possible if these electrodes are appropriately positioned and operate faultlessly [13]."

We confirmed the importance of stimulation in the area of the ureterovesical junctions. Future test, however, with different distances between electrodes and the ureterovesical junction might provide new evidence for optimal number(s) and locations of stimulation sites.

Electrode geometry is another electrode characteristic. The platinum-iridium disk stimulating surfaces used by Magasi *et al.* [12, 13] are different from the stainless-steel helical-wire stimulating surfaces used in this study. Effects of stimulating surface geometry should be compared in further studies using current-response tests. The type of metal for charge delivery, however, should not make a difference. For example, we use constant-current stimulation methods to deliver the same current for any difference in electrode resistance associated with the type of metal or electrode surface area. Thus, we propose to use bipolar electrodes with longer stimulating surfaces and greater separation of the electrodes in the bipolar sets in future studies.

Side Effects of Stimulation

Another discussion point for this study is side effects of stimulation. One side effect of stimulation was urethral skeletal sphincter contractions (Fig. **5**, Table **1**). Bladder-sphincter spinal reflexes appeared to have a primary role in this unwanted response. A reflex arc was indicated by: one, significant delays in increased urethral pressure after the start of stimulation; two, urethral pressures that were different from bladder pressures; three, bladder squeeze test that induced high urethral pressures; and, four, much smaller

contractions recorded from the anal sphincter which is not involved in the bladder, urethral-sphincter reflex arc. The urethral sphincter contractions to bladder squeeze were unexpected. Urethral responses to bladder squeeze are common in SCI models characterized by detrusor-sphincter dyssynergia, which presents as an over-active bladder-urethral, spinal reflex [5]. A possible explanation for our observed urethral sphincter contraction is a lack of inhibition of the bladder-sphincter reflexes due to the absence of spontaneous bladder contractions. If spontaneous bladder contractions had been present we would expect inhibition of the urethral sphincter contractions in the presence of elevated bladder pressures. Other studies of swine and minipigs have not observed increases in urethral pressures during elevated bladder pressures; bladder squeeze tests in these other studies, however, were not conducted [24, 25].

Another side effect of stimulation was leg muscle contractions which were most likely from stimulation of the sciatic nerve. The sciatic nerve courses through the pelvis relatively close to the bladder wall and innervates muscles that we observed contracting during stimulation including the back of the thigh, leg and paw. Leg muscle contractions were more common at caudal stimulation sites, higher stimulation currents, and after abdominal closure. Distended intestines pushing against the bladder after closure may have brought the electrodes closer to the sciatic nerve; implanted electrodes more rostral and ventral on the bladder wall should minimize the unwanted leg muscle contractions. Our results indicate that effective locations can be obtained on the bladder wall for inducing bladder contractions while avoiding leg contractions.

Implantable Bladder Stimulators and Proposed Development Work

Patients with SCI have several lower urinary tract problems that need to be managed in addition to activation of the bladder for urination. One problem is an overactive bladder causing urinary incontinence and this is managed through bladder inhibition. Possover *et al*, [28], using a bladder control system, showed in three SCI patients that pudendal nerve stimulation at 20 Hz could inhibit the bladder producing bladder filling volumes of 500 ml. Another problem for SCI patients is high urethral resistance; Possover *et al*, [28] demonstrated in one patient that a 1.2 KHz high-frequency blocking of the pudendal nerve could be used to decrease urethral resistance. In this study, we tested high-frequency blocking methods on the pudendal nerve, the results are reported in a parallel study publication [29].

A technical concern with the Permaloc^{TM} electrode used here was stretching during explantation, making it unusable for further testing. The monopolar Peterson^{R} electrode does not have this stretching problem because of a polypropylene suture in the middle of the lead that prevents stretching; thus, future work with Permaloc^{TM} electrodes should include a similar inner suture to prevent stretching. The bipolar Permaloc^{TM} electrode is similar to the monopolar Peterson^{R} electrodes that are currently implanted in the diaphragm of high-level-SCI patients for respiratory pacing [26] and implanted in SCI patients arms and legs for neuroprosthetic applications [27]. However, as noted above, a design change for the bipolar Permaloc^{TM} electrode is needed for our bladder application, a greater range of distances is needed between the two stimulating surfaces.

CONCLUSION

Bladder wall stimulation with four Permaloc^{TM} bipolar electrodes at high currents produced insufficient bladder pressures for urination. The limited responses may have been due to ineffective stimulation parameters, electrode location and geometry and the animal model. Side effects of stimulation were most apparent with electrodes close to the pelvic floor or at high stimulating current. Urethral sphincter contractions, another side effect, appeared to be activated primarily through a bladder-urethral, spinal reflex arc. Further modifications of the electrode such as greater separation of the bipolar stimulating surfaces or changes in the testing methods such as alternative animal models need to be investigated to induce high bladder pressures without side effects.

ACKNOWLEDGEMENT

Funded by Veterans Administration Merit Review Grant, Rehabilitation Research and Development, # B3254R.

CONFLICT OF INTEREST

Declared none.

ABBREVIATIONS

SCI = Spinal cord injury

DNCB = Dorsal neurovascular bundles

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Received: March 7, 2012 Revised: June 2, 2012 Accepted: June 3, 2012