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Bursting stimulation of proximal urethral afferents improves bladder pressures and voiding

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Abstract

Reflex bladder excitation has been evoked via pudendal nerve, pudendal nerve branch and intraurethral stimulation; however, afferent-evoked bladder emptying has been less efficient than direct activation of the bladder via sacral root stimulation. A stimulation method that improves activation of the urethra–bladder excitatory reflex with minimal sphincter recruitment may lead to improved bladder emptying. Fine wire electrodes were placed in the wall of the urethra in five cats. Placement of electrodes near the proximal urethra evoked bladder contractions with minimal sphincter activation. On these electrodes, lower frequency burst-patterned stimuli evoked greater bladder voiding efficiencies ($71.2 \pm 27.8\%$) than other stimulus patterns on the same electrodes ($50.4 \pm 41.5\%$, $p > 0.05$) or any stimulus pattern on electrodes that elicited urethral closure ($16.5 \pm 12.7\%$, $p < 0.05$). Fine wire electrodes specifically targeted afferent fibers in the urethra, indicating the feasibility of clinical evaluations using the same method. This work may improve the translation of next generation neuroprostheses for bladder control.

1. Introduction

Reflex bladder activation via peripheral afferent nerve stimulation has been a recent topic of interest for restoring voiding function. In anesthetized spinal intact preparations, bladder activation has been shown for electrodes on the pudendal nerve [1–3] and distal pudendal nerve branches [4–7], placement of a percutaneous lead near the pudendal nerve [8], stimulation on the ventral surface of the urethra with a needle [7] and excitation of urethral afferents via stimulation with a catheter in the urethra [9, 10]. The goal of reflex bladder excitation is effective bladder emptying through activation of the urethra–bladder micturition reflex [11, 12], restoring function for individuals with bladder voiding dysfunction. Reflex voiding efficiencies [13] of 50–65% have been reported in studies that directly stimulated the pudendal nerve or one of its distal branches innervating the urethra [1, 2, 5, 6]. These results are better than voiding during distension-evoked bladder contractions (25–45% [1, 2, 5, 6]). This approach has not matched voiding efficiencies for direct bladder activation through sacral root stimulation (77–79% in similar preparations [1, 14]).

Targeting proximal urethral locations indicated as excitable by intraurethral stimulation [9, 10, 15], rather than the pudendal nerve trunk, may lead to less concurrent activation of the external urethral sphincter than direct stimulation of the pudendal nerve. This potential reduction in the outlet sphincter pressure may yield higher voiding efficiencies. The use of a fine wire electrode provides a means to target a specific location, similar to the use of an electrode mounted on a catheter to target a specific region in the urethra for intraurethral stimulation. Wire electrode stimulation has been shown to evoke bladder contractions for placement near the dorsal penile nerve in cats [5] and percutaneous placement near the pudendal nerve in cats [8] and humans [16]. Those studies did not specifically target proximal urethral afferents.

Wire electrodes for reflex bladder excitation may be better received by potential subjects and are less invasive and more selective than nerve cuff electrodes. This approach is comparable to the use of stimulating wires in multi-day evaluations and permanent implant of Interstim leads (Medtronic, Minneapolis, MN) [17, 18], which are placed in a sacral foramen. Wire electrodes have been evaluated for reflex bladder control in humans near the pudendal nerve [16, 19] and the dorsal genital nerve [20]. In a similar minimally invasive technique, microstimulators have been placed near the pudendal nerve [21]. Evoked bladder contractions have not been consistent in humans due to possible co-activation of inhibitory bladder reflexes [16]. Prior to clinical evaluations using this method, it is necessary to investigate the placement of wire electrodes for bladder excitation and the relation to intraurethral stimulation in a preclinical model. While evaluating wire electrodes, the use of non-standard stimulus patterns such as pulse-bursting, which have been shown to evoke greater bladder pressures [3, 9], may lead to improved voiding.

The purpose of this study was to evaluate a methodology for evoking maximal reflex bladder excitation with minimal concurrent sphincter activation, thus leading to effective voiding. Our hypotheses were that targeting proximal urethral afferents closer to the bladder neck would result in less external urethral sphincter recruitment than targeting distal urethral afferents and that the use of burst-patterned stimuli would lead to improved bladder voiding. These results are an important step in the translation of neural prostheses for bladder dysfunction to clinical realization. These results indicate the feasibility of obtaining near complete voiding with afferent stimulation and the use of electrodes near the urethra for exciting the bladder.

2. Methods

2.1. Animal model

Experiments were conducted in mature, neurologically and urologically intact, purpose-bred cats. All animal studies were approved by the Institutional Animal Care and Use Committees of the Louis Stokes Cleveland Veterans Affairs Medical Center and Case Western Reserve University prior to initiation.

2.2. Experimental setup

An intramuscular injection of ketamine (35 mg kg^{-1}) was given for initial sedation, followed by induction of anesthesia with an intravenous dose of alpha-chloralose (65 mg kg^{-1}). Subsequent anesthesia was maintained with alpha-chloralose (15 mg kg^{-1}). Isoflurane (0.25–2%) was added during surgical procedures to maintain a full depth of anesthesia. Additionally, every 12 h, buprenorphine (0.01 mg kg^{-1}) was administered to ensure analgesia. For the duration of the experiment, vital signs were observed on a surgical monitor (V9204 Advisor Monitor, Surgivet, Waukesha, WI). A dual-lumen 6 Fr catheter (DLC-6D, Life-Tech, Stafford, TX) was placed through the dome of the bladder via a mid-ventral incision and secured with a purse-string suture. A disposable pressure transducer (Deltran I, Utah Medical Products, Midvale, UT) was connected to one lumen of the bladder catheter for recording bladder pressure. Infusion of saline through the other bladder catheter lumen was performed using a syringe pump (Genie, Kent Scientific, Torrington, CT). A custom-designed scale using a high-resolution single point load cell (ESP 0.6 kg, Load Cell Central, Monroeton, PA) was placed below the urethra outlet to record voided volumes. Bladder transducer outputs, voiding scale outputs and TTL signals from the current-controlled stimulator (DS7A, Digitimer, Hertfordshire, England or Pulsar 6bp-as, FHC, Bowdoinham, ME) were tracked using a custom-designed LabVIEW (version 7.1, National Instruments, Austin, TX) data acquisition system.

2.3. Stimulation

Monophasic (Digitimer) or biphasic (Pulsar) stimuli for bladder activation were given using cathode-leading, current-controlled pulses at a fixed pulse width of $200 \mu\text{s}$. Stimulus patterns were either applied continuously at a frequency of 2–33 Hz or were applied in bursts (e.g. a burst of 5 pulses at 200 Hz, with two bursts per second). This burst pattern example is described as $5 \times 200 \text{ Hz @ } 2 \text{ Hz}$. A detailed description of burst-patterned stimuli is given in Bruns *et al* [3]. Continuous or burst pulse train frequencies of less than 5 Hz were categorized as lower frequencies while frequencies of greater than 20 Hz were categorized as higher frequencies. For evaluating reflex bladder excitation, stimulus durations were approximately 20 s, varying between 15 s and 30 s.

2.4. Experimental protocol

A custom-assembled 3.5 F catheter was inserted into the urethra, such that a monopolar stimulating ring electrode on the catheter was near the mid portion of the urethra, which has been shown to be excitable in male cats [9, 10]. A large patch electrode or needle was placed on or in the skin of one leg or at the base of the tail to provide a current return path. A cystometrogram was performed to examine the excitability of the bladder, filling at $0.5\text{--}2 \text{ mL min}^{-1}$. During filling at 1–5 mL incremental volumes, the urethra was stimulated with the catheter electrode to evaluate whether reflex bladder contractions could be elicited. Throughout this initial excitability evaluation, the stimulus pattern was alternated between continuous 2 Hz and 33 Hz stimuli, using a current level two to three times the level for visual recruitment of the external anal sphincter. The bladder volume was recorded for the first reflex contraction elicited by stimulation (V_{STIM}). Once V_{STIM} was determined, the ability to excite the bladder via intraurethral stimulation was tested for several proximal

(closer to the prostate/bladder neck) and distal (closer to the external urethral sphincter) locations within the urethra.

Via a postero-lateral gluteal approach, the dorsal surface of the urethra was exposed. At several proximal and distal locations, the outer wall of the urethra was stimulated with a custom-made monopolar twisted-wire probe using successful intraurethral stimulation parameters, to verify observed intraurethral excitability. A fine wire electrode with an exposed metal tip (1512M, Life-Tech, Stafford, TX) was placed into the urethral wall at a proximal urethra location that was excited by stimulation on the surface of the urethra. When placing the wire electrode from the postero-lateral access, a longitudinal approach along the urethra was used for inserting the wire in the urethral wall. A transverse approach had a greater likelihood of either driving the wire needle completely through the urethra into surrounding tissue or missing the urethra completely. For comparison, a distal wire electrode was inserted in some experiments. From the postero-lateral access, fascia and vasculature surrounding the branching of the pudendal nerve toward the urethra, external urethral sphincter and external anal sphincter limited the visibility of the urethra, leading to a semi-blind transverse wire insertion for distal wire placements.

At or above V_{STIM} , several trials using lower and higher frequency patterned stimuli were performed on each electrode, while the intraurethral catheter was still in place. If an electrode did not evoke bladder contractions, a substitute was placed nearby after further testing with the twisted-wire probe. Next, the catheter was removed and voiding trials were performed. In each trial, the bladder was filled above V_{STIM} and a stimulus was applied to a wire electrode. If the bladder contracted and voiding occurred, stimulation was continued until the evoked pressure returned to the pre-stimulus baseline and voiding terminated. The volume of urine voided during the trial was tracked (V_{VOID}). Any residual urine (V_{RES}) left in the bladder was removed by the dual-lumen catheter. In this manner, voiding trials were performed for several lower frequency bursting patterns ($5\text{--}10 \times 200 \text{ Hz @ } 2\text{--}3 \text{ Hz}$), lower frequency continuous stimulation ($2\text{--}3 \text{ Hz}$) and higher frequency continuous stimulation ($20\text{--}33 \text{ Hz}$). Additionally, one or more control voids were performed in which the bladder was filled to a volume at which a fused distension-evoked contraction occurred (V_{TH}) and the bladder started voiding. V_{VOID} and V_{RES} were recorded for distension-evoked voids in the same manner as for stimulation-evoked voids.

The response of the external urethral sphincter to wire stimulation was determined for an empty bladder. A 4 F catheter with a solid-state pressure transducer (MMI, Hackensack, NJ) was inserted via the urethra to the level of the bladder neck. Outputs from the pressure transducer were recorded by the LabVIEW data acquisition system. The pressure catheter was moved in the urethra until a urethral location was found where maximal urethral pressure was observed for stimulation with an electrode. Then a continuous ($20\text{--}33 \text{ Hz}$) stimulus was applied to the wire electrode, while the pressure catheter was rotated and shifted to verify that the transducer was at the location of greatest evoked external urethral sphincter pressures. Across the range of stimulus current levels used to evoke bladder contractions, 33 Hz continuous stimulation was applied for $6\text{--}10 \text{ s}$ on each wire electrode that elicited bladder contractions and the resulting urethral pressure was recorded. The average increase in pressure between the end of the stimulus and the pre-stimulus level,

while using current amplitudes from bladder voiding trials, was defined as the urethral closure pressure.

In one experiment, after the completion of all wire electrode bladder excitation trials, the pudendal nerve was transected bilaterally. Previous trials that evoked bladder contractions were repeated to verify that the reflex pathway utilizes the pudendal nerve.

The urethral length and relative positions of the external urethral sphincter and the bladder neck were measured in a post-mortem dissection. Wire electrodes locations were normalized to these urethral landmarks and the urethral length, with respect to the average urethral landmark locations (in cm) as previously done for intraurethral stimulation [9].

2.5. Data analysis

For bladder excitation and voiding trials, each bladder response was examined. Once a bladder contraction of 15 cmH₂O or more above the baseline pressure could be evoked by stimulation, subsequent trials under similar conditions (bladder volume, stimulation location and amplitude) were analyzed. Average (P_{AVE-EV}) and maximum (P_{MAX-EV}) evoked pressures during each trial were calculated as the difference between the 3 s average pressure baseline before stimulus initiation and the average or maximum pressure recorded while the pressure was above the baseline plus three times the baseline standard deviation, as previously done [3, 9]. Unless indicated otherwise, only P_{AVE-EV} results are reported here, as P_{AVE-EV} and P_{MAX-EV} tracked each other during all comparisons. For all voiding trials, V_{VOID} and V_{RES} were measured, in addition to P_{AVE-EV} and P_{MAX-EV} . The voiding efficiency for each trial was determined by dividing V_{VOID} by the sum of V_{VOID} and V_{RES} . Evoked pressures and voiding results were accumulated for each stimulus pattern and urethral region (proximal, distal) within and across experiments. Tukey–Kramer HSD (highly significant difference) tests were performed for evaluations of statistical significance between group means ($\alpha = 0.05$) using JMP (version 6.0.3, SAS Institute Inc., Cary, NC). This test accounted for the multiple comparisons of unequal group sizes across the data set, for different animals, electrodes and stimulation patterns. When given, data were presented as mean $\pm$ standard deviation.

3. Results

3.1. Wire electrode placement

Reflex bladder excitation was evaluated in five adult cats (0.6 ± 0.1 years old; 3.4 ± 0.5 kg): four males and one female. Across experiments, 17 proximal wire electrodes were placed while evaluating reflex excitability. Three cats responded to stimulation with a single proximal electrode (two males—one with an additional proximal electrode that did not elicit contractions; one female). The other two male cats each responded to stimulation with two proximal electrodes, of the five and eight total proximal wire electrodes placed, respectively. For comparison, four cats had a single distal wire electrode placed, two of which evoked reflex bladder contractions (one male; one female).

The contact areas on the ten proximal and two distal wire electrodes which did not elicit bladder contractions were all located outside the urethra wall, as verified in post-mortem

dissections. The longitudinal locations of electrodes along the urethra were easily quantifiable, with average normalized proximal and distal wire electrode locations of 5.3 ± 0.7 cm and 3.5 ± 0.1 cm from the external meatus (figure 1), for electrodes that evoked bladder contractions. In the female cat ($\blacktriangle$ and $\triangle$, figure 1), locations of the external urethral sphincter at 0.3 cm and the bladder neck at 5.7 cm were normalized to the average male locations. The electrode distance from the urethra midline was not easily quantified due to surrounding soft tissue movement during dissection, so the effective total electrode distance to the external urethral sphincter was unknown. Thus, wire-evoked responses were quantified by the observed responses instead of the precise anatomical location of the electrode.

3.2. Bladder excitation

Under isovolumetric conditions, wire electrode stimulation-evoked bladder contractions (20.3 ± 5.9 cmH₂O, $n = 14$) were equivalent to intraurethral stimulation-evoked contractions (18.2 ± 7.0 cmH₂O, $n = 48$, $p > 0.05$), when comparing the same stimulus patterns at similar locations. Across all experiments, wire electrode stimulation current levels (1.2–5 mA) were equivalent to or less than intraurethral stimulation current levels (1–8.5 mA) when exciting the bladder. Lower frequency stimuli (2–3 Hz) and higher frequency stimuli (20–33 Hz) each elicited bladder contractions on seven of eight evaluated wire electrodes, while lower frequency bursting stimuli ($5, 10 \times 200$ Hz @ 2, 3 Hz) elicited bladder contractions for stimulation with all nine wire electrodes. Across all wire electrode stimulation trials without a catheter in the urethra, lower frequency bursting stimuli (20.3 ± 6.5 cmH₂O, $n = 111$) evoked consistently larger bladder contractions than lower frequency continuous stimuli (14.1 ± 8.9 cmH₂O, $n = 18$, $p < 0.05$) and higher frequency continuous stimuli (12.5 ± 9.1 cmH₂O, $n = 26$, $p < 0.05$). Stimulation with proximal placed wire electrodes evoked significantly larger bladder contractions (19.5 ± 8.1 cmH₂O, $n = 126$) than stimulation with distal placed wire electrodes (13.2 ± 4.7 cmH₂O, $n = 29$, $p < 0.05$).

3.3. Direct external urethral sphincter excitation

In general, urethral closure was larger for electrode positions closer to the external urethral sphincter (figures 1 and 2). At the stimulus current levels used to evoke bladder contractions, wire electrodes within 1.5 cm normalized distance from the external urethral sphincter evoked 80 cmH₂O or greater closure pressure. Wire electrodes at distances further from the sphincter evoked 25 cmH₂O or less closure pressure. In the female cat experiment, urethral closure was minimal (<10 cmH₂O).

3.4. Voiding

Stimulation-evoked reflexive bladder emptying was obtained in all experiments. Voiding efficiencies depended on urethral closure (figure 2). In four out of five wire electrode placements in which stimulation recruited less than 5 cmH₂O urethral closure pressure, the average voiding efficiency was 75% or greater for the best stimulus parameters. For all four wire placements which recruited more than 9 cmH₂O urethral closure pressure, the voiding efficiency was less than 50% for the best stimulus parameters. These voiding efficiencies were significantly different when comparing all best stimulus parameter per wire electrode voiding trials pooled together ($72.7 \pm 27.6\%$, $n = 29$, and $21.3 \pm 10.9\%$, $n = 23$, $p < 0.05$).

Comparing pooled voiding efficiencies across wire electrode averages, to limit potential bias due to an unbalanced numbers of trials across experiments, still yielded significant differences ($69.2 \pm 30.5\%$, $n = 5$, and $24.1 \pm 12.9\%$, $n = 4$, $p < 0.05$). The best stimulus parameters in each experiment were selected based on the stimulus type (lower frequency bursting stimuli, lower frequency continuous stimuli, and higher frequency continuous stimuli) that evoked an average voiding efficiency higher than for the other stimulus types. For eight of the wire electrodes, the best stimulus parameters were lower frequency bursting stimuli. For one wire electrode (□, figure 2), higher frequency continuous stimulation led to the best voiding efficiencies.

One wire electrode placement was an outlier, having both low urethral closure and voiding efficiencies (figure 2, ▼). Attempts at exciting the bladder with a variety of stimulus patterns and lower current levels to limit urethral closure were ineffective at increasing the voiding efficiency on this electrode. The P_{AVE-EV} (37.9 ± 4.5 cmH₂O) and P_{MAX-EV} (49.8 ± 3.9 cmH₂O) during voiding trials with this electrode were significantly greater than for voiding trials on all other electrodes (21.9 ± 7.5 cmH₂O, 33.1 ± 7.9 cmH₂O, $p < 0.05$). These higher pressures suggest an obstruction in the urethra, which would have limited bladder emptying. Omitting this outlier electrode results in a greater voiding efficiency for electrodes that recruited less than 5 cmH₂O urethral closure pressure, for all trials pooled together ($81.8 \pm 15.9\%$, $n = 25$) and for pooled voiding efficiencies across wire electrode averages ($82.6 \pm 7.0\%$, $n = 4$). The voiding efficiencies given in both reduced data sets are significantly greater than the voiding efficiencies obtained by stimulation with wire electrodes that recruited more than 9 cmH₂O urethral closure ($p < 0.05$).

Burst-patterned lower frequency stimulation ($5, 10 \times 200$ Hz @ 2, 3 Hz) led to better voiding than other stimulus patterns (figures 3 and 4). For wire electrodes that evoked minimal urethral closure pressure, the voiding efficiency evoked by lower frequency bursting stimuli ($69.7 \pm 28.0\%$, $n = 25$) was slightly greater than that evoked by lower frequency continuous stimulation, but the difference was not statistically significant ($61.5 \pm 44.8\%$, $n = 7$, $p > 0.05$). Lower frequency bursting stimulation led to a greater voiding efficiency than higher frequency continuous stimulation ($41.7 \pm 39.1\%$, $n = 9$, $0.10 > p > 0.05$), which may have had a significant difference if the sample size were larger. With these electrodes, lower frequency bursting stimuli evoked significantly greater voiding than bladder distension ($43.3 \pm 20.6\%$, $n = 31$, $p < 0.05$). For wire electrodes that evoked high urethral closure pressures, the voiding efficiency evoked by lower frequency bursting stimuli ($20.6 \pm 12.0\%$, $n = 22$) was not significantly different than that evoked by lower ($2.2 \pm 3.9\%$, $n = 3$, $p > 0.05$) and higher ($8.2 \pm 8.9\%$, $n = 6$, $p > 0.05$) frequency continuous stimulation and was significantly less than that evoked by bladder distension ($p < 0.05$).

3.5. Pathway verification

In one cat, proximal wire electrode stimulation trials were performed before and after bilateral pudendal nerve transection. After unilateral transection, reflex bladder contractions could still be evoked by wire stimulation. After bilateral pudendal nerve transection, proximal wire stimulation did not elicit bladder contractions, demonstrating that the proximal-stimulated pathway is pudendal nerve mediated.

4. Discussion

This work shows that reflex bladder excitation and emptying with wire electrodes placed in the urethra wall is feasible. In three of the experiments, voiding efficiencies greater than 75% were obtained. The two key factors were the placement of the electrode at proximal urethral locations that resulted in less urethral closure and the use of low-frequency pulse bursting to elicit larger bladder contractions than for other stimulus patterns.

4.1. Effective voiding

Voiding trials on wire electrodes that met the goal of reflex bladder excitation with minimal urethral closure (<5 cmH₂O) had efficiencies of $72.7 \pm 27.6\%$. This result is larger than previous work (50–65%) in similar spinal intact preps under alpha-chloralose anesthesia [1, 5, 6] and is near voiding efficiencies (73–91%) obtained in chronic spinalized cats under different testing scenarios [22, 23]. The improved voiding obtained in these results is not significantly different from voiding results obtained for efferent bladder excitation via sacral root stimulation coupled with sphincter block via high-frequency alternating current stimulation on the pudendal nerve ($78 \pm 17\%$, $p > 0.05$) [14]. Stimulus-evoked voiding in this experiment was greater than voiding evoked by distension-evoked contractions while under alpha-chloralose anesthesia, as previously observed [1, 5, 6]. If the outlier wire electrode (figure 2, ▼) is truly an outlier, then these reflex-evoked voiding results are even better ($81.8 \pm 15.9\%$) and more consistent with the other voiding efficiencies discussed.

4.2. Bladder excitation

The use of burst-patterned stimuli led to larger evoked bladder pressures and voiding efficiencies (figures 3 and 4). This improvement is a direct progression of previous work, which indicated greater bladder excitation for burst-patterned stimuli applied in the urethra [9] and on the pudendal nerve [3], to a functional output of improved voiding. The extra pulses in burst-patterned stimuli may increase the recruitment of post-ganglionic pelvic efferents, as occurs for higher rates of stimulation applied to pre-ganglionic fibers [24].

The duty cycle in lower frequency burst stimulation (5–15% for best bursting parameters used here: $5\text{--}10 \times 200$ Hz @ 2–3 Hz) is less than a higher frequency intermittent duty cycle (83% for 33 Hz 1 s on, 0.2 s off), previously reported to allow bladder voiding for direct pudendal nerve stimulation [1]. This shorter time interval of applied stimulation provides a longer time between stimuli for voiding if the sphincter is activated and reduces the stimulator power consumed with fewer pulses per second. Improved bladder emptying was seen for burst-patterned stimuli over higher frequency continuous stimuli even when there was urethra closure (figure 4). However, lower frequency stimulation does not elicit bladder contractions after spinalization [6, 9, 22, 25] so these benefits may only be available for individuals who do not have complete spinal cord injuries.

Reflex bladder excitation by fine wire electrodes at proximal urethral locations utilizes a pudendal nerve afferent pathway, as verified by pudendal nerve transection. This is consistent with previous work which reported the elimination of reflex-evoked bladder excitation via intraurethral stimulation after cutting or inhibiting the pudendal nerve [9, 26].

Thus, the urethra–bladder excitatory reflex is activated [11, 12, 27]. The cranial urethral sensory branch [6, 7] is likely the pudendal nerve branch activated by proximal urethral stimulation.

4.3. Urethral closure

Wire electrodes that were placed closer to the bladder neck, away from the sphincter, resulted in less urethral closure (figures 1 and 2). Excitation of the micturition reflex includes a reduction in the external urethral sphincter activity [27, 28]. Thus, while activating the reflex, limiting direct recruitment of the external urethral sphincter should allow improved voiding with minimal impedance. The selection of 5–9 cmH₂O as a threshold for minimal urethral closure provided a low cutoff point and appeared to have a functional basis as seen in the voiding elicited by stimulation with four out of five wire electrodes (figure 2).

Factors beyond the wire electrode location may have affected outlet resistance. For wire locations closer to the bladder neck that recruited urethral closure (3 out of 7 proximal electrodes; figures 1 and 2), indirect current paths, either through conducting urine in the urethra or through tissue surrounding the urethra, may have led to partial sphincter activation. Additionally, while alpha-chloralose is a standard anesthetic in reflex bladder excitation studies [1–10, 22, 23], it has been noted to limit bladder emptying by reducing reflex bladder contraction amplitudes and inducing dyssynergic sphincter contractions [29]. The direct effect of alpha-chloralose across these different experiments is unknown; however, it has been suggested that stimulation-evoked voiding will approach complete emptying in animals without alpha-chloralose [1], as has been indicated in non-anesthetized decerebrate cats [27].

4.4. Clinical implications

This work shows the clinical feasibility of a bladder neuroprosthesis using reflex bladder excitation targeting proximal urethral afferents. Bladder voiding efficiencies greater than 70% limit the likelihood of urinary tract infections [30]. Voiding efficiencies obtained here, in which minimal urethral closure was obtained, exceeded this clinical target for emptying the bladder. This work also suggests the clinical feasibility of using fine wire electrodes to excite the bladder. One clinical study with two subjects suggested the ability to excite the bladder with a percutaneous stimulating lead placed near the pudendal nerve [16]. However, this work did not indicate robust, extended bladder contractions, likely had simultaneous activation of the sphincter, and may have had concurrent activation of pudendal-to-bladder continence reflexes [16]. Selective activation [6] of the pudendal nerve may achieve clinically relevant bladder recruitment with minimal sphincter activation; however, the cranial sensory branch has yet to be identified in humans. Recent work evaluated percutaneous wire electrodes positioned near the dorsal genital nerve branch of the pudendal nerve to excite the continence reflex in women with incontinence [20]. A similar approach could be used in clinical evaluations of exciting the bladder, with a percutaneous wire placed near the urethra to specifically target the urethral sensory afferents with minimal external urethral sphincter recruitment, as was done here.

4.5. Wire placement

The approach taken here for placing the wire electrode presented some difficulties when accessing the distal urethra. Ventral access to the post-prostatic urethra in male cats, by splitting the pubic bone, has been reported [7]; however this invasive process is less likely to be clinically implemented. Percutaneous posterior approaches to the pudendal nerve have been evaluated in cats [8] and clinically [16, 19, 31]. This posterior approach may provide an easier method of targeting the urethra when placing stimulation leads in preclinical and clinical experiments.

5. Conclusions

Fine wire electrodes placed near the urethra in cats can evoke robust bladder contractions and effective voiding. Stimulation with wires at locations further from the sphincter led to bladder excitation with low urethral closure. Future evaluations of reflex bladder emptying should target electrode locations which limit sphincter activation. The use of lower frequency bursting stimuli evoked significantly larger bladder contractions than lower and higher frequency continuous stimuli and slightly greater, but not statistically different, voiding results. Neuroprosthetic applications targeting afferent nerves should evaluate bursting stimuli for obtaining maximal results. These results support the translatability of a bladder neuroprosthetic using electrodes placed near the proximal urethra and suggest that afferent-mediated approaches can produce voiding close to that produced by direct drive approaches.

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Figure 1.

Wire electrodes were placed at proximal urethral locations (closer to the prostate/bladder neck) to target the proximal urethral afferent branch of the pudendal nerve and to minimize direct external urethral sphincter (EUS) recruitment. For comparison, several wire electrodes were also placed more distally near the EUS. Urethral locations, normalized with respect to the urethral opening (external meatus), of wire electrodes that elicited bladder contractions are shown. Wire electrode icons used here correspond to icons used in figure 2, with same-shape icons indicating electrodes from the same animal experiment (one circle, three squares, one diamond, two triangles, two inverted triangles). Average normalized proximal and distal wire electrode locations were 5.3 ± 0.7 cm and 3.5 ± 0.1 cm from the urethral opening. The electrodes indicated by Δ and $\square$ represent the two distal electrode placements referenced in the text. The electrode indicated by ∇ was not a true distal placement, although it recruited urethral closure. Pudendal nerve innervation of the urethra is based on Yoo et al [7], with the non-urethral innervating branch of the pudendal nerve heading toward the external anal sphincter (EAS).

Figure 2.

Voiding efficiency depended on urethral closure. (a) For the best stimulus parameter on each wire electrode, increased urethral closure pressure led to a reduced voiding efficiency. Pulse bursting was the best stimulus parameter for all electrodes except one (□) in which higher frequency stimulation led to a higher voiding efficiency. (b) When pooled voiding trials were segregated by urethral closure, electrodes that produced lower urethral closure (<5 cmH₂O) evoked significantly greater voiding efficiencies ($72.7 \pm 27.6\%$, $n = 29$, $p < 0.05$) than those that produced higher urethral closure (>9 cmH₂O, $21.3 \pm 10.9\%$, $n = 23$). Urethral closure was defined as the maximal evoked urethral pressure recorded at the end of 6–10 s of 33 Hz stimulation. If the outlier electrode (▼) is removed (see text), the average voiding efficiency for electrodes with lower urethral closure was $81.8 \pm 15.9\%$ ($p < 0.05$ versus voiding efficiency for electrodes with higher urethral closure). (* $p < 0.05$)

Figure 3.

Pulse bursting induced larger bladder contractions and better voiding than the use of continuous stimuli. While 2 Hz (2.5 mA) continuous stimulation evoked a bladder contraction but no voiding in this example, burst-patterned stimulation (10×200 Hz @ 2 Hz, 2.5 mA) evoked a 30% larger bladder contraction and substantial voiding (81% voiding efficiency).

Figure 4.

Burst-patterned stimulation with wire electrodes that evoked lower urethral closure pressures (<5 cmH₂O) led to better voiding efficiencies than other stimulus parameters with the same electrodes and with electrodes that evoked higher urethral closure pressures (>9 cmH₂O).

For lower urethral closure electrodes, burst-patterned stimuli evoked slightly greater voiding ($69.7 \pm 28.0\%$, $n = 25$) than lower frequency stimuli ($61.5 \pm 44.8\%$, $n = 7$, $p > 0.05$) and higher frequency stimuli ($41.7 \pm 39.1\%$, $n = 9$, $p < 0.10$). For higher urethral closure electrodes, voiding evoked by burst-patterned stimuli ($20.6 \pm 12.0\%$, $n = 22$) was not significantly different than voiding evoked by either lower frequency ($2.2 \pm 3.9\%$, $n = 3$, $p > 0.05$) or higher frequency ($8.2 \pm 8.9\%$, $n = 6$, $p > 0.05$) continuous stimuli. Distension-evoked voiding ($43.3 \pm 20.6\%$, $n = 31$) was significantly less than for burst-patterned stimulus-evoked voiding on lower urethral closure electrodes ($p < 0.05$) but significantly greater than any voiding on higher urethral closure electrodes ($p < 0.05$). (* $p < 0.05$)