A pilot study investigating the effects of intraurethral stimulation and the potential to prevent urgency urinary incontinence episodes in women

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17 **Aims:** To determine the feasibility of intraurethral electrical stimulation to evoke increases in
18 urethral pressure and prevent urgency urinary incontinence (UUI) episodes in women.

19 **Methods:** Women with UUI based on the LUTS questionnaire were recruited. Stimulation
20 amplitude was varied at different locations along the urethra, different stimulation rates, and with
21 the bladder empty and filled to first sensation while measuring evoked urethral pressures and
22 noting sensation. Cystometry and micturition studies, with and without intraurethral stimulation
23 were performed to determine if stimulation prevented incontinence episodes. **Results:** Eleven
24 women (median age 70, range 27-85) with UUI participated in the study. Sensation thresholds
25 were higher for proximal urethral stimulation and for stimulation at lower frequencies (1 Hz).
26 Negligible increases in urethral pressure were observed despite large differences in tolerated
27 stimulation amplitudes between subjects. A correlation between sensory thresholds and
28 baseline urethral pressure was observed. Only one subject demonstrated phasic detrusor
29 overactivity incontinence (DOI). Two had urinary incontinence with provocative maneuvers. In
30 all three cases, intraurethral stimulation did not prevent urine loss. **Conclusions:** Intraurethral
31 electrical stimulation did not increase urethral pressures in women with UUI or prevent the
32 observed DOI. These findings suggest future studies should explore whether direct urethral
33 motor neuron stimulation increases urethral pressures sufficiently to prevent urgency
34 incontinence episodes, as well as if urethral stimulation prevents urethral relaxation in the
35 absence of increases in urethral pressure. Motor testing (e.g. urethral pressure profiles) should
36 be performed in conjunction with current perception testing to clarify whether patients have
37 sensory or general neurological impairment.

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39 **Keywords:** Urinary Urge Incontinence, Urethra, Electrical Stimulation, Current Perception
40 Threshold, Overactive Bladder

41 Introduction

42 Urgency urinary incontinence (UUI) may be treated with anticholinergics, $\beta 3$ agonists,
43 tibial nerve stimulation, sacral neuromodulation (SNM), and Onabotulinum Toxin A (Botox).
44 Although many patients improve with treatment they are often not completely satisfied with their
45 therapy, and additional therapies are needed to improve incontinence therapy.

46 Treatment of UUI focuses on detrusor overactivity and bladder dysfunction, to the
47 exclusion of urethral dysfunction, and this may contribute to the inadequate therapeutic relief
48 from current therapies. Incontinence results when the urethra fails to maintain adequate closure
49 pressure, and, for UUI, one might expect that this occurs when a detrusor contraction
50 overpowers a contracting urethra. However, there are numerous references to urethral failure in
51 UUI due to urethral relaxation during an incontinent episode¹⁻⁶. This may imply that UUI is not
52 always attributable to a lack of strength (structural weakness) in the presence of detrusor
53 overactivity, but rather to dysfunctional neural control (functional weakness). Webster et al.¹
54 found in 33% of UUI patients a seemingly inappropriate silencing of sphincter EMG that
55 “appeared to be the precipitating event of the [uninhibited] bladder contraction.” Similar
56 observations of urethral relaxation preceding rises in detrusor pressure during cystometry were
57 made by others with even higher prevalence rates (39%², 84%³, and 100%^{4,5}) as well as during
58 provocative maneuvers such as hand washing (77%⁶). These observations suggests that many
59 UUI episodes are actually inappropriate voiding events, as initiation of voiding usually starts with
60 a drop in urethral pressure, followed by an increase in bladder pressure⁷. Thus, functional
61 urethral weakness is likely to precipitate urine loss in at least a subset of women with UUI.

62 Observations of urethral functional weakness resulted in the suggestion of treatment of
63 UUI with alpha-agonists¹. Bergman et al.² reported a high rate of success treating UUI using
64 phenylpropanolamine. However, this therapy is not currently used, due to severe side effects

associated with the high required dosage⁸. Additionally, as alpha-agonist drugs are administered to increase baseline smooth muscle tone of the urethra (i.e., treatment of a structural weakness), their use may not always be appropriate for functional weakness, as dysfunctional neural control may still cause the urethra to relax inappropriately.

This pilot study evaluates the feasibility of using electrical stimulation to close the urethra when an impending UUI event is suspected. The envisaged solution would be an electrical stimulation device, with electrodes implanted peri-urethrally, to stimulate the urethra on demand, while attempting to reach a toilet. In this way a user could directly bypass their lack of urethral control and ensure adequate sphincter contraction until an appropriate time to void. This approach differs from and may be synergistic with current strategies directed at the bladder.

The aims of the study were to quantify the effects of stimulation parameters on intraurethral pressure, to determine the tolerability of stimulation, and to use this information to determine if intraurethral stimulation could prevent detrusor overactivity incontinence (DOI) in women with UUI.

Methods

Between January and May 2018, women with UUI were recruited from the Duke University Urogynecology clinic and completed the study. Prior approval was obtained from the Duke University Institutional Review Board and written informed consent was obtained from all subjects.

Inclusion/Exclusion Criteria

Inclusions were women ≥ 18 who answered “often” or “always” to question 6, “How often do you have a sudden need to rush to urinate”, and question 16b, “How often they leaked urine in connection with a sudden need to rush to urinate”, on the LUTS tool⁹. Additionally, subjects

had to be willing to stop their overactive bladder medications (i.e., anticholinergics and β 3 agonists) 3 weeks prior to the study. Exclusion criteria were: pregnancy, less than 6 weeks postpartum, or breastfeeding; pelvic cancer or irradiation; pelvic surgery in the past 3 months; multiple sclerosis, myasthenia gravis, Parkinson's Disease, or stroke within the past 6 months; positive urine dip ($>+1$ nitrites or >1 LE) with urinary tract infection symptoms at the study visit; unevaluated microscopic hematuria; morbid obesity (BMI > 40); posterior tibial nerve stimulation in the past month; intravesical Onabotulinum Toxin A in the past year; a sacral neuromodulation (InterStim) implant; or Interstitial Cystitis/Bladder Pain Syndrome.

Experimental Session

Subjects participated in a single session in the clinic which lasted approximately 2 hours. A custom setup was created for recording pressures, EMG, and delivering electrical stimulation, including: a laptop running custom Matlab software to view data and deliver stimulation; a stimulus isolator (ISO-STIM 01D-100 100 mA, NPI Electronic GmbH, Germany); EMG amplifier (ETH-256, iWorx, Dover, NH); pressure amplifiers (PCU-200, Millar); a custom switching box for connecting the catheter sites to the stimulator or EMG amplifier; a balance (GF-3000, A&D, Tokyo, Japan); and infusion pump (Delphis, Laborie). A custom 6 Fr catheter with multiple sensor and stimulation sites (Figure 1A, B) was manufactured by Gaeltec Devices Ltd. A NI-DAQ (USB-6218, National Instruments) was used to collect data and to control the stimulus isolator (via an analog output). All signals were sampled at 1 kHz, except the stimulus-output monitoring channel (20 kHz).

Subjects were in a semi-recumbent position during testing. The bladder was emptied via catheter. The custom catheter was inserted alongside a dual-lumen 6 Fr catheter for filling the bladder (Laborie, Figure 1B, C). Lubricating jelly (Cardinal Health) was applied to the tips of the catheters to ease insertion. A water-filled catheter (RPC-9, Laborie) was inserted into the vagina for measuring abdominal pressure. EMG electrodes (ELE428, Laborie) were placed on the

perineum. Two TENS pads (3"x5"), one for EMG ground and one for a stimulus return, were placed bilaterally just above the knee (RichMar MultiStim Cloth Electrodes, Chattanooga, TN). Catheters were held in place using tape (Transpore, 3M) and Gaeltec connectors were fixed to the subject's thigh using Coban wrap (3M).

Figure 1 Catheter setup and experiment outline. **A)** Picture of the custom catheter with four stimulation sites (each 3 mm length, stainless steel) and 4 pressure sites (each 7 mm length). Spacing between the majority of components is 1 mm with 14 mm spacing between the first stimulation site and the bladder pressure sensor. **B)** Picture of catheters used during cystometric testing after an experiment had ended. **C)** Illustration showing the placement of the two urethral catheters. The filling catheter was placed slightly ahead of custom catheter so that the filling outlet would not be occluded. With the distal urethra pressure sensor placed at the maximum baseline pressure position the fourth stimulus site was always inside the urethra. As the catheters were adjusted based on the maximum pressure location, the location of the other sensors with respect to the bladder neck was unknown. **D)** Experimental outline. Each block (in the diagram) was completed before moving onto the subsequent block.

For the last 4 subjects the distal urethra pressure sensor lacked reliable signaling, and in the last subject the mid-urethral pressure sensor also malfunctioned. In these cases, placement of the catheter was performed by finding the maximum urethral pressure on the adjacent pressure sensor and pushing the catheter into the urethra by a predetermined amount so that the stimulation sites were at the same location relative to the maximum pressure.

Urethral pressures were measured while varying stimulus amplitude, location, pulse repetition rate, and bladder fullness using charge-balanced 200 μ s per phase, biphasic stimulus pulses. For each combination of rate, location, and bladder state, the stimulation amplitude was increased from zero to either 1.5x (1 Hz, 20 Hz) the sensation threshold or to the maximum tolerable amplitude (10 Hz and 30 Hz). These sensations were logged to gain additional insight into how evoked sensations varied as a function of stimulus location, frequency, and bladder fullness. Step sizes of 0.1 mA were used until between 10 and 15 mA then step sizes of 1 mA were used to a maximum of 90 mA. Sensation threshold was evaluated by increasing the stimulation amplitude until the subject felt the stimulus, decreasing the amplitude until the sensation went away, then increasing the amplitude again until the subject felt the stimulus a second time, and averaging the resulting three values¹⁰.

The full experimental outline is shown in Figure 1D. Prior to cystometry the subject voided to empty their bladder. Their bladder was subsequently filled with room-temperature saline at 60 ml/min. The bladder was filled to maximum cystometric capacity at which point the pump stopped. Subjects then underwent a set of provocative maneuvers (standing, heel tapping, listening to running water) then sat to void on a nearby commode. This process was repeated twice, once with stimulation starting at first sensation of filling and once without stimulation (in randomized order). At the end all instrumentation was removed and the post-void residual was measured (via catheter).

Originally the experimental plan was to stimulate during cystometric testing using the stimulus location and frequency that generated the largest urethral pressure during parameter testing. However, given the lack of evoked pressures, all subjects received stimulation on site #3 at 10 Hz. Preliminary work in cats showed large evoked urethral pressures (> 100 cmH₂O) at ~10 Hz from intraurethral stimulation (unpublished data) and 10 Hz stimulation of the pudendal nerve inhibits the bladder in both rats and cats^{11,12}.

Data Analysis

ANOVAs were computed using the non-parametric Friedman test (*friedman* in Matlab). Correlations were computed using Pearson correlation (*corr* in Matlab). A paired t-test was used to assess differences in sensation thresholds before and after filling. Statistical significance was considered to be obtained at $p < 0.05$.

Results

Eleven women (8 Caucasian, 3 African-American, median age 70, range 27 – 85) were recruited from the Duke University Urogynecology clinic.

Sensation thresholds and maximum tolerable amplitudes at 10 Hz are shown for all subjects as a function of stimulus location in Figure 2A. Both sensation thresholds ($p < 0.001$, $n = 10$) and maximum tolerable amplitudes ($p = 0.001$, $n = 7$) were dependent on stimulation location, and both amplitudes increased from the distal urethra to the proximal urethra. One subject identified the stimulus as coming from inside the vagina and only at high amplitudes identified the sensation as originating from the urethra. Those values are shown in any Figure 2 but are not included in any statistical results. Three subjects were unable to tolerate the stimulus return placed at the leg at higher stimulus amplitudes before the urethral stimulus became intolerable, and they were also excluded from the statistical analysis.

Figure 2 Sensation threshold and maximum tolerable amplitudes as a function of location and stimulation frequency. Each line represents a single subject. The subject in green identified low-amplitude stimulation as coming from her vagina, and only identified urethral stimulation at higher amplitudes. Her values were excluded from averages and statistical analysis. **A)** Both sensation threshold ($p < 0.001$, $n = 10$) and maximum tolerable stimulus amplitudes ($p = 0.001$, $n = 7$) varied as a function of stimulus location. Missing data at the maximum tolerable amplitude is due to early stopping due to the leg return site becoming unpleasant. Averages are shown black. Both threshold and maximum tolerable amplitudes tended to increase moving from the meatus towards the bladder. **B)** Stimulation frequency also impacted sensation thresholds for two different stimulation sites (site #2: $p = 0.006$, $n = 9$ and site #3: $p = 0.004$, $n = 9$).

Sensation thresholds at both site 2 ($p = 0.006$, $n = 9$) and site 3 ($p = 0.004$, $n = 9$) were dependent on stimulation frequency (Figure 2B). In general, increasing the stimulation frequency decreased sensation thresholds, although this effect was minimal between 10 and 30

Hz, compared to the difference in threshold between 1 and 10 Hz. The first subject underwent a slightly different protocol and her data was omitted from this analysis.

Stimulation at 10 Hz on sites 2 and 3 was repeated after filling the bladder to first sensation to determine if the level of bladder fullness impacted thresholds. No clear trend was observed across subjects ($p = 0.81$ for site 2, $p = 0.56$ for site 3) despite generally consistent changes between the two sites within a subject (i.e. increases or decreases in thresholds after filling). Correlation of the two sensation ratios (sensation threshold with a full bladder vs. an empty bladder) between the two sites was 0.88.

Pressures were measured at five locations (bladder, vagina, and 3 urethral), and the largest observed increases in urethral pressure were less than 1 cmH₂O (Figure 3).

Figure 3 Demonstration of recording urethral pressure while increasing stimulation amplitude. In this example stimulation is delivered on site #3 at 30Hz. Evoked contractions of small amplitude (< 1 cmH₂O) can be seen on the right of the figure. These contractions are indicative of the largest evoked contractions observed during intraurethral stimulation. Top panel shows the specified stimulus amplitude sent to the stimulator. Since the stimulus pulses were biphasic, both positive and negative values can be seen. Zooming in would show the individual stimulus pulses.

The resting mid-urethral pressure (1.2 cm proximal to the maximum pressure) was correlated with sensation thresholds at 10 Hz for site 2 ($r = -0.69$, $p = 0.041$, $n = 9$) with a similar but not statistically significant trend at site 3 ($r = -0.53$, $p = 0.145$, $n = 9$) (Figure 4). These correlation values exceeded those for age (site 2: $r = 0.43$, $p = 0.22$, and site 3: $r = 0.32$, $p = 0.36$).

Figure 4 Scatter-plots of the mid-urethral pressure (sensor between stimulation sites 2 and 3 and 1.2 cm away from the maximum urethral pressure) at baseline versus sensation thresholds at sites 2 and 3 with linear fits shown. Each dot represents a single subject with the final subject omitted due to sensor damage and another subject due to sensations originating in the vagina. Correlations were $r=-0.69$ for site 2 ($p=0.041$, $n=9$) and $r=-0.53$ for site 3 ($p=0.145$, $n=9$). In comparison the correlation values between sensation thresholds and age were $r = 0.43$ ($p=0.22$, site 2) and $r=0.32$ ($p=0.36$, site 3).

Only 1 of the 11 subjects demonstrated DOI during bladder filling (Figure 5) and 2 subjects demonstrated urinary incontinence upon provocation. Stimulation did not prevent leaking for any of these 3 subjects.

Figure 5 Terminal detrusor overactivity incontinence event. Subject underwent filling at 60 ml/min starting at event #3 and stopping at event #5. Events are marked on the bottom of the figure. Event #4 indicates first sensation. Following first sensation intraurethral electrical stimulation is ramped up to 10 mA (sensation threshold) at site #3 at 10 Hz. Prior to reaching the target amplitude the distal urethral pressure (site of maximum urethral pressure closest to the meatus) starts to drop as vesical pressure is increasing. Shortly thereafter urine loss occurs. Urine loss occurred while still sitting.

225 Discussion

226 Intraurethral stimulation did not increase urethral pressure or prevent incontinence in
227 women with UUI. However, the results suggest approaches to treat UUI by targeting the urethra
228 and provide insight into how to potentially improve patient subtyping using current perception
229 testing.

230 Evoked Pressures

231 No parameter combinations evoked meaningful pressures to prevent urinary
232 incontinence episodes. Two methodological issues may have led to the lack of pressure
233 increases. First, the stimulus amplitude was gradually increased rather than starting at a large
234 amplitude as is typically done in animal studies. This was done to minimize discomfort from
235 rapid stimulation onset but may have led to sensory accommodation and prevented contractions
236 evoked by reflex mechanisms. Second, all testing was done with monopolar stimulation so that
237 the stimulus originated from a well-defined location along the urethra. Simultaneous stimulation
238 on multiple sites along the urethra to activate more urethral tissue may have evoked larger
239 increases in urethral pressure.

240 By recruiting those women reporting UUI episodes of “often” or “always”, we had
241 expected a high number of DOI episodes, but it is possible that urethral stimulation testing prior
242 to cystometry caused a neurological change that lessened the chance of a DOI episode.
243 However, our experimental setup did not lend itself to testing this particular hypothesis. There is
244 some evidence in female rats that intraurethral stimulation can be an inhibitory stimulus as
245 stimulation increased the rats’ bladder capacities¹³; however, it is unclear if the increases in
246 bladder capacity observed with urethral stimulation would also lead to decreases in UUI
247 episodes.

Moving Forward with the Proposed Therapy

The lack of evoked pressures from intraurethral stimulation suggests an alternative approach is needed to prevent decreases in urethral pressure and subsequent urgency incontinent episodes. Direct stimulation of motor neurons targeting the urethra, using a more invasive peri-urethral stimulation approach may be needed to maintain elevated urethral pressures. Additionally, it may be possible to drive urethral afferent activity not to increase pressures but rather to modulate neural control in a way that prevents inappropriate urethral relaxation. For example, increased baseline activation of urethral afferents, via electrical stimulation, may increase sensitivity to urethral fluid ingress, facilitating guarding reflexes.

Implications for Sensory Perception Testing and Patient Phenotyping

Sensory perception testing might improve patient subtyping that either guides new therapy development or improves the targeting of current therapies to patients. However, sensory perception testing is not a standard part of current diagnostic testing. In this study three factors that may impact current perception thresholds were assessed, including evaluating the impact of stimulus location, stimulation rate, and bladder fullness.

Stimulus sensation thresholds and maximum tolerable amplitudes varied as a function of stimulus location, with higher values towards the bladder and lower values towards the meatus. These results mirror those of Pauwels et al.¹⁴ who showed the lowest thresholds at the distal urethra, with higher thresholds at the proximal urethra, and even higher at the bladder. Despite the focus of our work on urethral function, there may be value in testing both urethral and bladder sensory function, as relative differences between the two may serve to sub-type patients¹⁵.

Increasing stimulation pulse repetition rate decreased sensation thresholds confirming previous results¹⁶. These results are expected if one considers that increasing stimulation rate

likely facilitates temporal integration at synapses. Note, this differs from sinusoidal stimuli where the strength of the stimulus itself varies as a function of frequency (lower frequencies are more powerful whereas the strength is constant for the fixed-duration pulses used in this study). Thus for sinusoidal waveforms thresholds tend to increase with increasing frequency¹⁷, rather than decrease as observed in this study.

Increasing the volume of fluid in the bladder to first sensation to void did not result in a consistent increase or decrease in sensation thresholds. Murray noted decreasing posterior urethra sensory thresholds as the bladders was filled, with a particularly sharp drop in thresholds for healthy patients at first desire to void that was absent in other patients (obstructive, hypersensitive, unstable)¹⁸. Those results suggest that changes in sensitivity as the bladder fills may also be useful for sub-typing patients, although this remains to be robustly tested in women with UI. Repeated measurements and additional levels of bladder fullness testing would help clarify the relationship between bladder fullness and thresholds.

Sensory thresholds were correlated with baseline urethral pressures. We had hypothesized that women with UI would have decreased sensory thresholds^{19,20}, and thus might tolerate larger stimulus amplitudes that might enable to direct activation of motor neurons innervating urethral striated muscle (and thus increases in urethral pressure). The large range of thresholds and maximum tolerable amplitudes between subjects suggests some degree of sensory impairment in at least a subset of the subjects we tested. An inability to activate motor neurons despite higher amplitudes suggests not only sensory impairment but also motor impairment, i.e. general neuropathy. Our results showing that reduced pressures are correlated with increased sensory thresholds (Figure 4) are also suggestive of combined sensory and motor impairment, and there is some evidence of urethral motor impairment during urgency urinary incontinence²¹.

Conclusion

Intraurethral electrical stimulation did not increase urethral pressures in women with UUI or prevent the observed DOI. These findings suggest future studies should explore whether direct urethral motor neuron stimulation increases urethral pressures sufficiently to prevent urgency incontinence episodes, as well as if urethral stimulation prevents urethral relaxation in the absence of increases in urethral pressure. Motor testing (e.g. urethral pressure profiles) should be performed in conjunction with current perception testing to clarify whether patients have sensory or general neurological impairment.

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