Published in final edited form as:

Proc Inst Mech Eng H. 2019 January ; 233(1): 100–113. doi:10.1177/0954411918754925.

Is submucosal bladder pressure monitoring feasible?

Anisha S. Basu^{1,2}, Steve Majerus^{2,3,4}, Liz Ferry⁵, Iryna Makovey⁶, Hui Zhu^{4,6}, and Margot S. Damaser^{2,4,6}

¹Dept of Biomedical Engineering, Case Western Reserve University, Cleveland, OH USA

²Dept of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH USA

³Dept of Electrical Engineering and Computer Science, Case Western Reserve University, Cleveland, OH USA

⁴Advanced Platform Technology Center, Louis Stokes Cleveland Dept. of Veterans Affairs Medical Center, Cleveland, OH USA

⁵Department of Urology, SUNY Upstate Medical University, Syracuse, NY USA

⁶Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH USA

Abstract

Introduction: There has been recent interest in placing pressure sensing elements beneath the bladder mucosa to facilitate chronic bladder pressure monitoring. Wired submucosal sensors with the wires passed through detrusor have been demonstrated *in vivo*, with limited chronic retention, potentially due to the cable tethering the detrusor. Published studies of submucosal implants have shown that high correlation coefficients between submucosal and lumen pressures can be obtained in caprine, feline, and canine models. We have developed a wireless pressure monitor and surgical technique for wireless submucosal implantation and present our initial chronic implantation study here.

Methods: Pressure monitors were implanted (n=6) in female calf models (n=5). Five devices were implanted cystoscopically with a 25-Fr rigid cystoscope. One device was implanted suprapubically to test device retention with an intact mucosa. Wireless recordings during anesthetized cystometry simultaneous with catheter-based reference vesical pressure measurements during filling and manual bladder compressions were recorded.

Results: Individual analysis of normalized data during bladder compressions (n=12) indicated high correlation ($r=0.85-0.94$) between submucosal and reference vesical pressure. The healing response was robust over 4 weeks; however, mucosal erosion occurred 2–4 weeks after implantation, leading to device migration into the bladder lumen and expulsion during urination.

Conclusions: Wireless pressure monitors may be successfully placed in a suburothelial position. Submucosal pressures are correlated with vesical pressure, but may differ due to biomechanical forces pressing on an implanted sensor. Fully wireless devices implanted beneath the mucosa have risk of erosion through the mucosa, potentially caused by disruption of blood flow to the

urothelium, or an as-yet unstudied mechanism of submucosal regrowth. Further investigation into device miniaturization, anchoring methods, and understanding of submucosal pressure biomechanics may enable chronic submucosal pressure monitoring. However, the risk of erosion with submucosal implantation highlights the need for investigation of devices designed for chronic intravesical pressure monitoring.

Keywords

urodynamics; wireless; catheter; incontinence; neuromodulation; closed-loop

Introduction

Urinary Incontinence (UI) is a bladder storage symptom defined by the involuntary leakage of urine.¹ It may be due to sphincter deficiency or loss of bladder control or function. Risk factors for UI include age, excessive alcohol intake, pregnancy, childbirth, bladder tumor/cancer, an enlarged prostate, as well as peripheral nerve or spinal cord injury.² The wide range of risk factors means that most individuals are at risk for UI at some point in their lives. More than 20 million women and more than 6 million men in the United States were estimated to have urinary incontinence in a 2008 study.³ Worldwide, UI affects over 200 million people.⁴ UI not only decreases the quality of life of patients but can also be linked to poor bladder compliance which could lead to renal dysfunction.^{5–8} Proper diagnosis of UI is a critical step in clinical management, since manifestation of UI can vary widely between individuals.

Urodynamics, the standard quantitative method of diagnosing UI, is an evaluation of bladder and urethra efficacy in the storage and emptying of urine.^{9,10} In filling cystometry, the urodynamic test that assesses storage function and dysfunction, the bladder is filled with room temperature saline retrogradely via a transurethral catheter placed within the bladder lumen. Bladder pressure is measured via the catheter, and simultaneous abdominal pressure is estimated via a vaginal or rectal catheter.⁹ The difference of these pressures is the detrusor pressure, or the pressure generated by the detrusor muscle through active contraction. The detrusor pressure during cystometry also depends on several factors including type of detrusor contraction, viscoelastic properties of the bladder wall, neurogenic control, simultaneous urethral behavior, and the presence of leakage.¹¹ Evaluating these factors can help narrow the causes of incontinence or bladder dysfunction.

The catheter-based nature of urodynamics has several disadvantages. Catheters increase the risk of urinary tract infections and may obstruct the urethra, affecting bladder pressure measurements.^{12,13} Urodynamics testing takes place in a clinical environment where patients are typically lying or sitting during the study and a clinician is in attendance to ask questions about sensations and observe any urine leakage. This situation can lead to embarrassment particularly in women, affecting bladder function and test results.¹⁴ Additionally, standard urodynamic measurements are recorded for only 20–40 minutes, during which time pathological changes in pressure may not appear.¹⁵ For example, in a study of patients with overactive bladder (OAB), conventional urodynamics did not reproduce patient symptoms 45–58% of the time.^{16,17} Therefore in many cases, patients are

diagnosed based on reported symptoms and medical history, while urodynamics is used to aid in complex diagnoses. However, if urodynamics accurately and reliably reproduced patient symptoms, it has the potential to lead to more objective and specific UI diagnoses.

Natural-filling, ambulatory urodynamics has the potential to better reflect physiological lower urinary tract function, since it monitors bladder pressure without superphysiologic bladder infusion. A longer period of measured activity could also lead to improved diagnostic efficacy because bladder function could be evaluated during daily activities.¹⁸ However, the need for catheters limits the duration of ambulatory monitoring and could affect the pressure measurements.¹⁹

In addition to improved diagnostics, continuous pressure monitoring could be a useful tool to improve quality of life since a device that monitors pressure in real-time could potentially alert an individual with loss of sensation of the need to void or empty the bladder.²⁰ In addition, bladder pressure feedback to neuromodulation systems could provide improved efficacy as well as reducing habituation and energy usage.^{21,22} Considering current clinical methods of assessment of lower urinary tract function, an innovative method of bladder monitoring is needed to accomplish these important goals.

Alternative measures of lower urinary tract function

It is widely accepted that measuring pressure is the best way to evaluate bladder function.¹¹ However there are alternative methods of evaluation, both as clinical and as research tools. Alternative methods used in conjunction with urodynamics, such as pelvic muscle electromyography (EMG), can help diagnose a variety of lower urinary tract conditions including detrusor-sphincter dysynergia.¹⁷ Imaging methods such as ultrasound (e.g. BladderScan²³) are used clinically to determine bladder volume non-invasively but can only be done as a snapshot rather than a continuous measurement.^{24,25} Similarly, near infrared spectroscopy (NIRS) has been studied as a method of noninvasively visualizing bladder microcirculation in real time during voiding.^{26,27} However, NIRS is only practical for short term measurement and is not appropriate for long term ambulatory, continuous bladder monitoring. Ongoing research into wearable imaging systems may address these shortcomings; Niestoruk et al have demonstrated long-term bladder ultrasound monitoring,²⁸ and it has also been suggested that NIRS instruments could be adapted for ambulatory monitoring.²⁹

Issues with these approaches, however, include the invasiveness of catheter-based measurements, monitoring in an artificial clinical environment, and limited data collection.³⁰ As such, these limitations generally mirror those posed by traditional urodynamics, in which data is gathered in limited-duration measurements in an artificial setting. Further, unambiguous detection of isovolumetric (non-voiding) bladder contractions may prove to be difficult using snapshot imaging methods, limiting the ability to diagnose UI.

Wireless pressure sensors

Wireless pressure sensors are an option to continuously evaluate bladder function long-term. Effectively, these sensors would provide the benefits of ambulatory urodynamics—continuous measurement of clinically-relevant vesical pressures within natural filling/

voiding cycles—while bypassing issues associated with catheters, wires, and high-energy imaging equipment. Wireless pressure sensors may be categorized as intravesical devices that remain in the bladder lumen or implantable devices that are tunneled through the detrusor or implanted within the bladder wall.

Intravesical devices

Intravesical devices currently used clinically or in clinical trials include the Vesair and LiRIS³¹, neither of which measures pressure or other physiological variables.^{13,32–35} Pressure-monitoring intravesical devices currently in development are inserted via the urethra and are exposed to urine and therefore measure vesical pressure directly. To reduce power consumption, some devices store data on the device; this data can only be accessed after device extraction and once the capsule is opened.^{33,35} One such device only stored pressure data if the current pressure reading differed from the previously stored value by a specific threshold value, or if it has been longer than 60 seconds since the last value was stored, to optimize device memory.^{32,35} As a result, these devices would be appropriate for long-term monitoring but not for feedback to notify an individual about the state of his/her bladder or control a neuromodulation or other electrical stimulation system in real-time.

Another intravesical wireless device currently in development, has no battery onboard, instead using the wireless transfer of energy through a magnetic field between coupled inductive windings, or coils.³⁶ For inductively-powered medical devices, a high current is passed through an external coil placed close to the skin surface, generating a short-range magnetic field that passes through the body. The small intravesical device scavenges energy from this magnetic field and transmits data to an external receiver via the same inductive link. Since the device is untethered and could be anywhere in the bladder lumen, it is proposed that this device be powered and the transmitted data collected by three external coils, one worn around the waist, one around the leg and a third coil placed vertically in front of the bladder on the assumption that at any point in time, one of the three coils will be close enough and sufficiently aligned to interface with the device.³⁶ However, no multi-day animal intravesical device studies in free-roaming animals have been reported to date.^{32–35}

Submucosal devices

The mucosa of the bladder, or urothelium, is the compliant lining of the inner wall and is thought to be sturdy enough to encapsulate and entrap small sensor devices, while being sufficiently compliant to enable bladder pressure measurement submucosally.³⁷ Devices that are submucosally implanted into the bladder involve a more invasive procedure than intravesical devices but may be more suitable for chronic use, as they are shielded from urine and therefore less likely to cause urine stone formation. Early attempts to develop implantable pressure sensors have struggled with sensor migration and infection in dogs and goats.^{4,38,39}

Submucosal devices, by and large, have been implanted via an abdominal incision, gaining access to the outer bladder wall. The detrusor is carefully dissected to the level of the urothelium, permitting implantation of a sensor element. Finally, the detrusor is sutured closed, enclosing a wired sensor within the bladder wall. Acutely, this implantation method

does not perforate the urothelium and places the sensor element within millimeters of the lumen but protected from the urine by the urothelium.^{4,40} The wire exits via the bladder wall and connects to either a battery pack in the abdomen or is exteriorized for connection to a power source and recording apparatus.³²

All published data in these wired submucosal implants have shown high correlation between intravesical and submucosal pressure in caprine,^{6,41} feline,^{32,42} and canine³² models. Pressure measurements showed that correlation coefficients in all animals were greater than 0.90, indicating high correlation in acute studies. Thus far, correlation coefficients have been reported, rather than absolute pressure values, due to an observed attenuation factor and nonlinear pressure transfer function through submucosal detection.^{13,42} Some investigators have suggested that the biomechanics of the detrusor/urothelium plays a role in this effect.³² Despite pressure attenuation, submucosal detection of bladder contractions appears to be feasible.^{32,41,42}

However, submucosal devices are susceptible to erosion through the detrusor in chronic studies. Placement of a submucosal device directly in the center of the detrusor is difficult to implement, and significant deviation is thought to increase the rate of device erosion.^{6,41} Erosion occurs over variable timescales from days to weeks, and may be influenced by surgical implantation method^{4,38,41} or accelerated by tethering of the detrusor by wires.³² Surgical complications such as hematuria and clots in the urine have also been linked to submucosal implants.^{40,43} However, it generally appears that the urothelial lining remains intact after abdominal implantation, with studies reporting an intact urothelium for up to 7 days³², 12 days⁴³, and three months⁴⁰ after successful submucosal implantation.

Previously published examples of such procedures involve wired devices, which left a wire protruding through the detrusor for connection to an intraabdominal module or external instrumentation.³² We have recently developed a novel submucosal sensor which is fully wireless, and can be fully enclosed within the submucosal plane, without a trans-detrusor wire. This wireless pressure monitor may reduce erosion and improve chronic sustainability of submucosal bladder pressure sensing.

The Wireless Implantable MicroManometer (WIMM)

An ideal chronic pressure sensor should be wireless, fully internalized, non-irritative, out of contact with the urine, and placed in a minimally-invasive manner. We have developed a wireless implantable micro-manometer (WIMM) that consists of a micro-battery, pressure transducer, and custom integrated circuit with instrumentation, telemetry, and power management circuitry. We aimed to evaluate the safety and feasibility of cystoscopic implementation of the WIMM into the suburothelium in a large animal model.

WIMM specifications

The specifications for the WIMM were chosen based on the desired functionality, implant location, and implant method^{42,44}, as well as a compromise between low power consumption and sensing accuracy. Because the bladder is located deep within the pelvis, continuous RF powering of the implant (as used in subcutaneous devices) would require a

large external power source which would limit patient mobility. Therefore, the WIMM was designed to be battery powered, with nightly wireless recharge occurring using a stationary system. An external radio receiver receives real-time pressure telemetry from the implanted WIMM.

Size constraints for the WIMM were chosen to enable cystoscopic implantation with standard urological instruments (Figure 1). Specifically, the device was sized to fit through a 25-French rigid cystoscope sheath—this required a device cross section less than $7\text{mm} \times 3.5\text{mm}$. Total device length was constrained to 18mm to reduce the total device volume in the suburothelial implant location. These constraints limited the size of the wireless charging antenna within the device, which in turn determined the daily power budget based on the efficiency of 6-hour wireless recharge periods. To maintain battery charge, an ultra-low-power application specific integrated circuit (ASIC) was designed for the WIMM. The ASIC measures pressure 100 times per second over a range of 0–200 cm H₂O. Additional circuitry tracks and subtracts very slow baseline (below 3 milli-Hertz) drifts up to 2,000 cm H₂O, which may be caused by package aging, device fabrication tolerances, or fibrotic tissue encapsulation effects.^{13,42} Therefore, the total absolute pressure range of the device is 0–2,200 cm H₂O, but at any moment, the device provides a dynamic sensing range of 200 cm H₂O with 0.5 cm H₂O precision. Data is transmitted adaptively to save energy, with a variable transmission rate of 1.5 – 100 samples/second to enable real-time detection of bladder events. The transmission rate of data is automatically calculated by a custom circuit which includes first- and second-order pressure derivatives to select an appropriate data rate based on bladder activity level.^{13,42} For example, during slow filling, data is transmitted less frequently, but during a contraction the data rate ramps up to maximum speed. The ASIC was combined with a silicon pressure sensor, data transmission and wireless recharge antennas, and a rechargeable battery to form a wireless microsystem (Figure 2a).

Chronic sensor encapsulation

We developed a nonhermetic polymer sensor package over a period of iteration using interdigitated electrodes soaked in high temperature saline to determine failure modes. Figure 2b shows a cross section of the final device packaging layers. Our key finding in these studies was that any inclusion of foreign particles provides water condensation points, leading to layer delamination and package failure. Our packaging process was performed in a Class-100 clean room to minimize contamination. Full details of the packaging process have been previously published⁴⁵, and are briefly summarized here. First, devices were cleaned thoroughly and coated in electronics-grade epoxy. The pressure sensor element was protected with poly-dimethyl siloxane (PDMS) gel and a conformal coating of Parylene-C produced a flexible pressure diaphragm and moisture barrier. Next, sensors were injection molded with biomedical-grade epoxy to provide device structural rigidity and waterproofing. Finally, devices were coated in centrifugally-cast PDMS to promote biocompatibility. In this procedure, PDMS was centrifuged under vacuum to remove entrapped air at the molecular level, which slows moisture ingress. Devices were dipped and centrifuged again at low speed to remove excess PDMS, leaving a thin polymer coating. This package was evaluated chronically in subcutaneous implantation in rats from 1–6 months.⁴⁵ Histological

confirmation of tissue samples indicated no foreign body reaction or biocompatibility concerns.⁴⁵

Implantation methods

Two different implantation methods were attempted; cystoscopic and transabdominal: Cystoscopic implantation of submucosal devices (n=5) was performed in female Jersey calves (n=4) weighing 50–60 kg (Figure 3). One calf received two serial device implantations with a one-week recovery period after device removal prior to the next implantation. Calves were initially anesthetized with ketamine (5mg/kg) and xylazine (0.1mg/kg) intramuscular followed by 2% isoflurane (inhalant) and were placed in a supine position. Cystourethroscopy was performed with a 25 French rigid cystoscope. A defect in the urothelium was made using electrocautery posterior to the trigone of the bladder. Flexible cystoscopic scissors were inserted beneath the mucosa and opened to develop a suburothelial plane without cutting action. Next, a 1.5-cc 5-Fr arterial embolectomy catheter was inserted into the pocket and expanded using saline to further dissect the mucosa without cutting. The cystoscope sheath and camera were placed into the pocket to verify the pocket depth and condition of dissection. Once pocket creation was completed, the nose of the sheath was held in the pocket while the camera was retracted. The sheath was then used as a delivery channel for the WIMM device measuring $6.8 \times 3.0 \times 15$ mm. The device was inserted into the cystoscope sheath and pushed into the pocket with the camera until it exited the sheath within the mucosal pocket (Figure 4). Finally, the sheath and camera were retracted to visualize the submucosal implantation. All devices were placed completely within the suburothelial pocket in the peri-trigone area, without urothelium interposition (Figure 5a).

Because the cystoscopic implantation relied on a submucosal pocket to retain the device, several methods were attempted to promote submucosal healing and device anchoring (Table 2). Devices were implanted either with a smooth, unmodified exterior surface (n=1), or with barbed absorbable sutures bonded to the device surface (n=5) to snare the mucosa. Additionally, biodegradable dermal glue (Derma-Bond) was applied with CO₂ cystoscopy to glue the mucosa (n=2).

In all cases, a Foley drainage catheter was placed immediately after implant to prevent detrusor distension and mucosa stretching. Intramuscular anchors on the WIMM were not used to avoid the risk of serious organ damage during device retrieval. Mucosa suturing was attempted but was ultimately too time-consuming and surgically difficult to be effective.

Surgical implantation (n=1) was performed with the calf anesthetized and placed in a supine position. A midline abdominal incision was made and dissection was performed down to the bladder. Perivesical fat was removed and a 1–2 cm incision was made in the detrusor, superficial to the urothelium, to create a pouch. The bladder was gently compressed to expose urothelium and verify integrity of the mucosa. The device was placed within the pouch oriented with the pressure sensor against the mucosa facing the bladder lumen (Figure 5b). The detrusor was then closed without tension using nonabsorbable suture and the abdomen was closed.

A Foley catheter was placed at the end of both implantation procedures to keep the bladder collapsed and promote healing for 1-week post-implant. To demonstrate that observed bladders spasms (painful episodes associated with small void) were due to the catheter and not the WIMM, one calf received the draining catheter for a week prior to device implantation. Repeat cystoscopy was performed at one-week intervals to monitor healing. The catheter was removed when cystoscopy showed positive healing and no interstitial redness.

Cystometric methods

During weekly anesthetized evaluations, bladder capacity was assessed and cystometry performed. Capacity was determined by gravity filling the detrusor using dilute contrast at 0 cm H₂O. After gravity filling, fluoroscopic cystograms were obtained to note bladder contour and integrity, as well as to align external data telemetry and battery recharging antennas with the implant location. A dual-lumen Foley was inserted into the bladder and was connected to a peristaltic pump and pressure reference transducer. Cystometry was performed by infusing saline at 100 mL/min while measuring vesical pressure. This fill rate was chosen for this animal model based on a typical gravity fill capacity of 800–1000 mL; cystometry at this rate took approximately 8–10 minutes per fill. Calves do not produce reflex voiding contractions under anesthesia, so cystometry was terminated when the bladder reached the gravity fill capacity or mean pressure exceeded 40 cm H₂O. Fluoroscopy was performed to verify device location (Figure 6).

Device measurement methods

Implanted wireless devices were tested both in anesthetized procedures and during ambulatory recording sessions. Sensor function was confirmed through anesthetized cystometry against a vesical reference. A data acquisition (DAQ) unit (National Instruments) simultaneously recorded vesical pressure and wirelessly-transmitted samples from the implanted pressure monitor. Abdominal compressions to create variable intraabdominal pressures were also conducted after bladder filling as an additional test for the implanted device.

Ambulatory device recording and wireless battery recharging was performed after a 2-day healing period. Battery recharging was performed three times weekly for four hours by placing the animal in a transport cart to limit movement and taping a recharge antenna to the animal skin. Alignment of the external charging antenna and functional battery recharge was confirmed with fluoroscopy at the time of implant and marked by shaving the animal's fur in an optimum location.

A second antenna was connected to wireless data reception instrumentation on a mobile cart. Ambulatory device recordings were performed by holding the data reception antenna approximately 25 cm from the implanted device at various positions on the animal's torso. Data was collected while the calves were conscious and standing, laying down, ambulating, and experiencing bladder spasms. Catheter-based vesical reference pressures were not collected during ambulatory procedures due to concern for catheter insertion in awake

animals and animal discomfort. Therefore, ambulatory pressure recordings are not presented here due to subjectivity in interpretation.

Data analysis

Matlab was used for data correction, filtering, and statistical calculations. Recordings from the DAQ were imported to obtain vesical pressure traces (from anesthetized cystometry only) and wireless device samples. Wireless data traces were visually inspected for data corruption (visible as large-scale noise). Highly corrupted spans of data were not selected for further analysis. Relatively noise-free data traces were further analyzed. Device binary data were error-corrected to account for single-bit errors which occur during wireless data reception. A first-order difference highlighted jumps in the data – any jumps in data greater than 8 (approximately 16 cm H₂O) were beyond physiologic speeds and likely caused by transmission corruption. Errors corresponding to binary powers (e.g. 8, 16, 32) were attributed to single-bit errors and corrected by flipping the relevant bit. Multi-bit errors were corrected using a zero-order hold of the last received valid sample.

After error correction, vesical reference and wireless device recordings were filtered using a 0.5-Hz, 4th-order low-pass Chebyshev filter. This low filter bandwidth was selected based on an analysis of human cystometry traces, which identified signal bandwidths for physiologic bladder events.⁴² Reference and device data were plotted and analyzed for correlation and root-mean-square difference. Data were also segmented to focus on device performance during manual abdominal compressions. Data segments were manually identified to have one compression per segment. Each segment was approximately 4 seconds long and processed in the same manner for analysis. Data were detrended in each segment and normalized to a range of zero to one. The correlation between reference pressure and device recorded pressure was calculated for the selected compression segments. Attenuation factor for each segment was also calculated based on the difference in min-max range between compression baseline and peak pressure.

Results

Implant summary

Although four different mucosal anchoring methods were attempted (Table 2), device retention in the mucosal plane was poor, with erosion occurring within 2–3 weeks. Eroded devices were expelled from the urethra during voiding, and were washed away during routine cage cleaning in the animal facility. Since expelled devices were not recovered, post-implant functionality could not be confirmed for 2 devices. Device electronic functionality during the implant period was maintained for all devices, with demonstrated wireless battery recharge. All devices transmitted low-power wireless radio signals, but data reception was noisy due to interference from imaging equipment in the operating theater and animal facility. Cystometric data recording from the first 2 devices was unsuccessful due to the unresolved interference; improvements to radio equipment allowed recording from the other 4 implants. Additionally, device recordings showed an attenuated pressure sensitivity, likely caused by the biomechanics of the submucosal implantation (Table 2).

Device retention

No device failures due to moisture ingress were observed, confirming efficacy of the nonhermetic package and device functionality throughout implant. Device retention within the bladder was poor, with a mean retention time of 2.5 ± 1.4 weeks. Subjective healing was observed 1–2 weeks after implantation, followed by device erosion into the bladder lumen occurring 3–4 weeks after implantation. Cystoscopy was used to assess retention and was done weekly, determining the precision of our retention duration outcome. Therefore retention durations of each device are given as a range of a week (Table 2). There was no notable difference in retention time for devices covered in barbed suture or for pockets additionally bonded with DermaBond adhesive.

Cystoscopically implanted devices were gradually pushed from the pocket as the urothelium healed behind the device. The surgically implanted device eroded into the lumen suddenly after 3 weeks, with fully intact urothelium behind the implant pocket. Devices that migrated into the bladder lumen were expelled during urination. Improvements to device anchoring may mitigate this effect, especially if intramuscular anchors are used. Additionally, adequate cystoscopic placement closer to the bladder dome was subjectively more difficult. Necropsy did not reveal perforation grossly, or on filling with toluidine blue.

Healing response

Bladder capacity showed recovery after implantation (Figure 7), almost returning to baseline values, indicative of a healing response. Weekly cystoscopy confirmed minimal bladder irritation and healing of the urothelium (Figure 8). After the device migrated into the bladder lumen, cystoscopy showed a healed urothelium (Figure 9).

Ambulatory wireless recharging

Successful battery recharge during ambulatory sessions was achieved in all animals and required 9–15 W of external charger power. Animals tolerated wireless charging without signs of pain or distress. Further, modulation of the wireless charging waveform communicated instructions to the WIMM—in this manner the WIMM was wirelessly activated or put into standby mode. Thus, within each charging cycle we confirmed proper function of the wireless charger by selectively activating and disabling the WIMM. This method was also used to tune the level of external charger power to the minimum required for effective charging and communication to the implant, based on implant distance and rotational alignment with the external antenna.

Cystometric suburothelial pressure measurement

Simultaneous pressure recordings from the WIMM and an intravesical water-filled catheter showed good agreement in pressure values at bladder volumes below 100 mL with root-mean-square error (RMSE) of 3.00 cm H₂O between device and reference. For bladder volumes greater than 100 mL, readings from the submucosal device diverged significantly from the reference catheter. This effect may have been caused by detrusor distension in which the submucosal biomechanics cause pressure differences between the lumen and mucosal plane, although we did not specifically study this property. This effect was apparent over two analyzed cystometric recordings (Figure 10). Abdominal compressions performed

at full bladder capacity produced high-speed pressure changes noted in both intravesical and submucosal pressure measurements (Figure 11). These compressions were used as surrogates for detrusor contractions, which do not occur under anesthesia in this animal model. Peak pressure values for each compression were highly attenuated compared to reference values. Again, this effect was likely caused by the effect of local tissues in the submucosal location. Due to this attenuation, accurate measurement of bladder pressure magnitude from the submucosal location was not possible.

Device readings during compressions—while attenuated—were highly correlated in time with vesical pressure. For applications such as contraction detection, e.g. for feedback to a neurostimulator, high correlation alone may be sufficient for real-time identification of detrusor contractions. To analyze this mode, correlation coefficients were calculated for 30-s windows of device and reference readings centered on each compression. Correlation between intravesical and submucosal pressure traces was observed for all compressions (n=12; Table 3), indicating high time alignment between vesical and submucosal pressures during compressions. Correlation for the full 300-s trace was lower, due to the inaccuracy in static pressure measurement above 100 mL caused by tissue attenuation (Table 3).

After explantation, devices (n=3) were tested in a pressure chamber to validate pressure sensing accuracy. Some devices were expelled and could not be recovered for the post-implant test. Tested devices showed good pressure linearity and accuracy within 3 cm H₂O. These tests suggested that devices were functioning properly while implanted, and that biomechanical effects caused by the implant location may have affected *in vivo* pressure accuracy.

Discussion

In this study, we demonstrated that devices can be delivered to a submucosal location using conventional cystoscopic tools, without a suprapubic incision. Healing response from this implantation method was rapid, with no evidence of long-term trauma or bladder irritation. The urothelium could not be sutured easily using conventional tools, suggesting that custom tools could be developed to enable more rapid implantation. Nevertheless, the use of a rigid cystoscope sheath as a delivery mechanism for intravesical devices may enable other applications in wireless bladder sensors.

We also demonstrated that modern microelectronics technology is sufficiently advanced to enable miniature, wireless electronic sensors capable of implantation in the bladder wall. Devices which were recovered for post-implant testing showed no loss of functionality, indicating that moisture ingress did not lead to device failures after 4 weeks of implantation. This study provides further evidence, beyond our prior biocompatibility studies in rats⁴⁵, that our packaging scheme and device architecture is sufficient. Furthermore, we demonstrated wireless recharge of implanted devices in conscious large animals, confirming that chronic sensors in the bladder can be reached using inductive powering techniques. Although we encountered difficulty in data reception from the implanted devices (due to interference from medical imaging equipment in the facility), we did receive data from all devices throughout the implant period. More careful selection of radio operating frequency,

antenna design, and implant transmission power could be performed, given implant dimensions and application.

Despite our successes in surgical implantation and device assembly, ultimately our study revealed several flaws with the submucosal implant location. The main obstacles which we identified were device erosion into the bladder lumen and vesical pressure attenuation in the submucosa. In all implants, the device eroded through the urothelium and into the bladder lumen within 1 month. Device fixation within the bladder or submucosa is important to achieve accurate, reliable data.⁴⁷

Despite our attempts to fix the device using barbed sutures and tissue adhesive, all devices eroded in a sudden manner after an initial period of observed healing. This effect was also noted in the suprapubically implanted device, in which the urothelium was fully intact at the time of implant. Critically, in all cases, an intact urothelium was present even after device erosion. From this, we conclude that the bladder's response to a submucosal device is to grow a new layer of epithelium while allowing disrupted epithelium to slough off. Several other attempts have been made to anchor devices to the urothelium with similar results.^{6,32,43} Anchoring of the device to the detrusor may reduce erosion, but due to this effect, it is possible that any submucosal device will eventually be exposed to urine. Once in the lumen, a device runs the risk of being swept from its desired placement, and becoming obstructive or being expelled during voiding.^{13,43}

The bladder is a dynamic environment with varying urine concentration, bacterial microbiome, and chemical properties that could influence pressure sensor function.² As with all bodily fluids, urine corrodes metallic surfaces galvanically⁴⁸, although the saline concentration c urine varies depending on diet and bladder/kidney health. In addition to corrosion, bladder implants can grow biofilms which can alter urine pH, allowing for crystallization of urine solutes. This process, known as encrustation, can lead to acute cystitis and urinary stone formation. For example, use of chronic indwelling Foley catheters is known to be associated wil urinary stone formation.^{49–53} However, it may be possible that much smaller devices, or device coatings which promote cell growth may address this effect.

Pressure attenuation in the submucosa was the second major obstacle to submucosal pressure measurement we observed. We had observed this effect acutely previously in smaller animal models.³² In the large animal model this effect was more prominent, although this may have been due to the less invasive (and less accurate) cystoscopic implantation technique. Although pressure is not a directional force (and hence intravesical pressure is the same at all points within the bladder lumen), local forces arising at the contact point between device and muscle can influence pressure readings. Based on this effect, accurate measurement of vesical pressure from a submucosal device may be challenging, or perhaps impossible, based on the variable mechanical properties of the tissue. In our model, at low distension (below 100 mL), pressures were accurately transduced submucosally. However, as the detrusor began to stretch, pressure accuracy dropped significantly. This may be attributed to changing tension in the detrusor which could “shield” pressure forces from acting on the implanted device. Nevertheless, the submucosal sensor showed a highly-correlated (but attenuated) response to manual bladder

compressions. For contraction detection alone, therefore, a submucosal sensor may have sufficient accuracy.

Although this study was limited in scope, we have identified pressure attenuation and device retention as challenges for chronic, submucosal pressure sensing. Long-term devices and clinical situations also need to consider the design challenges of sensor drift,^{43,54–56} reliable wireless communication^{57–59} and power consumption⁴⁷. By addressing these effects, a chronic pressure monitor capable of providing real-time pressure feedback for conditional neuromodulation may be realized. Although submucosal implantation would shield the device from the urine, due to erosion concerns it may be simpler to investigate new device encapsulation materials which can remain exposed to urine without forming stones. This would allow for both free-moving sensors in the bladder lumen, as suggested by several groups,^{32,35,43} or devices anchored to the detrusor with at least one face exposed to urine. The advantage of urine contact is a direct measurement of vesical pressure. Recent studies suggest that polymeric devices can remain in the lumen for lengthy time periods with minimal risk.^{60–62} Therefore, intraluminal wireless pressure sensors that are small enough for cystoscope deployment could be the solution to a chronic pressure monitor with real-time feedback.

Conclusion

Chronic monitoring of bladder pressure during activities of daily living (ambulatory monitoring) may enhance diagnosis of incontinence and possess several unique advantages to conventional urodynamic testing. A wireless, miniaturized pressure monitor would reduce the effect of the sensor on bladder function, and would potentially enable real-time bladder feedback for applications such as conditional neuromodulation. We developed a small wireless sensor, (6.8×3.0×15.0mm) suitable for implantation through a 25 Fr cystoscope. Sensors were implanted into submucosal pockets in animals of similar size to man using a novel surgical technique. Over 30 days of implantation, devices transmitted and were recharged wirelessly in conscious animals. However, all were expelled from the bladder wall within 4 weeks. Implantation in the bladder wall also resulted in pressure attenuation compared to simultaneous intravesical recordings. At present, these seem to be the two major obstacles to introducing this method for bladder pressure monitoring. Complications associated with devices implanted in the bladder wall may be avoided by design of a device for chronic intravesical placement.

Acknowledgments

Funding: This work was funded by the VA RR&D Merit Review, Grant F7422-R

References

1. Abrams PA,KE; Birder L; Brubaker L; Cardozo L; Chapple C; Cottenden A; al., et. 4th International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence. Paris2009.
2. Dakurah MN, Koo C, Choi W, Joung YH. Implantable Bladder Sensors: A Methodological Review. *Int Neurourol J* 2015;19:133–41. [PubMed: 26620894]

3. Landefeld CS, Bowers BJ, Feld AD, et al. National Institutes of Health state-of-the-science conference statement: prevention of fecal and urinary incontinence in adults. *Ann Intern Med* 2008;148:449–58. [PubMed: 18268289]
4. Powell CR. Conditional Electrical Stimulation in Animal and Human Models for Neurogenic Bladder: Working Toward a Neuroprosthesis. *Curr Bladder Dysfunct Rep* 2016;11:379–85. [PubMed: 27920880]
5. McGuire EJ. Urodynamics of the neurogenic bladder. *Urol Clin North Am* 2010;37:507–16. [PubMed: 20955902]
6. Melgaard J, Rijkhoff NJ. Detecting the onset of urinary bladder contractions using an implantable pressure sensor. *IEEE Trans Neural Syst Rehabil Eng* 2011;19:700–8. [PubMed: 21997323]
7. Davila GW, Neimark M. The overactive bladder: prevalence and effects on quality of life. *Clin Obstet Gynecol* 2002;45:173–81. [PubMed: 11862070]
8. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. *Neuroepidemiology* 2001;20:138–43. [PubMed: 11359083]
9. Mundy AR, and Stephenson TP. The Urge Syndrome. *Urodynamics: principles, practice, and application* 1984:212–28.
10. Fall M, Ohlsson BL, Carlsson CA. The neurogenic overactive bladder. Classification based on urodynamics. *Br J Urol* 1989;64:368–73. [PubMed: 2819387]
11. Artibani W. Diagnosis and significance of idiopathic overactive bladder. *Urology* 1997;50:25–32.
12. Gupta A, Defreitas G, Lemack GE. The reproducibility of urodynamic findings in healthy female volunteers: results of repeated studies in the same setting and after short-term follow-up. *Neurourol Urodyn* 2004;23:311–6. [PubMed: 15227647]
13. Majerus SJ, Garverick SL, Suster MA, Fletter PC, Damaser MS. Wireless, Ultra-Low-Power Implantable Sensor for Chronic Bladder Pressure Monitoring. *ACM J Emerg Technol Comput Syst* 2012;8:11. [PubMed: 26778926]
14. Yiou R, Audureau E, Loche C-M, Dussaud M, Lingombet O and Binhas M (2015), Comprehensive evaluation of embarrassment and pain associated with invasive urodynamics. *Neurourol. Urodyn*, 34: 156–160. doi:10.1002/nau.22521
15. Chapple CR. Primer: questionnaires versus urodynamics in the evaluation of lower urinary tract dysfunction—one, both or none? *Nat Clin Pract Urol* 2005;2:555–64. [PubMed: 16474599]
16. Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? *Neurourol Urodyn* 2003;22:105–8. [PubMed: 12579626]
17. Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol* 2006;175:191–4. [PubMed: 16406907]
18. van Koevinge GA, Rahnama'i MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. *BJU Int* 2010;105:508–13. [PubMed: 19673868]
19. Stickler DJ, Zimakoff J. Complications of Urinary-Tract Infections Associated with Devices Used for Long-Term Bladder Management. *Journal of Hospital Infection* 1994;28:177–94. [PubMed: 7852732]
20. Apostolos M, Georgios D, Spyridon K, et al. Comparison Between Ambulatory and Conventional Urodynamics of the Modified Orthotopic Hautmann Neobladder. *Int Neurourol J* 2015;19:265–71. [PubMed: 26739181]
21. Kirkham AP, Shah NC, Knight SL, Shah PJ, Craggs MD. The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. *Spinal Cord*. 2001; 39:420–428. [PubMed: 11512072]
22. Dalmose AL, Rijkhoff NJM, Kirkeby HJ, Nohr M, Sinkjaer T, Djurhuus JC. Conditional stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in patients with SCI. *Neurourol Urodyn*. 2003; 22:130.
23. Choe JH, Lee JY, Lee KS. Accuracy and precision of a new portable ultrasound scanner, the BME-150A, in residual urine volume measurement: a comparison with the BladderScan BVI 3000. *Int Urogynecol J Pelvic Floor Dysfunct* 2007;18:641–4. [PubMed: 17115233]

24. Ireton RC, Krieger JN, Cardenas DD, et al. Bladder volume determination using a dedicated, portable ultrasound scanner. *J Urol* 1990;143:909–11. [PubMed: 2184254]
25. Coombes GM, Millard RJ. The accuracy of portable ultrasound scanning in the measurement of residual urine volume. *J Urol* 1994;152:2083–5. [PubMed: 7966680]
26. Macnab AJ, Shadgan B, Stothers L, Afshar K. Ambulant monitoring of bladder oxygenation and hemodynamics using wireless near-infrared spectroscopy. *Can Urol Assoc J* 2013;7:E98–E104. [PubMed: 23671516]
27. Stothers L, Shadgan B, Macnab A. Urological applications of near infrared spectroscopy. *Can J Urol* 2008;15:4399–409. [PubMed: 19046493]
28. Niestoruk L, et al. A concept for wearable long-term urinary bladder monitoring with ultrasound. Feasibility study. Education and Research Conference (EDERC), 2012 5th European DSP; 2012 p. 134–8.
29. Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. *Can J Appl Physiol* 2004;29:463–87. [PubMed: 15328595]
30. Sadanand S, inventor Bladder monitoring device. Washington, DC, United States patent 9,037,211 2015.
31. Nickel JC, Jain P, Shore N, Anderson J, Giesing D, Lee H, Kim G, Daniel K, White S, Larrivee-Elkins C, Lekstrom-Himes J and Cima M. Continuous Intravesical Lidocaine Treatment for Interstitial Cystitis/Bladder Pain Syndrome: Safety and Efficacy of a New Drug Delivery Device. *Science Translational Medicine* 2012;4(143):143ra100
32. Wille S, Schumacher P, Paas J, et al. Catheterless long-term ambulatory urodynamic measurement using a novel three-device system. *PLoS One* 2014;9:e96280.
33. Philippe Jourand RP. The BladderPill: An in-body system logging bladder pressure. *Sensors and Actuators A: Physical* 2010;160–6.
34. Philippe Jourand RP. An Autonomous, Capacitive Sensor Based and Battery Powered Internal Bladder Pressure Monitoring System. *EuroSensors XXIII conference*; 2009 p. 1263–6.
35. Wille S, Tenholte D, Engelmann U. A system for long-term urodynamic studies without catheters. *Eur Urol* 2013;63:966–8. [PubMed: 23398766]
36. Coosemans RP J An autonomous bladder pressure monitoring system. *Sensors and Actuators A: Physical* 2005;155–61.
37. Kim J, and Bumkyoo Choi. Design and fabrication of implantable pressure sensing resistor sensor for human bladder monitoring system. *Microsystem technologies* 2011;1453–8.
38. Koldewijn EL, Van Kerrebroeck PE, Schaafsma E, Wijkstra H, Debruyne FM, Brindley GS. Bladder pressure sensors in an animal model. *J Urol* 1994;151:1379–84. [PubMed: 8158793]
39. Takayama K, Kitada S, Kumazawa J. New method for measuring bladder pressure. *Urology* 1987;29:632–4. [PubMed: 3576894]
40. Powell CR, Albert Kim, Mouhamad Alloosh, Michael Sturek, and Babak Ziaie. Wireless urodynamic device demonstrates submucosal sensor is comparable to urodynamic catheter. *Neurourology and Urodynamics* 2015:S6.
41. Melgaard JaR NJ Detecting urinary bladder contractions: methods and devices. *Journal of Sensor Technology* 2014:165.
42. Majerus SJ, Fletter PC, Damaser MS, Garverick SL. Low-power wireless micromanometer system for acute and chronic bladder-pressure monitoring. *IEEE Trans Biomed Eng* 2011;58:763–7. [PubMed: 20934942]
43. Kim A, Powell CR, Ziaie B. An Universal packaging technique for low-drift implantable pressure sensors. *Biomed Microdevices* 2016;18:32–0058. [PubMed: 26945864]
44. Fletter PC, et al. wireless ambulatory system for chronic bladder pressure monitoring. 2009 Sixth International Conference on; 2009 p. 1–4.
45. Wang P, et al. Long-term evaluation of a non-hermetic micropackage technology for MEMS-based, implantable pressure sensors. *International Conference on Solid-State Sensors, Actuators and Microsystems*; 2015 p. 484–7.
46. Karam R, Bourbeau D, Majerus S, et al. Real-Time Classification of Bladder Events for Effective Diagnosis and Treatment of Urinary Incontinence. *Ieee T Bio-Med Eng* 2016;63:721–9.

47. Wayne Burleson SSC, Benjamin Ransford, and Kevin Fu. Design challenges for secure implantable medical devices. Design Automation Conference; 2012 p. 12–7.
48. Williams DF. Corrosion of Implant Materials. Annual Review of Materials Science August 1976;237.
49. Larsen LD, Chamberlin DA, Khonsari F, Ahlering TE. Retrospective analysis of urologic complications in male patients with spinal cord injury managed with and without indwelling urinary catheters. Urology 1997;50:418–22. [PubMed: 9301708]
50. Donnellan SM, Bolton DM. The impact of contemporary bladder management techniques on struvite calculi associated with spinal cord injury. BJU Int 1999;84:280–5. [PubMed: 10468722]
51. Ku JH, Jung TY, Lee JK, Park WH, Shim HB. Risk factors for urinary stone formation in men with spinal cord injury: a 17-year follow-up study. BJU Int 2006;97:790–3. [PubMed: 16536775]
52. Welk B, Fuller A, Razvi H, Denstedt J. Renal stone disease in spinal-cord-injured patients. J Endourol 2012;26:954–9. [PubMed: 22356464]
53. Hall MK, Hackler RH, Zampieri TA, Zampieri JB. Renal calculi in spinal cord-injured patient: association with reflux, bladder stones, and foley catheter drainage. Urology 1989;34:126–8. [PubMed: 2789449]
54. Joung YH. Development of implantable medical devices: from an engineering perspective. Int Neurourol J 2013;17:98–106. [PubMed: 24143287]
55. Cleven NJ, Muntjes JA, Fassbender H, et al. A novel fully implantable wireless sensor system for monitoring hypertension patients. IEEE Trans Biomed Eng 2012;59:3124–30. [PubMed: 22955864]
56. Tan R, McClure T, Lin CK, et al. Development of a fully implantable wireless pressure monitoring system. Biomed Microdevices 2009;11:259–64. [PubMed: 18836836]
57. Akyildiz IF, et al. Wireless sensor networks: a survey. Computer Networks 2002;393–422.
58. Poon AS, O'Driscoll S, and Meng TH. Optimal frequency for wireless power transmission into dispersive tissue. IEEE Transactions on Antennas and Prop. 2010;1739–50.
59. Chow EY, Chlebowski AL, Chakraborty S, Chappell WJ, Irazoqui PP. Fully wireless implantable cardiovascular pressure monitor integrated with a medical stent. IEEE Trans Biomed Eng 2010;57:1487–96. [PubMed: 20172781]
60. Stone L. Incontinence: Stress less—balloon therapy is effective for SUI. Nat Rev Urol 2015;12:123.
61. Cox A, Golda N, Nadeau G, et al. CUA guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Canadian Urological Association Journal 2016;10:E136–E55. [PubMed: 27790294]
62. Zacche MM, Srikrishna S, Cardozo L. Novel targeted bladder drug-delivery systems: a review. Research and Reports in Urology 2015;7:169–78. [PubMed: 26649286]

Figure 1.
WIMM device, size comparison (a); WIMM device within cystoscope sheath (b)

Figure 2. System block diagram consisting of implanted device and external RF receiver and battery recharger (a); Cross-section showing packaging layers (b)

Figure 3.

Cautery used to create a defect in bladder mucosa (a,b); embolectomy catheter used to create submucosal pocket (c,d); submucosal pocket at the mouth of the cystoscope sheath (e); device in sheath (f); device in the pocket (g); device position adjusted with graspers (h)

Figure 4.

The cystoscopic implant procedure used a rigid cystoscope sheath as a channel to deliver the sensor into a prepared submucosal pocket.

Figure 5. Schematic of submucosal implant site cross-section for cystoscopic implantation (a) and suprapubic (trans-detrusor) implantation (b).

Figure 6.
Cystogram performed confirming location of the device and no bladder perforation.

Figure 7.
Change in bladder capacity over time (n=5, one outlier removed)

Figure 8.
Cystoscopy of device implantation immediately after placement (a); one week after placement (b); three weeks after placement (c)

Figure 9.
Implant site with healed urothelium after device expulsion.

Figure 10. Simultaneous catheter and wireless pressure monitor pressure recordings (a); Pressure readings from the implant were attenuated but correlated with manual compressions (b).

Figure 11. Trials 1 and 2 simultaneous catheter and wireless pressure monitor pressure data (a); Pressure readings from the implant were attenuated but showed correlation with manual compressions (b); Normalized pressure during compression segments (c)

Table 1.

WIMM pressure sensor specifications

Implantable device size	$6.8 \times 3.5 \times 17$ mm
Equivalent device French diameter	24 Fr
Pressure sensing range	0 – 2,200 cm H ₂ O
Pressure measurement precision	0.5 cm H ₂ O
Power draw *	9 – 105 μ A
Data transmission rate *	1.5 – 100 Hz
Typical battery life per recharge	20 – 48 hours

* variable based on rate of bladder pressure changes^{13,42}

Table 2.

Pressure correlation between device and reference pressure

Device	Submucosal Pocket Anchoring	Submucosal Retention	Implant data transmission and wireless battery recharge*	Cystometric wireless data collection*	Post-implant functionality
1	None	1–2 weeks	Functional through explant	Unsuccessful	Device lost
2	Barbed suture	3–4 weeks			Device lost
3		3–4 weeks		Successful	Confirmed
4	Barbed suture and mucosal adhesive	2–3 weeks			Confirmed
5		3–4 weeks			Confirmed
6	Suprapubic implant	3–4 weeks			Confirmed

* All implanted devices transmitted data and were calibrated prior to implant. Radio interference in the operating theater and animal facility caused data reception errors experimentally, although wireless data transmissions from the implant were apparent.

Table 3.

Pressure correlation between device and reference pressure

	Trial 1	Trial 2
Bladder Compression 1	0.85	0.90
Bladder Compression 2	0.85	0.88
Bladder Compression 3	0.90	0.88
Bladder Compression 4	0.86	0.91
Bladder Compression 5	0.99	0.81
Bladder Compression 6	0.94	0.94
Full Cystometric Tracing (300 s)	0.55	0.38