Diabetic Complications Consortium FINAL REPORT

Application Title: Progression of Diabetic Cystopathy in the Ossabaw Pig Using Bladder Monitor

Principal Investigator: Charles Powell, MD

1. Project Accomplishments:

The project is Finished accruing data. A No-Cost Extension has been granted 8/19/2014 Extending the project until 9/30/2015. Data is being analyzed. Tissue, blood, and urine have been stored for possible future use.

Metabolic syndrome (MetS) is common and has detrimental effects on the bladder, including detrusor underactivity. The progression and mechanism of disease are poorly understood. A large animal model for diabetic bladder dysfunction was developed. The primary hypothesis is that a decrease in bladder pressure at capacity will occur as MetS progresses.

The overall experimental design was to feed Ossabaw miniature swine hypercaloric, atherogenic diet for 10 months to develop metabolic syndrome (MetS), and compare the MetS animals after 10 months' treatment with themselves at 7 months' treatment and with an age matched set of Lean diet treated animals (controls) from the same breeding colony. Outcomes include urodynamic bladder pressure measurements as well as pressures measured with a novel device implanted in the wall of the bladder called UPLINK. Outcomes also included demographic data such as indices for MetS (blood pressure, body weight, total cholesterol, triglycerides, fasting serum glucose, and IV glucose tolerance testing in some cases). This was done simultaneous with an investigation on the effect of MetS on coronary atherosclerosis in the same animals to maximize use of resources (Sturek PI, NIH grant HL062552).

Briefly, the methods involved surgical implantation of the bladder sensor (UPLINK), invasive urodynamic studies using conventional techniques, blood draws, determination of body weight, and other interventions for purposes of atherosclerosis assessment, followed by 3 months recovery from surgery and monitoring on sustained MetS diet (10 months total treatment). To date we have performed invasive urodynamic studies on _12_ Ossabaw miniature swine after 7 months MetS and 5 lean (control) pigs and 11 MetS pigs after the 3 month recovery from surgery and continued MetS. Urodynamic studies were performed on 5 lean (control) pigs.

By the conclusion of the project we implanted 6 wireless pressure transmitters in MetS bladders and have explanted 6 devices. _7_ lean pigs were implanted.

Data have been collected on these animals with respect to blood pressure, insulin levels, body weight, fasting serum glucose testing to demonstrate MetS after the 7 month treatment.

MetS was verified by the ~2-fold greater body weight, hypertension, hypercholesterolemia, hypertriglyceridemia, and increased fasting plasma glucose ($p<0.05$). The summary of these results appears in TABLE 1.

	Metabolic Syndrome	Lean	
Body Weight (kg)	107.4 ± 2.4	81.4 ± 8.5	p= <0.001
BP-Systolic (mmHg)	163.2 ± 6.5	124.8 ± 4.4	p= 0.001
BP-Diastolic	92.8 ± 4.4	75.8 ± 2.5	p= 0.014
Fasting Blood Glucose	80.3 ± 2.4	69.2 ± 2.3	p= 0.007
Total Cholesterol	465.0 ± 54.3	73.6 ± 7.9	p= <0.001
Triglycerides	42.5 ± 5.8	37.5 ± 9.2	p= 0.313

Table 1. MetS Indices validate the Ossabaw Pig model. Numbers are mean +/- SEM, 1 tailed T-test for significance.

Bladder pressure data have been collected on both urodynamic bladder pressures using the reference urodynamic equipment (Laborie, Ontario, Canada) both after the 7 month MetS induction and at the end of 10 months' total MetS diet. The UPLINK device has taken measurements during this time as well and these data are still being analyzed. The urodynamic pressures appear in TABLE 2.

Urodynamic Bladder Pressure

	Pves EMPTY	Pves FULL	compliance
After 7 months MetS Diet	8.5 ± 2.0	63.8 ± 6.5	22.2 ± 3.2
After 10 months MetS Diet	10.0 ± 1.1	28.2 ± 4.6	67.1 ± 7.9
After 10 months LEAN Diet	7.6 ± 2.2	45.6 ± 6.1	28.3 ± 3.1

*mean ± SEM

Table 2. Urodynamic pressures of 3 groups of Ossabaw pigs: After 7 months MetS dietary treatment, after 10 months MetS treatment, and no treatment ("lean"). The differences in urodynamic bladder pressures were significant between the MetS pigs measured at 10 months vs. 7 months, $p=0.001$ and between the MetS pigs at 10 months vs. Lean pigs, $p=0.026$. The differences in compliance were also significant between these groups, $p=0.004$ and $p=0.006$ respectively. Urodynamics were according to ICS standards.

The wireless device, called UPLINK, has undergone extensive design modification since the beginning of the project. These will be detailed below under ENGINEERING ACCOMPLISHMENTS SPECIFIC AIM #3. The power system has been re-designed to take advantage of more reliable battery power and a more efficient circuit design that does not consume as much power. The in vitro testing has demonstrated an estimated lifetime of 13 years while sampling at a rate of once per hour. The cable connecting the power unit to the sensor has been re-designed to make it more reliable and flexible in the in vitro environment.

The previous cable utilized a socket that was a point of weakness, and the cable itself was prone to malfunction when subjected to the stresses of in vivo implantation. The package has been improved to decrease leaking.

The sensor has been modified to correct for a well-recognized phenomenon known as sensor drift, caused when body fluids saturate the relatively impermeable membranes that comprise the sensor and change their properties, introducing error. In so doing, we may have reduced the drift to lower levels than have previously been reported by other investigators. The manuscript has been submitted for publication. Although not the primary objective, this would be a major accomplishment in the field of bio-sensing.

Data also suggest that reading bladder pressure through the bladder wall, as opposed to placing the sensor within the lumen of the bladder, currently the standard of care, is an accurate and precise method of determining intra-luminal bladder pressure. This has been presented at a national meeting and won best Basic Science Poster 2015 (appendix 1 and 2). It is important to note that this could never have been accomplished in the rat bladder due to its small size. Rats and mice have been the primary experimental animal in the study of diabetic bladder dysfunction.

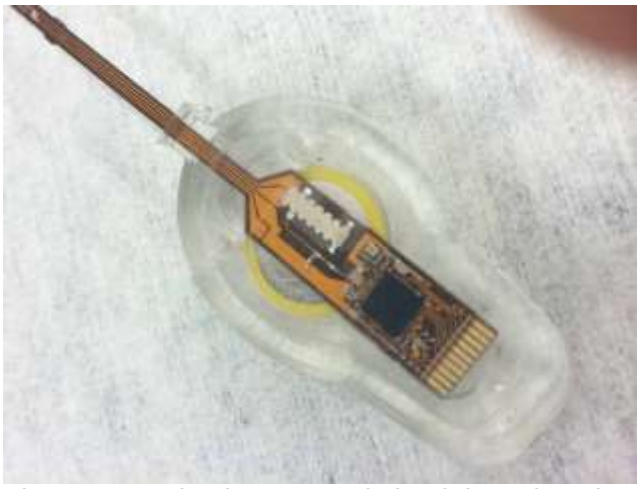


Figure 1. Device battery and circuit board packaged in acrylic.

2. Specific Aims:

Aim #1: PROGRESSION: We will document progression of diabetic cystopathy in the Ossabaw metabolic pig model through use of a novel ultrasound powered wireless implanted device to measure bladder pressure daily over 6 months. Bladder pressures will be compared to those measured in lean pigs (controls).

Results:

At the end of the dietary period, eleven Metabolic pigs demonstrated decreased bladder pressure at maximum capacity (28.2±4.6* vs. 63.8±6.5*cc, p=0.001) and increased compliance (67.1±7.9* vs. 22.2±3.2* cc/cmH2O, p<0.005). Increased compliance was also noted in the

Metabolic animals when compared with the 5 lean pigs (67.1±7.9*vs.28.3±3.1* cc/cmH2O, p<0.01) after 10 months on Metabolic diet. MetS was associated with detrusor underactivity an increased compliance when compared with animals at 7 months' treatment as well as lean controls (Table 2). The Aim was accomplished and the hypothesis was proven.

Additional histologic examinations are planned at the conclusion of the study to assess structural changes in the metabolic bladder. This will depend on additional funding.

Note that the study design was slightly different than originally proposed in Aims 1 and 2 involving only 6 months hypercaloric, atherogenic diet treatment to induce MetS. The reason is that this study "piggybacked" on an ongoing study with Drs. Alloosh and Sturek. The advantage was that the total duration of MetS was 10 months, thus increasing the likelihood of more robust MetS and cystopathy.

Aim #2: OSSABAW MODEL: The Ossabaw pig will be demonstrated as a valid animal model for the development of diabetic cystopathy. At the beginning and end of the 6 month study period a formal urodynamic study will be performed on the anesthetized pig to determine 1. Change in anesthetic bladder capacity (mL), 2. Increase in number of episodes of detrusor overactivity 3. Changes in bladder compliance. Serum creatinine and Blood Urea Nitrogen (BUN) content will also be assessed, as will fasting serum glucose (mg/dL) and glycosylated hemoglobin (Hgb A1c) as a measure of severity of diabetes. Bladder biopsies will also be taken.

Results:

MetS was demonstrated by increased body weight in the MetS animals, increased Systolic and Diastolic blood pressure, fasting serum glucose, total cholesterol, but not triglycerides (Table 1; data are mean ± SEM, all p<0.05 by 1 tailed student's t-test). **Change in anesthetic bladder capacity was not directly measured because the measurement involves filling the bladder almost to the bursting point and this was determined too risky for survival animals after the sensor was implanted in the wall of the bladder, theoretically weakening it. No bladder ruptures occurred. The study period was increased to 10 months but based on data in cardiac condition the interval between urodynamic study was decreased to 3 months because it was thought the morbidity of the MetS progression would be sufficiently heightened after this time period. This was demonstrated as hoped, suggesting the progression of cardiac morbidity parallels the onset of bladder dysfunction in this animal model for MetS. Sub-item 2: Episodes of detrusor Overactivity were not spontaneously observed in this animal model, which was unexpected, and so this end point was not practical once the investigation began. Sub-item 3: compliance was increased in the MetS animals suggesting either the detrusor muscle itself lost contractility or denervation decreased its ability to respond to increased bladder volume. Table 2 summarizes compliance results.**

Three of the MetS pigs died prior to completion of the protocol; 1 died of cardiac causes and 2 were sacrificed early due to infection. We worked closely with the veterinary staff and the IACUC to minimize risk to future animals, but acknowledge that the MetS conditions predispose these animals to infection and cardiac problems.

Five of the Lean animals (not fed diabetogenic high calorie "chow") completed the urodynamic study. Seven were implanted with the UPLINK wireless pressure sensor at the time of sacrifice but none carried it for 3 months like the MetS animals because the sister protocol changed so that these pigs were not allowed to undergo the first survival surgery as planned and only underwent the sacrifice surgery.

Three additional Lean animals (not fed diabetogenic high calorie "chow") completed the concomitant (unrelated) sister protocol, but did not undergo urodynamic study due to temporary failure of the Laborie reference urodynamic equipment. Data were collected on the blood pressure, serum creatinine, serum insulin, and weight, as well as bladder tissue collection. Bladder pressures were not collected on these animals.

Specimens of bladder have been collected from each animal and have been preserved in both formalin and liquid nitrogen. These will be analyzed at the end of the project, depending on funding.

Aim #3: UPLINK DEVICE: The investigators will demonstrate that the novel, ultrasound powered wireless bladder pressure sensor can accurately measure pressure over time, will not malfunction, and will not migrate out of the bladder or into the lumen of the bladder.

Results:

ENGINEERING ACCOMPLISHMENTS SPECIFIC AIM #3

No migration into the bladder has been noted during the 7 implanted MetS animals over a mean of 51.5 days. Figure 11 demonstrates the intact bladder mucosa underneath the UPLINK sensor. The body of the device has remained in place.
One device had a fractured lead, causing it to stop functioning, which occurred in vivo. This led to a design change.
One device became infected and another was explored for what turned out to be a superficial wound infection not affecting the device. Both had to be explanted. Both pigs required early sacrifice.
Design changes have been implemented to allow for an improved method to sterilize the device using ethylene oxide gas. Changes to the operative technique and device
Implantation location were made.
Two superficial wound infections not contacting the device have been noted.
Another animal developed a large organized blood clot filling the bladder and after 8 days the supervising veterinarian recommended sacrifice and so it was explanted early, no erosion through the bladder mucosa was noted. It was determined that a suture had perforated the bladder mucosa and bled into the lumen of the bladder on necropsy.

Four of seven animals with implanted devices survived to the completion of the protocol, but unfortunately packaging and software issues were responsible for three of the four long term devices failing before planned sacrifice. All of these animals received catheter based urodynamic studies (the gold standard) as were the remaining MetS and Lean animals described in Tables 1 and 2. Originally it was planned to implant all animals, but the change in the protocol as well as the infections prevented implantation in some but not urodynamic study using catheters.

The mechanical package design and circuit were changed extensively in the first year of the project. The second year was used primarily to finish feeding and growing animals, and so no opportunites to implant long term devices were available. Regardless, the devices were still built using the most current design and implanted at the time of sacrifice study so that the Intraclass Correlation Coeffecient (ICC) could be calculated to demonstrate the accuracy of the intramural sensor concept compared with the intra-vesical (bathed in urine) concept. The R^2 was 0.946. Figure 10 demonstrates the ICC combined plot.

During the first year of the project, we followed the original plan based on ultrasonically powered wireless interrogation scheme. Figure 1 shows the schematic view of proposed long-term urodynamic study. In an effort to develop the ultrasonically powered wireless bladder monitoring system, lead zirconate titnate (PZT-5H) was ordered as an ultrasonic receiver. A power and wireless interrogation switching circuit was designed. However, signal interference between ultrasonic receiver and RF signal was not negligible and its interrogation distance was not long enough to be practical in obese pigs (< 5 cm). This contributed to the decision to power the device with batteries. The new design allowed longer communication distance and more capability. The design incorported ultra low power consumption and automated Embed system. It has been tested both *in vivo* and *in vitro*. In this report, we included both designs.

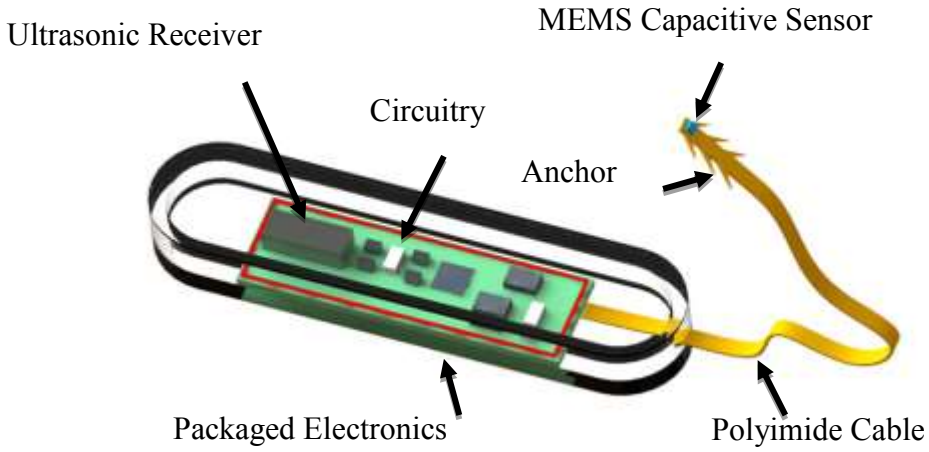


Figure 1: Proposed long-term monitoring system scheme.

New direction: Ultrasonically powered FM Transmitter and Battery powered automated Embedded system

Ultrasonically powered FM Transmitter: Further development of wireless interrogation circuitry was explored. The new and low power wireless circuitry was based on long neglected method, the Colpitts oscillator. An FM transmitter was designed and built, as shown in Figure 2.

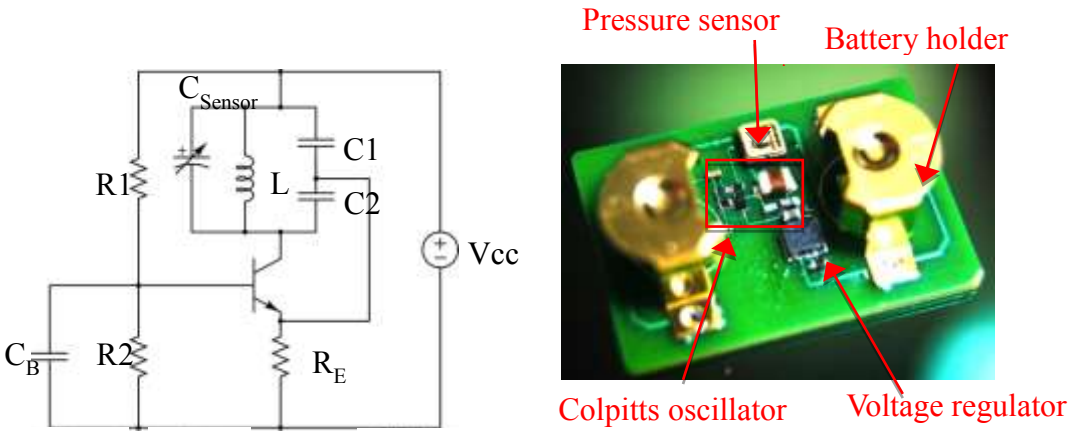
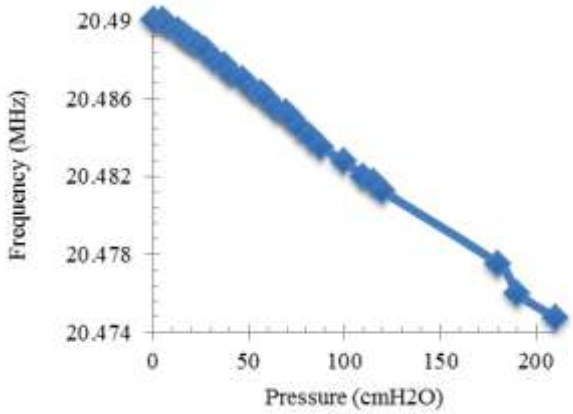


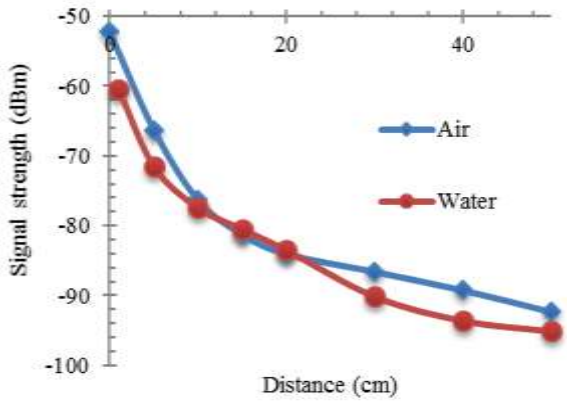
Figure 2: New wireless interrogation system

Unlike a traditional FM transmitter, the newly designed FM transmitter circuitry contains capacitive sensor (C4 in figure 2) and it is modulated at the resonant frequency ($f = 1/\sqrt{L_1 \times C_{eq}}$, $C_{eq} = 1/C_1 + 1/C_2 + 1/C_4$) of the incident RF signal. The rest of circuitry contains an NPN transistor and a couple of resistors (R1-R3) to sustain the modulation of resonant frequency, thus allowing the RF signal to transmit further (d = 1m) ([4]Maggio et. al. 1999). Developed circuitry has been tested with the battery for validation. Figure 3 summaries the results of Colpitts oscillator wireless interrogation system, with a linear frequency response to changes in fluid pressure and a significant signal strength dropoff as range increases beyond 10 cm in liquid and air. A spectrum analyzer with simple loop wire was used for the receiver in this stage.



Sensitivity: 73Hz/cmH_2O

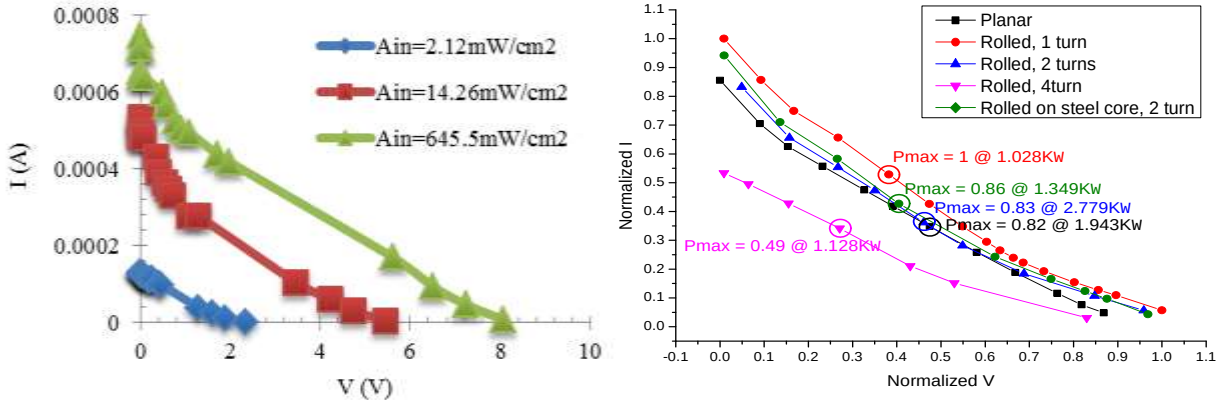
(b)



(a)

Figure 3: Characterization of FM Transmitter (a) pressure vs. received resonant frequency, (b) interrogation distance

Based on the results, the newly developed system could propagate RF signal up to 50 cm with 73 Hz/cm H_2O sensitivity in water, which mimics the soft tissue. After the validation, a prototype transmitter and receiver were built. As for the ultrasonic receiver, PZT-5H and PVDF (Polyvinylidene fluoride) were chosen. The PZT-5H has higher electromechanical coefficient (k = 0.72), so its form factor could be small, and PVDF has relatively low electromechanical coefficient (k = 0.2~0.31), but it is thin and flexible. The PZT was configured in a cube (2x2x2 mm^3), while PVDF was configured into a multi-turned coil (d = 11mm, h = 1cm). Power output in response to ultrasound stimulation of both ultrasonic receivers is illustrated in figure 4.



(a) (b)

Figure 4: IV characteristics of (a) PZT and (b) PVDF

Both designs were tested under FDA ultrasound power limits (P = 720 mW/cm^2). Since PZT had fixed size (2x2x2 mm), it was characterized at different acoustic input intensities, while PVDF could improve power capture / output by changing the number of turns to the coil: 1, 2, and 4 turns. Based on the figure 4, both ultrasonic receivers could serve as tangible power source for an interrogation system. However, PZT required a slightly higher ultrasound transmission power, which may improve by increasing the size of the cube.

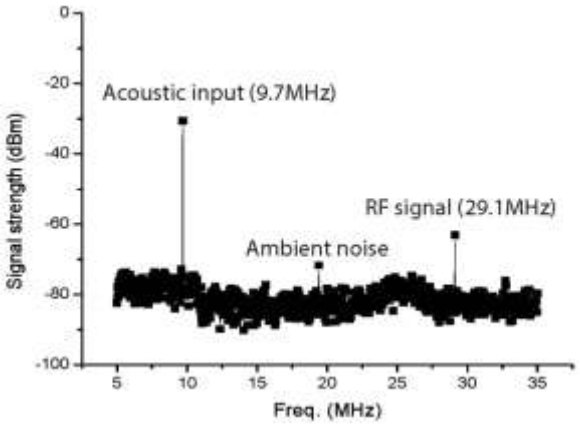


Figure 5: Spectrum analyzer output of an FM transmitter powered by a PVDF-roll

Embeded System: Although the ultrasonically powered FM transmitter operated and performed adequately, it was not suitable for practical use in pigs since trained personnel had to apply to transmitter/receiver daily for the measurement of bladder pressures. Thus, development of a more robust and automated system was necessary. The system we have developed was ultra-low power wireless embed system, called Uplink, figure 6.

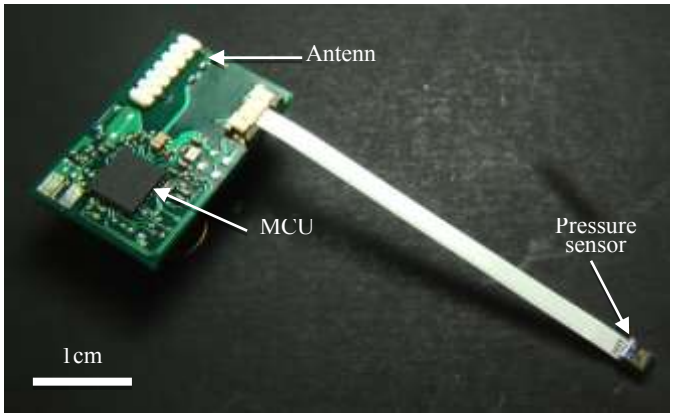


Figure 6: Battery powered automated Uplink

Uplink (the battery powered sensor) becomes active only intermittently and remains in sleep mode for most of time. As a result, the power consumed in the sleep mode plays a dominant role in determining battery life. Measured in the lab, it consumes only 1.5 μA in sleep mode and requires only 0.19 μAh for sensing and transmitting one sample of data. Given the measured power consumption of the hardware platform and the initial battery capacity of 560 mAh, it is possible to estimate the battery life of an implanted Uplink device. We adopt a very conservative approach and assume a safety margin of 65% in battery capacity due to variations in the initial capacity as well as other non-idealities that degrade battery performance. In other words, we assume that the batteries can only provide 196 mAh to the device (*i.e.,* 35% of the initial capacity). Assuming a scenario where Uplink performs one sensor measurement and data transmission every hour, 40.56 μAh of battery capacity will be required daily and it will operate for 4832 days (*i.e.,* 13 years) before it runs out of energy. The actual in-vitro testing has demonstrated a lifetime of 4 months while sampling at a rate of 3 seconds at first 3 days and converted to 15 minutes (the measurement is still going on). Since then, it has undergone extensive design modification in response to the early results of in-vivo testing.

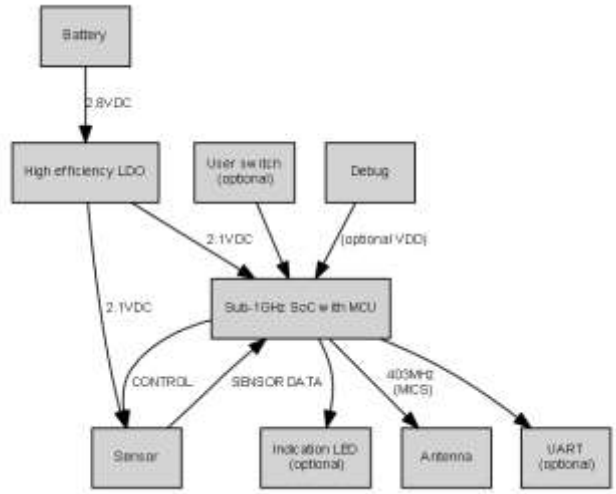
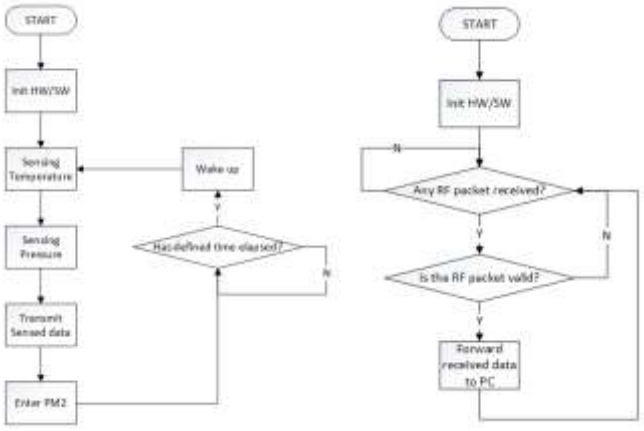


Figure 7: Hardware architecture of Uplink

Figure 7 shows the hardware architecture of Uplink. The platform mainly consists of a RF-SoC (CC1110F32, a sub-1GHz RF SoC with MCU from Texas Instruments) that contains sub-1GHz RF transceiver with 8051 MCU and a temperature/pressure sensor (MS5637-02BA03 from Measurement Specialties). The sensor gives 24-bit digital values for pressure and temperature with 0.016mbar and 0.002 degreeC resolutions, respectively. The temperature data is used to correct the pressure data, which is originally a digital representation of uncompensated analogue output voltage from the piezo-resistive pressure sensor. Mechanically, the sensor is connected to the RF-SoC using 5cm-long sensor catheter to provide surgical flexibility. However, the cable connecting the power unit to the sensor was re-designed after in-vivo testing to make it more durable. The previous cable utilized a socket that was a point of weakness, and the cable itself was prone to malfunction when subjected to the stresses of in-vivo implantation. The sensor is placed at a tip of the sensor cable and interfaced with the RF-SoC through standard I2C communication bus. Also the sensor has been modified to correct for a well-recognized phenomenon known as sensor drift, caused when body fluids saturate the relatively impermeable membranes that comprise the sensor and change their properties, introducing error. In so doing we may have reduced the drift to lower levels than have previously been reported by other investigators. In-vitro testing is ongoing to confirm this. Although not the primary objective, this would be a major accomplishment in the field of bio-sensing. Preliminary data also suggest that reading bladder pressure through the bladder wall, as opposed to placing the sensor within the lumen of the bladder, protecting it from urine, is an accurate and precise method of determining intra-luminal bladder pressure.

The RF-SoC measures and transmits the sensor data to a base station over MICS band (Medical Implant Communication Service, 402~405 MHz). The entire board is powered by two of size 13 coin-cell batteries (AC13, Size 13 battery from Energizer) connected in series to make 2.8V. The total capacity of the two coin-cell batteries is 560mAh, which is sufficient to operate it over 13 years. Output power of the battery can either be directly supplied to the platform or regulated to 2.1V to reduce active mode power consumption of the RF-SoC. According to the operation characteristics of applications, a DC/DC down-converter (TPS62730DRYT from Texas Instruments) can be selectively used by configuring a hardware jumper. For instance, the DC/DC

down-converter can be omitted in an application where standby or sleep duration is dominant since the quiescent current of the converter is greater than the lowest power consumption of the RF-SoC in sleep mode. Optionally, the Uplink also contains several user interfaces, such as user switch, LED, UART, for enhanced debugging. Although the RF-SoC is equipped with a RF transceiver, Uplink is only used as a transmitter to conserve power. Meanwhile, if connected to a PC, it can be used as a receiver as well. In receiver configuration, Uplink forwards received RF packets to the PC using USB port. While connected to a PC, Uplink can be permanently powered from USB port.



(a) (b)

Figure 8: Software flowchart for (a) implantable unit, and (b) receiver

Software is fully interrupt-driven and its structure is optimized to achieve ultra-low power operation. Since the Uplink platform can either be used as an implantable wireless sensor device OR a PC side RF receiver, it has different software execution flow depending on its role. The flowchart depicted in Figure 8 briefly shows the execution flow for each operation mode. In both modes, Uplink starts to execute by initializing software and hardware peripherals, such as clocks, timers, and I/O. If the Uplink is configured as an implantable wireless sensing device, it remains in power saving mode by default. It intermittently and regularly wakes up and becomes active using a sleep timer. The interval between each active mode can be defined by user as either constant or dynamic value. For instance, it is possible to have different sleep durations for the phases of surgery and monitoring to attain increased visibility about its operation while it is being implanted. In active mode, Uplink accesses the sensor through I2C bus to read out pressure and temperature data. After correcting the uncompensated pressure data with the temperature data, it transmits the pressure to a base station. Upon completion of the given task, it again enters and remains in sleep mode until next wake-up. Specifically, Uplink utilizes power down mode 2 (PM2) of the RF-SoC, which turns off all the peripherals except for the 32.768 KHz crystal oscillator, which is used to run the sleep timer that wakes up the RF-SoC. Since the contents of RAM are retained even in the power down mode, if necessary, it is possible to conduct uninterrupted processing for the sensor data (e.g., moving average) across each active mode. If configured as a receiver, Uplink is connected to a PC using UART-to-USB serial interface and works as a communication gateway for other implanted Uplink devices. In this case, Uplink is continually powered by the USB port and never goes into sleep mode so as not to miss any incoming RF packets. Received packets are forwarded to the PC.

After development, the battery powered automated Uplink underwent multiple *in vivo* implantation trials. The project is still accruing data. To date we have performed invasive urodynamic studies on 5 Ossabaw MetS pigs at 7 months of diet treatment and monitored for 3 months, 2 lean (control) pigs, and 4 Ossabaw metabolic swine after 3 months of recovery from surgery. The Uplink device has taken measurements during this time as well. Note that additional *in vivo* implants are planned, so data accrual is not yet completed.

Refinement of the implantation surgery technique was necessary since the Uplink will be implanted within the wall of the bladder to transfer intraluminal bladder pressure without contacting urine directly. Figure 9 shows the implant surgery technique. The sensor part of Uplink device will be placed on the wall of the bladder, and then it will be wrapped around by bladder muscle, which provides tunneled implantation. This surgery technique and the validity of pressure measurement were verified by comparing with reference urodynamic equipment (Laborie Delphis).

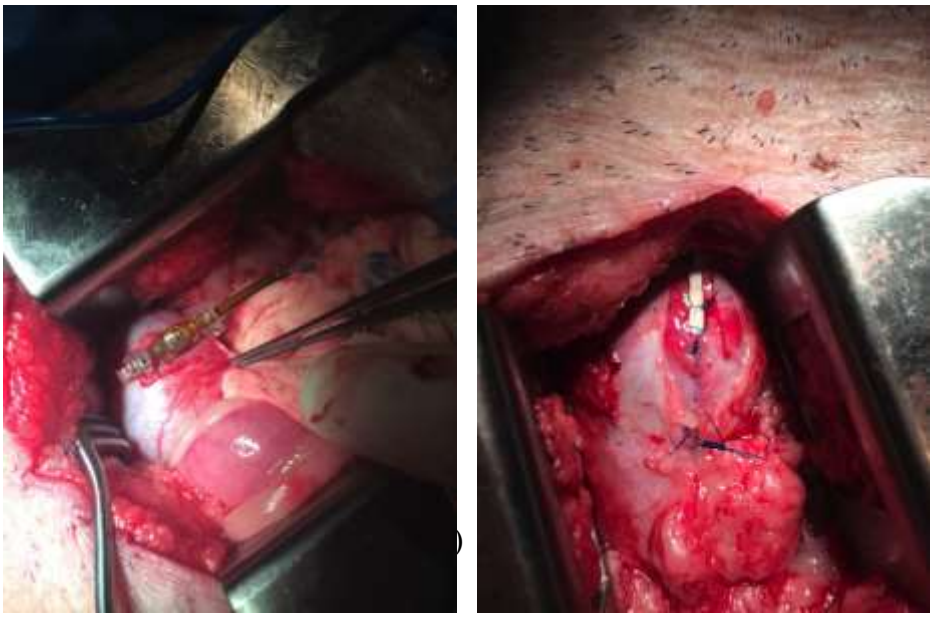


Figure 9: Uplink device implantation: (a) sensor cable on wall of bladder prior to closing bladder wall over device, (b) device tunneled into bladder wall and ready for urodynamic testing

Figure 10 depicts pressure data collection from urodynamic bladder pressures using both reference urodynamic equipment (Laborie Dephis, Laborie, Canada), and implanted Uplink *in vivo* experiments. The data from both systems have directly correlated. Intra-class correlation coefficients (ICCs) were calculated for concurrent measurement analysis of bladder pressure. From figure 10, strong validity was shown (R^2 of 0.946). Calculated ICCs was 0.979 as well.

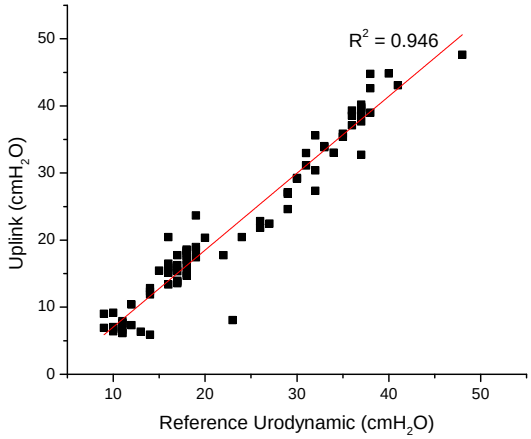


Figure 10: Uplink validation data comparing to reference urodynamic.

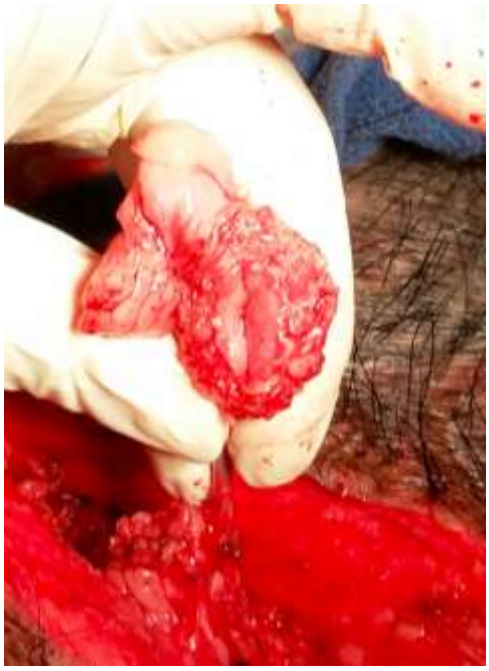


Figure 5: After 3 months no mucosal perforation was noted.

3. Publications and Abstracts Presented

1. CR Powell MD, Albert Kim MS, Mouhamad Alloosh MD, Babak Ziaie PhD, Mike Sturek PhD. OSSABAW PIG AS A LARGE ANIMAL MODEL FOR HYPOACTIVE DETRUSOR IN METABOLIC SYNDROME PILOT STUDY. 89th Annual Meeting of

the North Central Section of the AUA, 11/10/2015 - 11/14/2015. Amelia Island, FL, USA. Moderated Podium Abstract #67.

2. Powell C, Kim A, Alloosh M, Ziaie B, Sturek M; Ossabaw Pig as a Large Animal Model for Detrusor Underactivity in Metabolic Syndrome Pilot Study. International Continence Society, Montreal, Canada, 2015. Abstract #662. http://www.ics.org/2015/programme/abstract/662
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