



Mapping and Ablation Catheter for Overactive Bladder Condition

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All team members were involved in the editing of this report.

ABET Certification

An ability to design a system, component, or process to meet desired needs *within realistic constraints such as economic, environmental, social, political, ethical, health and safety, manufacturability, and sustainability* (ABET Criterion 3c) *while incorporating appropriate engineering standards* (ABET Criterion 5) (*need to assess each of these separately, but since 'or' and "such as" not all need to be met separately*).

- i) multiple realistic constraints (*economic, environmental, social, political, ethical, health and safety, manufacturability*) – **pages 41, 61-63**
- ii) appropriate engineering standards - **pages 39-44, 48**

An ability to function on multidisciplinary teams (ABET Criterion 3d). **pages 16-38**

An understanding of professional and ethical responsibilities (ABET Criterion 3f)

- i) Professional – **pages 39**
- ii) Ethical – **pages 62-63**

An ability to communicate effectively (ABET Criterion 3g). **pages 60-61, 75-76**

The broad education necessary to understand the impact of engineering solutions in a global, *economic, environmental*, and societal context (3h). (both economic AND environmental need to be addressed)

- i) Economic – **pages 63**
- ii) Environmental – **pages 63**

A knowledge of contemporary issues (ABET Criterion 3j). **pages 14-17**

Abstract

Overactive bladder (OAB) condition affects 200 million people world-wide (36 million U.S.). Currently, there are various treatment options, however each of these options has significant shortcomings ranging from ineffectiveness, cost and time efficiency to possibly causing incontinence. Overactivity in other tissues, such as the heart, has been shown to decrease after the tissue has been ablated. In this case, the electrical activity in the heart is mapped, and the identified overactive areas are ablated. No such mapping or ablating device, let alone a combined device exist for use in the bladder and the treatment of OAB. The major problem with adapting this design to the bladder is that the electrical activity of the bladder is significantly less than in the heart, and therefore it is more difficult to map and subsequently identify the overactive areas to ablate in the bladder. The team developed a device capable of recording the electrical signal in both static and dynamic testing. The device utilizes a multi-tiered balloon filling mechanism to conform to the shape of the bladder and maintain contact of the electrodes to the bladder wall. Additionally, the electrodes serve as individual ablation tips for the elimination of the signal propagation.

Chapter 1: Introduction

Overactive bladder condition (OAB) is a widespread and vastly under-reported condition that affects an estimated 200 million people worldwide. In the United States, it is estimated to affect more than 36 million individuals (National Association for Continence, 2014). The data for individuals with OAB may be skewed, however, due to under-reporting of the condition. Many people view it as an expected and accepted result of aging. Approximately 33% of the US population (aged 30-70) believes that incontinence is simply part of their bodies getting older and something that they have to accept (National Association for Continence, 2014). This accepted belief leads to under-reporting to their doctors, leading to individuals not receiving the appropriate treatment.

Beyond the detriments to quality of life caused by this condition, the uncomfortable, sometimes painful and frequent urges to void, and the inability to control voiding, there are numerous other ways that OAB can affect the individual. For example, a study performed in 2013 found that approximately 30% of affected individuals were depressed or slightly depressed because of their OAB (Sanford, 2013). Additionally, the study found that OAB can lead to urinary-specific work impairment, with 21.8% of men and 23.4% of women affected by OAB suffering from work impairment (Sanford, 2013).

Overactive bladder accounts for approximately \$65.9 billion of the United States economy. The cost of OAB breaks down into an estimated \$1,925 per individual OAB patient (Ganz, 2009). This number has risen greatly since 2003, when it was \$825 per affected person (Sanford, 2013). This increase is a result of an increase in various treatment types for OAB. Sacral nerve stimulation (SNS) for example costs an average of \$26,269 per patient for the first 3 years of treatment (Sanford, 2013).

The definition of overactive bladder condition begins with involuntary contractions of the bladder, which causes voiding, or emptying of the bladder, at undesirable intervals. An individual with a normal functioning bladder experiences urinary urges around 50% filling, and around 75% the bladder contraction is triggered (Urology Care Foundation). In an individual experiencing OAB, certain physiological disruptions will cause faulty signals leading to involuntary bladder contraction. Instead of feeling urges only at 50% full and above, a bladder with OAB will feel urges to void at much smaller volumes, eventually leading to the previously mentioned involuntary voids (Urology Care Foundation).

The client, Boston Scientific Corporation, helped transform the medical industry with many of their devices. Their goal is to, “transform lives through innovative medical solutions that improve the health of patients globally” (Boston Scientific Corporation). They have expertise in a variety of medical conditions including heart, digestive, pulmonary, vascular, urological, women's health, and chronic pain conditions. The area from which our project stems is the female pelvic medicine and urology sectors. Boston Scientific has come up with the idea to treat the common condition known as Overactive Bladder.

There are three origins of OAB: neurologic, myogenic, and idiopathic. The neurologic diagnosis results from an error of communication by way of electrical signals, which coordinate the controlled contraction of the bladder. When there is an interruption of electrical signal it can cause the smooth muscle cells in the bladder to conduct the signal incorrectly and in many directions, causing a result similar to an arrhythmia in the heart (Ellsworth, 2009). The myogenic diagnosis results from a problem with the muscles responsible for contraction of the bladder. The detrusor muscle is primarily responsible for controlling the contraction of the bladder. This type of the condition can arise from either muscle damage or faulty action potentials. When faulty action potentials are the cause of the condition, muscle signals will show a large imbalance of concentrations throughout the internal and external areas of the bladder. The final type of condition is idiopathic, which is simply categorized as any diagnosis that is not shown to have a root cause of either neurologic or myogenic purposes (Ellsworth, 2009). Boston Scientific Corporation's interest is primarily in developing technologies that can treat the condition regardless of the origin.

There are several treatments in development to help minimize the effects of OAB. The first line treatment is behavioral modification and medications. The patients will go through specific training and dietary alterations in order to lessen the OAB effects. Pelvic floor exercises are done to strengthen the pelvic floor muscles as the weakness of it could cause OAB symptoms (Kim, 2013). The second step of the first line treatment is to change the diet to eliminate the irritations and weight loss (Kim, 2013). Second line treatment drugs such as Darifenacin, Fesoterodine and Oxybutynin are given simultaneously or to patients when the behavioral modifications do not work. The side effects of these medications are dry mouth, constipation, upset stomach and blurry vision (Gulur et. al, 2010).

Third and fourth line treatments are the specialized therapies. There are four procedures that can relieve the OAB patients, however; effectiveness varies with the origin of the OAB symptoms being myogenic, neurologic or idiopathic. The Botulinum A treatment is Botox injections at random sites of the bladder in order to obstruct the neurotransmitters from sending many pulses to the central nervous system. (Gulur et. al, 2010). It also denervates the bladder muscles, resulting in decreased contractility. This method works for approximately three to six months before requiring re-injection (Kim, 2013). The major downside of this method is over-injections of the bladder with Botox, which could paralyze the organ causing urinary retention which then requires self-catheterization.

The next procedure is sacral neuromodulation. This procedure implants a stimulator that functions similarly to a pacemaker, but for the bladder. It will modulate the nerves connecting to the bladder and pelvic floor (Kim, 2013). This procedure, however, has some risks such as lead migration which could lead to another surgery, high cost, infection and many follow up appointments to confirm the device position and effectiveness.

The third procedure is posterior tibial nerve stimulation, a similar procedure to the sacral neuromodulation, although less invasive. The procedure requires the placement of an near the medial malleolus. The generated electrical impulses reach the sacral nerve roots.

This is a weekly, thirty minute session performed for twelve consecutive weeks. The patients experience immediate improvement, but when the treatment is over the patient could have a relapse (Kim, 2013).

The last procedure, which is more invasive than the others, is the augmentation cystoplasty surgery. It physically stretches out the bladder to have more volume by taking a part of the ileum or colon to weaken the contractility of the bladder. This procedure is not a popular one as it could cause urinary retention, perforation, malignancy, and mucus accumulation (Kim, 2013).

Boston Scientific Corporation tasked the team with exploring the feasibility of and developing a method for detecting overactive tissue within the bladder and a device to ablate overactive areas of tissue. The device must be able to accommodate bladders of varying sizes and enter the bladder through a natural orifice. The device must also be suitable for either gender and be safe for patients undergoing the procedure and physicians performing the procedure. The device must produce precise and accurate results as well as be marketable upon completion of the design.

In light of the client statement, the team focused on developing a method for mapping and ablation that is specific to the bladder. This client statement has led to two important goals. One of our goals is to develop an electrical signal detection technique. Abnormal electrical activity is causing the involuntary contractions in bladder. A method of detecting electrical activity inside the bladder is to, “map,” the bladder by an electrophysiology study. At the current stage, mapping techniques use catheters, which insert into the bladder, and are the main focus of all ongoing studies. However, we are aiming to design a system, which is as minimally invasive as possible.

Another important goal is designing an ablation component to the system. A hopeful way of correcting the irregularities in the electrical activity is to stop the abnormal electrical activity of the bladder. In the current treatment methods for other organs, mapping and ablation catheters are separate devices. The team is aiming to develop a device which has both mapping and ablation capabilities. The energy source is crucial in a successful ablation procedure. The team is considering a wide range of energy sources including thermal energy or radiofrequency. These energy sources have different properties and these different types of energies have shown successful results in ablating heart tissue. However, these energy sources require further investigation since the bladder has different anatomical features than the heart.

The team completed thorough research on the condition of overactive bladder and treatments that are the current state of the art. Additionally, the team obtained an understanding of mapping and ablation in order to advance in the design phase of the device. It was important to understand how these concepts correlate to the heart, then a comparison to the bladder will be made. Boston Scientific assisted the team in observing examples of mapping and ablation catheters and the handling of the medical devices. These steps helped move the project forward to create preliminary designs of the device using computer

software (SolidWorks). With the new design, the team procured prototypes for tissue experimenting and bench testing. The design concepts and prototypes underwent revision and the team evaluated the overall results, determined a final design and presented it to the client, Boston Scientific Corporation.

Chapter 2: Literature Review

2.1 The Clinical Significance of Overactive Bladder Condition (OAB)

Overactive bladder is a collection of symptoms that involves urinary urgency, frequency and nocturia (Wood, Ouslander, 2004). To classify a person with this condition, the patient must have one or more of the symptoms (Wein, 2002). This condition can be with or without incontinence, which is defined as involuntary urination, or voiding. The frequency of urination for an overactive bladder patient can vary, but is typically characterized by voiding more than eight times in a 24-hour period. Nocturia is the awakening of the patient to void more than twice in the same sleep cycle. These symptoms cause patients to have a decreased quality of life due to the inconvenience of the symptoms. Overactive bladder patients are more likely to experience depression because patients often isolate themselves and do not participate in social activity (Wood, Ouslander, 2004).

The National Overactive Bladder Evaluation Program (NOBLE) exists in order to clinically define the condition of overactive bladder and to explore the differences in patients with different symptoms. To assess the population of people for overactive bladder, the program conducts phone interviews or surveys. There are not any current diagnostic methods to define a patient with overactive bladder (Wein, 2002). The percent of the population with overactive bladder may be skewed because patients may feel embarrassed or depressed and do not report their symptoms.

2.1.1 The Population Affected by OAB

Overall, there has not been any widespread large-scale population based surveys on the prevalence of Overactive Bladder in the United States. NOBLE came to exist in order to assess the prevalence in the United States on a more defined scale. NOBLE used a clinically validated computer assisted telephone interview to survey the population based on gender, age, and other demographic factors. The percentage of population of patients with overactive bladder symptoms is 16.5%; 6.1% met the criteria for OAB with urge incontinence while the other 10.4% met criteria for OAB without urge incontinence. Of the patients who had overactive bladder with urge incontinence, 45% of patients had mixed symptoms. The prevalence of overactive bladder in men and women was not statistically significant; women represented 16.9% while men represented 16%. However, the prevalence of incontinence symptoms varied considerably between men and women and also increased with age (Stewart et al. 2002).

For women between the ages of 18-24, about 2% of them qualified as having OAB with incontinence, but as the age increased from 65-74, the number increased to 20% of women having OAB with incontinence. When it came to the male population, the prevalence of OAB with urge incontinence did not occur until 65 years of age, reaching 8.2% for ages 65-74 years, and 10.2% for those older than 75 years of age. This study showed that there

is no statistical difference between men and women who have overactive bladder, however, the difference lies between women being more likely to have incontinence than men. The likelihood that women will experience OAB with incontinence suggests that there is a sex-based predisposition for increased severity of expression of the condition. The reason for this sex-based difference could be because of the urinary mechanism differences between men and women, i.e. different pelvic floor anatomy. There was no statistical difference between men and women based on ranking quality of life, mental health and quality of sleep as the whole class of patients ranked poorly on these scales (Stewart et al. 2002).

Another study tested very similar OAB statistics in France, Germany, Italy, Spain, Sweden and the United Kingdom. Interviews were conducted by a clinically validated computer assisted telephone to survey the population, except in Spain where more households did not have access to a telephone, thus, the collected information came from direct interviews. The study determined the detailed symptomology by asking over 300 patients in each country a series of questions to help further understand the various symptoms patients have, as seen in Table 1 (insert key defining table). Over 16,500 subjects were assessed and 19% of patients reported overactive bladder symptoms. Of those patients, 85% of them experience the most commonly reported symptom, increased urination frequency. About 14% of men and women showed overactive bladder symptoms and the majority (>60%) of those patients reported that the symptoms of overactive bladder had an effect on their daily lives. Researchers believe that it is currently impractical to diagnose overactive bladder based on urodynamic investigation because the symptoms vary so widely among the general population. There is a need for diagnostic tests to encompass more bladder control problems to be able to compare across a wider population. This study showed the wide prevalence of overactive bladder in European countries and came to the conclusion that many of the subjects actively sought medical help, but few individuals were receiving treatment (Milsom et al. 2001).

2.1.2 Economic Impact of OAB

To further understand the impact of the costs of overactive bladder, NOBLE completed more surveys of a random population of people in the United States. From data collected in the 2003-2004 Medicare claims, annual expenditures for inpatient care, skilled nursing facilities, outpatient care, home health care, and physician services were generally much more for OAB patients. As symptoms worsened the costs increased and generally caused an OAB patient \$825 per person. This number increased when Medicare collected surveys again in 2007 to \$1,925 per person with a national cost of \$65.9 billion. They estimated the costs per person for 2015 and 2020 to be \$1,944 and \$1,969, respectively (Sanford et. al, 2013). Direct medical costs comprised about 75% of costs per capita for OAB patients and generally, national costs for women were higher than for men. Currently, total national costs due to OAB are the highest for those aged 45-54 years old, and lowest for those aged 18-24 years old. Costs for OAB exceed costs for osteoporosis, even though that

condition is thought to be more common. The conclusion in this study was that OAB will produce total national costs that are 25% higher than the current national cost by 2020 (Ganz et. al, 2009).

2.2 The Anatomy and Physiology of the Urinary Bladder

The urinary bladder is an organ which has the primary function of urine storage and release from the human body. The location of the bladder is near the pelvic bones, in the lower section of the abdominal region. Muscle and connective tissue comprise the bladder wall. When empty, the bladder wall relaxes and the inner wall creates folds to accommodate for the lack of pressure. During filling, the bladder wall expands and puts increasing pressure on these walls as they begin to stretch and thin out. Anatomically, the vertical axis (head to toe) of the bladder is longer than the side to side axis (hip to hip). When moderately distended the average bladder can measure at five inches wide and three inches high, which results in a capacity of about a pint (Gray, 2012). Figure 1 shows an illustration of the important features of the bladder. The detrusor muscle is primarily responsible for contraction of the bladder. During contraction, the external sphincter is engaged and opens due to the signal and pressure from the contraction of the detrusor.

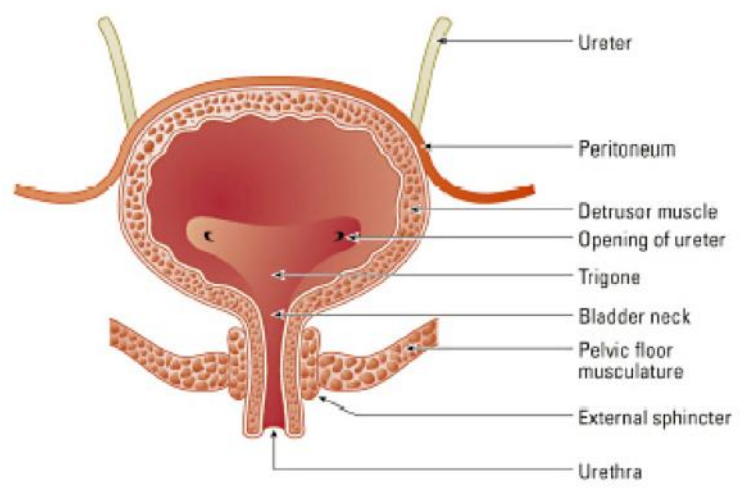


Figure 1: Bladder Anatomy (MedicaLook, Urinary Tract Infections)

The process of bladder filling begins in the kidneys, which filters the blood and removes impurities and waste for removal from the body. As this substance, urea, is created it flows out of the left or right kidney and down the left or right ureter. The ureters are tubes which connect the kidney and bladder in a vertical orientation. As the urine continues to transport from the kidneys, the bladder is gathering all of the fluid and holding it until it is told to contract. The signals given for contraction are sensations or urgency from reaching certain capacities within the bladder. When voiding is necessary, the bladder contracts and

the sphincters open, allowing the urine to pass through the urethra and out of the body. During filling, the sphincters close which prevents leakage of urine (Gray, 2012).

2.2.1 Bladder Tissue and Cell Types

There are four layers of cells that comprise the bladder wall, seen in Figure 2: serous, muscular, mucous, and submucosa. The serous layer comprises the outer layer of the bladder and protects the muscular layer, mostly in contact with the abdomen. The muscular portion of the bladder is split into three sections.

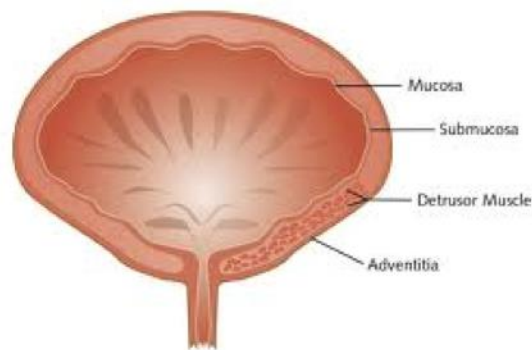


Figure 2: Bladder Tissue Layers (PromoCell, Bladder Cell Layers)

The orientation of the outer and inner layers is longitudinal, while the orientation of the middle layer is circular. These walls form a hollow formation with a mucous membrane, consisting of partly peritoneal serosa and partly fascia. The controlling of the contractile system is by the detrusor muscle which includes many bundles of nerves spread throughout the muscle, varying in size up to approximately two millimeters. Connective tissue surrounds these bundles, which assists in the spreading of signals throughout the organ. The next layer is the submucosa layer, which is a connective tissue between the muscular layer and the mucous layer. Finally, the mucous layer is the inner layer of tissue in the bladder, which is very thin and forms rugae, or folds in the tissue, when the bladder is empty. This layer provides an effective covering against urine in the bladder, also serving as another protection mechanism for the muscular layer, allowing the bladder to perform as needed (Gray, 2012).

2.2.2 Action Potential in the Bladder

The primary muscle involved in contraction of the bladder is the detrusor muscle. The detrusor muscle is controlled by the actin-myosin interactions, similarly to most other muscles in the human body. ATP (adenosine triphosphate) converts from chemical energy to mechanical energy to drive the contraction among individual smooth muscle cells in the bladder. The ATP energy will facilitate the sliding of actin filaments along myosin filaments.

This process shortens the sarcomere, a collection of linearly organized actin and myosin filaments, which on a large scale equates to cell contraction. Several factors influence the process of muscle contraction including many of the variable properties of smooth muscle cells. Sensation in the bladder initiates by stretching of the smooth muscle cells, which indicate bladder filling and communicate to the myovesical plexus and brainstem (Drake, 2007).

When the smooth muscle cells stretch the ion gates begin to open, causing freer flowing of ions, resulting in unbalanced, and sometimes undesired, ion concentrations on either side of the bladder wall. In some patients, overstretching during minor filling can cause hyperpolarization of the bladder wall, which can lead to undesirable detrusor overactivity. The ATP induced contraction is the preferred model and is usually the only effector in muscle contraction. This mechanism is called purinergic contractions, which is extracellular signaling, induced by ATP and accurately regulating the firing of muscle contractions for proper bladder voiding. Another mechanism that affects this process is cholinergic contraction, which is stimulation from the parasympathetic nervous system by way of acetylcholine. The bladder is very sensitive to acetylcholine, more so as the bladder fills over time. If a patient possesses excess amounts of acetylcholine it is possible to overstimulate through the parasympathetic nervous system which induces further bladder wall contraction, resulting in unwilling and unnecessary voiding (Ballaro, 2003).

2.2.3 Bladder Rhythm and Frequency

The contraction of the bladder can be considered as regulated by both muscle inhibitors and electrical signal inhibitors. Since the bladder is known to serve a very minimal role in the human body, filling and voiding, it is completely controlled by the Central Nervous System. In this manner, the brainstem's electrical communication is the source of bladder contraction initiation upon bladder filling and sensation. However, the physical distance in the human body from the brainstem to the bladder is far too inefficient to be the entire controlling mechanism of bladder contraction. Thus, the myovesical plexus identifies as the assisting complex in regulating and controlling the contracting and relaxing of the bladder (Andersson, 2004). Between the brainstem and the myovesical plexus, the contraction of the bladder walls is most efficiently organized and executed.

Sensation and urgency in the bladder varies depending on the fullness; they increase as the bladder fills. As soon as the bladder voids and remains empty, the sensation is very low due to minimal volume of urine. As filling occurs, the sensation increases due to increased levels of afferent activity, primarily acetylcholine. Increased sensation and urgency sends an electrical communication to the brainstem, which monitors the fullness in the bladder. Additional afferent activity creates excitation in the myovesical plexus, which serves as the intermediate step in communication from the brainstem to the bladder. When the brainstem senses the need to void the bladder, electrical communication is sent to the myovesical plexus. At this point, the myovesical plexus has high levels of excitation and uses

that along with the signal from the brainstem to initiate wave-like contraction of the bladder in order to systemically void all urine from the bladder (Andersson, 2004).

2.3 Origins of Overactive Bladder

The higher cortex of the brain, the pons, the spinal cord, the peripheral autonomic, somatic, and sensory afferent innervation of the lower urinary tract, and the anatomical components of the lower urinary tract itself control the bladder functions. There are a lot of factors that can contribute to overactive bladder, and these disruptions can occur at any point in the urinary system mechanism. As the bladder fills, pressure increases but still stays below the resistance of the urethral sphincter. Once the pressure is great enough, the bladder will void and the detrusor muscle will contract, forcing all urine out. The overactivity occurs mostly in the detrusor muscle and the types of the disease are neurogenic, idiopathic or myogenic (Wood, Ouslander, 2004).

2.3.1 Neurogenic Causes of OAB

A neurogenic cause of overactive bladder arises when there is nerve function disruption in the lower urinary tract. The ability of the bladder to void is dependent on nerve function in the lower urinary tract as well as the spinal cord and peripheral ganglia. Since the function of the bladder depends highly on the innervation throughout, a variety of neurological disorders can disrupt order and make overactive bladder a common issue. Controlling of the lower urinary tract is by three sets of nerves: pelvic nerves, hypogastric nerves and pudendal nerves. The pelvic nerves provide the majority of the excitatory input to the bladder. Any disruption to the spinal cord or subsequent nerves can cause overactivity, such as Parkinson's disease, which is a disorder of the basal ganglia function where dopamine-containing neurons rapidly degrade (de Groat, 1997).

2.3.2 Myogenic Causes of OAB

The bladder tissue consists largely of smooth muscle, and when there is a disturbance in the function of smooth muscle, there could be a myogenic cause of overactive bladder. The theory behind a myogenic cause is that an overall reduction in excitatory nerves to the smooth muscle causes the overactivity of the bladder. The bladder tissue must remain very compliant in the various stages of bladder filling and remain at a stable pressure when filling. The cells of the smooth muscle in the bladder are spontaneously active, which allows them to excite the necessary nerves when bladder pressure increases. However, the coupling of smooth muscle cells with a few other cells that are in direct contact which is quite unlike the heart, having all coupled cells. The excitation activity of the bladder is not homogenous and the activity of different areas of the bladder varies greatly. In overactive bladder tissue, there is an increase in abnormal spontaneous activity. Some patients have fused tetanic tension, which is when maximum stimulation of the motor neurons occurs and causes the muscle to twitch together at a high rate and result in a tetanic contraction. There are many more

factors that can contribute to detrusor instability like a change or increase in muscarinic agonists, or super sensitivity of agonist stimulation. The variety in which detrusor muscle instability occurs makes it difficult to diagnose a patient who has overactive symptoms when there is not one mechanism that can detect all of the changes that could possibly occur (Brading, 1997).

2.3.3 Idiopathic Causes of OAB

The last form of overactive bladder that can occur in a patient is idiopathic overactive bladder. Ruling out many of the other common factors of overactivity such as infection, inflammation, neoplasia, interstitial cystitis, and lithiasis, abnormal vesicourethral function is the most likely cause of overactive bladder. A variety of causes that could be the reason for bladder instability may start with congenital detrusor instability, which is a disorder in children related to delayed maturation of nervous control; behavioral detrusor instability, which relates to patients who have severe anxiety or a high level of constant distress; age related detrusor instability; and instability due to pelvic floor or urethral weakening. The bottom line is that often times, the cause of overactive bladder is unknown. To understand the idiopathic source of overactive bladder, researchers focus on what they do know about neurogenic and myogenic causes. The most useful way to address the patients with idiopathic overactive bladder is to subdivide the population based on possible etiopathogenesis, urodynamic patterns and response to treatment (Artibani, 1997).

2.4 Current Treatments and Limitations

The treatment options for OAB patients follow a standard chronology, based on the symptom severity and previous treatments. The first stage of treatment chronology is behavioral modification, which can include bladder training and dietary changes. The next phase of treatment uses pharmacological agents to address the muscles of the bladder and pelvic floor. The final step in the chronology is specialized treatment, which can include Botox injections, nerve stimulation via implant and cystoplasty augmentation surgery.

2.4.1 Behavioral Modifications

The first phase of the treatment chronology for OAB patients is behavioral modification, which can consist of therapies called the bladder drill, bladder training and modified behavioral training. The bladder drill and bladder training techniques have many similarities. Both therapies mainly target adjusting the voiding habits and patterns of the individual. The basic idea behind the two therapies is to achieve normal bladder function by extending the voiding interval, or the period between voids (Burgio, 2002). The bladder drill was the earliest therapy developed, and was an in-patient procedure. Bladder training evolved from the bladder drill, having a more gradual progression for adjusting the voiding habits and being an out-patient procedure. In both therapies, the patient must resist the

sensation of urgency, which postpones voiding of the bladder and gradually increases the voiding interval (Burgio, 2002).

The third technique for behavioral modification is the multicomponent behavioral training. The primary target of this treatment therapy is the re-training of the pelvic floor through exercise and the observation and analysis of the physiological responses of the bladder and pelvic floor muscles during urge sensations and voiding (Burgio, 2002). Patients are taught how to inhibit the bladder contractions that cause premature voiding through the use of biofeedback. Biofeedback allows the patient, and the physician, to observe the physiological responses of the bladder and pelvic floor through electrical sensors (Mayo Clinic, 2014). By seeing what the bladder and pelvic floor muscles are currently doing to cause the OAB, the patient and physician can gain a better understanding on how to adjust the activity to improve the condition.

While the behavioral modification techniques work for many patients with OAB, the results are heavily dependent on the individual patient. Active participation from the patient is necessary, as well as the ability to learn and retain the information and skills that are being taught to retrain the body. Additionally, the patient must be willing to make changes in his/her daily life activity in order to improve the condition. To offset these limitations of behavioral modifications, the therapies are often combined with pharmacological agents (Mayo Clinic, 2014).

2.4.2 Pharmacological Agents

The second phase of the treatment chronology is the addition of pharmacological agents to improve and treat the condition and its symptoms. There are a variety of types of drugs that are used in the treatment of OAB. Antimuscarinics, which selectively block the muscarinic receptors in the bladder, are widely used because they were the first developed and applied substances for the condition. Beta-agonists, which target and inhibit the adrenal receptors in the bladder, are receiving more and more attention as professionals conduct more research studying the advantages and disadvantages of using them (Andersson, 2004).

Antimuscarinics, as stated previously, target and selectively block the muscarinic receptors in the bladder. The primary function of the antimuscarinic drugs is to selectively block the muscarinic receptors, which act as end receptors for acetylcholine and cause the contraction of the muscles in the bladder, leading to voiding of the bladder (Andersson, 2004). They mainly act during the storage/filling stage of the bladder cycle, as the bladder wall stretches. The secondary function of antimuscarinics is to inhibit the release of acetylcholine from the cholinergic nerves within the detrusor muscle of the bladder (Andersson, 2004). The results of antimuscarinic treatment is that the voluntary and involuntary bladder contractions are initially suppressed to allow for greater bladder filling. While antimuscarinics have many advantages, there are negative side-effects associated with their use. Some of the more common side-effects are dry mouth and the threat of

tachycardia, though this is rare (Campbell, 2009). Also, high doses of the drugs can cause urinary retention as well as negative side-effects in other tissues of the body.

The development of a new drug in recent years is promising for the advancement of treatment for OAB. Beta-agonists differ from antimuscarinics by affecting the adrenoreceptors of the bladder rather than the muscarinic receptors. There is a high concentration of adrenoreceptors located in the bladder tissue which makes them a good target for OAB treatment. The mechanism of action for the beta-agonists is to relax the detrusor muscle by decreasing afferent nerve signals from the bladder (Ohlstein, 2012). The result is improved bladder compliance and an increase in bladder capacity. Similar to the antimuscarinics, beta-agonists have negative side-effects such as dry mouth and gastrointestinal disturbances. One of the more prominent beta-agonists is a drug called Mirabegron (Ohlstein, 2012). Mirabegron has been shown, in an animal study using rats, to reduce the frequency of contraction without affecting the strength of contraction (Tyagi, 2010). The study suggested that Mirabegron shows promising results in the treatment of OAB, targeting symptoms such as urgency, frequency and incontinence (Tyagi, 2010).

2.4.3 Specialized Treatment

The third phase of OAB treatment chronology is the use of more specialized treatments. These therapies are typically used when previous attempts to treat the condition have been unsuccessful. There are three main types of treatment: Botox injections, nerve stimulation and cystoplasty augmentation. This type of treatment is more involved than the previous two phases, as many of them require some amount of surgery.

2.4.3.i Botox (*Botulinum neurotoxins*) Injections

Botox injections are a popular method for treating OAB because it is reasonably simple and often produces good results in treating the symptoms of OAB. The injection of botulinum neurotoxins (BoNT) have the “ability to potently and selectively disrupt and modulate neurotransmission” (Smith p. 639, 2009). Research using BoNTs in the treatment of OAB has shown an increase in the maximum bladder capacity from 296mL to 480mL as well as a decrease in mean voiding pressure (Smith, 2009). The successful results from the injections lasted through both the 3 and 6 month follow up screenings in a study of 200 patients. In another study conducted to observe the effectiveness of multiple injections of BoNTs, the researchers found that after subsequent injections the patients experienced the same initial effects, a decrease in voiding pressure and increase in bladder capacity (Smith, 2009).

However, the subsequent injections did not have an additive effect, rather returned the bladder capacity and voiding pressure to the initial increased and decreased level of the first injection. This indicates that a patient would need repeated injections to maintain the level of treatment success. One major drawback to the application of repeated BoNT

injections for an extended length of time is the significant risk of long term catheterization due to the over-disruption and over-modulation of the bladder detrusor muscle, essentially completely inhibiting its ability to contract. A study of the long term effect of BoNT injections found that, in some trials, nearly 69% of patients needed to self-catheterize after the injections (Popat, 2005). While the effectiveness of BoNT injections is evident from the trials conducted in the above experiments, the significant risk of long term self-catheterization is a major drawback for the use of this treatment.

2.4.3.ii Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is a specialized OAB treatment that involves electrical pulses which modulate the reactions and reflexes of the bladder and pelvic floor muscles. A surgical procedure places an implantable device within the back of the patient, with the electrode leads connecting to the sacral nerve roots, seen in Figure 3 (Noblett, 2014).

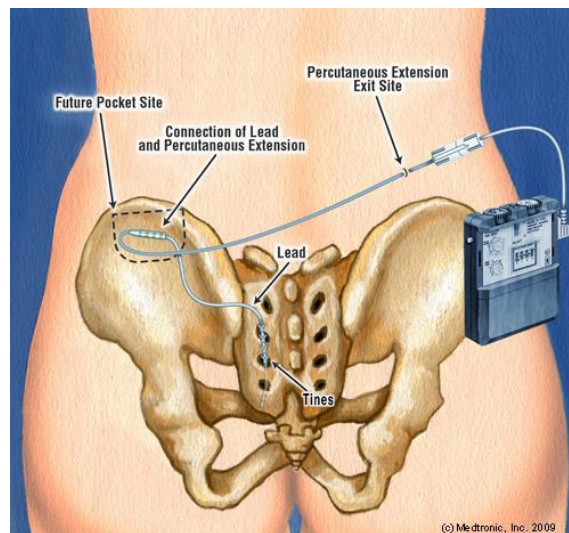


Figure 3: Sacral Nerve Stimulation (<http://www.uro.com/womens-services/interstim-virginia/>)

The device then acts as a “pacemaker for the bladder” (Noblett p.99, 2014), delivering non-painful electrical pulses to the sacral nerve roots. The SNS technique utilizes the depolarized somatic afferent nerves to produce inhibitory mechanisms in the interneurons in the sacral autonomic nucleus, which has been shown to be actively firing during bladder activity (Noblett, 2014).

During one study discussed by Noblett, treatment for the patients with OAB used the SNS therapy and the results were that the average number of incontinence episodes per day decreased from 10.8 to 2.9 and over 50% of the participants experienced a reduction in the number of voids per day (Noblett, 2014). However, after 6 months of treatment, the doctors turned the SNS device off in the patients, and the incontinence episodes per day returned to the original average of around 10.8 per day, while the number of voids per day also increased

(Noblett, 2014). This indicates that the therapy requires constant application and must be in working condition to maintain results. Another drawback of this therapy is that it requires a surgical procedure to implant the device within the patient.

2.4.3.iii Posterior Tibial Nerve Stimulation (PTNS)

The technique of posterior tibial nerve stimulation has a similar mechanism of action to that of the sacral nerve stimulation described in the previous section. PTNS involves inserting a needle just above the medial malleolus and using the needle to deliver an electrical impulse to the tibial nerve, seen in Figure 4 (Sherif, 2013).



Figure 4: Posterior Tibial Nerve Stimulation (<http://www.uroplasty.com/files/html/urgentpc.html>)

The impulse undergoes a transfer to the sacral autonomic nucleus via the tibial nerve. As in SNS, the delivery of impulses to the sacral autonomic nucleus helps to modulate the bladder activity and pelvic floor muscles. Performing of the treatment is typically once weekly for a duration of 12 weeks. The results of the study discussed by Sherif indicate that the therapy was successful in decreasing the number of voids per day as well as increasing the average voiding volume (Sherif, 2013). However, the data also shows that, after 3 months, the values begin to return pre-treatment levels (Sherif, 2013). For successful use in long term treatment of OAB, the patient would need treatments consistently performed every week. While this treatment is less invasive than SNS and does not require constant impulse delivery, it does require repeated treatment sessions continued success.

2.4.3.iv Augmentation Cystoplasty

Augmentation cystoplasty consists of reconstruction of the bladder via surgery using tissue grafts taken from the small intestine (ileum) (Veeratterapillay, 2013). This technique for the treatment of OAB is the most invasive option of those discussed in this section. The

removal of a section of tissue from the ileum in the small intestine allows for enlargement the patient's bladder, increasing the volume capacity of the bladder. In a study comparing augmentation cystoplasty and Botox injections for the treatment of OAB, the researchers reported significantly higher satisfaction scores in patients that underwent the reconstructive surgery (El-Azab, 2013). While the surgery may produce good results, the procedure does have its drawbacks. The main drawback is the necessity for major surgical operation on the patient. Additional drawbacks include metabolic disturbances, gastrointestinal and cardiovascular complications due to the surgery (Veeratterapillay, 2013). Many physicians are opting for less invasive therapies for the treatment of the condition.

2.6 Applying Mapping and Ablation in the Bladder

Currently, there are only imaging and ablation systems for the heart. We must compare the heart tissue to the bladder tissue to identify similarities and differences in relation to how catheters may work inside the body. The heart is an organ that has four separate chambers, with multiple orifices to enter the chambers. The heart is made up of thick muscle tissue, known as the myocardium, with an outer pericardium layer and an inner endocardium. The muscle in the heart is thick, largely interlocked and striated. These muscle fibers are connected with the cardiomyocytes between intercalated disks. All cells in the heart are couple so that the electrical signals in the heart form a wave to cause the heart to beat (Gray, 2012).

However, in the bladder, every cell is not coupled, only groups of cells because the bladder is modular. The thickness of the bladder wall is also much thinner, however there are four layers in the bladder, the serous, muscular, submucosa and mucosa layers. The muscular layer in the bladder is non-striated and the muscle fibers are not all arranged in the same order. The mucosa layer of the bladder is made up of transitional tissue with multiple different cell types so that the bladder has the ability to stretch. There is much easier access to the bladder because of the natural orifice as well as a different medium that moves through the bladder. In the heart there is blood, which is thicker and has the ability to coagulate, however in the bladder there is urine, which has the purpose of eventually being excreted (Gray, 2012). Although there are major differences in the heart and the bladder, the mechanisms for imaging and ablation could potentially be similar.

2.6.1 Cardiac Mapping

Mapping is an electrophysiological study, which shows the electrical activity of an organ and is the essential process performed before ablation to correct the irregularities in the heart rhythm. Cardiac mapping is a widely used technique that displays the electrical activities of the heart to detect the tissues responsible for the abnormal pattern of the heart rhythm. Figure 5 shows Rhythmia Mapping System from Boston Scientific Corporation. Figure 5 is an example of a cardiac mapping system.

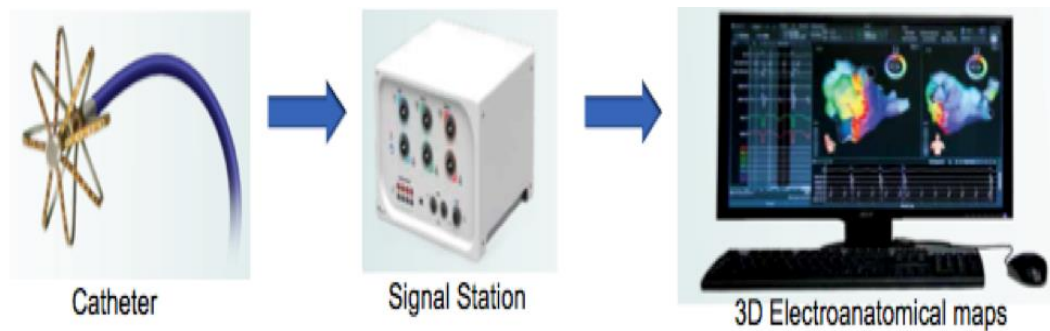


Figure 5 Rhythmia Mapping System (Rhythmia Brochure, 2013)

Mapping system includes a diagnostic catheter, a signal station and a localization system (Boston Scientific Rhythmia Brochure, 2013). Diagnostic catheters have different types of mechanisms and characteristics allowing physician's preference to be incorporated into the design, discussed later in this section. In a mapping procedure, a diagnostic catheter inserts through the vein or artery, depending on the chamber of interest, and guided carefully to the heart. These catheters have electrodes attached at the tip, which are sensors responsible for detecting the electrical signals inside the heart. Electrodes are the interface between the body and the electronic measuring apparatus. The electrodes carry out a transducing function by changing the ionic current in the body to an electric current (Webster, 2010).

There are many different types of electrodes used for collecting electrical activity signals, but catheters utilize internal electrodes, which detect the biopotentials in the body. With the help of a radio transmitter the electrodes record the signal and send it to the signal station where the proximal end of the catheter probe connects (Webster, 2010). The signal station is a closed box that has circuits inside. These circuits have the ability to perform signal conditioning on the data collected by the sensing electrodes. Signal processing includes amplification of the weak signal and filtering the noise in order to get a clear signal for diagnosis.

Another part of the mapping system includes the localization systems in which the diagnostic and ablation catheters can be seen inside the heart. Fluoroscopic guidance and 3D electroanatomical mapping are some common examples of localization systems. Fluoroscopy is an X-Ray technique used to guide the positioning of the catheter. Fluoroscopy technique has some limitations related to safety and performance. Since this process uses X-rays, it has the potential to increase the risk of malignancy to the patient and the operator. In addition, fluoroscopy does not provide the target sites of ablation to the operator so lesion formation cannot be completed by only using fluoroscopy since it only provides images of catheters (Edward et al., 1994).

Electroanatomic Mapping is another localization technique, which can determine the position of the catheter and shows the activation maps, which helps the physician in the formation of lesions. Using the electroanatomical mapping technique reduces the fluoroscopy time relying on its ability of catheter navigation. During the procedure a locator pad producing ultra-low intensity magnetic fields is placed under the operating table. The catheter used with this technique has an embedded sensor which measures the strength of the magnetic coils of the pad and helps to determine the position of the catheter. Besides reducing the fluoroscopy time, electroanatomical mapping provides 3D images of earliest activation site during arrhythmia (Friedman, 2002). Ablation of complex arrhythmias requires a more comprehensive mapping technique in order to be able to associate the intracardiac electrogram with a specific endocardial site previously mapped. Different techniques and mechanisms exist to overcome this problem and successfully ablate the site that is responsible for the disrhythmic electrical activity (Friedman, 2002).

2.6.2 Different Mapping Catheter Mechanisms

Diagnostic catheters detect the overactive tissues responsible for arrhythmia. All of the existing catheters specifically look for cardiac problems, but they all share different characteristics with different mechanisms to meet the expectations of physicians. There are many different types of diagnostic catheters and physicians choose the most suitable one depending on the surgery type. The main types are contact, non-contact and multi-electrode basket catheters (Friedman, 2002).

2.6.2.i Contact Catheters

Contact Catheters use a single point mapping technique. Physicians direct the tip of the catheter to the wall of the chamber of interest and map the chamber point by point. The contact catheters usually have four, six or eight electrodes. Contact catheters either have a fixed curve tip or a bidirectional curve tip as in Figure 6. These different features allow physicians to use the handle of the catheter and place the catheter tip around veins to get a high quality electrical signal for detection. For example, bidirectional catheters can form a ring shape around a vein for a good quality signal. Contact catheters provide a high resolution mapping as the electrodes pick up signals directly from the walls of the muscles of the heart. However, single point mapping takes a longer time to map the whole chamber (Friedman, 2002).

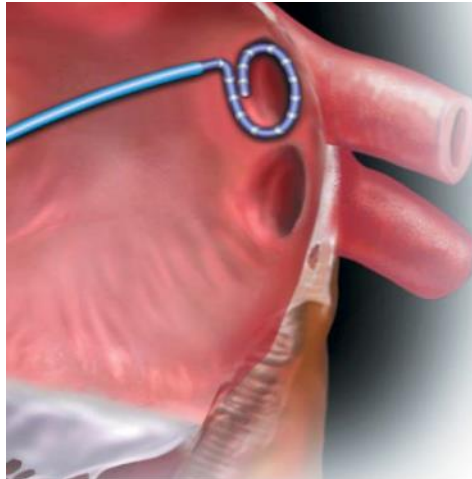


Figure 6: Contact Catheter (EP Bard, Orbiter PV Brochure, 2002)

2.6.2.ii Non-Contact Catheters

Non-Contact catheters allow simultaneous recording from multiple sites. These catheters map the organ by expanding once in the chamber of interest. Balloon catheters consist of a 7.5 ml balloon and usually 64 insulated wires with a diameter of 0.003m. The breaks in insulation act as a non-contact unipolar electrode. A unipolar electrode is an electrode attached to a single lead whereas bipolar leads have two conducting wires, Figure 7 (Friedman, 2002).



Figure 7: Non-Contact Catheter (Friedman, 2002)

2.6.2.iii Basket Catheters

Another catheter mechanism is multi-electrode basket catheters shown in Figure 8. Basket catheters have eight equidistant metallic arms providing a total of 64 unipolar or 32 bipolar electrodes.



Figure 8: Constellation Full Contact Mapping Catheter (Boston Scientific)

These catheters move inside the heart chamber and with the help of the high electrode numbers, map multiple sites at the chamber of interest. Having more electrodes allows a faster data acquisition however, at the same time, lowers the resolution of the signals recorded because of its poor spatial resolution (Friedman, 2002).

2.6.3 Cardiac Ablation

Ablation is the removal of material through vaporization, burning, or other mechanical erosive processes. Ablation is often used in the field of cardiology as the act of treating heart rhythm problems by creating a lesion to stop the abnormal electrical activity from travelling inside the heart. Ablation technique has become first line treatment for many causes of arrhythmia. In an ablation procedure, one or more catheters insert into the heart and a localization system identifies where to position the ablation catheter. Once the diagnostic catheter successfully locates the overactive tissue causing the abnormal electrical activity, an ablation catheter carefully inserts up the femoral vein or artery and guides into the heart chamber of interest. Physicians position the ablation catheter inside the chamber by using the localization systems, mentioned in the previous sections, and place the tip of the catheter over the tissue responsible for arrhythmia to start the ablation process. Ablation catheters generally use ring electrodes, placed around the shaft, and a large ablation tip to deliver the energy for the successful creation of a lesion. Ablation technique can utilize different types of energy sources, which is discussed in detail later in this section. The end of the ablation catheter connects to a power generator, which delivers the thermal energy used for ablation. Power generators are usually set to a limit of 50-60 degrees Celsius for cardiac ablation and energy is delivered to the tissue for period of time. The energy delivered from the tip of the ablation catheter causes a lesion at the point of interest and this prevents the

abnormal activity from continuing to move around the heart, thus preventing arrhythmia (Medtronic).

2.6.4 Sources of Energy

There are many sources of energy in use to treat cardiac arrhythmia and atrial fibrillations. Radiofrequency, microwave, laser, ultrasound and cryoablation are the most common energy sources for ablation in the treatment of atrial fibrillations. Each energy source has its advantages as well as its disadvantages, which will be discussed in detail in the following sections (Comas, 2007).

2.6.4.i Cryoablation

Cryoablation is the act of removing the heat from the tissue, which causes it to freeze and subsequently die. By freezing and destroying the targeted cardiac tissue, the electrical conduction through the heart returns to normal conditions (Medtronic). The freezing of the tissue causes lesions in the cell membrane, mitochondria, and cytoplasmic organelles. The lesion created around the tissue will disable it from sending any type of electrical activity, which means the tissue is isolated and results in stopping the random activity (Comas, 2007). The lesion's size changes by many technical factors such as the size and temperature of the probe, the temperature of the tissue and the cooling agent. The lower the temperature of the cooling agent, the shorter the time needed for the procedure to be done. In fact, the lesion can occur in a matter of minutes with a probe temperature of around -150 Celsius (Comas, 2007).

Table 1 below describes the advantages and disadvantages of the cryoablation technique. Cryoablation accurately targets the desired tissue, while the healthy, non-targeted tissue remains unaffected. In addition, it has a low risk for bleeding as well as it reduces the blood clots forming at the site of cryoablation. This method is also easy to use for surgeons as it is very stable. However, there are disadvantages to this technique as well. The cryoablation probes are stiff and cases of coronary artery stenosis have been reported as a rare complication from the procedure. Additionally, the large size of the catheter makes the therapy a moderately invasive procedure (Comas, 2007).

Table 1: Advantages and Disadvantages of Cryoablation (Comas, 2007)

Advantages	Disadvantages
Not harming the collagen and vasculature	Rare Complications could occur
Low risk of bleeding, perforation, collateral damage	Probes are stiff
Reduced blood clots forming at the cryoablation site	Large size of catheter
Ease of use	-
Stability at the endocardium	-

2.6.4.ii Radiofrequency Ablation

Radiofrequency (RF) ablation uses high-density alternating current (AC), with a frequency range of 350 to 1000 kHz that goes through the probe to the tissue of interest. The probes will heat up and apply at the tissue layer and the heat transfers to the deeper tissues as the surface tissue loses function. The probes typically heat to 50-60 Celsius in order to create lesions on the tissue, which inhibit the electrophysiological function by damaging the cell structure and destroying the collagen within the cell. Lesions can be created in 90 - 120 seconds, allowing for time efficient procedures using this ablation energy source. There are many factors that affect the lesion depth, such as electrode contact duration, electrode temperature, topical cooling, and tissue resistance (Comas, 2007).

Table 2 below displays the advantages and disadvantages of the RF ablation method. This method is popular among cardiologists due to its efficiency, as it takes around 10 to 20 minutes to complete the procedure. Also, it has many probes, which can be used in different approaches and configuration. However, there are disadvantages to the RF method as well. For example, many of the disadvantages focus on the complications of the RF as it has the potential to have thrombogenic effects, which could be a trigger for interactive thrombi. Also, a rare, but serious complication associated with RF ablation is atrio-esophageal fistula (Comas, 2007).

Table 2: Advantages and Disadvantages of Radiofrequency (Comas, 2007)

<i>Advantages</i>	<i>Disadvantages</i>
Time Efficient	Thrombogenic
Variety of Probes	Possible embolic complication
Simple and effective	Collateral Damage

2.6.4.iii

Microwave Ablation

Microwave ablation uses electromagnetic waves, generated between 300MHz and 300GHz. The electromagnetic field induces molecular dipoles which produce thermal energy. Catheters that utilize microwaves as an energy source for ablation, have a special design that includes a generator system, thermocouple and an antenna. Thermocouples monitor the temperature of the device and the antenna delivers the energy directly to the tissue. The size of the lesion created is dependent on the size of the antenna used to deliver the energy. Table 3 below displays the advantages and disadvantages of using microwave energy for ablation. Microwave ablation creates deeper lesions than RF ablation, however there are some disadvantages with these waves (Comas, 2007).

Table 3: Advantages and Disadvantages of Microwave Ablation (Comas, 2007)

<i>Advantages</i>	<i>Disadvantages</i>
Deeper Lesions	Less Experience with this technique
More penetrative	Probes are potentially dangerous

2.6.4.iv Laser Ablation

Lasers produce high-energy optical waves. Laser ablation is done by delivering laser beams from radiating fiber tip of the laser to the tissue of interest. With the beam directed the tissue gets heated and damages mechanically by shock waves. Laser beams can penetrate deeper into the tissue than Microwaves and causes cells to lose their normal shape and architecture. Besides being more penetrative than microwaves, lasers can give successful results using lower temperatures as seen in Table 4. Lasers are safe, however laser ablation does not have a safety mechanism to deal with increased high temperatures (Comas, 2007).

Table 4: Advantages and Disadvantages of Laser Ablation (Comas, 2007)

Advantages	Disadvantages
More penetrative than microwave	Lack of safety mechanism
Operates at lower temperature	

2.6.4.v High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a promising new ablation technique. In this ablation method, ultrasound waves heat the tissue of interest and induce lesions. There is not yet an effective study completed for this type of energy (Comas, 2007).

2.7 Current Technologies

This section explains some current examples of diagnostic and ablation catheters and their advantages.

2.7.1 Orbiter PV Catheter

The Orbiter catheter is an adjustable variable loop catheter with a deflectable shaft. The Orbiter catheter, Figure 9, maximizes the contact of electrodes with the tissue for better signal acquisition with the help of the variable loop. The pressure-based positioning feature of this design maximizes stability for the physician. This catheter has 14 internal electrodes with 5mm spacing (Orbiter Brochure, 2002).

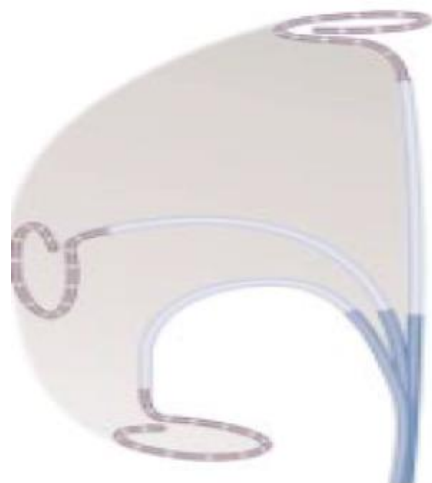


Figure 9: Orbiter PV Catheter (EP Bard)

2.7.2 Blazer Dx-20 Catheter

This catheter is a bidirectional steerable device intended to be used for diagnoses. The catheter has bidirectional steering, which is the ability of the device to respond to the physician's hand to move forward and backward. (Boston Scientific Brochure, 2014). The device has flexible soft tips to minimize the possibility of perforation of the organ. In addition, it has a curve lock that sustains the curve to prevent it from moving, creating stability and preventing error movement. As it can be seen in Figure 10, the flexibility of the tips and the ability to control the curves enabled the catheter to reach the targeted location smoothly.

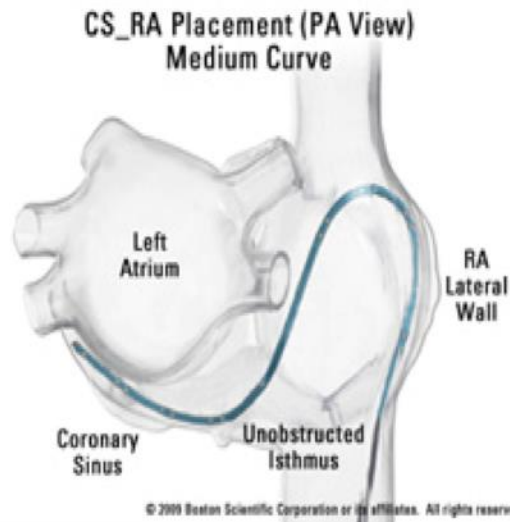


Figure 10: Blazer Dx-20 Catheter (Boston Scientific Brochure, 2014)

The handle, Figure 11, of the device helps the physician to control its movement inside the heart. Since it is bidirectional, the physician can move the tip into any position so that the electrodes receive electrical activities from all parts of the heart.

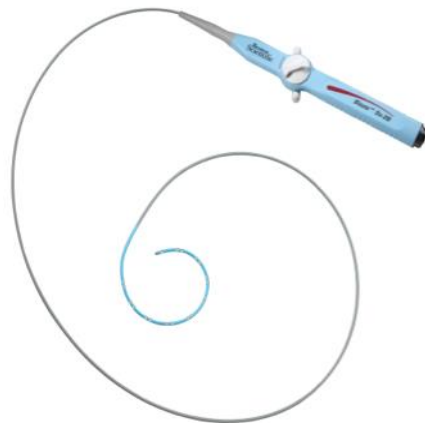


Figure 11: Blazer Dx-20 Catheter (Boston Scientific)

2.7.3 Chili II Ablation Catheter

The Chili II cooled ablation catheter is a product of Boston Scientific Corporation. This catheter uses Radio Frequency as the source energy and an internal cooling technique that does not include saline irrigation, as most ablation catheters use, which gives the Chili II an advantage as it prevents air bubbles going through the catheter. In addition, it is capable of bidirectional steering for better handling and tip stability. As it can be seen in Figure 12 below, the closed tip includes isolated thermocouples for temperature sensing, a RF delivery wire and cooling lumens. The cooling lumens are responsible for the internal cooling as one lumen sends out a cooling agent that circulates through the tip and then returns through the other lumen (Chili Brochure, 2013).

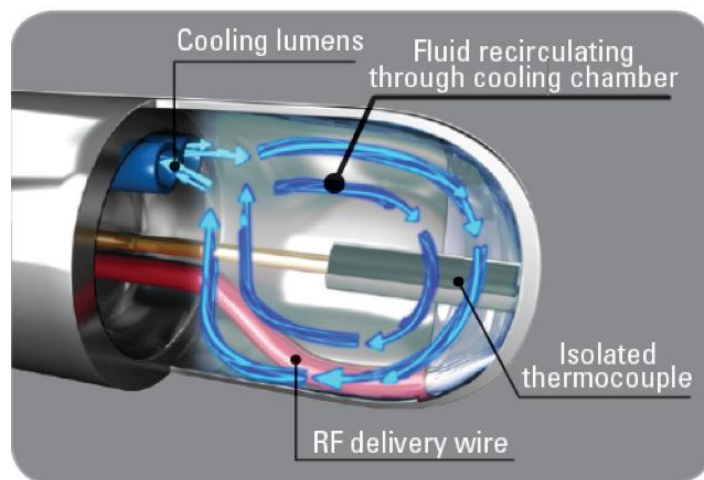


Figure 12: Chili II Ablation Catheter (Boston Scientific, 2013)

2.7.4 Achieve Catheter

The achieve catheter, shown in Figure 13 can map and ablate desired tissue by cryoablation. The electrodes on this catheter can create a ring shape around the pulmonary vein and map it through contact. The eight electrodes (1mm in length) are spaced 4 mm apart. Guiding of the catheter is by a wire lumen used to minimize the need to change catheters. The electrodes can stimulate and record the electrophysiological activity in the heart.

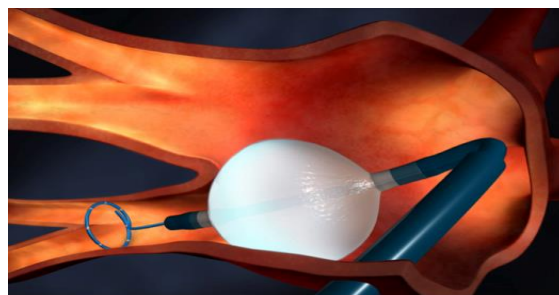


Figure 13: Achieve Catheter (Medtronic)

After completion of the mapping of the tissue, the electrodes will remain in contact with the vein. Simultaneously, the Arctic Front (cryoablation element of the device) will advance into the vein and inflates like a balloon. Figure 13 shows an illustration of this, and then application of the cryoablation against the tissue causes it to freeze. Afterwards, the balloon deflates and the catheter is removed (Medtronic Website).

Chapter 3: Project Strategy

3.1 Design Goals

After receiving our initial client statement from Boston Scientific Corporation, the team completed elementary literature review to better understand and assess the feasibility of the project. The team revised the client statement and developed objectives to frame the design process as reviewed in the following section.

3.1.1 Initial Client Statement:

Our client Boston Scientific Corporation, a company specializing in catheters, has tasked us with the challenge of exploring the feasibility of, and developing a device with the ability to be inserted through a natural orifice into the bladder. Once inserted, the device will be used to map the electrical signals of the bladder as well as ablate the overactive tissue.

Boston Scientific provided the initial client statement as their goal for the project. The team analyzed the initial client statement to identify areas where the client statement could be expanded on or details could be added. Our client allowed us freedom to think outside of the box for this project, as it is an exploratory topic. They did not want to limit us yet with specific details so that we are able to think of and consider all possible options and methods. As gathering of information occurred through a review of available literature, and through contact with Boston Scientific as well as the project advisors, the team was able to update and revise the initial client statement to produce a clear proposal for the project, described below in the Revised Client Statement.

3.1.2 Revised Client Statement:

Our client, Boston Scientific Corporation, a company specializing in catheters, is interested in exploring the feasibility of and developing a method for detecting over active tissue within the bladder and a device to ablate these specific over active areas. The device must be able to accommodate bladders of varying sizes (100-500 mL), both genders, and enter the bladder through a natural orifice.

3.2 Objectives:

The objectives of this project break down into several categories that summarize the most important achievements the team intends to accomplish in the completion of this project. The objectives were designing a device that had **easy access**, an **adaptable design**, is **gender neutral**, has **ability to map**, and can **eliminate signal propagation**. Each objective category has project specific details that further explain the purpose of each objective and how it incorporates in the project for Boston Scientific. The organization of the

objectives is from most important to least important, as according to the pairwise comparison chart.

Table 5 Pairwise Comparison Chart

Objectives	Easy Access	Adaptable Design	Gender Neutral	Effective	Eliminates Signal Propagation	Score
Easy Access	X	0	.5	0	0	.5
Adaptable Design	1	X	1	0	.5	2.5
Gender Neutral	.5	0	X	0	0	.5
Ability to Map	1	.5	1	X	.5	3
Eliminates Signal Propagation	1	.5	1	.5	X	3

3.2.1 Analysis of Design Objectives

One of the main functions of our device is the **ability to map** the whole bladder, which enables the physicians to identify the areas of overactive tissues with the help of real-time signals. The electrodes on the catheter act as the sensors and they pick up all of the signals inside the bladder and help the physicians to detect the irregular patterns in the electrical activity, which ablation stops.

Besides mapping, ablation is another important function of this device. Therefore, **eliminating the propagation of the overactive signal** is an important objective of this device. After mapping the whole bladder, the specific area of overactivity is detected and the device should ablate this overactive area and stop the propagation of the irregular electrical activity pattern from reaching the other nerves. Ablation is a crucial process and the device should ablate only the overactive areas without affecting other tissues or nerves. Recommended ablation source is Radiofrequency energy therefore the device will have a handle where it can connect to an RF generator for use as an ablation device.

Another objective of this project is the creation of a prototype that is an **adaptable design**. An important factor in dealing with many patients is anatomical differences in shape and structure of all body parts, in this case the human bladder. Patient specific designs are possible for the catheter devices, however the cost of manufacturing makes this option unfeasible, thus it is best to incorporate as many sizes as possible into the working device. Based on literature discussing anatomical sizes of the human bladder, this design will incorporate functionality for bladder volumes of 100mL to 500mL. That being established, it

will be important to choose the proper materials for this design that will be able to withstand repeated use. Things to consider are catheter strength and stiffness over several inserts through the urethra, material sterilization and how well it can reduce infection and contamination possibilities. Additionally, the device should be **gender neutral**, compatible with male and female anatomy, which will affect material choice and catheter design.

Easy access to the bladder is another objective of this device. The best method for utilizing easy access is to design a device that can insert through the natural orifice, through the urethra, into the bladder. One important aspect for easy access is the French size (mm diameter) of the catheter that will insert through the urethra. A French size that is too small will create liquid retention issues, but a French size too large could create discomfort in the patient and make the insertion process difficult.

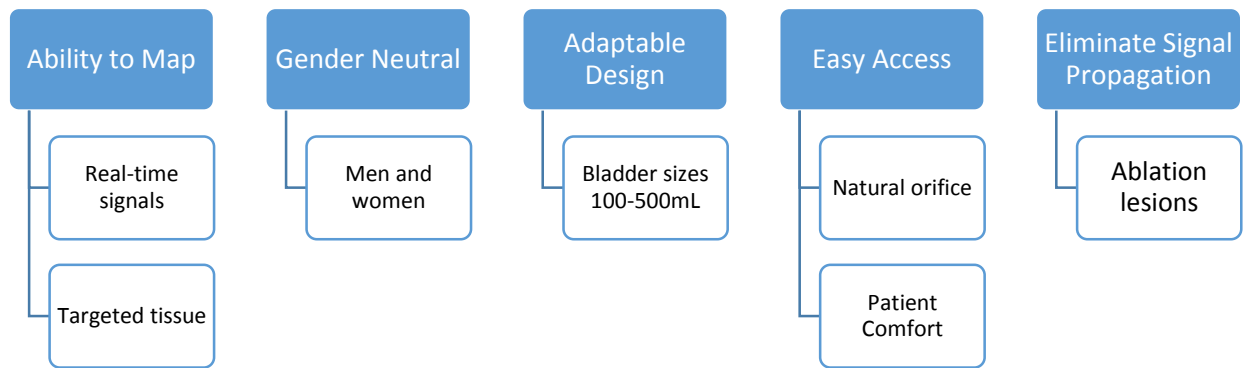


Figure 14 Objective Tree

In ranking the primary objectives, the specific details that define each of the primary objectives are labeled as the secondary objectives. The following table ranks each of the secondary objectives. In order to determine these ranks the secondary objectives were organized in the same priority order as the primary objectives, listed previously.

Table 6: Secondary Objectives

Rank	Secondary Objective	Primary Objective
1	Real-time signals	Ability to Map
2	Targeted tissue	Ability to Map
3	Bladder sizes from 100-500 mL	Adaptable design
4	Natural orifice	Easy access
5	Patient comfort	Easy access
6	Men and women	Gender Neutral
7	Ablation Lesions	Eliminate Signal Propagation

3.3 Constraints:

This project dealt with a variety of constraints and limitations that defined the mapping and ablation catheter project. The team worked with the WPI advisors, as well as Boston Scientific Corporation, the client, to develop a device that was conscious of these listed constraints.

Bladder Wall Thickness: The bladder wall is much thinner than the heart wall. The team is developing designs using similar ablation energy, so consideration of the tissue thickness is crucial. The bladder wall is much thinner than the heart and if the energy in the design method is too strong, then the bladder wall may be fully ablated or penetrated, which isn't safe for the patient.

Practitioner Capabilities: The designed device needed to be used with devices that many practitioners have access to. The design of the device needed commercial components, and not solely original components so that it could be used in many offices.

Tissue Availability: To test different components the team obtained porcine tissue from various slaughterhouses. The team was only able to use what was given to them on the specific sacrificing days for the animals.

Ablation Energy: There was a limitation of sources for ablation energy, such as not having access to Radio Frequency. Therefore, the team had to work with liquid Nitrogen as it was the only available source of energy.

Recording and Stimulating System: The use of the device must be compatible with the recording and mapping system. The Boston Scientific Catheters provided for us was not compatible with our stimulating and recording system.

Chapter 4 – Design Alternatives

4.1 Needs Analysis

Currently, a diagnostic device for OAB does not exist. Additionally, while some treatment options are currently in use, each of the options has its own shortcomings, which presents a large market opportunity in the field. One of the main areas in which the current treatment methods are lacking is the targeting of the area within the bladder that is causing the overactivity. Without the ability to identify the location within the bladder causing the overactivity, the treatments are non-targeted and non-specific. For example, the injection of Botox is performed by evenly distributing the injections throughout the bladder, rather than targeting in a specific location. This can lead to bladder paralysis if too much bladder tissue is affected, or an insufficient treatment of the condition if not enough bladder tissue is affected. If the physician had the means to locate the area of the bladder where the overactivity is most concentrated, they would be able to treat the patient more effectively and safely. The device developed through this project will satisfy the need of not only being capable of treating the overactivity through the use of ablation, but also the need for a means to detect and locate overactivity within the bladder.

4.2 Functions

The team developed a list functions that describe the operation of the device. The functions of the device helped the team develop multiple design alternatives and options to solve the given problem. Each function is something general that the device will need to perform in order to successfully reduce OAB symptoms. The functions include:

- Map the bladder
- Ablate overactive tissue
 - Target overactive tissue
- Maintain ablation temperature and surrounding tissue temperature
- Maintain stability
- Expand with the bladder

The functions are in a Functions-Means diagram in order to visualize the different aspects of the design (Appendix B).

4.3 Specifications

By performing different experiments and communicating with the sponsor, Boston Scientific Corporation, the team established specifications for the device's functions. The function's specifications are:

- The device must contain at least 64 electrodes in order to cover the entire bladder for electrical signal mapping.

- The device must use radiofrequency energy or cryoablation to ablate overactive tissue.
- The device must stay fixed in one position so the ablation can occur in exact same spot that overactive tissue is detected.
- Must contain a saline port to provide hydration to tissue.

The specifications for the device are subject to change with the continuation of the testing procedures. The purpose of each experiment is to test different design elements and functions of the device and optimize the specifications and design aspects.

4.4 Conceptual Designs

The team conducted various sessions of brainstorming with each other, their advisors, and their client. Through further discussion, a number of conceptual designs were drawn in order to assess the positives and negatives of each design with the client.

4.4.1 Catheter Design with Electrode Basket

The catheter design with an electrode basket, Figure 15, features both mapping and ablation capabilities. The head of the device is a retractable basket, having several wires that extend from inside of the catheter tube and meet at the very tip of the design. As the wires emerge from the catheter, they expand outward to form the basket shape. They are flexible wires, such that inside of the bladder they conform to the shape and maintain contact. The position of the electrodes is all along these wires, and have the ability to record and ablate the tissue. This design will use the wire contact to maintain basket fixation and to record and ablate at the same overactive tissue area in the bladder. The handheld portion of the device features two connection ports, one for liquid and one for electricity. The liquid is used to fill

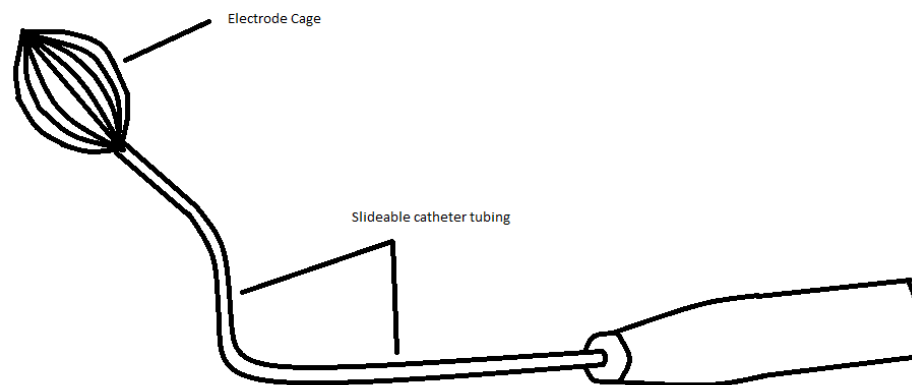


Figure 15 Updated Basket Catheter

the bladder and simulate inflation and induce contraction, while the electricity is to fuel the electrodes and ablation source.

4.4.2 Catheter Design with Electrode Balloon

The catheter design with an electrode balloon, Figure 16, features both mapping and ablation capabilities. The head of the device is an inflatable balloon into which water is held to simulate bladder inflation. As the balloon fills with water it takes the shape of the inside of the bladder, allowing for full contact with the bladder wall. The position of the electrodes is on the surface of the balloon, and have the ability to record and ablate the tissue. This design will use the balloon conformity to maintain contact and to record and ablate at the same overactive tissue area in the bladder. The handheld portion of the device features two connection ports, one for liquid and one for electricity. The liquid is for filling the bladder, simulating inflation, and inducing contraction, while the electricity is to fuel the electrodes and ablation source.

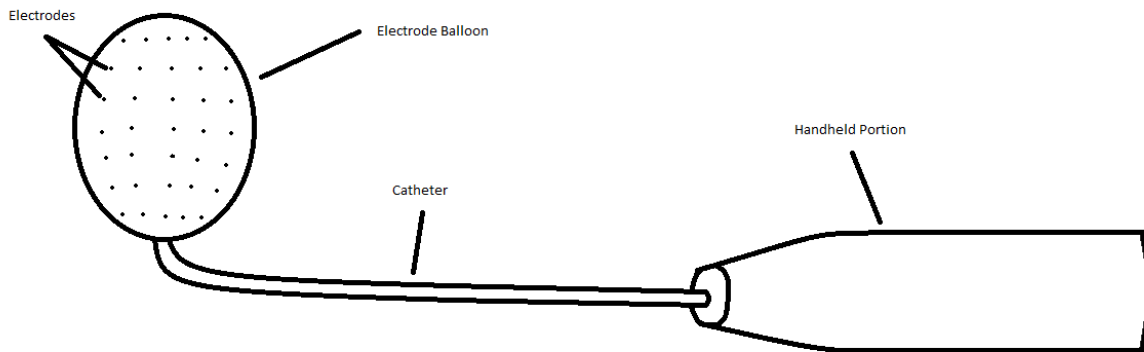


Figure 16 Balloon Catheter

4.4.3 Catheter Design with a Steerable Electrode Head

The catheter design with a steerable electrode head, Figure 17, features both mapping and ablation capabilities. The head of the device is a steerable, linear set of electrodes. The main function of this device is that it has the ability to enter directly into the bladder and rotates in multiple directions to conform to the wall of the bladder. A main advantage of this design is the size and ease of locating the overactive tissue regions. A disadvantage is that it takes several trials to fully map the bladder and search for any overactivity. The handheld portion of the device features one connection port for the electricity, controlling both the mapping and ablating capabilities of the design. Additionally, the handheld portion contains a manual control for the movement and adjustment of the catheter head. There are two controls, one which controls the frontward and backward movement of the head, and one

which controls the side to side movement of the head. These controls allow for coverage in any direction, and connect to the tip of the device by long, thin wires that extend through the body of the catheter.

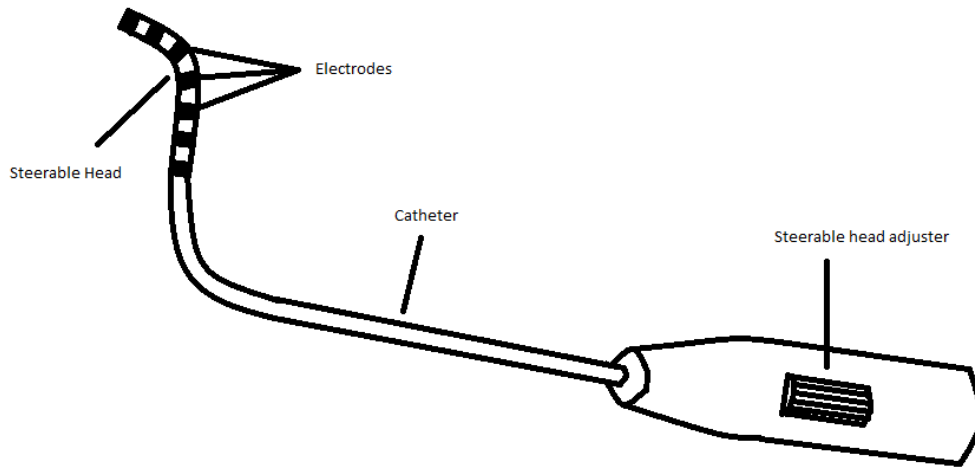


Figure 17 Steerable Catheter

4.4.4 External Pack with Skin Electrodes

This design, Figure 18, uses an external device system that a patient would wear on the pubic region. The external system is a soft, cotton-like material to increase comfort for the patient. The external device system uses skin electrodes that will attach to the pack and collect continuous data overtime. The skin electrodes are on specific spots that show bladder activity.

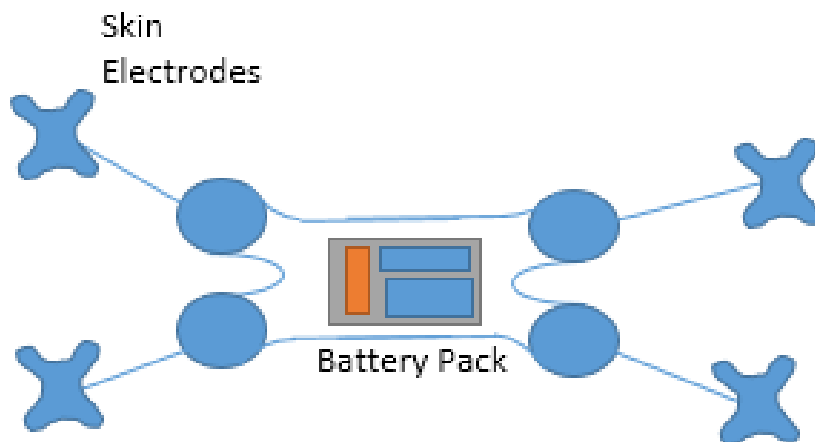


Figure 18 External Pack with Skin Electrodes

4.4.5 External Pack with Wireless Electrodes

This system, Figure 19, is modifying the external device that a patient would wear on the pubic region. This design uses wireless electrodes that insert into the bladder in various locations. The wireless electrodes are inside the bladder through the urethra. The electrodes provide a continuous monitoring for electrical activity that is recorded by the external pack for a physician to analyze.

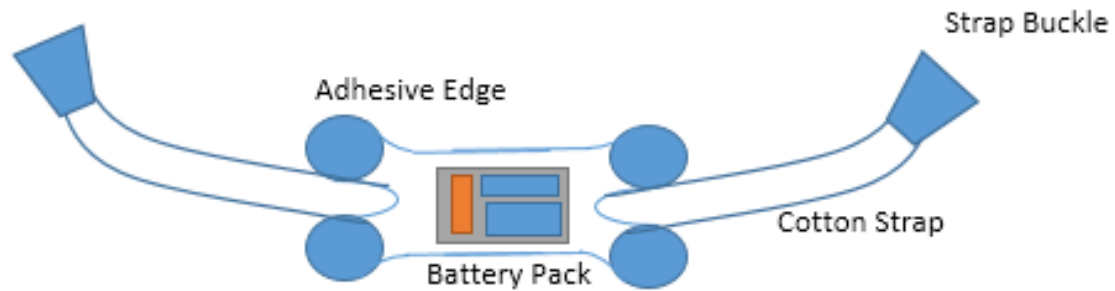


Figure 19 External Pack with Wireless Electrodes

4.5 Design Decision

After considering many design options, the team assessed each design listed above for various qualities pertaining the objectives and constraints. The team determined that the external packs would not be feasible because the bladder signal propagation was found to be too weak, and the time necessary to dedicate to designing a workable external pack was not available. The team then considered the remaining designs of the basket, balloon and steerable catheter. Through various brainstorming processes, newer designs were developed. The team considered an updated cage design that would be larger than the current Constellation Catheter, and expand with the bladder with excess nitinol wire. The second design considered was a donut balloon catheter because one of the functions of the catheter was to have the ability to fill and hydrate the bladder with saline, and with the bladder shaped balloon, the hydration would not occur, possibly causing tissue irritation. The third design that was considered was layered donut shaped balloons. This would allow more area of the bladder to be covered, still allowing hydration of the bladder, and allowing the catheter to expand with the bladder. The team evaluated each design in comparison to the objectives and constraints using a Decision Matrix, which can be seen below in Table 7. Each objective was given a score in order of importance that was determined from the Pairwise Comparison Chart (Table 5).

The final design that was chosen was the layered balloon catheter because it fit the team’s objective best. The initial design consisted of a number of layered balloons with electrodes attached the balloons by electrical wire. This design was chosen because it was determined to have the greatest ability to maintain contact with the bladder wall by adaptable design. The final drawing of the layered balloon is located in the Final Design Verification Chapter.

Table 7 Design Evaluation Matrix

Design Objectives: Required		Design 1: Updated Cage Design		Design 2:Donut Balloon		Design 3:Layered Balloon	
O: Ability to Map		✓		✓		✓	
O: Eliminate Signal Propagation		✓		✓		✓	
Convenient	Weight (%)	Score	Weighted Score	Score	Weighted Score	Score	Weighted Score
O: Easy Access (Minimally Invasive Procedure)	10	.9	9	.9	9	.9	9
O: Adaptable Design (Various Bladder Sizes)	25	.75	18.75	.75	18.75	1	25
O: Gender Neutral (Men and Women)	10	1	10	1	10	1	10
O: Effective (Accurate Signals and Lesions)	20	.8	16	.75	15	1	20
TOTAL:	100		87.5		77.75		98.5

4.6 Feasibility Study

The key to creating an effective design and solution to Overactive Bladder is to create a proof of concept experiment that shows how electrical activity in the bladder traces to a local point and how ablating to alter the activity and reduce symptoms is effective. The proof of concept experiment is an isolated bladder perfusion set-up. This allows the team to stimulate the bladder and detect overactive areas, and ablate those areas in tissue ex vivo. This set-up allows multiple experiments before going into animal study to prove that the theory is valid and that the designs work for the overactive bladder condition. This experiment will be difficult because there are not any isolated bladder perfusions systems for sale and the team built their own in order to accurately perfuse the organ.

4.7 Pig Bladder Tissue

Fresh pig bladder tissue used for perfusion experiments came from the Blood Farm in Groton, MA and Addams Farm in Athol, MA. Female and male pig bladders with vasculature are used in every experiment to keep results consistent. They are picked up immediately post mortem and are put in a cold solution of Krebs Buffer with heparin to prevent blood from clotting in the arteries and veins.

4.8 Perfusion Set-Up

To begin the testing for the mapping and ablation device for the bladder, the team needed a method for testing electrical signal collection in the bladder. For this, the team found the need for a bladder perfusion system. A perfusion system allows one to use saline, or Krebs solution, to cycle through the walls of the organ which simulates an in vivo condition. In order to assemble this system, many different parts and pieces needed obtaining. This collection of materials requires significant funding from the sponsor in order to purchase expensive equipment.

In this system, the bladder is held in an organ chamber, in which a cannula needle fixates a plastic tube in the main artery entering the bladder. This tube feeds Krebs solution through the bladder wall and simulates an in vivo condition for the bladder. By doing this, the bladder undergoes stimulation using electrical pulses which hopefully produce an electrical signal. The design of this testing setup is for a proof of concept regarding the collection of electrical activity in the bladder. By showing this through various experiments, detailed later, the team can move forward in designing a device that specifically locates overactive areas of tissue in the bladder.

To better understand the perfusion system and its components, the setup will be detailed part by part, including a diagram of the system. As mentioned previously, the bladder suspends in an organ chamber. At the bottom of the chamber is a valve, connected to plastic tubing, which drains the Krebs solution out of the chamber. The drained Krebs solution filters through the peristaltic pump, set at a flow rate of 10 milliliters per minute which pumps the Krebs solution up to the heated Krebs reservoir, set on a shelf in the lab. This reservoir is a jacketed reservoir that has water cycled through it, which is heated to 37 degrees Fahrenheit. The heated water is cycled through the jacketed reservoir from a water bath, situated on the shelf with the reservoir, keeping the Krebs solution warm. The reservoir is situated on the shelf at a height that will create a flow rate of 10 mm/min, to match the peristaltic pump. At this rate, the Krebs flows back down to the chamber containing the cannulated bladder. Along this length of tube is a heat exchanger. Since the water bath can only heat one of the reservoirs, the krebs loses heat and must reheat once more before entering the organ chamber. Another tube comes off of the elevated reservoir, and connects

to an open reservoir located on the lab bench. This open reservoir holds the rest of the Krebs solution and monitors the pressure head level throughout the perfusion experiments.

In order to assemble the system the team had to obtain parts from many different vendors. Harvard apparatus supplied the open reservoir and jacketed reservoir. For the organ chamber which holds the bladder the team contacted Radnoti LLC. The remainder of the parts for the system were obtained either through the Worcester Polytechnic Institute lab manager, Lisa Wall, or through the labs of Professor Glenn Gaudette and Yitzhak Mendelson. Using all of the gathered equipment the team constructed the system and used it to conduct many different experiments on pig bladders.

4.9 Krebs Buffer Solution

The main component of the perfusion system is the use of Krebs Buffer solution to provide nutrients to the bladder tissue to simulate an *ex vivo* environment so we can experiment on the bladder. To make a large stock of the solution, the team followed a previous study that validated a functional, isolated pig bladder model for physiological experimentation (Fry, 2012). The study gave a list of ingredients for use in a freshly made solution as follows: 118.3 millimolar (mM) NaCl, 24.9 mM NaHCO₃, 4.7 mM KCl, 1.15 mM MgSO₄, 1.15 mM KH₂PO₄, 1.9 mM CaCl₂, and 11.7 mM d-glucose. First, each solvent was converted from millimoles to moles, and then converted to grams/ mL and was weighed using a digital scale in grams. The equations for the Krebs's buffer solution are located in Appendix D.

The team scaled each component up by a factor of ten to have enough stock solution for multiple experiments. The team measured 1000 mL of deionized water and added each component besides the CaCl₂ to the water over a stir plate until it was fully dissolved. The CaCl₂ is added immediately before the perfusion experiments.

Chapter 5: Design Verifications

5.1 Materials

Once the team chose a final design, the different design components were broken down to look more closely at maximizing the efficiency and efficacy of the design. The components of the design include materials for the balloons, catheter tubes, and electrodes, as well as functionality of balloon inflation and electrical signal collection. Additionally, the team demonstrates different properties of porcine bladders through a variety of perfusion experiments. All of these considerations contribute to the validation of the chosen design. In the design process of this device, it was important to consider the advantages and disadvantages of different possible materials for each aspect of the device. The following sections describe possible materials for each aspect of the catheter device and what each material has to offer the design.

5.1.1 Balloon Materials

In our design, the material for the inflatable balloon part of the catheter needs to be flexible enough to inflate and deflate. However, the material needs to be stiff enough to maintain its inflated shape while in contact with the bladder wall. For this aspect of the design, the team narrowed down the material necessary to two options. The two options for the balloon material are polyurethane and nylon. Both materials can be manufactured to a variety of diameters, lengths and wall thicknesses.

Many balloon catheters are currently made with polyurethane. Polyurethane is a versatile material, with the capability of forming strong elastomers and rigid plastics. Additionally, they can be produced using a variety of techniques such as extrusion, injection molding, film blowing and solution dripping (Medical Plastics). The flexibility of the material comes from the long backbone, while the strength comes from the high degree of crosslinking between chains. The high tensile strength and flexibility are the main reasons that polyurethane would be an appropriate material for the inflatable balloon. Nylon shares many qualities with polyurethane for this application. However, one of the differences is that nylon can undergo repeated flexing without fatigue. However, nylon is less flexible than polyurethane. For our design, the flexibility of the balloon material is an important factor, as the balloons will need to be able to inflate to the appropriate size when inside the bladder.

5.1.2 Catheter Tubing

Given that the novel idea in this design focuses around the balloon for bladder filling, the catheter tubing materials are more synonymous with previous catheter designs for Boston Scientific. Products that are currently in production and in use from Boston Scientific successfully use the latest materials that are most beneficial for the function of this style of catheter.

5.1.3 Electrodes

There are two types of electrodes being, polarizable and nonpolarizable electrodes. Polarizable electrodes are more expensive electrodes such as Platinum and Nonpolarizable electrodes are inexpensive such as Ag/AgCl. Polarized electrodes are better preferred for biocompatibility reasons and nonpolarizable electrodes are more preferred for electrical performance aspect.

In our design, the electrodes will be collecting signals inside the bladder; therefore biocompatibility is the most important factor. Another important factor in choosing the right material is considering the functions of the electrode. In our balloon catheter, the electrodes will be responsible for both stimulation and recording the signal. Polarizable electrodes, such as Platinum electrodes, are more widely used in stimulating applications.

5.2 Demonstrating Design Concepts

Due to the limited manufacturing resources available, the team designed various experiments to test and demonstrate individual concepts of the total device. For example, a signal acquisition experiment was designed and conducted to demonstrate the ability of the electrode and electrode configuration to detect and collect electrical signal.

5.2.1 Signal Acquisition:

Signal acquisition, together with the perfusion system, from the bladder is the main modeling system of this project. Recording the electrical activity of the bladder requires an electrophysiology study, which includes signal acquisition by a sensor and a recording system that can process the acquired signal. Currently there are many different recording systems specifically designed for heart applications. These types of systems include software to gather data, a stimulator to stimulate the organ, a comprehensive signal conditioning system to remove noise and amplify the signal collected by the sensor, and a visualization system, which enables the physicians to locate the exact position of the electrical activity and the position of the catheter.

Due to set-up problems of existing recording systems and the cost of the portable recording systems, we decided to design and set up our own recording system. Since our primary goal is to measure the intravesical pressure of the bladder and detect any electrical patterns, a comprehensive system was not in need. Therefore, we set up a recording system using an amplifier and a stimulator, from BIOPAC Company, which can transfer data to Acqknowledge software for corresponding plots and settings related to signal acquisition. The external stimulator module, STM100C, provides pulse and waveform stimulus outputs for nerve and muscle stimulation through a Stimulus Isolator, which outputs the pulse through the needle electrodes that stick into the organ to be tested. The other part of the Biopac System is the ECG Amplifier, which is responsible for recording the electrical activity.

Electrodes connected to the amplifier collect the signal and the amplifier amplifies the signal by the amount of gain chosen by the user.

5.2.2 Pressure Measurements:

A pressure transducer from Harvard Apparatus was utilized to find the intravesical pressure of the bladder. It was calibrated using the Acqknowledge software. The two point calibration was measured first at the tube level being the same as the dome of the transducer and then scaled by the software to 0mmHg. Then the second point calibration was raising the tube 20cm from the dome and that should give us 20cmH₂O, which is equivalent 15.1 mmHg. The transducer works by converting the pressure to a DC voltage value. The sensing head has a button and an opening for the liquid to be tested. The liquid pressure acts through the opening and produce a force upon the button. This force is then converted to a DC voltage by the amplifier, which is connected to the sensing head by a cable that carries the electrical signal.

To measure the intravesical pressure of the bladder a tube, connected to the opening of the sensing head of the transducer, was inserted into one of the ureters and secured with a suture. The other ureter is secured with a Hoffman Clamp to ensure the isovolumetric conditions of the bladder. Then an 18G size catheter was inserted through the bladder and secured to help in emptying and filling the bladder. The bladder is filled with Krebs' solution and measurements are taken with 50 mL incremental and allowed to equilibrate for 5 minutes. The pressures inside the bladder at specific volumes were recorded.

5.2.3 Experiment 1:

We completed two different pressure experiments to check for consistency in our measurements. The two bladders used for these experiments are the smallest and the largest bladder the team experimented. The first experiment was done on a female bladder that weighed 22 g. The bladder was filled with saline with 50 mL incremental, up to 450 mL, and the pressure recorded after 5 minutes of the filling. The results were as followings:

Table 8: Volume and Pressure Measured in the Bladder

Volume mL	Pressure mmHg
50	1
100	2
150	3
200	4
250	4
300	5
350	6
400	7
450	8

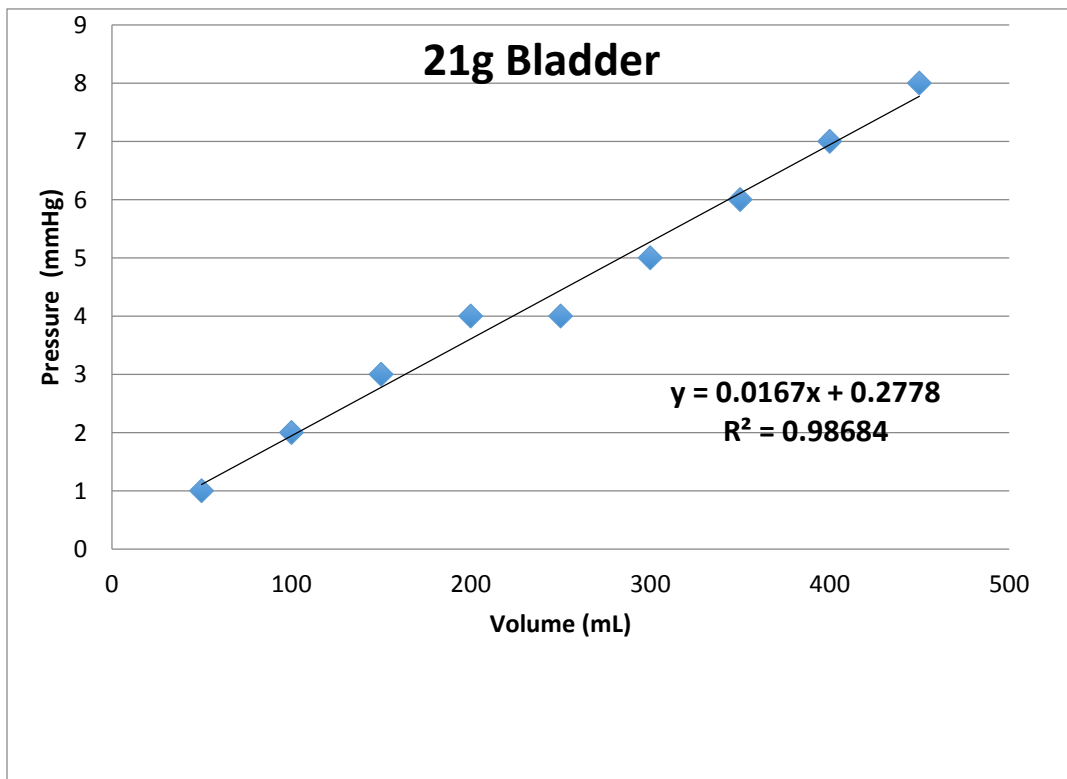


Figure 20 Pressure and Volume Relationship of the small bladder

As we can see from the table and the plot, there is a linear relationship between volume and intravesical pressure of the bladder. As volume of the bladder increases by 50

mL the pressure increases by 1 mmHg with an exception at 250 mL. The pressure graph for specific volumes and the test setup is detailed in Appendix D.

5.2.4 Experiment 2:

The team carried out another experiment to measure the intravesical pressure of a bladder, which was larger than the bladder that was previously experimented. The same experiment setup was completed and results obtained though BIOPAC System and Harvard Apparatus pressure transducer.

A female bladder, with a weight of 392 grams, was obtained from Adam Farms and filled with Krebs' solution. Since the bladder was larger than an average bladder size, the acquisition was lasted for 3 hours and the bladder was filled up to 3 Liters of Krebs's solution. The volume of the bladder is constantly increased by 100 mL in every 5 minutes and the results were as following:

Table 9 Volume vs Intravesical Pressure of the big bladder

Volume mL	Pressure mmHg	Volume mL	Pressure mmHg	Volume mL	Pressure mmHg	Volume mL	Pressure mmHg
50	-1	850	7	1650	10	2450	22
100	-1	900	9	1700	12	2500	21
150	-1	950	8	1750	13	2550	21
200	0	1000	9	1800	13	2600	22
250	0	1050	10	1850	13	2650	23
300	1	1100	10	1900	14	2700	22
350	1	1150	10	1950	15	2750	22
400	2	1200	9	2000	16	2800	23
450	3	1250	8	2050	17	2850	23
500	4	1300	10	2100	17	2900	24
550	5	1350	7	2150	17	2950	23
600	5	1400	9	2200	18	3000	23
650	6	1450	7	2250	19		
700	7	1500	9	2300	20		
750	8	1550	9	2350	21		
800	8	1600	11	2400	21		

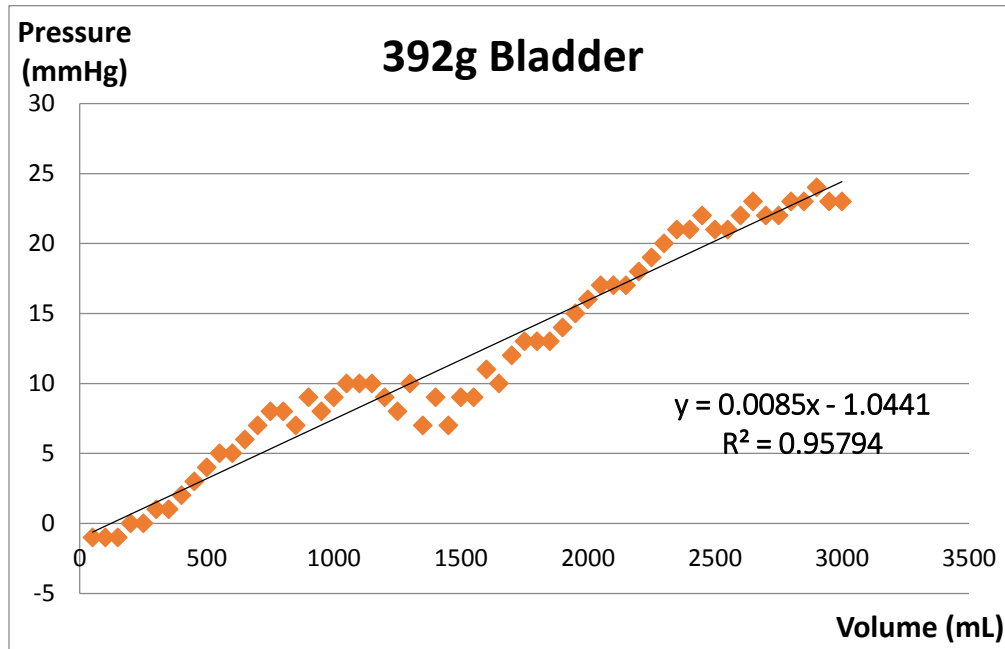


Figure 21 Large Bladder Pressure vs Volume

When we look at the volume and pressure relationship of the big bladder we see the same general trend that was observed for the small bladder. Although, the bladder was filled up to 3 L the general did not change and the slopes of both plots are very close to each other. However, this experiment demonstrated an important feature when we look at the results in detail.

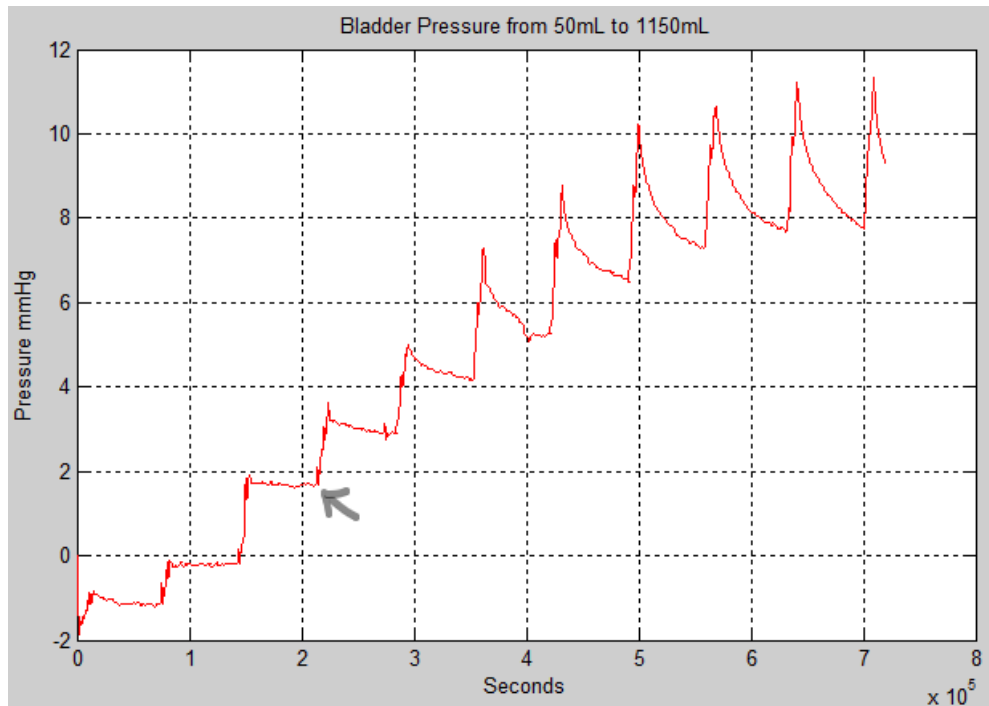


Figure 22 Increase in Pressure between 50mL and 1150mL

The volume of the bladder was constantly increased by 100 mL and pressure reflects a steep increase during filling. For the rest of the five minutes, the pressure stays the same until 200 mL, which is pointed by the grey arrow. After 200 mL the pressure increases instantly when the bladder is being filled and then the pressure decreases gradually during the next five minutes. This change in pressure is related with the ability of the bladder to accommodate pressure at high volumes.

5.2.5 Experiment 3:

Another important focus of our experiments was to test the feasibility of ablation on the bladder. Due to limiting resources we have only had access to Liquid Nitrogen so we mainly focused on cryoablation in our experiments. The goal of these experiments was to ablate a specific area of the bladder to see if we can stop the propagation of the signal in the bladder. As shown in Figure 23, a pair of stimulating electrodes was placed near the dome of the bladder and two sets of recording electrodes were placed to the left and right of the stimulating electrodes with 2cm and 4cm distance respectively. A bipolar, +5V and -5V, stimulation was applied on the bladder. Our main goal in these experiments was to isolate the further electrodes by performing a square ablation to eliminate the propagation of the signal to the ablated area. The acquisition was continuously running at the time the bladder being ablated.

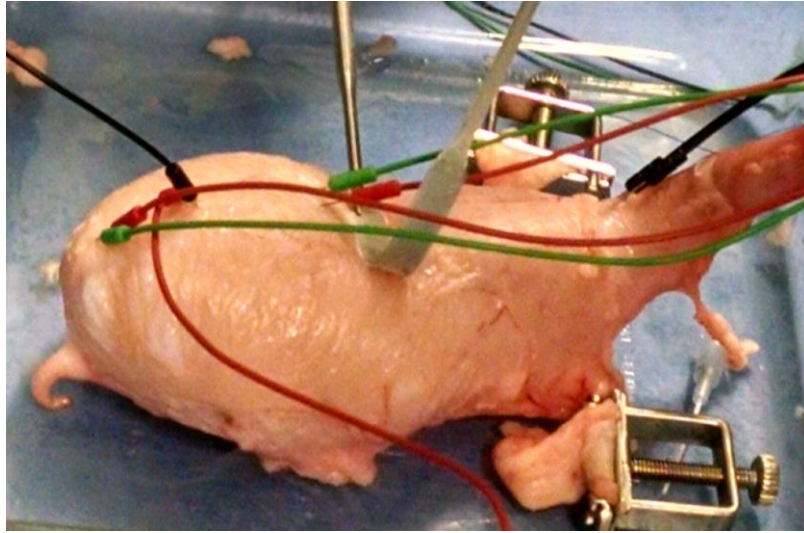


Figure 23 Electrode position and the ablation spot

The ablation process was using a metal that was put in liquid Nitrogen for around 20 seconds and then ablating by creating a square around the distant recording electrodes.

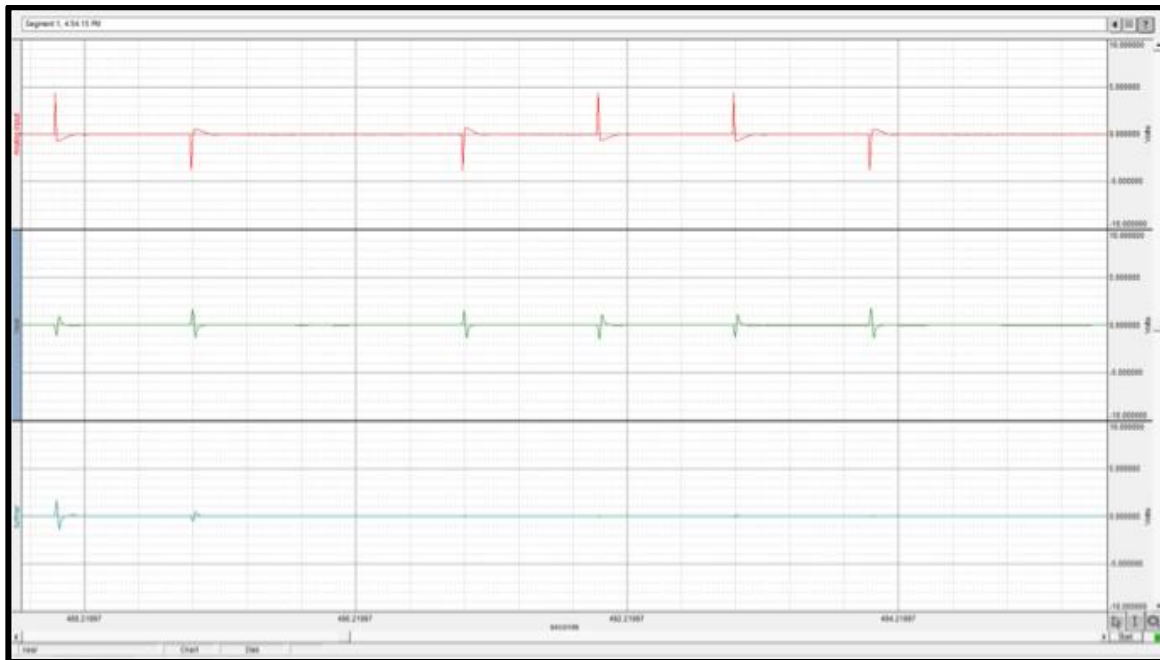


Figure 24 Plot showing the decrease in the signal amplitude after ablation. The top signal is stimulation, middle signal is from the near electrodes and the bottom signal is from the distant recording electrodes. Near electrodes were not affected because the ablation was done around the distant electrodes.

After performing the square ablation we were able to stop the propagation of the stimulated signal to reach to distant electrodes, which is the ablated area, without affecting

the signal level of near electrodes. This experiment demonstrated the feasibility of ablating a specific area of the bladder without damaging to other areas of the bladder.

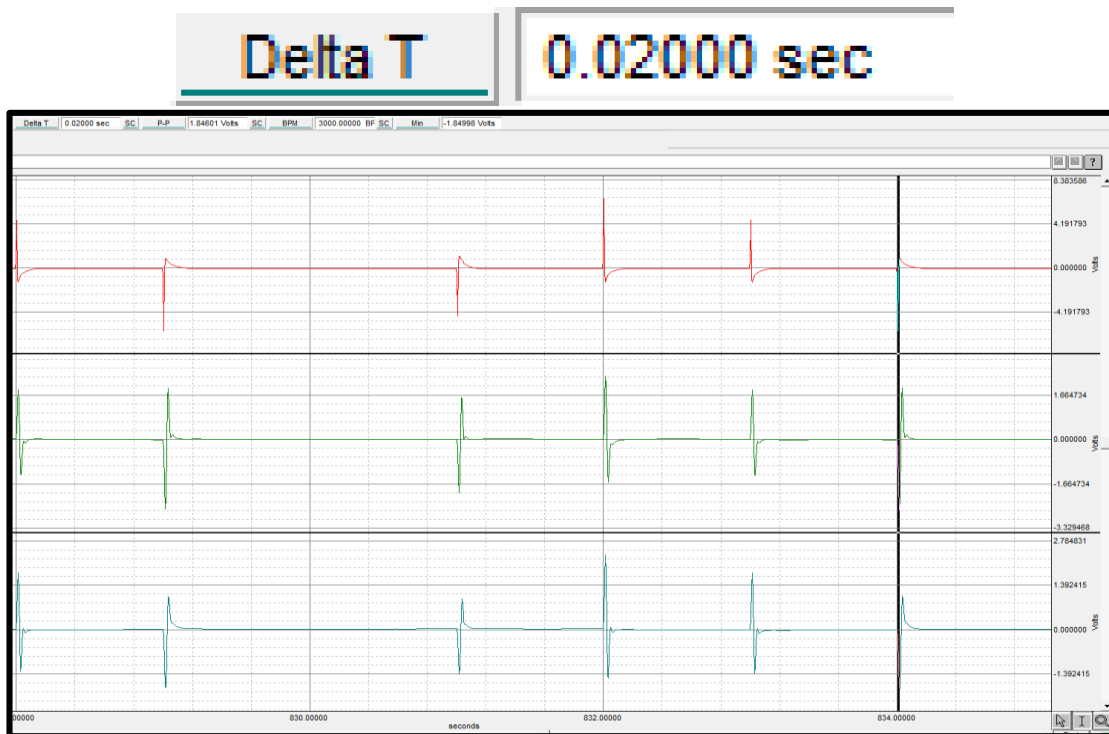


Figure 25 Conduction velocity of the signal

Another important outcome of this experiment was related to the conduction velocity of the signal in the bladder. This experiment demonstrated that there is a 20 ms of time delay between the stimulated and the recorded signal. The time delay is consistent throughout the whole data set regarding the distance of the recording electrodes but we recommend to our sponsor to repeat this experiment with a more reliable recording system since we were expecting a different time delay for distant and near electrodes because of the difference in the distance.

Chapter 6: Discussion

Due to limited resources, all objectives of the project were examined separately through different testing mechanisms. Through electrical, ablation and perfusion testing, the device was designed piece by piece as each concept was solidified. The team was unable to test the final prototype, but was able to examine the conceptual design and analyze the different components. The first objective that was focused on was making sure the design could function with an easy access approach, by making it a catheter that was to be inserted through a natural orifice. The team discussed different ideas about the possibility of having an external monitor for detection, however, through further research, the accuracy of the bladder mapping could not be achieved in time. The benefit of having this balloon catheter design is that the mapping and ablation could be completed through one process instead of two different mechanisms.

The next objective that had to be accomplished through our design decision was the ability to have the device be gender neutral, meaning that it would work for both men and women, regardless of age or size. Designing the device to be gender neutral will promote and increase marketability for our client when they move to enter the product into commerce. It was designed to be gender neutral because the catheter will be manufactured to be small enough to fit through a male or female urethra. Through research, the team found ideal French sizes for urethral catheters and will provide the ideal sizes through recommendations.

The team achieved the objective for an adaptable design for the mapping and ablation catheter by incorporating various design components that allow variations in size, shape, and function of the catheter. The use of individually filled balloons gives the design the ability to conform to many volumes of bladder size, or shapes of bladders. This design component is very important because the success of electrical signal collection is contingent upon maintaining contact between the electrodes and the bladder wall. Another important aspect of the electrodes on the balloon is that as the balloon inflates or deflates, the electrodes remain centered on the balloon, which means the catheter can map consistent locations throughout the bladder. Additionally, the use of electrodes capable of both recording and stimulating allows the entire procedure to occur without having to remove and replace the catheter, making the design adaptable and the process efficient.

One of the objectives was to design a catheter that can map the electrical activity of the bladder with real-time signals. Having the 64 electrodes distributed over the different tiers in the catheter, the catheter should obtain mapping from various places simultaneously of the bladder. The electrodes penetrating the expandable tiers can ensure contact with the bladder as it will shape/expand accordingly. Another aspect of the mapping is the individual wiring of the electrodes, which each electrode can be monitored through the recording system.

The last major objective for the design was to create a way to eliminate signal propagation through ablation. The ablation process can easily be completed by our catheter design by use of electrodes. When the catheter is connected to any kind of energy source generator, the individually controllable 64 electrodes can be ablated to perform the process. In our design each of the electrodes has a separate wire connection so they can be connected to the ablation source generator via a custom made connector. To validate the ablation technique, the team used cryoablation to show that by harming the bladder tissue, the signal propagation from stimulating electrodes was eliminated. This mechanism could potentially be applied to all forms of ablation on the bladder. The team wanted to use an RF generator, but due to limited resources, the RF generator could not be used.

6.1 Impacts of Device

As OAB is a condition affecting a significant portion of the population, the impact of a device of this nature will extend to many aspects of society. The main impacts that this device will have are described in the following sections.

6.1.1 Economics

One aspect of the economic impact of this device will be felt by the patients who suffer from OAB. This device will potentially allow for patients to cut out unnecessary surgical procedures and extended therapy with this one-time treatment. This will save the thousands of patients both time and money by offering the one-time treatment for their OAB.

On the other side is the economic impact felt by the manufacturer of this device, Boston Scientific. As mentioned previously, OAB consists of a \$65.9 billion industry of the United States economy. By being the first company with an effective, one-time, minimally invasive treatment for this condition, it will allow Boston Scientific to control the field in the immediate future.

6.1.2 Societal Influence

The introduction of an effective one-time treatment for OAB would be significant once it hits the market. A therapy capable of successfully knocking down the symptoms of OAB in a one-time, minimally invasive treatment would allow thousands of people to regain control of their bladder and the pain, discomfort, embarrassment and possible medical complications associated with the condition. OAB is estimated to affect over 36 million people in the United States alone, so a therapy of this type would have a widespread impact, not only in the U.S., but also across the world where the condition affects over 200 million individuals.

6.1.3 Political Ramifications

The major political ramifications that could result from the introduction of this device to market would be in the new regulation standards that would need to be established for use of this type of device within the bladder. Mapping and ablation catheters have been approved through the FDA for uses in other areas of the body, such as in the heart, but not yet in the bladder. The correct procedures would need to be followed to obtain FDA approval for this device. Additionally, the device would need to be compliant with other regulatory organizations in foreign countries for international use of the product.

6.1.4 Ethical Concerns

There are aspects of this project that minimizes previous ethical concerns. The perfusion system was developed so that testing different devices did not need to occur in canine animal studies. The future success of the perfusion study will allow all tests to be completed on a bench prior to animal study, minimizing the suffering and sacrificing of lab animals.

6.1.5 Health and Safety Issues

There are health and safety concerns with any new medical device, but with proper testing and validation, the issues should be minimized. Some concerns will be related directly to the procedure with the device. For example, one of the bigger concerns that will not be well understood until clinical application, is if the ablation of the bladder will harm the patient, either long term, short term, or cause urinary retention. Another lesser concern is the sterility of the catheter, and if it will be able to be sterilized without harming the electrical components. The catheters may have to be manufactured sterile, and they might not be multiple use products. Another health concern is that this product could might not work as well as it is hoped. Long-term effects of this product will not be evident for years to come, and it is work that will be done by future teams, or just our client. However, if this product does work exceptionally well, then it could change the face of overactive bladder treatments, meaning that the overall health issue and frequency of this issue would be reduced.

6.1.6 Manufacturability

The ability to manufacture this product will be key to the success of the catheter. The final design of the project has key aspects that have not been developed before, but the client, Boston Scientific, has the manufacturing capabilities to achieve all facets of the design. There are multiple ways that the catheter can be manufactured, depending on the type of electrodes that is chosen, or the orientation of the balloon. Another aspect that needs to be considered while manufacturing is the generators, saline pumps, and recording system that will be used with the catheter. Another focal point of this project was making the catheter

universally usable, amongst any office setting, so it would be necessary to make the catheter compatible with multiple systems, or at least a system that many offices would have.

6.1.7 Economic Sustainability

In order to evaluate the economic sustainability of this device, one must first evaluate the financial impact of current treatments for the OAB condition. The cost of current OAB treatments is estimated to be about \$1,925 per patient per year (Ganz, 2009). Currently, there is no available treatments for this condition that permanently reduce the symptoms of OAB, so the patients need to repeatedly have the treatments performed, increasing the total cost of care over time. The estimated price of our device, based on manufacturing estimates as well as comparisons to similar products currently on the market, will be around \$500-\$700. Even taking into account added expenses, such as the visit and stay in the hospital or doctor's office, our device will cost a patient significantly less than a current treatment costs in one year. Additionally, our device aims to permanently decrease the overactivity within the bladder in a one-time treatment. This will reduce the total cost of care over the lifetime of the patient significantly.

6.1.8 Environmental Sustainability

The device will be environmentally sustainable because the materials being used can be recycled. The wires and electrodes can be reused for devices because they can be sterilized. The silicone balloon components, as well as the tube components can either be sterilized again, or reprocessed into a new catheter.

Chapter 7: Final Design and Validation

7.1 Design Process

The team followed a Gantt chart and used multiple work breakdown task lists to split up the work and stay on task as the project was being completed. Various conceptual designs were developed during brainstorming sessions, and by the use of design matrices, but the team's final design was chosen because it fit all the needs and objectives, and stayed within the constraints. The following sections details the various parts to the team's final design and how the design was verified.

7.2 Final Design Description

Our final design consists of a seven-layered balloon, with electrodes surrounding each balloon. The total number of electrodes is 64, with a breakdown, starting from the top, to be 8, 8, 10, 12, 10, 8, 8, respectively on each layer. The electrodes will follow the same material as current Boston Scientific electrodes, which are made of platinum iridium. There will be one major saline port to keep the bladder hydrated that exists from the top of the catheter, so that the saline is able to cascade down around the bladder in full. The material of our balloons will be polyurethane, which are a tough, heat resistant, biocompatible material. These components will come together to make a successful mapping and ablation catheter for the bladder.

7.2.1 Balloons

The organization of balloons on the final design is a tiered structure of balloons, specifically three tiers in the final prototype. Each balloon is controlled by an individual filling mechanism in which the amount of water or saline filling the balloons is adjustable at any point of the procedure. When un-inflated, the balloons rest against the catheter tube and are covered by a protective sheath for insertion and removal through the urethra. In the final prototype the balloons were glued around the catheter tube, with the opening of the balloon covering a small tube poking through a hole of the catheter tube surface. By closing off this area the smaller tube can control individual filling.

For the final design the adhesion method for the balloon needs improvement. Additionally, the balloons would attach to the catheter tube such that the cylindrical balloon, open on both ends, will slide over the tube and be sealed around the top and bottom edges of the respective balloons. This method allows for any hole in the catheter tube to be open to the inside of the balloon. This method still requires individual tubes leading to each balloon in order to maintain individual filling.

7.2.2 Electrodes

Our final design has 64 electrodes in total. The breakdown of electrodes will be 8,14,20,14 and 8 respectively on each layer. The electrode numbers are proportional to circumference of each balloon layer. The electrode wires will be insulated and wires will be placed inside of the each tier of the balloon to where the tip of the wire will be exposed to outside of the 5 balloons. With this idea the electrodes will individually be controlled with the help of individual connections.

The material chosen for the electrodes is platinum iridium. Considering the biocompatibility issues and the functions of the catheter, the electrodes will be made from platinum similar to Boston Scientific's Constellation Catheter. The Electrode tips will be able to contact with the bladder wall as the balloons get filled for the best signal connection.

7.2.3 Saline Port

The saline port is a feature concerned with filling of the space in between the balloons. Saline is a liquid that can be used to best simulate urine in the bladder, thus in order to collect electrical activity in the most efficient way in a patient, filling the bladder with saline may trigger overactive signal or voiding and show the doctor the location of the overactive signal. For the final design the saline port is a single tube that runs up through the catheter, surpassing all outlets to the balloons, and the end of the port is at the end of the catheter, which is open directly to the bladder. As the balloons are being filled the port can be used to fill the bladder with saline, and similar to the balloons the bladder volume can be adjusted with this saline port to simulate different environments and volumes for the bladder.

7.2.4 Final Design CAD Drawing

The team sketched the final design in CAD as seen in Figure 26. The design has five layered balloons and a total of 64 electrodes. Each balloon has a different circumference, and the number of electrodes will vary between each balloon so that they are equally spread. There is a reference electrode located at the top for unipolar function. There is also a saline port at the top, but multiple ports can also be placed in between balloons for bladder hydration during procedures. The electrodes are protruding through the balloon so that a point electrode is the only visible component and that will help maintain contact while allowing the balloons to expand without having the wire constrain the balloons. The wires are each insulated so that the electrical performance is increased and they can be individually controlled for mapping and ablation purposes.

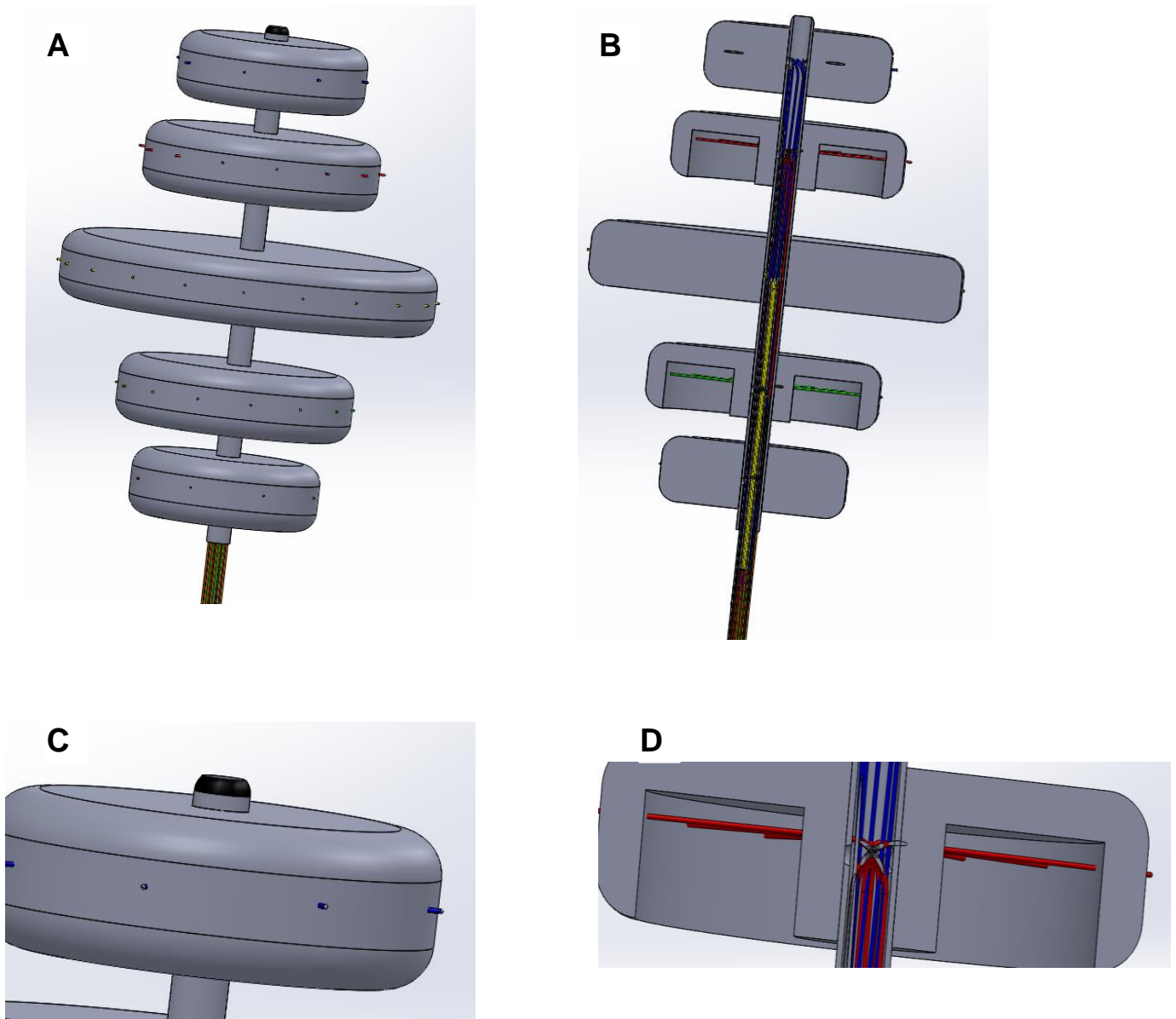


Figure 26 A: Outside view of design B: Inside view of Design C: Close-up of Reference Electrode D: Insulated Wires through Balloon

7.3 Prototyping

The goal of this project is primarily to develop a catheter that can collect and identify electrical signal in the bladder and ablate identified overactive tissue areas. To provide this solution the team needs to complete several experiments that show the validity of the chosen

design concept. The team approached each aspect of the design individually in order to prove the concept of the chosen design step by step. Each step is organized in chronological order for this section, which details the team's work towards creating a functional prototype.

The team used multiple methods, as previously described, to validate the selection of the final design concept. The decided design is the tiered balloon catheter, in which the balloons are filled separately, forming a donut shape with eight electrodes equidistantly placed around each balloon. The number of tiers was experimented with during these trials and is a variable aspect of the design. With this information prototypes were developed as follows in order to create a functional prototype.

7.3.1 First Prototype

The team created the first catheter prototype as a visual of balloons on a catheter sized tube and how the functionality of the idea would initially work. Figure 27 shows the first prototype procured by the team. The team purchased generic balloons from a local party store, so the quality of balloon may be questioned regarding consistent thickness. The maximum volume of these balloons is 250 mL and in the picture they are wrapped around a catheter-like length of tubing that is 1/8" outer diameter. Since these are normal balloons, the team did not expect to see equivalent distribution of water, forming donut rings, as is expected in the conceptual design. The concept of this prototype was to analyze the way in which the balloons expanded when individually filled with water. The outcome of this prototype was that the team could not obtain enough stop stopcocks to individually control the seven balloon openings as seen in Figure 27, and it was determined it would be more efficient to find an alternative design to test balloon inflation.



Figure 27 First Balloon Catheter Prototype

7.3.2 Balloon Catheter with Same-time Filling

The next prototype focused on redesigning the method used for attaching the balloons in order to provide a more efficient filling mechanism. Figure 28 shows the prototype that was made as a solution to this problem. The prototype used the same bladder shaped balloons as the first prototype and two stopcocks in order to control the flow of water into the tube. To test this catheter the team attached two syringes, one to each stopcock, and attempted to fill the balloons at the same time. In order to achieve this, there were seven equidistant holes made along the length of the tube and the openings of the balloons were glued over these holes. Thus, by pumping water into the tube, the tube fills and the water should then filter into the balloons. An issue that arose with this design was the inconsistency with the balloon wall thickness such that the orange balloon in particular was taking most of the water, as the path of least resistance, and the other balloons remained relatively empty.



Figure 28 Same-Time filling of tiered Balloon catheter

7.3.2.i Individually Filled Tiered Balloon Catheter

From the previous prototype, the team learned that filling all of the balloons at the same time was a design aspect that could be improved, and this was the direction taken for the individually filled tiered balloon catheter. Figure 29 depicts the prototype which features a three tiered balloon setup on a tube with an outer diameter of $3/8$ ". The figure also shows three much smaller tubes ($1/32$ " outer diameter) coming out of the larger tube which functions as the filling mechanism for the three balloons individually. To create this prototype three holes were made equidistant from one another along the length of the catheter. The next step was to feed the smaller tubes through the holes that were made, as can be seen in the figure. Approximately $1/8$ " of the small tube was left protruding through the hole, around which the balloons were adhered and then wrapped around the catheter. The testing for this prototype involved the use of tube plugs and plastic connectors. Two

plugs were always used to block flow of water out of the balloons, while the third connection used a tube adaptor to allow a syringe to be attached. Using this system, each balloon was filled separately in order to analyze the effectiveness of individual filling of balloons. The results of this prototype showed that individual filling is much more effective to achieve constant contact and shape adaptability, but the bladder shaped balloons cannot fill in a donut-like shape.



Figure 29 Three Tiered Balloon catheter that fills balloons individually

7.3.2.ii Single Cylindrical Spiraling Balloon Prototype

The main point of improvement as identified by the previous prototype was solving the ineffectiveness of the bladder shaped balloons for the concept of this design. The solution to this problem was solved by doing some research on cylindrical balloons. The team found cylindrical balloons with the purpose of creating animal balloons, but the shape was ideal for the prototype idea. Although the balloons were quite long, the idea was still pursued and the solution was to wrap the balloon around the catheter in a spiral fashion as seen in Figure 30. Similar to the previous design, a hole was made for the smaller tube that is seen in at the right portion of the prototype. The cylindrical balloon was glued over the opening filled by the tube, and then the balloon was spirally wrapped around the balloon and adhered at the end. The functional test performed on this prototype was to attach a syringe by way of a plastic adaptor and fill the balloon to analyze its ability to equally fill and expand the balloon. At a low volume of injected water, the balloon filled equally and showed what the team expected.



Figure 30 Cylindrical balloon wrapped around wide catheter tube

7.3.2.iii Tightly Wrapped and Loosely Wrapped Spiral Balloon Catheter

To further test the cylindrical balloon the team then used a smaller catheter, more equivalent to the size of a functional bladder catheter. For this design there were two experimental setups to analyze the difference of inflation success. For the first design the green balloon is tightly spiraled around the catheter tube as seen in Figure 31 (top). Alternatively, the same design was procured using a yellow balloon, yet this time the balloon was more loosely spiraled around the catheter, hopefully giving more space for inflation of the balloon, also seen in Figure 31 (bottom). Each design was moderately successful, but given more room for inflation, the yellow balloon provided a more functional prototype.



Figure 31 Tightly wrapped cylindrical prototype (top) and loosely wrapped cylindrical prototype (bottom).

7.3.2.iv Tiered Balloon Catheter with Variation of Radii

Once the team verified that the cylindrical balloons could function in the way we intended to use them, the spiral design was eliminated and the focus went back to the tiered balloon design. This prototype focused on the difference in length of the balloon that wraps around the catheter. In order to build this prototype the long cylindrical balloons were cut to predetermined lengths. The yellow balloon is 1.5", the green balloon is 2", and the red balloon is 2.5". The catheter tube is 3/8" outer diameter and the tube used for liquid filling is 1/32" outer diameter. Each balloon has one of the smaller tubes connected to the balloon's opening, allowing for individual filling of the balloons. The results of this prototype testing showed that the middle balloon, 2" length, was most effective for providing an adequate donut shaped balloon for filling the bladder.

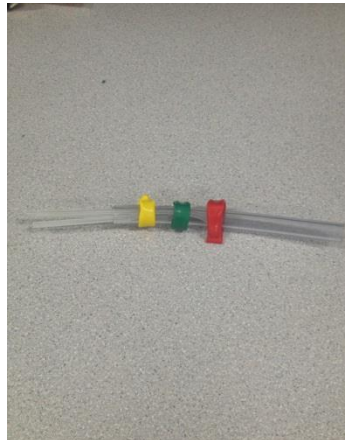


Figure 32 Three Balloons tiers that vary in radius length

7.3.2.v Tin Foil Electrode Catheter

Once the balloon concepts had been validated as pertaining to the chosen design, the team moved forward with the incorporation of electrodes to the design. Figure 32 shows the catheter prototype, which contains four individual tin foil wraps, serving as electrodes. Underneath the tinfoil are four holes in the tube that each holds one wire, as seen at the bottom of Figure 32. The wires in the figure are meant to be connective tools to pass any collected electrical signal down through the shaft of the catheter and to the signal collection device that can process the data. The tube that was used for this prototype was cut from a stethoscope and is 1/4" in outer diameter. The testing for this prototype involved the use of a heart rate simulator and the prototype was able to detect a low level signal from the simulator. The lack in strength of signal might be attributed to the lower-level quality of the electrode design, but the concept was a success in this experiment.

We used a heart rate stimulator, which we connected to the BIOPAC to see the amplitude of the signal. The amplitude was 0.7V. The second step was to test the catheter we created by hooking it up to the heart rate stimulator. The alligator clips from the heart rate stimulator were connected to the foil electrodes and the conducting wires coming out of the tube were connected to the BIOAC system. The signal that was recorded had lower amplitude however it depicted a heart wave signal. This demonstrates the successful implementation of the catheter.

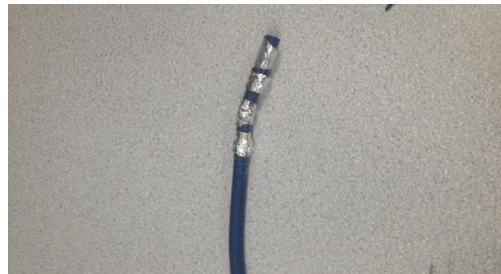


Figure 33 Catheter made with tin foil to serve as electrodes

7.3.2.vi Ring Electrode Balloon Catheter

Since the electrode catheter concept was successful, the team attempted to create the first prototype combining the balloon design with the electrode design. The first prototype that accomplished this is seen in Figure 33. The catheter is the blue tube, the same material and outer diameter as the previous design, and the pink balloons are all of the same material and size. At the bottom of the figure one finds the three wires, each one leading through separate holes in the catheter.

The end of each wire was stripped and wrapped around the tube, underneath the balloon to create a circular conducting mechanism. Figure 34 is a photograph of the ring electrode used to connect the conducting wire to the outside of the balloon in order to contact the bladder wall. This ring is made from the same wire and allows space for inflation of the balloon. An issue with this prototype is that the ring, as is, could not fit inside of the bladder, but instead would need to be collapsed initially, and expand inside of the bladder. For functional purposes, this design was a successful attempt to understand and visualize the complications of this design concept and the team was able to begin brainstorming alternative solutions for electrode exposure inside of the bladder.



Figure 34 Close-up of ring electrodes

7.3.2.vii Electrode Balloon Catheter

In exploring alternative electrode designs to implement with the balloon design, the team created a prototype that incorporates a more feasible electrode design, based on the testing and experimentation performed. Figure 35 shows the entire prototype, making it difficult to see some of the minute details, but further figures will show the different aspects. As can be seen from Figure 35, the left portion of the picture shows the three smaller tubes that are used for individual inflation of the balloons. The green, blue, and red stripes towards the middle of the figure are the balloons, wrapped once around the catheter tube.

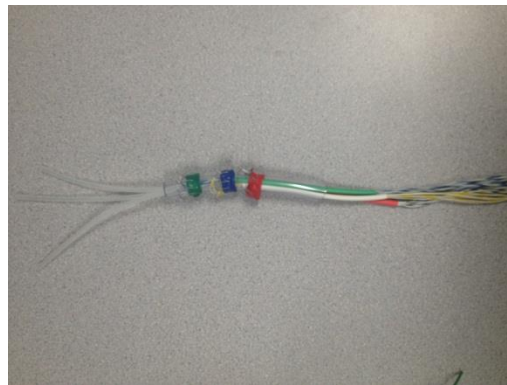


Figure 35 Balloon catheter featuring 8 electrodes on each balloon

On the right side of the figure is a collection of 24 wires. The wires are in collections of eight wires, which are identified by color (eight black, eight blue, eight yellow). Figure 36 shows these wires from a better angle, and one can see that a small thin tube, to maintain separation inside of the catheter, corrals each collection of eight wires. Two holes can be

found underneath each balloon in the design. One hole contains the liquid filling tubes for each balloon, and the other hole contains the eight wires. The wires were fed through the hole and adhered equidistantly around the circular balloon. Figure 37 shows a closer look at the connection of the wire electrodes, which are designed to move freely with the inflation of the balloon and slide in and out of the catheter tube during inflation and deflation. Given the transparency of the catheter tube, Figure 37 shows the tubes as they go from inside of the tube to outside. The yellow wires accurately depict the design concept, which has the wires come out and curl down over the balloon.

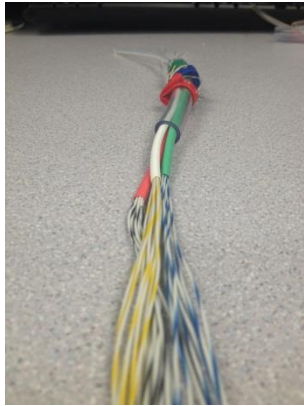


Figure 36 Electrode wires as seen along length of the catheter

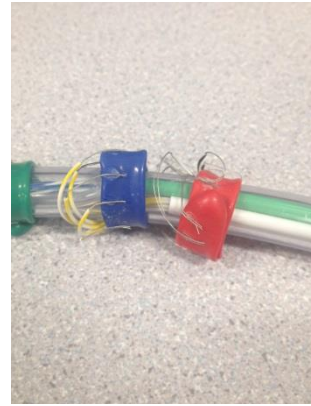


Figure 37 Up close look at electrodes on balloons

The team used a strong adhesive to connect the wire to the balloon and hold it in place. The design should keep the electrode tips in place as the balloon expands and the wire should slide in and out of the catheter as needed.

Chapter 8: Conclusions and Recommendations

The catheter concepts and design that have been developed in this project will be an effective method for mapping and ablating the bladder in cases of severe OAB syndrome. The primary goal of this project was to develop a new catheter design that could be used in the bladder with mechanisms that allow for the catheter to be expandable in size and adaptable, while keeping the mapping electrodes in the same location. Another goal of this project was to develop a perfusion system that could be used to detect electrical activity in the bladder, as well as testing catheter devices prior to animal study. The team completed tests to prove the individual concepts of the catheter design, however, the team was unable to fully manufacture a usable catheter, with all components, for a study. The team accomplished different validation protocols that can be used again for further testing after manufacturing a usable catheter.

The perfusion system that was developed could ideally be used in a more professional setting, a place that has all necessary tools and resources readily available to make the perfusion successful. For example, the ability to obtain pig bladders with the desired vasculature hindered the team because proper cannulation could not occur without arteries that were large enough. If there was a way to obtain a bladder with more specific appendages, such as the distal aorta, cannulation would occur more easily, and therefore, perfusion would be more successful.

There are variables in the design that need to be modified so that the catheter can function to its maximum potential. Our limitations in regard to time, materials and facilities prevented us from manufacturing anything more than an over-sized conceptual prototype, as well as performing various testing. As a result, we have compiled various recommendations for Boston Scientific to continue the development of this device.

One of the more significant recommendations is to conduct testing to confirm and demonstrate that the balloons effectively force the electrodes to maintain contact as the bladder expands. This test can be performed by inserting the catheter into a perfused bladder and then recording the electrical signal. As the electrode comes into contact with the bladder wall, the impedance value recorded will change. As the bladder is filled, the impedance should remain constant if the electrodes maintain contact with the bladder wall as it fill.

The diameter of the catheter must remain between 10 French to 28 French depending on the patient's anatomy and gender of the patient. The French unit conversion is .33 mm to 1 French. The actual diameter of the urethra is 6 mm and can vary between patients. We cannot make the diameter of our catheter wider than 9 mm (Urethra Gauge, 2014). The length is also a consideration, as common catheters now are longer due to access point. This device will be entering through the natural orifice and presumably the length can be shorter. Male and female urethras vary in length, so we must tailor our catheter length to be applied

to both. The length can be between three to four cm in females and up to 20 cm in males (Marieb et. al, 2013).

Another recommendation is to perform ablation testing to demonstrate elimination of the electrical signal using RF energy. The team was limited to using liquid nitrogen to mimic cryoablation to demonstrate that this is possible, but the final device would utilize RF energy to accomplish this task. The same experiment can be performed that the team conducted with the cryoablation technique, simply switching the cryoablation with RF ablation.

After the RF ablation experiment is conducted, we recommend to take histological samples of the ablated tissue and observe the effects of the ablation. Observations can be made from this analysis to determine the total area of tissue affected by the ablation, as well as the ablation depth into the tissue. Additionally, detailed observations can be made to determine if the bladder wall was perforated from the ablation.

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Appendix A: Gantt Chart

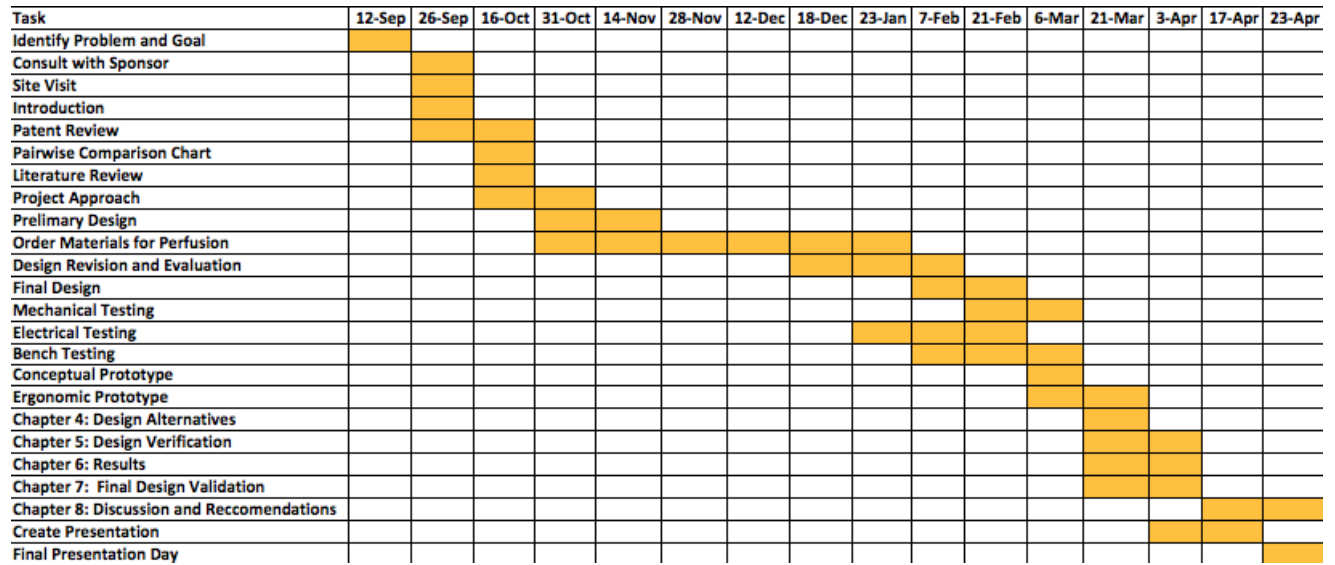


Figure 38 Gantt Chart

Appendix B: Functions Means Chart

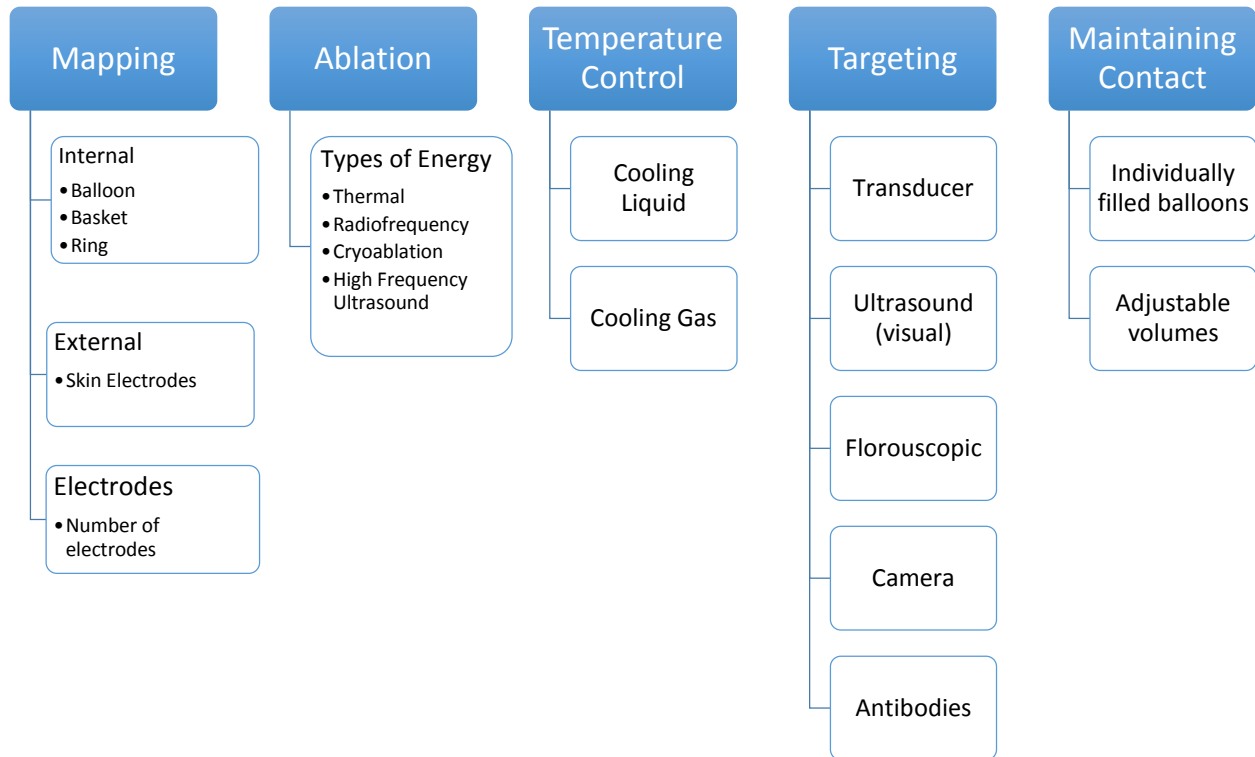


Figure 39 Functions-Means Chart

Appendix C: Krebs Buffer Equations

$$\frac{\text{moles}}{\text{liters}} * \frac{\text{Atomic Mass(grams)}}{\text{moles}} = \frac{\text{grams}}{\text{liter}}$$

$$\frac{.1183\text{moles}}{1L} * \frac{\text{NaCl} \quad 58.443g}{1\text{mole}} = 6.9138 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.0249\text{moles}}{1L} * \frac{\text{NaHCO}_3 \quad 84.0089g}{1\text{mole}} = 2.0918 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.0047\text{moles}}{1L} * \frac{\text{KCl} \quad 74.551g}{1\text{mole}} = .3504 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.00115\text{moles}}{1L} * \frac{\text{MgSO}_4 \quad 120.37g}{1\text{mole}} = .1384 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.00115\text{moles}}{1L} * \frac{\text{KH}_2\text{PO}_4 \quad 136.0728g}{1\text{mole}} = .1565 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.0019\text{moles}}{1L} * \frac{\text{CaCl}_2 \quad 110.984g}{1\text{mole}} = .2109 \frac{\text{grams}}{\text{liter}}$$

$$\frac{.0017\text{moles}}{1L} * \frac{\text{D-glucose} \quad 180.1559g}{1\text{mole}} = 2.1078 \frac{\text{grams}}{\text{liter}}$$

Appendix D: Pressure Experiment 1

Pressure Set Up:

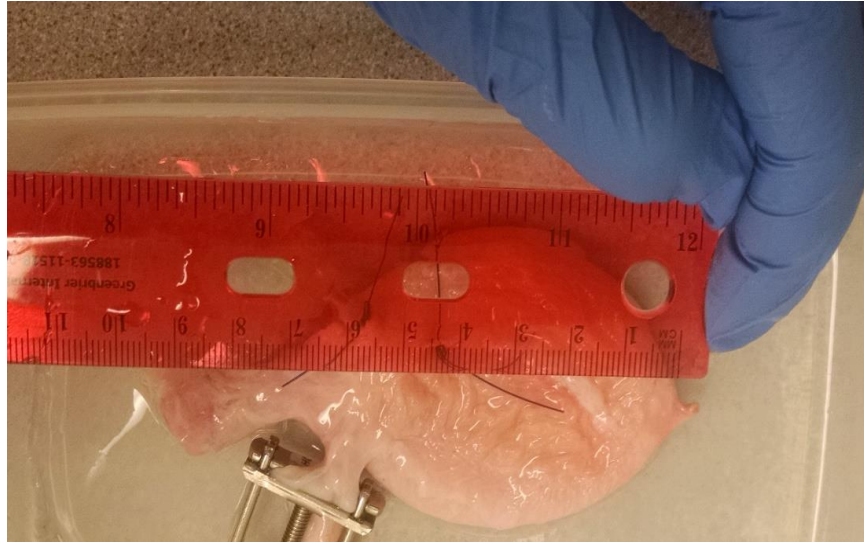


Figure 40: Female Bladder Measurements. Length was 9cm.

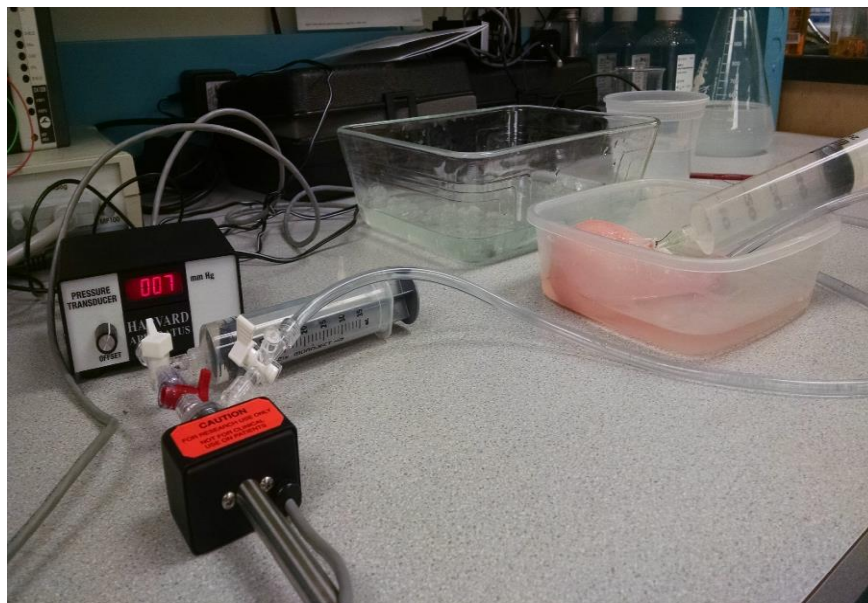


Figure 41: Pressure Test Setup for the Bladder

Results:

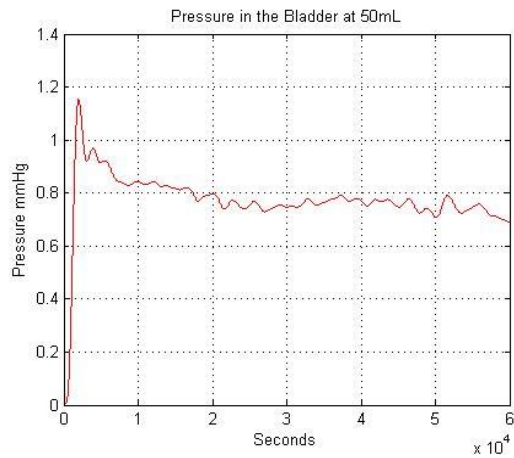


Figure 42: 50mL bladder and corresponding pressure-volume plot

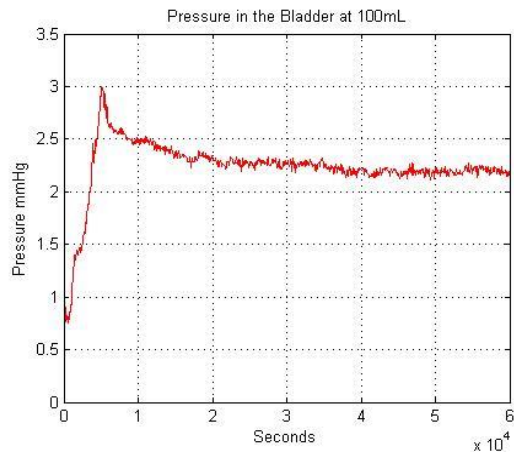


Figure 43: 100mL bladder and corresponding pressure-volume plot

At 100 mL, the acquisition was started before filling the bladder. We can see a sudden change at the time the bladder is being filled. The pressure rises up to 3 mmHg but then drops to 2mmHg and stays the same.

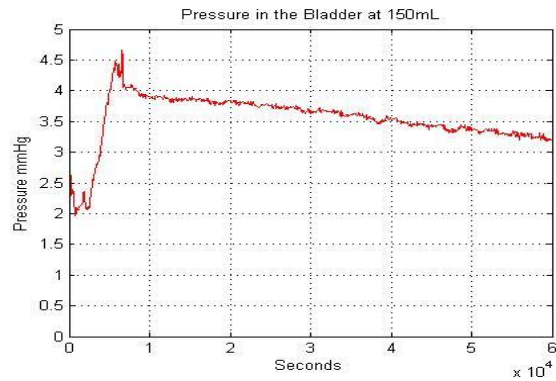


Figure 44: 150mL bladder and corresponding pressure-volume plot

Pressure at 150 mL shares the same features with 100 mL. Again there is a steep increase in the pressure at the beginning but then it drops and stays constant for 5 minutes. The pressure value was 3 mmHg after the 5 minutes.

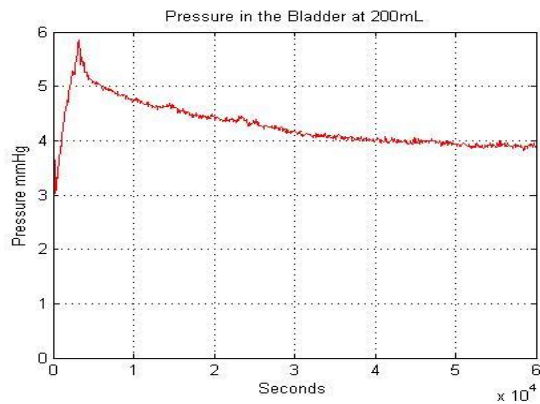
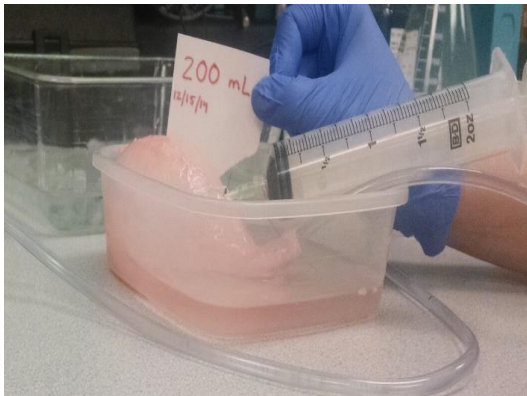


Figure 45: Bladder at 200mL and corresponding pressure-volume plot

At 200 mL the bladder showed the same steep increase at the time of filling as before. The pressure value noted after 5 minutes was 4 mmHg.

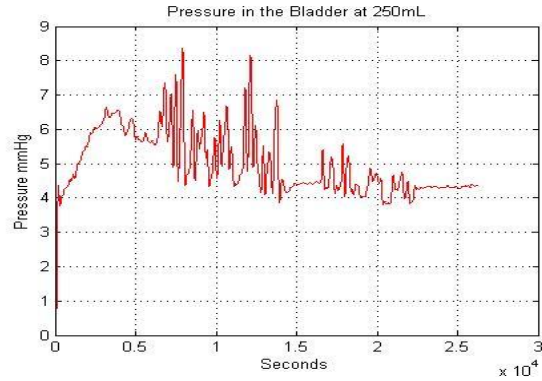


Figure 46: Bladder at 250mL and corresponding pressure-volume plot

At 250 mL, the pressure increased and then decreased to 4mmHg as it was at 200mL. Throughout the middle of the data, we were concerned with a leakage causing the pressure to drop to a constant value so the noise in middle of the data indicates the times we exerted an external pressure on the bladder to check for any leakage.

After making sure that there is not any leakage causing a drop in the pressure of the bladder the experiments continued up to 450 mL. The results displayed the same changes. For every 50 mL, there was a change of 1 mmHg in the pressure.

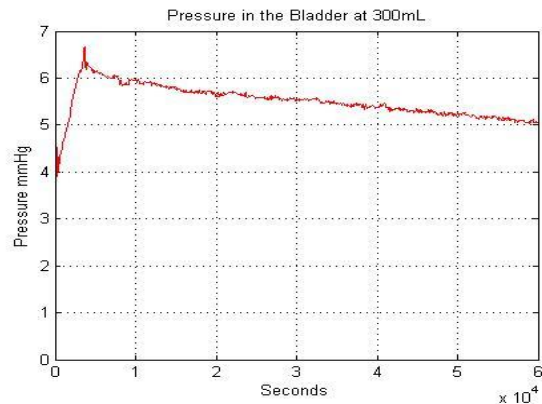
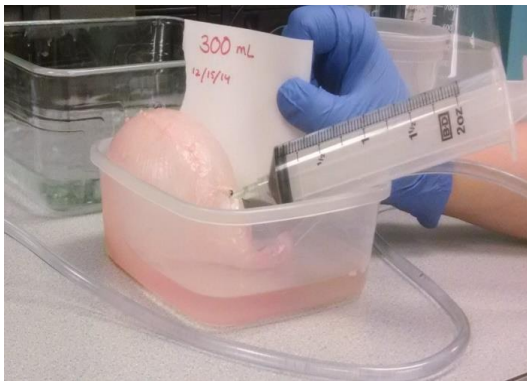


Figure 47: Bladder at 300mL and corresponding pressure-volume plot

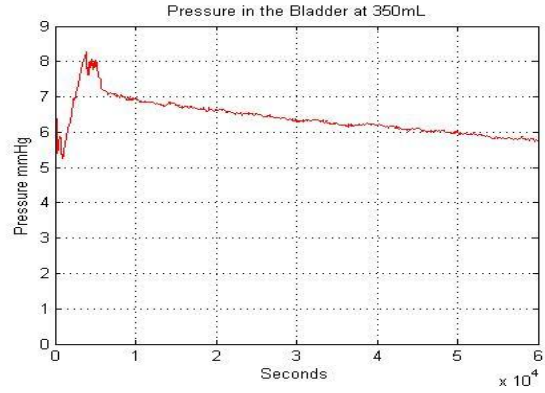
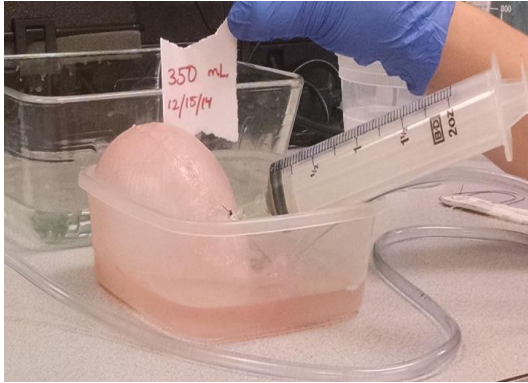


Figure 48: Bladder at 350mL and corresponding pressure-volume plot

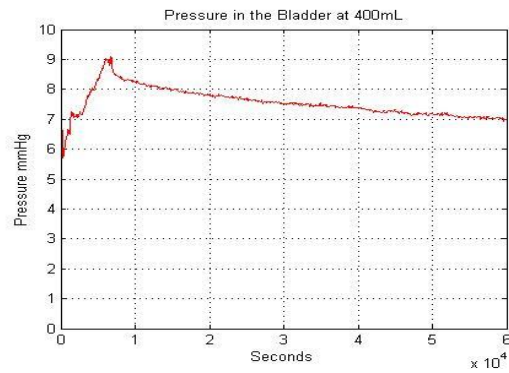


Figure 49: Bladder at 400mL and corresponding pressure-volume plot

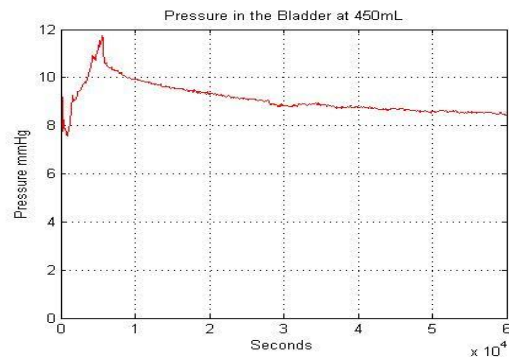


Figure 50: Bladder at 450mL and corresponding pressure-volume plot

Appendix E: Pressure Experiment 2

Bladder Measurements:

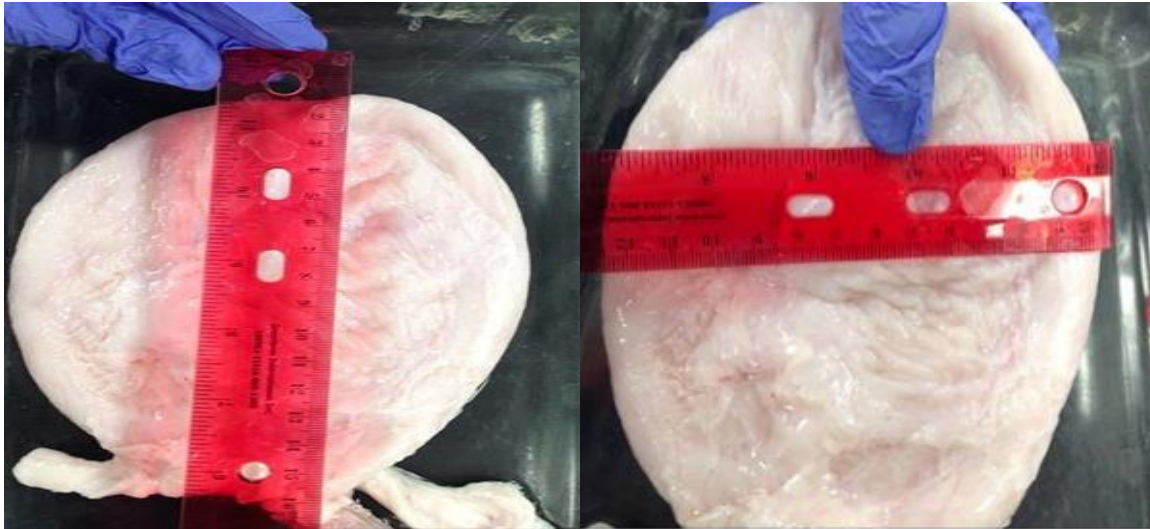


Figure 51 Length of the bladder is 12.5 cm

Figure 52 Length (side-side) = 16.5 cm

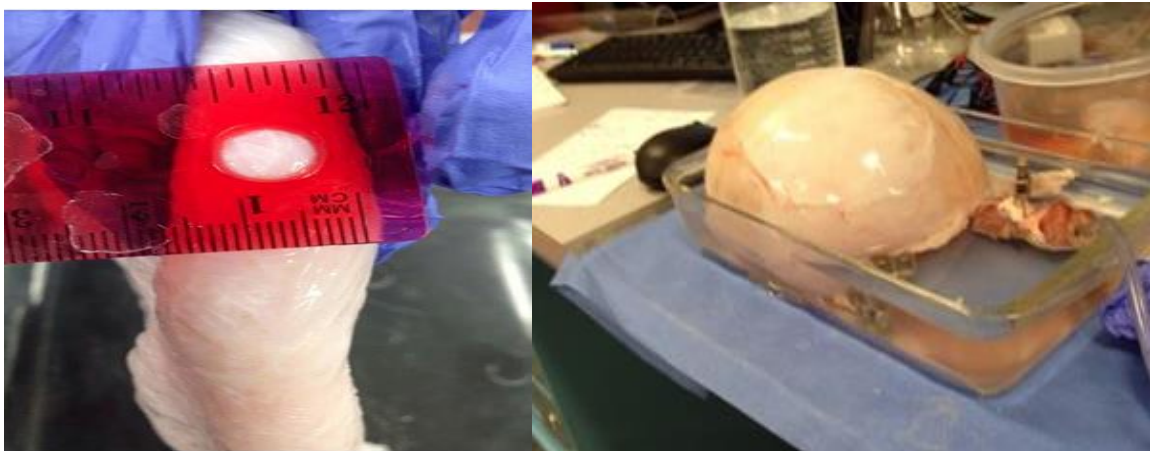


Figure 53 The thickness of the bladder (1.8 cm) and bladder filled with 3 L of saline.

Appendix F: Liquid Nitrogen Ablation Experiment (Cryoablation)

Results:

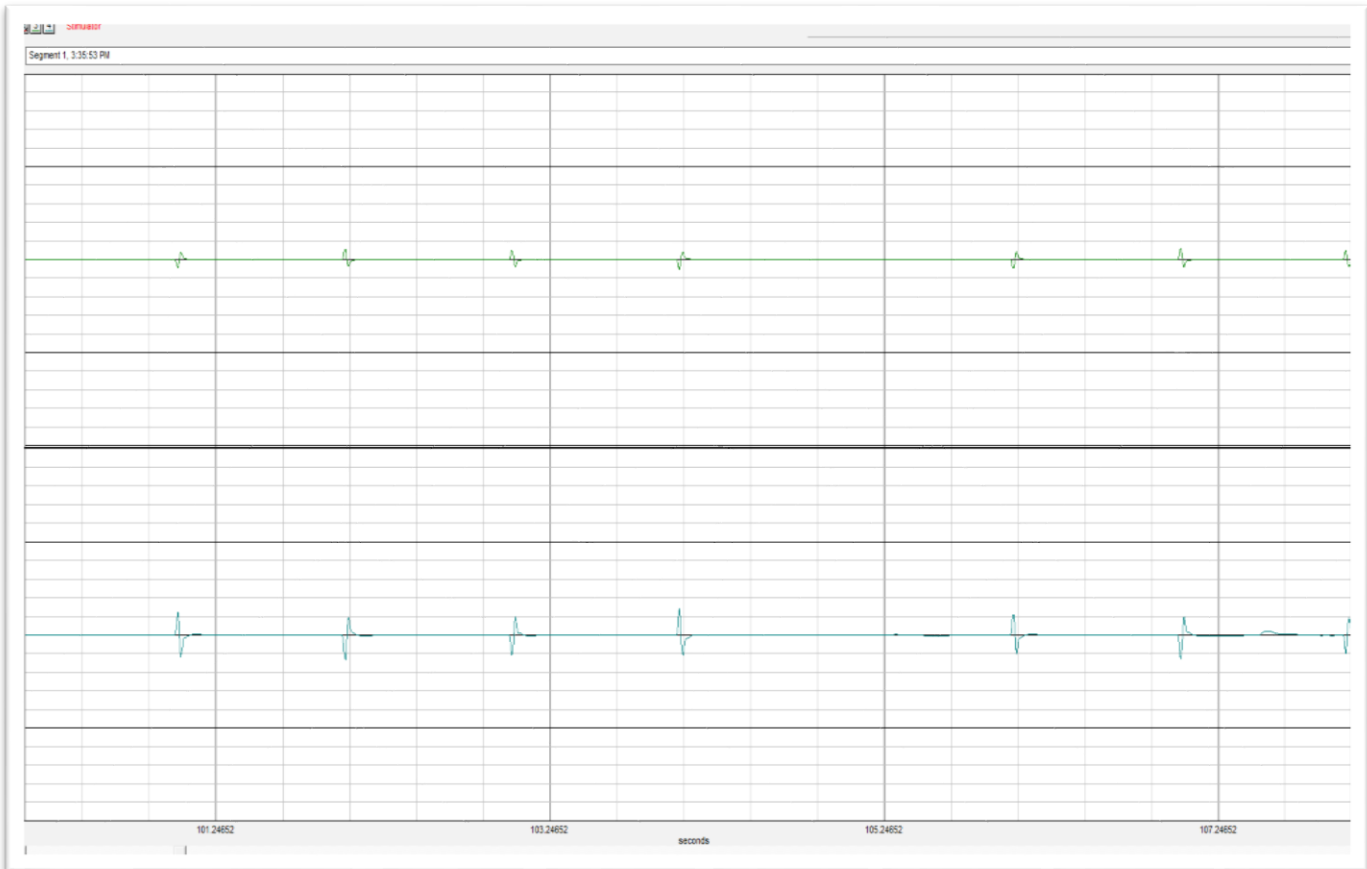


Figure 54 Plot showing the difference between amplitudes of the near (bottom) and further (top) electrodes.

The electrodes were intentionally placed by different distances. The near electrodes pick up more signal than the distant ones.

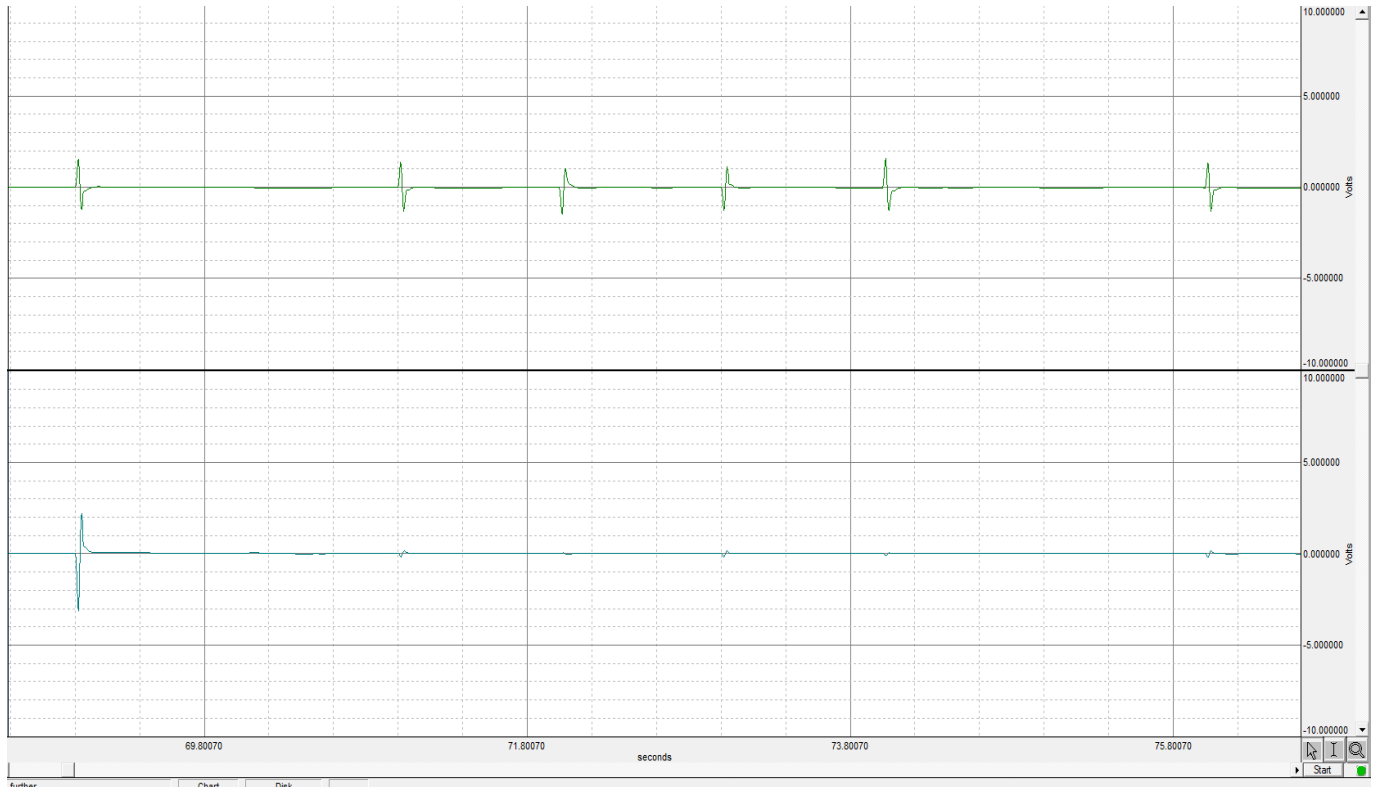


Figure 55 Plot showing the decrease in amplitude after ablation. The top electrode was not affected because the ablation was done around the bottom one.

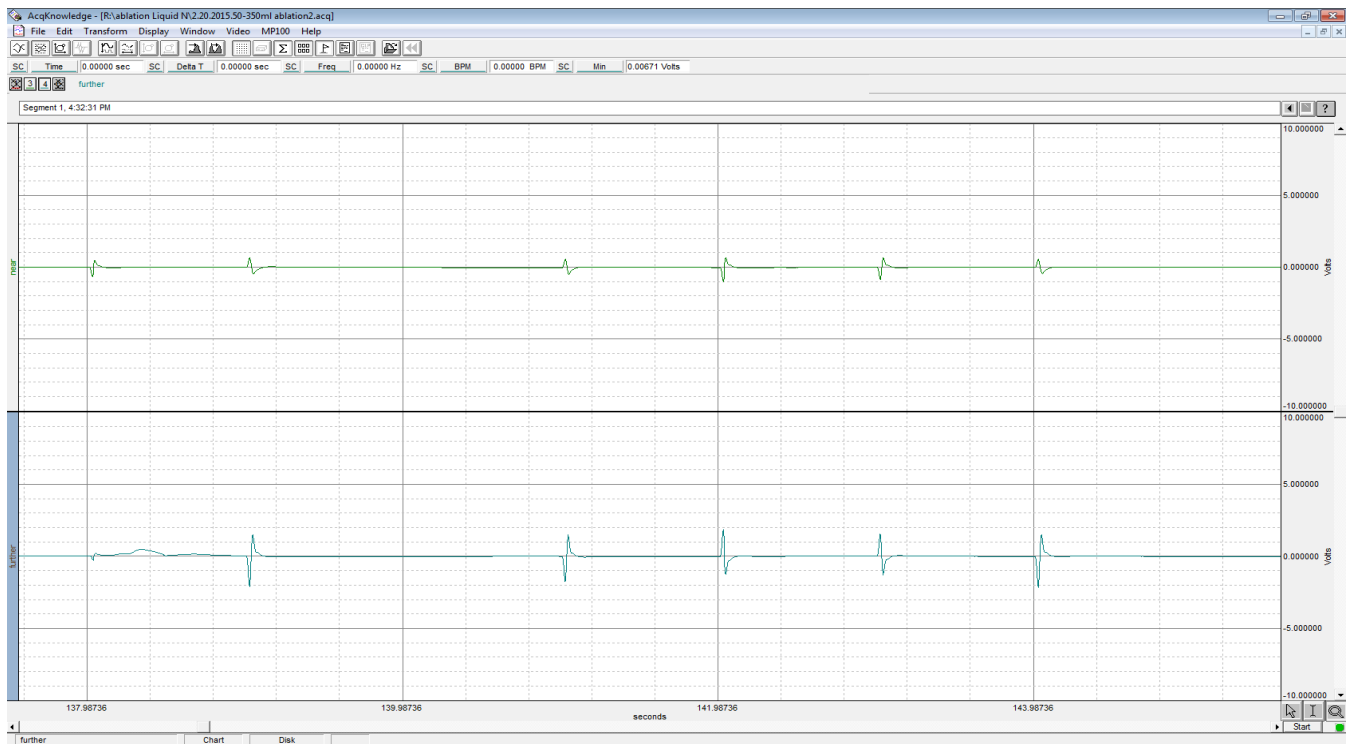


Figure 56 Gain in amplitude after ablation. Signal recovers after a minute.

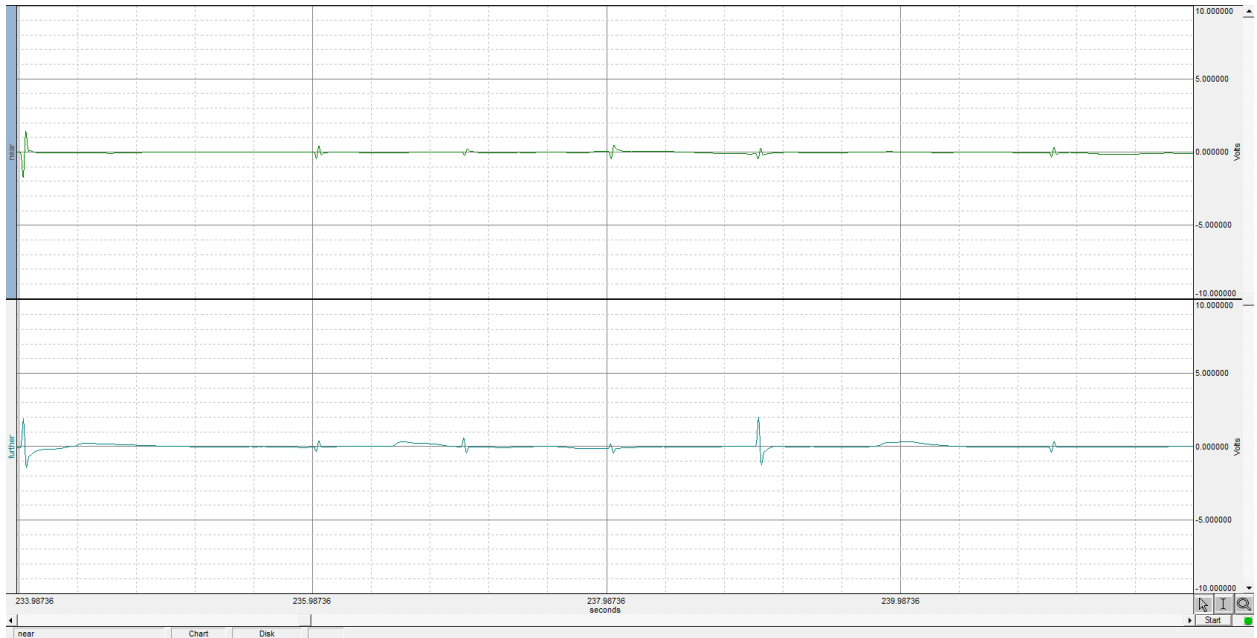


Figure 57 Decrease in amplitude of both electrodes while filling

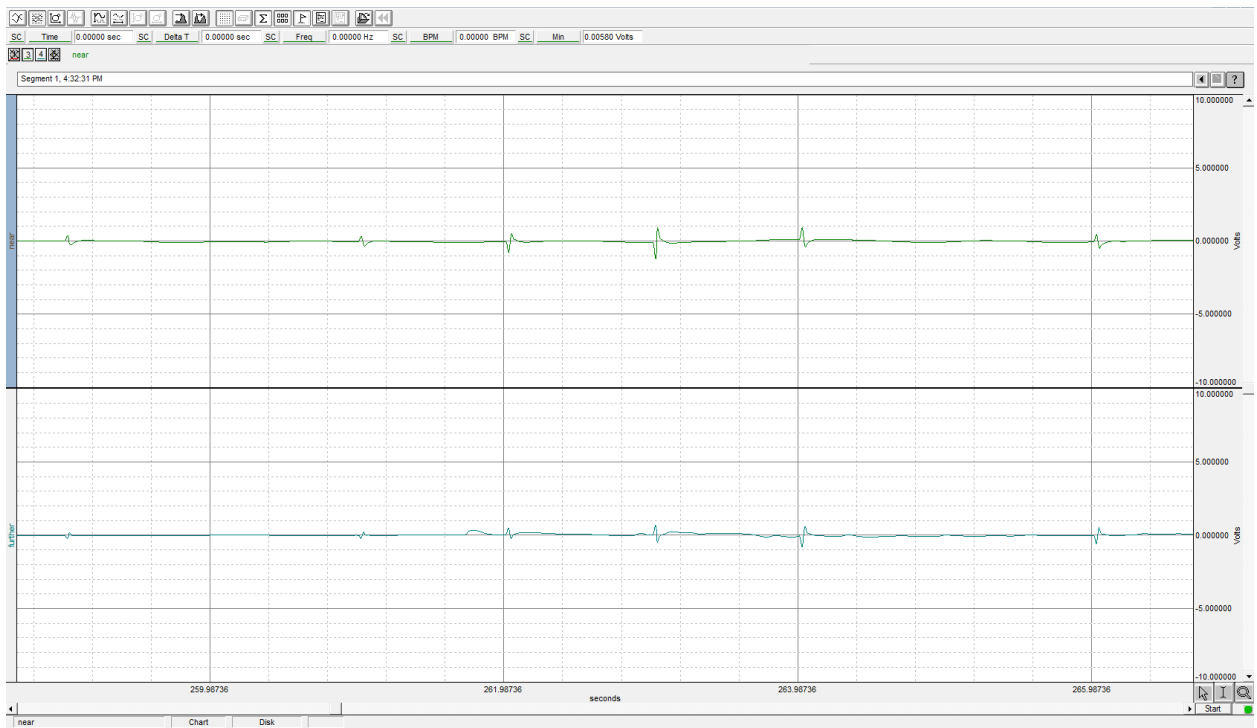


Figure 58 Signal after 30 seconds filling the bladder. The amplitude is recovering again.

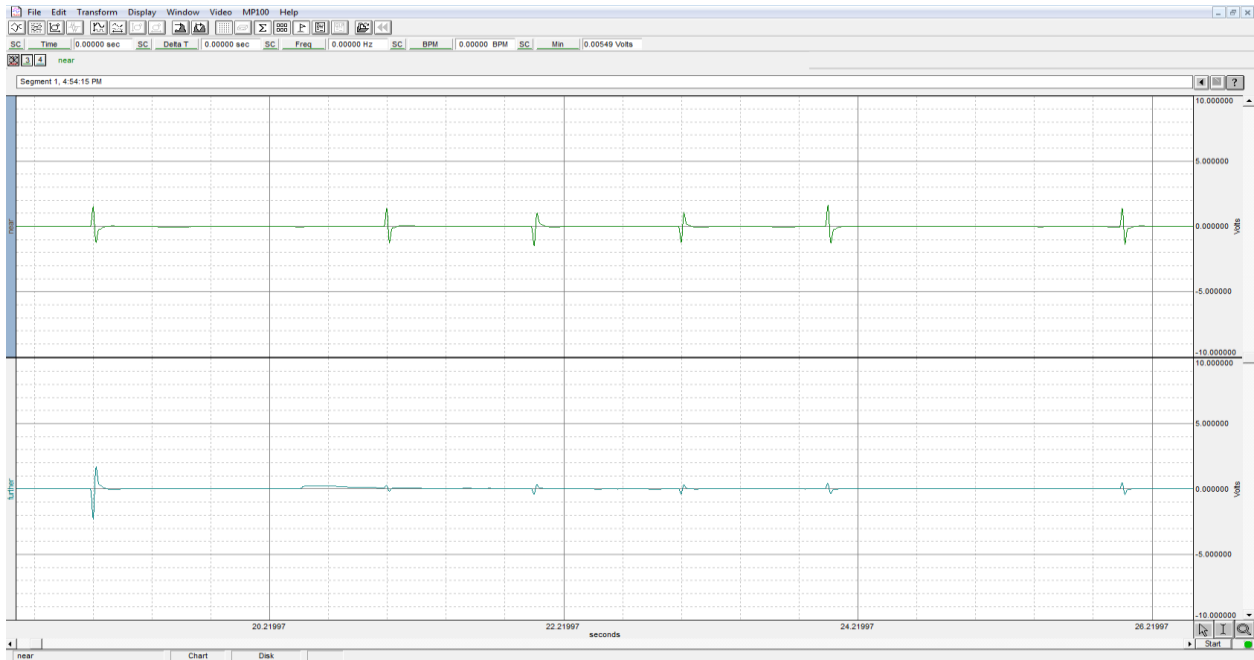


Figure 59 Ablation started at 19s around the further electrodes (bottom) and the signal was blocked.

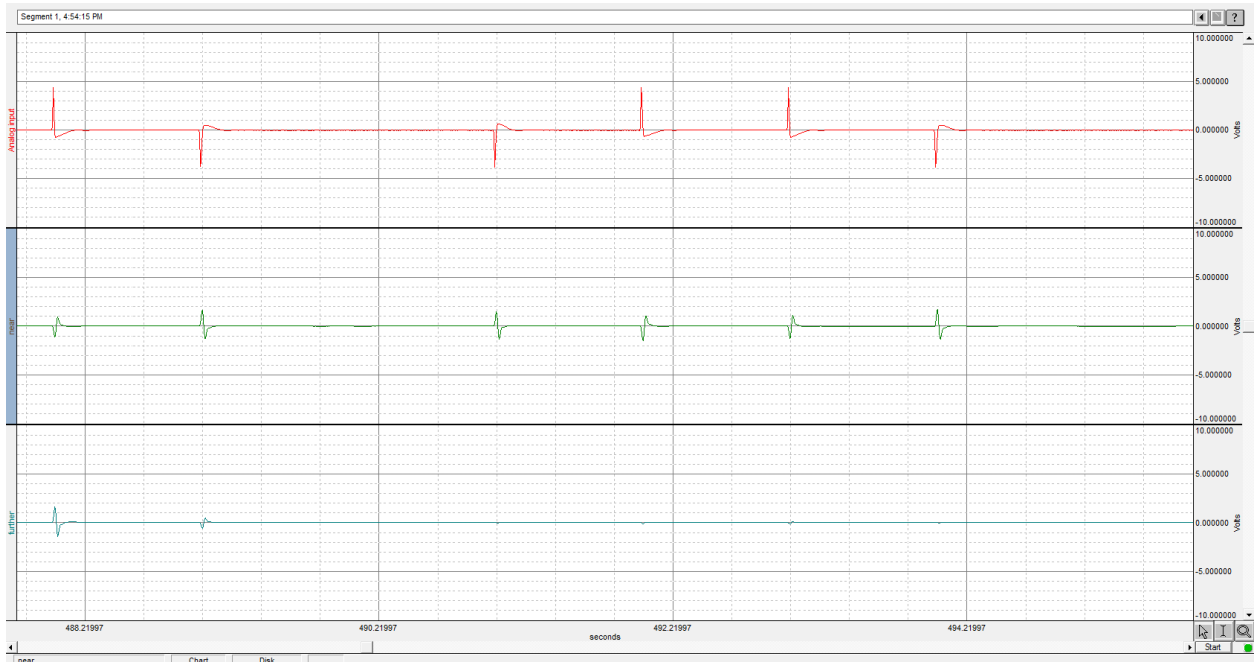


Figure 60 We poured the liquid nitrogen in the middle of further recording electrodes and stimulating electrodes. The lowest signal was observed and the signal was blocked and did not recover.



Figure 61 Dissected Bladder.

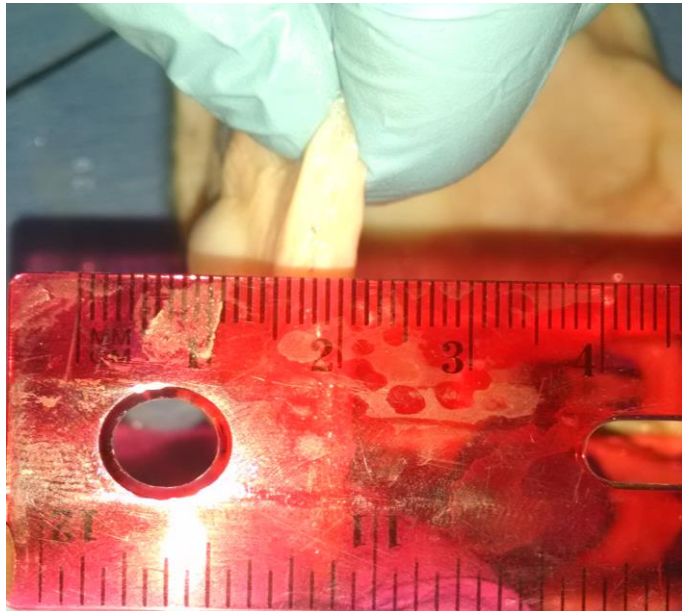


Figure 62 Width of the bubble is 5 mm.

Appendix G: Perfusion Schematic

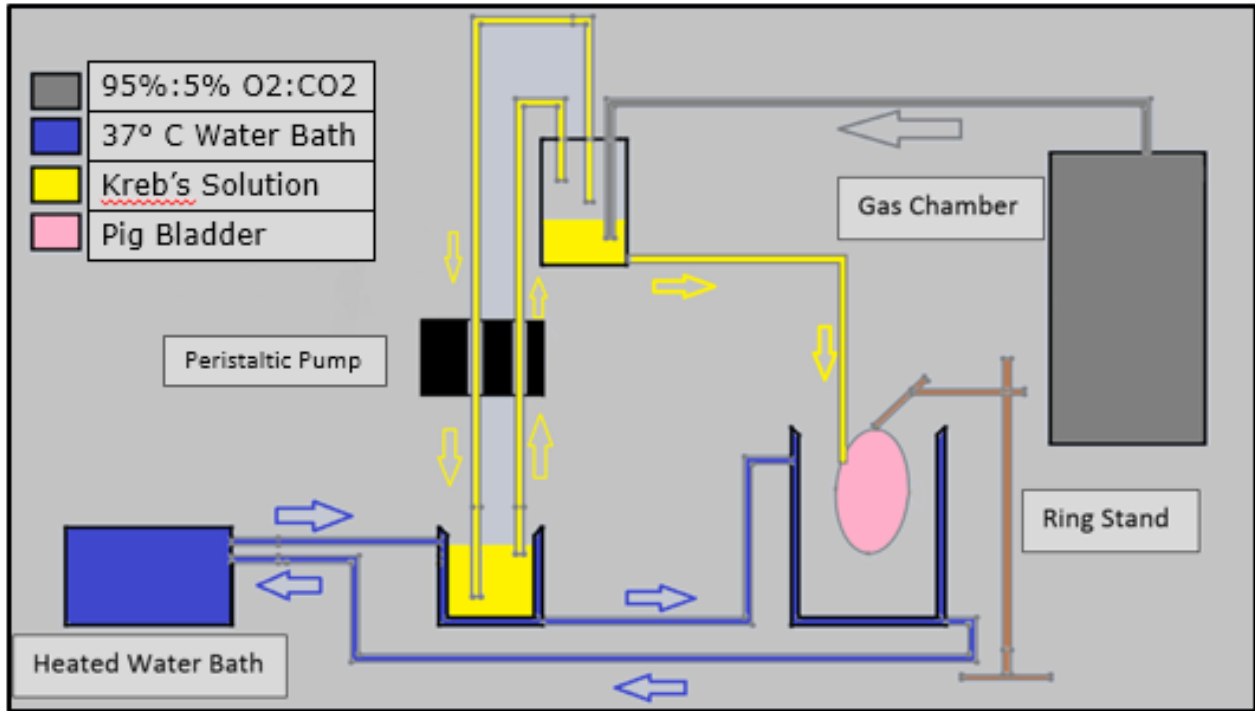


Figure 63 Perfusion Schematic