



## An Implantable Pressure Sensor to Detect the Onset of Bladder Contractions

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# **AN IMPLANTABLE PRESSURE SENSOR TO DETECT THE ONSET OF BLADDER CONTRACTIONS**

**BY  
JACOB MELGAARD**

DISSERTATION SUBMITTED 2016



**AALBORG UNIVERSITY**  
DENMARK



# An Implantable Pressure Sensor to Detect the Onset of Bladder Contractions

Ph.D. Thesis by  
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January 2016

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## Preface

This thesis is based on work carried out from September 2006 to September 2012 at the Center for Sensory-Motor Interaction (SMI) at Aalborg University. The work was made possible by a grant from the Danish National Advanced Technology Foundation.

## Acknowledgements

First, I would like to thank my supervisor Nico Rijkhoff for his support and guidance throughout the extended period of this work. Next, I will express my deepest gratitude to Dorthe Deding, for demonstrating the experimental procedure for exposing the pelvic nerve in the pig model. Without this help, the work would not have been possible. I am also grateful to the Torben Madsen, Ole Sørensen and Jens Sørensen at the Biomedical Lab of Aalborg Hospital, where the animal experiments were carried out. Their help and advice with the experiments is highly appreciated. Morten Fjorback and Thomas Borup from Neurodan A/S are also acknowledged for help and advice regarding the animal experiments. Last, but not least, I would like to thank my wife, Line, and my sons, Walther and Karl, for their love, patience and support throughout this project.

Jacob Melgaard, Jan 2016





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- **Melgaard, J**; Rijkhoff, NJM: "Detecting Urinary Bladder Contractions: Methods and Devices." *Journal of Sensor Technology*, **4**, 165-176, 2014 (doi: [10.4236/jst.2014.44016](https://doi.org/10.4236/jst.2014.44016)).
- **Melgaard, J**; Rijkhoff, NJM: "Detecting the onset of urinary bladder contractions using an implantable pressure sensor." *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, Vol: 19(6), pp. 700-708, 2011.

### *Journal papers (submitted)*

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### *Peer-reviewed conference abstracts*

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- **Melgaard, J**; Rijkhoff, NJM: "An implantable pressure sensor to detect the onset of urinary bladder contractions." *Neurourology and Urodynamics*, Vol: 30(6), pp. 934-936, 2011.
- **Melgaard, J**; Rijkhoff, NJM: "Detecting the onset of bladder contractions." In: *Proceedings of the 28<sup>rd</sup> Annual Meeting of the Danish Biomedical Society*, 21-23 September, Brædstrup, Denmark, 2010.

*Popular Science*

- **Melgaard, J;** Rijkhoff, NJM: “En neural protese mod inkontinens.” Medicinsk Teknologi & Informatik, Vol: 8(1), pp. 8-10, 2011. (In Danish)

## English Summary

A wide range of conditions such as spinal cord injury, multiple sclerosis, Parkinson's disease, stroke and several others may lead to neurogenic detrusor overactivity (NDO). NDO is characterized by involuntary detrusor contractions during the filling phase. In layman terms, the nerves or brain centers controlling the bladder are damaged, resulting in loss of bladder control. In most patients, detrusor-sphincter-dyssynergia, which is the concurrent contraction of the detrusor and the urethral sphincter, also develop. Despite of concurrent sphincter contractions, involuntary detrusor contractions may lead to both incontinence episodes and to vesicoureteral reflux, which in the long term can cause renal failure.

It has been shown that involuntary detrusor contractions can be abolished by electrical stimulation of the dorsal genital nerve (DGN). While DGN stimulation can be applied continuously, it may be painful, the reflex loop may habituate to stimulation, and the bladder fullness is unknown. These problems can be overcome by using a sensor to detect the onset of bladder contractions, and use a scheme known as conditional stimulation. In this scheme, stimulation is only applied at the onset of contractions, and this offers a number of advantages. Firstly, a larger capacity than when using continuous stimulation can be obtained. Secondly, the charge injection is reduced, and so is the risk of habituation of the reflex loop. Thirdly, a warning signal can be issued to the patient, informing that it is time to empty the bladder when convenient.

However, for this type of conditional stimulation to work, a sensor capable of robustly detecting the onset of involuntary contractions is needed. Using a transurethral catheter it was demonstrated that intravesical pressure can be used to determine the onset of contractions. This project focused on the development and experimental test of an implantable pressure sensor, which would enable a complete implantable neuroprosthesis for treating NDO. In an acute animal model ( $n=6$ ) implantable pressure sensors were placed in the bladder wall. The signals obtained from these sensors were as good as intravesical pressure measured using a transurethral catheter and external equipment in detecting the onset of contractions. In chronic animal models ( $n=4$ ), signals from implantable sensors could be obtained only for up to three weeks. Improvements of the sensor towards long-term implantation may improve these figures. In conclusion, using an implantable pressure sensor to detect the onset of detrusor contractions is feasible; for chronic applications further development of the sensor is needed.



## Dansk Resumé

En lang række lidelser så som rygmarvsskade, sklerose, Parkinsons og cerebrovaskulære blodpropper kan føre til neurogen overaktiv blære (NDO). NDO er kendetegnet ved ufrivillige blæresammentrækninger i fyldningsfasen. I lægmandstermer kan man sige, at de nerver, eller de centre i hjernen som styrer blæren, ødelægges, og dermed mistes kontrollen med blæren. De fleste med NDO udvikler også detrusor-sphincter-dyssynergi, hvilket vil sige samtidige sammentrækninger af både blæremusklen (detrusoren) og lukkemusklen (sphincteren). Til trods for denne samtidige sammentrækning af sphincteren, kan ufrivillige blæresammentrækninger føre til både inkontinens og til at urin presses tilbage i nyrerne, hvilket på sigt kan forårsage nyresvigt.

Man har vist at man ved at påføre penis- eller klitorisnerven (engelsk: dorsal genital nerve, DGN) elektrisk stimulation kan stoppe eller undertrykke ufrivillige blæresammentrækninger. Man kan i princippet påføre DGN elektrisk stimulation kontinuerligt, men det kan være smertefuldt, refleksbanen kan vænne sig til stimulationen (hvorved effekten går tabt), og den relative fyldning af blæren er ukendt. Disse problemer kan forhindres ved at bruge såkaldt behovsstyret stimulation. Her bliver stimulation kun påført i begyndelsen af de ufrivillige blæresammentrækninger, hvilket stadig får blæren til at slappe af. Man opnår dog også en række andre fordele. For det første kan man opnå større fyldning med denne metode end med kontinuerlig stimulation. For det andet reduceres mængden af tilført strøm, og risikoen for tilvænnning af refleksbanen reduceres ligeledes. For det tredje kan man give brugeren en advarsel om at blæren nu er ved at være fuld, og at vedkomne bør tømme den ved førstkomne lejlighed.

For at kunne udføre behovsstyret stimulation er det nødvendigt med en sensor, som på en robust måde kan registrere begyndende blæresammentrækninger. Det er med urinvejskatetre vist, at man kan bruge blæretryk til at registrere sammentrækninger, og dermed til at styre stimulationen. I dette projekt har der været fokuseret på udvikling og eksperimentel test af en implanterbar tryksensor, som potentielt kunne gøre det muligt at lave et fuldt implanterbart system til behandling af NDO. I akutte griseforsøg ( $n=6$ ) blev implanterbare tryksensorer indsat i blærevæggen. Signalerne fra disse sensorer var lige så gode som blæretryk målt med et urinvejskateter til at registrere blæresammentrækninger. I kroniske forsøg ( $n=4$ ) kunne signaler fra de implanterede sensorer kun måles i op til 3 uger. Det forventes at dette vil kunne forbedres med sensorer forbedret med kronisk implan-

tation for øje. Som konklusion kan siges at brugen af en implanterbar tryksensor til at registrere blæresammentrækninger er mulig, dog er yderligere udvikling påkrævet før sådan en sensor kan benyttes som kronisk implantat.

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# Chapter I

## Introduction

### I-1 Background and purpose

Voluntary control of the bladder is learned during early childhood, and is so integrated into daily life that it occurs mostly on a sub-conscious level. And while the basic on-off function of the bladder might seem simple, neural control is complex and distributed, and consequently, many conditions may lead to loss of control.

In clinical terms, Overactive Bladder (OAB) is defined as “urgency, with or without incontinence, usually with frequency and nocturia” [1]. Patients with this syndrome may receive an urodynamic examination with the purpose establishing a diagnosis. Detrusor Overactivity (DO) is a diagnosis, based on urodynamic examination, characterized by involuntary detrusor contractions during the filling phase. If the cause of DO is determined to be a neurological disorder, the diagnosis is termed neurogenic detrusor overactivity (NDO).

Thus, NDO is the loss of voluntary control of the bladder due to neural lesions, causing frequent involuntary bladder contractions. It develops in most patients with spinal cord injury (SCI), multiple sclerosis (MS) and Parkinson’s disease (PD) [2]. It can also be caused by congenital defects such as spina bifida. Additionally, stroke may cause NDO, although the exact neurological cause is still debated [2].

The field of bladder management is relatively new. SCI, for instance, was practically fatal until the 2<sup>nd</sup> World War. After the war survival increased dramatically, but until the introduction of “Clean Intermittent Self Catheterization” (CISC) in the 1970’s, kidney failure caused by poor management of NDO was the primary cause of death in this patient group [3, 4]. Now, life expectancy is much longer, and management has changed from life-saving to improving the quality of life, and maximizing the independence of the patients. Individual patient needs differ, but most people with SCI rank bladder and bowel function and sexual function and much higher than for instance walking [5]. This demonstrates the significant morbidity caused by the condition. There is no data available on the total cost of NDO [6]. OAB and incontinence in general are two related symptoms, however, less severe, with higher prevalence and lower cost per patient. In 1995, the societal cost of incontinence (both urgency and stress incontinence) for individuals aged 65 years

or older was found to be \$26.3 billion in USA alone [7]. In 2000, the direct cost of medication, supplies and care related to OAB was estimated to be \$12 billion, also in USA [8]. It was found that in the USA, the cost to treat NDO with conventional therapy was approximately \$100.000 for 10 years, and that by using a neural prosthesis, this cost could be halved [9]. With a prevalence of SCI patients in the USA of 150.000 (see section I-4 in this chapter for further details), this means a potential saving of \$7.5 billion during a 10 year period, just for SCI patients. The prevalence of NDO will be looked at more thoroughly in section I-4 of this chapter.

One treatment option is a neural prosthesis that applies stimulation to the penile or clitoral nerve at the beginning of involuntary bladder contractions. This abolishes the contraction and maintains continence for the patient. However, it requires a sensor that is able to detect the onset of bladder contractions.

The aim of this thesis is to investigate whether chronic bladder sensing is possible using an implantable pressure sensor placed in the bladder wall. This could enable a neural prosthesis based on on-demand nerve stimulation.

The rest of this first chapter details the anatomy of the lower urinary tract, the pathophysiology of NDO, and the conservative treatment options. At the end of the chapter, neural prosthesis for treating NDO are described. The second chapter is a review of state-of-the-art sensing techniques, together with a discussion of the most promising techniques. The third chapter describes the investigation of whether a wired pressure sensor in the bladder wall could be used to detect bladder onset in an acute animal model. The fourth chapter follows with corresponding chronic animal model experiments. The fifth chapter describes analysis and design of a passive wireless implantable pressure sensor. Finally, the thesis is concluded with a chapter containing a discussion of the obtained results, future perspectives of the research, and summarizing remarks.

## I-2 The Lower Urinary Tract

### I-2.1 Anatomy

The urinary tract consists of the kidneys, ureters, bladder and outlet. The kidneys produce droplets of urine, which are led by the ureters down and into the bladder. The role of the bladder is low pressure storage and periodical release of the urine. The outlet consists of the urethra, and the internal and external sphincters. The sphincters, together with the smooth muscle of the urethra, functions to open or close the outlet as desired. The kidneys and ureters are referred to as the upper urinary tract (UUT), while the bladder and the outlet is termed the lower urinary tract (LUT). The anatomical details of the UUT are outside the scope of this thesis. The anatomy of the LUT is illustrated in Figure 1.

The bladder consists of three layers. The inner layer is the urothelium, which is a specially adapted epithelium lining the inside of the bladder. The middle layer of the bladder consists of smooth muscle, and is termed the detrusor. The outer layer is a fascia termed the serous coat. The outlet consists of the urethra, the internal urethral sphincter (IUS) and the external urethral sphincter (EUS). The IUS is placed

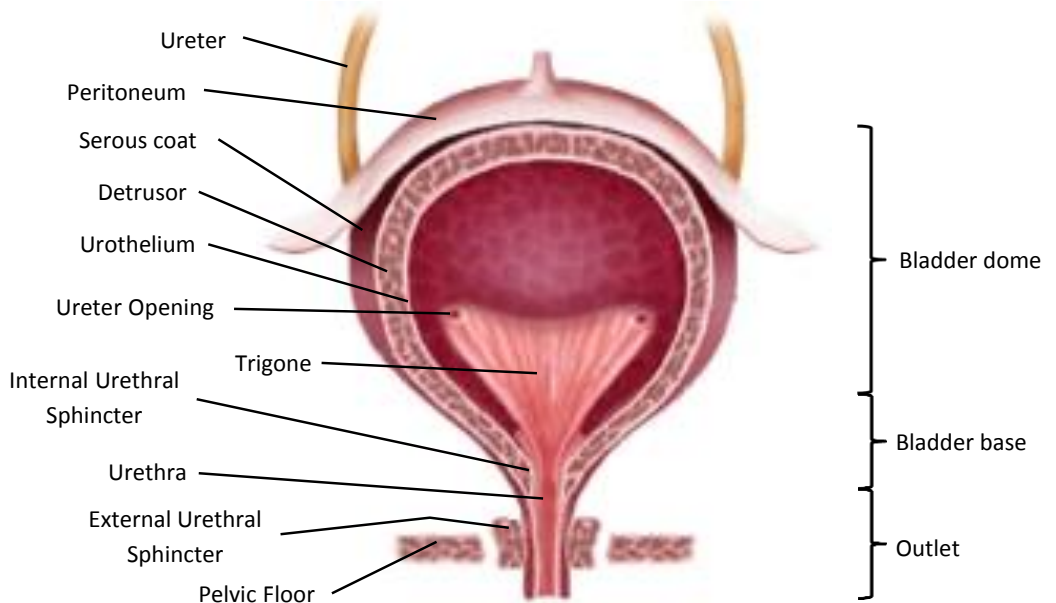


Figure 1: Anatomy of the Lower Urinary Tract (LUT).

at the junction between the bladder and the urethra, while the EUS is placed more distal at the same level as the pelvic floor. The pelvic floor musculature is not part of the urinary tract, but supports the LUT, and can work synergistically with the sphincters to maintain continence.

### **I-2.2 Neuroanatomy and physiology**

Peripheral innervation of the bladder originates from the thoracic, lumbar and sacral segments of the spinal cord. Anatomically, the bladder and urethra are visceral organs, and are innervated by branches of the autonomous nervous system. The external urethral sphincter (EUS), however, is under direct voluntary control and is innervated by somatic fibers.

#### ***Overview***

The LUT has 2 functions, storage and periodical elimination of urine. These two are mutually exclusive; the system works in an on-off fashion. During storage, afferent sensory information about bladder distension is conveyed to the CNS as the bladder fills. At some critical point, the input becomes so strong that reflex voiding occurs. During normal voiding, positive feedback from flow-receptors in the urethra act to augment the bladder contraction to ensure complete emptying of the bladder with no post-void residual urine. When voluntary control of micturition is learned, tonic input from higher brain centers act to suppress the reflex, until at some point this is no longer possible, or voiding is initiated voluntarily.

#### ***Efferent innervation of the LUT***

The detrusor is commonly said to be innervated by the hypogastric nerve, and the pelvic nerve. The hypogastric nerve is a sympathetic nerve originating at the T<sub>10</sub>-L<sub>2</sub> level of the spinal cord. Fibers run from the spinal cord, through the inferior mesenteric plexus, and either via the hypogastric nerve trunk to the bladder dome, or through the pelvic plexus to the bladder base and urethra [10, 11]. The fibers are active in the storage phase; their mechanism of action is the release of Nor-Epinephrine (NE), which binds to  $\beta_3$ -adrenergic receptors of the detrusor, causing the detrusor to relax, and which binds to  $\alpha_1$ -receptors in the urethra, causing contraction. The pelvic nerve is a parasympathetic nerve originating at the S<sub>2</sub>-S<sub>4</sub> level of the cord; the fibers run through ganglia in the pelvic plexus, or in the bladder wall. Post-ganglionic fibers originating these two places constitute the parasympathetic innervation of the bladder. They act by releasing Acetyl-Choline (ACh) that binds to M<sub>3</sub>-receptors, causing detrusor contraction. The urethra is also innervated by parasympathetic fibers; they cause relaxation by releasing nitric oxide (NO). Thus, although it simplifies the matter, strictly speaking one cannot say the bladder is inner-

**Table 1:** Schematic representation of the *efferent* nerve activity and corresponding action during storage and voiding. Nerves that are shown in light grey are inactive. EUS: External Urethral Sphincter; IUS: Internal Urethral Sphincter; ACh: Acetyl-Choline; NE: Nor-Epinephrine; NO: Nitric Oxide; N: Nicotinic receptor.

	Part of Nervous System	Nerve	Level of origin	End organ	Neuro-transmitter	Recep-tor	Function
Storage	Somatic	<b>Pudendal</b> nerve	S <sub>2</sub> -S <sub>4</sub>	EUS	ACh	N	Contraction
	Sympathetic	<b>Hypogastric</b> nerve	T <sub>10</sub> -L <sub>2</sub>	Detrusor Urethra/IUS	NE NE	β <sub>3</sub> α <sub>1</sub>	Relaxation Contraction
	Parasympathetic	<b>Pelvic</b> nerve	S <sub>2</sub> -S <sub>4</sub>	Detrusor			
Voiding	Somatic	Pudendal nerve	S <sub>2</sub> -S <sub>4</sub>	EUS			
	Sympathetic	Hypogastric nerve	T <sub>10</sub> -L <sub>2</sub>	Detrusor Urethra/IUS			
	Parasympathetic	<b>Pelvic</b> nerve	S <sub>2</sub> -S <sub>4</sub>	Detrusor Urethra	ACh NO	M <sub>3</sub>	Contraction Relaxation

vated by the hypogastric or the pelvic nerve, but by sympathetic and parasympathetic fibers running in these nerve trunks, at least part of the way.

Contrary to the rest of the LUT, which is under autonomic control, the EUS is innervated by somatic fibers. They originate at the S<sub>2</sub>-S<sub>4</sub> level of the spinal cord, and run via the pudendal nerve to the EUS. They act by releasing ACh that binds to nicotinic receptors, causing contraction. A schematic view of the neuroanatomy of the LUT is shown in Figure 2.

In healthy persons, the storage phase is characterized by synergistic activity of hypogastric nerve fibers to relax the detrusor muscle and hypogastric and pudendal nerve fibers to contract the sphincters. This ensures low pressure continent storage. In the voiding phase of the micturition cycle, efferent activity in these nerves ceases, and the efferent fibers of the pelvic nerve become active, causing detrusor contraction. This is summarized in Table 1.

### ***Afferent innervation of the LUT***

Sensory afferent fibers run in all three nerves (hypogastric, pelvic, pudendal). Sensory Aδ-fibers originating from the bladder wall relay wall distention information to the CNS. These fibers run mainly in the pelvic nerve, but also in the hypogastric nerve [10, 12]. In addition, C-fibers carry information about noxious or chemical

stimuli [13]. Since they do not respond to distention, these fibers are called ‘silent C-fibers’ in healthy. The urothelium has been found also to play a role in the sensory and signaling properties of the bladder. In the suburothelial layer, a network of sensory fibers was identified together with a layer of interstitial cells, dense at the bladder neck, and sparse at the bladder dome. Further, from the suburothelial neural network, terminal fibers were found to project into the urothelium. The urothelium, in turn, was found to contain both a range of different receptors, and the ability to release neurotransmitters such as ATP and ACh. It is believed, that the urothelium, the interstitial cells, afferent nerves and smooth muscle might collectively act as the stretch-receptor organ of the bladder [12, 14, 15], although the precise mechanism of action is still not well established.

### *Central centers involved in bladder control*

In voluntary voiding, the decision to void is believed to be made in the prefrontal cortex; the signaling probably also includes the anterior cingulate cortex, the thalamus, the hypothalamus, the basal ganglia and cerebellum [12]. Although several higher centers are involved, they merely control whether to store, or to void. The

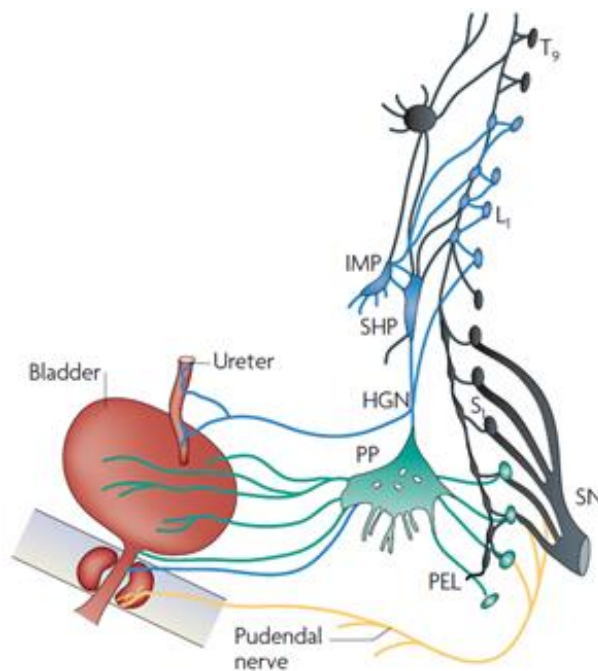


Figure 2. Innervation of the Lower Urinary Tract (LUT). From Ref. [1] with permission.

area believed to be responsible for the transition between the phases is the Periaqueductal Grey (PAG). In the pons there is functional imaging evidence of two distinct centers: a lateral center commonly termed the Pontine Storage Center (PSC), and a medial center termed the Pontine Micturition Center (PMC). The role of the PSC is not clear; it might simply help to facilitate the storage 'reflex' by adding excitatory input to the reflex loop. When the decision to void has been made, the PAG activates the PMC. This causes a sequence of actions. Firstly, an inhibitory effect on the pudendal nerve is asserted, causing the EUS to relax. Then, the activity of the hypogastric nerve is inhibited, simultaneously with excitatory input to the pelvic nerve. This causes the outlet to open, and the detrusor to contract. Flow receptors in the urethra activate an additional positive feedback spinal reflex arch, augmenting the detrusor contraction until the bladder has been completely emptied. In the storage phase, tonic suppression of the PAG from the higher brain centers prevents activation of the PMC. When, at a socially acceptable time and place voiding is desired, this suppression is interrupted, and the PAG provides excitatory input to the PMC, initiating voiding and suppressing the storage reflex until the bladder is empty.

### **I-3 Etiology and Pathophysiology of NDO**

Most of the time is spent in the storage phase; about 23 hours and 40 minutes each day. Consequently, disorders related to the storage phase have the largest impact on patients. As mentioned previously, NDO can be caused by SCI, MS, Parkinson's disease and stroke [2]. It is also often present in patients with spina bifida [16]. Other diseases that are characterized by neural lesions or degeneration may also lead to NDO. Most patients with NDO also develop detrusor sphincter dyssynergia (DSD) [17-19]. DSD is the concurrent contraction of the detrusor and the sphincter, which causes high transient intravesical pressures. Despite the activation of the outlet, incontinence episodes may also occur.

To patients, the symptom of incontinence episodes is detrimental to their quality of life [20]. Patients with cauda equina lesions often suffer from areflexive bladder; they prefer this condition to "normal" bladder function with incontinence episodes [21]. In fact, bladder and bowel function, and sexual function, are the ones prioritized the highest among patients with SCI, much more than e.g. walking [5]. From a clinical perspective, the high transient pressure and post-void residual urine are the main problems. They can cause recurrent urinary tract infection (UTI), vesico-ureteral reflux, and ultimately renal failure [22-24]. Previously, renal failure was the

most frequent cause of death in patients with SCI; despite considerable improvements in management it still ranks as the fourth most frequent cause of death [4].

In layman's terms, NDO is the lack of control and coordination of the spinal reflex loops, due to nerve damage. However, the pathophysiology varies somewhat between the different conditions. In suprapontine lesions (e.g. Stroke, Parkinson's disease), the tonic inhibition of the PAG, and hence the PMC, is destroyed. This results in decreased bladder capacity and NDO [2, 12].

After SCI the bladder initially becomes areflexive; this is followed by development of NDO. This type of neurogenic DO is mediated by the emergence of a capsaicin-sensitive, C-fiber-mediated spinal micturition reflex due to reorganization of synaptic connections in the spinal cord [2, 25].

In patients with MS the neurological lesions may be either spinal or cerebral. Spinal lesions are the most common, but the emergence of a new reflex similar to SCI has not been shown. Instead, the demyelination of the spinal nerves may cause uncoordinated control. With cerebral lesions a pathophysiology similar to Stroke or PD may be expected.

## **I-4 Prevalence and Incidence of NDO**

The prevalence of NDO among the general population was recently surveyed. It was concluded that "Neurologic dysfunction of the LUT occurs in many patients with neurologic disease but exact [prevalence] figures are seldom available." [6]

The most common causes of NDO are SCI and MS. Despite narrowing down to two diseases, exact prevalence figures do not exist. For SCI, prevalence estimates vary from 223–755 per million [26], with one study mentioning a range of 110-1120 per million [27]. Assuming a mean prevalence of SCI of 500 per million in the Western world, the number of SCI patients is approximately 400.000. Regarding MS, a worldwide prevalence of 1 million has been estimated [28].

It was shown that electrical stimulation of pudendal afferents caused bladder relaxation in both healthy and NDO patients. Thus, a neural prosthesis for treating NDO could also be used to treat non-neurogenic DO. This is one of the pathologies of OAB with Urinary Urgency Incontinence (UUI) in the general population.

Looking at the broader OAB syndrome, two large studies have examined the prevalence. These are the NOBLE study [29], and the EPIC study [30]. Just before the 2002 definition of OAB [1], another large scale study was published; the SIFO study



[31]. While overall prevalence of OAB cannot be compared between the SIFO study and the other two studies, prevalence for the sub-pathologies can. There is agreement between all studies, that the overall prevalence of OAB is approximately 16 %. Further, approximately 6 % of the population was found to have OAB with UUI, and approximately 10 % had OAB without UUI. It was reported that up to 90 % of patients with NDO become continent with antimuscarinics and catheterization [32]. If the same number applies to the general population, 0.6 % or 4.8 million in the EU and USA would still suffer from refractory OAB, and could potentially benefit from a neural prosthesis.

## **I-5 Management of NDO**

Treatment options for NDO include behavioral modification, pharmacological treatment, surgical treatment and neuromodulation. In stress urinary incontinence, physiotherapeutical training is a very effective treatment option [33], however, there is no evidence that this has any benefit in urgency incontinence patients [34].

### **I-5.1 Behavioral modification**

First line treatment is education and behavioral modification. This implies educating patients about bladder function and appropriate fluid intake. General guidelines for fluid intake are to avoid caffeine, to maintain adequate hydration throughout the day, and to time fluid intake according to daily routines. A regime of “Bladder training” would generally include patient education, scheduled voiding, urge-suppression techniques and pelvic-muscle exercises. [35]. The value of the educational part alone has been hypothesized to underlie the marked placebo effect observed in drug trials (up to 30 % improvements in symptoms) [36].

### **I-5.2 Pharmacological treatment**

#### ***Antimuscarinics***

First line pharmacologic treatment of NDO is the administration of antimuscarinics (also known as anticholinergics). They are typically targeted at blocking the  $M_2$  or preferably the  $M_3$ -receptors of the detrusor, thereby preventing or at least diminishing the strength of detrusor contractions [37].

A limiting factor of antimuscarinic treatment is that  $M_3$ -receptors (and  $M_1$ - $M_5$ -receptors, to which the drugs also bind, albeit with a lower affinity) are found in other organs as well. Thus, common side-effects include dry mouth, constipation, gastroesophageal reflux, blurry vision, urinary retention and cognitive side effects.

[32, 36, 38]. While antimuscarinic treatment is adequate for some, many continue to have problems even after maximal therapy is applied [39].

There are several other drug classes under investigation, e.g. GABA-receptor agonists, potassium channel openers [36] potassium channel blockers, calcium channel blockers and  $\beta$ -adrenoceptor agonists [40]. However, none of these are currently used in routine management of NDO.

### *Capsaicin and Resiniferatoxin (RTX)*

Resiniferatoxin (RTX) is an analog of capsaicin; they belong to the group of substances known as vanilloids. Their mechanism of action is that they desensitize vanilloid receptors of unmyelinated sensory C-fibers. As described in section I-2.1, a C-fiber mediated micturition reflex arises in patients with spinal NDO. Administration of capsaicin or RTX, and the subsequent desensitization of the C-fibers, reduces neural firing and inhibits the micturition reflex [41, 42]. Capsaicin was first used to treat NDO with success, despite acute pain and bladder irritation. RTX is more potent than capsaicin, and appears to share the efficacy of capsaicin albeit with less side effects [43].

### *Botulinum Toxin-A (BoNT-A)*

Botulinum toxin (BoNT) is a highly potent neurotoxin that blocks the release of neurotransmitters from nerve endings. This causes a prolonged period of paralysis, during which the affected nerve endings become inactive, and new endings sprout to re-innervate the affected organ [42, 44]. There are seven serotypes of botulinum toxin, named A to G that attain the same effect by different mechanisms. Serotype A (BoNT-A) is the most used for treatment of NDO. It acts by cleaving the SNAP25 protein, which normally allows vesicles containing neurotransmitters to fuse with the membrane. Without SNAP25, the vesicles can no longer fuse with the cell membrane, and release of the transmitter substance is prevented [45]. The first larger study of BoNT-A as treatment for NDO was a European multicenter study with 200 participants [46]. Participants had BoNT-A injected into the detrusor, and after 3 months, mean volume at first reflex contraction and maximal capacity had both increased by more than 50 %, and 73 % of patients achieved full continence between catheterizations. The efficacy of BoNT-A was later confirmed by a randomized, double-blind placebo-controlled study [47]. The treatment needs to be repeated at 6-9 month intervals, but repeated injections seems to be as effective as the first [48]. There has been raised concerns about the cost of treatment, the long term effects, and the risk of urinary retention [44, 49]. The latter, however, is most-

ly relevant to patients with idiopathic DO; patients with NDO almost universally use a catheter to empty their bladder.

### **I-5.3 Surgical Treatment**

#### ***Augmentation cystoplasty***

Augmentation cystoplasty is the surgical augmentation of the bladder. Usually, a patch of the sigmoid colon (sigmoidocystoplasty) or the ileum (ileocystoplasty) is used [50]. Such bowel patches are extremely compliant; the result is increased bladder capacity and low pressure storage. As a consequence, natural voiding becomes impossible, and a catheter must be used to empty the bladder. Due to high rates of complications, alternative methods (patches from other intestines or organs, and the use of artificial materials) are under constant investigation [51].

#### ***Detrusor myectomy***

Detrusor myectomy is based on a somewhat similar principle. Instead of augmenting the bladder with a patch of bowel, part of the detrusor muscle is removed. The remaining urothelium is, similar to a bowel patch, very compliant, and the procedure results in increased capacity and low pressure storage, with the need for catheterization to empty. The efficacy of the procedure is not as high as for augmentation cystoplasty, however, complication rates are lower [52, 53].

### **I-5.4 Neuromodulation**

Neuromodulation has the potential of becoming a preferred treatment modality for patients with NDO. Currently, however, there are only two systems available in the clinic. The first, and the only approved treatment option for NDO, is the Fine-tech-Brindley bladder system. The second is the InterStim system, which is approved for UII, and used experimentally in patients with NDO. However, the system is not yet approved, and as of 2004 was implanted only in 83 patients [54].

Neuromodulation requires the implantation of at least a pulse generator (stimulator) and an electrode. A system as proposed in this thesis also requires the implantation of a sensor. Even with minimally invasive surgery, this may seem radical compared to pharmacological treatment. However, there are two arguments why neuromodulation may still be an attractive alternative to drugs. The first is the efficacy. Upon successful initial screening of the patient, most patients have higher rates of symptom relief using neuromodulation than pharmacological treatment. In addition, there are also fewer side effects. The other is more of a societal than a

patient concern; it relates to the cost of treatment. For the specific case of the Finetech-Brindley Bladder system, it was found that the break-even time between the initial cost of the device and the implantation procedure, and the cost continued conventional treatment, was 5 years [9].

Because of the potential benefits, a range of different systems have been proposed in the research literature. On the other hand, bringing a neuroprosthesis to market is expected to cost 80-100 million US dollars, and the research part is expected to take 5-7 years. Thus a considerable investment must be made, even beyond large research grants, for this to happen. This may be one of the obstacles for breaking the barrier between research and commercial systems.

### *Interstim*

The most widely used neuroprosthesis for restoring continence is the Medtronic Interstim. It is used to treat urgency incontinence, but also urgency-frequency incontinence, urinary retention and fecal incontinence. The therapy is based on sacral root stimulation; a quadripolar electrode is placed in the S3 foramen, and stimulation is applied continuously below sensory threshold. Clinical trials started in 1993, CE-marking was obtained in 1994, and FDA approval for treating urgency incontinence was obtained in 1997 [55]. The use of Interstim therapy has increased exponentially; the 10.000 implant milestone was reached in 2004 [54], in 2011 implant number 100.000 was celebrated.

Both screening and implant technique has improved significantly since the introduction [56]. Initially a so-called percutaneous nerve evaluation (PNE) was performed to assess the efficacy of treatment. This consisted of the placement of a percutaneous temporary lead at the S3 foramen close to the S3 root. This lead was connected to an external stimulator where stimulation parameters could be adjusted. This was followed by a 3 to 7 day testing period; at baseline and during this testing period the user kept a voiding diary, to document any effect. Patients with a documented 50 % or higher reduction in at least one symptom would get the Interstim system implanted. With this technique, a 3 year follow-up showed that 59 % of patients reported a 50 % or larger decrease in symptoms, and 46 % reported turning completely dry [55]. However, an average of  $5.0 \pm 6.1$  leaks per day was still reported, and only around 50 % of patients had a successful PNE.

The evaluation scheme has changed to what is called a two-stage implant. In this scheme, the permanent quadripolar tined lead is implanted, and connected to a percutaneous extension cable. This cable is connected to an external stimulator. This avoids any problems of lead migration, and allows for a prolonged evaluation period. Follow-up studies showed that 80-90 % had at least a 50 % symptom reduction [57-59]; leakage episodes decreased from average 9.5 to 3.3 [58].

In light of the efficacy and popularity, it is paradoxical that the same implant is used to treat both urinary incontinence and urinary retention. In fact, the mechanism of action is not at all clear [60]. Different stimulation parameters are typically used for the different conditions, and current hypotheses evolve around this. Some parameter sets might cause direct action (neurostimulation) while other parameters modulate reflex activity (neuromodulation). A better understanding of the neurophysiology of the LUT, combined with improved functional imaging techniques, may lead to an understanding [60].

### *SARS/SPARSI (Finetech-Brindley Bladder System)*

The only neuroprosthesis to become widespread for the treatment of NDO was the Sacral Anterior Root Stimulator (SARS), also known as the Finetech-Brindley Bladder System. The first implants were performed in 1978, and by 2004 more than 2.500 implants were performed [54]. It is a system to restore voiding, it does not by itself inhibit involuntary detrusor contractions. In order to abolish involuntary contractions the sacral posterior roots are cut, a procedure known as a posterior rhizotomy [Brindley1986]. This renders the bladder areflexive, but also causes loss of reflex defecation and erection if present. For voiding, the system takes advantage of the differences in smooth and striated muscle tissue properties. When stimulation is on, contraction of both the detrusor and the external sphincter occur. When stimulation is turned off, the striated sphincter relaxes instantaneously, whereas the smooth detrusor muscle fibers keep tension for a considerable period of time. This results in urine flow, as long as the intravesical pressure is larger than the urethral pressure. Once the flow stops, another stimulus bout is given. This results in a pattern called post-stimulus voiding, and while not very similar to physiological voiding, residual volumes of less than 30 ml are generally possible [61].

The loss of reflex erection and defecation (if present) due to the posterior rhizotomy has been the primary limiting factor for the acceptance of the system. In order to accommodate this, the system was configured as a Sacral Posterior Anterior

Root Stimulator Implant (SPARSI) [62]. In addition to the traditional SARS configuration, a lead for stimulating the posterior roots is included. This was evaluated in five patients with complete SCI. All 5 retained reflex erection after the implant, and 3 had persistent NDO. Continuous stimulation was applied to the posterior roots in these 3 patients, and this was remarkably effective; bladder capacity more than doubled in two of three patients. High pressures ( $> 70 \text{ cmH}_2\text{O}$ ) could still be generated for voiding, but persistent DSD prevented complete emptying. The mechanism of action of the posterior root stimulation expected to be similar to that of Interstim therapy.

### *The Bion*

The Bion is a wireless injectable microstimulator. Several versions exist; they are similar in that they consist of a small glass cylinder (the first version was 2 mm in diameter and 10 mm in length), with coils and electronics in the cavity, and an electrode at each end. It was described by Loeb et al. in 1991 [63], and has been used for various applications such as pressure ulcer prevention, knee osteoarthritis, and correction of foot drop, shoulder subluxation and post-stroke hand contractures [64]. For treatment of NDO a larger version was used. It measured 3.3 mm in diameter and 27 mm in length, and was implanted in Alcock's canal adjacent to the pudendal nerve. Stimulation was applied continuously, at a 50 % duty cycle (5 s on, 5 s off).

One study included 14 women, who underwent a percutaneous screening test (PST). A cystometrogram was performed at baseline, the patients received stimulation for 10 min, and if they showed at least 50 % increase in either volume at first involuntary contraction, or maximum cystometric capacity, they received the implant. 6 women had a positive PST. At 6 months follow-up, they all had improved in incontinence episodes; the average decrease was from  $6.2 \pm 2.5$  to  $2.4 \pm 2.1$  incontinence episodes a day. Similarly had the pad usage decreased from on average  $5.2 \pm 2.7$  a day to  $2.8 \pm 2.1$  [65]. Another study included only 2 women, one with UUI and one with frequency. Both passed the PST, and received the implant. At 1 month follow-up, the first had a reduction in number of incontinence episodes of 31 %; the other lowered her voiding frequency from 12 to 7 times a day [66]. These small studies suggest an efficacy similar to the Interstim therapy, however larger, long term trials are required to verify this. The Bion has received the European CE mark for use in treating UUI.

### *Miniaturio*

The Miniaturio is an electrostimulator with the stimulation lead placed paraurethrally. The implant works by stimulating the EUS, thereby activating an inhibitory reflex as described by Shafik [67]. It delivers continuous stimulation “with an interrupted cycle of 16 s every 5 s (15 s pause)” [68]. An initial study on the efficacy in treating OAB included 7 women with refractory OAB manifested by both frequency of more than 10 a day and urgency incontinence. At 12 months follow-up all measured parameters had improved; frequency decreased from median 15.2 a day to 9.4 a day, and incontinence episodes decreased from 9.1 to 1.8. One woman had to have the implant removed after 10 months due to infection at the implant site [68]. The Miniaturio received the CE mark as treatment modality for interstitial cystitis (IC) and OAB in 2005 [69].

### *PTNS*

Another option for treating NDO is to apply therapeutic percutaneous tibial nerve stimulation (PTNS). A small needle electrode is inserted near the ankle to stimulate the tibial nerve. Stimulation is continuous at 20 Hz, with current levels of 0.5 to 9 mA. Treatment consisted of weekly sessions of 30 min each for 13 weeks. PTNS was compared to validated sham stimulation [70]. A total of 220 patients were enrolled in the study, 110 in each group (PTNS vs. Sham). In the PTNS group, 54.5 % indicated moderate or marked improvements in symptoms, compared to 20.9 % in the sham group [71]. It was later shown, that the effect could be maintained by one 30 min session every fourth week [72].

## **I-6 Conditional stimulation to treat NDO**

All currently accepted treatment options use continuous, intermittent (based on therapeutic carry-over effects) or manually triggered stimulation. As described in the previous section, they all improve symptoms, but they do not effectively cure the condition. It has been shown that genital nerve stimulation can suppress nascent bladder contractions [73-77]. Conditional stimulation also increases the maximum cystometric capacity compared to continuous stimulation [78].

A system intended to completely treat symptoms of NDO based on conditional stimulation has been proposed [Hansen2005]. The described system consists of

external equipment, and is based on a pressure sensor, a control unit, and a stimulator connected to surface electrodes placed above the dorsal penile or clitoral nerve. The system works by continuously analyzing the pressure signal, and once an involuntary contraction is detected, stimulation is applied, causing the bladder to relax. At the same time, the patient is warned that he or she should consider emptying the bladder as soon as convenient.

The system was evaluated in 16 patients with SCI during a filling cystometrogram session. 13 responded to stimulation, and had at least one involuntary contraction suppressed (mean  $\pm$  SD was  $16 \pm 17$ ). Maximum cystometric capacity improved in all patients, on average by 53 %. On average, there was 20 min from the first suppressed contraction, until leakage occurred. Assuming that patients empty their bladder during this period, they would become symptom free.

The missing component in making such an implantable system is an implantable sensor capable of detecting the onset of bladder contractions in a chronic setting. Several sensors have been proposed, as reviewed in the next chapter. The work described in the remainder of this thesis relates to the development of an implantable pressure sensor intended to be placed in the bladder wall.



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## **Chapter II**

# **Detecting Urinary Bladder Contractions: Methods and Devices**

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# **Chapter III**

## **Detecting the onset of urinary bladder contractions using an implantable pressure sensor**

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## Chapter IV

# Bladder pressure sensors in a chronic animal model

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### Abstract

This study investigated whether signals, obtained from a pressure sensor chronically implanted in the urinary bladder wall of pigs, could be used to detect the onset of bladder contractions. The sensor was encapsulated with a thin layer of silicone; it was lens shaped with a diameter of 13.6 mm and height of 2.0 mm. Experiments were performed in 5 pigs with duration from 4 weeks to 3 months. Sensors were either fully implanted for 3 months ( $n=2$ ) or the leads were left transcutaneously to enable weekly follow-up experiments for 4 weeks ( $n=3$ ). For follow-up, pigs were mildly sedated with propofol, after which a double-lumen transurethral catheter was placed for reference measurement of the intravesical pressure, and for artificial filling. Contraction evoked by filling distention occurred in one pig; the signals obtained from the implanted sensor in this pig could be used to detect the onset of contraction. In the other pigs, it was not possible to obtain contractions. The propofol anesthetic, a too low filling volume and a too slow filling rate may all have contributed to this. In the transcutaneous group, 4 of 6 sensors were in place at the time of termination; in the fully implanted group none of the 4 sensors were in place. This success rate needs to be improved for the application to become feasible.

## IV-1 Introduction

Neurogenic detrusor overactivity (NDO) is a diagnosis characterized by involuntary bladder contractions at low intravesical volumes. NDO is generally caused by neurological lesions related to spinal cord injury, multiple sclerosis, Parkinson's disease or similar conditions [1]. In addition to NDO, most patients also develop detrusor-sphincter-dyssynergia, which is the concurrent contraction of the detrusor and the urethral sphincter. Despite this antagonistic action, involuntary detrusor contractions often lead to incontinence episodes. From a patient perspective, incontinence episodes are embarrassing, and have a detrimental impact on the quality of life [2]. However, from a clinical perspective the high transient pressure during concomitant contractions is of more importance, since it can lead to vesicouretral reflux and ultimately renal damage [3].

One treatment modality for NDO is to apply electrical stimulation to the dorsal genital nerve (DGN), as this is able to suppress bladder contractions. Stimulation can be applied both continuously and conditionally [4-6]. Continuous stimulation is able to suppress contractions until a certain intravesical volume is reached. At this critical point, stimulation no longer has any effect. The disadvantage of continuous stimulation is primarily that the patients do not know how close to maximal capacity they are, and thus when stimulation will cease to show an inhibitory effect. In addition, stimulation may cause an unpleasant sensation, and habituation of the reflex loop may occur over time, limiting or even abolishing the effect of stimulation. Conditional stimulation is a scheme where stimulation is applied at the onset of an involuntary bladder contraction, thereby abolishing the contraction before the intravesical pressure reaches a pathologic level. Such conditional stimulation requires a sensor capable of detecting the onset of bladder contractions, but it offers several advantages compared to continuous stimulation. The most important advantage is that an estimation of bladder fullness is obtained. Involuntary contractions occur more and more frequently as intravesical volume increases [7]. Typically, contractions can be suppressed for at least 30 minutes from the first contraction [8], providing the patient time to empty his bladder in a controlled manner. Thus, high transient pressures can be avoided altogether. Previously, chronic implantation of pressure sensors has been studied [9], but only the implant stability was evaluated. The ability of such implanted sensors to detect the onset of bladder contractions was never assessed. Recently, a sensor for detecting the onset of bladder contractions was developed and tested in acute animal experiments [10]. The objective of this study was to investigate whether it was possible to detect the onset of detrusor contractions using pressure sensors implanted chronically in the

bladder wall for periods of up to 3 months. As a secondary outcome measure the number of eroded sensors and the state of the remaining sensors during this period were also reported.

## **IV-2 Methods**

### **IV-2.1 Outline and protocol**

All experimental procedures were approved by the Danish Animal Welfare Committee. Chronic experiments were performed in minipigs to obtain both intravesical pressure and pressure in the bladder wall simultaneously during bladder contractions evoked by artificial filling of the bladder. The experimental series consisted of one pilot experiment and additional four experiments. In the pilot experiment, two pressure sensors were implanted in bilateral aspects of the bladder wall near the bladder dome. The wires from one sensor were tunneled to the back of the pig and brought through the skin. Wires from the other sensor were placed in a pouch between the abdominal cavity and the skin. In the four additional experiments, two pigs had the wires from one sensor similarly tunneled to the back and through the skin, the other two had the sensors and wires completely implanted.

Weekly follow-up experiments were conducted in the pigs with transcutaneous leads for a period of four weeks. They were anesthetized and put to the operating table, where the impedances of the sensors were measured to indicate proper electrical functioning of the sensors. Then a transurethral double-lumen catheter was placed in the bladder; this was used for artificial filling and measurement of intravesical pressure using an external sensor. Contractions were evoked (if possible) by the artificial filling, and bladder pressure was recorded during the entire filling session. The two pigs with sensors completely implanted were put in their booths for 3 months before a terminal experiment.

Identical terminal experiments were conducted in all animals, similar to the acute experiments described in an earlier study [10]. In brief, the pelvic nerve was accessed by a posterior approach as described by Wen et al. [11], and a cuff electrode was placed unilaterally to evoke hemispheric bladder contractions by electrical stimulation. Intravesical pressure, measured by an external sensor via a transurethral catheter, and pressure in the bladder wall was recorded simultaneously.

### **IV-2.2 Animal Model**

The study was performed on five Göttingen minipigs weighing 30 to 40 kg. Due to difficulties evoking bladder contractions, two anesthetic schemes were used. In

scheme one induction consisted of Ketamine (15 mg/kg), Stresnil (2.2 mg/kg) and Atropine (0.04 mg/kg) given I.M. as a bolus injection. The pig was intubated and ventilated, and anesthesia was maintained with Propofol i.v. (6 ml initial bolus, 10-14 ml/h following) ("Propofol scheme").

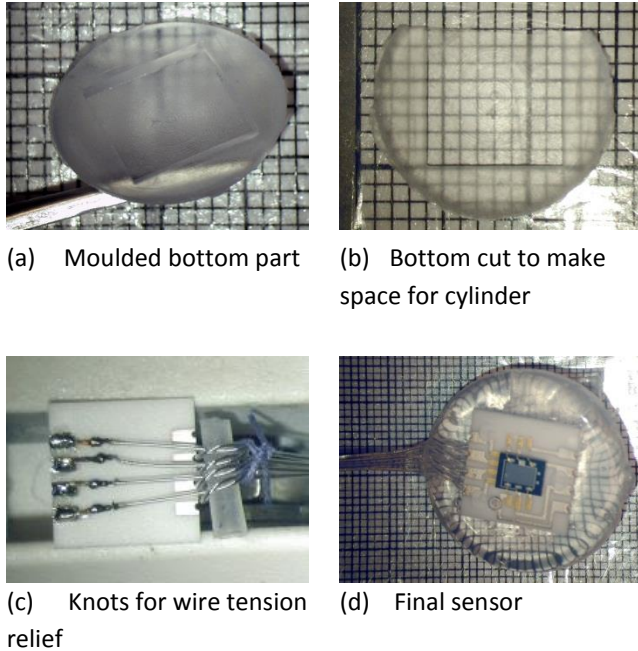
In the second scheme induction consisted of Ketamine (10 mg/kg) and Midazolam (1 mg/kg) given I.M. as a bolus. The pig was subsequently intubated and ventilated, and anesthesia was maintained using Sevoflurane (1–1.5% vol) ("Sevoflurane scheme").

For implantation a mixture of Zoletil, Rompun, Ketaminol and Turbogesic was used; for details see [10]. Heart rate and oxygen saturation was monitored in all experiments. The experiments were approved by the local ethical committee.

#### **IV-2.3 Sensor and Equipment**

The sensor itself and the silicone encapsulation of the sensor was identical to what is described in an earlier study [10]. Compared with the described sensor, the wires were changed to small single-lead Teflon-coated MP35N wires (Fort Wayne Metals, Fort Wayne, IN; Wire specification: 1x19 strand, FEP coated, outer diameter 0.3 mm). With the choice of sensor, the MP35N could not be welded on the soldering pad, as the temperature required destroyed the pads. Instead, a small piece of copper wire was welded on the end of each of the four leads, and this small piece of copper was soldered to the pads. The copper was completely covered with the soldering tin, except for one case where this was not possible. To relieve stress from the solders and welds, a simple mechanism was used. A small silicone cylinder was placed adjacent to the sensor transversal to the direction of the wires, and a knot was tied around it with each wire. This cylinder with the knots of all four leads was then encapsulated together with the sensor, as illustrated in Figure 3. After moulding, dip-coating was done twice with a low-viscosity dip-coat solution (28 g heptane to 35 g silicone (NuSIL, Carpinteria, CA; MED 1137)), to fill any creases especially around the wire exits.





**Figure 3:** (a)-(d) The steps for modifying the moulding process to include a wire tension relief mechanism. The thread knot on figure (c) was only used to keep the four wires together during handling; it was removed before the final moulding.

A continuous infusion pump (Carefusion, San Diego, CA; IVAC 598) was used for artificial filling at a rate of 999 ml/hour (pump max), corresponding to 16.7 ml/min. Maximum infused volume was set to 400 ml. If contractions did not occur at this point, a second filling was attempted. If still no response was obtained, the recording session was terminated. The rest of the setup was described in a previous study [10], it is repeated below for clarity.

Intravesical pressure was used as reference signal. This was measured through a transurethral catheter (Medtronic Functional Diagnostics A/S, Skovlunde, DK; 2-way Catheter, 10 Fr., 400 mm) using an external pressure transducer (Edwards Lifesciences, Irvine, CA; TruWave PX600F, relative-type transducer).

Both the implanted sensor and the reference sensor are full-bridge sensors. Using custom made connectors they were connected to an amplifier (Molecular Devices, Sunnyvale, CA; Axon CyberAmp 380) that also provided a +5.000 V precision output to drive the sensors. Data acquisition was done with a USB acquisition box (Nation-

al Instruments, Austin, TX, Model NI USB-6009) controlled by custom software written in Matlab. The signals were amplified (2000x for the implantable; 500x for the reference sensor), lowpass filtered at 10 Hz (amplifier built-in 4<sup>th</sup> order Bessel filters), and sampled at 100 Hz. For offline viewing, a 2<sup>nd</sup> order Butterworth lowpass filter with a cutoff frequency of 0.5 Hz was applied digitally.

#### IV-2.4 Surgical Procedure

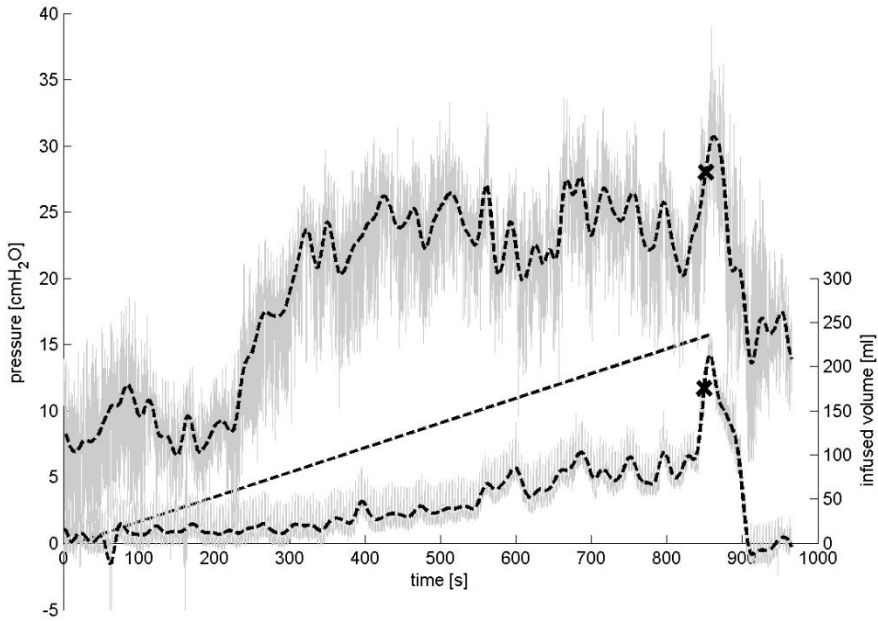
With the pig in the prone position, a transurethral catheter was placed in the bladder. A midline incision was made to expose the bladder. Using a syringe, urine was removed or saline was infused in the bladder to obtain a volume of approximately 200 ml. Two pouches were made in the middle of the detrusor, one on each lateral aspect of the bladder near the bladder dome. Sensors were placed in the pouches, and the pouches were closed using a string purse suture. Wires from one sensor were cut at lengths 12, 13, 14 and 15 cm, to be able to distinguish between them, and placed uncoiled in a subcutaneous pouch. Wires from the other sensor were tunneled to the back of the pig, where they were simply left transcutaneously through small incisions. Finally a two-layered closure of the midline incision was done, one layer being the peritoneum, second layer the abdominal muscles and the skin. All pigs were treated with Gentamycin post implant.

#### IV-3 Results

In the pilot experiment, bladder contractions were evoked by artificial filling under the propofol anesthetic scheme. After 2 week experiment duration, a good recording of a contraction was made; this recording is shown in Figure 4. After experiment durations of 3 and 4 weeks, reliable signals could no longer be obtained from the implanted sensor. In the remaining experiments bladder contractions could not be evoked. On occasion the pigs were brought out of anesthesia with a full bladder, and it was observed that they voided immediately after waking up. In total, 12 filling experiments were made. Only the first four were successful in the sense that distention evoked contractions occurred. After another four unsuccessful experiments using the propofol scheme, the sevoflurane scheme was used. Using this scheme we also failed to generate any contractions.

In the one good recording that was made, the automatic detection algorithm previously described [10] was applied, and detection occurred in both traces without false positives. Onset was detected after 849.4 s using the intravesical pressure signal, and after 851.3 s using the wall pressure signal; detection using the wall signal was delayed by 1.9 s compared to the intravesical pressure. Intravesical pressure at the time of detection was 11.7 and 12.7 cmH<sub>2</sub>O for the intravesical and wall

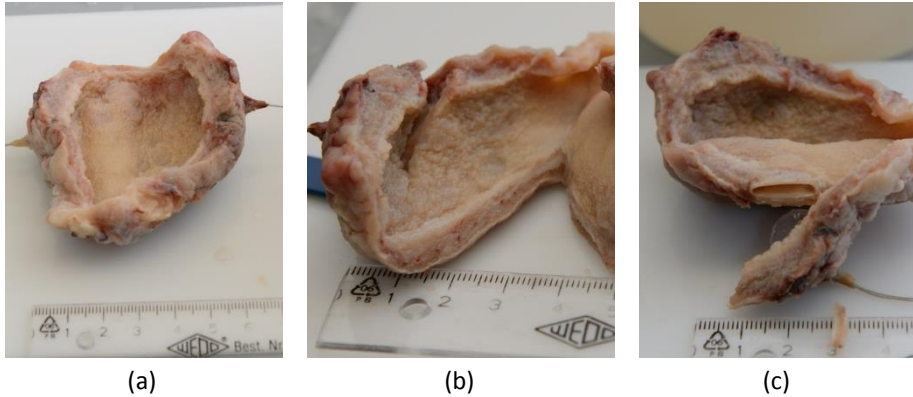
signal, respectively. Bladder compliance was 37 ml/cmH<sub>2</sub>O in the recording obtained.



**Figure 4** Recording of one successful filling experiment. Top trace is the bladder wall pressure, bottom trace is intravesical pressure. The straight line is the infused volume, according to the scale on the right-hand side of the graph. Crosses mark the points of onset detection by the automatic detection algorithm.

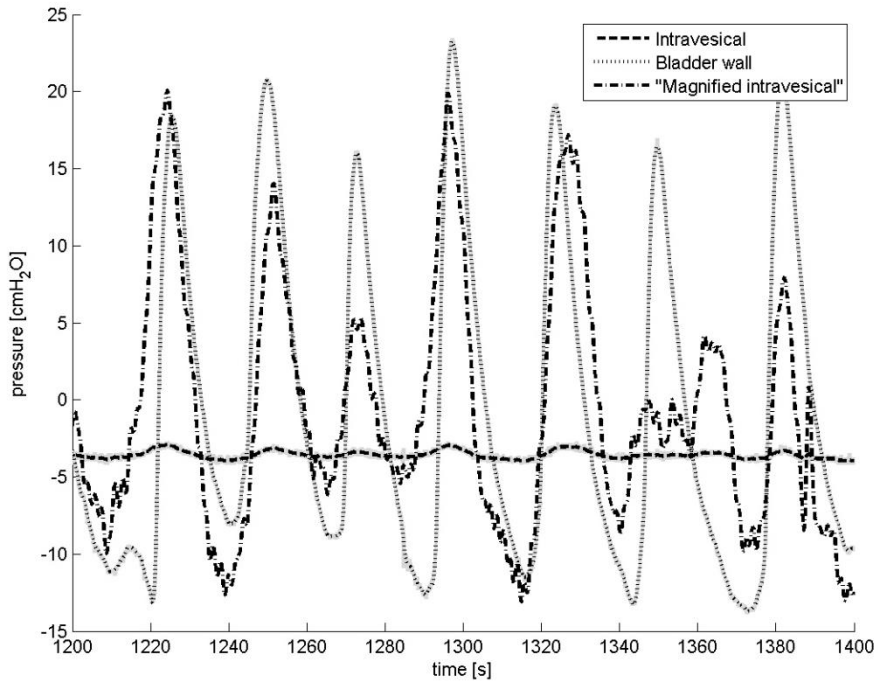
Upon termination of the experiments, all bladders were dissected out and fixed with formalin. In the relaxed fixed state, bladder wall thickness was approximately 9 mm on the ventral aspect, and approximately 5 mm on the dorsal aspect, with thickness decreasing uniformly from the ventral aspect to the dorsal. The urothelium was found to constitute approximately one third of the wall thickness. Capsule formation was clearly seen around all sensors; thickness of this capsule was approximately 1 mm. With the very limited recorded pressure data at hand, it was not possible to assess the influence this capsule had on the sensitivity of the pressure

sensors. In addition to the capsule, an increase in urothelial thickness below the sensors was observed. These findings are illustrated in Figure 5.



**Figure 5** Illustration of bladder wall thickness and capsule formation. (a) shows the wall thickness of the ventral aspect of the bladder. One cut was made at the ventral midline, and the bladder was held 'open' by sutures. Wall thickness was measured to 9 mm. (b) shows the thickness of the dorsal aspect of the bladder, by extending the cut. Here, wall thickness was measured to 5 mm. (c) illustrates the thickness of the connective tissue encapsulating the implanted sensor, the thickness of the connective tissue was approximately 1 mm.

In several experiments large rhythmic pressure increases were seen in the bladder wall pressure signal for periods of 50 to 200 s. This occurred with bladder volumes ranging from an estimated 200 ml to 400 ml. Figure 6 shows an example of this. In the figure, the “magnified intravesical” pressure is obtained by multiplication and level shift; parameters were chosen manually for illustrating the similarity.



**Figure 6** Slow rhythmic pressure increases observed particularly pronounced in experiment 3.

The transcutaneous lead-out did not cause any infection, nor was it observed to annoy the pigs. Four wires in total were led out at 2 different positions (2 power leads at one position, 2 signal leads at another). Impedance of the sensors (Wheatstone bridge topology) was checked before all experiments, and did not change over the course of any of the experiments. Since pressure measurements were inaccurate and inconsistent, despite good impedance measurements, impedance measurements could not be used to verify proper functioning of the sensors. The simple method of wire stress relief worked well; no leads broke, and no leads detached from the soldering pads.

**Table 2** Position of recovered sensors and their level of corrosion. None of the eroded sensors were recovered; hence their corrosion level could not be assessed. This is noted n/a in the table.

#		Position		Corrosion	
		1 <sup>st</sup> sensor	2 <sup>nd</sup> sensor	1 <sup>st</sup> sensor	2 <sup>nd</sup> sensor
1	Pilot study	in place	eroded	severe	n/a
2	1 <sup>st</sup> w/leads out	in place	in place	minor	minor
3	2 <sup>nd</sup> w/leads out	in place	eroded	minor	n/a
4	1 <sup>st</sup> fully implanted	inside bladder	eroded	minor	n/a
5	2 <sup>nd</sup> fully implanted	eroded	eroded	n/a	n/a

In the experiments with transcutaneous leads, 4 of 6 sensors stayed in place. The two sensors that eroded out of the bladder both had short wires placed in a subcutaneous pouch. In one of the two experiments with sensors completely implanted (i.e., without transcutaneous leads), both sensors had eroded out of the bladder wall. In the other, one sensor had eroded out of the bladder wall, the other had eroded into the bladder lumen. The sensor recovered from the pilot experiment was severely corroded, whereas the rest only showed minor signs of beginning corrosion. These findings are summarized in Table 2.

#### IV-4 Discussion

The aim of this study was to evaluate in a chronic setting, whether signals obtained from sensors implanted in the bladder wall could be used to detect the onset of detrusor contractions. The experimental series were only partly successful. In 4 of 5 pigs, it was not possible to evoke contractions by artificial filling; in addition reliable signals could only be obtained from the sensors the first 2-3 weeks after implantation.

A similar animal model was used by Greenland and Brading [12]. Landrace pigs were sedated with propofol at rates of 2 to 8 mg/kg/h, and bladders were filled with warm saline at a rates of 20 to 110 ml/min; predominantly 50 ml/min. For propofol infusion rates less than or equal to 4 mg/kg/h, there was no effect on the cystometrogram compared to non-sedated animals. At rates of 6 mg/kg/h or more, the bladders showed low compliance. They did not state a maximal infused volume in their paper; however, in the low-compliance example they showed that an in-

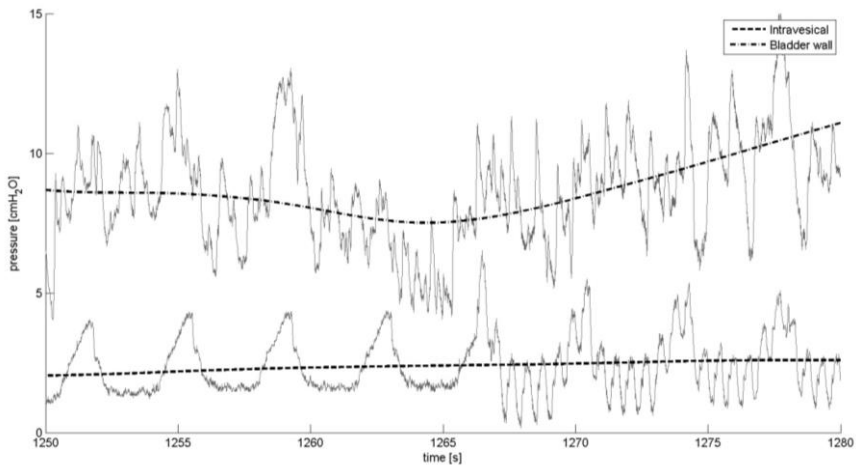
fused volume of 550 ml was necessary before contraction. In the normal compliance example only half of this, 225 ml, was necessary. Regarding the infused volumes, it is relevant to note that the pigs they used were larger, weight range 58 to 95 kg.

Propofol infusion rates of 2.5 to 4.7 mg/kg/h was used in this study. This lies mostly within the 'normal compliance' range suggested. Despite this, the compliance in the one recording obtained in this study was only 37 ml/cmH<sub>2</sub>O. For comparison, in the study of Greenland and Brading, mean compliance was  $620 \pm 160$  ml/cmH<sub>2</sub>O in the 'normal' case, and  $58.7 \pm 5.8$  ml/cmH<sub>2</sub>O in the 'low compliance' case. In the low-compliance cases, contractions were still reported, although at higher intravesical volumes. From the above it can be inferred that propofol has an inhibiting effect on the voiding reflex, and based on the very low compliance measured in this study, one could speculate that minipigs are more sensitive to propofol than land-race pigs. However, in the last unsuccessful experiments using the propofol scheme, infusion rates were kept at an absolute minimum, eliminating the option of further lowering the infusion rate. The filling rate used in this study (16.7 ml/min) was much lower than reported by Greenland and Brading, but it was the maximum rate of the available pump. A faster filling rate might produce increased afferent firing, increasing the change of triggering the voiding reflex. Also, a larger maximal infused volume could be used, if it could be asserted that it would not overdistend the bladder tissue. Altogether, the propofol infusion rate, the low bladder filling rate and the set maximum infused bladder volume may all collectively have prevented the evoked contractions. Different provocative maneuvers are suggested for human urodynamic studies, e.g. infusion of ice water. This was not attempted in the pigs, but could be an option for future studies.

One proper contraction was recorded in the pilot experiment, shown in Figure 4. The increase in pressure perceived by the implanted sensor at around 250-300 s may well be the unfolding of the bladder. At low volumes the bladder wall collapses into rugae. When it fills, the rugae first unfolds, and after this, the bladder wall starts to stretch. This transition is likely what is seen at 250-350 s, where the initial stretching of the bladder wall around the sensor will yield a "static" pressure increase.

As seen in Figure 4, there is a large amount of background noise in the recorded signals. This is primarily generated by the ventilator, and the infusion pump. Figure 7 shows this at a smaller time scale. The 3-4 cmH<sub>2</sub>O pressure increases seen from 1250 to 1265 are pressure increases of the entire abdominal cavity caused by the ventilator. At 1265 the infusion pump was turned on, adding to the signal a low-frequency noise (approximately 1.8 Hz) with an amplitude of 2 to 3 cmH<sub>2</sub>O. It is also seen that the noise level of the implanted sensor is larger than that of the external sensor. Some of the noise could arise from the smaller sensitivity of the implanted sensor compared to the external sensor (amplification was 2000x and 500x, respectively).

It was also observed, that the noise level of the implanted sensor was larger when implanted, than in the lab. During manufacture and storage, the sensors were kept dry. Only during testing and calibration were they submerged. Tests were performed using vials of demineralized water, for two reasons. One was to avoid unnecessarily contaminating the sensors, although they were sterilized (by autoclave) before implantation. The second was that by making a small slit in the rubber lid of the vials, and passing the sensor wire in this slit, a "pressure chamber" could easily be made, since no pressure chamber was available at our lab. During all lab measurements, sensors behaved as expected.



**Figure 7** Illustration of the “noise” generated by external equipment. The larger spike-like noise is from the ventilator, the low-frequency oscillations starting at around 1265 are caused by the infusion pump.



During the animal experiments, we experienced large fluctuations (noise) in the recordings from the implanted sensors. This was explored in the lab, where sensors were submerged in saline for 24 hours. During measurements with these sensors, similar noise fluctuations were seen. It is speculated, that the reason for this noise is caused by volume conduction between the tracks and/or leads of the sensor. Ideally, silicone is not permeable to salts, but ions may be present in the saline solution causing this effect. However, this is purely speculation. It was not a concern before the studies, but proved detrimental to the recording quality during experiments. All together, this suggests a sub-optimal sensor design for this application.

The pressure increases shown in Figure 6 are difficult to see directly from the intravesical pressure signal. If, however, the intravesical signal is amplified and offset artificially, a pattern similar to the bladder wall pressure emerges. This suggests that there is some form of non-voiding contractions occurring in the bladder. Looking at the intravesical pressure signal, the contractions have an amplitude of approximately 1 cmH<sub>2</sub>O, and there are 8 contractions during a 200 s period. This corresponds very well with what was described by Drake et al. [13] even though they used excised guinea pig bladders. In addition to intravesical pressure, they measured relative movements of fixed points on the surface of the bladder; they did not look at intramural pressure. Data from this study support the existence of such non-voiding contractions, and suggest that localized intramural pressure can be as much as 20 cmH<sub>2</sub>O during these bladder waves. Looking at Figure 4, a similar pattern of small (approximately 1 cmH<sub>2</sub>O in amplitude) pressure increases are seen in the intravesical pressure signal throughout the filling. The corresponding pressure fluctuations in intramural pressure have amplitudes of approximately 5 cmH<sub>2</sub>O. This corroborates the existence of local non-voiding contractions in the pig bladder.

The sensors used in this experiment were not built with implantation as an intended application, but rather modified for use as implantable sensors. The sensor die is made of silicon and glass, and mounted on a ceramic substrate. The tracks and bond pads of the die are of aluminum; the soldering pads and tracks on the substrate are gold. The die is connected to the substrate with gold wirebonds. The attached leads were made from biocompatible MP35N wire. The sensors show vulnerability to the harsh implanted environment at two points. One is the small pieces of copper used to connect the MP35N to the soldering pads, and the tin solder used for the attachment. The other is the aluminum tracks and bondpads on

the top of the sensor die. This is also where corrosion was seen to various degrees on all sensors. Despite this, sensor impedance remained constant over the course of the experiments, even after reliable signals could not be obtained any longer. Also, the wire stress relief mechanism proved very efficient. The Teflon coated wire used may have helped in this as the connective tissue was not able to attach to the Teflon.

In the fully implanted pigs, 3 of 4 sensors had eroded out of the bladder wall after 3 months. Post-terminal inspection showed that not all sensors were placed in the middle of the bladder wall, and that some were placed almost transverse to the bladder wall when the bladder was in the relaxed state, and parallel with wall as intended. It is expected that the number of eroded sensors could be reduced, had the sensors been placed in the middle of the wall, and parallel with it. An experienced surgeon would be able to do this.

In conclusion, problems with the animal model generally prevented recording of bladder pressures. However, one single experiment showed that recording is possible, and that the signal even can be used for automatic detection of contractions. Thickness of connective tissue encapsulation did not increase from 4 weeks to 3 months, but was approximately 1 mm in all experiments independent of duration. In total, 4 of 10 sensors stayed in place, during the 4 weeks to 3 months duration of the experiments. This rate needs to be improved for application to become feasible.

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# **Chapter V**

## **Minimizing a wireless passive LC-tank sensor to monitor bladder pressure – a simulation study**

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## Chapter VI

### General Discussion and Perspectives

#### Discussion

Conditional stimulation of the dorsal genital nerve would provide a near ideal modality to treat NDO. Side-effects known from medication would be eliminated, and efficacy is near 100 %. Financially, it is also more viable than medication [1]. Compared to continuous stimulation, conditional stimulation provides higher bladder capacity [2], reduces the risk of habituation of the reflex loop, and reduces charge injection. This further reduces the risk of tissue damage, and prolongs electrode life. Finally, a signal can be given to the patient at the time of stimulation, to warn the patient that it is time to empty the bladder when convenient. This is particularly important to patients, and may help them become completely dry.

However, a sensor that can reliably detect the onset of contractions is needed. Part of the work of this thesis was to review the current state of the art regarding bladder sensing. Based on this, recommendations are given on preferred sensing modalities. The list of proposed methods include blood flow, O<sub>2</sub> saturation, Near Infra-red Spectroscopy (NIRS), bladder sound, bladder EMG, anal sphincter EMG, urethral sphincter EMG, pelvic nerve ENG, sacral root ENG, pudendal nerve ENG, bladder pressure, skin potentials and bladder shape changes. Table 3 highlights the most important pros and cons of each method, from the perspective of being suitable for detecting the *onset* of bladder contractions.

The review (study 1) showed that many methods, e.g. O<sub>2</sub> saturation, blood flow and NIRS, are less suited for detecting the onset of bladder contractions, since they are all related to the restricted blood flow during contractions. Hence, deflections in these signals develop gradually with contraction duration, and for all these methods there is a considerable lag before contractions can be detected. ENG based methods are elegant in that they use the natural sensors of the bladder, but signal amplitude and noise from other (and larger) fibers in the same nerves makes this approach difficult. Velocity-selective recording could help improve on this, but

this requires a quite long electrode. Such an electrode would have to be implanted on a dorsal root, making the surgical procedure very invasive.

Bladder EMG was measured with a complex setup; improvements in both equipment and processing methods are needed before this modality can be considered a candidate. However, proxies of the bladder EMG often exist in NDO patients. Thus, external anal sphincter EMG and pelvic floor EMG were investigated by different groups. In acute trials, these modalities could be used to detect bladder contractions. However, the measurement setup is basically a noise-free environment, which is very different from the real life of patients, even if they are largely sedentary. Firstly, the equipment needs to be tested in chronic models, and secondly, the performance in a real life patient setting needs to be assessed.

The most promising method is to base detection on bladder pressure. A few studies reported on catheter-based monitoring of intravesical pressure. Recordings were obtained for as long as 6 months. Risks of sensor migration, bladder rupture or simply encrustation of the catheter, all speak against this approach, but no conclusive evidence that rule out catheter-based monitoring exists. Two independent groups have recently proposed devices for ambulatory monitoring of bladder pressure. One device is intended for buoyant placement within the bladder lumen [3], while the other is placed surgically in a pouch between the detrusor and the urothelium [4, 5]. Both of the proposed systems are active systems that need to be recharged often. Further, they are placed at locations that may not be feasible for long term implantation, cf. the results of Koldewijn et al. [6].



**Table 3** Pros and cons of each potential method for detecting the onset of bladder contractions.

Method	Pros	Cons
Bladder EMG	Direct measurement of onset (if EMG can be obtained)	Very difficult to obtain, if exists
Anal Sphincter EMG	Non- or minimally invasive stable interface	Noisy signal, many false positives
Urethral Sphincter EMG	Non- or minimally invasive interface	Noisy signal, many false positives
Sacral Root and Pelvic Nerve ENG	Chronically stable interface	SNR too low to detect contractions
Pudendal Nerve ENG	Chronically stable interface	SNR too low to detect contractions
Pressure Based Sensors	Reliable low noise signal	Currently no stable interface
Detrusor Blood Flow Changes	Can be non-invasive or placed at a distance to the bladder	Signal is delayed compared to contraction onset
Detrusor Blood O <sub>2</sub> Changes	Can be non-invasive or placed at a distance to the bladder	Signal is delayed compared to contraction onset
Near-Infrared Spectroscopy	Can be non-invasive or placed at a distance to the bladder	Very sensitive to movements
Skin Potential Changes	Non-invasive	Only very few have clear responses
Bladder Sounds	Stable interface	Method unclear
Capacitive Flexor	Can also measure volume	Very invasive, chronic stability unknown
Patient Controlled Stimulation	No sensor needed	Only few have sensation, it is often delayed and concurrent with flow

In order to determine whether a pressure increase stems from an involuntary bladder contraction or a general pressure increase of the abdominal cavity as might occur when e.g. coughing or laughing, the differential pressure between abdomen and bladder needs to be evaluated. This can be done in a number of ways. Brindley, who was the first to apply this principle [7], made a “double-sided” sensor connected to a mechanical switch based on a conducting fluid. The sensor consisted of two fluid-filled capsules on opposite sides of a common rigid wall, connected by tubes to a mechanical switch. One side faced the bladder, and one side faced the abdominal cavity. If pressure on the abdominal side exceeded pressure on the bladder side, a membrane in the switch would close a fluid duct, turning the switch off. Conversely, if pressure was highest on the bladder side, the membrane would be pressed away from the duct, allowing current to flow, thus turning the switch on. Hence, differential pressure was automatically obtained, and the switch could be used directly to control a stimulator. In case of involuntary bladder contractions the switch would turn on, but it would be left off in case of general abdominal pressure increases. The system worked well initially, however, in all four patients with the system, the sensors detached from the bladder within one year [6].

Differential pressure can also be computed from the signals from two separate sensors. This was done by e.g. Hansen et al. [8] and Fjorback et al. [9]. Both studies used catheters and external relative-type pressure sensors, to measure intravesical and abdominal pressure. The signals were fed into a computer, which computed the differential pressure, and from this signal a stimulator unit was controlled. In both studies this worked well, with an average of 16 and 12, respectively, inhibited bladder contractions without leakage. A thorough analysis of this method, and the ability to abolish nascent contractions has also been published by Fjorback et al. [10].

As demonstrated by the results of the studies of both Brindley and Koldewijn [6], the main problem with implantable pressure sensors has been that they erode away from their implantation site. Sensors placed *on* the bladder generally detached, as did sensors placed between the detrusor and the urothelium. Sensors placed between the peritoneum and the detrusor provided the best chronic stability for a sensor implant. In addition, the use of prolene (non-absorbable) sutures provided the most stable implants, a finding that was corroborated by Picha and Drake [11].

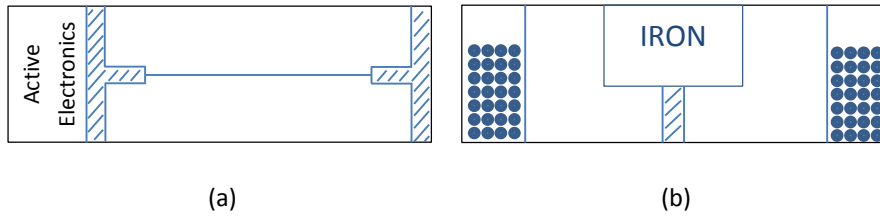
Based on this, a wireless sensor placed in the bladder wall, was hypothesized to be the optimal solution. It was speculated, that if it was possible to implant a sensor in

the bladder wall that was chronically stable, it would also be possible, and most likely easier, to implant a sensor somewhere in the abdominal cavity to monitor abdominal pressure. The differential bladder pressure could then be derived easily in a given stimulator implant.

Another option is to use a differential sensor in a setup similar to that used by Brindley and Donaldson [7]. Two options for this principle will be described briefly.

- One design would be a central membrane with a pressure chamber on each side. Such type of sensor is typically resistive. Resistive sensors are often wired, or alternatively equipped with embedded active electronics to measure the signal and send it out wirelessly. This is sketched in Figure 8 (a). This type of sensor could be powered inductively by adding a coil (not shown), or an internal battery. Schemes for operating resistive sensors without active electronics also exist, but are not well characterized.
- Another possibility would be to use a modified LC tank sensor. In order to distinguish which side of the sensor is exposed to the highest pressure, a design with a cylindrical coil and capacitor plates on each end could be used. An iron bar could be attached to one plate, and the distance between the plates could be fixed. Movement of the bar further into the coil would increase inductance, while movement out of the coil would lower inductance. This is sketched in Figure 8 (b). (This principle of a variable inductance was the first principle used for telemetric pressure sensors [12, 13].)

The benefit of such designs would be that the electronics needed in the stimulator unit could be made simpler, and that only one sensor is needed, which compared to the two needed for the indirect differential method, would reduce the risk of device failure. However, both designs would be more difficult to fabricate, and there would likely be a higher risk of erosion. In this scheme, the anchoring to the bladder would have to resist the force applied to the membrane facing the bladder, and although the forces are rather small, it would still promote, rather than prevent, erosion.



**Figure 8** Sketches (cross-sections) of differential sensor designs. (a) Shows an example of a wireless active resistive-type sensor. It could be powered by a battery, or a coil for inductive powering could be added. (b) Illustrates a wireless passive LC-type sensor. An iron core is moved further into or out of the center of a coil (windings represented by small circles), depending on pressure, changing the inductance of the coil. This can be detected as a change in impedance using various techniques described later in this chapter.

Based on these considerations, it was decided to focus on an absolute pressure sensor intended for implantation in the bladder wall. It is to be used in combination with a similar sensor for measuring abdominal pressure, enabling computation of the differential bladder pressure. There is, however, no clear evidence this is the optimal solution.

The aim of study 2 was to develop an implantable pressure sensor capable of detecting the onset of bladder contractions. The second study of this thesis demonstrated, in an acute animal model, that this principle is feasible. A wired sensor coated with silicone to form a lens shape with diameter 13.6 mm and height 2 mm was made. Experiments were conducted in 6 pigs, where the sensor was placed in pouches in the bladder wall. Pouches were made at different positions (base and dome, medial and lateral), and with the sensor membrane both facing the bladder lumen and away from it. Across 114 contraction epochs of 90 second duration, contractions could be detected in 101. The correlation coefficient between the sensor signal and the intravesical pressure as measured by an external sensor was above 0.9 in 91 epochs. Keeping the explorative nature of the study in mind, these results are very promising. The peak pressures during evoked contractions were lower than expected. As a result, the threshold for detecting contractions was lowered from 10 cmH<sub>2</sub>O to 5 cmH<sub>2</sub>O. This was still considered to be of general applicability, since the aim of the study was to investigate whether signals obtained from pouches in the bladder wall could be used equally well as the intravesical pressure. Given that intravesical pressure has been used successfully to detect the onset of

bladder contractions in humans [8], the point of interest was whether an equal performance could be obtained, and not whether the a certain threshold would be suitable for human application. Hence, number of detections, time delay of detection, and correlation with intravesical pressure were the parameters of interest. Good agreement in all three parameters for both sensor signals indicates that either signal may be used.

Chronic animal experiments were also conducted using a slightly modified sensor (study 3). For the chronic implantation, the sensor leads were made of four individual 0.3 mm diameter Teflon coated MP35N stranded wires. Reliable signals could be detected for only up to 3 weeks. This was due to problems with the sensor die, which was not developed for chronic implantation. When immersed in conducting (ionic) fluid for prolonged time, signals became unstable. Another problem was that of migration or erosion, as described by Koldewijn et al. [6]. In total, only four of ten sensors stayed in place during the chronic experiments. It was found that the sensors that stayed in place were implanted as intended, approximately in the middle of the detrusor, and an orientation parallel with the wall. Many parameters may have influenced migration. It is hypothesized, that the sensors that eroded were implanted either too superficially or too deep. This means that in order to erode, they needed only to penetrate the serous coat or the urothelium, not the detrusor fibers. Having the surgery done by an experienced surgeon, combined with a systematic investigation of different anchoring techniques is expected to increase this number of sensors that stay in place substantially.

Other parameters that could be adjusted is size and surface texture of the sensor. This is a major discussion in itself, but a few points will be made here. It has been known at least since the 1980's that the implant surface topography plays a significant role in determining the foreign body response of an implant. [11, 14, 15]. Despite this, there has been more attention on surface chemistry than topography, or implant biomechanics in general, in the literature [16]. In addition, most research within the area of biocompatibility has traditionally been related to hard-tissue implants, i.e. implants into bones. However, some reviews of the importance of biomechanical factors on soft tissue implants have been published recently, e.g. Hilborn and Bjursten [16] and Helton et al. [17, 18]. Still, acknowledging the im-

portance is not the same as understanding the interaction. An initial theoretical framework for this understanding was given by Helton et al. [17].

The biomechanical interaction with tissue is now believed to be an equally important factor as surface chemistry, for achieving chronically stable implants. Mechanical loading causes bones to remodel and muscles to grow. Mechanical forces are also involved cellular signal transduction [16]. Hence, it would only be natural that biomechanics play an integral role in defining the foreign body response of an implant.

For implanted devices, mechanical stresses may stem from several sources. Besides the tissue motion caused by movement in general, it could also be scratching over the area of an implanted sensor, pressure from lying on the area where the sensor is implanted, or from muscle contractions in the vicinity of the sensor. There seems to be general consensus that the most stable state for chronic implantation is that of maximal tissue adhesion, which also results in the thinnest capsule. This importance of size and shape may for long have been an underappreciated factor, which has led to differing conclusions in several studies investigating surface topography and chemistry.

Generally, the smaller the sensor implant is, the lesser foreign body reaction it will cause [19]. However, the orientation of the implant is crucial in this relation. Most tissues have an extracellular matrix where the large collagen fibers are arranged mainly in layers. For such tissues, the height of the implant is much more critical than either length or width. This suggests that implants should be sheet-shaped, if possible, and placed parallel with fiber orientation [20].

In order to reduce the response due to shear stresses experienced by an implant, it has been suggested to increase the surface area, thus reducing the force per unit area. In an extensive study, Picha and Drake showed that there were significant differences with respect to specific topography, implant site and implant anchoring [11]. Currently, surface topography in the nanoscale (irregular or patterns with features less than 100 nm) are considered most beneficial for cell adhesion and growth [21]. Such features can be made using a range of different techniques, all with their respective pros and cons, and different process requirements. For irregular patterns, the sol-gel thin film coating is relatively easy to apply [22]; for specific patterns techniques such as electron based lithography, nano-imprint lithography and many others may be used [23].

Based on the above, the following recommendation for a pressure sensor design is given. In the following, a passive wireless sensor is considered. This is due to the previous arguments for choosing this type of sensor. The sensor should be as small as possible, but this contradicts with the possibility of inductive powering. It was found that a sensor diameter (or side length) of approximately 1 cm would fulfill this requirement. Using MEMS techniques, a thickness of 0.5 mm should be possible. This is in line with the finding, that height is more critical than length or width. In order to achieve chronic stability, a textured or porous surface coating should be added. This could be done using the sol-gel technique, which preserves sensor roughness, and adds (unstructured) nanoscale roughness [24]. Preservation of sensor roughness may aid in anchoring the sensor, however, sharp edges should be avoided in order not to cause further trauma.

In light of this, the sensor design employed in the chronic studies was not optimal. Even if a hermetically sealed MEMS sensor could not be manufactured, different techniques could be used to improve the chronic stability of the sensor. This was not possible within the limits of this project.

In addition to the studies using wired sensors, wireless sensors were investigated. A wireless sensor was designed and realized, but did unfortunately not work due to problems with the fabrication process sequence. Owing to this, read-out circuitry was designed and the sensor system was analyzed by means of simulations (study 4). It was found that distance between antenna and sensor is a critical factor, but that operation should at least be feasible for distances up to 12 mm. The wireless sensor is hypothesized to be superior to a wired sensor with respect to both migration and long term operation. This is because the lack of wires ensures that there are no pulling forces acting on the sensor. Similarly, because of the lack of wire connections, it can be completely sealed, so corrosion, lead detachment or similar events are avoided. Several operating principles have been described in the literature. For use with a fully implantable system, the problem is keeping the circuitry simple and keeping power consumption low. The system described in this study should fulfill these requirements.

## Perspectives and future work

The most important single step is to make a sensor that is not only biocompatible, but can sustain operation for a prolonged period of time in the harsh environment that the body is. This imposes that all 'internal' wiring of the sensor, e.g. strain gauges and wire bonds if they exist, should be hermetically sealed. The sensor used in this work was only covered with silicone, and although the impermeability to salts should create a sustained osmotic pressure 'out of' the sensor [25], strange behavior of the recorded signal was noticed after 3 weeks of implantation. This was even if only minimal corrosion was seen on post experimental sensor retrieval. The only explanation found was that current paths altering the behavior of the sensor arise through the body fluids. In light of this, a simple LC-tank type wireless sensor may prove superior, since it can be sealed better. In addition to this, the wireless sensor will, at least theoretically, have a reduced risk of migration, making is a very attractive option.

Once a proper sensor is constructed, there are still two unknowns that need to be clarified. They are firstly, if the sensor will stay in place chronically, and secondly, if the sensor performance remains intact during this period. In case both of the above can be confirmed, a fully implantable system for use in humans can be made. Given such a system, the next step is to investigate whether bladder contractions can be detected reliably. Pressure increases may be detected due to non-voiding contractions, coughing, laughing, changes in position and several other events. Characteristic features (e.g. morphology, rate of increase) of bladder contractions may be found, that can help distinguish them from the other mentioned events. Finally, if proof-of-concept is shown in a pilot study, larger studies are still needed to show the general efficacy of such a system.

In conclusion, it was shown that it is possible to detect bladder contractions using a pressure sensor placed in the bladder wall. Positive results were obtained in acute experiments, but only for up to 3 weeks in chronic experiments. Evidence from laboratory measurements indicate that these problems were with the sensor, and not due to the host response to implantation. One natural bladder contraction was recorded after 3 weeks of implantation. A slow filling of the bladder was done, until



a distention-evoked reflex contraction occurred. The contraction was detected using an automatic detection algorithm based on the signal from the implanted sensor. Although there is a cascade of developments needed before a neural prosthesis can be realized, this demonstrates proof-of-concept for this approach.

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