When ‘I’ is replaced with ’We’, even ‘illness’ becomes ‘wellness’
– Malcom X

Master Thesis.

A new way to prevent bedwetting

W.M.J. Kwinten, BSc.

Master of Science Thesis

"A new way to prevent bedwetting"

January 31, 2019

W.M.J. Kwinten, BSc.
Technical Medicine
Medical Sensing & Stimulation
University of Twente
UMC Utrecht - Pediatric urology
Novioscan

UNIVERSITY OF TWENTE. UMC Utrecht Wilhelmina Children's Hospital novioscan wearable ultrasound care

Technical supervisor (chair): Prof. dr. ir. B. ten Haken
Medical supervisor: Dr. P. Dik
Process mentor: Drs. B.J.C.C. Hessink-Sweep
External member: Dr. F.J. Siepel
Additional member: P.G. van Leuteren, Msc.

Preface

This master thesis is the result of my graduation internship at the Wilhelmina Children's Hospital, UMC Utrecht, at the department of pediatric urology. I focused on optimization of the SENS-U® Bladder Sensor for children with nocturnal incontinence.

Finally, the end of my Master's degree of Technical Medicine is here. Well, it was a hell of a ride for which I am so grateful. This final report feels more like a new beginning as an end. Seven years ago, I started my Bachelors with the intend to heal people and taking care of them. I always was amazed by the way the body worked and how technique could help to be more effective in healing.

This clear mission faded during my study period. Becoming a Bachelor of Science, the most logical step of that moment was starting my Masters. Without a clear intend, I struggled through my years as a master student. Until.. September 2017. I went to Spain and came back connected with myself and my vision again. I started my last M2 internship at the pediatric urology department under supervision of dr. Dik. This time it was different from previous internships. I felt confident and worthy and my colleagues gave me a warm welcome.

A funny thing is that I knew I wanted to do an internship at this department, since my Bachelor's. It turned out that this was the place I wanted to graduate. Nowhere else would have been a better option for me. In February the final trip of my studies started.

And here it is. I am so proud of the result! The last year has been amazing. The best year of my life so far. I took a major leap in personal growth, reconnected with my soul and my souls calling: healing people. I rediscovered my core values and found out what was important to me in living my life. My main lesson: don't try so hard to fit in, create your own rules.

Because dr. Dik allowed me to have a lot of freedom, I could do this graduation my way. For me this internship was experiencing with flow and resistance. I stepped on a boat that knew its destiny and it was my task to hoist the sails. Sometimes, I sailed on a rapids, sometimes I tried to change course against the current. Turning around in literature not knowing where to go. Or trying to figuring out step five, while I forgot to start at step one. But every time, I was willing to let go and let the boat sail its own course.

Focusing on my dreams and future, made me feel inspired to finish my graduation well. I did what I had to do and took care of my well-being. I want to thank myself for that. Thank you Pieter for your inspiration and for expanding our minds together. Thank you Paul for guiding me through the hospital structures and being the solid land in the storm. Thank you Bennie for tickle my brains and let me think in new ways. Thank you colleagues of Novioscan for making this study available and the weekly lunch breaks. And thank you Bregje for planting the seed of my personal development processes. I am so grateful to present this work to you. Think in possibilities and miracles will happen.

Enjoy reading.

Wenche Kwinten
's-Hertogenbosch, January 2019

Summary

Introduction

Nocturnal enuresis (NE) is a common problem in school-aged children, with huge psychological and emotional impact. Currently, the wetting alarm, based on negative feedback, is used for treatment. The SENS-U Bladder Sensor is developed to help children stay dry based on positive feedback and its feasibility is successful in day-time incontinence. The sensor measures the anterior-posterior (A-P) bladder dimension based on ultrasound.

Objectives

The aim of this thesis was to investigate feasibility and optimization of the SENS-U for children with NE. An MRI study was performed to gain insight in the full bladder shape changes in different positions and the effect on the theoretical SENS-U measurement. Next, a clinical study focused on the feasibility of the SENS-U in ambulatory care in children with NE to examine if the SENS-U was able to measure natural nocturnal bladder filling (NNBF) cycles.

Full bladder deformation

MRI scans were made in three healthy adults in four positions; standing, supine, left side and prone. Next to voided volume using a measurement cup, the theoretical SENS-U volume was determined. Results showed that bladder shape did change due to gravitational force and that inter subject differences (i.a. age and presence of internal abdominal fat) had effect on the theoretical SENS-U measurement. The theoretical volume was underestimated, most likely caused by difference in A-P and left-right bladder dimension.

SENS-U in ambulatory care for NE

In this home-based observational pilot study, fifteen children (6-12 years) were measured with the SENS-U during one night. The sensor measured A-P bladder dimension and body position every 30 seconds. Voided volume was collected and filled in in a voiding diary with corresponding time by the parents. In addition, a sub children's sleep habit questionnaire (CSHQ) was filled in. Results showed that fifteen out of eighteen NNBF cycles were measured successfully, a success rate of 83%.

Wearing the SENS-U did not have major effects on the children's sleep. The theoretical notification success rate, based on 80% of the patient's expected bladder capacity, was 17 %. In addition it was seen that the SENS-U overestimated bladder volume and that its measurement depended on body position which caused the bladder to move outside the field of view of the SENS-U. When the position dependency is solved, the SENS-U might be a new way to prevent bedwetting.

Abbreviations

AG	Abdominal Girth
A-P	Anterior-Posterior
BBD	Bladder Bowel Dysfunction
C-C	Cranial-Caudal
CSHQ	Children's Sleep Habit Questionnaire
EAU	European Association of Urology
EBC	Expected Bladder Capacity
EMV	Early Morning Volume
FBC	Functional Bladder Capacity
FOV	Field Of View
ICCS	International Children's Continence Society
L-R	Left-Right
MNE	Monosymptomatic Nocturnal Enuresis
MRI	Magnetic Resonance Imaging
NNBF	Natural Nocturnal Bladder Filling
NMNE	Non-Monosymptomatic Nocturnal Enuresis
PTF	Position Transition Factor
UBM	URIKA Bladder Monitor

Contents

Chapter 1

Introduction

This master thesis, performed during the final graduation internship, is all about the use of the SENS-U® Bladder Sensor and its optimization for ambulatory care in patients with nocturnal enuresis.

The bedwetting alarm, designed in 1904, is a widely used device for treatment of nocturnal enuresis. This biofeedback system is based on negative feedback. Over the years, researchers tried to develop a new device to treat bedwetting with positive feedback. They wanted to develop a wearable device that was able to measure bladder filling status non-invasively. A few bladder monitors were developed, which automatically detected a full bladder based on ultrasound.[1–4]

In 1998, a study was performed with one of these ultrasonic bladder volume monitors to investigate whether the device was able to treat nocturnal enuresis in children. The low accuracy of the device resulted in a success rate of only 50 %. The SENS-U was successfully validated (success rate of 90%) for infused bladder filling[5] and results of the feasibility study of the SENS-U in day-time incontinence were promising.[6] Therefore, this research was focused on the use of the SENS-U for nocturnal enuresis.

The SENS-U is a wearable ultrasound device which measures anterior-posterior bladder dimensions and intends to help children stay dry during day and night. The main positive aspect is the simplicity of its working mechanism and the intention to change children's behavior in a positive way. We also believe that positive stimulation is the best way to bring about behavioral change. The SENS-U might be a new way to prevent bedwetting.

1.1 Clinical Significance

Nocturnal enuresis is a common problem in school-aged children. 5-10 % of the seven-year old suffer from this condition which has huge psychological and emotional impact.[7–9] Children with enuresis have a lower perceived competence and lower self-esteem, which can be increased by successful treatment.[10] Alarm treatment (based on negative reinforcement) is successful in two-thirds of the children with nocturnal enuresis, which is relatively high. Most importantly, the chance of success depends on the childs motivation and the parental tolerance.[9] We think that child and parents will be rewarded if the alarm treatment is based on positive reinforcement, resulting in an increased effectiveness of this "new way" of biofeedback treatment. Before we can investigate the effectiveness of the SENS-U, we have to gain more insight in the operation of the sensor in different body positions and to investigate if the sensor is able to measure natural nocturnal bladder filling cycles in children with enuresis. This resulted in the research questions described below.

1.2 Research Question

The aim of this thesis was to investigate possibilities and optimization of the SENS-U for use in ambulatory care in children with nocturnal enuresis. This thesis exists of two parts. We wanted to cover a broad perspective of the issues concerning US bladder detection with the SENS-U. Part I is a magnetic resonance imaging (MRI) study concerning the shape of the full bladder in different positions. The main questions are:

"Does a full bladder shape change in different body positions?"
"What is the effect of the body position on the theoretical (volume) measurement of the SENS-U® ?"

Two sub questions which are answered in this thesis are:

- Is there a difference in the full bladder shape between men and women?
- Does the presence of internal abdominal fat have effect on the full bladder shape?

Part II is a home based observational study examine the usability of the SENS-U for ambulatory care in children with nocturnal enuresis. The main questions are:

"Is the SENS-U® able to measure correct natural nocturnal bladder filling cycles?"
"Does the anterior-posterior bladder dimension depend on body position?"

The sub question which was answered in this thesis:

- What is the theoretical notification success-rate for expected bladder capacity?

1.3 Thesis Outline

In chapter 2, the clinical background of enuresis will be introduced, starting with the anatomy of the lower urinary tract focused on the bladder, its shape and its change due to bladder filling. In addition, the neurophysiology of bladder filling and voiding will be explained. After that, the concept of enuresis will be accompanying with definitions, diagnosis and treatment. Chapter 3 will explain background information about the technical aspects of this study, mainly the the working principles of the SENS-U bladder sensor. Then, part I of this thesis wil describe the background and hypothesis of the MRI study in chapter 4. Next, to that the study design will be explained in chapter 5 and in chapter 6 the results of the full bladder MRI study will be described. The results will be discussed in chapter 7 after which the conclusion will be stated in chapter 8. In Part II, chapter 9 a short background will be described about the home-based observational pilot study for natural nocturnal bladder filling in children with nocturnal enuresis. Its design will be discussed in chapter 10 and the results will be presented in chapter 11. The discussion and conclusion will be presented in chapter 12 and 13, respectively. Lastly, the bibliography and the appendices with additional information will be presented at the end of this thesis.

Chapter 2

Clinical Background

2.1 Anatomy of the lower urinary tract system

Figure 2.1 presents an overview of the lower urinary tract system anatomy in females. The most cranial part of the system exists of the kidneys, which are bean shaped organs and lie in the abdominal cavity. They are responsible for production and excretion of urine. Blood passes through the structural and functional unit of the kidney: the nephron. Here, filtration, reabsorption, secretion and excretion of the blood plasma takes place, resulting in production of urine. Urine is transported via the ureters to the bladder where it is stored.[11]

The bladder is an extraperitoneal organ[12] which exists of a bladder dome consisting of smooth muscle fibers (mainly known as the detrusor muscle), and the trigone. The smooth muscle fibers of the dome extend in many directions to allow it to expand during urine storage and to contract during voiding.[13]The trigone is a triangular region which exists of two ureteric orifices and the internal urethral orifice. Urine leaves the bladder via the urethra. The internal and external sphincter act as a closure mechanism to protect unintentional release of urine.[14,15]

The internal sphincter is located at the transition of the bladder to the urethra. Because it is a continuation of the detrusor muscle, consisting of smooth muscle, this sphincter is autonomic innervated like the bladder. In contrast to the internal sphincter, the external sphincter is part of the pelvic floor muscles and exists of skeletal muscle. This explains why the external sphincter is innervated somatically, meaning that this sphincter is under voluntary control.[16]The pelvic floor consists of two muscles: levator ani muscle and coccygeus muscle. It prevents the bladder neck to move downwards during jumping, running, coughing and other physical activities.[16]

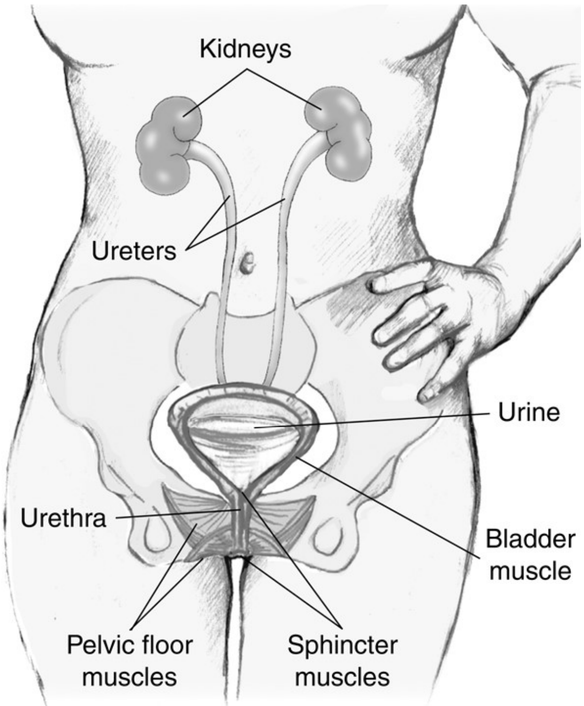

Figure 2.1: Anatomy of lower urinary tract system[15]

2.1.1 Bladder shape and location

There is anatomical difference between man and woman, see figure 2.2. This applies to both the bladder and the external sphincter. The bladder lies behind the pubic bone and in front of the rectum in males, while the bladder lies in front of the uterus in females. MRI images showed that the female bladder lies more caudal that the male bladder.[17] In females, the external sphincter is located at the distal inferior end of the bladder, while in males it is located inferior to the prostate gland.[18] In adults, when the bladder is emptied, the bladder lies in the lesser pelvis and is completely hidden behind the pubic bone.

The difference in anatomy between adults and children is significant. The most important difference is that children do have a smaller pelvic cavity which results in a higher positioned bladder compared to adults.[18] Especially in females, the difference between adults and children is noticeable. Due to the growth of the uterus the bladder is positioned lower in the adult pelvis than in that of the children. The uterus is thin and the fundus and cervix are of comparable length during pre-puberty, while in adult women the fundus of the uterus is substantially present and is two to three times longer than the cervix[19] and is positioned on top of the bladder.

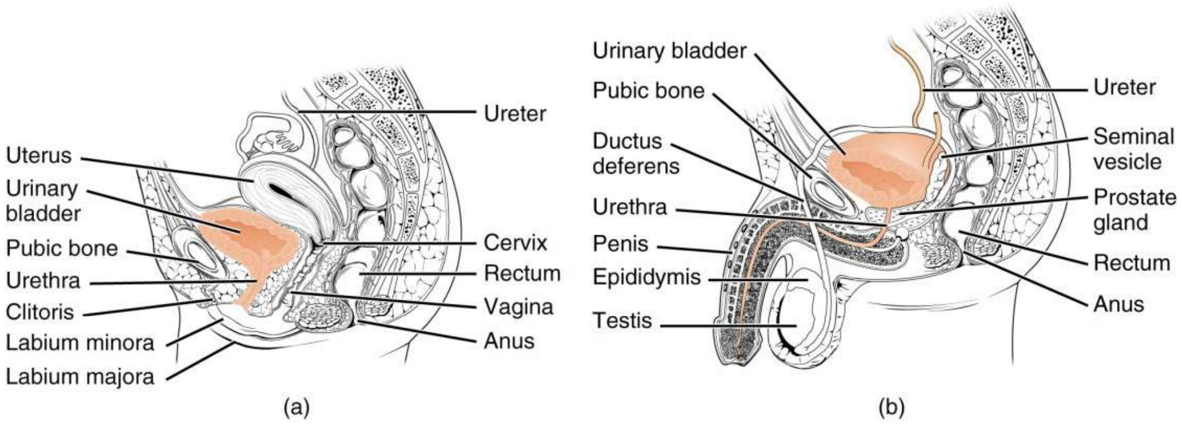

Figure 2.2: The shape and location of the adult bladder, (a) female (b) male[20]

2.1.2 Bladder filling during day and night

A study from Companion et al. showed that the bladder fills according to a specific trajectory. First, the bladder expands in the direction of the upper abdomen and than forward to the abdominal wall.[1] Although the bladder is an extraperitoneal structure and is able to expand in cranial direction, the base of the bladder does not transform during filling because it is fixated in the lower pelvis. According to a study of Lotz et al., the caudal bladder shape is most reproducible during individual bladder filling. They investigated bladder shape changes with MR imaging. Figure 2.4 shows a model of the bladder shape in three different filling statuses of a healthy volunteer.[21]

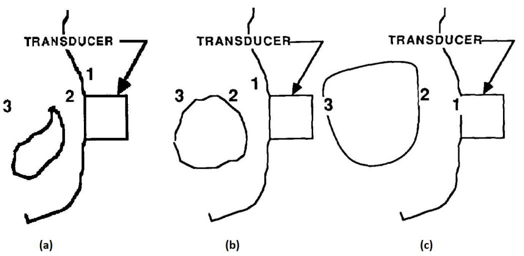

Figure 2.3: The bladder filling trajectory measured with a single element ultrasound sensor. The filling status is: (a) almost empty, (b) partially filled and (c) full bladder

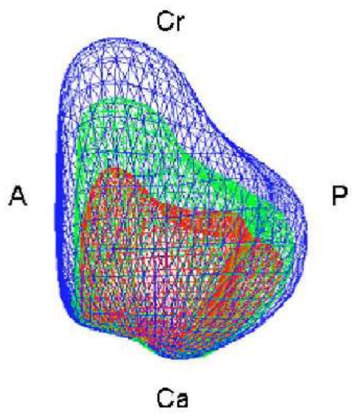

Figure 2.4: Bladder shape model, based on MR images, with three different volumes. A = anterior, Ca = caudal, Cr = cranial, P = posterior[21]

Obviously there is a difference between day-time and nocturnal bladder filling. One of the reasons is the fluid intake, which is variable during day-time and absent during the night. This is assumed to result in a variable urine production during the day and a relatively constant nocturnal urine production. One of the other reasons for the difference between day-time and nocturnal bladder filling is the presence of the circadian rhythm,[22] which will be explained later in this chapter. The study of Watanabe et al. found an interesting phenomenon during nocturnal bladder filling. They found that a considerable amount of urine in the bladder diminished without micturition during sleep. They suggest that water is reabsorbed from the urine in the human body.[23] This study showed that the urine production increased when the volume was below the functional capacity of the bladder (FBC), while the volume stopped increasing when it was more that the FBC. The functional bladder capacity is defined as the volume of urine collected in the bladder prior to voluntary micturition. This, again, is a significant difference between adults and children. The expected bladder capacity (EBC) of adults is between 300 - 600 mL.[12] For children up to 12 years old, the EBC in mL can be calculated by the formula of Hjalmäs, shown in equation 2.1,[24] and is prepared by the International Children's Continence Society (ICCS).[8]

$$\mathrm{EBC\ [mL]} = 30 * \mathrm{AGE\ (years)} + 30 \tag{2.1}$$

2.2 Neurophysiology

Innervation of the bladder and the sphincters are both autonomic and somatic. Three nerves are involved: the *sympathetic* hypogastric nerve (Th11 L2), the *parasympathetic* pelvic nerve (S2-S4) and the somatic pudendal nerve (S2-S4). In short, involuntary urine retention is provided by the hypogastric nerve and voluntary urine retention is provided by the pudendal nerve, while involuntary and voluntary voiding is provided by the pelvic and the pudendal nerve respectively. The cortex, from which conscious decisions can be made (for example whether it is a suitable time to void) sends signals to the pontine micturition center. From this center, impulses are sent to the sacral continence center: Onuf's nucleus where the pudendal nerve and pelvic nerve are stimulated.[13,16]

Filling phase Figure 2.5 shows the neurophysiology of the filling phase in more detail. Stretch receptors in the detrusor muscle send slow impulses via the afferent part of the pelvic nerve. This leads to stimulates of the hypogastric nerve, resulting in relaxation of the detrusor muscle via beta-3 receptors and contraction of the bladder neck via alpha-1 receptors. When it is not the right place and time to void, the micturition center stimulates both pudendal and pelvic nerves. This results in contraction of the pelvic floor via nicotine receptors, and contraction of the rhabdosphincter. At the same time, the pelvic nerve inhibits via M3 receptors and causes the detrusor muscle to relax. Relaxation of the detrusor muscle and contraction of the sphincter complex prevent urine loss and allows the bladder to fill.

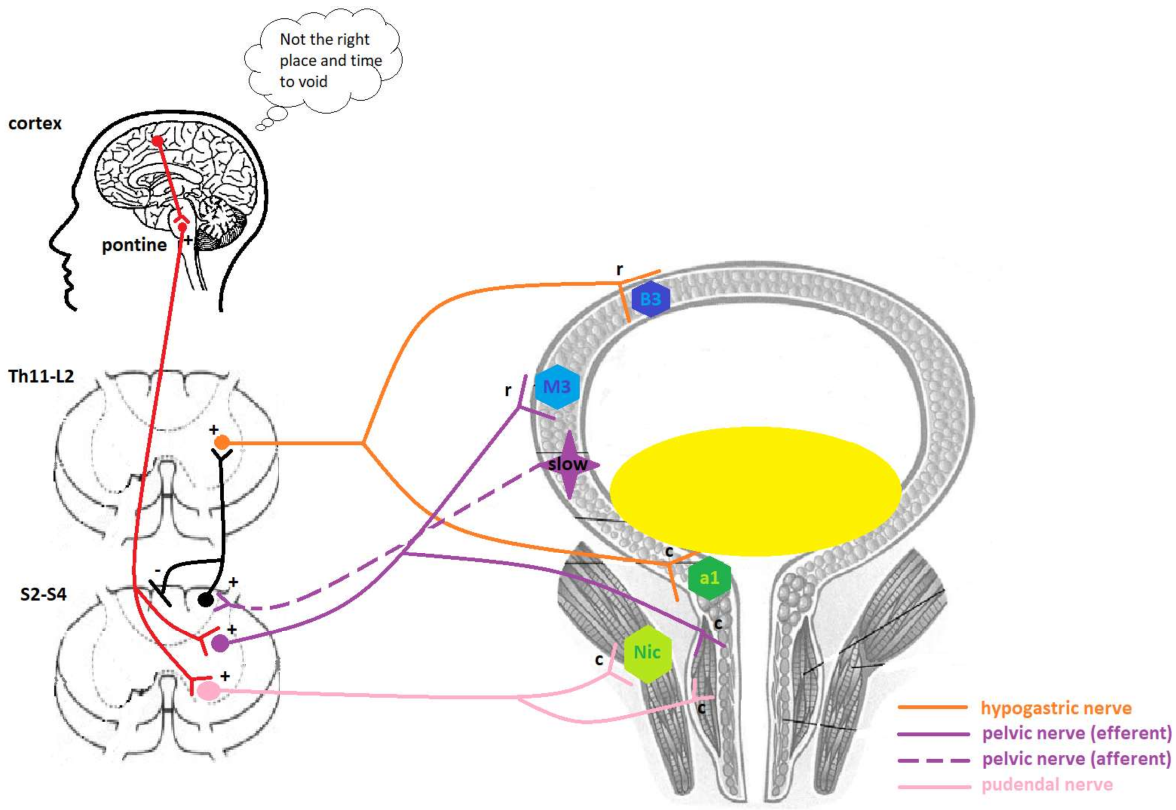

Figure 2.5: Innervation and neurophysiology during bladder filling phase.

Voiding phase When the bladder is full, stretch receptors in the bladder wall send fast impulses via afferent fibers of the pelvic nerve and the voiding phase begins, see figure 2.6. A signal is sent to the cortex. When voiding is suitable, the pontine micturition center send impulses to the sacral pontine center which inhibits the efferent fibers of both the pudendal and the pelvic nerve.[13] This result in relaxation of the rhabdosphincter and the pelvic floor, while the detrusor is activated via M3-receptors. Fast impulses, directly inhibit the hypogastric nerve via the afferent pelvic nerve. The detrusor muscle will contract and the bladder neck will relax, allowing micturition to start.[16] An important part of this circuit is the voiding reflex. The efferent pelvic nerve is directly inhibited via the afferent pelvic nerve and an interneuron. This ensures that voiding continues. During voiding, the sensory part of the pudendal nerve is activated and sends signals to the cortex to check if voiding is appropriate.

2.3 Enuresis

According to the European Association of Urology (EAU) Guidelines, enuresis is synonymous to intermittent nocturnal incontinence and is equal to the terminology of the ICCS.[7,8,25] 5-22% of the seven-year olds suffer from enuresis.[7,8] This heterogeneous problem is caused by three main factors: 1) high night-time urine output

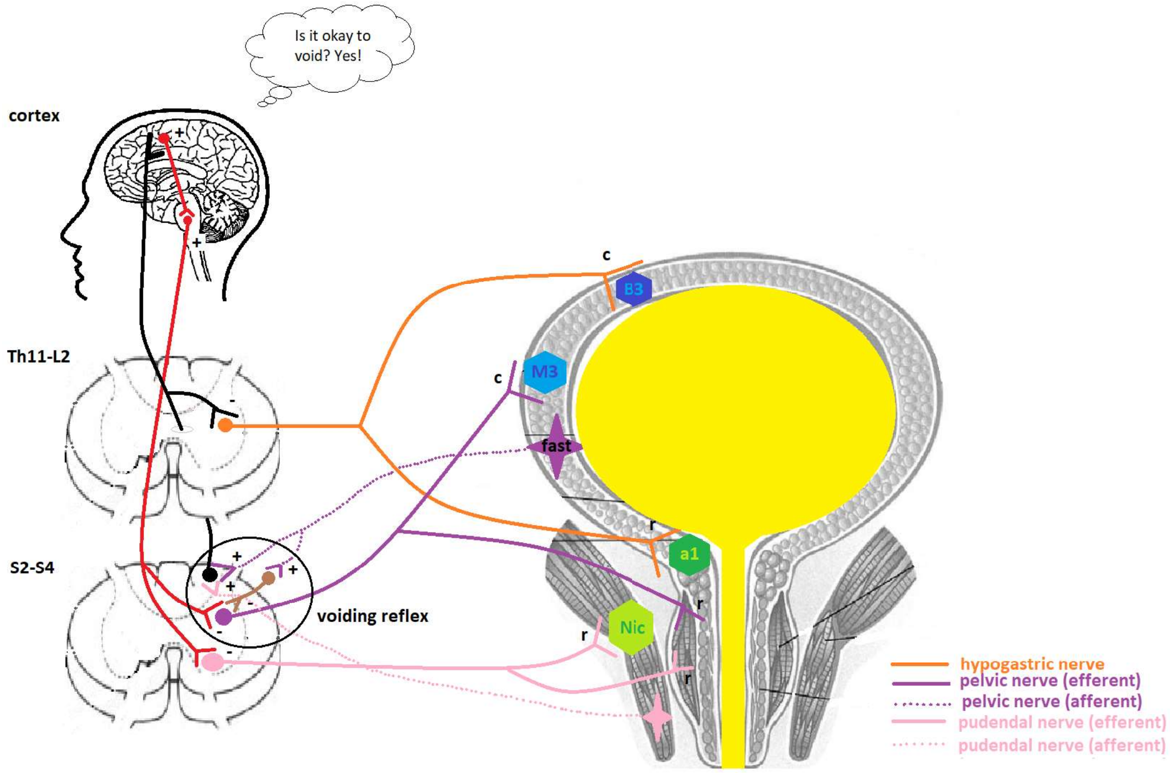

Figure 2.6: Innervation and neurophysiology during bladder voiding phase.

(polyuria defined as a BC of greater than 135% EBC[8]), 2) low night-time bladder capacity (defined as less than 65% of the EBC[8]) or high detrusor activity and 3) arousal disorder.[7,25] It was shown that the arousal threshold in enuretic boys was increased and that they were wet during the first two thirds of the night.[26] This was probably caused by delayed maturation of the brain cores. In addition, studies showed that the circadian rhythm of micturition plays a major role on the abovementioned factors.[22,27] Besides, circadian rhythm influences the voiding volume.

It is seen that healthy children and children with enuresis have the same day-time holding exercise volume, while the early morning volume (EMV) is significantly lower in nocturnal incontinence patients.[22] In 1993, urodynamic studies were preformed in children with MNE, which showed that 73% of the children had a decreased functional bladder capacity during the night.[28] This could explain the reduced EMV.

2.3.1 Definitions and guidelines

When problems occur in the anatomy and/or physiology described in sections 2.1 and 2.2, incontinence can be the result. Two types of incontinence can be distinguished: continuous incontinence (uncontrollable leakage of urine caused by a defect of the sphincter complex) and intermittent incontinence. Intermittent incontinence is diagnosed from the age of five, because from that moment it is accepted

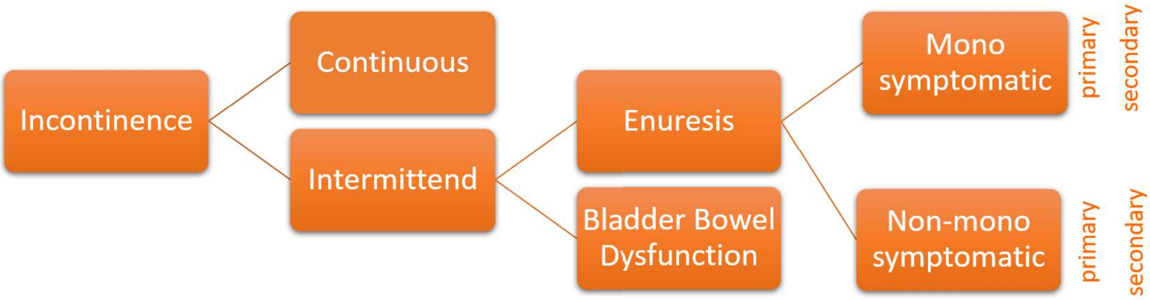

Figure 2.7: Incontinence definitions according to the ICCS[8]

that children are dry. This category is divided in daytime and nocturnal incontinence, also called enuresis.[8,25] An overview of incontinence classification is presented in figure 2.7

When lower urinary tract symptoms (LUTS) such as urgency, incontinence or recurrent urinary tract infections, or neurological or anatomical problems are the cause of nocturnal bedwetting it is called non-monosymptomatic enuresis (NMNE). Wetting during sleep above the age of five years without other symptoms is called monosymptomatic enuresis (MNE) and is part of the Bladder Bowel Dysfunction (BBD) class.[25] Besides (N)MNE, primary and secondary enuresis is distinguished, see figure 2.7. In secondary enuresis, a child was dry during the night for a period of at least six months, otherwise it is primary.[29]

The degree of NE is defined according to the following guidelines: little ($<$ 2 nights per week), moderate (2-3 nights per week) and severe ($\geq$ 3 nights per week).

2.3.2 Diagnosis

Consultation and information gathering are an essential part to diagnose incontinence and enuresis. It is the details of the patient's and his parent's story which gives most clearity of the condition. The most important tool is the history-taking. Micturition/defecation frequency and fluid-intake are important parameters. Next to physical examination, uroflowmetry gives insight in the voiding pattern and voiding volumes. In contrast to day-time urine production, nocturnal urine production can be determined based on the EMV and the weight of a possible wetted diaper. All additional tools give more information about the type and the cause of enuresis. This can be beneficial for the choice of treatment, which is performed from an age of five years.[7]

2.3.3 Treatment

In children with NMNE, the underlying problem is the main target for treatment.[30] When this problem is treated successfully, but bedwetting remains, the conditions will automatically be defined as MNE. The first choice of treatment for this class is explanation of the condition to the child and his parents. It is very important for them to understand the problem. Information is given about eating and drinking habits. Despite the effectiveness of the supportive treatment, medication and alarm therapy is proven to be more effective.[7]

Desmopressin is used in children with polyuria. This medicine is a surrogate for hormonal vasopressin, which supports water reabsorption in the kidneys and thus reduces urine production. Anticholinergic medicine, such as oxybutynin, is prescribed in case of a small functional bladder.[7,31] Anticholinergic oxybutynin inhibits detrusor contraction, providing a possibile increase of the FBC.[7,32] The commonly used non-medical treatment is the use of a wetting alarm and is most effective for arousal disorder.[7,30] In general, this is based on negative reinforcement where pelvic floor contraction is taught when there is leakage of urine. In the next section (2.3.4), alarm treatment will be discussed in more detail.

2.3.4 Wetting Alarm

In 1904 the German pediatrician Pfaundler developed equipment that gave an alarm when an infant needed changing. Initially, he designed the alarm system for nurses, knowing when they had to change bedding. After using the system for one month, they discovered that children who did wet their bed regularly became dry within a month. Around 1930, Mowrer and Mowrer introduced the wetting alarm based on conditioning. It was not until the sixties that alarm therapy was acknowledged as a reliable treatment by peadiatricians.[33,34] Today, the wetting alarms is used for ambulatory care and in the Wilhelmina Children's Hospital this home-based therapy is regularly prescribed.

This highly effective treatment device is based on biofeedback and exists of an alarm box and a special pants or an inlay, which are physically or wirelessly connected. A few drops of urine will be detected by the sensor in the inlay/pants, resulting in activation of the alarm. All kinds of alarms exist; alarm clock, an alarm watch and alarms based on vibration. This technique encourages pelvic floor contraction dur-

Figure 2.8: Wireless bedwetting alarm with sensor[36]

ing urine leakage, a form of negative reinforcement. Figure 2.8 shows an example of a wetting alarm. The sensor in the right lower corner is placed in the underwear and is wireless connected to the alarm left in the figure.

This is an intense treatment for both child and parents. Motivation of both parties is required. Besides, it is essential for the child to be dry with normal day-time fluid intake.[33] 65-75% of the children with NE (not differentiated between MNE and NMNE) are dry for 14 consecutive days when using alarm treatment.[9,35]

Chapter 3

Technical background

In daily clinical practice, imaging techniques have been used since 1963[37] and it is also used to examine the lower urinary tract system. Trans-abdominal ultrasound is the gold standard to examine the bladder and bladder volume, which is previously described in section 2.3. For years, scientists struggled with the question: how can we continuously, non-invasively measure the bladder to examine the bladder filling? Therefore a wearable device had to be developed. In 1979, the ultrasonic bladder-volume sensor was developed which determined an empty bladder or a full bladder based on wearable ultrasound.[4] The device was non-invasive, simple to use but had to be improved to decrease the amount of false positive measurements (full bladder while it was empty in reality). From a binary device which only could measure empty or full bladder, the next step was to develop a device which could measure bladder distention.

3.1 A wearable bladder monitor

In 1986, Companion et al. developed a non-invasive bladder distention monitor based on reflection of the back wall position.[1] An ultrasound signal was sent and the reflection of both anterior and posterior wall of the bladder determined the bladder distention. In the following sections, this principal will be explained in more detail. This anterior-posterior reflection principal was very promising and lots of wearable bladder volume devices have been developed over the years. Although the principal was very promising in general, a number of conditions make continuous bladder filling measurement using ultrasound complex.

- Bladder shape
- Bladder location
- Thickness of the abdominal wall
- Hold the measurement device in place

- Comfort of the wearable device

A lot of adjustments and smart methods have been developed to tackle the above mentioned issues. From a one-dimensional ultrasound method[4] to an advanced seven phased-array ultrasonic transducers in a circular pattern.[2] Different positioning methods of the device had been tried. However, most of the devices were not clinically evaluated and those who were showed poor and unstable results.[38] Two different bladder monitors are presented in figure 3.1. Currently, continuous bladder monitoring is not used (for treatment or diagnosis) in daily practice.

Figure 3.1: A bladder volume detector[3]

Figure 3.2: The BladderManager ®[38]

Novioscan (Novioscan, Nijmegen, The Netherlands) has developed the SENS-U® Bladder Sensor in association with the UMC Utrecht hospital. This sensor, which measures bladder filling status, is specially designed for children. That is one of the reasons why they were able to meet the conditions mentioned above. The anatomy of the children ensures that the bladder is positioned high in the pelvis, and will rise above the pubic bone during in the initial phase of the bladder filling. In addition, the SENS-U has a specific field of view (FOV) pointing downwards, therefore issues about bladder shape have been overcome. Next to that, most children have less supra-pubic fat than adults and therefore a thinner abdominal wall. This is beneficial for the quality of the US signal and measurability of the bladder wall. Novioscan was also able to develop a skin-friendly adhesive to comfortably hold the SENS-U in place on the lower abdomen of the user. During a clinical evaluation van Leuteren et al. showed that the SENS-U is able to accurately measure an infused full bladder with a success-rate of 90 %.[5] The development process of the SENS-U will be explained in the next section.

3.2 SENS-U® Bladder Sensor: product development

In 2016, the first version of the SENS-U was developed, the so-called URIKA Bladder Monitor (UBM), shown in figure 3.3. It existed of a transducer assembly with one single-element US transducer at an angle of 0°. The assembly was connected to an electronic case where digital data were stored.[39] Despite the UBM was able to detect a full bladder with proper sensitivity, specificity and detection rate, the device was not able to tackle the issues mentioned above in section 3.1 and improvement of the device was necessary. This resulted in the Noviomini (the name changed to SENS-U with CE-certification), shown in figure 3.4. The SENS-U consists of a casing which is, in combination with standard ultrasound gel, fixated on the lower abdomen with a skin-friendly adhesive and therefore it is a small light-weighted wearable device. In contrast to the UBM, the SENS-U uses four small ultrasound crystals creating a FOV of 30° pointing downwards into the pelvic region. The device is small and comfortable to wear. Positioning is stable and due to the increased FOV, the likelihood of detecting bladder distention is increased. In addition, the SENS-U has a built-in position sensor to determine position of the patient during the use of the device. A recent study showed that the SENS-U was able to detect a full bladder during (video) urodynamic research with a detection rate of 90%. When excluding erroneous data due to sensor misplacement or an (relative) obese abdomen, a full bladder was detected in all patients.[5]

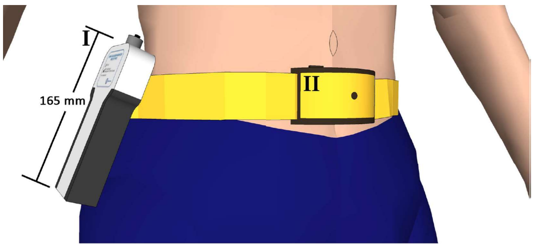

Figure 3.3: URIKA Bladder Monitor existing of electronic case (I) and transducer assembly (II)[39]

Figure 3.4: SENS-U is a small light-weighted wearable ultrasound device, that intends to help children stay dry during day and night

3.3 Anterior-posterior reflection principal

The basic working mechanism of the SENS-U is based on the anterior-posterior reflection principal (as all the other bladder monitors described above). Due to difference in acoustic impedance between two materials, the US wave will be reflected at the boundaries of the transition with different time delays. Acoustic impedance (Z) is defined as the product of the density and the acoustic velocity of the material.[40] The bigger the difference in impedance between two materials, the higher the energy of the reflected US wave. In the lower abdomen, the biggest impedance difference is between detrusor muscle (tissue: Z = 1.71 e^6 $\frac{kg}{m^2 s}$) and urine (water: Z = 1.48 e^6 $\frac{kg}{m^2 s}$).[40] Figure 3.5 shows this mechanism. An US wave is transmitted (TX pulse) from the abdominal wall in posterior direction. First, a reflection of the

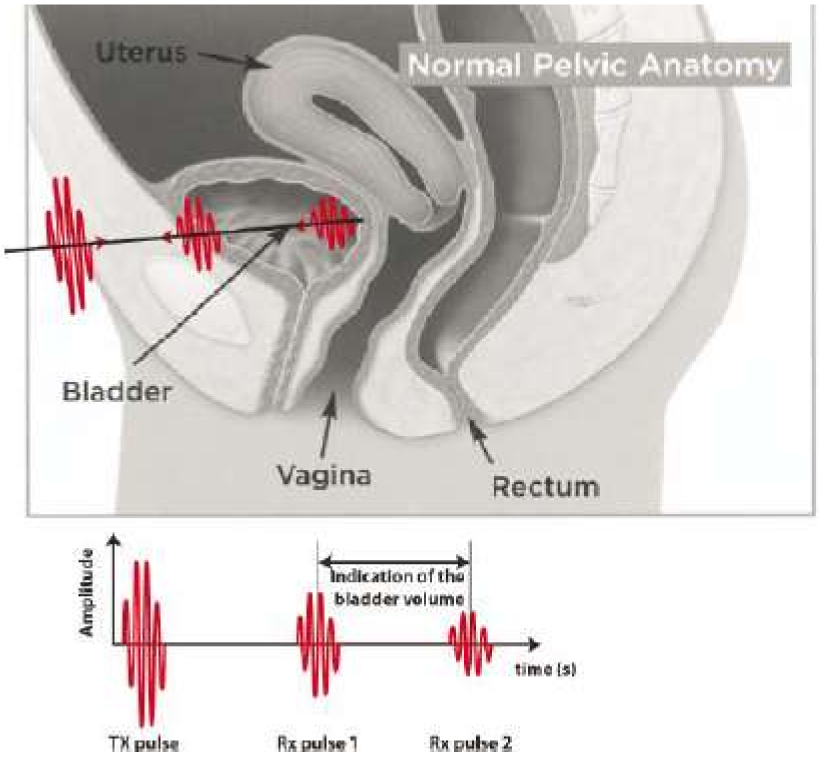

Figure 3.5: Anterior posterior reflection principal: the US waves are transmitted and the reflection of the anterior and posterior bladder wall serve as an indication of the bladder filling status

anterior bladder wall is received (Rx pulse 1) and a time frame later a reflection of the posterior bladder wall is received (Rx pulse 2). According to van Leuteren et al. 2018, the position of the anterior and posterior bladder wall is determined every 30 seconds "by comparing the received ultrasound reflections with a threshold based on the maximum amplitude of the reflection".[5] This anterior posterior reflection principal is very useful in bladder filling detection.

Part I

Full bladder shape in different positions based on MRI

Chapter 4

Background and hypothesis

In this part, we will go deeper into the full bladder shape in different positions based on MRI. In 2004, Kirstiansen et al. performed a study in which they investigated the influence of body position on the shape and position of the urinary bladder in adults.[41] They concluded that change in position and shape of the bladder due to body position change was negligible. However, the volumes were small, between 156 - 370 mL, while the EBC of an adult bladder is between 300 - 600 mL. The underfilled bladders of the participants could be the explanation why body position did not have a significant effect.

Because the extraperitoneal urinary bladder is only attached to the trigone, urethra and vascular system (in the lower part of the pelvis), we expect that gravity will have a major effect on the bladder shape as the bladder fills and when the bladder is at its maximum capacity. Assuming that the user changes sleeping position during the night, it is important to know whether the bladder shape changes in different position for the accuracy of the SENS-U. The SENS-U is validated during urodynamic research in which the child is in sitting position. And therefore, maybe, less accurate in other body positions.

To gain insight into nocturnal measurement possibilities of the SENS-U, we performed a nocturnal trial measurement in a healthy adult subject. The subject slept with the SENS-U placed on the lower abdomen. The notifications were turned OFF during the measurement nocturnal and early morning volumes with corresponding time were notated.

Figure 4.1 presents data of this measurement. Two bladder filling cycles were measured and during the night, the subject changed sleeping position. The first natural nocturnal bladder filling (NNBF) cycle was measured from 23:45 hr until 01:53 hr when the subject voided 530 mL which corresponded to a median A-P bladder dimension of 167 mm. The second NNBF cycle started at 02:02 hr and ended at

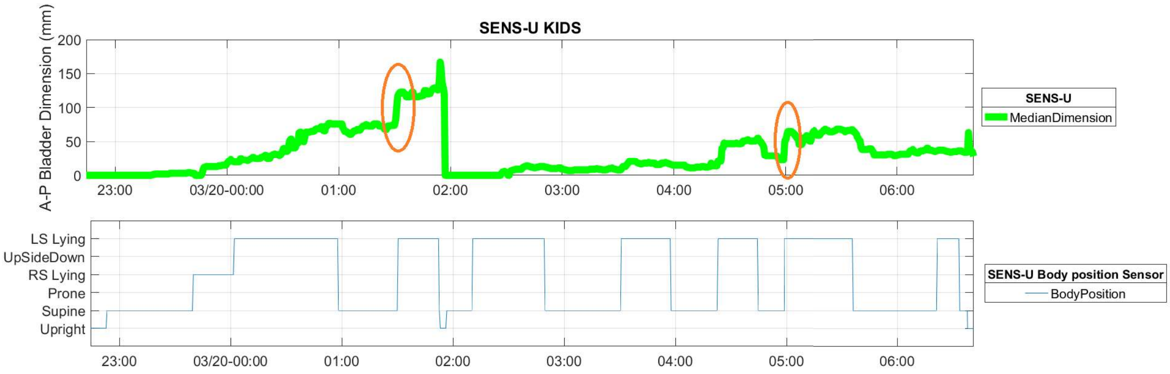

Figure 4.1: Nocturnal bladder filling measurement in a healthy adult, measured with the SENS-U. Two bladder filling cycles are measured with position dependency at 01:30 hr and 05:00 hr.

06:37 hr. The voided volume was 430 mL corresponding to a 63 mm median A-P bladder dimension. Remarkably, it was seen that the mean A-P bladder dimension increased 65% and 209% after position change (supine to left side) at respectively 01:30 hr and 05:00 hr. In addition, it was noticed that the ratio volume/A-P dimension was different in the first and second filling cycle. Therefore, questions described below are investigated in this part of the master thesis.

"Does a full bladder shape change in different body positions?"
"What is the effect of the body position on the theoretical (volume) measurement of the SENS-U® ?"

Chapter 5

Methods

In this pilot study we have collaborated with the department of Magnetic Detection & Imaging of University of Twente (Enschede, The Netherlands). A 0.25T MRI system was used to visualize the full bladder shape in different positions. The Esaote G-scan Brio (Esaote, Genoa, Italy) was used, shown in figure 5.1. This scanner was able to make scans in a vertical position of the subjects with an angle of 81°.

5.1 Subjects

Three healthy adults participated in this study. A few categories were important to vary between subjects: gender, age and presence of internal abdominal fat. We performed MRI on 1) a young man ($\leq$ 35 years) with relatively little abdominal fat, 2) an old man ($\geq$ 60 years) with relatively much internal abdominal fat and 3) a young woman ($\leq$ 35 years) with relatively little suprapubic fat. The subjects were instructed to void two hours before the start of the MRI research and in the meantime take 300-400 mL of fluid to ensure a full bladder during the moment of scanning. A SENS-U® dummy was placed on the lower abdomen, 1 cm above the pubic bone, by the investigator while the subject was in supine position. This dummy exist of a 3D printed SENS-U casing filled with EcoFlex™ 00-30 silicone (Smooth-On, Macungie, United States). The silicone contained sufficient fluid for visibility in the MRI. All patients wore a loose-fitting pants.

5.2 Scan protocol

All patient were scanned with the same coil; the flex Coil (Esaote, Genoa, Italy), shown in figure 5.2. The coil was used as lumbar spine coil and was placed with the hard side in cranial direction and with the hole of the coil at the height of the SENS-U to generate less pressure on that region. Four 3D ”T2 weighted images” were

Figure 5.1: Example of the 0.25T MRI system (Esaote G-scan Brio) with an angle of 45° [42]

Figure 5.2: Esaote flex coil used as lumbar spine coil.[42]

created per subject with a resolution of 1.2x1.2x1.2 mm and a window of 111 slices. The difference between "T2 weighted images" and "T1 weighted images" was that fluid had a high intensity on a T2 image and was presented brightly, while muscle tissue had a lower intensity and was presented in dark grey scale. For "T1 weighted images" it was the other way around.

The four different scans correspond to different positions: I) standing upright, II) supine, III) left side lying and IV) prone. The MRI system was rotated to an angle of 81° for a comfortable standing position. After that, the system was rotated backward to an angle of 0° for the other positions. It was assumed that there was no difference between left and right side lying. Before the start of each 3D scan, a scout scan was made to check the position of the bladder, repeatedly in every position. In addition, extra cushions were used to up level the position of the subject, as close as possible to the scanner, especially in supine and prone position. Cushions of choice were used for comfort of the subjects. After the scan protocol was finished, the voided volume was collected in a measuring cup and noted along with age, length, weight and abdominal girth (AG).

5.3 Anatomical orientation of MRI scans in different positions

Usually, MR scans were made in upright and supine position. For these positions, the MR cross-section was chosen to be the reference, because these cross-section correspond to the anatomical planes. Figure 5.3 shows the anatomical planes. How-

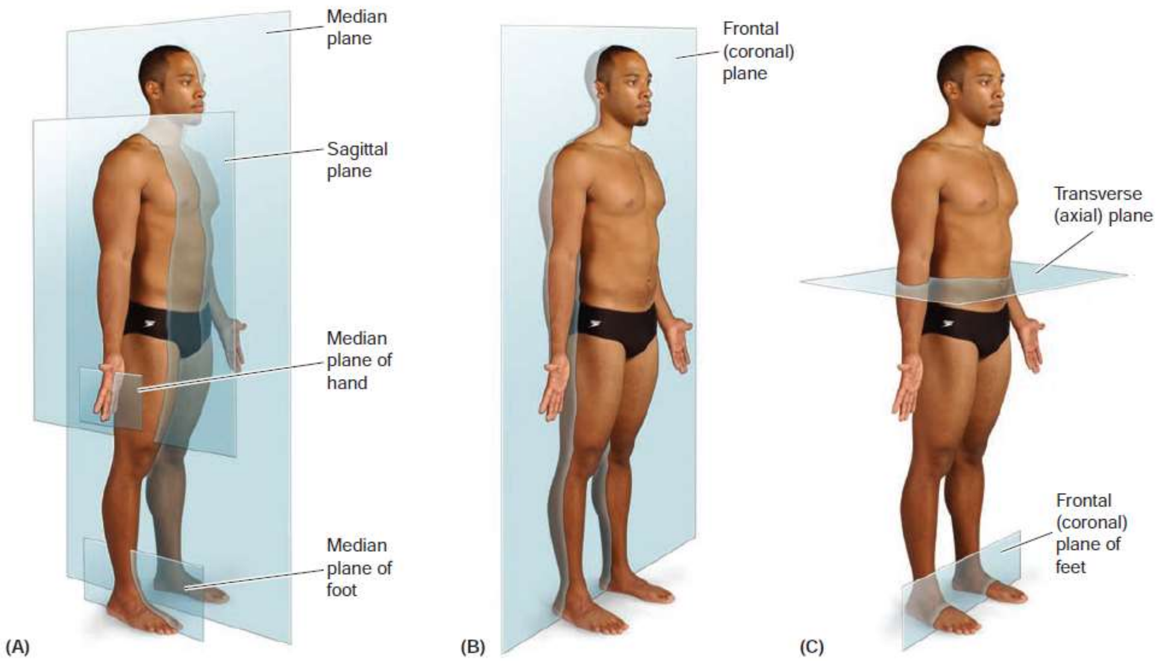

Figure 5.3: Standard anatomical planes[11]

ever, the anatomical interpretation was different when the subject was in the left side lying position. The frontal MR cross-section was equal to the sagittal anatomical plane and vice versa and the left and right interpretation was switched. In addition, in the transversal MR cross-section the image was rotated a quarter of a turn clockwise with respect to the upright and supine position. For the prone position, the anatomical planes were equal to the MR corss-section. However, the anatomical orientation was inversed with respect to upright and supine position. In other words, anterior and posterior were switched as well as left and right. In the transversal plane the SENS-U dummy was turned 180° with respect to the upright and supine position. The changes of the anatomical interpretation are shown visually in figure 5.4.

5.4 Data analysis

All images were processed using RadiANT DICOM viewer (Medixant, Poznan, Poland) and Adobe Photoshop CS6 (Adobe, San Jose, United States).

Full bladder shape To be able to compare the full bladder shapes in different positions, sagittal section of the bladder was chosen to be a starting point for comparison. This was chosen because the SENS-U measures in this plane as well. Because the gold standard in medical MRI is the supine position, this position is used as a reference to describe the changes in bladder shape.

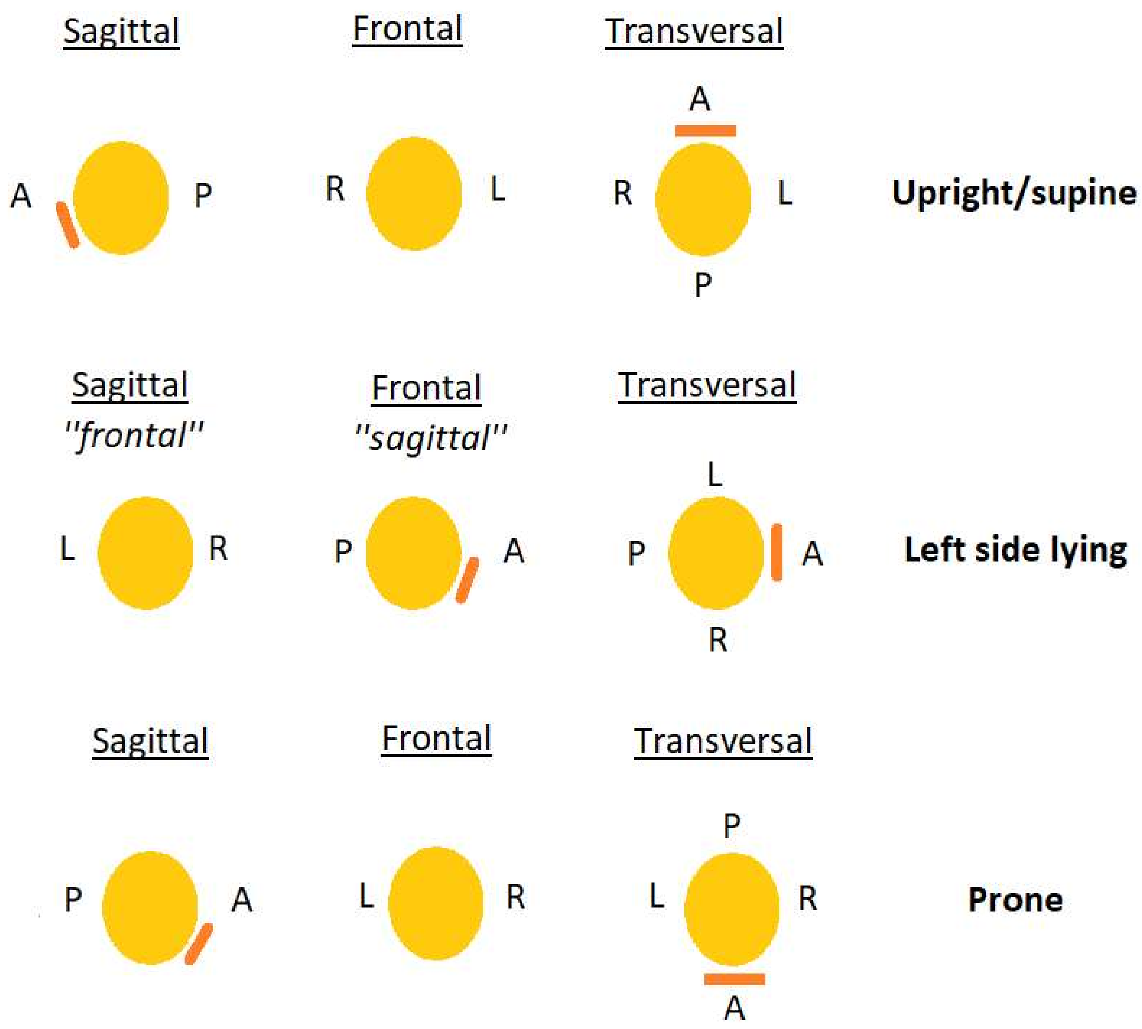

Figure 5.4: Interpretatioin of the anatomical orientation in different positions. The bladder is presented as a yellow sphere and the SENS-U is presented as an orange line. The MR crossections are presented with its anatomical orientation and anatomical plane within "quotations marks".

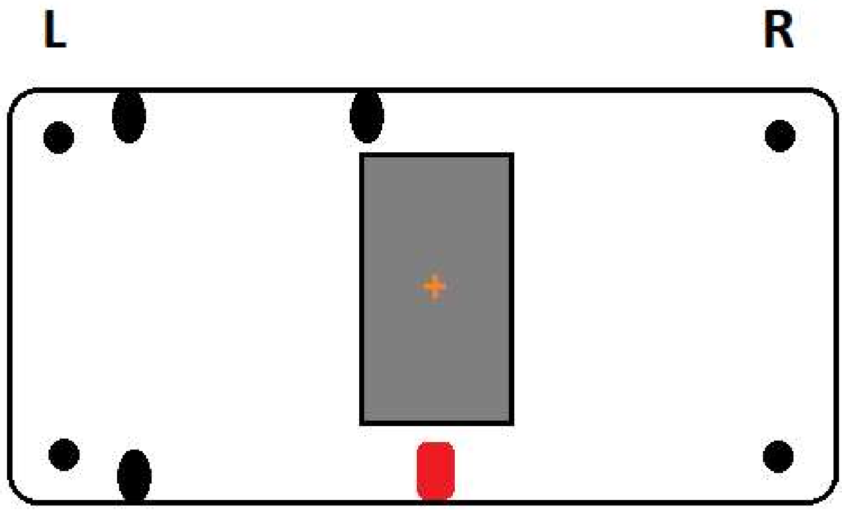

Figure 5.5: Schematic overview of the SENS-U silicone dummy with the middel whole (red) used as a reference point.

Selection of the images for analysis was the most important step. The SENS-U silicone dummy was used as a reference point. In a similar research, bone structure (e.g. lumbar spine or femur head) was used as landmark to create reproducible images.[41] However, due to the different positions in this study, femur and spine could not be held in the same position. Therefore, bone structure was unreliable to use as reference point. Figure 5.5, represents a schematic overview of the imprint of the silicone SENS-U dummy. Screwing holes of the device and the measurement window in the middle were represented black in the MR images and therefore a reliable reference point. We chose the red marker point in figure 5.5 as reference point, because it was in the middle of the SENS-U which was placed in the umbilical midline of the subject. Therefore we assumed that the red marker point represented the mid-sagittal view in the sagittal plane.

5.5 Theoretical volume measurement of SENS-U®

To determine the theoretical SENS-U volume, the FOV was drawn in the multiplanar reconstruction of the MR scans. These reconstructions were made using RadiANT DICOM viewer. The MRI was presented in the three MR cross-sections, as described in section 5.3. Orientation of the images was based on the middle of the SENS-U measurement window (the orange cross in the grey window, shown in figure 5.5). The slice was chosen in which the middle of the window was visible and in which the indicated axes in radiant were set perpendicular to the measurement window.

After that, images were imported in Photoshop CS6, where the direction of the four US channels corresponding to the FOV were drawn in the MR scans. The A-P bladder dimension for each US channel was determined † and with these values the theoretical estimated volume was calculated using a simple formula shown in equation 5.1. t is the time of each measurement, A_n is the distance to the anterior wall of the bladder measured by transducer n, P_n is the distance to the posterior wall of the bladder measured by transducer n, n is the numbering of the four transducers.

The difference between theoretical volume ans measured volume as calculated using equation 5.2. Equation 5.1 assumed that the A-P bladder dimension was equal to the Left-Right (L-R) bladder dimension. The multiplanar reconstructions were used to measure both A-P and L-R bladder dimension in the transversal plane. From these dimension, the A-P/L-R deviation, expressed in $\%$, was calculated between A-P and L-R, using equation 5.3. An A-P/L-R deviation of $\geq \pm$ 10 $\%$ was defined as significant.

$$V_{measurement}(t) \sim \sum_{n=1}^{4}[A_n(t) - P_n(t)]^2 \tag{5.1}$$

$$\Delta\text{volume}[\%] = \frac{\text{theoretical volume}-\text{voided volume}}{\text{voided volume}} * 100\% \tag{5.2}$$

$$\text{A-P/L-R deviation}[\%] = (\frac{\text{A-P bladder dimension}}{\text{L-R bladder dimension}} - 1) * 100\% \tag{5.3}$$

†A scaling factor of 2.89 was used to express MRI distances in Photoshop to veracious values.

Chapter 6

Results

In this study three participants were scanned. Two men and one woman for whom the baseline characteristics and voided volume after the scan protocol are presented in table 6.1.

6.1 Full bladder shape in different positions

Generally, all participants showed the same changes in bladder deformation. Figure 6.1 shows the MR images of participant I in the four different positions: supine, standing upright, prone and left side. The scans in supine and upright position showed an open bladder neck.

Relative to the supine position, it was seen that the in the upright position the bladder shape was compressed due to gravitational forces. The cranial-caudal (C-C) bladder dimension was decreased, while the A-P bladder dimension was increased over the entire height of the bladder.

In contrast to the upright position, the prone position had an increase in C-C bladder dimension and a decrease in A-P dimension. For these positions, gravity worked in

Parameters		**Participant I**	**Participant II**	**Participant III**
Gender	M/F	M	M	F
Age	$years$	28	60	32
Length	cm	192	193	172
Weight	kg	75	90	73
BMI	kg/m^2	20.3	24.2	23.7
Abdominal girth	cm	88	98	80
Voided volume	mL	950	450	400

Table 6.1: An overview of the baseline characteristics and the voided volume of the three participants.

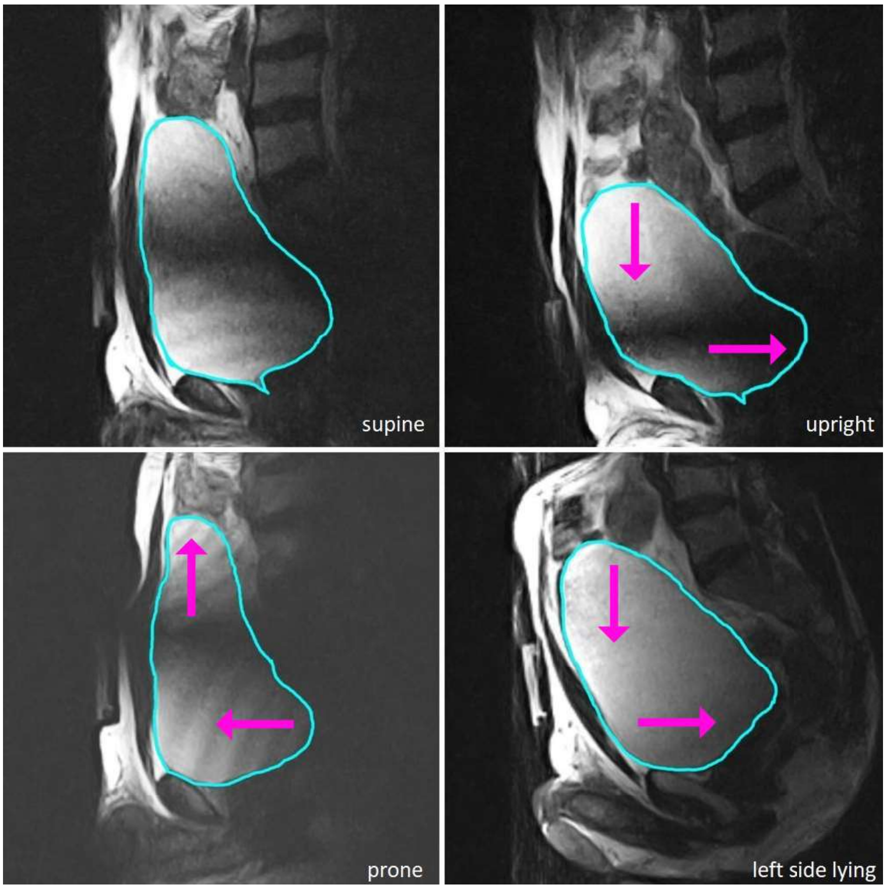

Figure 6.1: Four mid-sagittal MR scans of the bladder in positions: supine, standing upright, prone and left side lying. The light blue line indicates the bladder of participant I with a bladder volume of 950 mL. The pink arrows indicates the direction of the bladder deformation.

a different direction. In the standing position gravity pressed on the C-C direction, while it pressed on the P-A direction in prone position.

For the left side lying position it was seen that the bladder shape was different than the supine position as well. The C-C bladder dimension was decreased and the A-P bladder dimension was increased, equal to changes in the upright position. In the transversal plane of the left side lying position, it was seen that the bladder moved in the direction of the "free" side, right side in the left side lying position. Figure 6.2 presents the multiplanar reconstruction of the left side lying position.

Appendix A shows the mid-sagittal MR scans of the other participants in all four positions.

6.2 Inter participant differences

There was also difference between the subjects. In women, the bladder was expected to be positioned lower in the pelvis. Figure 6.3 shows the difference in the

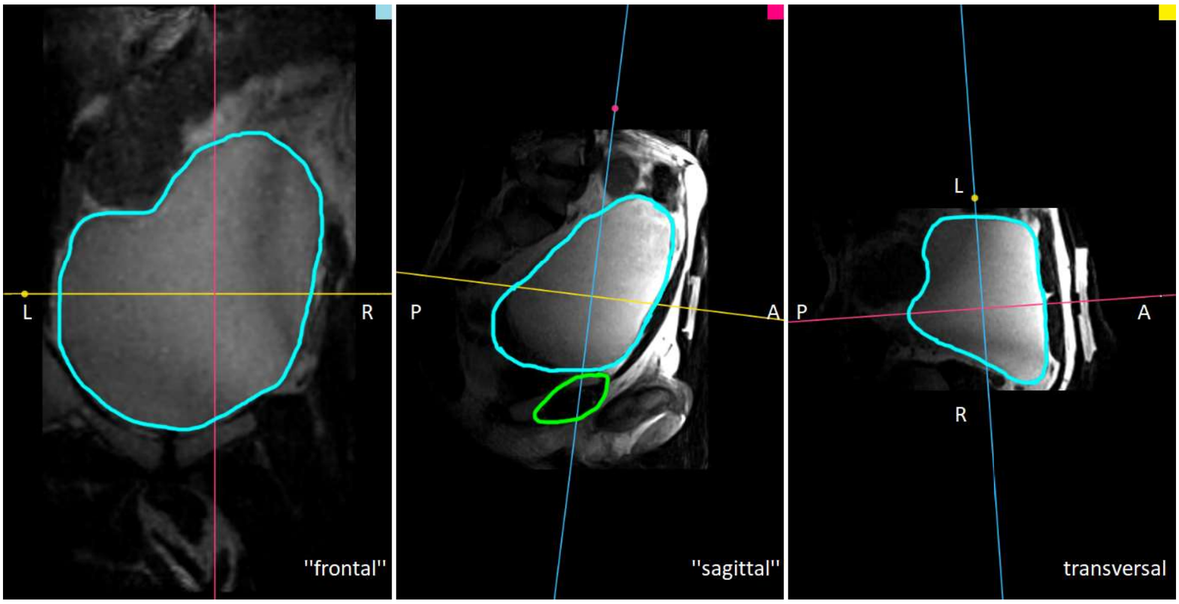

Figure 6.2: Multiplanar reconstruction of the bladder in left side lying position. The transversal plane shows that the bladder moves through the right side. The light blue and green line indicates the bladder and the pubic bone respectively.

bladder position between man and woman. Despite the volume differences, the majority of the female bladder was located behind the pubic bone and therefore positioned lower in the pelvis compared to the male bladder of comparable age.

In the participant with relatively much internal abdominal fat, it could be seen that the presence of fat was of big influence on bladder shape. It had less room of maneuver in the direction of the fat. Figure 6.4 shows the difference between relatively less and relatively much internal abdominal fat in the upright position. Abdominal fat caused an increase of gravitational effect on the bladder shape. The bladder expanded extra in the dorsal direction and therefore had a major effect on the A-P bladder dimension as well.

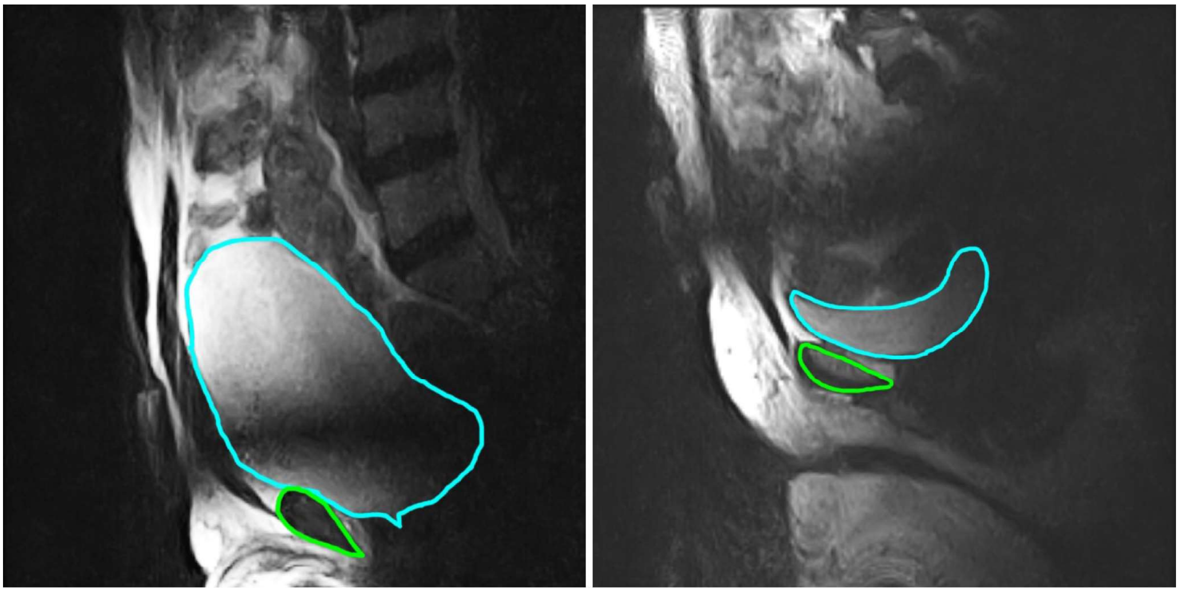

Figure 6.3: The bladder position of a male $<$ 35 years with volume of 950 mL (left) and a female $<$ 35 years with volume of 400 mL (right). The female bladder is positioned lower in the pelvis. The light blue line represents the bladder and the green line represents the pubic bone.

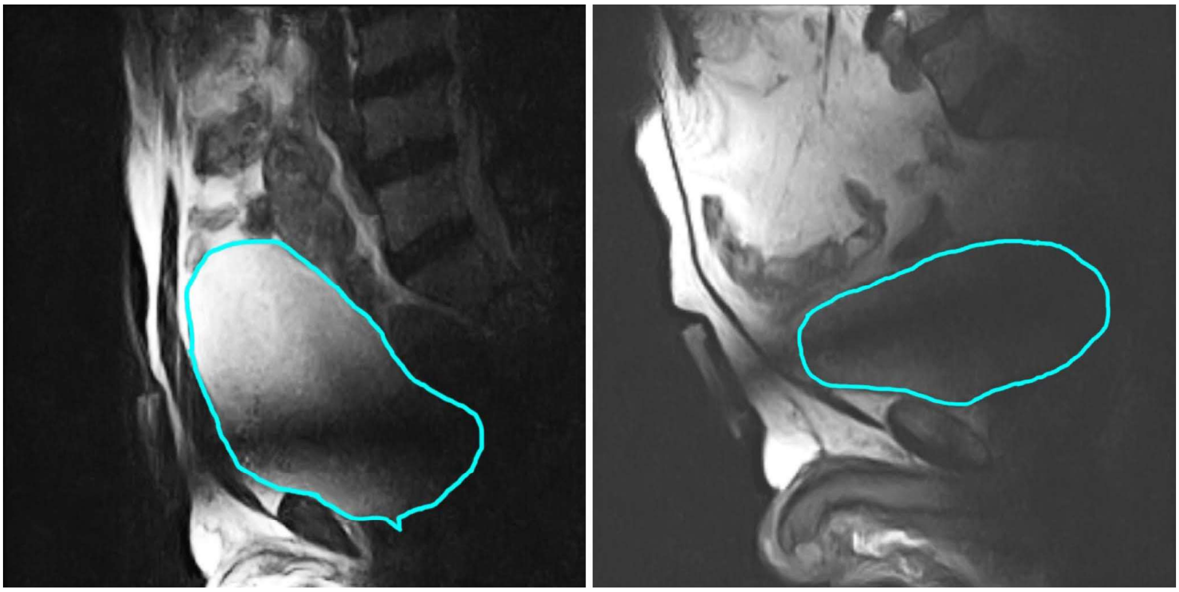

Figure 6.4: The bladder shape of adults with relatively less abdominal fat (left) and relatively much abdominal fat (right) in an upright position. The bladder expands extra in the dorsal direction with the presence of internal abdominal fat.

		upright	supine	left side lying	prone
	Participant I				
# US channels		4	4	4	4
volume $[mL]$	950	232	399	539	363
Δ volume [%]		-75%	-58%	-38%	-62%
	Participant II				
# US channels		3	4	2	4
volume $[mL]$	450	275	312	232	301
Δ volume [%]		-39%	-31%	-48%	-33%
	Participant II				
# US channels		1	1	1	3
volume $[mL]$	400	10	3	9	100
Δ volume [%]		-98%	-99%	-98%	-75%

Table 6.2: Overview of theoretical SENS-U data for each participant. Number of active US channels and theoretical volume are presented for each position separately. The measured voided volume is presented as well as the difference between the measured and the theoretical volume.

6.3 Theoretical SENS-U® volume measurement

Figure 6.5, 6.6 and 6.7 present multiplanar reconstructions of the three participants in upright position with the FOV of the SENS-U indicated. The bladder, pubic bone and the SENS-U were outlined in different colors. In every participant, the theoretical SENS-U measurement would be different. The bladder of participant I was visible in four channels of the theoretical SENS-U, while in participant II and III the bladder was visible in only three and one US channels respectively. This had major consequences for the theoretical volume measurements. An overview of the number of active US channels with corresponding theoretical volume for every participant for all positions is presented in table 6.2. In all participants the theoretical volume measurement was considerably underestimated independent of the position in which was measured.
Due to the large volume of participant I, a major part of the bladder outreached the FOV (figure 6.5) which was the cause of the underestimation. In the standing and left side lying position, the FOV was tilted upwards in participant II due to the presence of internal abdominal fat. Because the FOV changed in upward direction, it was not able to measure the bladder in the four US channels, which resulted in an underestimation of the theoretical volume (figure 6.6). The low positioned bladder of participant III (female) did not fall within the FOV or only partly. Therefore the theoretical volume was underestimated (figure 6.7).

In the transversal plane of the A-P and L-R bladder dimensions were visible. The theoretical volume measurement assumed that these dimensions were equal. Fig-

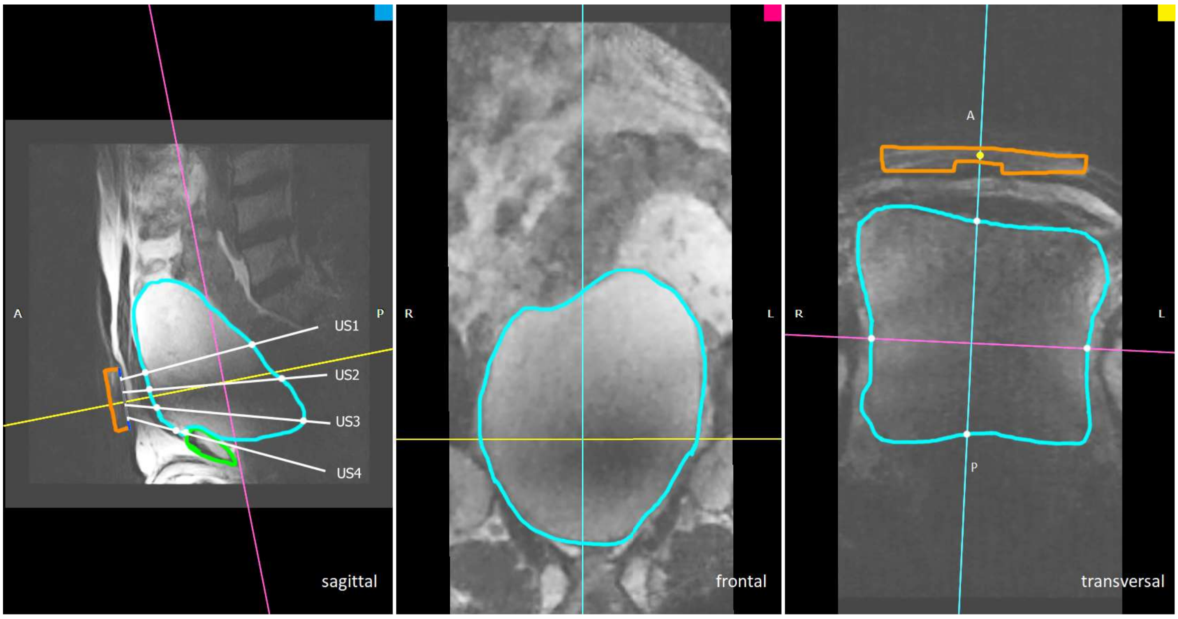

Figure 6.5: Participant I: multiplanar reconstruction of the bladder in the upright position with the theoretical FOV of the SENS-U. The bladder is outlined in blue, the pubic bone in green and the SENS-U dummy in orange.

	upright	supine	left side lying	prone
A-P/L-R deviation				
Participant I	-1%	-31%	-8%	-36%
Participant II	+79%	+30%	+41%	+14%
Participant III	–	–	–	–

Table 6.3: Overview of the A-P/L-R deviations for all participants in all positions.

ure 6.5 showed that this was the case in participant I. The A-P and L-R bladder dimension were 18.8 cm and 19.1 cm respectively, which was equal to a 1 $\%$ deviation. However, in participant II (figure 6.6) the A-P bladder dimension of 19.9 cm is much larger than the L-R bladder dimension of 11.1 cm. In this case, the bladder dimension deviated 79$\%$. For participant III and (figure 6.7), the bladder fell outside the FOV. As a result, the bladder was not visible in the transversal plane. For each position, the bladder dimensions deviated. In general there was seen that participant I had a slightly larger L-R bladder dimension, while participant II had a significant greater A-P bladder dimension. Table 6.3 shows the A-P/L-R deviation. Appendix B shows specified theoretical SENS-U data, including the A-P bladder dimension for each US channel, the theoretical SENS-U volumes and the A-P and L-R dimensions form the transversal plane.

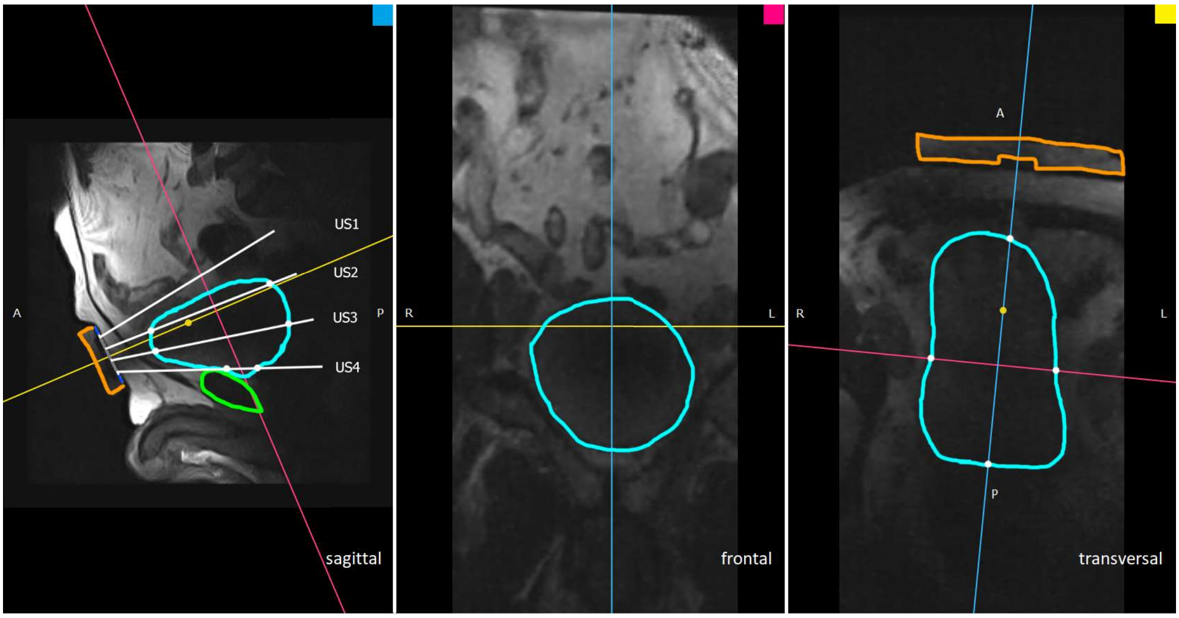

Figure 6.6: Participant II: multiplanar reconstruction of the bladder in the upright position with the theoretical FOV of the SENS-U. The bladder is outlined in blue, the pubic bone in green and the SENS-U dummy in orange.

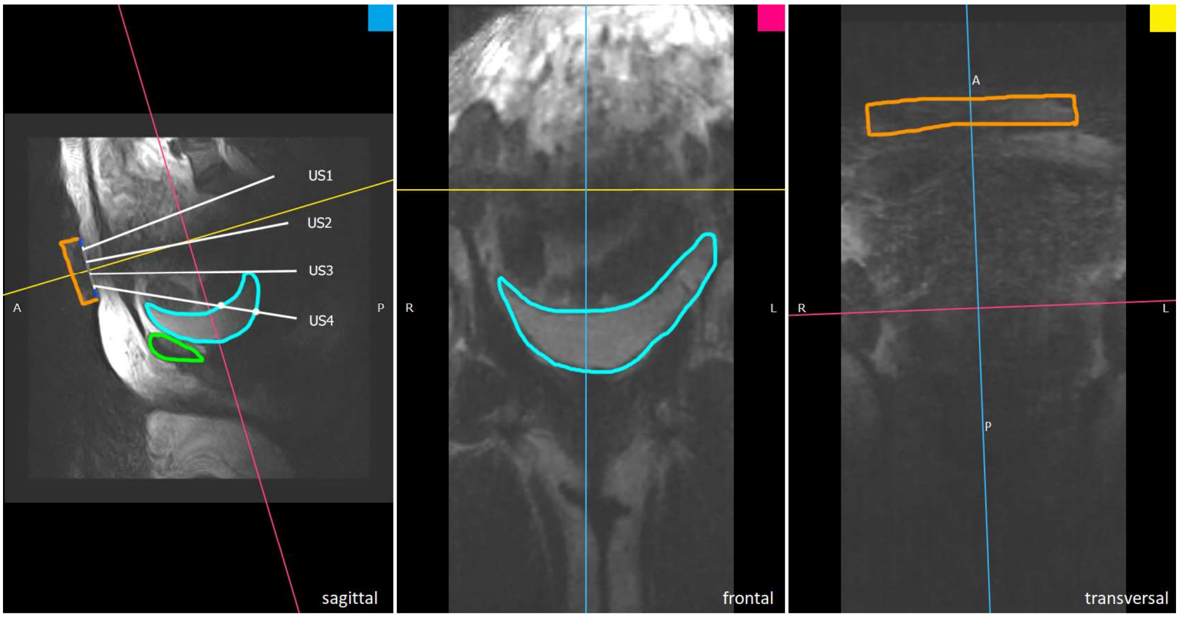

Figure 6.7: Participant III: multiplanar reconstruction of the bladder in the upright position with the theoretical FOV of the SENS-U. The bladder is outlined in blue, the pubic bone in green and the SENS-U dummy in orange.

Chapter 7

Discussion

The purpose of this pilot study was to determine if the full bladder shape changed in different body positions and to determine the effect of these positions on the theoretical SENS-U® measurement. In contrast to the study of Kristiansen et al.,[41] we have seen that the shape of the full bladder did change in different positions. In addition, we saw that this affected the A-P bladder dimension in particular. This was a great insight for the interpretation of the SENS-U measurement. We have seen before, in the trial measurement (chapter 4), that the SENS-U measured different A-P dimensions with, the same voided volumes. Next to that, we have seen a position dependency of the SENS-U data, which can now be explained by the full bladder deformation in different positions.

Originally, the SENS-U was designed for children, because of their compact anatomy. There is a big desire to develop an adult version of the SENS-U to solve incontinence problems in elderly. However, the anatomy was more complicated because of the lower positioned bladder and the likelihood and presence of internal abdominal fat. We have seen that in men with less abdominal fat, the SENS-U measured with all four US channels, meaning that the current FOV is accurate in this group. On the other hand, results show that the SENS-U would not measure accurately with the presence of internal abdominal fat. We have seen that the current FOV was sufficient in this type of participant, but that it led to a major underestimation for the volume calculation. Practically, this means that the SENS-U measures a large bladder dimension, resulting in a large bladder volume, while in reality the bladder not full.

Also, we have seen that the bladder in women was positioned lower in the pelvis, behind the pubic bone. Therefore, the current measurement method is not usable for adult women. Optimization of the FOV, pointing more than 30° downwards into the pelvis could be a solution for the use of the SENS-U in women. In addition, results showed that the A-P and L-R dimensions were not always equal, which was assumed in the theoretical SENS-U volume measurement. Therefore, adjusting the FOV in the L-R direction, next to the C-C direction, might improve the accuracy of the SENS-U.

7.1 Limitations

This study had some limitations of the scan protocol. First, this protocol had to use the Flex Coil to scan on the left side lying position. The original lumbar spine coil was not suitable. Unfortunately, this resulted in a lower image quality because the flex coil had only surface view of the patient, while the original lumbar spine coil was placed all around the participant. Second, the participants were placed in the MRI scanner with a full bladder. Therefore, it was necessary that the duration of the scan protocol was limited. There was decided to do less accurate scans and shorten the single scans to 5 minutes with the disadvantage that the image quality was reduced.

Despite the short scans, the total duration of the protocol was still $\pm$ 60 minutes. This caused a the third limitation of the scan protocol. During this 60 minutes, there could have been urine production and that the bladder volume was possibly increased during the scan protocol. Last, the theoretical volume equation was based on SENS-U data from a sitting position. In this scan protocol. the sitting position was not included due to limited time and the impractical implementation. Therefore, calculation of the theoretical volumes could not be compared with the theoretical volume in sitting position, on which the calculation was based. In other words, there was no gold standard for the theoretical volume calculation.

In addition, there were remarks and comments on the participants. First, only three participants were included in this study and they had clear inter participant differences. Therefore, it might not describe the healthy adult group as a whole. Second, because the study was performed in adults, it gained only generally insight in the working mechanism of the SENS-U for children. We assumed that the gravitational effect on the bladder in different positions would be the same in children and adults. Third, participant two fell in the category $\geq$ 60 years and had presence of abdominal fat. Therefore, we were not able to distinguish between these two categories. On the other hand, we can assume that in elderly the presence of abdominal fat is more to be expected. The main insight in this type was that the internal fat had a significant increasing effect on the A-P bladder dimension and resulted in volume underestimation. Fourth, volume underestimation was also seen in the young adult with relatively little abdominal fat. This participant had an unhealthy large volume of 950 mL, which was $>$ 150 $\%$ of the adult EBC for which the FOV of the SENS-U was not designed. Probably, this participant had not strictly follow the drinking instructions of 300-400 mL two hours before the start of the scan sessions.

A study, which investigated bladder shape and bladder filling, stated that rectal filling is a significant phenomenon which influenced the bladder shape.[21] This phenomenon was also clearly visible in several MRI scans of this study. We did not investigate the effect of rectal filling on the A-P bladder dimension in detail. However, depending on the amount of rectal filling, we can assume that this has effect on the bladder dimension.

7.2 Feature research

Feature research should give more insight in the effect of the changes in bladder shape on the A-P (and L-R) bladder dimension and the theoretical SENS-U measurement. For this research, it is important to perform this study in children to optimize and see the effect of the current SENS-U. On the other hand, this research gave insight in the bladder measurement in adults. It was seen that an adjusted FOV (pointing downwards more than 30° and adding L-R view) of the SENS-U is a possible solution to solve formerly ”adult” problems. Future research can be performed on a similar data set, in which the theoretical FOV can be drawn in to the MR images. For this study, a lot more participants and a wider range of adults should be included. From this data, the most optimal FOV change could be determined. For extra insights, it is recommended to create 3D models of the full bladder shape and the pubic bone. Based on that model, an optimal FOV could be determined for an adult SENS-U.

Chapter 8

Conclusion

This pilot study showed that a full bladder shape did change due to different body positions. It showed that, in general, the bladder shape changed in equal direction for every different position. There were inter participant differences which showed that the bladder was positioned lower in females and that the presence of inter abdominal fat had a major increasing effect on the A-P bladder dimension. In addition, it showed that the theoretical SENS-U® volume was underestimated in all participants. This was not caused by position change, but was likely due to deviations in the measured bladder and the differences between A-P and L-R bladder dimension.

Part II

SENS-U® Bladder Sensor: continuous home monitoring of natural nocturnal bladder filling in children with nocturnal enuresis

Chapter 9

Background and hypothesis

In this second part, we wanted to examine the usability of the SENS-U for ambulatory care in children with NE. In a recent study, results showed that the SENS-U was able to detect a full bladder during (video) urodynamic research, with a detection rate of 90%. When excluding erroneous data due to sensor misplacement or an (relative) obese abdomen, a full bladder was detected in all patients.[5] Based on that, we expect the SENS-U will be able to detect NNBF cycles. However, based on research described in chapter 4, the A-P bladder dimension is highly expected to be position dependent. In this pilot study the following research questions will be answered:

"Is the SENS-U® able to measure correct natural nocturnal bladder filling cycles?"
"Does the anterior-posterior bladder dimension depend on body position?"

Chapter 10

Methods

This home-based observational pilot study was performed in collaboration with the department of pediatrics of the Jeroen Bosch Hospital ('s-Hertogenbosch, The Netherlands).

10.1 Patients

Fifteen children with mono-symptomatic nocturnal enuresis, between the age of 6 to 12 years, were included in this study. Their parents agreed to let their children participate in the study and all the children were capable of understanding the study procedure. Exclusion criteria were 1) patients with a small bladder capacity ($< 65\%$ of the EBC), 2) patients with breached skin, open wounds, sutures or major scar tissue in the suprapubic region and 3) patients that used a (suprapubic) catheter during the night. When parents signed informed consent, an appointment was scheduled for a nocturnal measurement at home.

10.2 Data acquisition

The study protocol, presented in figure 10.1, was used during this study. Before the measurement started, the incontinence evaluation data (see appendix D) and patient characteristics (differential diagnosis, gender, age, length, weight and AG) were collected. Unknown patient characteristics were gathered during the measurement appointment. AG was measured between the bottom of the ribs and the top of the pelvis, directly on the skin. Measurements were performed with the SENS-U® Bladder Sensor (Novioscan, Nijmegen, The Netherlands) which used Sonogel ® (Sonogel Vertriebs GmbH, Camberg, Germany) for signal transmission.

At the day of the measurement, the investigator visited the child at home before bedtime. Parents and child were asked to fill in selected questions from the children's

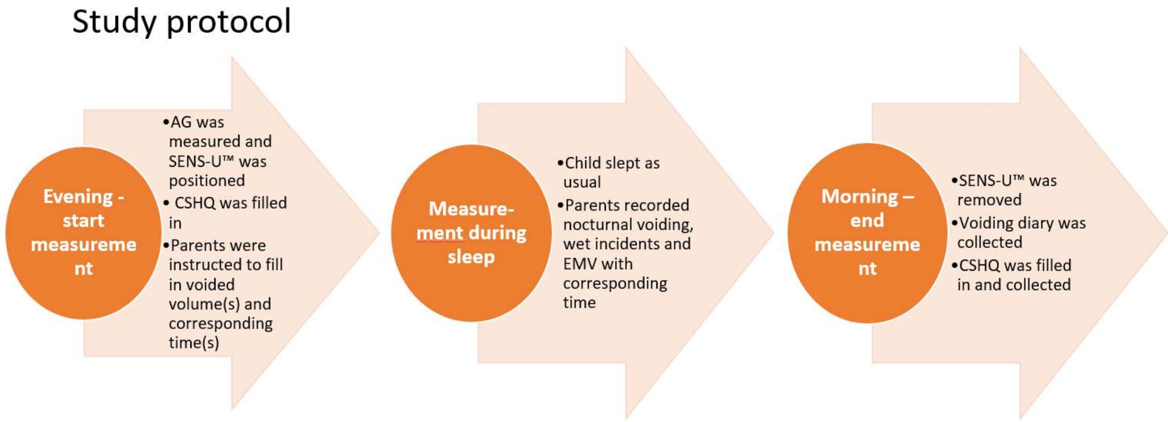

Figure 10.1: Flow chart of the study protocol.

sleep habit questionnaire (CSHQ)[43,44] (for a translated Dutch version, see appendix E). According to the user manual, the SENS-U with US gel was positioned, with an adhesive, on the lower abdomen, in line with the umbilicus and 1 cm above the pubic bone. Position check was performed to determine whether the bladder was positioned within the field of view of the SENS-U.

From this moment, the anterior-posterior bladder dimension and the body position (upright, upside down, supine, prone, left or right side) were measured every 30 seconds until the researcher stopped the measurement the next morning. Importantly, the full bladder notification of the SENS-U were turned OFF during this study to prevent disturbing the child's night rest unnecessarily. During the night, the parents were asked to report the time and volume of nightly voiding, wetting incidents and EMV.

In the early morning of the next day, the investigator visited the patient to remove the SENS-U and examined possible skin reactions of the adhesive or the US-gel. After the nightly measurement, the selected questions of the CSHQ were filled in again about the measurement night.

10.3 Data analysis

Descriptive statistics . The acquired data was saved at an online platform for capturing high quality medical research data: Castor EDC (Amsterdam, the Netherlands. Descriptive statistical analysis was performed using Excel (Microsoft, Washington, United States). Data were expressed as mean $\pm$ standard deviation. The SENS-U contained data about the quality of contact between the sensor and the patient. Based on these data, the time that the SENS-U was worn was calculated.

Based on the body sensor data, the moment of sleep was determined. This was defined as the start of a period $\geq$ 10 samples in a non-upright position with the exception of 1 sample. This could be a "sitting position", caused by a position transition from left to right side via an apparent sitting position. A NNBF cycle was defined as a bladder filling cycle during the nocturnal phase, from the moment of sleep to the moment of the first morning void. The voiding diary was used to determine the moments of nocturnal and early morning voiding. These moments were added to the visual SENS-U data in addition to the moment of sleep.

The total number of NNBF cycles based on the voiding diary were determined and the number of successful detected NNBF cycles by the SENS-U as well. The success rate was calculated according to equation 10.1. The SENS-U data converted from dimension to volume by dividing by 0.21 mm/mL based on previous research.[5] The accuracy of the SENS-U was analyzed as well. Acceptable accuracy was around a linear trend line with the mean slope of 0.21 mm/mL with a spread of $\pm 20\% \pm 20mL$.

$$\text{NNBF success rate} = \frac{\text{Number of NNBF cycles of voiding diary}}{\text{Number of successfully detected NNBF cycles by SENS-U}} \tag{10.1}$$

Theoretical notification success rate The theoretical notification success rate was determined as well. The notification threshold was defined as 80$\%$ of the EBC of the patient. The conversion factor from bladder capacity (mL) to A-P bladder dimension (mm) of $0.21mm/mL$, described before, was used to determine the notification threshold as a dimension. The notificaton success rate was calculated by dividing number of voiding moments which were equal or greater than the threshold by the total number of voiding moments, see equation 10.2.

$$\text{Theoretical notification success rate} = \frac{\text{Number of successful notifications during voiding}}{\text{Total number of voiding moments}} \tag{10.2}$$

Position dependency Position dependency was determined based on the position transition factor (PTF). This factor was calculated using equation 10.3. A PTF $\leq$ 0.8 or $\geq$ 1.2 was defined to be significant. In other words, a deviation of $\geq$ 20 $\%$ between two positions was significant.

$$\text{PTF} = \frac{\text{A-P dimension new position}}{\text{A-P dimension old position}} \tag{10.3}$$

Position	Correction factor
Supine	0.73
Left side lying	0.87
Right side lying	1.02
Prone	0.70
Standing	1.55

Table 10.1: Overview of the correction factors for each position with respect to the sitting position.

When the bladder dimension was depended on the position, correction could be performed based on correction factors. These factors were calculated in a study performed by a master 2 student of technical medicine. In this study, the A-P bladder dimension was measured with the SENS-U of 25 healthy adults with a full bladder in different positions. For one minute each, the bladder dimension is measured in the positions: 1) supine, 2) left side lying 3) right side lying 4) sitting 5) standing 6) supine and 7) prone. Based on the voided volume and the position dependent A-P bladder dimension the correction factor was calculated using the sitting position as a reference. The correction factors for each position are represented in table 10.1. An other attempt to solve position dependency, was removal of accelerated measurements. Details can be found in appendix C.

Chapter 11

Results

A total of fifteen patients participated in this study, 13 (87 $\%$) boys and 2 (13 $\%$) girls. In one patient (study number: 01), contact between the SENS-U and the skin was suboptimal, so the bladder dimension could not be measured by the SENS-U. Therefore, this patient was excluded before conducting (descriptive) analysis. Another patient woke-up during the night, using a wetting alarm, and immediately went voiding. The urine loss was negligible and therefore this patient was considered dry.

11.1 Descriptive statistics

The mean age of the patients was 8.6 $\pm$ 1.5 years and they had an BMI of 16.7 $\pm$ 1.7 kg/m^2 and an AG of 61.5 $\pm$ 5.9 cm. The bladder volume during holding exercise, based on the incontinence evaluation, data was 240 mL $\pm$ 75 mL and the children had moderate to severe NE.

The SENS-U was worn for about 12 $\pm$ 1 hr. During the measurement night six children (43 $\%$) were dry during, while eight children (57 $\%$) had bedwetting incidents. The children with wet incidents had urine loss of 128 $\pm$ 82 mL (8 - 244 mL) over the night. During the night the patients slept in different positions; 33 $\pm$ 18$\%$ supine, 20 $\pm$ 12$\%$ on the left side, 24$\pm$ 14$\%$ on the right side, 19 $\pm$ 11$\%$ prone.

11.2 Individual measurements

In this section, a few individual examples of the over-night measurements were described. The patients were categorized in two groups: dry and wet incidents. The upper graph with the red line presents the A-P bladder dimension and the lower graph (blue) presents the body position, both measured by the SENS-U. The grey areas wiped out SENS-U data when the sensor was not attached to the patient.

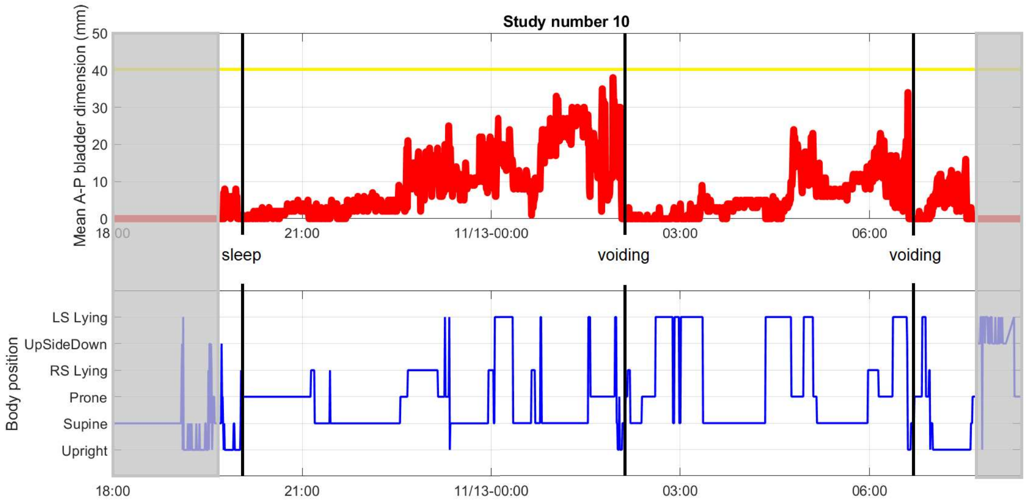

Figure 11.1: Subject 10 (boy, 7 years) was dry during the measurement night. Sleep at 20:00 hr; nightly void at 02:20 hr, volume = 160 mL and A-P bladder dimension = 30 $mm \sim$ 143 mL. First morning void at 06:30 hr, volume = 140 mL and A-P bladder dimension = 34 $mm \sim$ 162 mL. Total number of NNBF cycle(s) = 2, successfully detected = 2. Threshold level: 40 mm.

The yellow line represent the threshold level for notification based on 80$\%$ of the EBC and the black lines indicate moments of sleep and moments of voiding. Other measurements can be found in Appendix F.

11.2.1 Dry

Study number 10 This boy of 7 years old went to sleep at 20:00 hr and did a nightly void at 02:20 hr with a volume of 150 mL. The first morning void was at 06:30 hr and had a volume of 140 mL. Both were successfully detected by the SENS-U. This patient had two NNBF cycles. Data is shown in figure 11.1

11.2.2 Wet incidents

Study number 05 This girl of 8 years old went to sleep at 20:10 hr with a filled bladder according to the SENS-U and slept through the night. The overnight urine loss was 244 mL. Looking at the A-P bladder dimension data in more detail, it could be assumed that there was a bladder emptying at 21:35 hr and probably at 02:55 as well. The first void in the morning was at 07:45 and had a volume of 65 mL which represented an incomplete bladder filling cycle. Despite the incompleteness, the bladder filling was successfully detected by the SENS-U. This patient had one (incomplete) NNBF cycle. Other possible nocturnal bladder filling cycles could not be determined due to missing voiding diary data. Figure 11.2 shows the data of this patient.

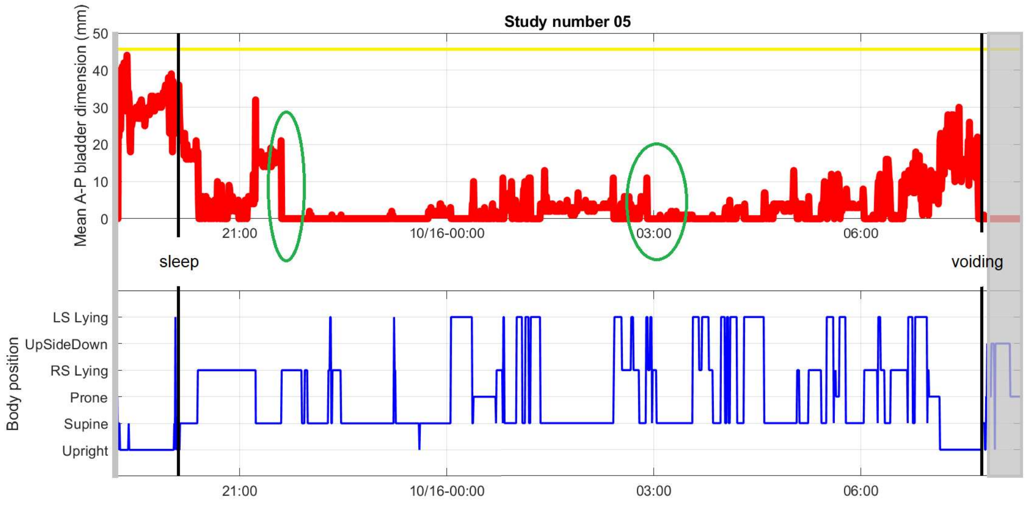

Figure 11.2: Subject 05 (girl, 8 years) was wet during the measurement night. Sleep at 20:10 hr; first morning void at 07:45 hr, EMV = 65 mL and A-P bladder dimension = 22 $mm \sim$ 105 mL. Nightly urine loss = 244 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Possible urine loss is presented by the green sphere. Threshold level: 46 mm.

Study number 06 This patient was a boy of 8 years old and went to sleep at 20:50 hr and slept through the night. At 07:00 hr, the first void in the morning had an EMV of 145 mL and there was urine loss of 100 mL over the night. Based on the EMV, the bladder capacity of the patient was greater than the urine loss over the night. Therefore, it was possible that this urine loss was caused by nightly over activity, although the patient was not familiar with over activity. Looking at the bladder dimension data in more detail, it seemed that the patient loses urine in shoots around 01:30 hr and 04:00 hr. However, this could not be stated with great certainty because of missing voiding diary data and position dependency of the A-P bladder dimension (explained later in this chapter). At least, this patient had one NNBF cycle, based on the voiding diary which was successfully detected by the SENS-U as well. Figure 11.3 shows data of this patient.

11.3 NNBF cycles measured by the SENS-U®

Appendix F showed the mean A-P bladder dimension and body position over the measurement night of all patients individually. The NNBF cycles based on the voiding diary were represented in the SENS-U measurement data with the corresponding volume. In total, eighteen NNBF cycles were defined based on the voiding diary. Three patients (21$\%$) had more than one NNBF cycle based on the voiding diary. The SENS-U observed fifteen of the NNBF cycles, resulting in a success rate of 83 $\%$. The three missed NNBF cycles by the SENS-U had a volume of less than 30 mL, which was at the lower limit of the sensitivity of the sensor.[5] When the NNBF

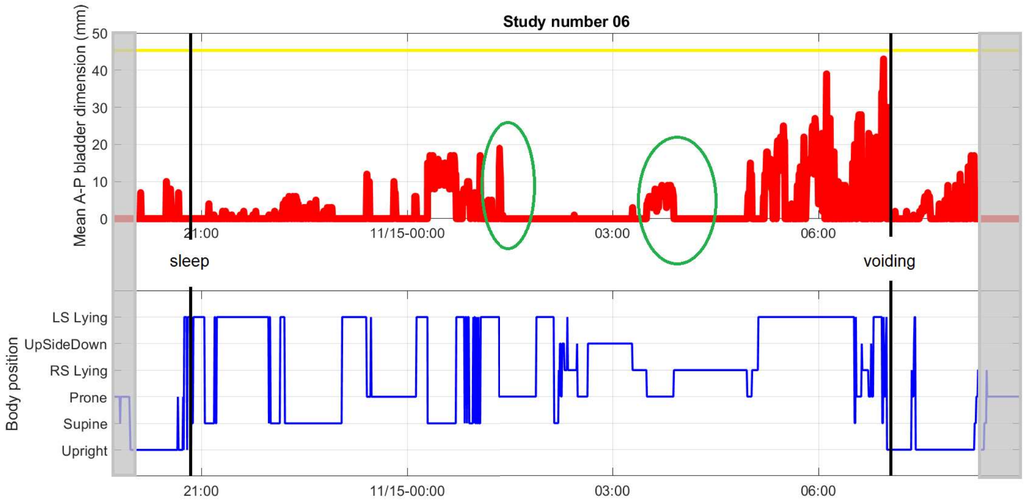

Figure 11.3: Subject 06 (boy, 8 years) was wet during the measurement night. Sleep at 20:50 hr; first morning void at 07:00 hr, EMV = 145 mL and A-P bladder dimension = 30 $mm \sim$ 143 mL. Nightly urine loss = 100 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Possible urine loss is presented by the green sphere. Threshold level: 46 mm.

cycles with a volume $\leq$ 30 mL were excluded, the success rate of the SENS-U was 100 $\%$.

Figure 11.4 shows the measurements of the SENS-U and the corresponding EMV. The graph shows that half of the measurements were measured accurate, while the other measurements mainly measured a too high A-P bladder dimension for the EMV which was actually present in the bladder.

11.4 Theoretical notification success rate

As described in the previous section, the total number of NNBF cycles based on the voiding diary was eighteen. From these voiding moment, three A-P dimensions were bigger or equal to the set theoretical notification level, while fifteen moments were not. The theoretical notification success rate was 17 $\%$. Remarkably there were bladder dimensions seen during the measurement which were bigger or equal to the notification level, when there was no indication of voiding. An example can be seen in appendix F, figure F.2.

11.5 Position dependency

Figure 11.5 shows one example of the mean A-P bladder dimension and the body position of a patient that was dry during the measurement night. In other words, there was one NNBF cycle without leakage. The cycle started at the moment of

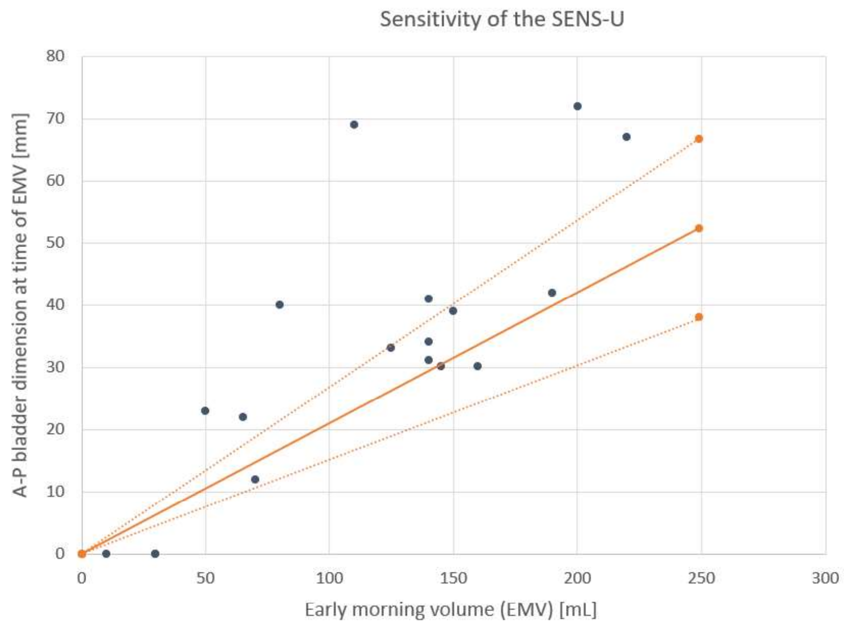

Figure 11.4: Accuracy of the SENS-U for measuring the A-P bladder dimension that correlates to the voided volume. The mean slope is 0.21 mm/mL with a spread of $\pm 20\% \pm 20mL$

sleep at 22:20 hr and ended at the micturition time at 08:30 hr. In this period, the A-P bladder dimension did decrease, despite the increase of bladder volume without leakage. At different times (green lines) the A-P bladder dimension changed together with the position. Table 11.1 presents the position transition and the corresponding PTF for the specified times in figure 11.5. The bladder was within the view or outside the view of the sensor, explaining ∞ and 0 respectively. This was a common phenomenon in the SENS-U measurement over the night. It was also seen that there have been a change in A-P dimension within the same position (yellow lines). The bladder was also within or outside the view of the sensor, shown in table 11.1

Time (hh:mm)	Transition	PTF
02:10	supine - prone	0
02:40	prone - supine	0
06:10	supine - left side	∞
06:25	left side - supine	0
06:45	supine - right side	∞
02:25	*supine - supine*	∞
05:55	*prone - prone*	0

Table 11.1: Overview of change in A-P bladder dimension and body position with corresponding PTF.

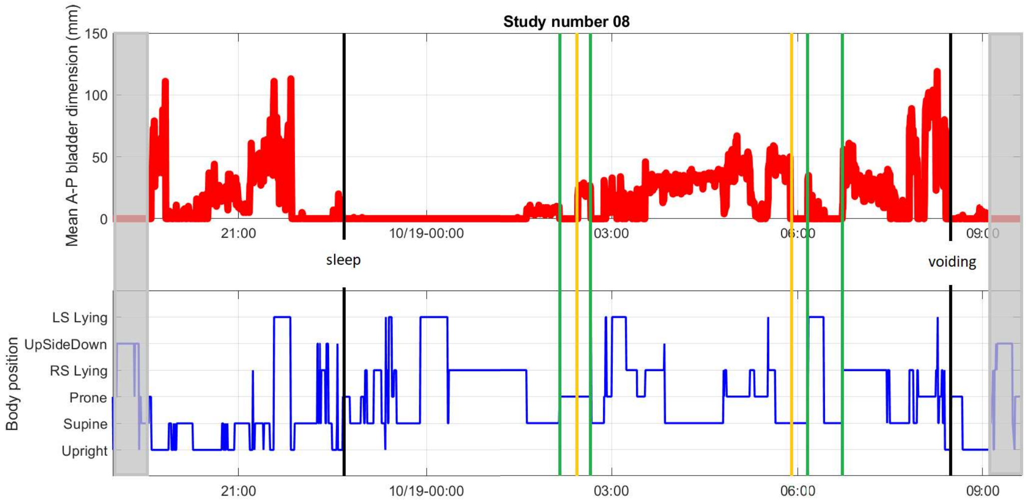

Figure 11.5: SENS-U measurement of study patient 08, who was dry during the measurement night. The mean A-P bladder dimens ion and the body position are presented. The time of sleep and micturition are reflected by the black lines and the position transitions are reflected by the green and yellow lines.

11.6 Correction of the position dependency

Figure 11.6, shows the correction of the A-P bladder dimension using the correction factor described in chapter 10. There can be seen that there was still position dependency of the new A-P bladder dimension. Obviously, this correction method did not work when the bladder was outside of view of the sensor, with an A-P bladder dimension of 0 mm. This phenomenon was the main issue for position dependency in this study.

11.7 Wearing the SENS-U® during the night

The questionnaires showed that wearing the SENS-U had no effect on falling asleep and the duration of the the sleep. Four children (29%) woke-up during the night once, using the SENS-U, while they did not wake up generally.

Five children (36 %) had visible pressure points of the SENS-U and another five children (36%) had skin irritations. One patient (7%) had both pressure points and skin irritations. In three children (21%) the US gel was slightly sprouted to the outside of the measurement window, but that did not adverse effect on the measurement.

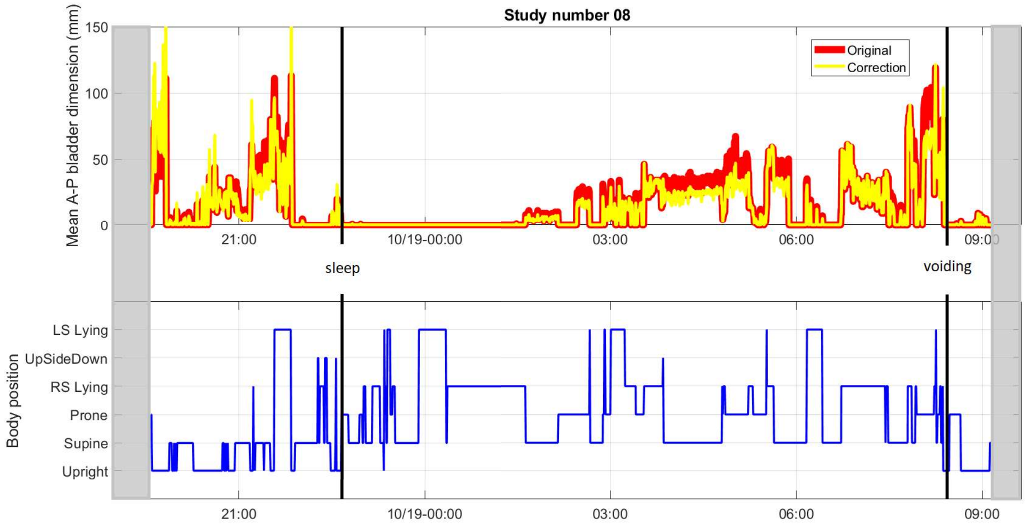

Figure 11.6: SENS-U measurement of study patient 08. The red line representing the original mean A-P bladder dimension and the yellow line representing the corrected measurement data.

Chapter 12

Discussion

The aim of this study was to examine the usability of the SENS-U® Bladder Sensor for ambulatory care in children with NE. This study showed that the SENS-U was able to measure NNBF cycles successfully, but that the theoretical notification and the accuracy of the sensor in this study were poor to moderate. It also showed that the A-P bladder dimension was dependent on body position and up to now, we were not able to solve this position dependency, mainly because the bladder was (often outside the field of view. If the position dependency can be solved, which is likely to cause an increase in successful theoretical notifications, the SENS-U might be a successful new device for bedwetting ambulatory care.

In all the measurements, a trend of the bladder dimension was visually perceptible. This indicated that the SENS-U measured a bladder filling indeed. Because the bladder was sometimes out of view, a trend line of the data could not be estimated with curve fitting. To solve position dependency, it might be an option to estimate the trajectory of the bladder filling, possibly using a Kalman-filter. However, this is an extensive method which probably is not suitable for the simple working mechanism of the SENS-U and its limited memory capacity.

The current sample frequency of the SENS-U was 0.033 Hz. In other words, every 30 seconds, a measurement was performed, while the patient was asleep. This sample frequency was determined for day-time measurement with a faster bladder filling than a nocturnal bladder filling. So, this sample frequency is too high for nocturnal measurements. This might also be of influence of the position dependency. A possible method to solve position dependency is to increase the sample frequency. To increase the sample frequency in this data set, it is recommended to select windows of ten minutes and determine its median bladder dimension. Why using the median? Because the main problem was that the bladder fell outside of view and therefore the bladder dimension was zero. When the median is calculated over a window of ten minutes, these zero's will be neglected.

In this study, it was seen that the theoretical notification rate, with a threshold level of 80% of the EBC, was very poor. On the one hand, this was caused by missed NNBF cycles, probably because the low nocturnal bladder capacity of the patients. In addition, children that did have wet incidents have lost urine during the night, before they reached their 80% EBC threshold. On the other hand, there should have been a lot of false positive notifications. This might by caused by the unstable, position dependent bladder dimension. In this status of research, the theoretical notification rate was not accurate. To improve the notification rate, especially for children with NE, the threshold could be based on the average EMV, which can be collected over a number of nights. Next, the position dependency must be solved to reduce the false positive notifications and to gain more insight in the (theoretical) feasibility of the SENS-U.

The accuracy of the SENS-U measurement, in correlation to the EMV, was moderate. Only half of the bladder dimensions measured at times of the EMV correlated to the EMV as expected. In other words, the SENS-U overestimated the bladder volume. One reason for this could be the position. The accuracy of the sensor was determined in a sitting position, while the children were lying during most of the measurement. In the MRI study, part I, we have seen that the gravitational force had a major influence on the A-P bladder dimension. It is expected that the bladder dimension in an upright position, during voiding, will be larger than a bladder dimension in a lying position. This might explain the over estimation of the SENS-U in this study. On the other hand, the highest bladder dimension at the time of voiding (with a deviation of maximal 2 minutes) was selected for analysis. This might explain the bladder dimensions that were too high for correlation with the EMV. It might be better to select an average A-P bladder dimension from a window of 3-5 minutes backwards from the time of EMV.

12.1 Limitations

There were some limitations regarding the protocol of this study. The parents were asked to fill in the voiding diary during the measurement. They all were devoted, because (early morning) volumes were collected in all patients. However, the time notation was not always accurate and in accordance with the SENS-U. Sometimes, there was a difference between the voiding diary and the time of voiding according to the SENS-U with a maximum of almost 15 minutes. This made the determination of the bladder dimension at the time of voiding inaccurate.

In additions, 57% of the children had bedwetting accidents. Unfortunately, these children did not wake up during the night nor did the parents to notate the time and volume of the wet accident. Because of this missing voiding diary data, not all NNBF cycles, which seemed to be measured with the SENS-U, could be verified. For future research it is recommended to use a bedwetting alarm in addition to the protocol, to wake up children during a wet accident and to collect its time and volume.

According to the SENS-U manual, children with a body mass index higher than the 95^{th} percentile are contraindicated. However, this was not included in the exclusion criteria of this study and it turned out that two children (patient 06 and patient 11) fell within this category. Remarkably, the measurement of these children was not diverging from other measurements.

During the measurements, it turned out that a few children had a relapse of their incontinence and suffered from day-time incontinence as well. According to the guidelines, these children should be categorized as NMNE.[7] Despite the mismatch in categorization of the protocol, these children were analyzed like the others. SENS-U data showed that one of these children, went to sleep with a filled bladder. Another patient had possible nocturnal over activity based on the SENS-U data. In children with NMNE that had wet incidents, there were clear differences visible compared to children that were dry. This implies that the SENS-U data give insight in the pathofysiology of bedwetting and might be able to use as a diagnostic tool or the gain more insight in the condition nocturnal enuresis in general.

Surprisingly, the A-P dimension did not change significantly during a position transition, but within one position. This can be explained by the definitions of the body positions. Conditions of the tri-axial measurement of the body position sensor, defined the body position. Definitions were defined to determine each body position separately. It was possible that the tri-axial data conditions were an edge case for the body position. In other words, a patient changed its position a little bit, with associated with a change in bladder dimension, but the body positions was defined equal. For future research it is advisable to look at the tri-axial acceleration in stead of the body positions itself.

It was remarkable that the children in this study did move a lot during their sleep. They changed sleep position a lot more than what was expected based on the adult trial measurement. Besides, there were some pseudo positions measured, meaning a position measured in one sample between two sleep positions. For, this reasons, we were not able to measure a PTF for each position transition. The correction factors form a previous study, did not have effect on the position dependency. It is expected that solving position dependency with PTF calculated from the data has a low chance of success. The reason why the correction factors did not succeed, was mainly caused by the fact that they were obtained in adults and were not reliable for children.

Wearing the SENS-U involved little inconveniences. Some patients had pressure points after the measurement night, others had skin irritations. The main problem was with the adhesive. It was hard and sometime painful to remove from the patient. Besides, the device-adhesive connection was too strong, so it was not practical to change adhesives and keep the sensor clean. It is strongly recommended to improve the adhesive for patients comfort.

12.2 Future Research

Solving the position dependency is the most important focus in future research. This could be done based on software improvements that decrease the amount of measurements by selecting data over a window of 10 minutes, as described before. It might be not enough to solve the position dependency completely, but the most important thing is that the theoretical notification success rate will increase and false positive notifications will be resolved. With these conditions, children will wake up when their bladder is full and their sleep will not be interrupted by false notifications.

Software based improvements might not solve the false positive or missed notifications. The bladder shifting outside the FOV has the most effect on position dependency and is complicated to solve with an algorithm. Looking at the research described in part I, increasing the FOV in the L-R direction is an option which gives additional information about the bladder size and will give extra information to solve position dependency as well. Please note that the software improvements are prefered, for both the costs and the simple working mechanism to which the SENS-U mainly owes its success.

Chapter 13

Conclusion

This home-based observational pilot study showed that the SENS-U® was able to measure correct NNBF cycles in children with NE with a high success-rate. However, the A-P bladder dimension depended on body position and therefore the theoretical notification success rate was very poor. In addition, the SENS-U overestimated the bladder volume in half of the cases. It appeared that the bladder sometimes fell out of view and therefore the bladder dimension could not be corrected due to a correction factor. Software improvements, e.g. selecting samples over a window of 10 minutes, might solve the position dependency whether or not good enough to improve the notification success rate and decrease false positive notifications. If it is necessary to solve position dependency, the FOV can be enlarged in the L-R direction. When the position dependency is solved, the SENS-U Bladder Sensor might be a new way to prevent bedwetting.

Bibliography

[1] J Companion, S Heyman, T Blalock, A Cavalier, B Mineo, F Klien, and L Fox. Bladder distension sensor for the handicapped. *IEEE 1986 Ultrasonics Symposium*, pages 953–956, 1986.

[2] NK Kristiansen, Jens Christian Djurhuus, and Hans Nygaard. Design and evaluation of an ultrasound-based bladder volume monitor. *Medical and Biological Engineering and Computing*, 42(6):762–769, 2004.

[3] Paul Petrican and Mohamad A Sawan. Design of a miniaturized ultrasonic bladder volume monitor and subsequent preliminary evaluation on 41 enuretic patients. *IEEE Transactions on Rehabilitation Engineering*, 6(1):66–74, 1998.

[4] MT Rise, WE Bradley, and DA Frohrib. An ultrasonic bladder-volume sensor. *IEEE Transactions on Biomedical Engineering*, 12:709–711, 1979.

[5] PG van Leuteren, AJ Klijn, TPVM de Jong, and P Dik. Sens-u: validation of a wearable ultrasonic bladder monitor in children during urodynamic studies. *Journal of pediatric urology*, 14(6):569–e1, 2018.

[6] Paul van Leuteren, Anka Nieuwenhof-Leppink, Tom de Jong, and Pieter Dik. Sens-u: clinical evaluation of a full bladder notification - a feasibility study. *ICCS 2018 - Abstract book*, 2018.

[7] Stein R. Tekgul S, Riedmiller H, Dogan HS, Hoebeke P, Kocvara R, Nijman R, Radmayr C. Guidelines on paediatric urology. *The Netherlands: European Association of Urology, European Society for Paediatric Urology*, 2015.

[8] Tryggve Nevéus, Alexander von Gontard, Piet Hoebeke, Kelm Hjälmås, Stuart Bauer, Wendy Bower, Troels Munch Jørgensen, Søren Rittig, Johan Vande Walle, Chung-Kwong Yeung, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the standardisation committee of the international childrens continence society. *The Journal of urology*, 176(1):314–324, 2006.

[9] Richard J Butler and Sarah L Gasson. Enuresis alarm treatment. *Scandinavian journal of urology and nephrology*, 39(5):349–357, 2005.

[10] Marleen Theunis, Eline Van Hoecke, S Paesbrugge, Piet Hoebeke, and J Vande Walle. Self-image and performance in children with nocturnal enuresis. *European urology*, 41(6):660–667, 2002.

[11] Keith L. Moore, Arthur F. Dalley, and Anne R.M. Agur. *Clinically Oriented Anatomy 6th Eedition*, volume 6. Lippincott Williams & Wilkins, 2010, 2009.

[12] Medscape. Bladder anatomy, August 2018.

[13] Lars Viktrup and Richard C. Bump. Simplified neurophysiology of the lower urinary tract. *Primary Care Update for Ob/Gyns*, 10(5):261–264, 2003.

[14] Anne R.M. Agur and Arthur F. Dalley. *Grant's Atlas of Anatomy, 12th Edition*, volume 12. Lippincott Williams & Wilkins, 2008.

[15] Urology and Kidney. Urodynamic testing. Kidneyurology.

[16] P. Dik and R. Nijman. Neuro-anatomie van het sfinctercomplex en de m. detrusor. In *Incontinentie bij kinderen: een handboek voor de praktijk*, pages 75–80. Prelum, 2012.

[17] Niels Kristian Kristiansen, Steffen Ringgaard, Hans Nygaard, and Jens Christian Djurhuus. Effect of bladder volume, gender and body position on the shape and position of the urinary bladder. *Scandinavian journal of urology and nephrology*, 38(6):462–468, 2004.

[18] Vishram Singh. *Textbook of anatomy abdomen and lower limb*, volume 2. Elsevier Health Sciences, 2014.

[19] Laurent Garel, Josée Dubois, Andrée Grignon, Denis Filiatrault, and Guy Van Vliet. Us of the pediatric female pelvis: a clinical perspective. *Radiographics*, 21(6):1393–1407, 2001.

[20] OpenSTax College. Anatomy and physiology ii, August 2018.

[21] Heidi T Lotz, Marcel van Herk, Anja Betgen, Floris Pos, Joos V Lebesque, and Peter Remeijer. Reproducibility of the bladder shape and bladder shape changes during filling. *Medical physics*, 32(8):2590–2597, 2005.

[22] Hiromitsu Negoro, Akihiro Kanematsu, Koji Yoshimura, and Osamu Ogawa. Chronobiology of micturition: putative role of the circadian clock. *The Journal of urology*, 190(3):843–849, 2013.

[23] Hiroki Watanabe and Yuji Azuma. Periodical measurement of urine volume in the bladder during sleep: Temporary volume reduction suggestive of absorption. *International Journal of Urology*, 23(2):182–187, 2016.

[24] A. Bael and R. Sukhai. Fysiologie en pathofysiologie van bedplassen. In *Incontinentie bij kinderen: een handboek voor de praktijk*, pages 159–1665. Prelum, 2012.

[25] Paul F Austin, Stuart B Bauer, Wendy Bower, Janet Chase, Israel Franco, Piet Hoebeke, Søren Rittig, Johan Vande Walle, Alexander von Gontard, Anne Wright, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the international children's continence society. *The Journal of urology*, 191(6):1863–1865, 2014.

[26] K.A. Busby N.M. Wolfish, R.T. Pivik. Elevated sleep arousal thresholds in enuretic boys: clinical implications. *Acta Paediatrica, nurturing the child*, 86(4):381–384, 1997.

[27] S Rittig, Ulla Breth Knudsen, JP Norgaard, Erling Bjerregaard Pedersen, and Jens Christian Djurhuus. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *American Journal of Physiology-Renal Physiology*, 256(4):F664–F671, 1989.

[28] J.M. Nijman R.J. Scholtmeijer. Routine urodynamic studies is not indicated in children with enuresis. *Nederlands Tijdschrift Voor Geneeskunde*, 137(16):808–810, 1993.

[29] A. Raes and D. Creemers. Bedplassen: definities en diagnostiek. In *Incontinentie bij kinderen: een handboek voor de praktijk*, pages 167–174. Prelum, 2012.

[30] J. Vande Walle J. van Deure. De behandeling van bedplassen. In *Incontinentie bij kinderen: een handboek voor de praktijk*, pages 167–174. Prelum, 2012.

[31] Kennisinstituut van medisch specialisten. Anticholinergica bij overactieve blaas bij urine-incontinentie, February 2018.

[32] Zorginstituut Nederland. Oxybutinine - farmacotherapeutisch kompas, February 2018.

[33] S. van Overbeek and M. Deterink. De plaswekker. In *Incontinentie bij kinderen: een handboek voor de praktijk*, pages 167–174. Prelum, 2012.

[34] WI Forsythe and RJ Butler. Fifty years of enuretic alarms. *Archives of Disease in Childhood*, 64(6):879, 1989.

[35] Koen van Hoeck, An Bael, Hildegard Lax, Herbert Hirche, and Jan D van Gool. Circadian variation of voided volume in normal school-age children. *European journal of pediatrics*, 166(6):579–584, 2007.

[36] Rodger. Wireless bedwetting system, June 2018.

[37] Joseph H Holmes and Douglass H Howry. Ultrasonic diagnosis of abdominal disease. *The American journal of digestive diseases*, 8(1):12–32, 1963.

[38] Niels Kristian Kristiansen, Hans Nygaard, and Jens Christian Djurhuus. Clinical evaluation of a novel ultrasound-based bladder volume monitor. *Scandinavian journal of urology and nephrology*, 39(4):321–328, 2005.

[39] PG van Leuteren, BA de Vries, GCJ de Joode-Smink, B ten Haken, TPVM de Jong, and P Dik. Urika, continuous ultrasound monitoring for the detection of a full bladder in children with dysfunctional voiding: a feasibility study. *Biomedical Physics & Engineering Express*, 3(1):017005, 2017.

[40] Dr. Yuranga Weerakkody and Dr. Matt A. Morgan. Acoustic impedance, June 2018.

[41] Niels Kristian Kristiansen, Steffen Ringgaard, Hans Nygaard, and Jens Christian Djurhuus. Mri assessment of the influence of body position on the shape and position of the urinary bladder. *Scandinavian journal of urology and nephrology*, 38(1):53–61, 2004.

[42] Esaote. G-scan brio, September 2018.

[43] Judith A Owens, Anthony Spirito, Melissa McGuinn, et al. The children's sleep habits questionnaire (cshq): psychometric properties of a survey instrument for school-aged children. *SLEEP-NEW YORK-*, 23(8):1043–1052, 2000.

[44] Raphaële Reine Lydie van Litsenburg, Ruth C Waumans, Gerrit van den Berg, and Reinoud JBJ Gemke. Sleep habits and sleep disturbances in dutch children: a population-based study. *European journal of pediatrics*, 169(8):1009–1015, 2010.

Appendix A

Mid-sagittal MR scans of the bladder

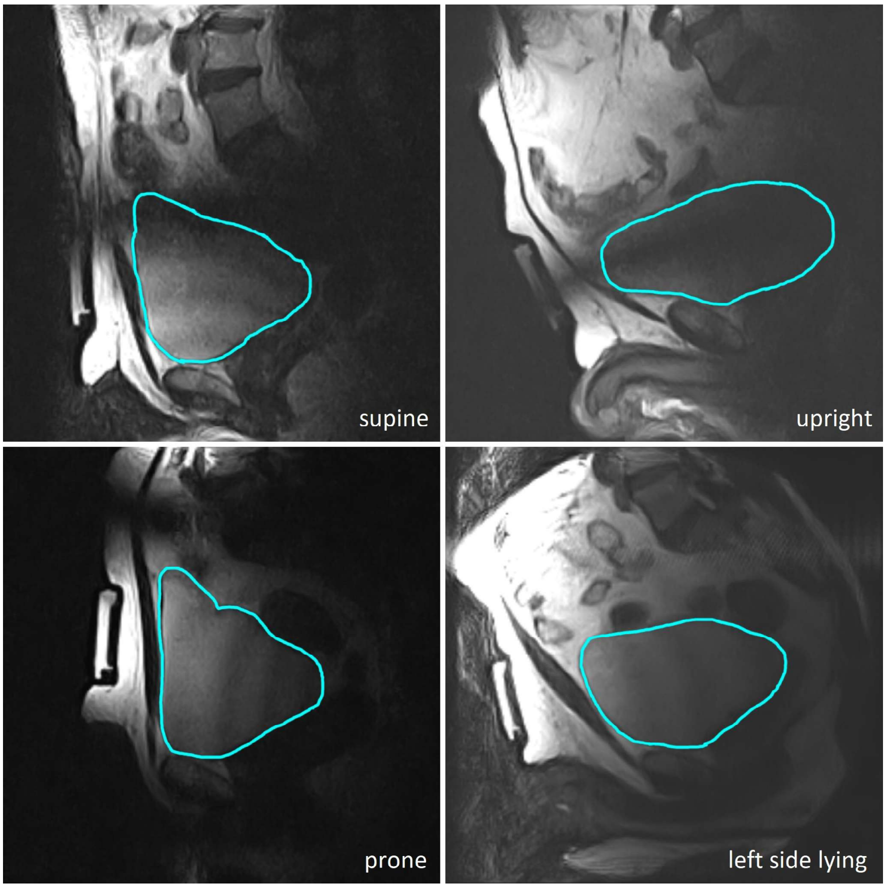

Figure A.1: Four mid-sagittal MR scans of the bladder in positions: supine, standing upright, prone and left side lying. The light blue line indicates the bladder of participant II.

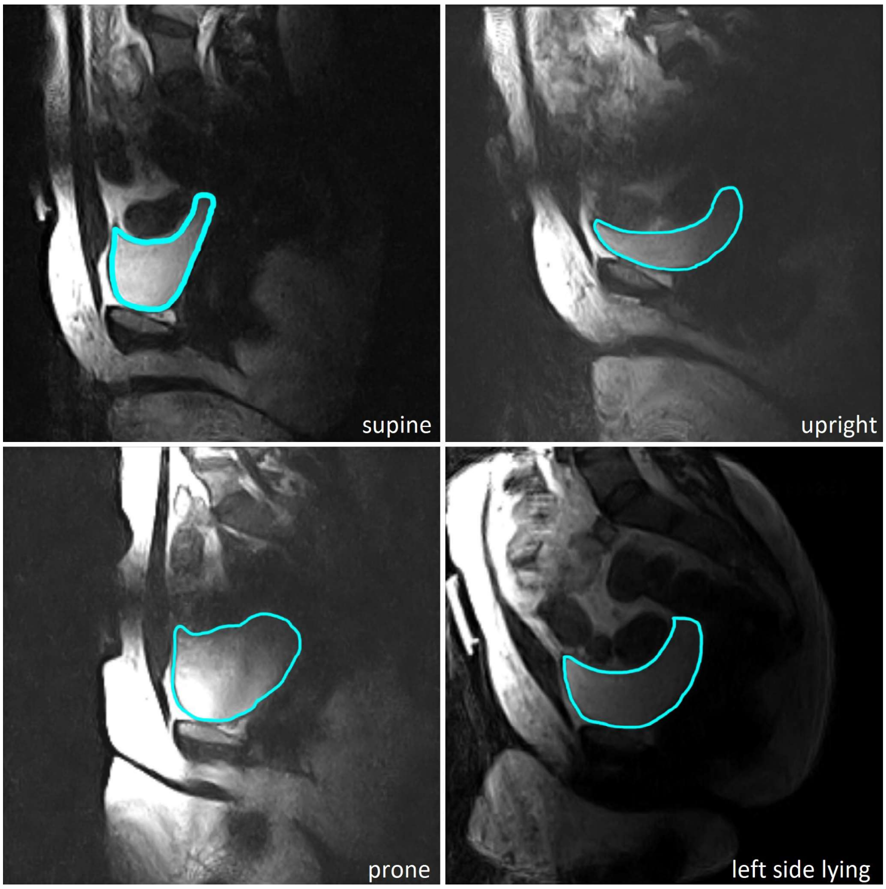

Figure A.2: Four mid-sagittal MR scans of the bladder in positions: supine, standing upright, prone and left side lying. The light blue line indicates the bladder of participant III.

Appendix B

Theoretical SENS-U® data

	upright	supine	left side lying	prone
Participant I				
A-P US1 $[cm]$	9.16	8.41	10.64	8.15
A-P US2 $[cm]$	11.10	11.53	13.03	10.32
A-P US3 $[cm]$	12.66	11.42	13.58	10.78
A-P US4 $[cm]$	0.64	8.06	8.67	8.58
Theoretical volume $[mL]$	232.31	399.02	539.00	362.74
A-P transversal $[cm]$	18.81	5.21	4.14	5.2
L-R transversal $[cm]$	19.05	7.52	4.50	8.07
Participant II				
A-P US1 $[cm]$	–	8.01	–	4.83
A-P US2 $[cm]$	11.18	12.05	12.31	9.25
A-P US3 $[cm]$	11.94	8.55	8.99	11.39
A-P US4 $[cm]$	2.80	5.43	–	7.95
Theoretical volume $[mL]$	275.41	312.02	232.35	301.64
A-P transversal $[cm]$	19.85	20.40	2.12	14.77
L-R transversal $[cm]$	11.07	15.72	8.97	12.92
Participant III				
A-P US1 $[cm]$	–	–	–	–
A-P US2 $[cm]$	–	–	–	3.01
A-P US3 $[cm]$	–	–	–	6.53
A-P US4 $[cm]$	3.18	1.62	–	6.96
Theoretical volume $[mL]$	10.11	2.62	8.52	100.20
A-P transversal $[cm]$	–	–	–	–
L-R transversal $[cm]$	–	–	–	–

Table B.1: Overview of theoretical SENS-U data for each participant. Number of active US channels and theoretical volume are presented for each position separately. The measured voided volume is presented as well.

Appendix C

Accelerated measurements

The SENS-U has a sample frequency of 0.033 Hz. The software is designed such that, at times, the SENS-U measures faster to obtain optimal bladder filling tracking. Therefore, the sample frequency is unstable. In addition, this raw signal is filtered to reduce fluctuations in bladder dimension. This filtered signal is the final A-P bladder signal on which alarming is based. These measurements could be of influence of the final A-P bladder dimension on which could be alarmed. For this reason, the number of accelerated measurements were determined and removed. It turned out that 0.57 $\pm$ 0.25 $\%$ of the time, the SENS-U measured accelerated. This was considered to be a negligible part, so this was also a dead end to solve position dependency.

Appendix D

Incontinence evaluation data

Scoringsformulier incontinentie start- tijdens- en evaluatie van de behandeling

Patiëntensticker

DIAGNOSE

MEDICATIE *(+start/einde)
-
-

Hebben ouders de vragenlijst ingevuld?	☐ JA ☐ NEE				
	Start behandeling	**Tijdens Behandeling**	**Na behandeling/training**		
Meetmoment Datum	-1-2 mnd ----------	.... mnd ---------	6 mnd ---------	12 mnd ---------	
MICTIE					
Infecties	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	Nooit infecties gehad. Infecties in het verleden (>1jr geleden) Recent infecties (< 1 jaar) Infecties met koorts/ziek Geen infecties met profylaxe Regelmatig infecties met profylaxe
Mictiefrequentie	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 – 3 keer per dag 4 – 7 keer per dag 8 – 12 keer per dag Meer dan 12 keer per dag
Natte incidenten	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	droog 1 keer per week 2 a 3 keer per week 1 keer per dag 1 x en/of meerdere keren per dag
Mate van incontinentie	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	Druppelnat (> 2 euro) Flinke natte onderbroek Natte buitenbroek Wisselt Draagt luier
Urge klachten bij OAB	☐ ☐	☐ ☐	☐ ☐	☐ ☐	Geen Soms (1x per week of minder)

Scoringsformulier incontinentie start- tijdens- en evaluatie van de behandeling

	☐ ☐	☐ ☐	☐ ☐	☐ ☐	meestal (2-6 per week) altijd (meerdere keren per dag)
Urge klachten door uitstel	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	Geen Zelden (1x per week of minder) Soms (2-5 per week) Vaak (dagelijks)
Enuresis nocturna					
	☐	☐	☐	☐	nooit
	☐	☐	☐	☐	1x per week of minder per week
	☐	☐	☐	☐	Meerdere nachten per week
	☐	☐	☐	☐	Elke nacht
Defecatie					
Ontlastingspatroon	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	Frequentie 2x of minder per week Houdt de ontlasting op Pijnlijke of harde, keutelige defecatie Grote hoeveelheid ontlasting/olifantendrol
Vieze broeken	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	Niet aanwezig <3 keer per week, 3 of meer keer per week Poepvegen in broek Poep in broek Zowel vegen als poep
Parameters					
Blaasvolume (ml)	....	....	....	....	Maximaal ophouden (V)UDO (datum..............)
Echografie	....	....	....	....	Blaaswanddikte (mm) Rectumdiameter (cm)
Flowmetrie	....	....	....	....	Volume (ml) Max.Flow (ml/sec) Mictie duur (sec)
Flowpatroon	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	Klokvormig Staccato Gefractioneerd Piek Obstructief
Residu (ml)	.... ☐ ☐	.... ☐ ☐	.... ☐ ☐	.... ☐ ☐	Volume (ml) < 10 % geplaste volume > 10 % geplaste volume

Appendix E

Children's Sleep Habit Questionnaire

Studie ID: Datum:

Vragenlijst slaapgewoonte (CSHQ)

1. **Valt de uw kind binnen 20 minuten na het naar bed gaan in slaap?**

Normaliter	Tijdens gebruik van de SENS-U
○ Ja ○ Nee ○ N.v.t.	○ Ja ○ Nee ○ N.v.t.

2. **Slaapt uw kind de juiste hoeveelheid?**

Normaliter	Tijdens gebruik van de SENS-U
○ Ja ○ Nee ○ N.v.t.	○ Ja ○ Nee ○ N.v.t.

3. **Wordt uw kind 's nachts een keer wakker?**

Normaliter	Tijdens gebruik van de SENS-U
○ Ja ○ Nee ○ N.v.t.	○ Ja ○ Nee ○ N.v.t.

4. **Wordt uw kind meer dan een keer wakker?**

Normaliter	Tijdens gebruik van de SENS-U
○ Ja ○ Nee ○ N.v.t.	○ Ja ○ Nee ○ N.v.t.

5. **Wordt uw kind (van)zelf wakker?**

Normaliter	Tijdens gebruik van de SENS-U
○ Ja ○ Nee ○ N.v.t.	○ Ja ○ Nee ○ N.v.t.

Appendix F

SENS-U® measurement data

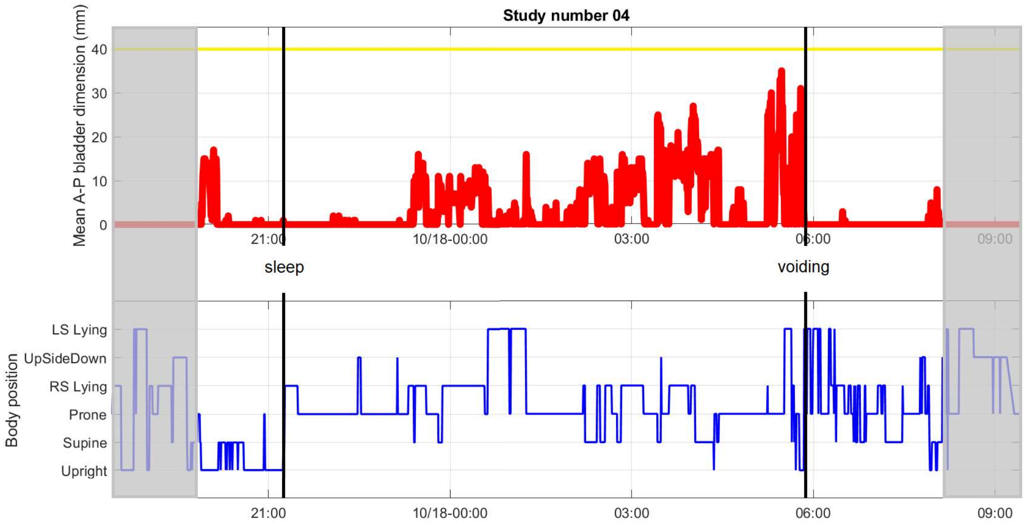

Figure F.1: Subject 04 (boy, 7 years) was dry during the measurement night. Sleep at 21:15 hr; first morning void at 05:50 hr, EMV = 140 mL and A-P bladder dimension = 31 $mm \sim$ 148 mL Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 40 mm.

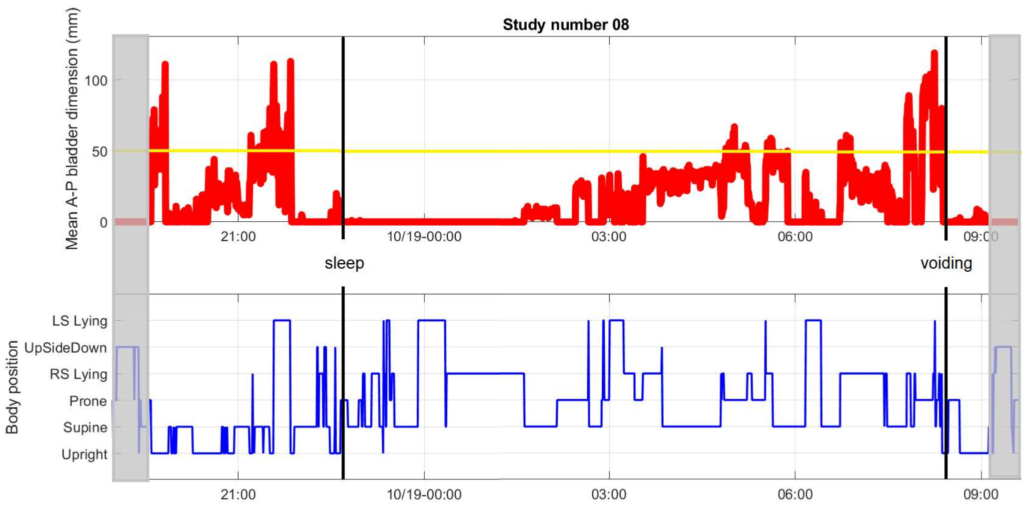

Figure F.2: Subject 08 (boy, 9 years) was dry during the measurement night. Sleep at 22:40 hr; first morning void at 08:30 hr, EMV = 200 mL and A-P bladder dimension = 72 $mm \sim$ 343 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 46 mm.

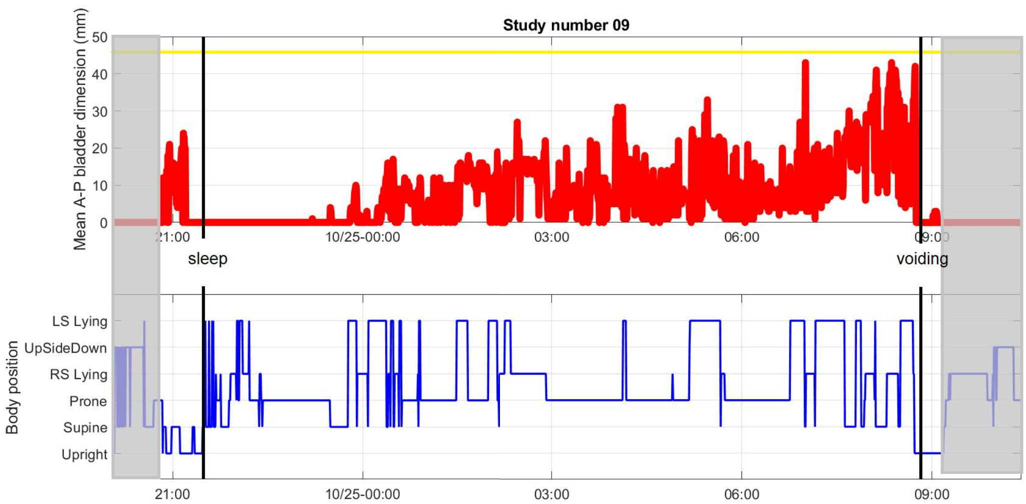

Figure F.3: Subject 09 (boy, 8 years) was dry during the measurement night. Sleep at 21:30 hr; first morning void at 08:45 hr, EMV = 190 mL and A-P bladder dimension = 42 $mm \sim$ 200 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 46 mm.

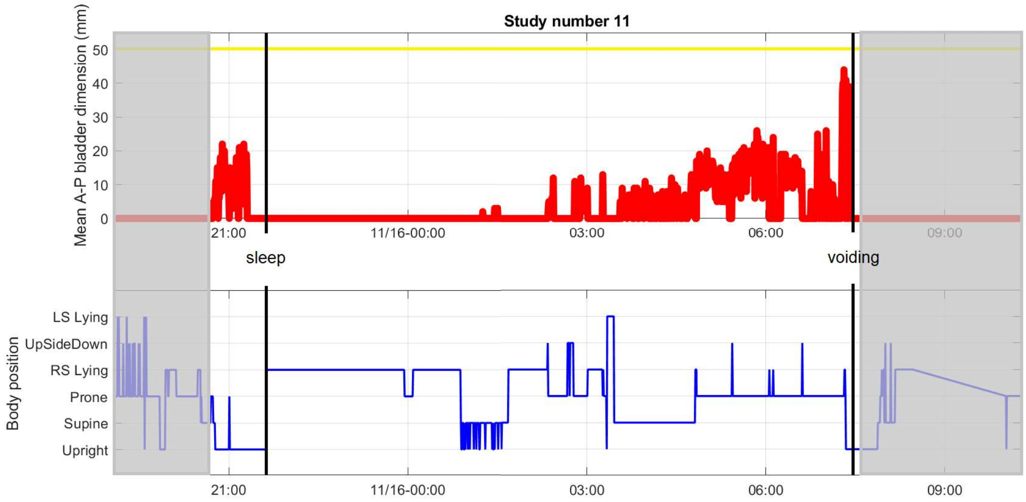

Figure F.4: Subject 11 (girl, 9 years) was dry during the measurement night. Sleep at 21:30 hr; first morning void at 07:25 hr (voiding diary = 07:10 hr), EMV = 150 mL and A-P bladder dimension = 39 $mm \sim$ 186mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 50 mm.

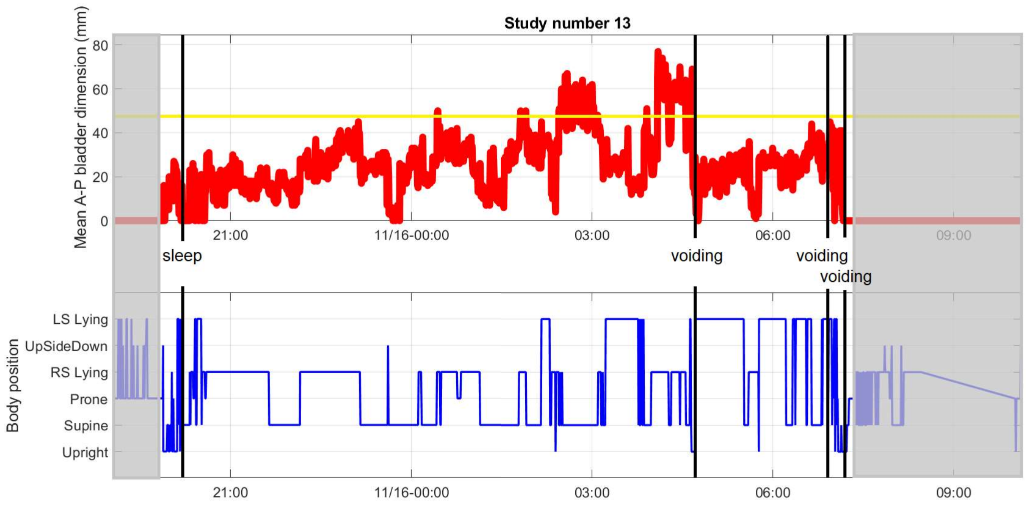

Figure F.5: Subject 13 (boy, 8 years) was dry during the measurement night. Sleep at 20:10 hr; nightly void at 04:50 hr, volume = 110 mL and A-P bladder dimension = 69 $mm \sim$ 329 mL. First (incomplete) morning void at 07:00 hr, volume = 10 mL, but the A-P bladder dimension was not reliable for this bladder filling. Complete morning void at 07:10 hr, EMV = 140 mL and A-P bladder dimension = 41 $mm \sim$ 195 mL. Total number of NNBF cycle(s) = 3, successfully detected = 2. Threshold level: 46 mm.

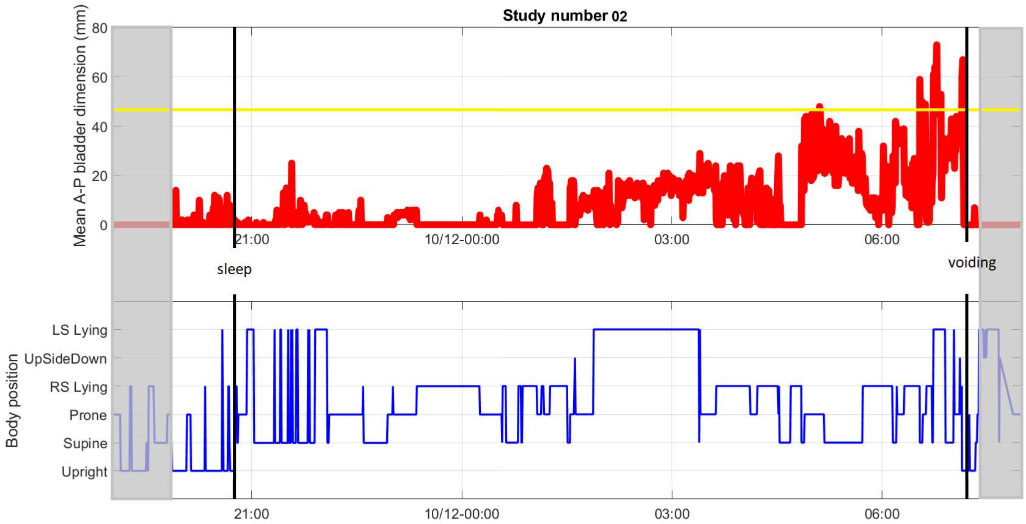

Figure F.6: Subject 02 (boy, 8 years) was wet during the measurement night. Sleep at 20:45 hr; first morning void at 07:00 hr, EMV = 220 mL and A-P bladder dimension = 67 $mm \sim$ 319mL. Nightly urine loss = 8 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 46 mm.

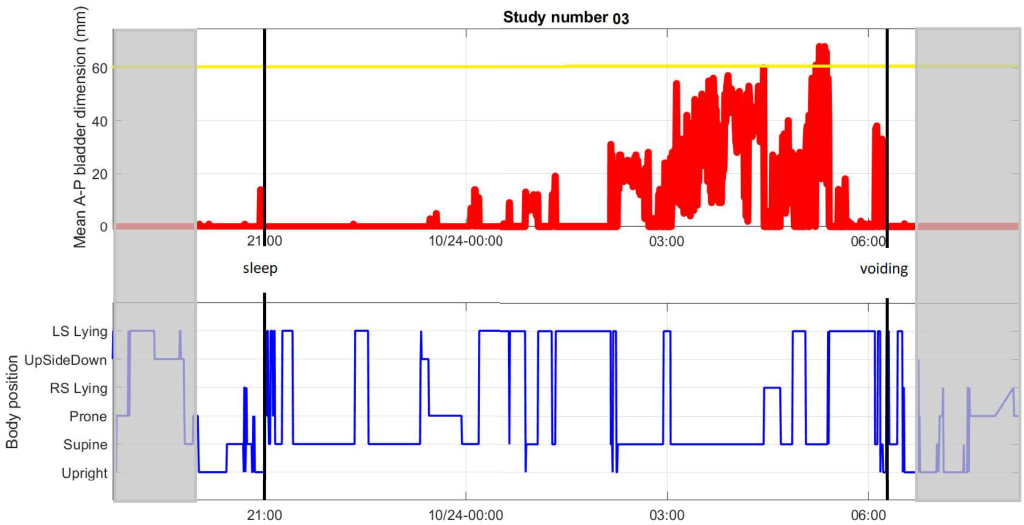

Figure F.7: Subject 03 (boy, 11 years)was wet during the measurement night. Sleep at 21:00 hr; first morning void at 06:30 hr, EMV = 125 mL and A-P bladder dimension = 33 $mm \sim$ 157 mL. Nightly urine loss = 48 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Threshold level: 61 mm.

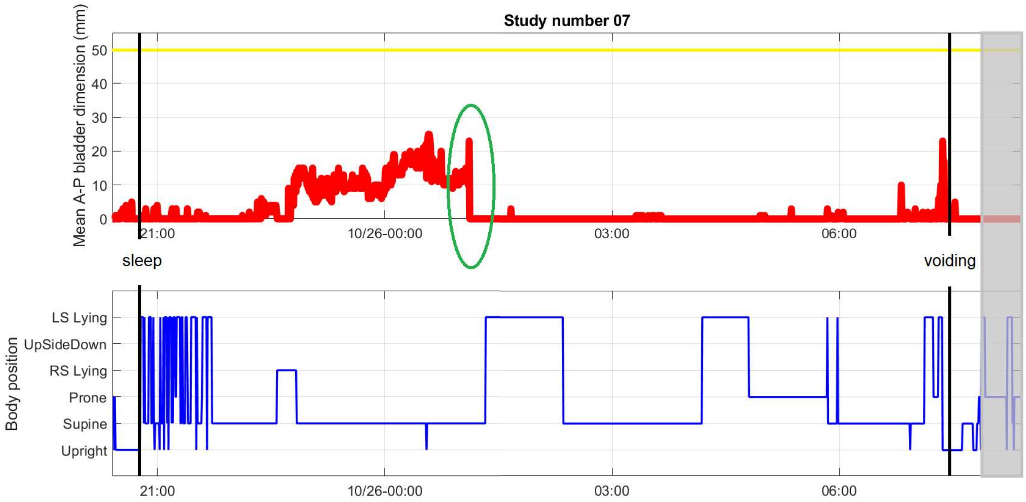

Figure F.8: Subject 07 (boy, 9 years) was wet during the measurement night. Sleep at 20:45 hr; first morning void at 07:25 hr, EMV = 50 mL and A-P bladder dimension = 23 $mm \sim$ 110 mL. Nightly urine loss = 100 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Possible urine loss is presented by the green sphere around 01.00 hr. Threshold level: 50 mm.

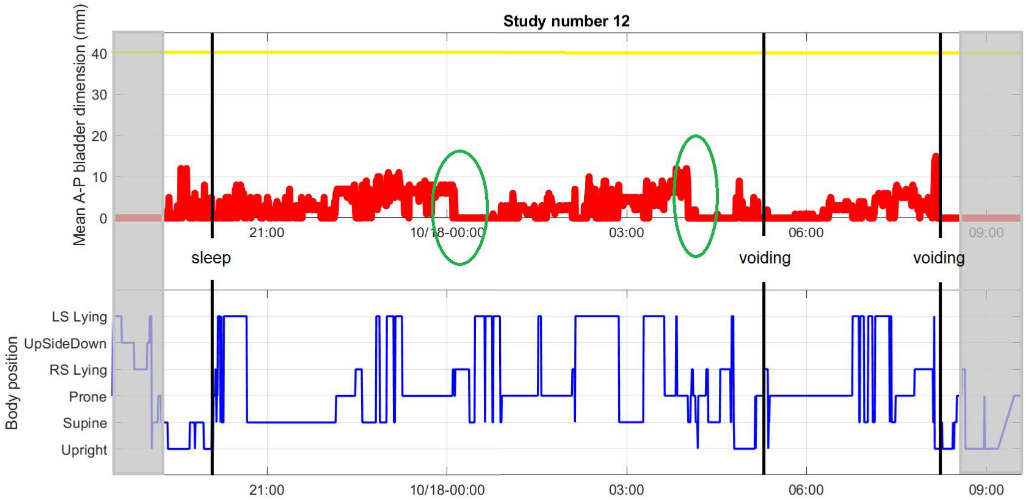

Figure F.9: Subject 12 (boy, 7 years)was wet during the measurement night. Sleep at 20:00 hr; nightly void at 05:00 hr, volume = 30 mL but the A-P bladder dimension was not reliable for this bladder filling. First morning void at 08:10 hr, EMV = 70 mL and A-P bladder dimension = 12 $mm \sim$ 57 mL. Nightly urine loss = 138 mL. Total number of NNBF cycle(s) = 2, successfully detected = 1. Possible urine loss is presented by the green sphere around 00.00 hr and 04.00 hr. Threshold level: 40 mm.

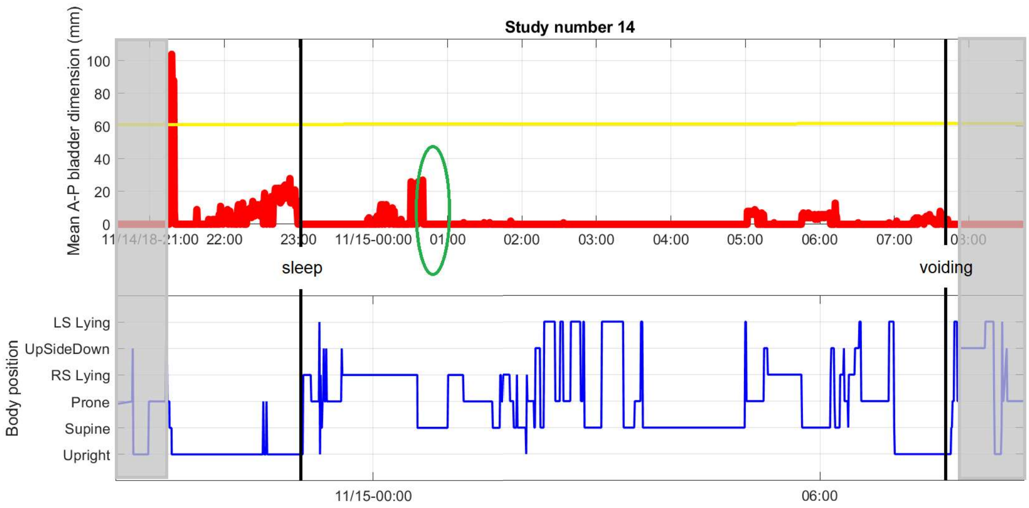

Figure F.10: Subject 14 (boy, 11 years) was wet during the measurement night. Sleep at 23:00 hr; first morning void at 07:40 hr, EMV = 30 mL but the A-P bladder dimension was not reliable for this bladder filling. Nightly urine loss = 158 mL. Total number of NNBF cycle(s) = 1, successfully detected = 0. Possible urine loss is presented by the green sphere around 01.30 hr. A remark was that the amount of urine loss was more than 158 mL, because the bed of this patient was wet next to the diaper. Threshold level: 61 mm.

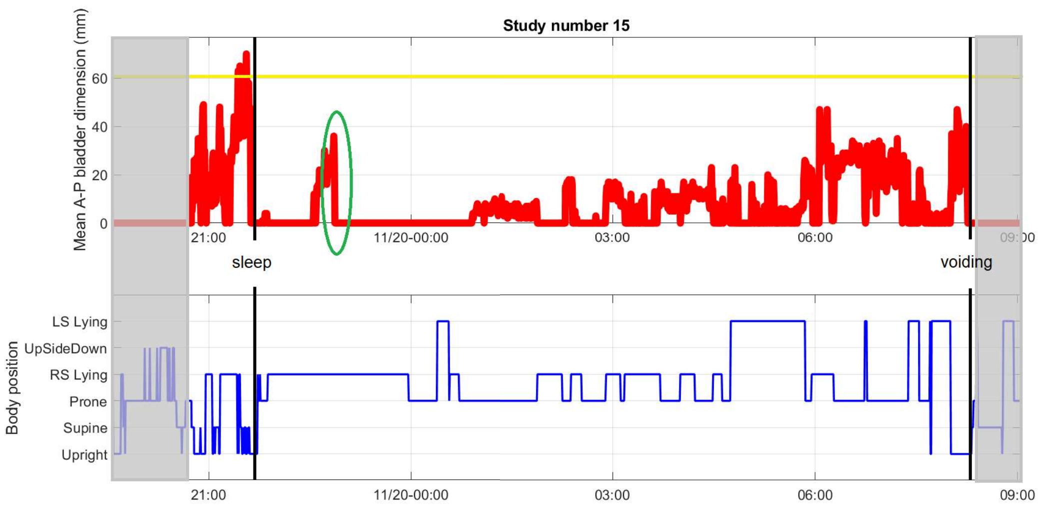

Figure F.11: Subject 15 (boy, 11 years) was wet during the measurement night. Sleep at 21:45 hr; first morning void at 08:15 hr, EMV = 85 mL and A-P bladder dimension = 40 $mm \sim$ 190 mL. Nightly urine loss = 232 mL. Total number of NNBF cycle(s) = 1, successfully detected = 1. Possible urine loss is presented by the green sphere around 23.00 hr.Threshold level: 61 mm.