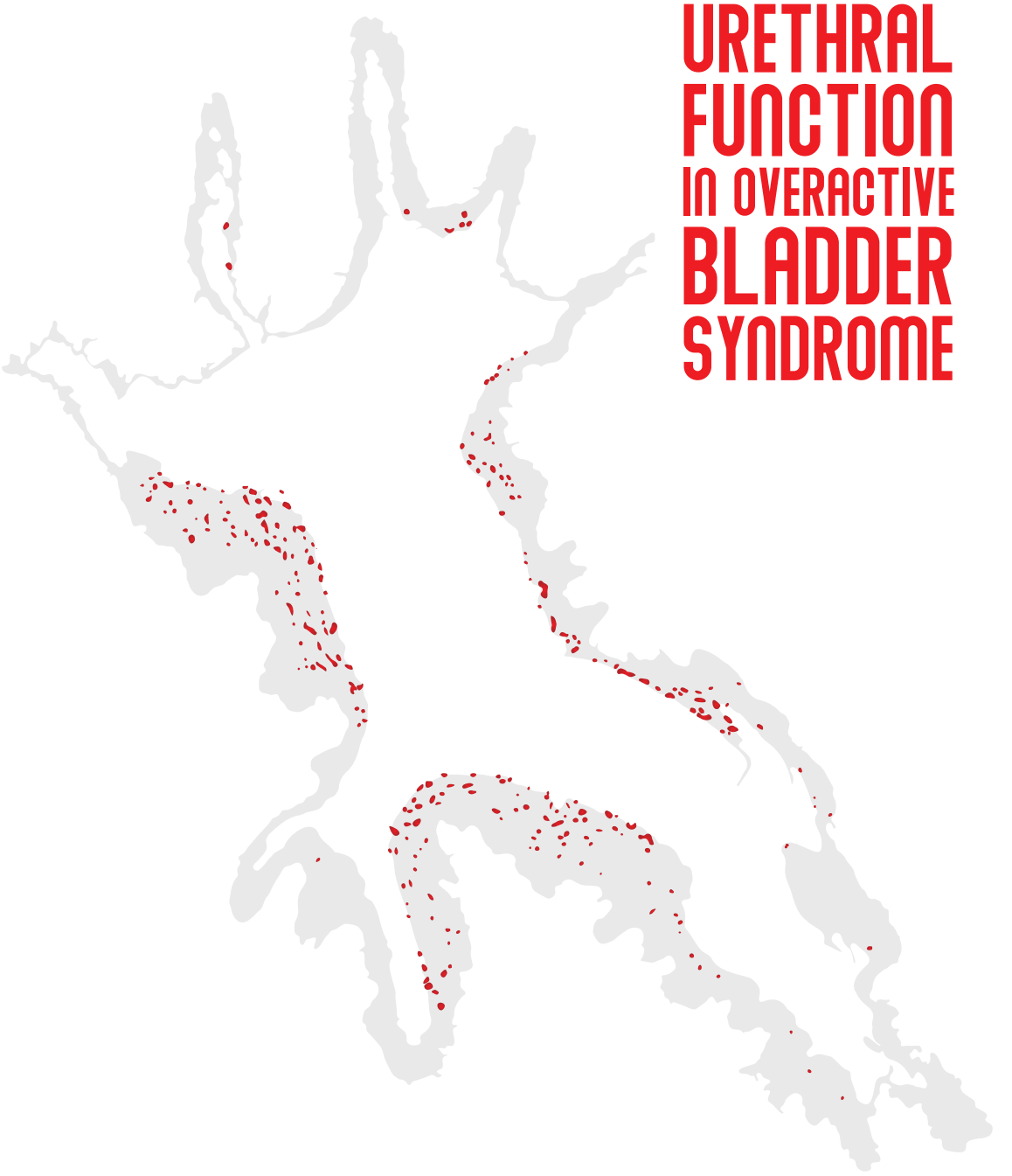
Urethral function in overactive bladder syndrome

Kummeling, M.T.M.

URETHRAL FUNCTION IN OVERACTIVE BLADDER SYNDROME



MAXIME KUMMELING

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COLOFON

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CHAPTER 1

GENERAL INTRODUCTION

1

GENERAL INTRODUCTION AND OUTLINE THESIS

Overactive bladder syndrome (OAB) is a common lower urinary tract disorder with a prevalence increasing with age[1]. OAB was defined in 2002 by the International Continence Society (ICS) as the urgency to void, usually accompanying frequency and nocturia, with or without urge urinary incontinence (UUI)[2]. If infection, urolithiasis, neoplasm or neurological bladder dysfunction as the cause for the symptoms are excluded, the condition is yet idiopathic.

According to investigation of Dutch central statistical agency (CBS) in 2004, about 16% of the Dutch population above the age of forty years old suffers from OAB syndrome. This indicates that at least one million people may be affected[3], however not all seek medical attention[4]. The college for health insurances (CVZ) estimated costs for urinary incontinence material in 2011 at 148 million euro. The total costs for treatment of urinary incontinence were estimated at 256 million euro. OAB syndrome has a negative impact on health-related quality of life (QoL)[5, 6] and the worse the symptoms, the greater the negative effect[7]. Prevalence of OAB increase with age and increase up to 30% in the population older than 75 years[3]. With the increasing average life span of the population, the socioeconomic burden of OAB will rise in the future[8].

Currently there a several treatment options for OAB. Guidelines for treatment propose a pathway from conservative treatment, then drugs, then minimally invasive surgery and last invasive surgery. For a start, conservative treatment can be initiated, consisting of lifestyle advice, and/or pelvic muscle floor therapy. Second, there a several forms of neuromodulation therapies, like percutaneous tibial nerve stimulation, transcutaneous electrical nerve stimulation, transvaginal electrical stimulation or sacral neuromodulation. The advantage of neuromodulation treatment are very low rates of adverse events. The disadvantage of neuromodulation treatment modalities, except the sacral form, is that the effect diminishes over time when treatment is not applied anymore. Third there is the possibility of pharmacotherapeutic treatment. The predominant treatment option consists of oral antimuscarinics. Treatment with antimuscarinics result in reduction in voiding frequency, urgency episodes and or urgency urinary incontinence[9, 10]. However, treatment persistence is low, with around 30% of patients continuing therapy after one year[11, 12]. Adverse events, the most bothersome associated with

antimuscarinic drugs being a dry mouth, are often a reason for treatment discontinuation[13]. Since 2014 a beta 3 adrenoceptor (ADRB3) agonist is available in pharmacological treatment of OAB. It has been proven clinically and urodynamically effective in the treatment for OAB and is well tolerated[14]. In a recent retrospective observational study, the persistence and adherence of mirabegron versus antimuscarinic agents was compared[15]. Although persistence of mirabegron was better than the persistence of antimuscarinic agents, persistency rates after one year were 38% for mirabegron and 20% for antimuscarinic drugs. The combination of mirabegron and the antimuscarinic agent solifenacin in treatment for OAB was reported in the BESIDE-study[16]. Combined treatment resulted in better outcome than single agent treatment and was well tolerated in older patients as well[17]. In conclusion, pharmacotherapeutic treatment in its current form needs improvement.

Fourth, OAB can be treated with botulinum A toxin (Bont-A) injections. Bont-A is the most potent neurotoxic poison known. The first administration in the bladder in treatment for lower urinary tract dysfunction was reported in 2006[18]. Bont-A blocks acetylcholine release in the presynaptic membranes, resulting in paralysis at the injected location. In 2011, the FDA approved this treatment for neurogenic bladder dysfunction, later it was also approved for treatment of idiopathic OAB, when pharmacological treatment has failed. Common adverse events in the treatment with BontA-injections are the need for clean intermittent self-catheterization and urinary tract infections. The advantage of this treatment is the local application, systemic side effect as in pharmacological treatment do not occur.

From the abovementioned data can be concluded that unfortunately no therapy is beneficial and applicable for all OAB patients. This is due to the fact that patients with OAB represent a very heterogeneous group of patients, with the same social invalidating symptom complex in common. Until recently, research on OAB has mainly focused on detrusor overactivity (DO) as a cause for the symptoms. However, DO is present in only 50% of female OAB patients and can also be present in asymptomatic patients. In the past decade, further research has been performed to the existence of alternative underlying mechanisms leading to OAB. There is growing evidence that increased activity of bladder afferent signaling, originating from the urothelium or suburothelium and influenced by the urinary microbiome, contributes to OAB symptom complex[19]. Research to the role of the urethra within micturition reflex was initiated in the early 20th

century by Barrington in an animal model. He described seven reflexes involved in bladder storage and micturition in cat, of which four had their afferent origin in the urethra[20, 21]. Later, Jung et al hypothesized that leakage of urine into the urethra can stimulate urethral afferents, causing stress induced urgency with or without urinary incontinence[22]. In patients surgically treated for stress urinary incontinence (SUI), storage function improves in some patients with mixed urinary incontinence. Unfortunately, de novo urgency and or increased urgency is also reported after surgery for SUI. In the last 20 years of the 20th century, various studies were performed to further elucidate the role of urethral function in lower urinary tract dysfunction on the basis of urethral pressure variations during filling cystometry of urodynamic studies[23-25].

Urodynamic studies are part of the work-up of patients with OAB syndrome. Detrusor overactivity (DO) is defined as detrusor contractions of any extent during filling phase of urodynamic investigation. However, this phenomenon can also be observed in symptomatic patients. In association and apart from detrusor overactivity, urethral pressure variations (UPV) can been observed during urodynamic investigation. The clinical relevance of UPV, although associated with urinary urgency, in the pathophysiology of OAB syndrome is not yet precisely established. In 1980, the ICS defined urethral instability (URI) as a condition in which there is involuntary fall in urethral pressure during filling, resulting in urinary leakage in the absence of detrusor activity. URI was abandoned within terminology shortly after because of the rarity of this condition. Opponents consider urethral pressure variations as an artefact during filling cystometry and for a long time, research on OAB has focused on detrusor function as a cause. Maintaining urinary continence however requires a coordinated function between the bladder as storage room for urine and the urethra as gatekeeper. Recently, a think tank session of the ICI-RS was dedicated to urethral pressure variations urethral instability[26] . This session was followed by a summarizing report based on literature review and discussions during this ICI-RS meeting[27]. This report also concluded that UPV certainly is associated with LUTS and thus, future research on this topic is relevant.

ANATOMY

With an average length of 3-4cm, the female urethra is shorter than the male urethra with an average length of 17cm. In both sexes, is a distensible, partly muscular tube. Differences in length, pelvic floor anatomy and the absence of the prostate result in a different functionality. The urethra is composed of striated and smooth muscles. The smooth muscles bundles within the urethral wall have a relatively thick inner layer, arranged predominantly longitudinal. Outside this is layer, there is a thinner circular muscle layer. The urethral smooth muscle layer extends to the bladder neck, where they merge in detrusor smooth muscle bundles. Contrary to the male anatomy, a well-defined circular smooth muscle component comparable with the preprostatic sphincter is absent in the female bladder neck. As a consequence, active smooth muscle contraction in the female bladder neck region will not have a major contributing role in maintaining urinary continence. In male, the striated muscle layer extends from the bladder base and the anterior urethra tot the full length of the membranous urethra. In females, the striated muscle layer extends from the proximal urethra and is horseshoe shaped. The muscle arrangement forming the distal sphincter has an additional muscle structure termed the compressor urethrae. When there is adequate support from the pelvic floor, the posterior wall remains rigid. In males there is no striated component posteriorly. Despite the limited length of the female urethra, anatomical and functional differences exist. The proximal urethra, above the urogenital diaphragm is subject to abdominal pressure while the distal parts are not. From proximal to distal, the transitional epithelium changes into a non-keratinizing stratified squamous epithelium. At the external meatus, this epithelium is keratinized and becomes continuous with the skin of the vestibule.

INNERVATION

Both the autonomic and somatic nervous system are involved in the innervation of the bladder and urethra[28]. The autonomic nervous system is under unconscious control and typically acts on smooth muscles. The somatic nervous system is under conscious control and typically acts on striated muscles. The autonomic nervous system consists of sympathetic adrenergic nerves and parasympathetic cholinergic nerves.

Branches of the nervous system here are referred to by the names of the chemical transmitters responsible for transmitting signals from the nerves. The chemical transmitter of the sympathetic system is noradrenaline or a similar substance. The nerve branches of the sympathetic system are divided in alfa adrenergic and beta adrenergic subtypes. For the parasympathetic system the chemical transmitter is acetylcholine or a similar substance. For the lower urinary tract, sympathetic innervation is through the hypogastric nerve bundles, initiating from spinal cord segments thoracic 12 to lumbar 2. The parasympathetic innervation is through pelvic nerve bundles, originating in second to fourth sacral spinal cord segments. The somatic innervation through the pudendal nerve, also originates from this part of the spinal cord. All abovementioned nerve bundles contain afferent or sensory axons, transmitting information from the lower urinary tract back to the lumbosacral spinal cord up to higher central brain centers. From the central nervous system, motor or efferent impulses are transmitted back to the lower urinary tract. Afferent and efferent impulses are transmitted by different bundles of the same nerve. For micturition, the most important afferent bundles are the myelinated Ad-fibers and the unmyelinated C-fibers. Pelvic nerve afferents monitor the volume of the bladder and mediate the sensation associated with normal bladder filling and pain[29]. In storage phase, the pelvic nerve has a low level of vesical afferent activity and the hypogastric nerve afferent activity is high. This results in a stimulated sympathetic outflow to the bladder base outlet and pudendal flow to the external urethral sphincter by spinal reflex pathways (guarding reflex). Detrusor muscle contraction and transmission in bladder ganglia are also inhibited. When voiding phase is initiated, the level of afferent activity of abovementioned nerves are switched. This results in inhibition of the spinal guarding reflex and stimulation of parasympathetic outflow to the lower urinary tract, resulting in detrusor contraction. The urethral smooth muscle tonus and intra-urethral pressure is predominantly regulated by adrenergic sympathetic nerves. In their review on neural control of the lower urinary tract, Birder and Andersson[29, 30] concluded that the urothelium itself also contributes in afferent signaling. As a response to sensory or mechanical stimuli, the neurotransmitters nitric oxide (NO), adenosine triphosphate (ATP) and acetylcholine can be released by the urothelium, resulting in afferent activity allowing the micturition reflex to be initiated.

URETHRAL PRESSURE

The urethral closure pressure is defined as the difference between the urethral pressure and the intravesical pressure. The urethral pressure varies along the length of the urethra and can be measured continuously or as a plot of pressure against distance. The latter is defined as the urethral closure pressure profile. The functional urethral length is length of the urethra where urethral pressure is higher than intravesical pressure. Since the urethra is not a closed reservoir like the bladder and since it's not filled with liquid at rest, it is difficult to understand what is measured. Besides, the urethra has a different shape of cross-section from point to point. What we do know is that as long as the urethral pressure is higher than intravesical pressure, leakage of urine should be resisted. In the literature, two controversies exist about the urethral pressure profile. First about the role of urethral pressure within lower urinary tract symptoms and second about the contributing role of the urethral smooth, striated circular muscles and the lamina propria to urethral pressure profile. In addition there is also controversy about the role of urodynamic investigation, since so far it has not been so successful in suggesting treatments for OAB or predicting postoperative results in surgery for urinary incontinence or for urogenital prolapse [31]. However, these studies mainly focused on bladder-function related outcomes, and far less on urethral function. Especially urethral pressure variations as measured in urodynamics correlated to clinical symptoms has not so extensively been investigated and as aforementioned, may be of clinical importance. In 2007, Groenendijk concluded that URI appeared to be a valuable urodynamic parameter for predicting the outcome of SNS[32].

URETHRAL INSTABILITY

When continuous urethral pressure is measured during filling cystometry of urodynamic investigation, sudden pressure variations can be observed. Different patterns[33] and definitions have been described in the past. The lower the cut-off value used, the higher the mentioned prevalence, with variations in prevalence reported from 2 to 95% [32, 34]. The chance to demonstrate UPV will be higher when multiple urethral sensors are used and possibly also dependent on which type of urodynamic catheter is used. Measurements with dual air-balloon sensor, with one

sensor in the urethra- is the most reported technique, but measurements with up to 5 urethral sensors have been reported[35]. For this study, two different types of catheters have been used. In the centers in The Hague, continuous urethral measurements have been performed with a dual air-balloon catheter, with the urethral sensor catheter positioned at the point of maximal pressure. In the LUMC, measurements have been performed with a multi urethral sensor catheter, with three urethral sensors and one bladder sensor. The mid-urethral pressure sensor is positioned at the maximal pressure point. Urethral and detrusor pressure are continuously measured during storage and during voiding phase. The use of three urethral sensors reduces the chance of measurement artifacts due to movement of the catheter. Past research proposed that for the definition of URI, pressure variations of at least 15cm H2O should be present in all urethral sensors. The question is whether a fixed cut-off value is relevant in all measurement points and whether it is not more important that the pattern of pressure variations is registered in all measurement points, regardless of the absolute value. For this study, we have defined URI as follows. In the measurements performed with the dual air-balloon sensor catheter we have used a cut-off value of an urethral pressure drop of 30cm H2O or more. For measurements performed with the three urethral sensor catheter, urethral pressure drops exceeding 30cm H2O must be demonstrated in at least one sensor and the pattern of the urethral pressure drops should be demonstrated in at least two out of three measurement point, because in some cases it was not possible to obtain registration in measurement points due to the anatomy of the urethra. In addition, the urethral pressure drop should be independent of detrusor contraction. In other words, when DO occurred, the preceding drop in urethral pressure was considered physiological. EMG recordings were performed in all measurements but were not considered of any importance in the definition of URI. Examples of urodynamic investigations with URI, with and without accompanying DO are shown in figures 1.1 and 1.2.

In figures 1.3 and 1.4, examples of urodynamic investigation with three urethral sensors are demonstrated. Figure 1.3 shows a normal urodynamic investigation, figure 1.4 shows an urodynamic investigation with URI.

If further research can confirm that URI is good predictor for successful clinical outcome of certain treatments in a subgroup of patients with OAB, or that patients with URI should be considered as a different group of patients within OAB, we can make an important contribution to tailored-treatment of patients with OAB.

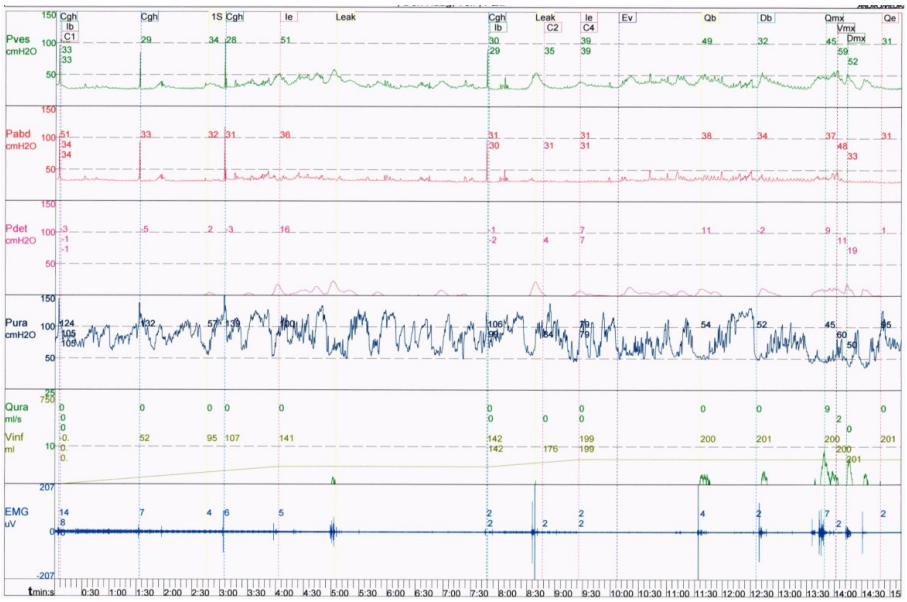

Figure 1.1 Example of filling cystometry with dual microtip catheter, demonstrating URI and DO

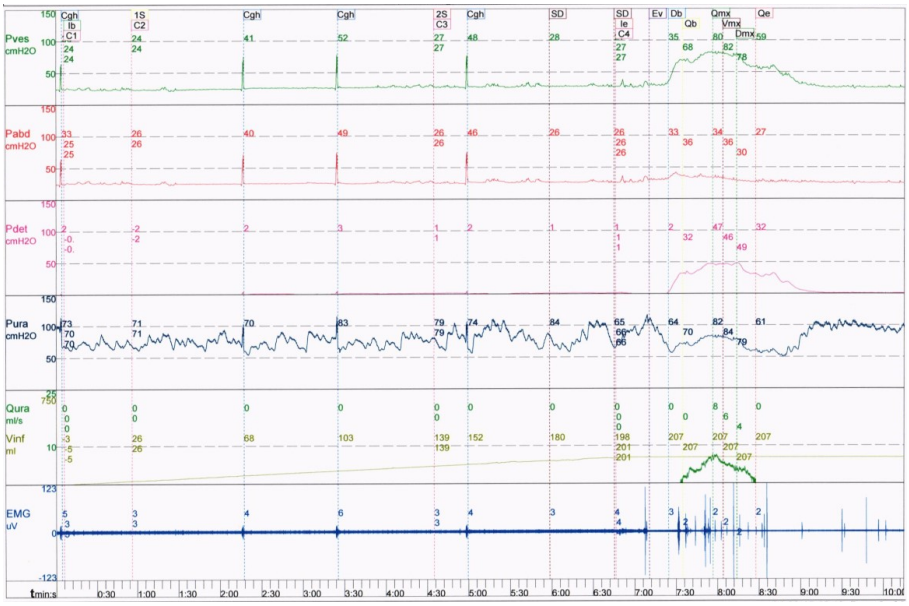

Figure 1.2 Example of filling cystometry with dual microtip catheter, demonstrating URI

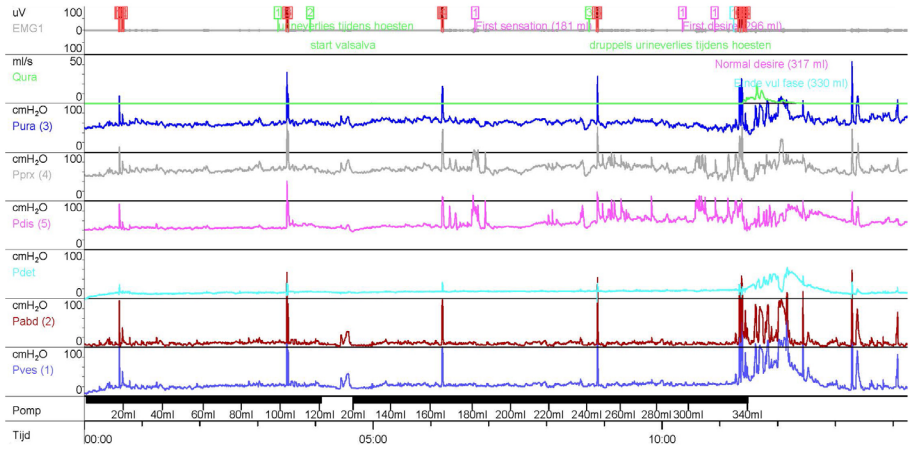

Figure 1.3 Example of a normal filling phase of urodynamic investigation with three urethral sensors

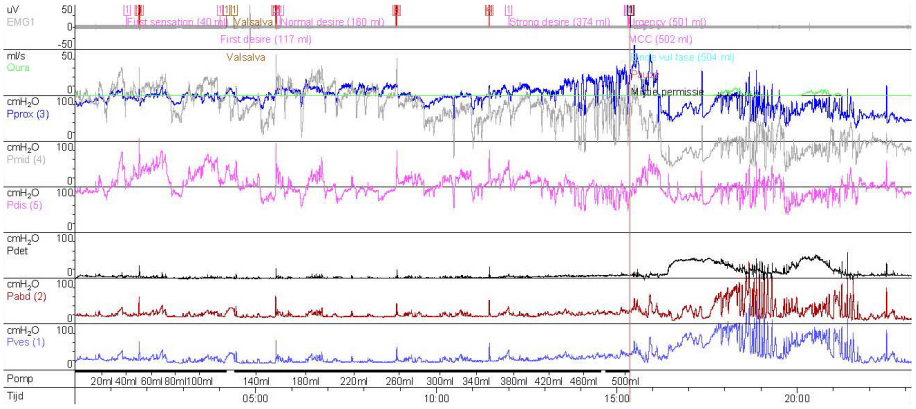

Figure 1.4 Urethral pressure variations exceeding 30 cm H2O are present in two out of three urethral pressure sensors.

OUTLINE OF THE THESIS

The aim of this is to further elucidate the role of urethral function within OAB to contribute to better targeted therapy in patients with OAB. This thesis consists of seven chapters and contains the results of an anatomical study, a review of the literature on this subject, a functional urodynamic study and a combined clinical and urodynamic study to the effect of pharmacotherapy in patients with urethral pressure variations and a pilot study to the efficacy of a localized treatment for patients with urethral pressure variations (UPV). The question is whether urethral pressure variations should be seen as an own entity within OAB with possibilities of tailored therapy, or whether it is a prognostic factor which can be used for prediction of success for certain treatment modalities, or whether it should be considered as a rare phenomenon of which it is difficult to establish clinical significance.

In Chapter 2 the results of the anatomical study to the presence and distribution of beta 3 adrenoceptor (ADRB3) in the female human urethra are described. The maintaining of urethral tonus is considered to be mainly under sympathetic control. Since five years, a beta 3 adrenoceptor (ADRB3) agonist is available for treatment of OAB. If ADRB3 is present in the urethra, an ADRB3 agonist will have a local influence which possibly is of importance in patients with urethral pressure variations.

Chapter 3 describes a systematic review of the literature on urethral instability. We have assessed the various measurement methods, materials used, definitions and the methodological quality of reported studies in current literature. This background information is essential to put UPV in perspective of OAB and to define a working definition for this thesis.

Chapter 4 describes a prospective study to determine the additional value of triple-sensor urethral catheter in demonstrating urethral pressure variations during filling cystometry. For further research and definition of UPV, it is important to determine how this condition can best be demonstrated and if the use of a single urethral sensor catheter is as representative as the use of triple urethral sensor catheters in the demonstration of UPV.

In Chapter 5, we present the results of a prospective study to the effect of the beta 3 adrenoreceptor agonist (Mirabegron) on urodynamic sensation parameters and urethral pressure variations during filling cystometry. Previous studies have demonstrated no effect of antimuscarinic agents on urethral function [36]. The aim of this study was to assess the influence

of mirabegron on urethral pressure variations during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

In the five years since ADRB3 agonist has been available, no studies have been performed to effect of ADRB3 agonist on urethral function.

In an attempt to develop localized treatment for patients with UPV, we performed a pilot study to the effectiveness of subtrigonal Botulinum A toxin injections in the treatment of patients with high urethral pressure and/or urethral pressure variations. These results are described in Chapter 6.

Chapter 7 summarizes the results of abovementioned chapters by their abstracts in English.

In Chapter 8 the main findings and recommendations for future research are discussed

In Chapter 9 the Dutch summary of this thesis is provided.

REFERENCES

1. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I: National community prevalence of overactive bladder in the United States stratified by sex and age. *Urology* 2011, 77(5):1081-1087.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003, 61(1):37-49.
3. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU international* 2001, 87(9):760-766.
4. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I: Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. *BJU international* 2009, 104(7):954-959.
5. Lagro-Janssen T, Smits A, Van Weel C: Urinary incontinence in women and the effects on their lives. *Scandinavian journal of primary health care* 1992, 10(3):211-216.
6. Dmochowski RR, Newman DK: Impact of overactive bladder on women in the United States: results of a national survey. *Current medical research and opinion* 2007, 23(1):65-76.
7. Vaughan CP, Johnson TM, 2nd, Ala-Lipasti MA, Cartwright R, Tammela TL, Taari K, Auvinen A, Tikkinen KA: The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. *European urology* 2011, 59(4):629-636.
8. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I: Economic burden of urgency urinary incontinence in the United States: a systematic review. *Journal of managed care pharmacy : JMCP* 2014, 20(2):130-140.
9. Chapple C, Cruz F: Open to debate. The Motion: antimuscarinics are the mainstay of therapy for overactive bladder. *European urology* 2008, 54(1):226-230.
10. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ: Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev* 2012, 1:CD005429.
11. Wagg A, Compion G, Fahey A, Siddiqui E: Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU international* 2012, 110(11):1767-1774.
12. Sicras-Mainar A, Rejas J, Navarro-Artieda R, Aguado-Jodar A, Ruiz-Torrejon A, Ibanez-Nolla J, Kvasz M: Antimuscarinic persistence patterns in newly treated patients with overactive bladder: a retrospective comparative analysis. *Int Urogynecol J* 2014, 25(4):485-492.
13. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D: The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *European urology* 2008, 54(3):543-562.
14. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC: Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014, 33(1):17-30.
15. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, Khemiri A, Siddiqui E, Wagg A: Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *European urology* 2017, 72(3):389-399.

16. Drake MJ, Chapple C, Esen AA, Athanasiou S, Cambronero J, Mitcheson D, Herschorn S, Saleem T, Huang M, Siddiqui E *et al*: Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). *European urology* 2016, 70(1):136-145.
17. MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, Saleem T, Huang M, Siddiqui E, Stolzel M *et al*: Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy: Responder Analyses and Patient-Reported Outcomes from the BESIDE Study [corrected]. *J Urol* 2016, 196(3):809-818.
18. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006, 49(4):644-650.
19. Merrill L, Gonzalez EJ, Girard BM, Vizzard MA: Receptors, channels, and signalling in the urothelial sensory system in the bladder. *Nat Rev Urol* 2016, 13(4):193-204.
20. Barrington F: The components reflexes of micturition in the cat, Parts I and II. *Brain* 1931, 54:177-188.
21. Barrington F: The component reflexes of micturition in the cat: Part III. *Brain* 1941, 64:239-243.
22. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB: Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999, 162(1):204-212.
23. Vereecken RL: Physiological and pathological urethral pressure variations. *UrolInt* 1996, 57(3):145-150.
24. McLennan MT, Melick C, Bent AE: Urethral instability: clinical and urodynamic characteristics. *Neurourol Urodyn* 2001, 20(6):653-660.
25. Groenendijk PM, Heesakkers JP, Ouwerkerk TJ, Lycklama ANAA: Urethral instability: current pathophysiological concept. *Urol Int* 2009, 83(2):125-133.
26. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R: Do we need better methods of assessing urethral function: ICI-RS 2013? *Neurourol Urodyn* 2014, 33(5):587-590.
27. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.
28. de Groat WC, Griffiths D, Yoshimura N: Neural control of the lower urinary tract. *Compr Physiol* 2015, 5(1):327-396.
29. Birder LA, Andersson KE, Kanai AJ, Hanna-Mitchell AT, Fry CH: Urothelial mucosal signaling and the overactive bladder-ICI-RS 2013. *Neurourol Urodyn* 2014, 33(5):597-601.
30. Birder L, Andersson KE: Urothelial signaling. *Physiol Rev* 2013, 93(2):653-680.
31. Kummeling MT, Rietbergen JB, Withagen MI, Mannaerts GH, van der Weiden RM: Sequential urodynamic assessment before and after laparoscopic sacrocolpopexy. *Acta Obstet Gynecol Scand* 2013, 92(2):172-177.
32. Groenendijk PM, Heesakkers JP, Lycklama ANAA: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol* 2007, 178(2):568-572.

33. Farrell SA, Tynski G: The effect of urethral pressure variation on detrusor activity in women. *Int Urogynecol J Pelvic Floor Dysfunct* 1996, 7(2):87-93.
34. Sand PK, Bowen LW, Ostergard DR: Uninhibited urethral relaxation: an unusual cause of incontinence. *ObstetGynecol* 1986, 68(5):645-648.
35. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
36. Thind P, Lose G, Colstrup H, Andersson KE: The influence of beta-adrenoceptor and muscarinic receptor agonists and antagonists on the static urethral closure function in healthy females. *Scand J Urol Nephrol* 1993, 27(1):31-38.

CHAPTER 2

INITIAL REPORT ON DISTRIBUTION OF β3-ADRENOCEPTOR IN THE HUMAN FEMALE URETHRA

Kummeling MT, Buijs JT, Wisse LJ, van Uhm JI, Elzevier HW, Ruiter MC, Groenendijk PM

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INTRODUCTION

The micturition cycle consists of a storage phase and a voiding phase. The bladder functions as the reservoir where urine is storaged, as long as the urethral pressure withstands the pressure in the bladder[1]. When this coordinated function is disturbed, lower urinary tract symptoms (LUTS) or overactive bladder symptoms (OAB) can occur. Barrington was the first to describe seven reflexes involved in bladder storage and micturition in the cat[2, 3], of which four have their afferent origin in the urethra. Therefore, a disturbance in urethral function can probably result in OAB symptoms as well. When outlet resistance suddenly changes because of urethral pressure variations, leakage of urine into the urethra can occur, which in turn may stimulate urethral afferents inducing an involuntary voiding reflex[4]. In the past, a functional disturbance in urethral function leading to OAB was defined as urethral instability (URI)[5]. Yet, since the initial reports the clinical relevance of URI has been controversial and because lack of consensus, the condition was abandoned in terms of the International Continence Society (ICS). A recent review together with the report from the ICS Research Society meeting in 2014 concluded that urethral instability may be regarded a potentially pathophysiological entity of its own within cohorts of patients with OAB[6, 7]. In addition, a recent review of overactive bladder pathophysiology underlined the importance of identifying subgroups of patients within OAB to optimize tailor treatment[8].

Studies to urethral closure function in female patients in the past concluded that the sympathetic nerve system dominates in regard to maintaining the tonus in the urethra[9, 10]. Throughout the entire length of the urethra, administration of noradrenaline or β2-adrenoceptor agonist resulted in a contractile response. Currently, the ADRB3 agonist mirabegron has an important role in the treatment of OAB. Recently, Coelho et al described bladder structures expressing ADRB3[11]. The presence of ADRB3 within the human urethra has not been demonstrated to date. The aim of this study is to investigate the presence of ADRB3 in the human female urethra to contribute to elucidating the effect and side effects of current therapy with mirabegron.

MATERIAL AND METHODS

We performed anatomical studies in 5 female specimen. We started our experiment with three urethra specimen from the body donation program. These results were presented at the annual ICS-meeting in Tokyo in 2016. However, because of tissue decay, the quality of tissue sampling wasn't optimal. We then continued our study with tissue from two female patients with muscle invasive bladder cancer, where radical resection of bladder and urethra was performed. Pre-operatively, the patients were not treated with intravesical or systemical chemotherapy. Patients consented to use the tissue for scientific research anonymously. When bladder neck and urethra were macroscopically tumor free, the urethra up till the bladder neck was separated from the rest of the bladder and freshly obtained for this research. The urethra was transversely divided in 4 areas from meatus to bladder neck. The areas are the bladder neck, the proximal urethra, the mid-urethra and the distal urethra/meatus. Half of the tissue was embedded in optimal cutting temperature compound (OCT) (TissueTEK OCT) and stored at -80°C or directly fixed in 4% paraformaldehyde overnight and processed for paraffin-embedding. For demonstrating ADRB3 expression, we used rabbit polyclonal anti-human ADRB3 LS-A4198.

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Paraffin-embedded tissues were sectioned at 5 μm and deparaffinized. OCT-embedded tissues were cut at 5-μm using a cryomicrotome, and fixed in 4% paraformaldehyde for 10 min at room temperature. All sections were permeabilized in 0.1% Triton-100 in Tris Buffered Saline (TBS). Endogenous peroxidase was blocked by incubation in 1% H2O2/ TBS. Parafin-embedded sections, but not the cryosections, were boiled for 7 minutes in citrate buffer (0.01M) for antigen retrieval. Sections were blocked with 10% Fetal Calf Serum (FCS)/TBS for 30 minutes at room temperature, before O/N incubation with the primary antibody: a rabbit polyclonal anti-human β3AR (LS-A4198, Life Span Biosciences), directed against the N-terminus, and diluted 1:400 in 1%BSA (Sigma)/TBS, and no first antibody served as negative controls.

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The polyclonal anti-human β3AR (LS-A4198, Life Span Biosciences, 1:200) and the mouse monoclonal α-beta III Tubulin (SC-80005, Santa Cruz, 1:1000) in PBS-T with 1% BSA (PBST/BSA) were incubated overnight. Next morning slides were rinsed in 2 times PBS and PBS-Tween. Then the sections were incubated with a mixture of donkey anti-rabbit-Alexa-555 (A-31572, Life technologies) and donkey anti-mouse-Alexa-488.(A-21202, Life technologies) for 60 minutes. Both antibodies were diluted 1:200 in PBST/BSA. After rinsing again the sections were incubated with a 0,3 μM DAPI (D3571, Molecular probes) for 5 minutes. The slides were rinsed with 2 times PBS and mounted in ProLong Gold antifading Reagent (P36930, Molecular probes). The imaging was performed with the panoramic 250 Flash (3DHISTECH)

RESULTS

In the adult female, the urethra has a length of 3-4 cm average and consists of three layers[12]. From inside to outside the first layer is the mucosal layer. In the region of the bladder neck and proximal urethra this is lined by urothelium (figure 2.1B, TE). In the middle and distal part, the urethra is lined by stratified squamous epithelium (figure 2.1D). The second layer is the submucosal layer (figure 2.1D), consisting of connective tissue, elastic tissue, a vascular plexus and periurethral glands (figure 2.1F). The third layer is the muscular layer, consisting of an inner longitudinal and circular smooth muscle layer (figure 2.1E) and an outer circular striated muscle layer, also referred to as EUS. The EUS has its thickest part in the middle third section of the urethra, where striated

Figure 2.1 HE-staining of transverse cross-sections of the urethra and bladder neck. **A:** bladder neck with transition to the proximal urethra. L=lumen. Square box indicates transitional epithelium. **B:** Detailed image of the square box in A. L=lumen bladder, SM=submucosal layer, TE=transitional epithelium. **C:** transverse cross-section of mid-urethra. L=lumen. Square box D demonstrates stratified squamous epithelium and is in detail in image 1D. Square box F refers to figure 1F, an example of a peri-urethral gland. **D:** Detailed image of the square box in C. L=lumen. SE= squamous stratified epithelium. SM=submucosal layer **E:** able- fluorescence image of C. L=lumen. LSMC=longitudinal smooth muscle layer. CSMC=circular smooth muscle layer. **F:** detailed image of the peri-urethral gland. Scale bar A,C,E=1000μm. B,D,F=50μm

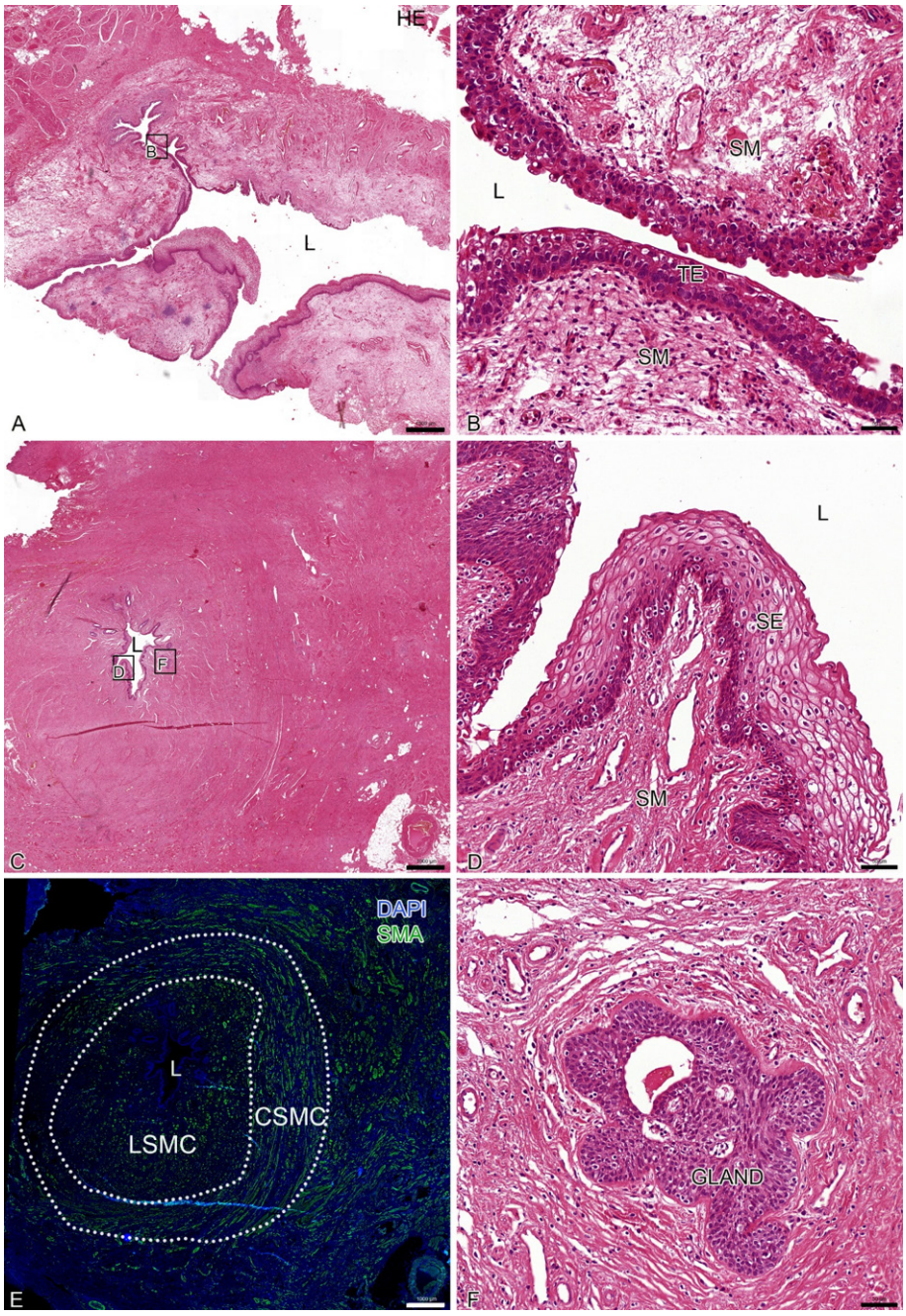

Figure 2.1 For caption see left page

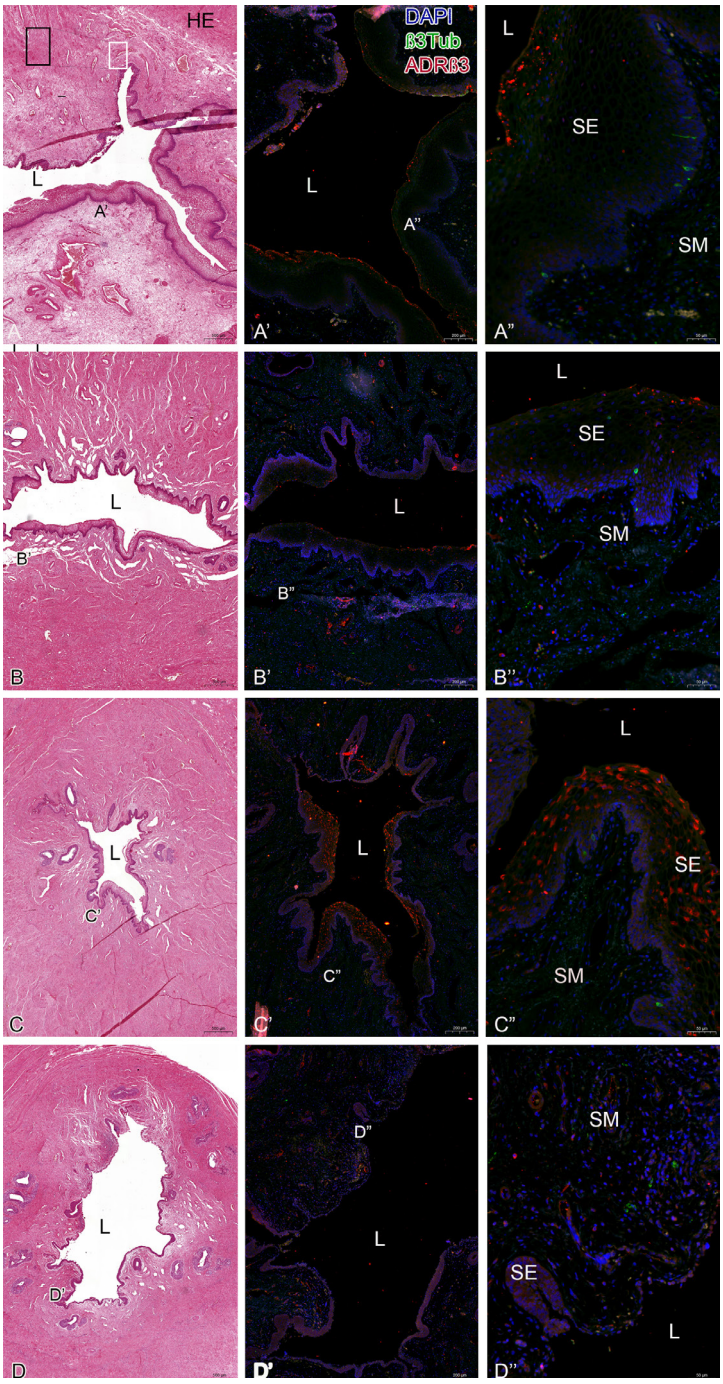

Figure 2.2 For caption see right page

muscle completely surrounds the urethra, although the posterior part is relatively thin. In the proximal and distal part of the urethra, no striated muscle is present in the posterior part.

ADRB3-expression

Expression of ADRB3 was demonstrated in the urothelium and squamous stratified epithelium in all urethral parts, except at the meatus. The pattern and degree of ADRB3 expression differs between urethral regions. At the bladder neck, ADBR3 is expressed in the superficial layer of the transitional epithelium only (fig 2A'). In the proximal urethra, there is a lower level of ADRB3 expression in the superficial layer of the transitional epithelium and the expression is more scattered than at the bladder neck (fig 2B'). The highest level of ADRB3 expression is present in the mid-urethra (fig 2C'). In the distal urethra, at the meatus and the pelvic floor, there is no intraluminal expression of ADRB3 (fig 2D'). ADRB3-expression is also demonstrated in the stratified muscular layer (fig 3). This stratified muscular layer represents the EUS and is the only urethral part with stratified muscles. The other urethral parts contain smooth muscle cells only, where ADRB3-expression is absent. Within the periurethral glands no ADRB3 expression was demonstrated.

Figure 2.2 Distribution of ADRB3 and beta III tubulin in the female urethra with LS-A4198. **A** transverse cross- section of the bladder neck with HE-staining. L=lumen. **A'** able-fluorescence staining for ADRB3 of A. Red spots represent ADRB3 expression in the superficial layer of transitional epithelium. L=lumen. **A''** able-fluorescence staining with beta III tubulin. Arrows indicate the course of neurons in the lamina propria. L=lumen SM=submucosal layer. SE=stratified squamous epithelium **B** transverse cross-section of the proximal urethra with HE-staining. L=lumen **B'** immunofluorescence staining for ADRB3 of B. SM=submucosal layer. SE=stratified squamous epithelium **B''** immunofluorescence staining of B' with beta III tubulin. Arrows indicate expression of beta III tubulin positive neurons. **C** transverse cross-section of the mid-urethra with HE-staining. L=lumen. **C'** able-fluorescence staining of C for ADRB3. L=lumen. **C''** able-fluorescence staining of C' with beta III tubulin. Arrows indicate expression of neurons. L=lumen SM=submucosal layer. SE=stratified squamous epithelium **D** transverse cross-section of the distal urethra with HE-staining **D'** immunofluorescence staining of D for ADRB3 is negative. **D''** immunofluorescence staining of D' with beta III tubulin. Arrows indicate beta III tubulin positive neurons in the submucosal layer. L=lumen SM=submucosal layer. SE=stratified squamous epithelium. Scale bar A,B,C,D=500 μm A'BÇ'D'=200 μm A"B"C"D"= 50 μm

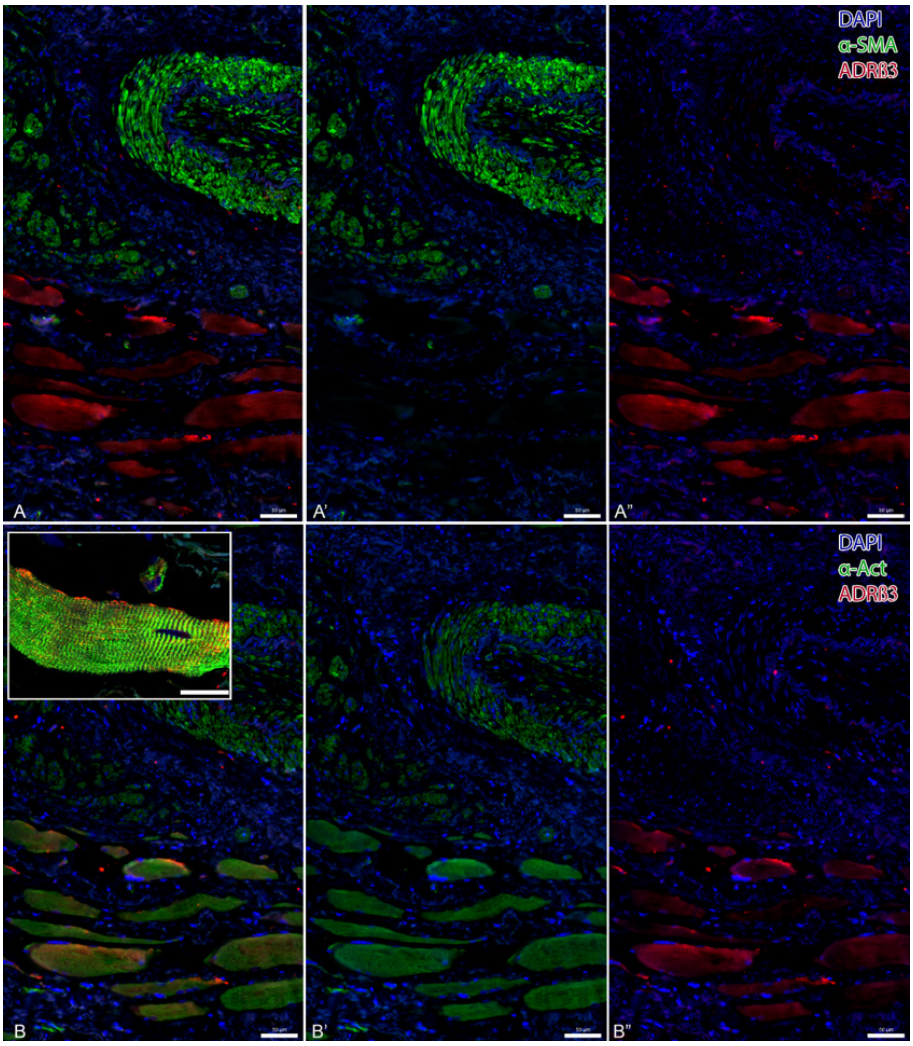

Figure 2.3 Transverse images of the muscular layers of the urethra.
A: fluorescent image of smooth muscle cells, **A'** staining αsmooth muscle actin(αSMA = green) **A''** no ADRB3-expression in smooth muscle cells could be found.
B: Fluorescent image of stratified muscular cells. In the upper left corner detailed image of a stratified muscular cell with scale bar 20μm **B'** demonstrates positive actin staining, **B''** demonstrates ADRB3-expression within the stratified muscular cells. Scale bar all images 50μm

Beta III tubulin staining

Staining with beta III tubulin is positive in the lamina propria of the bladder neck (fig 2A"). There is no direct contact between the cells that express the ADRB3 receptor and the neurons. In the proximal urethra, there is a scattered presence of neurons within the distal part of transitional epithelium and in the submucosal layer (fig 2B"). In the mid-urethra, there is expression of few neurons both in the distal epithelial layer as in the submucosal layer (fig 2C"). The distance between ADRB3 in the squamous stratified epithelial layer and beta III tubulin positive neurons in the submucosal layer is smallest in this section. At the distal urethra, there are few neurons in the submucosal layer(fig 2D").

DISCUSSION

In this study, we performed an anatomical mapping of ADRB3 in five human female urethras. This resulted in two main findings. First, we demonstrated the presence of ADRB3 in the superficial epithelial layer of the urethra. Second, we found that there was no direct contact between ADRB3 receptor and nerve endings.

The predominating β-adrenoceptor in the human bladder is the ADRB3-receptor[13, 14]. Although presence of adrenergic nerves and of ADRB3-receptor have been demonstrated in the striated human urethral sphincter in the past[15], this is the first report on epithelial presence of ADRB3 in the human female urethra.

In animal studies, attempts to identify the subtype beta-adrenoceptor (ADRB) mediating urethral relaxation were based upon the response of urethral pressure to a non-selective agonist, and to selective ADRB1, ADRB2 and ADRB3 agonists and their inhibition by subtype selective antagonists[16]. In rats, bladder pressure was reduced by ADRB2 and ADRBR3 agonist, but urethral pressure reduction was different between ADRB2 and ADRBR3 agonist. The pressure reduction was highest in response to ADRB2 agonist. The effect of ADRB3 agonist on urethral pressure was comparable to the effect of saline. Michel and Vrydag conclude in their review that relaxation of the urethra of rat, dog and pig appear to involve a strong ADRB2-component[17]. The lack of response of urethral pressure to ADRB3 agonist could be due to dominance of ADRB2 in the urethra in rats. We want to address that many adrenoceptor antibodies lack specificity[18], but that the LS-A4198 antibody used in

the current study has been tested and described as most promising[19] to best validated ADRB3 antibody available[14].

Previous studies mainly focused on the role of alfa-adrenoceptor subtypes and the effect of α-adrenoceptor agonists in urethral pressure. However, a randomized placebo-controlled pilot study in female patients with LUTS demonstrated that the alfa blocking agent terazosine was not effective in treating symptoms[20]. The use of α-adrenoceptor agonists in the treatment of LUTS is limited because of adverse effects on the cardiovascular system. Nowadays, with the selective β3 agonist mirabegron available in treatment with patients suffering from OAB, the question rises if and how urethral pressure is influenced by this agent.

Our second finding, the lack of contact between ADRB3 and neurons in the submucosal layer, could suggest the presence of an extra afferent signaling network originating from the urethral epithelial layer. From previous studies is learned that in the bladder, the urothelium itself has neuron-like properties, contributing to sensory transduction mechanisms[21]. The release of the neurotransmitters nitric oxide (NO) and ATP by the urothelium in response to chemical and mechanical stimuli has been demonstrated [22-24]. Activation of ADRB3 receptor on urothelial cells triggers production and release of nitric oxide (NO). For the urethra, no similar findings have been reported. Although urothelium only is present in the proximal urethra, maybe the presence of ADRB3 in other parts of the urethral epithelial layer could result in NO release as well when stimulated. Past studies suggested that alterations in NO-levels may play a role in urothelial signaling in the bladder[25, 26]. The female urethra has a rich vascular plexus and vascular smooth muscle cells are recognized as targets for NO. Activity of the enzyme cyclic nucleotide phosphodiesterase 5 (PDE5) rapidly inactivates the degradation of cGMP and thus increases the effect of NO stimulation. If a similar afferent signaling pathway from the urethra exists, this could be of interest for future research to the role of pharmacotherapy in regard to urethral function. Previous research demonstrated that PDE5 inhibitors promote potent relaxation of animal and human urethral smooth muscle [27]. Male patients with erectile dysfunction and LUTS treated with PDE5 inhibitors may experience a beneficial effect both on erectile function as on their LUTS [28]. Extrapolation of these data suggest that PDE5 inhibitors could have an effect on female urethral function as well, an interesting hypothesis for future research. Given the hypothesis of an additional local mechanism in afferent signaling, future research could

also focus on therapy with a local mechanism of action, as we recently did in a pilot study with paraurethral injections of botulinum toxin-A in patients with URI [29].

The major limitations of this study are the lack of a quantitative analysis, of positive controls, of a functional evaluation and of course the small sample size. Future research should elucidate the optimal protocol for demonstrating the presence of functional ADRB3, combined with functional research, as well as exploring the role of NO pathway in the urethra.

Conclusion

In this study, for the first time expression of ADRB3 is demonstrated in the epithelial layer of the human female urethra. The expression of ADBR3 is present in almost the entire length of the urethra, with the highest level in the mid-urethra. No direct connection between ADRB3 and nerve endings was observed. These findings contribute to better a better understanding of action mechanisms of ADRB3 agonists. Future research should elucidate the local effect of pharmacotherapy.

Acknowledgements

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REFERENCES

1. de Groat WC, Griffiths D, Yoshimura N: Neural control of the lower urinary tract. *Compr Physiol* 2015, 5(1):327-396.
2. FJF Barrington: The component reflexes of micturitionin the cat, Parts I and II. *Brain* 1931, 54:177-188.
3. FJF Barrington: The component reflexes of micturition in the cat. Part III. *Brain* 1941, 64:239-243.
4. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB: Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999, 162(1):204-212.
5. Bates CP, Bradley WE, Glen ES, Melchior H, Rowan D, Sterling AM, Sundin T, Thomas D, Torrens M, Warwick RT *et al*: Fourth Report on the Standardisation of Terminology of Lower Urinary Tract Function: Terminology related to neuromuscular dysfunction of the lower urinary tract: produced by the International Continence Society*. *Br J Urol* 1981, 53(4):333-335.
6. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.
7. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
8. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, Amarenco G, Game X, Kirby R, Van Der Aa F *et al*: A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment. *Eur. Urol.* 2019, 75(6):988-1000.
9. Thind P, Lose G, Colstrup H, Andersson KE: The influence of beta-adrenoceptor and muscarinic receptor agonists and antagonists on the static urethral closure function in healthy females. *Scand J Urol. Nephrol.* 1993, 27(1):31-38.
10. Taki N, Taniguchi T, Okada K, Moriyama N, Muramatsu I: Evidence for predominant mediation of alpha1-adrenoceptor in the tonus of entire urethra of women. *J Urol* 1999, 162(5):1829-1832.
11. Coelho A, Antunes-Lopes T, Gillespie J, Cruz F: Beta-3 adrenergic receptor is expressed in acetylcholine-containing nerve fibers of the human urinary bladder: An immunohistochemical study. *Neurourol Urodyn* 2017, 36(8):1972-1980.
12. Gosling JA: Gross and microscopic anatomy of the urethra II - the female urethra. Edinburgh: Gower Medical Publishing Ltd; 1984.
13. Takeda M, Obara K, Mizusawa T, Tomita Y, Arai K, Tsutsui T, Hatano A, Takahashi K, Nomura S: Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. *J Pharmacol Exp Ther* 1999, 288(3):1367-1373.
14. Limberg BJ, Andersson KE, Aura Kullmann F, Burmer G, de Groat WC, Rosenbaum JS: beta-Adrenergic receptor subtype expression in myocyte and non-myocyte cells in human female bladder. *Cell Tissue Res* 2010, 342(2):295-306.
15. Morita T, Iizuka H, Iwata T, Kondo S: Function and distribution of beta3-adrenoceptors in rat, rabbit and human urinary bladder and external urethral sphincter. *J Smooth Muscle Res* 2000, 36(1):21-32.

16. Takeda H MA, Igawa Y, Yamazaki Y, Kaidoh K, Akahane S, Kojima M, Miyata H, Akahane M, Nishizawa O: Functional characterization of beta-adrenoceptor subtypes in the canine and rat lower urinary tract. *J Urol.* 2003, 170:654-658.
17. Michel MC, Vrydag W: Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol* 2006, 147 Suppl 2:S88-119.
18. Kirkpatrick P: Specificity concerns with antibodies for receptor mapping. *Nat Rev Drug Discov* 2009, 8(4):278.
19. Cernecka H OP, Lamers WH, Michel MC: Specifity evaluation of antibodies against human beta-3-adrenoceptors. *Naunyn Schmiedebergs Arch Pharmacol* 2012, 385:875-882.
20. Lepor H, Theune C: Randomized double-blind study comparing the efficacy of terazosin versus placebo in women with prostatism-like symptoms. *J Urol* 1995, 154(1):116-118.
21. de Groat WC: The urothelium in overactive bladder: passive bystander or active participant? *Urology* 2004, 64(6 Suppl 1):7-11.
22. Birder LA, Apodaca G, De Groat WC, Kanai AJ: Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. *Am J Physiol* 1998, 275(2):F226-229.
23. Sun Y, Keay S, De Deyne PG, Chai TC: Augmented stretch activated adenosine triphosphate release from bladder uroepithelial cells in patients with interstitial cystitis. *J Urol* 2001, 166(5):1951-1956.
24. Birder L, Andersson KE: Urothelial signaling. *Physiol Rev* 2013, 93(2):653-680.
25. Ozawa H, Chancellor MB, Jung SY, Yokoyama T, Fraser MO, Yu Y, de Groat WC, Yoshimura N: Effect of intravesical nitric oxide therapy on cyclophosphamide-induced cystitis. *J Urol* 1999, 162(6):2211-2216.
26. Caremel R, Oger-Roussel S, Behr-Roussel D, Grise P, Giuliano FA: Nitric oxide/cyclic guanosine monophosphate signalling mediates an inhibitory action on sensory pathways of the micturition reflex in the rat. *Eur Urol* 2010, 58(4):616-625.
27. Werkstrom V, Svensson A, Andersson KE, Hedlund P: Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. *BJU Int* 2006, 98(2):414-423.
28. Sun HY, Lee B, Kim JH: Factors affecting the efficacy and safety of phosphodiesterase 5 inhibitor and placebo in treatment for lower urinary tract symptoms: meta-analysis and meta-regression. *Int Urol Nephrol* 2018, 50(1):35-47.
29. Kummeling MT DV, van Uhm JI, de Vries L, Groenendijk PM, van Koeveringe GA, Elzevier HW: Initial report on subtrigonal Botulinum toxin-A (BoNT-A) therapy for female patients with urethral instability - results of a pilot study. *Urol. Nephrol. Open Access J* 2018, 6(2):69-72.

CHAPTER 3

CONTINUOUS URETHRAL PRESSURE MEASUREMENTS: A SYSTEMATIC LITERATURE ANALYSIS

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INTRODUCTION

Normal adult lower urinary tract (LUT) storage function requires a detrusor muscle that is relaxing and adapting to volume -increment with low pressure. On the other side, the outlet should remain closed, to prevent incontinence. Passive as well as muscle outlet factors play a role and, crudely; 'outlet muscles' should remain contracted, to a certain degree during urine storage phase, to ensure continence(1, 2). Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome (OAB), urge syndrome or urgency-frequency syndrome(3)

OAB is urodynamically associated with both presence and absence of detrusor overactivity (DO). Urethral pressure variations (UPV) are observable with continuous intra urethral pressure measurement and have been observed during urodynamic investigation as well in association with DO in patients with lower urinary tract symptoms (LUTS) (4, 5) as in individuals without LUTS(6, 7) The clinical relevance of UPV, also referred to as urethral instability, in the pathophysiology of OAB has remained controversial since the initial reports,(8-10) Furthermore it is unknown whether patients with UPV have specific symptoms, hidden in-, or separate from OAB, and as a consequence specific management for patients with 'significant' UPV is not yet available.

In the period 1978-1996 various studies have described UPV and discussed whether this is an isolated entity apart from DO or not, without an unambiguous conclusion.(5, 8-12). The international continence society (ICS) defined unstable urethra in 1981 as the condition where urinary loss is solely caused by a fall in urethral pressure(13). The condition defined by this definition is however rare and as a consequence various propositions for definition have been made. The ICS did reach a new compromise for the definition and for a relatively long time, no studies have been performed on this subject. Recently, the International Consultation on Incontinence Research Society (ICI-RS) recommended new clinical research to be performed on this topic.(14)

We have performed a systematic review of the available evidence with regard to UPV with the aim to provide an overview of the measurement methods and the (proposed) definitions as well as the reported prevalence. The scientific quality of the studies was systematically evaluated.

On the basis of this systematic review we suggest for urodynamic practice and future research and hope that this may contribute to targeted management and therefore may optimize the treatment of patient suffering from OAB or LUTS.

METHODS

In September 2014, the electronic databases Pubmed, Embase, Web of Science, Cochrane, Central, Cinahl, Academic Science Premier, Science Direct and WileyOnline were searched using the search strategies as shown in Fig. 1. The articles were screened by title, abstract or by full article, when necessary, to select the studies that met the predefined selection criteria. Initial selection criteria were; Urethral pressure variations / urethral instability as the predominant outcome, performed with adult female patients, without relevant neurological conditions in a cohort study or randomized controlled trial and reported full text available in English, German, French or Dutch. We excluded case studies or cohorts less than ten patients and expert reviews were also not included. Reference screening and citation tracking were performed on the identified articles.

All authors have independently reviewed and scored all full text papers that met the inclusion criteria, according to the STARD-checklist(15). Consensus about methodological quality was obtained in an open discussion meeting according to Oxford Level of Evidence (LoE, version March 2009).

The items reviewed were selection bias, description and specifications of urodynamic evaluation (type and position of catheter used, position of patients, filling speed, EMG), informed consent, approval by medical ethics committee, definition of urethral pressure variation and reported prevalence.

RESULTS

487 articles were identified and no paper was excluded because of the language. Among the list of excluded papers were papers in Japanese, Chinese, Spanish and Italian, but the main topic of these papers was not about urethral pressure variations or had a too small sample size. Five papers were excluded because they reported on non-adult patients

also.(16-19). Six papers were excluded because of mixed gender studies. (9, 20-23). Six expert opinion reviews were excluded(24-28) (29). When multiple papers were published on the basis of a single patient cohort, only one paper of those, with the largest cohort, was included, others were considered duplicate and excluded.(7, 29-31) Twenty-five papers met all predefined selection criteria and were included. Only two of the studies(32, 33) were performed after approval of local ethics committee and with informed patient consent.

The reported incidence of UPV has varied between 2 and 95%.(34, 35) Definition of UPV, as well as measurement methods and techniques, patient position, cystometry and catheter type and position show a large variety and are shown in tables 1 and 2. The papers report studies of weak methodological quality with Oxford LoE scores of 3B or 4, an overview is shown in table 3(4-6, 8, 12, 16, 18, 32-50). Striking is that all studies have reported and or concluded an association of DO/OAB with UPV although patients selection at entry or at evaluation may have played a role in this.

Table 3.1 Reported (urodynamic) technique (N studies =25)

Catheter used	N	Position sensor	N
Dual microtip sensor, (1 urethra)	18	Ventral	2
2 separate catheters	2	Lateral	6
3 sensors urethra	2	Not specified	17
5 sensors urethra	1		
Open water filling	1		
Microtip, not specified	1		

Table 3.2 Overview study types and variables of urodynamic investigation

Study	Study type	Filling rate	Postion of patients	EMG
Bergman et al (36)	Prospective Cohort	60 ml/min	NA	N
Demoulin et al (37)	Limited cohort	50 ml/min	NA	Y (some)
Farrell and Tynski(38)	Retrospective case series	80 ml/min	Sitting + standing	Y
Groenendijk et al. (34)	Prospective case series	NA	NA	Y
Hilton (33)	Retrospective case series	Fixed vol. 250ml	Supine	N
Kulseng-Hanssen (18)	Retrospective case series	Fixed 100+50ml/min	Semirecumbent	NA
Kulseng-Hanssen and Kristoffersen (6)	Selected cases	Fixed 100+30ml/min	Semirecumbent	NA
Low et al. (39)	Selected cases	20 ml/min	Supine	N
McLennan et al. (4)	Prospective case series	80 ml/min	Sitting	N
Penttinen (43)	Retrospective case series	50 ml/min till 300ml	Supine	N
Plevnik and Janez (44)	Retrospective case series	NA	Supine	N
Sorensen (45)	Retrospective case series	NA	NA	Y (nothing reported)
Sorensen et al. (46)	Retrospective case series	Diuresis	NA	Needle
Sand et al. (35)	Prospective case series	"medium filling"	Supine + sitting	Y
Schaer et al. (47)	Case series	60 ml/min	Supine	N
Sorensen et al. (40)	Prospective case series	Fixed vol. 250 ml	Supine + sitting	Y
Tapp et al. (32)	Prospective case series	Fixed vol. 250 ml	Supine	N
Ulmsten et al. (41)	Prospective case series	50 ml/min	Sitting + standing	N
Venema and Kramer (48)	Retrospective selected cases	50 ml/min	Sitting + standing	Y
Vereecken (5)	Retrospective case series	NA	NA	Y
Vereecken et al. (49)	Case series	28 ml/min	Supine + sitting	Y
Vereecken and Das (8)	retrospective selected casses	28 ml/min	Sitting	Y
Versi and Cardozo (50)	Prospective case series	Fixed vol. 250 ml	NA	N
Weil et al. (12)	Prospective case series	50 ml/min	Supine	N

Table 3.3 Overview Oxford Level of Evidence, definitions and reported prevalence

Study	Oxford LoE	Inclusion def.	Exclusion def.	Definition UPV	Prevalence
Bergman et al (36)	3B	poor	poor	probably one type	39% ?
Demoulin et al (37)	4	poor	selected series	types / patterns	?
Farrell and Tynski(38)	4	selected	selected	patterns	73% UDI
Groenendijk et al. (34)	3B	yes	no	16-30 or >30cm-H2O	95%
Hilton (33)	4	poor	no	continuous	not dichotomous
Kulseng-Hanssen (18)	4	no	no	>20cmH2O	20%
Kulseng-Hanssen and Kristoffersen (6)	4	no	no	continuous	?
Low et al. (39)	4	selected	selected	>20cmH2O drop	selected
McLennan et al. (4)	3B	consecutive	consecutive	ratio, 4 patterns	13%
Penttinen (43)	4	consecutive?	No	posthoc 3 patterns	63%
Plevnik and Janez (44)	4	no	no	posthoc 10-40cm-H2O	67%
Sorensen (45)	3B	poor	poor	all variation	?
Sorensen et al. (46)	4	poor	healthy	all variation	?
Sand et al. (35)	4	selected	selected	all variation	2%
Schaer et al. (47)	3B	selected	no	15-30 and 30-130cmH2O	17%
Sorensen et al. (40)	4	selected	healthy	posthoc 3 types	?
Tapp et al. (32)	4	yes	yes	variable	not dichotomous
Ulmsten et al. (41)	4	consecutive	consecutive	posthoc 3 types	12%
Venema and Kramer (48)	4	yes	poor	>15cmH2O	?
Vereecken (5)	4	no	posthoc	posthoc typing	8%
Vereecken et al. (49)	4	no	selected	>15cmH2O	18%
Vereecken and Das (8)	4	no	selected	>15cmH2O	14%
Versi and Cardozo (50)	3B	yes	poor	posthoc	14%
Weil et al. (12)	3B	poor	poor	posthoc	16%
Wise et al. (16)	4	poor	poor	ratio	42%

DISCUSSION

The generalizability of the performed studies is limited because all studies have been performed with very heterogeneous and poorly defined –retrospective single centre- patient populations with poorly defined in- and exclusion criteria. The results of the studies are difficult to combine since a wide variety of measurement methods and patient populations is reported. Clinical relevance of UPV and consequences for management of patients with LUTS are yet to be established and we suggest that this is of relevance since epidemiological studies in the US and in Europe show prevalence figures for OAB of 16% to more than 50% of the population(51-53). Estimated is that 29.8 million adults aged ≥40 years in the United States have bothersome OAB symptoms(54) but not all affected people seek medical attention.(55) In the year 2007, estimated total national cost in US of OAB with urinary incontinence was $65.9 billion, with projected costs of $76.2 billion in 2015 and $82.6 billion(56). OAB syndrome has a negative impact on health-related quality of life (QoL)(57, 58) and the worse the symptoms, the larger the negative effect(59).

Considering fundamental and clinical research, there exists a phenomenon of UPV, apart from detrusor overactivity, which may be a distinguishable pathophysiological entity, probably within the cohort of persons with OAB. That the normal outlet remains closed during urine storage is not only dependent on outlet anatomy and passive mechanics but also on muscular contraction activity. Especially when related to physical stress with intra- abdominal pressure rises, the passive properties play a role. With regard to the muscle activity component of urinary continence, both voluntary striated pelvic muscle as well as autonomic internal sphincter / bladder -neck smooth muscle activity is relevant. Voluntary pelvic -striated- muscle relaxation –physiologically- allows (or initiates) smooth muscle internal sphincter relaxation and detrusor dome muscle contraction that, in turn, opens the urethra and prompts passage of urine. The internal sphincter and detrusor dome act as autonomic antagonists under the 'guidance of' somatosensory innervated pelvic muscles'.(2) Failure of the detrusor to relax during the entire storage phase is a deviation from normal physiology referred to as detrusor over activity (DO), observable as pressure increment(s) during cystometry. Failure of the bladder outlet to remain closed (maybe observable as UPV) in the storage phase will result in symptoms of LUT dysfunction and or urinary incontinence.

Although the clinical relevance may be obvious continuous intra urethral pressure during storage is technically not easy to measure. An element of continuous urethral closure is intra urethral pressure and continuous intra urethral pressure measurement could give information about urethral muscular closure function alike continuous detrusor pressure measurement gives information about detrusor relaxation and volume adaptation. However, because the closed urethra during LUT storage phase has no lumen, pressure cannot be measured in the physical sense. Intra-urethral pressure recording, with contemporary available techniques can, at best only, provide surrogate observations and provide circumstantial evidence, for the urethral closure function. The techniques that are applied for intravesical (or rectal –abdominal) pressure measurement are fundamentally imperfect to measure the physics of urethral closure. As a consequence, those results are prone to intrinsic artefacts, or just 'only artefacts' in the eyes of its opponents. The catheter by itself, the measuring fluid and orientation of catheter measuring opening, or the sensor-stiffness or orientation, are causing artefacts simply by their position and the space that is occupied inside the urethral lumen. Moreover also a slightly moving or displacing sensor may mimic UPV because the 'pressure' inside the urethra is unequally distributed, even when the total muscle activity around the outlet is not changing during the time of that movement. In the studies performed with multiple urethral pressure sensors, all sensors register urethral pressure variations simultaneously, they have however been best recognized at the point of maximal urethral pressure.

Small amplitude pressure variations have arbitrarily always been considered normal. Abrupt pressure variations have been interpreted as movement artefacts. Bearing this in mind evaluation of research articles reporting UPV should include much caution. We have nevertheless evaluated the existing evidence for UPV, for measuring techniques and methods to evaluate outlet function during storage and UPV.

In the included studies three different patterns are consistently reported: Slow wave pattern UPV's, with relatively small amplitude; UPV's of varying amplitude, prior to DO and third: Fast and brief UPV's with relatively large ($>$ 40cmH_2O) amplitude, observed during the entire filling cystometry.

The discussion whether or not UPV are a realistic phenomenon is probably not the question to debate. Just like the observation of DO during filling cystometry in normal persons that not bother or perceive symptoms, UPV's can be observed in healthy individuals without obvious LUTS. The fact that the detrusor muscle can fail to (adapt and) relax during bladder

filling makes it plausible that its antagonist, the smooth urinary sphincter and or the striated urethral sphincter may fail to maintain contracted, and clinical studies that falsify this are never published. The focus of attention should be to distinguish between the phenomenon within normal limits and phenomenon leading to signs and symptoms and or pathophysiology. The current scientific evidence is too weak to answer this question in a way that allows generalizable conclusions.

For the future research for UPV we suggest that clinical urodynamic testing is standardised. Patients should be investigated in sitting position during continuous, medium (30-50mL/min) filling rate cystometry. Continuous urethral pressure should be registered, ventrally oriented in the urethra (12 o'clock position) minimally at the point of maximal urethral pressure, however we acknowledge that it is difficult to maintain urethral pressure measurement at a fixed point in the urethra with the commonly available techniques. Certainly improved techniques to monitor (active and or passive maintenance of) urethral closure function during cystometry are much needed in this regard. Future research may validate if single urethral sensor is as representative as multisensory urethral catheters in diagnosing urethral pressure variations.

CONCLUSION

Systematic analysis or the literature regarding UPV shows large variation in technique and low Oxford level of evidence research. Different patterns and definitions of urethral pressure variations / urethral instability have been reported. Despite the poor methodological quality of the performed studies and the inherent measurement problems, UPV may be regarded a –potentially pathophysiological- entity of its own within cohorts of patients with OAB. We suggest that future prospective research needs to be performed with better-standardized urodynamic technique and focuses on the fast and brief pattern of UPV. Obviously, a well-defined patient population and urodynamic measurement methods according to ICS standard of good urodynamic practises are of utmost relevance. Studies should be performed in both symptomatic and asymptomatic patients. Urodynamic observations should be combined with validated clinical questionnaires. Further research should aim to better instigate personalised management for patient suffering OAB and more systematic evaluation of UPV may help in this regard.

REFERENCES

1. de Groat WC, Yoshimura N. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Progress in brain research. 2006;152:59-84.
2. de Groat WC. Anatomy and physiology of the lower urinary tract. The Urologic clinics of North America. 1993;20(3):383-401.
3. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):37-49.
4. McLennan MT, Melick C, Bent AE. Urethral instability: clinical and urodynamic characteristics. NeurourolUrodyn. 2001;20(6):653-60.
5. Vereecken RL. Physiological and pathological urethral pressure variations. UrolInt. 1996;57(3):145-50.
6. Kuseng-Hanssen S, Kristoffersen M. Urethral pressure variations in women with and without neurourological symptoms. Neurourology and Urodynamics. 1987;6(4):299-306.
7. Sorensen S. Urethral pressure variations in healthy and incontinent women. Neurourology and Urodynamics. 1992;11(6):549-91.
8. Vereecken RL, Das J. Urethral instability: related to stress and/or urge incontinence? J Urol. 1985;134(4):698-701.
9. McGuire EJ. Reflex urethral instability. Br J Urol. 1978;50(3):200-4.
10. Obrink A, Bunne G. Urethrocystometric findings in urgency. Urologia Internationalis. 1978;33(6):377-80.
11. Colstrup H, Lose G, Jorgensen L. Pressure variations in the female urethra measured by the infusion technique: Is it an artifact? Neurourology and Urodynamics. 1988;7(5):457-60.
12. Weil A, Miege B, Rottenberg R, Krauer F. Clinical significance of urethral instability. ObstetGynecol. 1986;68(1):106-10.
13. Bates CP, Bradley WE, Glen ES, Melchior H, Rowan D, Sterling AM, et al. Fourth Report on the Standardisation of Terminology of Lower Urinary Tract Function: Terminology related to neuromuscular dysfunction of the lower urinary tract: PRODUCED BY THE INTERNATIONAL CONTINENCE SOCIETY*. British Journal of Urology. 1981;53(4):333-5.
14. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R. Do we need better methods of assessing urethral function: ICI-RS 2013? Neurourol Urodyn. 2014;33(5):587-90.
15. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Annals of internal medicine. 2003;138(1):W1-12.
16. Wise BG, Cardozo LD, Cutner A, Benness CJ, Burton G. Prevalence and significance of urethral instability in women with detrusor instability. Br J Urol. 1993;72(1):26-9.
17. Penders L. [Simultaneous urethrocystometry and urethral instability in female incontinence]. Acta UrolBelg. 1984;52(2):200-6.
18. Kulseng-Hanssen S. Prevalence and pattern of unstable urethral pressure in one hundred seventy-four gynecologic patients referred for urodynamic investigation. Am J ObstetGynecol. 1983;146(8):895-900.
19. Penders L, de LJ, Petit R. Enuresis and urethral instability. Eur Urol. 1984;10(5):317-22.

20. Yamanishi T, Yasuda K, Suda S, Ishikawa N. Effect of functional continuous magnetic stimulation on urethral closure in healthy volunteers. Urology. 1999;54:652-5.
21. Yalla SV, Resnick NM. Initiation of voiding in humans: the nature and temporal relationship of urethral sphincter responses. J Urol. 1997;157(2):590-5.
22. Penders L. [Urethral instability. Clinical and physiopathological observations]. Acta UrolBelg. 1987;55(3):401-16.
23. Kulseng-Hanssen S. Urethral pressure variation. International Urogynecology Journal. 1993;4(6):366-72.
24. Khullar V, Cardozo L. The urethra (UPP, MUPP, instability, LPP). Eur Urol. 1998;34 Suppl 1:20-2.
25. Trifa M. [Urethral instability in women. Etiopathogenesis and therapeutic approach]. J Urol(Paris). 1994;100(1):36-9.
26. Plante P, Soulie M. [Urethral instability]. ProgUrol. 2000;10(2):200-4.
27. Groenendijk PM, Heesakkers JP, Ouwerkerk TJ, Lycklama ANAA. Urethral instability: current pathophysiological concept. UrolInt. 2009;83(2):125-33.
28. Elia G, Bergman A. Urethral pressure changes in women with detrusor instability. International Urogynecology Journal. 1994;5(2):98-101.
29. Koonings PP, Bergman A. Urethral pressure changes in women with detrusor instability. Bladder or urethral pathologic process? Urology. 1991;37(6):540-2.
30. Sorensen S. Urethral pressures during bladder filling. Scand J UrolNephrol Suppl. 1989;125:45-51.
31. Sorensen S, Norgaard JP, Knudsen LM, Rittig S, Djurhuus JC. Urethral pressure variations in healthy females during rest and sleep. J Urol. 1987;137(6):1287-90.
32. Tapp AJS, Cardozo LD, Versi E, Studd JWW. The Prevalence of Variation of Resting Urethral Pressure in Women and its Association with Lower Urinary Tract Function. British Journal of Urology. 1988;61(4):314-7.
33. Hilton P. Unstable urethral pressure: Toward a more relevant definition. Neurourology and Urodynamics. 1987;6(5):411-8.
34. Groenendijk PM, Heesakkers JP, Lycklama ANAA. Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? J Urol. 2007;178(2):568-72.
35. Sand PK, Bowen LW, Ostergard DR. Uninhibited urethral relaxation: an unusual cause of incontinence. ObstetGynecol. 1986;68(5):645-8.
36. Bergman A, Koonings PP, Ballard CA. Detrusor instability. Is the bladder the cause or the effect? J Reprod Med. 1989;34(10):834-8.
37. Demoulin JY, Kunst D, Pigne A. [Urethral instability]. J GynecolObstetBiol Reprod (Paris). 1987;16(6):723-7.
38. Farrell SA, Tynski G. The effect of urethral pressure variation on detrusor activity in women. Int UrogynecolJ Pelvic Floor Dysfunct. 1996;7(2):87-93.
39. Low JA, Armstrong JB, Mauger GM. The unstable urethra in the female. ObstetGynecol. 1989;74(1):69-74.
40. Sorensen S, Kirkeby HJ, Stodkilde-Jorgensen H, Djurhuus JC. Continuous recording of urethral activity in healthy female volunteers. Neurourology and Urodynamics. 1986;5(1):5-16.
41. Ulmsten U, Henriksson L, Iosif S. The unstable female urethra. American Journal of Obstetrics and Gynecology. 1982;144(1):93-7.

42. Vereecken RL, Proesmans W. Urethral instability as an important element of dysfunctional voiding. J Urol. 2000;163(2):585-8.
43. Penttinen J. Urethral pressure variations diagnosed by multiple urethral pressure transducers. A common phenomenon in women suffering from urinary incontinence. Eur J ObstetGynecolReprod Biol. 1989;33(3):259-65.
44. Plevnik S, Janez J. Urethral pressure variations. Urology. 1983;21(2):207-9.
45. S++rensen S. Urethral pressure and pressure variations in stress incontinent women and women with unstable detrusor. Neurourology and Urodynamics. 1991;10(5):483-92.
46. S++rensen S, N++rgaard JP, Djurhuus JC. Continuous urethral pressure measurement in women with unstable detrusor. Neurourology and Urodynamics. 1986;5(6):525-34.
47. Schaer GN, Koechli OR, Schuessler B, Haller U. Can simultaneous perineal sonography and urethrocystometry help explain urethral pressure variations? NeurourolUrodyn. 1997;16(1):31-8.
48. Venema PL, Kramer AEJL. Treatment of female incontinence with or without urethral instability. World Journal of Urology. 1986;4(1):27-31.
49. Vereecken RL, Cornelissen M, Das J, Grisar P. Urethral and perineal instability. UrolInt. 1985;40(6):325-30.
50. Versi E, Cardozo L. Urethral instability: Diagnosis based on variations of the maximum urethral pressure in normal climacteric women. Neurourology and Urodynamics. 1986;5(6):535-41.
51. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20(6):327-36.
52. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU international. 2001;87(9):760-6.
53. Vaughan CP, Johnson TM, 2nd, Ala-Lipasti MA, Cartwright R, Tammela TL, Taari K, et al. The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. European urology. 2011;59(4):629-36.
54. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National community prevalence of overactive bladder in the United States stratified by sex and age. Urology. 2011;77(5):1081-7.
55. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I. Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. BJU international. 2009;104(7):954-9.
56. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I. Economic burden of urgency urinary incontinence in the United States: a systematic review. Journal of managed care pharmacy : JMCP. 2014;20(2):130-40.
57. Lagro-Janssen T, Smits A, Van Weel C. Urinary incontinence in women and the effects on their lives. Scandinavian journal of primary health care. 1992;10(3):211-6.
58. Dmochowski RR, Newman DK. Impact of overactive bladder on women in the United States: results of a national survey. Current medical research and opinion. 2007;23(1):65-76.
59. Diokno AC. Epidemiology and psychosocial aspects of incontinence. The Urologic clinics of North America. 1995;22(3):481-5.

CHAPTER 4

ADDITIONAL VALUE OF TRIPLE-SENSOR URETHRAL CATHETER IN DEMONSTRATING URETHRAL PRESSURE VARIATIONS DURING FILLING CYSTOMETRY

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INTRODUCTION

Urodynamic evaluation is often performed in the work-up of patients with lower urinary tract symptoms (LUTS). During filling cystometry, urethral pressure variations (UPV) can be observed if continuous intra urethral pressure measurement is performed. Continuous intra urethral pressure is technically not easy to measure, since the closed urethra during filling phase has no lumen like the bladder, the vagina or the rectum. In the period 1978-1996 various studies have described urethral pressure variations, and discussed whether this is an entity on its own, apart from detrusor overactivity[1-4]. The International Continence Society (ICS) defined urethral instability (URI) in 1981 as a condition in which there is an involuntary fall in urethral pressure during filling phase, resulting in urinary leakage in the absence of detrusor activity. This definition was abandoned shortly after because this is a rare phenomenon. In a recent review was concluded that studies on this subject have a diversity in measurement techniques and materials [5]. Urodynamic catheters with variation of one to six sensors in the urethra have been used in the literature[6-9]. In the studies performed with multiple urethral pressure sensors, all sensors registered the urethral pressure variations simultaneously, they have however been best recognized at the point of maximal urethral pressure[9]. Recently, a think tank session of the ICI-RS was dedicated to urethral pressure variations urethral instability[10]. This session was followed by a summarizing report based on literature review and discussions during this ICI-RS meeting[11]. This report also concluded that UPV certainly is associated with LUTS and thus, future research on this topic is relevant.

If clinical relevance of urethral pressure variations is to be further examined, a consensus about the definition of URI is necessary and the demonstrating of this condition has to be widely applicable. Therefore, research is needed to demonstrate if measurement with a single urethral sensor catheter is as representative as measurement with a multi sensor urethral catheter in diagnosing UPV. Continuous urethral pressure measurement is usually performed with the use of a dual air-balloon sensor urodynamic catheter with only one sensor in the urethra. In our centre, urodynamic studies have been performed with both the "standard" dual sensor catheter, as with a catheter with three urethral sensors. The purpose of this study is to compare the results of continuous urethral pressure measurements with a single urethral sensor catheter and a triple urethral sensor catheter in demonstrating UPV during filling cystometry.

MATERIALS AND METHODS

This prospective observational intervention study was performed at the outpatient urology department of Leiden University Medical Centre. Between May 2016 and July 2018, seventy-five consecutive patients enrolled in this study. All adult female patients, mentally fit to consent and requiring urodynamic evaluation for analysis of their LUTS were asked to participate in this study. Ethical committee approval was granted and all patients provided written informed consent. Declaration of Helsinki was followed. All patients had a normal urine microscopy before urodynamic investigation. All patients underwent two series of filling and voiding cystometry. One series was performed with the regular dual-air balloon sensor urodynamic catheter (Laborie T-DOC® air-charged dual sensor catheter, distance from bladder sensor to urethral sensor 6cm, shore hardness 65±5D, 7Fr), positioned at maximum urethral pressure. The other series was performed with a urodynamic catheter with three urethral sensors (Unisensor, UniTip catheter, three urethral sensors 7mm apart, distance from bladder sensor to middle urethral sensor 7cm, shore hardness of 65D, 8Fr), with the midurethral pressure sensor positioned at the maximum urethral pressure. It was decided at random which type of catheter was used for the first filling series, the second measurement series was performed with the other type. Cystometry was carried out in a semi-upright sitting position with a continuous filling rate of 30-50ml/min. All urodynamic investigations were performed by the same specialized nurse according to ICS standard good urodynamic practices and terms 2016. During filling cystometry, the sensory markers first sensation of filling (FSF), normal desire (ND) and strong desire (SD) and maximal filling capacity (MMC) were marked. Pelvic floor electromyography (EMG) was performed with surface patch electrodes. In the measurement with single urethral sensor catheter, UPV was defined as an urethral pressure drop exceeding 30 cmH2O. Although to date pressure variations larger than 15 cm H2O have appeared to be most clinically relevant, we deliberately used a relatively higher cut-off value to rule out movement artefacts. In the measurement with the triple urethral sensor catheter, UPV was defined as an urethral pressure drop present in at least two out of three sensor measurements, with a pressure drop exceeding 30 cmH2O in at least one sensor measurement. Confidence intervals for correlation were calculated to a sample size of 75 patients.

RESULTS

The patients' mean age was 54 years with a range of 19-90 years. The median volumes during filling cystometry measured with both catheters are shown in Table 4.1.

The prevalence of UPV is 37.3% (28 out of 75 patients). In 8 patients UPV was seen in both single and triple urethral sensor catheters, in 18 patients only in the triple urethral sensor catheter and in 2 patients only in the single urethral sensor catheter. Examples of urodynamic tracings showing the 30cm H2O pressure drop with each of the two catheter types in the same patient are shown in figure 4.1 and 4.2 respectively. An overview of the prevalence of UPV in measurements with both catheters is shown in table 4.2. The triple sensor catheter detected a significant larger amount of UPV (26/28) compared to dual air-balloon catheter (10/28, p-value <0.001). Detrusor overactivity (DO) was seen in 13 patients (17.3%) and a combination of UPV and DO in 4 patients (5.3%). As shown in Table 4.3, there are no significant differences in volumes during filling cystometry between patients with and without UPV. As shown in table 4.4, neither was there a significant difference in median volumes during filling cystometry between patients who underwent the first measurement with single sensor catheter compared to triple sensor catheter.

Table 4.1 Median volumes during filling cystometry

N=75	Dual microtip Median (IQR)	Missing	Triple sensors Median (IQR)	Missing	P-value*
FSF	97 ml (55 – 214)	2	123 ml (67 – 198)	0	0.790
ND	245 ml (121 – 386)	6	198 ml (133 – 316)	6	0.013
SD	303 ml (167 – 455)	11	264 ml (169 – 411)	9	0.030
MMC	334 ml (210 – 502)	10	327 ml (195 – 499)	7	0.493

* Wilcoxon signed ranks test

Table 4.2 UPV in dual microtip versus triple sensor catheter (30cmH2O)

		Triple sensor No UPV	UPV	Total
Dual microtip (one urethral sensor)				
	No UPV	47	18	65
	UPV	2	8	10
	Total	49	26	75

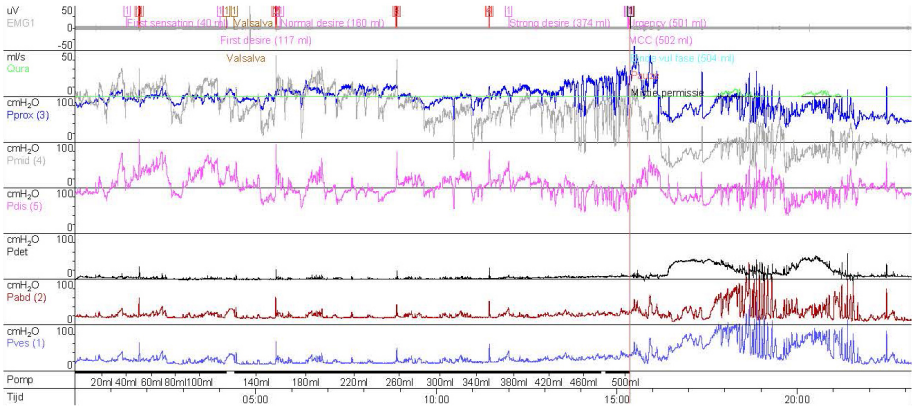

Figure 4.1 Sample tracing UPV with 3 urethral sensor catheter

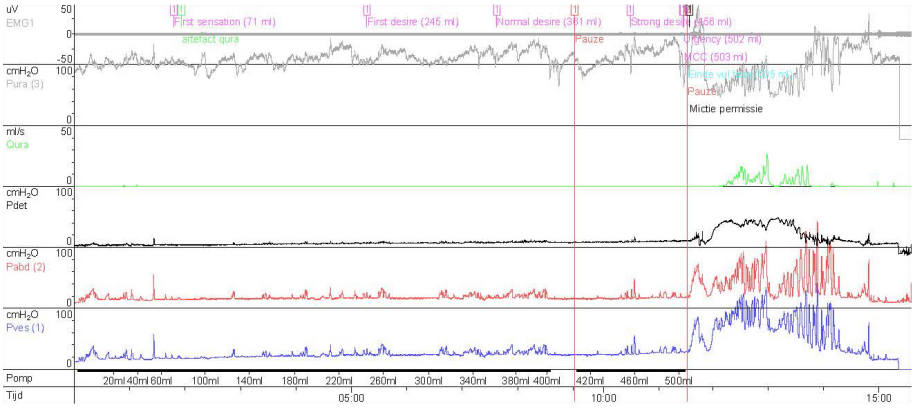

Figure 4.2 Sample tracing UPV single urethral sensor catheter

Table 4.3 Median volumes during filling cystometry compared in patients with and without UPV

		UPV (n=28)	Missing	No UPV (n= 47)	Missing	P-value*
FSF	*1 sensor*	90ml (65 – 309)	0	99ml (51 – 205)	2	0.434
	3 sensors	115ml (65 – 193)	0	124ml (69 – 201)	0	0.935
SD	*1 sensor*	349ml (181 – 501)	2	272.5ml (155 – 433)	9	0.346
	3 sensors	322ml (169 – 501)	1	249ml (169 – 369)	8	0.300
MMC	*1 sensor*	463ml (209 – 524)	2	323ml (210 – 491)	8	0.328
	3 sensors	412ml (202– 550)	1	299ml (195 – 481)	6	0.284

*Mann- Whitney U test

Table 4.4 Median volumes during filling cystometry compared in order of measurements

		1-3 (N= 20)	Missing	3-1 (N=55)	Missing	P-value*
FSF	*1 sensor*	99 (56 – 263)	1	95 (53 – 213)	1	0.624
	3 sensors	135 (74 – 232)	0	113 (63 – 176)	0	0.229
ND	*1 sensor*	226 (121 – 375)	2	264 (120 – 415)	4	0.779
	3 sensors	226(150 – 525)	4	194 (125 – 311)	2	0.196
SD	*1 sensor*	251 (137 – 403)	2	312 (183 – 471)	9	0.442
	3 sensors	273 (176 – 588)	4	260 (162 – 408)	5	0.487
MMC	*1 sensor*	319 (206 – 487)	3	400 (213 – 503)	7	0.681
	3 sensors	308 (196 – 599)	4	342 (195 – 498)	3	0.603

*Mann- Whitney U test

DISCUSSION

In the present study, we found two things. First, despite the use of a relatively high cut-off value for the definition of UPV, the prevalence still was 37%. This is much more common than the prevalence of DO. Opponents of UPV in the past have argued that UPV is a physiological phenomenon prior to voiding reflex in DO or as a result of voluntary holding to suppress the desire to void [8, 12, 13]. However, the prevalence of both conditions in the same measurement series was even more rare in this series. The relatively high prevalence and the presence in healthy asymptomatic females have also been used as arguments against a pathophysiological entity[14]. In other words, on the one hand the definition of URI was abandoned because of the rarity of the condition, and on the other hand URI is rejected because of the high prevalence when detected apart from urinary incontinence. At the same time is accepted that DO can be demonstrated in asymptomatic patients. Since the urethra is not a closed reservoir like the bladder and since it's not filled with liquid at rest, it is difficult to understand what is measured. Besides, the urethra has a different shape of cross-section from point to point. The possibility of movement artefacts can never be completely excluded, but is demonstrated too consistent to be labelled as artefact only. By performing pelvic floor EMG - not showing any movements when UPV occurred- we have tried to exclude the movement artifacts to the best of our ability, but off course there might be better methods to do so. By performing two measurement series, one with each catheter, in the same patient, we made the patients their own control. To reduce the risk of bias, we have performed the measurements with the different catheter types in random order, however this doesn't exclude the within-patient

variability of pressure measurement completely. However, there were no significant differences in the two measurements within the same patients and between patients undergoing three urethral-sensor measurement first or single urethral-sensor measurement first.

It is time to evaluate the complete functional unit of bladder and urethra together in the analysis of LUTS.

Second, we found that there is additional value in measurement with triple urethral sensor catheter for the demonstration of UPV during filling cystometry. The use of three urethral sensors reduces the chance of measurement artifacts due to movement of the catheter. The direction of the three sensors are the same, so we hypothesized that if there is any movement of the catheter, it will be registered in all leads.

Before the start of the study it was considered that there could be advantages as well as disadvantages in using the triple sensor urethral catheter. An advantage is that the chance of missing UPV because of dislocation of the catheter is minimized since the presence of two other sensors being able to so. A possible disadvantage is that the triple sensor urethral catheter is a reusable one, with a slightly larger diameter (8Fr versus 7Fr) and maybe a slight greater degree of stiffness (65D versus 65±5D). The use of a triple urethral sensor catheter during filling cystometry was non-inferior to the single urethral sensor catheter in first sensation of filling and bladder capacity, thus demonstrating the possible disadvantage of use not to be present.

The advantage has been proven true, since the triple sensor urethral catheter detected UPV significantly better. This observation is not so favorable for the applicability in daily practice. In many centers, continuous urethral pressure measurement is not performed at all, let alone with a custom-made triple urethral sensor catheter. On the other hand, the majority of previous studies are performed with a standard dual micro tip catheter, with a similar prevalence as seen here. The larger the pressure variation, the greater the chance that the dual sensor will demonstrate it as well. Therefore, we suggest to start with standard measurement of continuous urethral pressure measurement with a standard single urethral sensor catheter and to refer patients for measurement with a multi urethral sensor catheter when no abnormalities are demonstrated but clinical suspicion of UPV still is present.

The cut-off value for UPV we used were pressure variations of 30cm H2O or more. In the literature a diversity of cut-off values and categories have been used to describe UPV. Definitions have been used with a fixed

cut-off value between 10-30 cm H2O[3, 7, 15], dependent on pattern, peak-to-peak time[16-18] and as percentage or difference with maximum urethral pressure[4, 19-21]. While the air balloon measurements have less variability than other measurement types, there are no normal ranges for the technology used, maybe varying pressure amounts may need to be adjusted for which type of sensor is used, although no significant differences between the two measurements in the same patient occurred in this series. As long as there is no definition of UPV within terms of ICS, this is still a matter of debate as well. Because the aim of this study was primarily to investigate the applicability and outcomes of the two different urodynamic catheters, a relatively high fixed cut-off point was used.

CONCLUSION

In this study we found that UPV is a quite common phenomenon, demonstrated in one third of all patients during filling cystometry. Although the clinical consequences have yet to be established, these results underline the importance of further research to urethral function. Currently, measurement of urethral pressure during filling cystometry is not defined within ICS standard good urodynamic practices and terms. The single urethral sensor catheter is useful for a start, but detection of UPV is significantly better with triple urethral sensor catheter. There is an additional value in measurement with triple urethral sensor catheter during filling cystometry.

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REFERENCES

1. Hindmarsh JR, Gosling PT, Deane AM: Bladder Instability. is the Primary Defect in the Urethra? *British Journal of Urology* 1983, 55(6):648-651.
2. Colstrup H, Lose G, J++rgensen L: Pressure variations in the female urethra measured by the infusion technique: Is it an artifact? *Neurourology and Urodynamics* 1988, 7(5):457-460.
3. Low JA, Armstrong JB, Mauger GM: The unstable urethra in the female. *ObstetGynecol* 1989, 74(1):69-74.
4. McLennan MT, Melick C, Bent AE: Urethral instability: clinical and urodynamic characteristics. *NeurourolUrodyn* 2001, 20(6):653-660.
5. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
6. Kulseng-Hanssen S: Prevalence and pattern of unstable urethral pressure in one hundred seventy-four gynecologic patients referred for urodynamic investigation. *Am J ObstetGynecol* 1983, 146(8):895-900.
7. Plevnik S, Janez J: Urethral pressure variations. *Urology* 1983, 21(2):207-209.
8. Penttinen J: Urethral pressure variations diagnosed by multiple urethral pressure transducers. A common phenomenon in women suffering from urinary incontinence. *Eur J ObstetGynecolReprod Biol* 1989, 33(3):259-265.
9. Groenendijk PM, Nijeholt AALA, Ouwerkerk TJ: Urethral instability and Sacral Nerve Stimulation (SNS). *Journal of Urology* 2002, 167(4):200-200.
10. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R: Do we need better methods of assessing urethral function: ICI-RS 2013? *Neurourol Urodyn* 2014, 33(5):587-590.
11. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.
12. Ulmsten U, Henriksson L, Iosif S: The unstable female urethra. American Journal of Obstetrics and Gynecology 1982, 144(1):93-97.
13. Sorensen S: Urethral pressure and pressure variations in stress incontinent women and women with unstable detrusor. *Neurourology and Urodynamics* 1991, 10(5):483-492.
14. Kulseng HS: Prevalence and pattern of unstable urethral pressure in one hundred seventy-four gynecologic patients referred for urodynamic investigation. *American Journal of Obstetrics and Gynecology* 1983, 146(8):875-900.
15. Vereecken RL: Physiological and pathological urethral pressure variations. *UrolInt* 1996, 57(3):145-150.
16. Sorensen S, Kirkeby HJ, Stodkilde-Jorgensen H, Djurhuus JC: Continuous recording of urethral activity in healthy female volunteers. *Neurourology and Urodynamics* 1986, 5(1):5-16.
17. Demoulin JY, Kunst D, Pigne A: [Urethral instability]. *J GynecolObstetBiol Reprod (Paris)* 1987, 16(6):723-727.
18. Bergman A, Koonings PP, Ballard CA: Detrusor instability. Is the bladder the cause or the effect? *J Reprod Med* 1989, 34(10):834-838.

19. Versi E, Cardozo L: Urethral instability: Diagnosis based on variations of the maximum urethral pressure in normal climacteric women. *Neurourology and Urodynamics* 1986, 5(6):535-541.

20. Hilton P: Unstable urethral pressure: Toward a more relevant definition. *Neurourology and Urodynamics* 1987, 6(5):411-418.

21. Wise BG, Cardozo LD, Cutner A, Benness CJ, Burton G: Prevalence and significance of urethral instability in women with detrusor instability. *Br J Urol* 1993, 72(1):26-29.

CHAPTER 5

EXPLORATORY ANALYSIS OF THE EFFECT OF MIRABEGRON ON URODYNAMIC SENSATION PARAMETERS AND URETHRAL PRESSURE VARIATIONS

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INTRODUCTION

Urinary continence requires a coordinated function of the bladder as a low pressure reservoir while the outlet resistance is maintained by the urethra.]In storage phase, sympathetic and pudendal nerve activity are responsible for this.. When voiding is initiated, sympathetic stimulation is inhibited and parasympathetic activation results in the contraction of the detrusor muscle and in relaxation of the urethra[1]. Patients with overactive bladder syndrome (OAB) have symptoms of frequent voiding and the sudden need to void, with or without urinary incontinence[2]. OAB is a very common problem with a negative impact on health-related quality of life[3-5].]This condition is often idiopathic, with no responsible anatomical substrate. Urodynamic testing is used to evaluate bladder function in these patients. Detrusor overactivity can be demonstrated during filling cystometry in these patients, but in asymptomatic patients as well. The involuntary initiation of voiding phase can lead to urge urinary incontinence. Research on OAB so far, has mainly been focused on detrusor dysfunction and less on the potential contribution of urethral function. A sudden fall in urethral outlet resistance due to urethral pressure variations (UPV) could result in stimulation of urethral afferents by leakage of urine into the urethra, thereby causing OAB as well[6, 7]. Urge urinary incontinence only due to a sudden fall in urethral pressure has in the past been defined by the International Continence Society (ICS) as urethral instability (URI). Because of the rarity of this condition and lack of consensus about the clinical importance of this phenomenon, the definition was never adjusted and no longer included within ICS terminology and definitions. A recent systematic review on URI concluded however that URI may be regarded a potential pathophysiological entity of its own within cohorts of patients with OAB[8]. This was supported by a recent report based on a literature review and discussions during the ICI-RS meeting on urethral function in 2014[9]. In addition, a recent review underlined the importance of identifying subgroups of patients within OAB to optimize tailor treatment and improve outcomes[10]

Medical treatment options for the management of OAB consists of oral antimuscarinics and a beta 3 adrenoceptor (B3AR) agonist (Mirabegron). Treatment with antimuscarinics result in reduction of voiding frequency, urgency episodes and/or urgency urinary incontinence[11]. However, treatment persistence is low, mainly because of bothersome side effects, with around 30% of patients continuing therapy after one year[12-14].

Past research demonstrated that antimuscarinics had no significant influence on static urethral urethral closure function[15, 16].

Mirabegron is approved for the treatment of overactive bladder symptoms in the last decade. It has been proven clinically and urodynamically effective in the treatment for OAB[17, 18]. The effect of mirabegron on the urethral pressure and on urethral pressure variations during filling cystometry is however unknown. In addition, the presence of B3AR was recently demonstrated in the human female urethra[19]. The aim of this study was to assess the influence of the B3AR agonist mirabegron UPV during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

MATERIALS AND METHODS

Between May 2015 and May 2018 consecutive female patients with OAB symptoms for whom conservative therapy was unsuccessful enrolled in this prospective study. The study was performed in two centers in the Hague. Ethical committee approval was granted and all patients provided written informed consent. Inclusion criteria were female, >18 years of age, mentally fit to consent, bothersome OAB symptoms, voiding diary with total urine production in 24 hours < 2200ml, willing to stop medication for lower urinary tract (LUT) dysfunction 2 days before urodynamic investigation at entry of the study and willing to start mirabegron after initial urodynamic investigation. Exclusion criteria were cystocele POP-Q stage 2 or more, necessity to perform CIC or significant post void residual volume (> 100ml),; bladder outlet obstruction or underactive or acontractile detrusor, unwilling or unable to stop current treatment for LUT dysfunction, treatment with intravesical botulinum toxin A less than one year before investigation and contra indications for using mirabegron. All women underwent clinical evaluation, including history and physical examination. Urinary tract infection was excluded and a cystoscopy was performed to rule out bladder neoplasm. At entry of the study patients were evaluated with a voiding diary, two validated questionnaires for the Dutch language and an urodynamic investigation. The used questionnaires were the Urogenitary Distress Inventory (UDI-6) and the Incontinence Impact short form (II-Q). Cystometry was carried out in a semi-upright sitting position with a continuous filling rate of 30-40ml/min. After urodynamic investigation, patients started with a daily

dosis of 50 mg mirabegron and six weeks later, a second evaluation was performed with a voiding diary, the same questionnaires and urodynamic investigation. The urodynamic investigations were performed with a dual-air balloon sensor urodynamic catheter (Laborie T-DOC® air-charged dual sensor catheter, distance from bladder sensor to urethral sensor 6cm, shore hardness 65±5D, 7Fr), positioned at maximum urethral pressure. During filling cystometry, the sensory markers first sensation of filling (FSF), normal desire (ND) and strong desire (SD) and maximal filling capacity (MMC) were marked. Pelvic floor electromyography (EMG) was performed with surface patch electrodes. URI was defined as UPV exceeding 30 cmH2O. The main endpoint was defined as the number of patients with a reduction of UPV on urodynamic investigation while on treatment with beta 3 adrenoreceptor agonist. The secondary endpoints were individual differences in urethral pressure before and on treatment and to explore association of symptoms before and on treatment with mirabegron. A McNemar test power analysis was performed. A sample size of 60 patients was calculated. Statistical analysis was performed with SPSS statistics (IBM, version 23). Data were analyzed using descriptive statistics and Wilcoxon test for paired samples.

RESULTS

Fifty-one patients were eligible, of which forty-nine patients underwent complete evaluation at entry. Flowchart of the study population is shown in figure 5.1. Two patients cancelled all further appointments and were lost to follow-up after inclusion. Forty-two patients completed the study with two urodynamic investigations. One patient discontinued because of side effects of mirabegron (tachycardia). One patient withdrew participation because eventually she did not want to use medication at all, one patient was referred for pelvic muscle floor training based on the results of her urodynamic evaluation, one patient had an urinary tract infection after the first urodynamic investigation and did not want a second urodynamic investigation and one patient was withdrawn because of her language barrier. Two other patients were lost to follow up. Two patients used antimuscarinics at entry of the study and discontinued use at least 2 days before urodynamic evaluation.

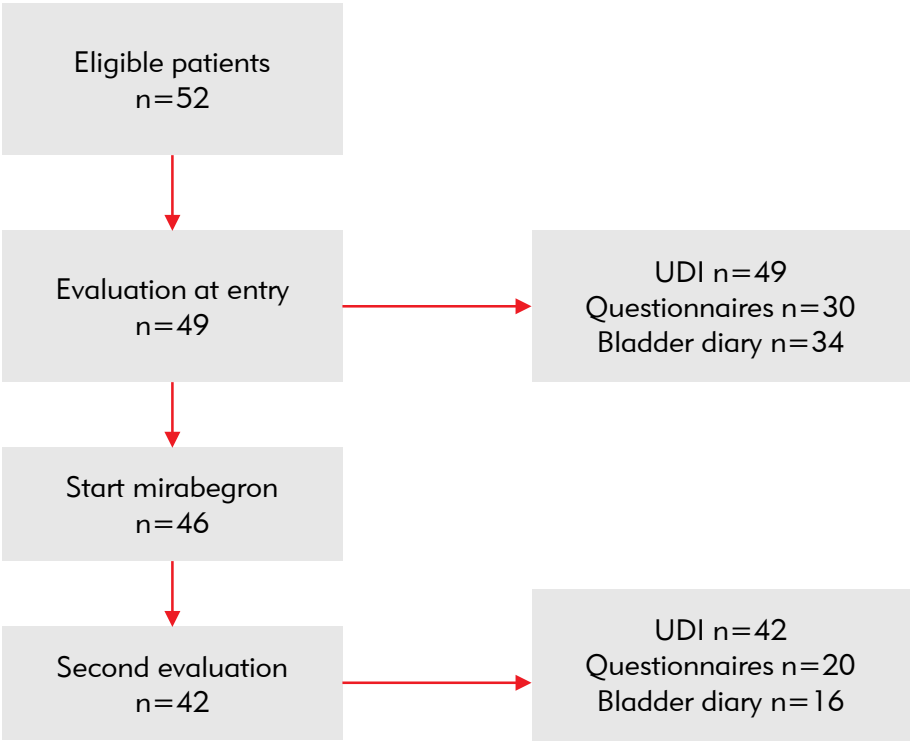

Figure 5.1 Flowchart of study population

Prevalence of URI was in 15 patients (31%) at initial urodynamic investigation, and in 8 patients (19%) at second investigation. DO was present in 9 patients (18%) at initial urodynamic investigation, and in 11 patients (26%) at second investigation. In figure 5.2, an example of urodynamic tracing in a patient with URI, before and after treatment with mirabegron is shown.

Since the aim of our study was to assess the influence of a B3AR agonist on urethral pressure variations we performed a separate analysis of patients with and without URI. The analysis of these subgroups was performed only in patients who completed both urodynamic studies, so that they could serve as their own control. Results of the urodynamic parameters for the complete cohort and subgroups are shown in table 5.1. The difference in maximal and minimal urethral pressure was significantly changed in the URI-group and not in non URI-group after treatment with mirabegron.

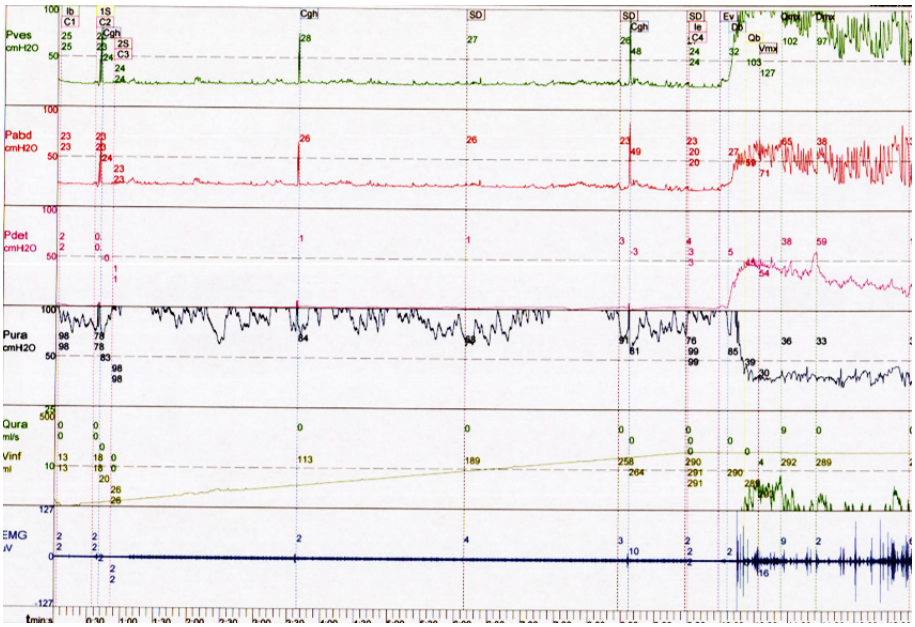

Figure 5.2a Filling cystometry in patient with URI before treatment with mirabegron

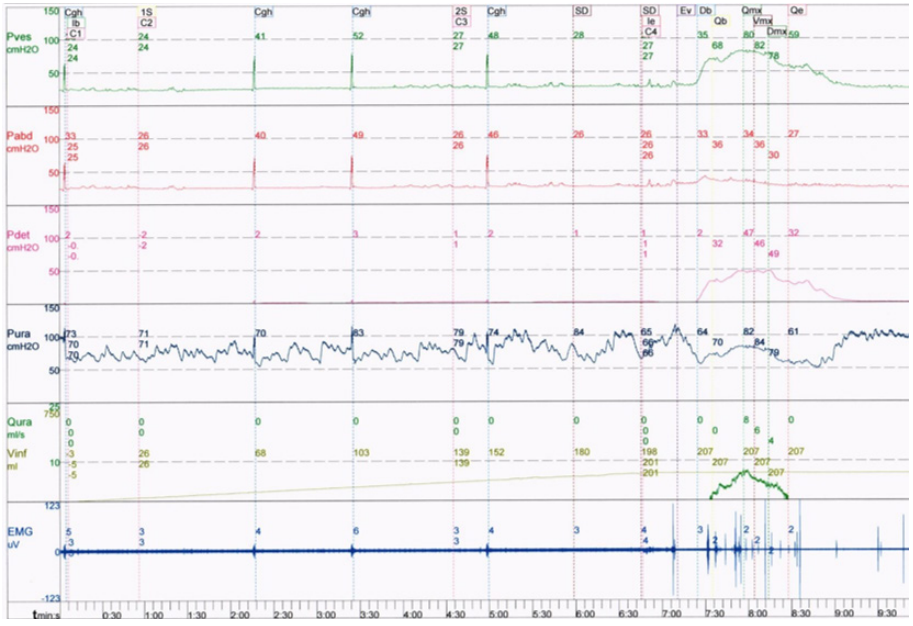

Figure 5.2b Filling cystometry in the same patient aftertreatment with mirabegron

Table 5.1 Urodynamic parameters before and after mirabegron

	Urodynamic parameters – average (range)								
	All patients - before mirabegron (n= 42)	URI-patients –before mirabegron (n=15)	Non-URI-patients – before mirabegron (n=27)	All patients – after mirabegron	URI-patients – after mirabegron	Non-URI-patients – after mirabegron	P-value – all patients	P-value – URI-patients	P-value – Non-URI-patients
Bladder capacity (ml)	303 (85-662)	340 (130-662)	279 (85-495)	330 (0-661)	392 (161-661)	292 (0-561)	0.066	0.087	0.354
Residue (ml)	44 (0-307)	8 (0-307)	10 (0-233)	66 (0-535)	15 (0-421)	11 (0-535)	0.823	0.722	0.987
First desire (cm H2O)	112 (16-288)	71 (16-258)	77 (16-288)	151 (13-372)	208 (32-372)	110 (13-305)	0.023*	0.005*	0.416
Normal desire (cm H2O)	192 (50-459)	182(58-456)	175 (50-459)	231 (49-478)	298 (97-450)	190 (49-478)	0.008*	0.010*	0.087
Strong desire (cm H2O)	267 (74-580)	321 (131-580)	236 (74-495)	302 (57-620)	379 (159-620)	238 (57-526)	0.016*	0.046*	0.141
Qmax (ml/s)	21.8 (1.9-341)	9.7 (1.9-341)	16.5 (4.1-31.9)	16.0 (4.2-40.5)	14.8 (7.7-40.5)	19.9 (4.2-34)	0.788	0.272	0.904
Qav (ml/s)	14.9 (0.9-188)	5.0 (2.9-188)	8.5 (0.9-29)	7.3 (0.3-21.5)	6.1 (0.3-21.5)	7.1 (2.2-20.1)	0.465	0.46	0.955
Max. urethral pressure (cm H2O)	95 (47-150)	95 (75-130)	89 (47-150)	86 (29-153)	90 (40-143)	90 (29-153)	0.150	0.099	0.368
Min. urethral pressure (cm H2O)	62 (25-110)	50 (26-110)	57 (25-109)	60 (16-130)	57(16-101)	58 (16-130)	0.918	0.196	0.659
Urethral pressure difference (cm H2O)	34(6-103)	40 (8-95)	24 (6-103)	26 (3-80)	25 (8-46)	24 (3-80	0.200	0.010*	0.745

Wilcoxon test for paired samples, $p < 0.05$ is significant

A striking finding is that in the URI group, the urodynamic sensation markers all improved while in the non URI-group, none of the sensation markers were changed.

For the entire group of patients, treatment with mirabegron resulted in a reduction of symptoms in the questionnaires on the domains of active relaxation (IIQ p=0,005, UDI-6 p=0,031) and emotional health (IIQ, p=0,011) and in frequency of small amounts urinary incontinence (UDI-6 p=0,011). Results are show in table 5.2. In the URI-group, treatment with mirabegron resulted in a reduction of leakage of drops urine and of urine leakage due to physical activity (UDI-6, question 3 and 4). Results are shown in table 5.3. In the non-URI group, there were no changes in the questionnaires.

In regard to urodynamic parameters, treatment with mirabegron resulted in an improvement of FSF(p=0,019), ND (p=0,015) and SD (p=0,020) demonstrated in urodynamic investigation. Bladder capacity was improved, but not significantly (p=0.07).

Unfortunately, only thirty-four patients adequately completed their voiding diary. After treatment, seventeen of these thirty-four handed in a second complete diary. We only performed analysis on these patients, so that they served as their own control. Results are shown in table 5.4. Voiding frequency improved on treatment with mirabegron, both during the day and in the night. Maximal functional capacity also improved.

Table 5.2 Results from questionnaires – all patients

Domain	Before mirabegron (n=17)	After mirabegron (n=17)	P-value
IIQ-7 Q1	1.18	0.47	***0.03***
IIQ-7 Q2	1.71	1.00	***0.01***
IIQ-7 Q3	1.35	0.88	0.09
IIQ-7 Q4	1.35	1.06	0.25
IIQ-7 Q5	1.19	0.82	0.11
IIQ-7 Q6	1.18	0.65	***0.03***
IIQ-7 Q7	1.38	1.12	0.45
UDI 6 Q1	2.00	1.56	0.25
UDI 6 Q2	1.65	1.44	0.59
UDI 6 Q3	1.12	0.75	***0.03***
UDI 6 Q4	1.76	1.13	***0.02***
UDI 6 Q5	1.00	0.75	0.23

Wilcoxon test for paired samples, $p < 0.05$ is significant

IIQ-7; Incontinence Impact Questionnaire short form, UDI 6; Urogenital Distress Inventory

Table 5.3 Results from questionnaires for patients with urethral instability

Domain	Before mirabegron (n=7)	After mirabegron (n=7)	P-value
IIQ-7 Q1	0.86	0.29	0.180
IIQ-7 Q2	1.57	1.29	0.317
IIQ-7 Q3	1.43	1.14	0.480
IIQ-7 Q4	0.71	1.00	0.414
IIQ-7 Q5	1.00	0.86	0.564
IIQ-7 Q6	1.00	0.71	0.414
IIQ-7 Q7	1.43	1.29	0.783
UDI 6 Q1	2.00	1.43	0.357
UDI 6 Q2	1.29	1.29	0.705
UDI 6 Q3	1.00	0.57	0.083
UDI 6 Q4	1.43	0.71	0.059
UDI 6 Q5	0.86	0.43	0.180
UDI 6 Q6	0.57	1.14	0.102

Wilcoxon test for paired samples, $p < 0.05$ is significant

Table 5.4 Results voiding diaries

N=17	Before mirabegron (avg (range))	After mirabegron (avg (range))	P-value
Voiding frequency day	9.6 (3-18)	7.71 (4-16)	0.034*
Voiding frequency night	1.3 (0-3)	0.9 (0-3)	0.047*
Maximal portion (ml)	298 (100-500)	324 (150-650)	0.001*
Average portion (ml)	186 (90-310)	211 (122-333)	0.136

Wilcoxon test for paired samples, $p < 0.05$ is significant

DISCUSSION

This is the first study to date presenting the effect of treatment with a B3AR agonist on continuous urethral pressure during filling cystometry. Previous studies have reported subjective efficacy and tolerability of treatment with mirabegron alone or in combination with solifenacin[20]. In 2016 Vecchiolo Scaldazza was the first to report urodynamic results of treatment with mirabegron or solifenacin in 60 patients with OAB [18]. Urodynamic parameters as first, normal and strong desire and continuous urethral pressure measurement were not mentioned and/or performed in aforementioned study.

The present study also demonstrates, in line with previous studies[17, 18], that treatment with mirabegron results in a significant improvement of symptoms and quality of life. In contrast to these studies, changes in bladder capacity and DO were not significant.

An important finding is that this study demonstrates that patients with URI have a different response to mirabegron than patients with the same clinical symptoms without URI.

Treatment with mirabegron had a significant effect on all sensation parameters during urodynamic investigation in patients with URI. The changes in first, normal and strong desire are of clinical importance, since these moments will determine when patients will look for a toilet in their daily lives, probably even more than the maximal bladder capacity. The difference in maximal bladder capacity before and on treatment was greater in the URI group, but this change was not statistical significant. The maximal urethral pressure decreased more than the minimal urethral pressure. The difference between maximal and minimal urethral pressure decreased significantly in the URI-group. However, some caution is required considering the loss of power. Theoretically, this could implicate that treatment with mirabegron could be beneficial in patients with high urethral pressure and/or UPV, while maintaining minimal pressure and thus stabilize UPV. UPV is a more common urodynamic phenomenon than detrusor overactivity, demonstrated in one third of the female patients at presentation with OAB in this study. Kirschner-Hermanns et al.[21] even reported a prevalence of 54% in a consecutive series of female patients and a prevalence of 79% in the subgroup of patients with OAB within this cohort, but this was with a lower cut-off value of pressure drops of 15cm H2O or more during filling cystometry.

The main limitation of this study is the small, underpowered sample size. At initiation the study in 2014, mirabegron was just approved for medical treatment of OAB in our country. As time went on, more patients already received mirabegron treatment from their general practitioner and were not willing to use it again for research purposes. In addition, the questionnaires and bladder diaries were unfortunately completed by a limited number of patients, which limits the correlation of urodynamic findings with clinical symptoms so caution is required in interpreting the results. Nevertheless it is important that, apart from prevalence, urodynamic effects of medical treatment are reported. Another limitation is the lack of results of an asymptomatic control group.

This is the first prospective clinical study comparing OAB patients with and without URI. Patients with URI have a different response on mirabegron than patients without OAB. In the past was already demonstrated that presence of URI was a better predictor of outcome in sacral nerve stimulation than DO[22]. The question remains if URI is a separate entity within OAB, or that it should be considered as a predictor for effectiveness of certain treatments. With current insights and recommendations on urethral function, the results of the present study contribute to optimizing treatment choices in patients with OAB. Future research should elucidate the correlation of experienced complaints with urodynamic parameters after treatment and confirm our results in a bigger cohort of patients.

CONCLUSIONS

In this small study we demonstrated that urethral pressure differences are significantly reduced by treatment with the beta 3 adrenoceptor agonist mirabegron in patients with URI. Although the prevalence of URI was reduced with 12% after six weeks of treatment, this difference was not significant. URI seems to have a predictive value in treatment choices for OAB. Taken into consideration the amount of studies performed to the effect and influence of different treatment modalities on detrusor overactivity in patients suffering from OAB, these results confirm the need for future research to the role of urethral function within OAB. We propose that the ICS will include URI again within her definitions and terminology.

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REFERENCES

1. de Groat WC, Griffiths D, Yoshimura N: Neural control of the lower urinary tract. *Compr Physiol* 2015, 5(1):327-396.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003, 61(1):37-49.
3. Lagro-Janssen T, Smits A, Van Weel C: Urinary incontinence in women and the effects on their lives. *Scandinavian journal of primary health care* 1992, 10(3):211-216.
4. Diokno AC: Epidemiology and psychosocial aspects of incontinence. *The Urologic clinics of North America* 1995, 22(3):481-485.
5. Dmochowski RR, Newman DK: Impact of overactive bladder on women in the United States: results of a national survey. *Current medical research and opinion* 2007, 23(1):65-76.
6. Geirsson G, Fall M: Reflex interaction between the proximal urethra and the bladder. A clinical experimental study. *Scand J Urol Nephrol* 1999, 33(1):24-26.
7. Robain G, Combrisson H, Mazieres L: Bladder response to urethral flow in the awake ewe. *Neurourol Urodyn* 2001, 20(5):641-649.
8. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
9. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.
10. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, Amarenco G, Game X, Kirby R, Van Der Aa F *et al*: A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment. *European urology* 2019, 75(6):988-1000.
11. Chapple C, Cruz F: Open to debate. The Motion: antimuscarinics are the mainstay of therapy for overactive bladder. *Eur Urol* 2008, 54(1):226-230.
12. Basra RK, Wagg A, Chapple C, Cardozo L, Castro-Diaz D, Pons ME, Kirby M, Milsom I, Vierhout M, Van Kerrebroeck P *et al*: A review of adherence to drug therapy in patients with overactive bladder. *BJU Int* 2008, 102(7):774-779.
13. Wagg A, Compion G, Fahey A, Siddiqui E: Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012, 110(11):1767-1774.
14. Sicras-Mainar A, Rejas J, Navarro-Artieda R, Aguado-Jodar A, Ruiz-Torrejon A, Ibanez-Nolla J, Kvasz M: Antimuscarinic persistence patterns in newly treated patients with overactive bladder: a retrospective comparative analysis. *Int Urogynecol J* 2014, 25(4):485-492.
15. Thind P, Lose G, Colstrup H, Andersson KE: The influence of beta-adrenoceptor and muscarinic receptor agonists and antagonists on the static urethral closure function in healthy females. *Scandinavian journal of urology and nephrology* 1993, 27(1):31-38.
16. Thind P, Lose G, Colstrup H, Andersson KE: The effect of pharmacological stimulation and blockade of autonomic receptors on the urethral pressure and power generation during coughing and squeezing of the pelvic floor in healthy females. *Scand J Urol Nephrol* 1993, 27(4):519-525.

17. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC: Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014, 33(1):17-30.

18. Vecchioli Scaldazza C, Morosetti C: Comparison of Therapeutic Efficacy and Urodynamic Findings of Solifenacin Succinate versus Mirabegron in Women with Overactive Bladder Syndrome: Results of a Randomized Controlled Study. *Urol Int* 2016, 97(3):325-329.

19. Kummeling MT, Buijs JT, Wisse LJ, van Uhm JI, Elzevier HW, de Ruiter MC, Groenendijk PM: Initial report on distribution of beta3-adrenoceptor in the human female urethra. *Neurourol Urodyn* 2019.

20. Sebastianelli A, Russo GI, Kaplan SA, McVary KT, Moncada I, Gravas S, Chapple C, Morgia G, Serni S, Gacci M: Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: Comparison with placebo and tolterodine. *Int J Urol* 2018, 25(3):196-205.

21. Ruth KH, Ralf A, Nariman G, Ing G, Adele C, Nadine H: Urethral Pressure Variation: A neglected contributing factor in patients with overactive bladder syndrome? *Int Braz J Urol* 2017, 43(2):272-279.

22. Groenendijk PM, Heesakkers JP, Lycklama ANAA: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol* 2007, 178(2):568-572.

CHAPTER 6

INITIAL REPORT ON SUBTRIGONAL BOTULINUM TOXIN-A (BONT-A) THERAPY FOR FEMALE PATIENTS WITH URETHRAL INSTABILITY - RESULTS OF A PILOT STUDY

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INTRODUCTION

Overactive bladder syndrome (OAB) is a common, often under-diagnosed and under-treated condition that significantly affects the quality of life of patients[1].

Unfortunately, in large part of the patients the underlying etiology of OAB is unknown. Urodynamic evaluation can be performed to learn more of the underlying etiology, but unfortunately symptoms of OAB are also present in patients without urodynamic abnormalities. Therefore, patients with OAB are a very heterogeneous patient population for whom a standard treatment protocol is difficult to establish. The treatments offered to patients are usually by preference and experience of the treating physician and effectiveness is established by trial and error.

During filling cystometry of urodynamic evaluation for OAB, detrusor over activity (DO) is often observed. Urethral pressure variations – referred to as urethral instability (URI) by the International Continence Society (ICS)- have also been observed and associated with OAB[2,3]. However, the clinical relevance of this phenomenon is still controversial. DO can be observed in patients suffering from OAB, but also in asymptomatic patients. For urethral instability (URI), the presence of the phenomenon in asymptomatic volunteers was one of the major reasons to abandon this as a pathophysiological phenomenon. It never made it to stay a within the International Continence Society (ICS) terminology.

Urinary continence is maintained by a low pressure reservoir and adequate resting pressure in the urinary sphincter. Therefore, the scope of research on OAB should not be limited to (over)activity of detrusor muscle, but should also take urethral function in consideration. This opinion is shared by the International Consultation on Incontinence Research Society (ICIRS), who recommended new clinical research to be performed on urethral pressure variations[4]. In a recent review was concluded that despite the poor methodological quality of the performed studies UPV may be regarded a –potentially pathophysiological- entity of its own within cohorts of patients with OAB[5]

Nowadays treatment options for OAB include lifestyle modifications, pelvic floor muscle exercises, pharmacotherapy with anticholinergics or beta-3 receptor agonists, pudendal or sacral nerve stimulation and intravesical Botulinum toxin-A (BoNT-A) therapy[6]. In the past, surgical bladder denervation has been performed as treatment modality for OAB.

This was first described in 1935 by Richer and afterwards modified by several colleagues[7,8].

All the above mentioned treatments have in common that they interfere in any part of efferent and afferent signaling from the bladder to the brain, the difference is in the localization and extent of interference. In the present day invasive surgical denervation is rarely performed. The signaling from the nerves is blocked by intravesical injections of Botulinum toxin A, it is a chemical denervation. Botulinum toxin A treatment in OAB has evidence based good results[9], however there are still patients suffering from refractory OAB. The former surgical denervation was performed outside the bladder wall, and thus had a different location of action than the current chemical intravesical injections.

We hypothesized that patients with OAB symptoms and URI are more likely to benefit from a treatment with the mode of action at the urodynamically identified problem.

In this pilot study we present the clinical and urodynamic results of subtrigonal / paraurethral chemical denervation treatment with BoNT-A injections in 5 patients with refractory OAB symptoms and URI.

MATERIAL AND METHODS

This is a retrospective description of the pilot study we performed in 5 female patients. All patients were referred to the Urology department of Leiden University Medical Center and received already several treatments for OAB without success. Four patients had a long history of refractory idiopathic OAB symptoms. One patient was diagnosed with Bladder Pain Syndrome (BPS). All patients were evaluated by an urodynamic study with urethral pressure measurement. All urodynamic studies demonstrated urethral pressure variations.

In the past, improvement of OAB after subtrigonal injections with local anesthetics were a positive predictive factor for success of surgical denervation7. Prior to the surgical procedure, local instillation with xylocaine / adrenalin or bupivavcain solution was performed. First unilaterally, subtrigonal, into the anterior fornix lateral, one cm to the cervix and at a depth of about 3 cm. When there was an improvement of compliance or DO on cystometry and post void residual volume was less then 150ml, there was a favorable result and treatment was continued with surgery. Resection of nerves was performed unilaterally or bilaterally

through an incision in the anterior vaginal wall. Therefore we started treatment with subtrigonal / paraurethral injections of 10cc lidocaine 1%. The patient was positioned in dorsolithotomy position. After disinfection, a urinary catheter was introduced. Traction on the balloon of the catheter was used to localize the position of the bladder neck and the trigonum. Here, 10mL of lidocaine was injected using a 22 gauge spinal needle. The patients were contacted the following day by telephone to evaluate the efficacy of the injections. An improvement of 50% or more in the complaints of urgency and/ or urge urinary incontinence was considered as a positive response. If the response was positive, treatment was continued with subtrigonal injections BoNT-A, 100IU in 10ml solution of NaCl 0,9%. A description of the patients is mentioned below.

Patient 1

Female nulliparous patient of 57 years old referred with urge urinary incontinence. History of slow transit constipation and bowel outlet obstruction, abdominal uterus extirpation and PDDNOS. Patient was referred with refractory OAB with urinary incontinence. She had pelvic floor muscle therapy (PFMT) and anti-muscarinic therapy without effect. Physical examination demonstrated no pelvic organ prolapse (POP). Cystoscopy revealed no abnormalities. Urodynamic evaluation demonstrated bladder capacity (BC) of 380ml, no detrusor overactivity (DO), normal compliance, high urethral pressures till 100 cmH2O and urethral pressure variations (UPV). After repeated PFMT without success, treatment with alpha blocking agent was started, without success. She was treated with subtrigonal lidocaine injections, which improved her symptoms with more than 50%. Treatment was continued with subtrigonal BoNTA injections.

Patient 2

Female nulliparous patient of 38 years old. History of fibromyalgia. Patient was referred with OAB. She already received anti-muscarinic treatment, PMFT and intravesical glycosaminoglycanes (GAG)-replacement therapy with our success. Physical examination demonstrated no POP. Urinary test were clear. Cystoscopy revealed no intravesical abnormalities. Urethra was dilated with short relieve of symptoms (2 days). Bladder diary mentioned total volume 1120ml. Urinary portions of 60-250ml. Daytime frequency

of 7 times, 1 time nocturia. Urodynamic evaluation demonstrated BC of 329 ml, no DO. First sensation of filling (FSF) at 64ml with urethral pressure drop. High urethral pressures and UPV of > 40 cm H2O. She had a very good response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections.

Patient 3

Female patient of 69 years old referred with urge urinary incontinence. History of Stamey procedure, TVT-O and later TVT. Physical examination demonstrated no POP. Patient reported daytime frequency of 8 times and at night 1 time, volumes 75-200ml. Three to four incontinence episodes per day. Cystoscopy demonstrated trabeculation. Urodynamic evaluation demonstrated BC of 407ml, no DO, FSF at 199ml with high pressure drops of urethral pressure and observation of urinary incontinence occurring at lowest pressure point. After successful treatment with lidocaine injections, treatment was continued with subtrigonal BoNT-A injections.

Patient 4

Female multiparous patient of 62 years old referred with mixed urinary incontinence. No relevant medical history. Physical examination demonstrated POP. Urinary test were clear. Bladder diary demonstrated daytime frequency of 12 times and at nighttime frequency of 3 times. Nine tot ten incontinence episodes per day. Cystoscopy demonstrated trabeculation. Urodynamic evaluation demonstrated BC of 337ml, no DO, FSF at 116ml. High urethral pressures up to 180 cmH2O UPV of > 40 cm H2O. Post void residual volume was 225ml. She had a good response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections.

Patient 5

Female patient of 62 years old referred with urethral- and bladder pain syndrome. History of fibromyalgia, chronic fatigue syndrome, cardiac arrhythmias and nocturnal enuresis in her childhood. Patient suffered from urethral pain since 2010, she was treated with alpha booking agents, anti-muscarinic therapy without any effect and local depomedrol application with partial response. Physical examination demonstrated no

POP or other abnormalities. Urinary tests were normal. Her bladder diary showed daytime urinary frequency of 11 times with volumes of 300-450ml. Nocturia 2-3 times. Cystoscopy revealed trabeculation. Urodynamic evaluation demonstrated BC of 730ml, no DO, normal compliance, FSF at 113ml, high urethral pressures up to 150 cmH2O and UPV of > 40 cm H2O. There was no post void residual volume. The pain worsened after micturition. She had a positive response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections

RESULTS

The urodynamic evaluations before and after the subtrigonal BoNT-A injections and the clinical efficacy were compared. In table 1, results of pre- and post-treatment urodynamic results are summarized.

Patient 1

There was a good response to BoNT-A injections for four months. Urodynamic evaluation after the second series of injections demonstrated BC of 480 ml, no DO, still there was high urethral pressure around 100 cmH2O, but no pressure variations were demonstrated. Treatment has been successfully repeated.

Patient 2

Urge complaints responded good on this treatment. Urodynamic evaluation after treatment demonstrated BC of 363 ml, no DO, FSF of 200ml and 114ml. UPV were still present, but with variations of maximal 20 cmH2O. Subtrigonal BoNT-A treatment has been repeated several times, with good response.

Patient 3

Patient had a good response after subtrigonal BoNT-A-injections. Urodynamic evaluation after BoNT-A treatment demonstrated BC of 687 and 756ml, no DO, FSF at 613 and 645ml. UPV were observed, but with maximal pressure drops of 20cm H2O and not related to FSF.

Patient 4

Patient had a good response after subtrigonal BoNT-A-injections. Because of hip replacement surgery, post-treatment urodynamic evaluation has not been performed yet.

Patient 5

Patient had no positive response. After a few days she developed a urinary tract infection. After treating this infection, her complaints were as worse as before treatment.

DISCUSSION

In this heterogeneous group of patients with urethral instability (URI), we demonstrated an improvement of complaints in four out of five patients treated with subtrigonal BoNT-A injections. An interesting finding, apart from the increased bladder capacity, is the increased bladder volume at FSF.

Groenendijk et al concluded that presence of URI was a positive predictive factor for success of sacral neuromodulation therapy (SNM) for OAB[10] and a better predictive factor then presence of DO in pretreatment urodynamic evaluation. Patients with URI responded well on SNM, however, URI was still present in post treatment urodynamic evaluation. Consistent with these findings, in our study, UPV were still present in post-treatment urodynamic evaluation, but with a decreased amplitude of the variations. Sixty years ago, in the time of Ingelman-Sundberg, a group of 34 patients treated with surgical denervation was already split into 6 different categories, indicating how heterogeneous the patient population with OAB is and has been over the years. Thirty patients were cured of their symptoms, with mean follow up of seven years[7]. At that time, changes in cystometry and in compliance of the bladder were observed. Urethral pressures were not measured in those days.

Classification based on clinical and urodynamic characteristics of OAB patients would contribute to targeted therapy. To debate is the question whether OAB is from urodynamic point of view a bladder-only problem or not. In the recent decades, urodynamic evaluation of patients have been further developed. An effort has been made to define what

observations are normal or physiological and when to speak of abnormal or pathophysiological findings. However, the bladder has been the center of attention. If assumed that the feeling of imminent micturition has its origins in the urethra[11], intervening in afferent sensory input from the urethra could have a positive effect on OAB symptoms of patients. It might be that efferent motor response is being of lesser importance. Apparently, sensory input is influenced by neuromodulation and surgical or chemical denervation.

Local injections with lidocaine temporarily and reversibly prevent the formation and transmission of stimuli along the peripheral nervous pathways and nerve endings, creating a temporary numbness. BoNT-A results in inhibition of exocytosis of acetylcholine containing vesicles at the motor endplate, making transmission of the nerve impulse to the motor endplate of the muscle impossible and resulting in a weak paralysis. Despite the differences in mechanism of action of BoNT-A and lidocaine, local injections with lidocaine have been of predictive value in regard to response on BoNT-A treatment[7,8].

Probably, we should see OAB as a form of neuropathy or bladder nerve supply dysfunction that has different forms of expression. Depending on the affected branches, different complaints will be reported as major complaint of the patients, resulting in a heterogenous population with multiple complaints within pudendal nerve supply area.

CONCLUSIONS

Chemical denervation by subtrigonal BoNT-A injections resulted in improvement of refractory OAB symptoms in four out of five patients. The largest improvement was in FSF. Further prospective research is necessary to define the condition of URI in patient with OAB. Besides, new treatment modalities like chemical denervation with subtrigonal BoNT-A injections should be explored by correlation of bladder diaries, validated questionnaires and urodynamic evaluations, with special attention for FSF.

REFERENCES

1. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National community prevalence of overactive bladder in the United States stratified by sex and age. Urology. 2011;77(5):1081-7.
2. Wise BG, Cardozo LD, Cutner A, Benness CJ, Burton G. Prevalence and significance of urethral instability in women with detrusor instability. Br J Urol. 1993;72(1):26-9.
3. McLennan MT, Melick C, Bent AE. Urethral instability: clinical and urodynamic characteristics. NeurourolUrodyn. 2001;20(6):653-60.
4. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R. Do we need better methods of assessing urethral function: ICI-RS 2013? Neurourol Urodyn. 2014;33(5):587-90.
5. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM. Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. Neurourol Urodyn. 2017;36(1):51-6.
6. Allahdin S, Oo N. An overview of treatment of overactive bladder syndrome in women. J Obstet Gynaecol. 2012;32(3):217-21.
7. Ingelman-Sundberg A. Partial denervation of the bladder, A new operation for the treatment of urge incontinence and similar conditions in women. Acta Obstet Gynecol Scand. 1959;38:487-502.
8. Cespedes RD, Cross CA, McGuire EJ. Modified Ingelman-Sundberg bladder denervation procedure for intractable urge incontinence. J Urol. 1996;156(5):1744-7.
9. Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG. Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature. J Urol. 2010;183(6):2258-64.
10. Groenendijk PM, Heesakkers JP, Lycklama ANAA. Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? J Urol. 2007;178(2):568-72.
11. Andersson KE. Bladder activation: afferent mechanisms. Urology. 2002;59(5 Suppl 1):43-50.

CHAPTER 7

SUMMARY (ABSTRACTS)

CHAPTER 2

Introduction:

Past research has demonstrated that the urethral tonus is mainly under sympathetic control. Since five years, a beta 3 adrenoceptor (ADRB3) agonist is available in treatment of overactive bladder syndrome. The presence of ADRB3 within the human urethra has not been demonstrated to date. Presence of ADRB3 in the urethra could influence urethral tonus. The aim of this study is to investigate the presence of ADRB3 in the human female urethra.

Material and Methods:

We performed anatomical studies in 5 female specimen. Three specimen were obtained from the body donation program, two from female patients with muscle invasive bladder cancer, where radical resection of bladder and urethra was performed. The urethra up till the bladder neck was separated from the rest of the bladder and freshly obtained for this study. For demonstrating ADRB3 expression, we used rabbit polyclonal anti-human ADRB3 LS-A4198 .

Results:

Expression of ADBR3 was demonstrated in the epithelial layer of all urethral parts, except at the level of the meatus. The level of ADRB3-expression was highest in the mid-urethra. There was no direct contact between ADRB3 and nerve tissue. ADRB3 expression was also demonstrated in the stratified muscle layer at the level of external urethral sphincter.

Conclusions:

This is the first study to demonstrate expression of ADRB3 in the human female urethra. There is absence of a direct connection between ADRB3 and nerve tissue.

CHAPTER 3

Introduction:

The clinical relevance of urethral pressure variations (UPV) in the pathophysiology of over active bladder syndrome (OAB) has remained controversial to date. Some studies report an association with OAB and/or detrusor over activity (DO). Recently the International Consultation on Incontinence – Research Society recommended new clinical research to be performed on this subject. We provide a systematic review of the literature to specify this recommendation.

Methods:

Literature search was performed in PubMed, Embase, Web of Science, Cochrane, Central, Cinahl, Academic Science Premier, ScienceDirect and WileyOnline using a sensitive search string combination. All authors independently reviewed and scored full text papers and consensus about methodological quality was obtained according to Oxford Level of Evidence (LoE).

Results:

487 abstracts were screened, 25 papers met all predefined inclusion selection criteria. Incidence figures of UPV varied between 2 and 95%. Studies are of poor methodological quality with Oxford LoE scores of 3B and 4. Measurement methods and techniques show a large variety. The abovementioned association of DO/OAB with UPV is however rather consistently reported.

Conclusions:

UPV, and detrusor (over-) activity, may exist as separate entities, may coincide or may be pathophysiologically associated and may or may not be a cause of OAB syndrome. A large variation in measurement techniques for UPV in a variety of patient populations is reported, which hinders fundamental research as well as clinical progress. Clinical relevance of UPV and consequences for treatment therefore are yet to be established. Future prospective research with well-defined patient population and standardised urodynamic measurement techniques is needed. Results of standardized and objective evaluations should be compared to clinical signs and symptoms by validated questionnaires to be able to offer personalised management for OAB patients.

CHAPTER 4

Introduction:

During filling cystometry, urethral pressure variations (UPV) can be observed. The clinical relevance and a clear definition of this phenomenon are still matter of debate. For further research and definition of UPV, it is important to determine how this condition can best be demonstrated. The purpose of this study is to compare continuous urethral pressure measurements with a single urethral sensor catheter and a triple urethral sensor catheter in demonstrating UPV.

Methods:

75 adult female patients requiring urodynamic investigation enrolled in this prospective study. All patients underwent two series of filling and voiding cystometry. One series was performed with a dual air-balloon sensor urodynamic catheter, the other series with a triple urethral sensor catheter. Urethral pressure variations (UPV) were defined as urethral pressure drop exceeding 30 cmH2O.

Results:

The prevalence of UPV was 37.3% (28 out of 75 patients), more common than detrusor overactivity. The triple urethral sensor catheter was more sensitive than the single urethral sensor catheter: In 8 patients UPV was demonstrated with both catheters and in 18 patients only in the measurement with the triple urethral sensor catheter. This difference in detection was significant ($p<0,001$).

Conclusion:

There is additional value in measurement with triple urethral sensor catheter for demonstration of UPV during filling cystometry. Currently, continuous measurement of urethral pressure during filling cystometry and UPV are not defined within ICS terminology. The single urethral sensor catheter is useful for a start, however it demonstrates less than half of all UPV

CHAPTER 5

Introduction:

Urethral instability (URI) has in the past been defined by the International Continence Society (ICS) but was excluded of ICS terminology and definitions shortly after because of lack of consensus about the clinical importance of this phenomenon. Recently, interest for URI and its possible role in overactive bladder (OAB) increased again. In the last decade, a beta 3 adrenoreceptor agonist (mirabegron) is approved for treatment of OAB. The effect of mirabegron on urethral pressure during filling cystometry is unknown. The aim of this study was to assess the influence of mirabegron on urethral pressure variations during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

Methods:

This prospective study included 51 consecutive adult female patients, referred with OAB. Patients were evaluated with a voiding diary, two validated questionnaires and two urodynamic investigations, one before and one after six weeks of treatment with mirabegron. URI was defined as an urethral pressure drop exceeding 30 cmH2O during filling cystometry.

Results:

The prevalence of URI was 31% at initial urodynamic investigation, and 19% at second investigation. URI is more common than DO with 18% prevalence at initial evaluation. Treatment with mirabegron resulted in significant changes in symptoms and urodynamic sensory markers in patients with URI.

Conclusion:

Urethral pressure variations are significantly reduced by treatment with mirabegron in patients with URI. URI seems to have a predictive value in treatment choices for OAB. Future research should elucidate this.

CHAPTER 6

Introduction:

We present the results of a pilot study performed in 5 female patients with overactive bladder symptoms (OAB), combined with urethral instability (URI), treated with subtrigonal Botulinum toxin-A (BoNT-A) injections. Treatment modalities for OAB have in common that they interfere in any part of efferent and afferent signaling from the bladder to the brain, the difference is in the localization and extent of interference. We hypothesized that patients with OAB symptoms and URI could benefit more from a treatment with the mode of action at the urodynamically identified problem.

Methods:

This a retrospective description of the pilot study we performed. Four patients had a long history of refractory idiopathic OAB symptoms, in one patient the main complaint was painfull bladder syndrome. In all patients URI was demonstrated during filling cystometry. Treatment was started with subtrigonal injections of 10cc lidocaine 1%. If OAB symtoms improved with more than 50%, treatment continued with subtrigonal injections with BoNT-A.

Results:

Four out of 5 patients OAB symptoms improved more than 50% after subtrigonal BoNT-A injections. URI disappeared in one patient after treatment. In three other patients, the maximum amplitude of the urethral pressure variations decreased from more than 40cm H2O up to a maximum of 20 cm H2O. The most remarkable change was the improvement in first sensation of filling.

Conclusions:

Chemical denervation by subtrigonal BoNT-A injections in patients with OAB combined with URI, resulted in improvement of refractory OAB symptoms in all patients with refractory OAB as their main complaint in this study.

CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

The aim of thesis was to elucidate the role of urethral function in overactive bladder syndrome (OAB). In the last decade, there has been more awareness that the underlying cause of OAB does not necessarily have to come from the bladder, but could lie within the urethra as well. The knowledge about various influencers on afferent signalling from the bladder has increased, especially by reports on the active role of the urothelium in afferent signalling.

At the annual conference of the EAU in 2019, an expert panel explained that the pipeline for drug therapy for treatment of OAB in the near future is empty and that there especially is a great need to improve efficiency in treating urgency and nocturia. With this assumption that no new treatment modalities will be introduced in the foreseeable future, the existing treatment options will therefore have to be used more efficiently, to achieve better clinical outcome. In other words, if this very heterogeneous group of patients could be further divided by analogy of the underlying cause, proposals for targeted therapy will be easier to define.

With this assumption and the knowledge that Groenendijk et al demonstrated in the past that URI was a better predictor of success for treatment with sacral neuromodulation in patients with OAB[3], we wanted to elucidate the phenomenon of urethral pressure variations (UPV) or urethral instability (URI). If the detrusor muscle can fail to adapt and relax in storage phase, it is plausible that its antagonist, the smooth urinary sphincter and or the striated urethral sphincter may fail to maintain contracted.

One of our assumptions was that if there can be an active role from the urothelium in the bladder, the urothelium and the stratified squamous epithelium in the urethra could have an active role as well. In the past, studies to urethral closure function in female patients concluded that the sympathetic nerve system dominates in regard to maintaining the tonus in the urethra[18, 19]. Nowadays, with a sympathomimetic in the form of a selective β3 receptor (ADRB3) agonist available in drug therapeutic options for patients with OAB, it is important to know what the targets are in the urethra. If ADRB3 is present in the urethra, this could have consequences for the urethral pressure. We demonstrated for the first time expression of ADRB3 in the epithelial layer of the female urethra. The expression of ADBR3 is present in almost the entire length of the urethra, with the highest level in the mid-urethra. No direct connection between

ADRB3 and nerve endings was observed, suggesting the existence of an extra afferent signaling pathway originating in the epithelial layer of the urethra.

By conducting a systematic review, we aimed to define a clear working definition for URI, to use for our clinical studies. Unfortunately, the generalizability of the performed studies was limited because the very heterogeneous and poorly defined patient populations and measurement methods. In the past, opponents have set aside URI as movement artefacts. The closed urethra in storage phase has no lumen, so current techniques applied for intravesical or abdominal pressure measurement are probably imperfect to measure the physics of urethral closure. On the other hand, abdominal pressure measurement is often performed with a vaginal sensor and the vagina has no closed lumen either. In the studies performed with multiple urethral pressure sensors, all sensors registered UPV simultaneously, which argues against an artefact as the cause of these findings.

In the past, Venema and Kramer described results of urodynamics in patients with and without urethral instability[9]. During the urethral pressure measurement in the filling phase, both urethral and anal electromyography (EMG) were performed simultaneously by the use of a thin intramuscular needle sensor. Urethral pressure measurement was performed with three urethral sensors. In this measurements, UPV were seen in all leads. A striking difference was seen in urethral EMG in patients with URI and without URI. In normal cystometry was seen that at the start of voiding phase, both anal and urethral EMG demonstrated relaxation, followed by a gradual relaxation of the urethral pressure and a gradual increase in detrusor pressure until urinary flow initiated (Figure 8.1). In patients with UPV, a sudden stop in the EMG occured during the filling phase, followed by a rapid drop in urethral pressure (Figure 8.2). If a pattern of rapid successive pressure variations was observed, changes in urethral EMG were seen simultaneously (Figure 8.3). This argues against a movement artefact as well.

We then conducted a prospective study to determine if and to what extend the use of a multi-sensor urethral catheter contributes in demonstrating UPV. If measurement with a single urethral sensor catheter is as sensitive as a multi-sensor urethral catheter, the applicability will be greater in daily practice. We demonstrated that despite the use of a relatively high cut-off value for the definition of UPV, the prevalence still was 37% and therefore much more common than the prevalence

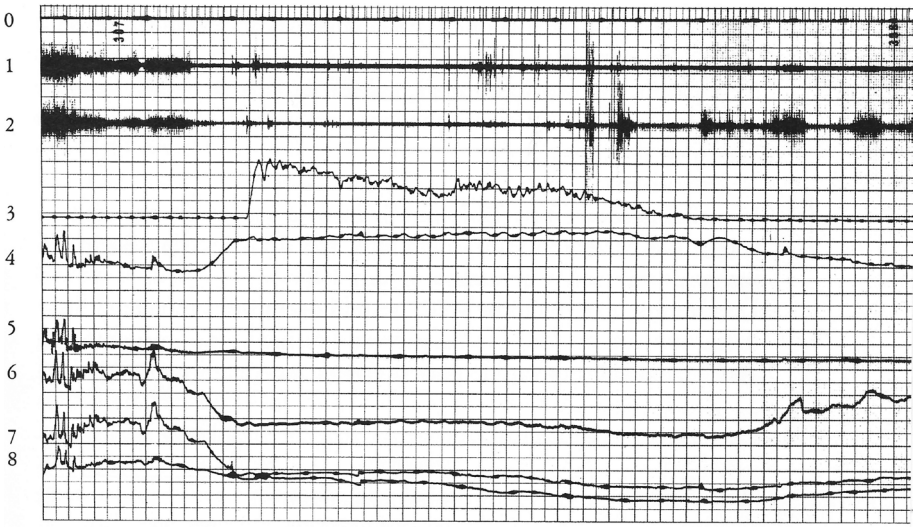

Figure 8.1* Example of normal cystometry 0. Time-scale (seconds) 1. Urethral EMG 2. Anal EMG 3.flowmetry 4. Intravesical pressure 5. Abdominal pressure 6-8 urethral pressure

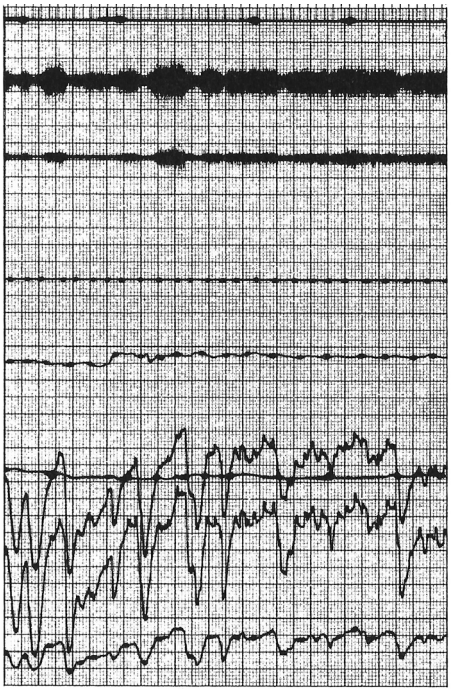

Figure 8.2* Sudden drop in urethral pressure

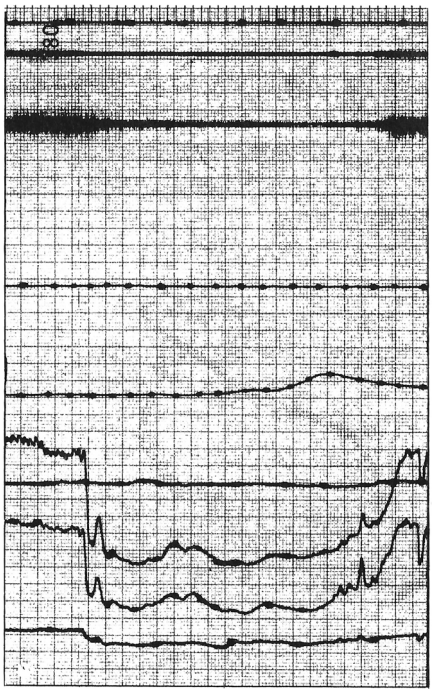

Figure 8.3* Rapid urethral pressure variations

* From P.L. Venema, clinical importance of the unstable urethra in females

of DO. If UPV was demonstrated, it was visible in all urethral sensor derivations. We found that there is additional value in measurement with triple urethral sensor catheter for the demonstration of UPV during filling cystometry. Opponents of UPV in the past have argued that UPV is a physiological phenomenon prior to the voiding reflex in DO or as a result of voluntary holding to suppress the desire to void [8, 12, 13]. If you assume that the rapid decrease in urethral pressure is caused by a sudden inhibition in the sympathetic system, but compensated via the somatic system by contraction of the external sphincter, the opponents are partly right. However, the fact that the sudden pressure drops occur, is not explained by this.

Now that we demonstrated expression of ADRB3 in the urethra, the next question was whether and to what extent urethral pressure is influenced by the ADRB3-agonist mirabegron. To date, Vecchiolo Scaldazza and Morosetti have reported the only study with urodynamic results of treatment with mirabegron in 60 patients with OAB [18]. Urodynamic parameters as first, normal and strong desire and continuous urethral pressure measurement were not mentioned and/or performed in this study. In line with our study to the additional value of using a multi-sensor urethral catheter in demonstrating UPV, we demonstrated that UPV is a more common urodynamic phenomenon than detrusor overactivity with an incidence of one third in female patients at presentation with OAB. In this study, urethral pressure measurements were performed with a single urethral sensor catheter, so the prevalence could be underestimated. An important finding of this study is that patients with UPV have a different response to mirabegron than patients with the same clinical symptoms without UPV. Treatment with mirabegron had a significant effect on all sensation parameters and the difference between maximal and minimal urethral pressure decreased significantly in the UPV-group.

This fits in the above-mentioned hypothesis that urethral pressure drops occur when a sudden inhibition in the sympathetic system (hypogastric nerve) occurs. Because of this inhibition, the contraction of bladder outlet is no longer maintained. If the sympathetic system is subsequently stimulated with the ADRB3 agonist with demonstrated target receptor in the urethra, the urethral pressure can recover.

Finally, a pilot study was performed to determine whether local chemical denervation by subtrigonal botulinum toxin-A injections in patients with UPV, result in a relief of symptoms. If assumed that the feeling of imminent micturition has its origins in the urethra[11], intervening in

afferent sensory input from the urethra could have a positive effect on OAB symptoms of patients. This pilot study was performed in four patients with a long history of refractory idiopathic OAB and in one patient with painful bladder syndrome. After treatment with subtrigonal botulinum toxin-A injections, UPV were still present in post-treatment urodynamic evaluation, but with an decreased amplitude of variations. Treatment was successful in 4 of 5 patients. The largest improvement was in the urodynamic sensation marker first sensation of filling.

CONCLUSIONS AND FUTURE PERSPECTIVE

UPV is a more common urodynamic phenomenon than DO within the described cohort of OAB-patients in this thesis. The demonstration of UPV is best performed by the use of a multi-sensor urethral catheter. UPV appears to be an underlying cause or expression marker of sensory urgency complaints in the studies we performed and it improved significantly in treatment with ADRB3 receptor agonist and in treatment with local (subtrigonal) Botulinum toxin-A injections. Patients with OAB and UPV differ from patients without UPV in their response to same medical treatment. This makes an important contribution to improving targeted therapy in patients with OAB. Future research will have to test these findings in a larger prospective population. Further anatomical research will also have to be carried out to further explore the afferent signalling routes and thus explore further possibilities of targeted local treatment options. The ICS should reintroduce UPV in its terminology to enable standardized research.

REFERENCES

1. Birder LA, Andersson KE, Kanai AJ, Hanna-Mitchell AT, Fry CH: Urothelial mucosal signaling and the overactive bladder-ICI-RS 2013. *Neurourol Urodyn* 2014, 33(5):597-601.
2. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, Amarenco G, Game X, Kirby R, Van Der Aa F *et al*: A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment. *European urology* 2019, 75(6):988-1000.
3. Groenendijk PM, Heesakkers JP, Lycklama ANAA: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol* 2007, 178(2):568-572.
4. Thind P, Lose G, Colstrup H, Andersson KE: The influence of beta-adrenoceptor and muscarinic receptor agonists and antagonists on the static urethral closure function in healthy females. *Scand J Urol Nephrol* 1993, 27(1):31-38.
5. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
6. Sorensen S, Norgaard JP, Knudsen LM, Rittig S, Djurhuus JC: Urethral pressure variations in healthy females during rest and sleep. *J Urol* 1987, 137(6):1287-1290.
7. Tapp AJ, Cardozo LD, Versi E, Studd JW: The prevalence of variation of resting urethral pressure in women and its association with lower urinary tract function. *Br J Urol* 1988, 61(4):314-317.
8. Sorensen S: Urethral pressure variations in healthy and incontinent women. *Neurourology and Urodynamics* 1992, 11(6):549-591.
9. Venema PL, Kramer AEJL: Treatment of female incontinence with or without urethral instability. *World journal of urology* 1986, 4(1):27-31.
10. Vecchioli Scaldazza C, Morosetti C: Comparison of Therapeutic Efficacy and Urodynamic Findings of Solifenacin Succinate versus Mirabegron in Women with Overactive Bladder Syndrome: Results of a Randomized Controlled Study. *Urol Int* 2016, 97(3):325-329.
11. Andersson KE: Bladder activation: afferent mechanisms. *Urology* 2002, 59(5 Suppl 1):43-50.

CHAPTER 9

NEDERLANDSE SAMENVATTING

SAMENVATTING

Overactieve blaasklachten (OAB) zijn een veelvoorkomende klacht. In 2002 heeft de International Continence Society (ICS) OAB gedefinieerd als de aandrang om te plassen (urgency), meestal gepaard gaand met een frequente mictie (frequency) en nycturie[1]. Als een urineweginfectie, stenen, een neoplasma of neurogeen blaaslijden zijn uitgesloten spreekt men van een idiopathische overactieve blaas. De incidentie neemt toe naarmate de leeftijd vordert[2], volgens een Europese prevalentiestudie[3] komen deze klachten voor bij 30% van de populatie boven de 70 jaar.

Volgens onderzoek van het Centraal Bureau voor Statistiek (CBS) in 2004, ondervond 16% van de Nederlandse bevolking boven de 40 jaar klachten van OAB. Dit betekent dat minstens 1 miljoen mensen last hebben van deze klachten, alhoewel maar een deel van deze patiënten daar aandacht voor zal vragen[4] Het college van zorgverzekeraars schatte in 2011 de kosten voor incontinentiemateriaal op 148 miljoen euro, de totale kosten voor incontinentiezorg werden geschat op 256 miljoen euro. Klachten van OAB hebben een negatieve invloed op de kwaliteit van leven[5, 6] en hoe erger de klachten, hoe groter de negatieve impact[7]. Met de toenemende levensverwachting en vergrijzing van de bevolking, zal de sociaaleconomische last van dit probleem alleen maar toenemen[8].

Momenteel zijn er verschillende behandelingsmogelijkheden voor OAB. Allereerst wordt gestart met conservatieve therapie in de vorm van levensstijl adviezen en/of bekkenfysiotherapie. Indien bovenstaande modaliteiten onvoldoende effect hebben gehad, kan behandeling vervolgd worden met verschillende vormen van zenuwstimulatie, verschillende vormen van medicamenteuze therapie of met botuline toxine-A injecties.

De meest toegepaste vorm van zenuwstimulatie in de dagelijkse urologische praktijk is de percutane posterior tibiale zenuwstimulatie (PTNS). Andere vormen zijn transvaginale elektrostimulatie, transcutane elektrostimulatie en sacrale zenuwstimulatie. Zenuwstimulatie behandelingen hebben als grote voordeel dat er weinig bijwerkingen zijn. Het grootste nadeel is dat bij de meeste patiënten het effect van de behandeling afneemt naarmate de tijd verstrijkt sinds de laatste behandelsessie. Dit geldt overigens niet voor de sacrale zenuwstimulatie, aangezien daar via een implantaat 24/7 gestimuleerd wordt.

De medicamenteuze behandeling van OAB bestond tot 6 jaar geleden uit antimuscarinica. De behandeling met antimuscarinica

leidt tot vermindering van urgency en frequency-episodes als ook een vermindering in incontinentie-episodes[9, 10].

Helaas blijkt slechts 20-30% van de patiënten deze medicatie na een jaar nog te gebruiken vanwege de vele bijwerkingen[11, 12]. Sinds 2014 is er een nieuwe vorm van medicamenteuze therapie beschikbaar in Nederland, de beta-3 agonist Mirabegron. Dit middel is klinisch en urodynamisch ook effectief gebleken en heeft een gunstiger bijwerkingenprofiel dan antimuscarinica[13]. De therapietrouw van mirabegron is groter dan die van antimuscarinica, maar met 38% ook niet optimaal[14].

OAB kan ook behandeld worden met botuline toxine-A injecties (BontA). BontA is het meest potente neurotoxische gif. Het blokkeert het vrijkomen van acetylcholine in de presynaptische membraan, hetgeen resulteert in een paralyse op de geïnjecteerde plaats. De eerste behandeling met BontA in de blaas vond plaats in 1990. In 2011 werd het gebruik voor neurogeen blaaslijden goedgekeurd door de FDA, later volgde ook de goedkeuring voor toepassing binnen idiopathisch OAB, als medicamenteuze therapie met antimuscarinica onvoldoende heeft geholpen. Nadelige effecten van deze behandeling zijn de kans op een periode zelf-katheterisatie als op recidiverende urineweginfecties. Het voordeel is de lokale toepasbaarheid, systemische bijwerkingen als in medicamenteuze therapie treden hier niet op.

Geconcludeerd kan worden dat geen enkele behandeling in de huidige vorm voor iedereen met OAB toepasbaar is en voor verbetering vatbaar is. Patiënten met OAB vertegenwoordigen een zeer heterogene groep patiënten die hetzelfde sociaal invaliderende symptomencomplex gemeen hebben. Tot voor kort heeft onderzoek naar de etiologie van deze klachten zich gefocust op een uitlokkende oorzaak binnen de blaas, zoals bijvoorbeeld detrusor overactiviteit (DO) en toename van afferente stimuli vanuit het urotheel. Echter, DO wordt gezien bij ongeveer 50% van de patiënten die een urodynamisch onderzoek ondergaat vanwege OAB en wordt ook gezien bij asymptomatische patiënten.

Onderzoek naar de rol van de urethra in de mictiereflex werd in het begin van de 20ste eeuw geïnitieerd door Barrington in een diermodel[15, 16]. Hij beschreef 7 reflexen die betrokken zijn bij de opslagfase en de mictiefase van de kat. Vier van deze zeven reflexen hadden hun oorsprong in de urethra. Later werd door Jung et al beschreven dat lekkage van urine in de urethra kan leiden tot stimulatie van urethrale afferente banen, hetgeen kan leiden tot stress-geïnduceerde urgency al dan niet gepaard

met urine incontinentie[17]. In de laatste 20 jaar van de 20ste eeuw hebben verschillende klinische studies getracht de functionele rol van de urethra binnen OAB te verduidelijken door middel van continue urethrale drukmetingen tijdens urodynamisch onderzoek. Een consensus hierover werd echter nooit bereikt. Tijdens deze continue urethrale drukmetingen zijn in vullingsfase plotselinge drukvariaties (UPV) aangetoond. In 1980 heeft de ICS een definitie urethra instabiliteit (URI) gedefinieerd als urine incontinentie die optreedt als het gevolg van plotse UPV, in de afwezigheid van een detrusor contractie. Omdat dit fenomeen zeldzaam is, werd de term na een jaar weer verlaten en is er vervolgens weinig over dit onderwerp gepubliceerd. In 2007 beschreef Groenendijk dat de aanwezigheid van UPV een betere voorspeller is dan de aanwezigheid van DO voor het voorspellen van succes met behandeling door sacrale zenuwstimulatie[18].

In 2014 heeft de denktank van de ICS-research society een sessie gewijd aan UPV, gevolgd door een rapport dat concludeerde dat UPV zeker geassocieerd is met mictieklachten en het belang van verder onderzoek naar urethrale functie werd onderstreept[19, 20]. Als verder onderzoek kan bevestigen dat UPV een goede voorspeller voor succes van bepaalde behandelingen is, of als blijkt dat patiënten met UPV beschouwd moeten worden als subgroep binnen OAB, kunnen we een belangrijke bijdrage leveren aan therapie op maat bij patiënten met OAB.

Het doel van dit proefschrift was om de rol van urethrale functie binnen OAB te verduidelijken. In **hoofdstuk 1** wordt de achtergrond, zoals hierboven uitgebreider geschetst. In **hoofdstuk 2** worden de resultaten van de anatomische studie naar de aanwezigheid en verdeling van beta-3 receptoren (ADRB3) in de urethra beschreven. Het handhaven van de urethrale druk staat voornamelijk onder controle van het sympathische zenuwstelsel. Zoals hierboven beschreven is er sinds 2014 een (adrenerge) beta-3 agonist, mirabegron, beschikbaar voor de behandeling van OAB. In onze praktijk hebben we bij een aantal patiënten verslechtering van hun klachten gezien tijdens behandeling met mirabegron. Dit impliceert een mogelijk oorzaak in de urethra gemedieerd door mirabegron. De aanwezigheid van ADRB3 in de urethra is tot op heden niet beschreven. Het doel van dit hoofdstuk is om de aanwezigheid van ADRB3 in de urethra te onderzoeken. Hiervoor werden 5 humane vrouwelijke anatomische preparaten gebruikt. Het urethra-specimen werd transversaal in vieren gedeeld, op het niveau van de blaashals, de proximale urethra, de mid-urethra en de distale

urethra en werden kleuringen verricht om de aanwezigheid van ADRB3 aan te tonen. Vervolgens hebben we ADRB3-expressie aangetoond in de epitheliale laag van de urethra op alle niveaus, behalve op het niveau van de meatus. De mate van expressie van ADRB3 was het grootst in de mid-urethra. Er werd geen direct contact gezien tussen de ADRB3-receptoren en zenuwweefsel. In de dwarsgestreepte spierlaag op niveau van externe urethrale sfincter werd ook ADRB3-expressie gezien. Dit is de eerste studie die ADRB3-expressie in de humane urethra aantoont. De afwezigheid van een directe verbinding tussen ADRB3-receptoren en zenuwvezels duidt op een extra, onbekende afferente signaleringsroute uitgaande van de urethra.

In **hoofdstuk 3** zijn de resultaten van een systematische review van de literatuur over urethra instabiliteit beschreven. De klinische relevantie van UPV binnen OAB is tot op heden controversieel gebleven. We hebben de verschillende meetmethoden, gebruikte materialen, definities en de methodologische kwaliteit van de gerapporteerde studies in de huidige literatuur beoordeeld. Deze achtergrondinformatie is essentieel om UPV in perspectief van OAB te plaatsen en om een werkdefinitie UPV voor dit proefschrift te definiëren. Literatuuronderzoek werd uitgevoerd in PubMed, Embase, Web of Science, Cochrane, Central, Cinahl, Academic Science Premier, ScienceDirect en WileyOnline. In totaal werden 487 abstracts gescreend, waarvan 25 artikelen voldeden aan de vooraf gedefinieerde inclusiecriteria. Alle auteurs beoordeelden alle full text papers onafhankelijk, consensus over methodologische kwaliteit werd verkregen volgens Oxford level of evidence. De gerapporteerde incidentie varieerde van 2 tot 95%, hetgeen tekenend is voor het gebrek aan consensus en meetmethoden. Studies waren van matige methodologische kwaliteit. De associatie tussen DO, OAB en UPV werd wel consistent gerapporteerd. We concludeerden dat UPV een eigen entiteit binnen OAB zou kunnen zijn, maar dat de grote variatie in meetmethoden en definities zowel fundamenteel onderzoek als klinische vooruitgang belemmert. De klinische relevantie zal dus nader moeten worden onderzocht, in een goed gedefinieerde studiepopulatie met gestandaardiseerde urodynamische meetmethode. Resultaten van gevalideerde subjectieve en objectieve evaluaties zullen met elkaar moeten worden vergeleken.

Hoofdstuk 4 beschrijft de resultaten van de prospectieve studie naar de toegevoegde waarde van een multi-sensor urethrale katheter in het aantonen van UPV tijdens vullingscystometrie. Voor verder onderzoek en definitie van UPV, is het belangrijk om te bepalen hoe deze aandoening

het best kan worden aangetoond en of het gebruik van een enkele urethrale sensor katheter net zo representatief is als het gebruik van een katheter met drie urethrale sensoren (triple-sensor) in het aantonen van UPV. De studie werd verricht in het LUMC waar 75 patiënten met een indicatie voor urodynamisch onderzoek prospectief werden geëvalueerd. Alle patiënten ondergingen twee maal een vullingscystometrie. Een serie werd uitgevoerd met een standaard dual air-balloon sensor urodynamische katheter, de andere serie met een triple-sensor katheter. UPV werd gedefinieerd als een urethraal drukverval van meer dan 30 cm H2O. De prevalentie van UPV bleek 37,3% te zijn en daarmee hoger dan die van DO. De triple-sensor katheter was gevoeliger dan de dual air-balloon katheter: in 8 patiënten werd UPV aangetoond met beide katheters en bij 18 patiënten alleen in de meting met de triple-sensor katheter. Dit verschil in detectie was significant ($p < 0001$). De dual air-balloon katheter is nuttig om mee te starten, echter, het meten met triple-sensor katheter heeft duidelijk toegevoegde waarde voor het aantonen van UPV. Als er een klinische verdenking op UPV bestaat is het aan te raden patiënten te verwijzen naar een tertiair centrum voor urodynamisch onderzoek met een triple-sensor katheter.

Zoals beschreven in hoofdstuk 2 hebben we geconstateerd dat een aantal patienten die werden behandeld met mirabegron, een verergering van hun klachten ondervond. Het effect van een mirabegron op de urethrale druk tijdens de vullingsfase is onbekend. Het doel van de prospectieve studie beschreven in **hoofdstuk 5**, was om de invloed van mirabegron op urethrale drukvariaties tijdens urodynamisch onderzoek vast te stellen, gecombineerd met klinische symptomen en klachtenbeleving, vóór en na behandeling. Uit eerder onderzoek is gebleken dat antimuscarinica geen effect hebben op de urethrale druk. Het effect van mirabegron op de urethrale druk is nooit eerder beschreven. Met de kennis van de bevindingen uit hoofdstuk 2, verwachtten we een effect te zien van mirabegron op de urethrale druk, zeker bij patienten met UPV. Er werden 51 patiënten geïncludeerd in het Haaglanden Medisch Centrum en het HAGA ziekenhuis. Patienten werden geëvalueerd met een plasdagboek, twee gevalideerde vragenlijsten en twee maal urodynamisch onderzoek, een onderzoen voor en een na 6 weken behandeling met mirabegron. De prevalentie van UPV was met 31% ten tijde van het eerste urodynamisch onderzoek, conform de bevindingen in hoofdstuk 4, hoger dan de prevalentie van DO. Voor de complete groep gold dat behandeling met mirabegron resulteerde in significante verbetering van klachten en in

significante urodynamische veranderingen. Vervolgens hebben we de groep gesplitst in patienten met en zonder UPV. De bovengenoemde significante veranderingen gelden dan nog steeds voor patienten met UPV, maar niet voor patienten zonder UPV. De grootste verandering trad op in de urodynamische parameter "first sensation of filling" (FSF). De studie is helaas underpowerd gesloten, maar deze bevindingen vormen voldoende fundament voor verder klinisch onderzoek.

In een poging om een gelokaliseerde behandeling voor patiënten met UPV te ontwikkelen, werd in het LUMC een pilot-onderzoek verricht naar de effectiviteit van subtrigonale botuline-A toxine injecties bij de behandeling van patiënten met een hoge urethrale druk en/of UPV. Deze resultaten worden beschreven in **hoofdstuk 6**.

Alle beschikbare behandelingen voor OAB hebben gemeen dat ze interfereren in de afferente of efferente signaleringsroute tussen de blaas en de hersenen. Het verschil zit in de lokalisatie en de mate van interferentie. We veronderstelden dat patiënten met UPV meer zouden kunnen profiteren van een gelokaliseerde behandeling op de plaats van het urodynamisch geïdentificeerde probleem. Retrospectieve resultaten van 4 patiënten met een lange historie van idiopathisch refractaire OAB en 1 patiënt met blaaspijn syndroom worden beschreven. Bij alle patiënten werd UPV urodynamisch aangetoond met een triple-sensor katheter. Naar analogie van vroegere chirurgische denervatie behandelingen werd de behandeling gestart met een para-urethrale, subtrigonale lokale injectie met lidocaïne. Als OAB klachten met meer dan 50% verbeterden werd de behandeling vervolgd met botuline-A toxine injecties. Bij 4 van de 5 patiënten resulteerde deze behandeling in een subjectieve verbetering van meer dan 50%. In 1 patiënt was UPV niet meer aanwezig op het controle urodynamisch onderzoek. Bij 3 andere patiënten veranderde de amplitude van UPV van meer dan 40cm H2O naar maximaal 20cm H2O. De grootste verandering trad, net als in hoofdstuk 5, op in een verbetering van FSF.

In conclusie kunnen we stellen dat UPV een veelvoorkomend urodynamisch fenomeen is binnen de patiëntenpopulatie met OAB. Patiënten met OAB en UPV verschillen in respons op bepaalde behandelingsmodaliteiten van patiënten met OAB zonder UPV.

Op het jaarlijkse congres van de EAU in 2019 werd door een expert-panel uiteengezet dat de pijplijn voor medicamenteuze therapie ten behoeve van behandeling van OAB in de nabije toekomst leeg is en dat grote behoefte is aan het verbeteren van de efficiëntie in het behandelen

van urgency en nycturie. UPV lijkt een goede verklaring te zijn van sensore urgeklachten, deze verbeterden significant in behandeling met ADRB3-receptor agonist en in behandeling met lokale BontA-injectie. Dit levert een belangrijke bijdrage aan het verbeteren van therapie op maat bij patiënten met OAB.

Toekomstig onderzoek zal deze bevindingen in een grotere prospectieve populatie moeten toetsen. Ook zal er verder anatomisch onderzoek moeten worden verricht om de afferente signaleringsroutes en daarmee ook verdere mogelijkheden van toegespitste lokale behandelingsmogelijkheden verder te exploreren. De ICS moet UPV weer opnemen in haar terminologie om gestandaardiseerd onderzoek mogelijk te maken.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003, 61(1):37-49.
2. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I: National community prevalence of overactive bladder in the United States stratified by sex and age. *Urology* 2011, 77(5):1081-1087.
3. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU international* 2001, 87(9):760-766.
4. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I: Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. *BJU international* 2009, 104(7):954-959.
5. Lagro-Janssen T, Smits A, Van Weel C: Urinary incontinence in women and the effects on their lives. *Scandinavian journal of primary health care* 1992, 10(3):211-216.
6. Dmochowski RR, Newman DK: Impact of overactive bladder on women in the United States: results of a national survey. *Current medical research and opinion* 2007, 23(1):65-76.
7. Vaughan CP, Johnson TM, 2nd, Ala-Lipasti MA, Cartwright R, Tammela TL, Taari K, Auvinen A, Tikkinen KA: The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. *European urology* 2011, 59(4):629-636.
8. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I: Economic burden of urgency urinary incontinence in the United States: a systematic review. *Journal of managed care pharmacy : JMCP* 2014, 20(2):130-140.
9. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D: The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *European urology* 2008, 54(3):543-562.
10. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ: Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev* 2012, 1:CD005429.
11. Wagg A, Compion G, Fahey A, Siddiqui E: Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012, 110(11):1767-1774.
12. Sicras-Mainar A, Rejas J, Navarro-Artieda R, Aguado-Jodar A, Ruiz-Torrejon A, Ibanez-Nolla J, Kvasz M: Antimuscarinic persistence patterns in newly treated patients with overactive bladder: a retrospective comparative analysis. *Int Urogynecol J* 2014, 25(4):485-492.
13. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC: Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014, 33(1):17-30.
14. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, Khemiri A, Siddiqui E, Wagg A: Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *European urology* 2017, 72(3):389-399.
15. Barrington F: The components reflexes of micturition in the cat, Parts I and II. *Brain* 1931, 54:177-188.
16. Barrington F: The component reflexes of micturition in the cat: Part III. *Brain* 1941, 64:239-243.

17. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB: Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999, 162(1):204-212.
18. Groenendijk PM, Heesakkers JP, Lycklama ANAA: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol* 2007, 178(2):568-572.
19. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R: Do we need better methods of assessing urethral function: ICI-RS 2013? *Neurourol Urodyn* 2014, 33(5):587-590.
20. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.

APPENDICES

VRAGENLIJSTEN

LIST OF PUBLICATIONS

CURRICULUM VITAE

VRAGENLIJSTEN

Vragenlijsten mirupress

II-Q

IIQ-7: vragenlijst impact van incontinentie

Sommige mensen vinden dat ongewild urineverlies invloed kan hebben op hun activiteiten, relaties en gevoelens. De onderstaande vragen gaan over facetten van uw leven die misschien zijn beïnvloed of veranderd door uw probleem.

Kruis bij elke vraag het antwoord aan, dat het best omschrijft in hoeverre uw activiteiten, relaties en gevoelens zijn beïnvloed door urineverlies.

Heeft urineverlies invloed gehad op uw….

(Kruis één vakje per regel aan)	Helemaal niet	Een beetje	Redelijk wat	Zeer veel
1. vermogen om huishoudelijke taken te doen (koken, schoonmaken, de was doen)?	☐	☐	☐	☐
2. lichamelijke activiteiten zoals bijv. wandelen of zwemmen of andere oefeningen?	☐	☐	☐	☐
3. uitgaansactiviteiten (films, concerten, etc.)?	☐	☐	☐	☐
4. vermogen om langer dan 30 minuten van uw huis met de auto of bus te reizen?	☐	☐	☐	☐
5. deelname aan sociale activiteiten buitenshuis?	☐	☐	☐	☐
6. emotionele gezondheid (nervositeit, depressie, etc.)?	☐	☐	☐	☐
7. gevoel van frustratie?	☐	☐	☐	☐

Einde van vragenlijst IIQ-7

Utomo E. et al Validation of the urogenital distress inventory (UDI-6) and incontinence impact questionnaire (IIQ-7) in a Dutch population. Neurourol Urodyn doi 10.1002/nau.22496

UDI-6

UDI-6: Urogenitale Klachten Lijst

In hoeverre heeft u van het volgende last:

(Kruis één vakje per regel aan)	Helemaal niet	Een beetje	Redelijk wat	Zeer veel
1. Vaak plassen	☐	☐	☐	☐
2. Urineverlies dat verband houdt met het gevoel van aandrang	☐	☐	☐	☐
3. Urineverlies dat verband houdt met lichamelijke activiteit, hoesten of niezen	☐	☐	☐	☐
4. Kleine hoeveelheden urineverlies (druppels)	☐	☐	☐	☐
5. Moeite uw blaas te legen	☐	☐	☐	☐
6. Pijn of ongemak in de onderbuik of rond het kruis	☐	☐	☐	☐

Einde van vragenlijst UDI-6

Utomo E. et al Validation of the urogenital distress inventory (UDI-6) and incontinence impact questionnaire (IIQ-7) in a Dutch population. Neurourol Urodyn doi 10.1002/nau.22496

LIST OF PUBLICATIONS

Kummeling MT, Buijs JT, Wisse LJ, van Uhm JI, Elzevier HW, Ruiter MC, Groenendijk PM "Initial report on distribution of β3-adrenoceptor in the human female urethra" *Neurourology and Urodynamics 2020;39:125-132 doi: 10.1002/nau.24183. [Epub 2019 Oct 14]*

Kummeling MT, Bovelander E, van Uhm JI, van Koeveringe GA, Elzevier HW, Putter H, Groenendijk PM "Additional value of triple sensor urethral catheter in demonstrating urethral pressure variations during filling cystometry" *Neurourol Urodyn 2019;38:2368-2373 doi:10.1002/nau.24157 [Epub 2019 sep 4]*

Kummeling MT, Dolmans VE, van UJI, et al. Initial report on subtrigonal Botulinum toxin-A (BoNT-A) therapy for female patients with urethral instability - results of a pilot study. *Urol Nephrol Open Access J. 2018;9(2):69-72.*

Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM. "Continuous urethral pressure measurements, measurement techniques, pressure variations, clinical interpretations and clinical relevance. A systemic literature analysis" *Neurourol Urodyn. 2017 Jan;36(1): 51-56. Epub 2015*

Kummeling MTM, Rietbergen JBW, Withagen MIJ, Mannaerts GHH, van der Weiden RMF "Sequential urodynamic assessment before and after laparoscopic sacrocolpopexy" *Acta Obstet Gynecol Scand. 2013 Feb;92(2):172-7. doi: 10.1111/aogs.12045. Epub 2012 Dec 14.*

Kummeling MTM, de Jong BW, Laffeber C, Kok DJ, Verhagen PC, van Leenders GJ, van Schaik RH, van Woerden CS, Verhulst A, Verkoelen CF. "Tubular and interstitial nephrocalcinosis" *J Urol. 2007 Sep;178 (3 Pt 1):1097-103*

CURRICULUM VITAE

Maxime Kummeling werd op 8 november 1976 geboren te Eindhoven als dochter van Gerard en Marie-Thérèse Kummeling-Eijsbouts. Samen met haar broers Hendrik, Klaas en Gijs groeide zij op in Eindhoven. Na het behalen van haar VWO diploma in 1995 aan Scholengemeenschap Augustinianum te Eindhoven startte zij met haar studie geneeskunde aan de Rijksuniversiteit Groningen. Tijdens haar studietijd was zij werkzaam als onderzoeksassistent bij de vakgroep thoraxchirurgie in het Universitair Medisch Centrum Groningen onder leiding van Dr. J.G. Grandjean.

Na het behalen van haar doctoraal diploma in december 1999 maakte zij de overstap naar de Rijksuniversiteit Leiden voor haar coschappen. Na het afronden van haar artsexamen in februari 2002 werkte zij achtereenvolgens als arts-assistent chirurgie en urologie in het Haaglanden Medisch Centrum (HMC) in Den Haag. Haar vooropleiding chirurgie volgde zij aansluitend in het HMC (opleider Dr. J.C.A. de Mol van Otterloo). In het Erasmus Medisch Centrum volgde zij het academisch gedeelte van de opleiding tot uroloog (opleider dr. G.R. Dohle) van januari 2007 tot januari 2010. Het perifere gedeelte van haar opleiding volgde zij van januari 2010 tot september 2011 in het Franciscus Gasthuis & Vlietland te Rotterdam (opleider Dr. J.H.M. Blom). Hier ontstond de interesse voor functionele urologie. Vanaf mei 2012 is zij werkzaam als uroloog in het HMC te Den Haag. Nadat haar collega Pieter Groenendijk de Astellas European unrestricted Grant for Urogynecology in 2013 had gewonnen, besloot zij naast haar klinische werkzaamheden aan dit onderzoek te starten, met dit proefschrift als eindresultaat. Binnen de NVU maakt ze deel uit van de Commissie Kwaliteit en de Commissie Kwaliteits Visitatie.

Maxime is in 2007 getrouwd met Thijs van der Laan, samen hebben zij 3 dochters en een zoon, Emma (2008), Mara (2010), Fien (2011) en Max (2014).