Detrusor underactivity

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Section I
General Introduction

Detrusor underactivity (DU) is a challenging and largely uninvestigated topic in functional urology which has received increasing attention during the last five years. DU refers to an impaired contractile function of the bladder, which may result in incomplete bladder emptying or even in urinary retention. DU has been defined by the International Continence Society (ICS) as a bladder contraction of reduced strength and/or duration resulting in prolonged or incomplete bladder emptying during pressure-flow assessment[1]. DU, in contrast to detrusor overactivity (DO), is primarily a problem of the voiding phase. However, both DU and DO may originate from inadequate coordination of bladder afferent and efferent signalling and, therefore, may share the same pathophysiology[2]. DO refers to urodynamically proven (involuntary) contractions during the storage phase of the bladder, possibly resulting in bladder storage symptoms such as urinary incontinence, urgency and frequency[1]. Combined presence of both DO and DU has been described and classified as detrusor hyperactivity-impaired contractility (DHIC)[3].

DU is one of the reasons for lower urinary tract symptoms (LUTS) associated with voiding and incomplete bladder emptying in both women and men[4]. Figure 1 shows the additional two other entities which may occur separately or in combination. It is assumed that there is an overlap in the clinical presentation of all three entities but exact epidemiological numbers of the individual or combined problem(s) remain to be elucidated.

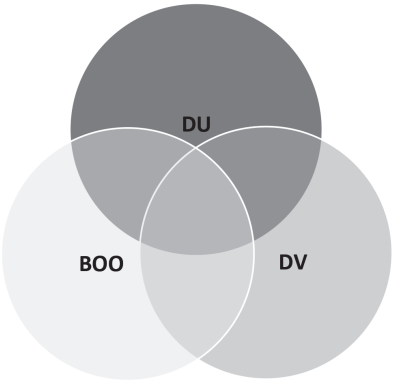

Figure 1. Major causes for incomplete bladder emptying and post-void residual urine in non-neurological men or women based on pressure-flow studies. An overlap in the pathophysiology of incomplete bladder emptying is suspected in the majority of patients1. The amount of overlap between the three identities is currently unknown.

1.1 Clinical problem and relevance of the disease

A day consists of 1440 minutes of which humans usually use only less than 5 minutes for voiding. Although voiding represents only a small duration during the day-or nighttime, voiding phase-related problems are common and may even be debilitating. Particularly in men, voiding LUTS are a common cause for outpatient consultations in physician offices. Men have a lifetime risk of approximetaly 45% to develop LUTS[5]. The prevalence of voiding LUTS in men increases with ageing, ranging from 2.7% in men aged 45-59 years to 24% in those aged >80 years[5].

LUTS can be caused by various conditions. Amongst this heterogeneous group of conditions, detrusor underactivity is one of the causes for voiding LUTS[4]. DU is often hidden behind other clinical phenotypes such as bladder outlet obstruction (BOO) or dysfunctional voiding; it may also coincide with the presence of urinary tract infections (UTIs) or urinary incontinence. Symptomatology includes prolonged voiding time, altered bladder filling sensation, (feeling of) post-void residual urine and/or slow urinary stream. Acute urinary retention (AUR) - as an extreme clinical presentation of DU - has a low incidence in young men with an incidence of 0.2 per 1000 man-years[6]. However, the incidence increases with age and the debilitating effect of catheterisation may impact a patient's quality of life[6-10].

Urinary incontinence is a relevant problem in both men and women in all age groups. Incontinence associated with DU can present as stress, urgency or overflow urinary incontinence and may even appear in combination. Within the group of elderly patients, voiding dysfunction is estimated to affect approximately two-thirds of the incontinent nursing home residents[11]. Overflow urinary incontinence or the relation between post-void residual (PVR) and urinary incontinence is often not recognised as such and may result in false management of patients. In addition and specifically in the elderly, impaired bladder emptying may coincide with the development of UTIs[12]. Amongst community dwelling elderly women, UTIs is the second most common cause of infectious diseases and are in the group of frail elderly patients responsible for substantial morbidity[13]. Moreover, UTIs represent the most common cause of infection in hospitalised subjects and patients in long-term care facilities[14]. Aside from the patient's burden, these demographics result in a significant increase in health care expenses because of the ageing population in Europe. UTIs are estimated to be responsible for more than 100,000 hospital visits and costs of $ 3.5 billion annually in the USA[15]. UTI-related additional costs might even be higher in frail elderly patients in whom UTIs more frequently results in hospitalisation[16]. It still remains unclear whether there is a causal relationship between UTIs and development of PVR. A part of patients with PVR needs clean intermittent catheterisation (CIC) to (completely) empty the bladder. However, CIC or indwelling catheters are also related to infectious complications and/or potential upper urinary tract deterioration in the long-term[17].

1.2 Debate on terminology

The original definition on DU was written in the year 2002[1]. In addition to the ICS definition of DU, an ICS working group has proposed in the year 2015 a working definition for a more clinical approach of the topic in order to enable screening of patients based on symptoms and signs rather than pressure-flow measurement. This Underactive Bladder (UAB) working hypothesis includes: '*A symptom complex suggestive of detrusor underactivity and is usually characterised by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling and a slow stream*'[18]. Theoretically, a partial overlap between UAB, DU and BOO is considered but the purpose of the working hypothesis is to clinically identify patients who are suspicious of having DU (in pressure-flow analysis)[18,19]. However, there is a lack of scientific data particularly on the clinical symptom complex and its relation to urodynamically defined DU. The absence of robust data makes it impossible to accept the above mentioned clinical hypothesis already as a definition. A recent study of Gammie *et al.* exposed that the use of only LUTS in the diagnostic route might not have enough discriminative power to differentiate UAB from other causes of voiding dysfunction[20].

1.3 Epidemiology

The exact prevalence of the DU/UAB is difficult to define due to the ongoing debate of the definitions. The reader has to keep in mind that the occurrence of the condition(s) is dependent on the definition and the used threshold values as well as on the available assessment tools for identification and differentiation. Therefore, researchers are currently only able to make a rough estimation of the prevalence of DU and UAB.

Patients with PVR due to DU are often difficult to identify because symptoms and signs are often masked behind identical or similar symptoms or signs of voiding dysfunction presented in Figure 1. To complicate matter, men or women with DU may even be without PVR or LUTS. Based on current literature, the prevalence of DU in men has been estimated to be 9-23% and as high as 48% in men aged <50 years and >65 years, respectively (Table 1). In women, prevalence of DU is estimated to be between 4% and 45%. However, more recent studies suggested prevalence rates between 10 and 20% (Table 2).

Until now, DU has only been characterised by the presence of PVR in the absence of BOO. Therefore, the previously published studies on the epidemiology of DU have not considered the coexistence of DU and BOO. Though, urologists frequently see men with LUTS and PVR after unsuccessful treatment of BOO (for example after transurethral resection of the prostate, TURP) or female patients with LUTS complaints or PVR after urinary incontinence surgery. DU is known to have an unfavourable influence on the outcome of both TURP[37-39] and mid-urethral slings[40].

Table 1. Data on DU prevalence in the literature divided for men

	Investigated patients (n)	Age (mean, yr)	Clinical/ pressure-flow	Criteria	Prevalence (%)
Resnick 1989[21]	17	89	Pressure-flow	Absence of BOO	41.2
Ameda 1999[22]	193	69	Video-urodynamics	P_{iso} <60 cm H_2O or unsustained isovolumetric contraction	41.9
Abarbanel 2007[23]	82	≥70	Pressure-flow	Q_{max} <10 ml/s at $P_{det.Qmax}$ <30 cm H_2O	48
Kuo 2007[24]	1407	45-96	Video-urodynamics	'Relaxed sphincter EMG with open membranous urethra during voiding and low flow rate'	10.6
Jeong 2012[25]	632	>65	Pressure-flow	BCI<100	40.2
Lee 1999[26]	96	>50	Pressure-flow	Q_{max} ≤10 ml/s at $P_{det.Qmax}$ ≤30 cm H_2O	37
Fusco 2001[27]	541	64	Video-urodynamics	Q_{max} ≤12 ml/s at $P_{det.Qmax}$ ≤30 cm H_2O	10
Nitti 2002[28]	85	18-45	Video-urodynamics	Q_{max} <12 ml/s and BOOI <20	9
Wang 2003[29]	90	18-50	Video-urodynamics	Q_{max} <15 ml/s at $P_{det.Qmax}$ <30 cm H_2O	10
Kaplan 1996[30]	137	18-50	Video-urodynamics	Q_{max} <12 ml/s at $P_{det.Qmax}$ <45 cm H_2O	23
Karami 2011[31]	456	18-40	Pressure-flow	ICS definition	12.9
Jamzadeh 2014[32]	87	<40	Video-urodynamics	Q_{max} <12 ml/s at $P_{det.Qmax}$ <30 cm H_2O	11.9
Gammie 2015[20]	507	63	Pressure flow	BCI <100 and BOOI <20 and VE <90	25.0

BOO: bladder outlet obstruction, P_{iso}: isovolumetric detrusor pressure, Q_{max}: maximum flow rate based on catheterised uroflowmetry, $P_{det.Qmax}$: pressure at maximum flow rate, EMG: electromyography, BCI: bladder contractility index, BOOI: bladder outlet obstruction index, ICS: international continence society, VE: voiding efficiency.

Table 2. Data on DU prevalence in the literature for women

	Number of patients (n)	Age (mean, yr)	Clinical/ pressure-flow	Criteria	Prevalence (%)
Resnick 1989[21]	77	89	Pressure-flow	'Failure to empty in the absence of an increase in abdominal pressure.'	37.7
Resnick 1996[33]	97	87	Pressure-flow	'Reproducible failure of the involuntary contraction to empty at least half of bladder contents in the absence of straining, urethral obstruction, and detrusor-sphincter dyssynergia'	45
Choi 2013[34]	102	61	Pressure-flow	Q_{max}<15 ml/s at $P_{det.Qmax}$ <20 cm H_2O	12.8
Groutz 1999[35]	206	62	Pressure-flow	Q_{max}<12 ml/s and PVR >150 ml	19
Abarbanel 2007[23]	99	>70	Pressure-flow	Q_{max}<10 at $P_{det.Qmax}$ <30 cm H_2O	12
Valentini 2011[36]	442	>55	Pressure-flow	'Impaired detrusor contraction leading to prolonged voiding time and high residual volume'	13.8
Jeong 2012[25]	547	>65	Pressure-flow	Q_{max} ≤12 ml/s at $P_{det.Qmax}$ ≤10 cm H_2O	13.3
Gammie 2015[20]	1281	59	Pressure-flow	Q_{max} <15 ml/s at $P_{det.Qmax}$ <20 cm H_2O and VE <90	24.0

Q_{max}: maximum flow rate based on catheterised uroflowmetry, $P_{det.Qmax}$: pressure at maximum flow rate, VE: voiding efficiency.

1.4 Pathogenesis and factors involved in detrusor underactivity

The exact cause of DU or UAB has yet to be determined[41]. Regulation of 'normal' voiding requires multiple processes involved at different levels of the bladder-brain-bladder axis (Figure 2)[1,42]. Afferent function includes sensory modulation and local regulatory mechanisms involved in sensation. Afferent information is transferred to the periaqueductal gray matter (PAG) in the midbrain. From there, information is relayed to the pontine micturition centre (PMC). The PMC contains neurons from the spinal cord which control motor outflows to the detrusor and sphincter muscles. Forebrain regions, predominantly the prefrontal cortex, are of importance to control basic pontine and sacral voiding circuits[43]. Efferent function reflects local implementation of signals mediated from central or peripheral control areas through three major nerves: (1) the striated urethral sphincter is innervated by somatic nerves which are bunched mainly in the pudendal nerve; (2) the hypogastric nerve is responsible for sympathetic innervation of the bladder wall and urethra, and (3) the pelvic nerve is responsible for parasympathetic innervation of the smooth muscle cells of the detrusor. Dysfunction at any level of the peripheral or central nervous system or the bladder muscle may eventually lead to a disturbed voiding cycle, leading to the development of DU.

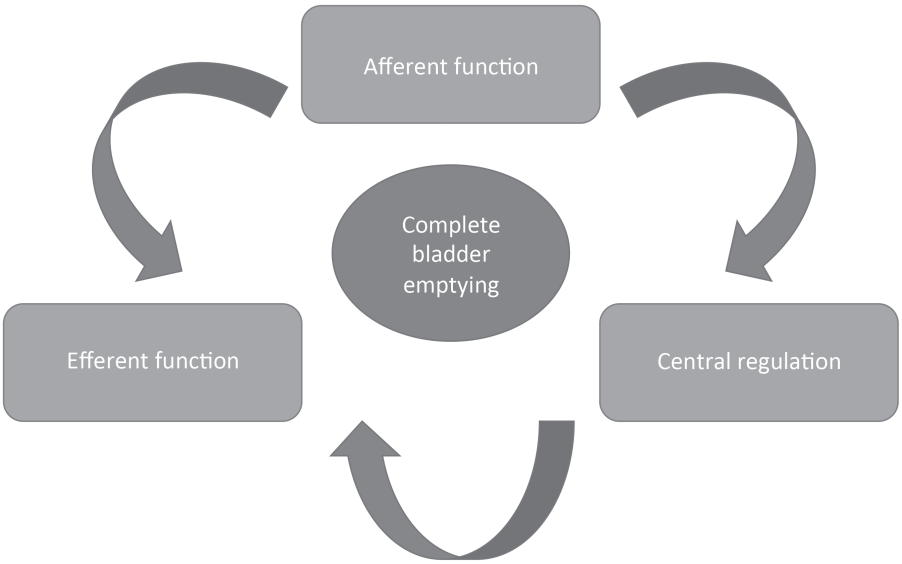

Figure 2. Factors involved in voiding. Voiding to completion can only be achieved if the three components of the model (afferent function, central regulation/control, efferent function) work properly and synergistically.

Factors that may underlie or influence development of DU can be divided into several broader categories: ageing as a natural process, BOO, diabetes mellitus, neurogenic disorders, cardiovascular disease, or psychosocial influence. These specific factors have all been investigated with respect to their presumed influence on DU in both experimental animals and humans.

1.4.1 Ageing

Bladder function can change due to several processes in ageing individuals, such as alteration in vascularisation, nervous supply and changes bladder receptor function and expression[44]. To date, it is unknown whether degeneration of detrusor smooth muscle plays a significant role in age-related voiding dysfunction. A morphological study by Elbadawi and colleagues compared detrusor biopsies in urodynamically 'normal' individuals (without DO or BOO) with impaired and normal contractility during pressure-flow studies. The electron microscopy specimens showed degeneration of smooth muscle and axons in the group with impaired contractility during pressure-flow study[45]. Recently, a functional study by Fry *et al.* found no differences in decline of detrusor smooth muscle contractility or excitability as a function of age in a muscle strip study[46].

The literature shows that only approximately 50% of the male patients with LUTS actually have BOO[47]. A large Brazilian cohort study demonstrated that only 25% of the symptomatic patients above 80 years of age have BOO[10,48]. However, an age-related degradation of detrusor contractility has not yet been identified as the primary cause of impaired bladder emptying[39,49].

In vitro studies showed that detrusor contractility alters with ageing in rats and mice[50,51]. In vivo studies in experimental animals showed that afferent nerve density declines with ageing[52]. Additionally, Smith *et al.* confirmed that altered volume sensation may play a role in unobstructed, non-neurogenic bladder patients with voiding dysfunction[53]. Nevertheless, the exact role of central regulatory system dysfunction in ageing humans remains to be elucidated and, in addition the role of altered bladder contractile ability with ageing remains a topic under investigation. Currently, the most likely explanation is that not only bladder contractility alone but also the altered relationship of the contractile force and the outlet resistance, together with a diminished afferent function, causes defective voiding in ageing patients with LUTS[47,54]. The former implies that ageing is not a stand-alone process.

1.4.2 Bladder Outlet Obstruction (BOO)

Increased bladder outlet resistance caused by benign prostatic enlargement (BPE), i.e. benign prostatic obstruction (BPO), is considered to be the most common cause of LUTS or bladder dysfunction in the ageing male population, which may eventually lead to filling and/or voiding phase complaints. In women, anatomical as well as functional causes of BOO may evoke LUTS and also inefficient voiding. However, whether a patient develops

LUTS may only be partially dependent on the grade or severity of BOO[47]. There is most probably only a narrow margin in which the grade of BOO and the patient's capacity to overcome this increased outlet resistance by increasing contractility is balanced (acutely or chronically)[55]. The margins of the contractile reserve of the detrusor have not been investigated and may also be variable in individuals. Several in vitro studies have shown a consistent relationship between increased bladder mass and altered contractile responses in muscle strips after prolonged BOO in rats, rabbits and cats[56-58]. Alterations in bladder outlet resistance may evoke a diminished emptying capacity of the bladder because the bladder is not able to compensate for this 'additional' obstruction. In addition, studies in experimental animals also suggest the presence of sensory denervation caused by prolonged partial BOO[59].

1.4.3 Diabetes mellitus (DM)

The pathophysiology of DM and the effects on the urinary tract are considered multifactorial, involving neuronal, smooth muscle and urothelial alterations[60]. Animal studies showed that end-stage diabetic cystopathy potentially results in an underactive or even acontractile detrusor[61] due to hyperglycaemia-related oxidative stress and polyuria[62,63]. In addition, a recent study of Wang *et al.* highlighted the potential influence of DM on urothelial modulation and afferent sensory function[64].

Diabetes Mellitus (DM) type 1 or type 2 may be the cause of urinary tract symptoms because of neuropathy, myopathy and vasculopathy. Diabetic cystopathy has been observed in 80% of the patients with DM complications. In contrast, peripheral neuropathy and nephropathy have been reported in 50 and 60% of the DM patients, respectively[65]. The term diabetic cystopathy is not only referred to as an end-stage disorder with irreversible loss of sensation resulting bladder distension and development of urinary retention, but also includes symptoms of different degrees of bladder dysfunction[66-68]. Diabetic cystopathy may be asymptomatic or can include storage and voiding problems, as well as other less well defined clinical phenotypes such as decreased sensation and increased bladder capacity[69,70]. Aside from the association between DM and storage symptoms, DM is frequently related to incomplete bladder emptying or diabetic cystopathy, especially in a late phase of DM. A recent study in 1,640 women showed that diabetic cystopathy was present in 54% of these patients[71].

1.4.4 Neurogenic disorders

Incomplete bladder emptying is also a common phenomenon in patients with specific neurological diseases, such as multiple sclerosis (0-40%)[72], Parkinson's disease (53%)[73,74], and multiple system atrophy (MSA) (52-67%)[75]. A recent study of Kim *et al.* showed that PVR and detrusor hypocontractility were pathognomic findings for MSA when comparing this neurological disease with Parkinson's disease[74].

Multiple animal studies have been published that focussed on reproducing these specific neurogenic situations and its influence on the bladder[76], but it is difficult to translate these results of these animal studies to the human situation[55]. However, some translational aspects have been implemented such as reinnervation strategies used in experimental animals that have already been applied in humans. An example is the spinal root transection model in canines in which the genitofemoral nerve was used to reinnervate the bladder[77]. Xiao *et al.* performed comparable artificial somatic-autonomic reflex pathway re-routing in neurogenic bladder dysfunction patients to restore voluntary bladder control[78].

1.4.5 Cardiovascular disease

Based on research in experimental animals, there are strong indications that cardiovascular comorbidity can induce bladder ischaemia and successive oxidative damage. Several animal studies clearly showed a correlation between oxidative stress and impaired contractility[54,79]. A recent study of Radu *et al.* concluded a beneficial effect of antioxidant treatment in delaying the onset of progressive loss of bladder function in rabbits[80]. However, it remains unclear in humans to what extent these experimental results can be translated into the potential use of antioxidants as a therapeutic agent[44,81].

1.4.6 Psychosocial influence

The regulation of lower urinary tract function is also dependent on the influence of local, spinal, bulbar and cortical reflexes[1]. It is known from research reports that it is possible to completely inhibit the voiding reflex in a situation of psychological stress[82,83]. One of the most likely causes of absent detrusor contraction during in-hospital conventional urodynamics but visible contractions on ambulatory (outpatient) urodynamics appears to be psychological[84,85]. Therefore, the level of cortical inhibition is responsible for the measurable amplitude of the bladder pressure in conscious humans, and this effect is also very likely to occur in experimental animals. Intra-subject variability in urodynamic outcomes may partially be explained by these psychological factors. Also psychological traits in specific patient groups can prove to be responsible for voiding dysfunction due to DU/UAB[86]. It has been proposed that psychological and psychiatric assessment should be considered and, in some situations, even standardised in functional urology[87].

1.5 Assessment of detrusor function and detrusor underactivity

The European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend pressure-flow measurement only in selected men during LUTS work-up in order to distinguish between DU, BOO and dysfunctional voiding (Figure 1)[88,89]. A recent Cochrane systematic review showed that invasive urodynamic testing did change clinical

decision making in male patients with LUTS before desobstructive treatment, for example by TURP. However, whether this led to symptom reduction or improvement of voiding dysfunction is still uncertain[90]. Most of the studies were done in men and the exact diagnostic value of invasive urodynamics for the LUTS work-up in women and children remains to be investigated[91].

Conventional interpretation of pressure-flow studies has clear limitations for the measurement of contractility in both men and women and may not identify DU correctly. Surprisingly, a majority of the studies published on epidemiological data with regard to DU solely use a cut-off value for Q_{max} combined with $P_{det.Qmax}$ to define DU (Table 1). The combination of Q_{max} and $P_{det.Qmax}$ is generally used to determine BOO grading rather than estimation of bladder contractility. The potential misuse of this pressure-flow assumption without any clinical measurement values may lead to incorrect epidemiological data on DU[47].

1.5.1 Evaluation of bladder contractility in men

DU is a urodynamic diagnosis and is therefore based on the result of pressure-flow analysis. Healthy individuals void with a low detrusor pressure and high urinary flow, patients with BOO void with high detrusor pressure and high urinary flow, and patients with DU void with low detrusor pressure and low urinary flow rate[1]. The most widely known indices are:

1. Maximum Watts factor (W_{max})

The Watt Factor (WF) calculation is based on the Hill equation and consist of a complex computed formula[92,93]. The first step is to re-write the equation in pressure (P_{det}) developed by the complete bladder and velocity of the detrusor circumference[94]. The resulting final equation of volume-independent contraction strength is $WF = [(P_{det} + a)(v_{det} + b) - ab]/2\pi$. This equation contains a correction for a point 'zero' (where there is no contraction at all) and correction for the strength per unit area. WF is considered the contraction strength per unit area of bladder surface of which W_{max} represents the highest value, corrected for straining and other pressure-flow related artefacts[94].

2. 'linPURR detrusor' extracted from the Schäfer nomogram

The Schäfer concept is based on the passive urethral resistance relation (PURR) assumption, which is helpful to analyse the pressure-flow relation only at the low-pressure flank of the pressure-flow plot. PURR consists of the minimal urethral opening pressure (P_{muo}) and lumen size (Q_{max} at $P_{det.Qmax}$) (Figure 3). The use of a linear PURR (linPURR) instead of the more complex fitting curve (quadratic PURR) on the pressure-flow plot appeared to have similar results[95,96]. The Schäfer nomogram defines linPURR 'urethra' (resistance) and 'detrusor' (contractility) in one nomogram (Figure 3). However, the Schäfer classification only roughly distinguishes between obstruction and contractility classes and cannot provide detailed information on small differences within or in between the classes.

3. The Bladder Contractility Index (BCI)

The length of the linPURR detrusor can be expressed using the BCI formula ($P_{det.Qmax}$ + $5Q_{max}$)[97]. BCI >150 represents strong contractile strength, BCI between 100-150 is considered as normal contractility and BCI <100 as low contractility.

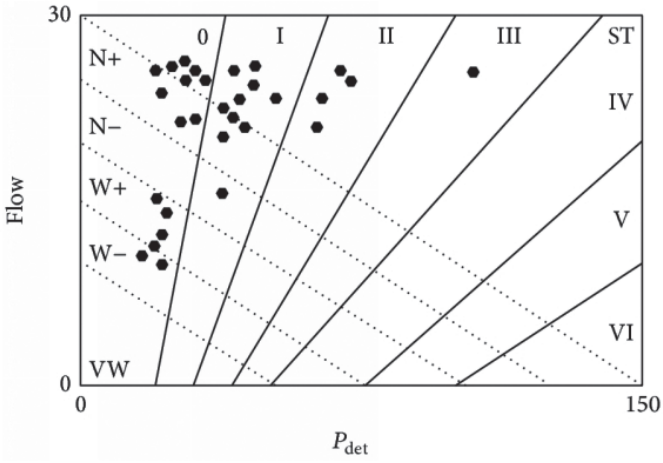

Figure 3. Schäfer nomogram indicating both detrusor contractility and bladder outlet resistance. Detrusor contractility is based on the concept of the length of the linPURR (i.e. linPURR-detrusor; thresholds indicated as red lines: ST: strong detrusor, N: normal detrusor, W: weak detrusor, VW: very weak detrusor). Bladder outlet resistance is also based on the linPURR concept (i.e. linPURR-urethra; thresholds are indicated as green lines)

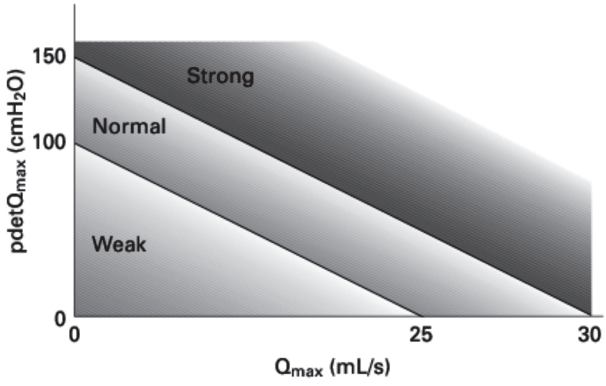

Figure 4. Bladder Contractility nomogram by Abrams[97].

Multiple indicators and threshold values for DU are used in current literature but there is a lack of evidence especially for the threshold values[98-101]. Most of these values are based on specific assumptions and, therefore, may not be applicable or validated for all patients. The latter seems to be true for the threshold values of BCI (<100) and W_{max} (<7 W/m^2); these seem to be incorrect for at least part of the obstructed male bladders[47]. Even less evidence exists for the maximum flow threshold values that have been used in clinical studies on impaired bladder emptying. The problem in these situations lies most probably in the fact that the specific indices are not correlated to clinical parameters and do not take the increasing bladder outlet resistance of the increasing BOO grade into account[47].

1.5.2 Evaluation of bladder contractility in women

Women are capable of voiding in the presence of lower or even no detrusor pressures - often by simply straining together with pelvic floor relaxation - and, at the same time, generating higher flow rates compared to men. A study in healthy women aged 28-45 years showed that the range of contraction strength in healthy women varies from 24 W/m^2 (ideal voids) to 5 W/m^2 (non-ideal voids)[94]. Aside from men, the pressure-flow based Schäfer nomogram, the projected isovolumetric pressure (PIP), detrusor coefficient (DECO) and BCI have also been used in studies with regard to women without definition of specific threshold values. The projected isovolumetric pressure has initially been proposed for women, using the formula $P_{det.Qmax} + 5Q_{max}$. The same formula is used in men (BCI), but the fixed constant named K should be 5[102] in men and 1 in women[95]. Therefore, Tan *et al.* proposed an alternative to PIP, PIP_1 ($P_{det.Qmax} + Q_{max}$) using a constant K of 1 cm H_2O/ml/s [103]. This constant K value appears to overestimate the detrusor contractile strength in women[102,103]. Until now, PIP_1 is the only valid contractile function pressure-flow parameter developed for women. However, until now there is no age-stratification because the value of constant K in women is only based on limited data in older women.

1.5.3 Non-invasive indicators of bladder function

In order to deliver a better estimation of the bladder emptying capability, parameters such as voiding efficiency (VE = voided volume / (voided volume + post-void residual) x 100), amount of PVR, bladder capacity and bladder filling sensations may be taken into account in combination with the conventional urodynamic parameters. Aside from providing a pressure-flow relationship, these parameters can inform the physician about the clinical consequences of DU. The addition of symptoms to the diagnostic algorithm does not seem useful to increase diagnostic accuracy[20,104]. This is likely caused by the overlap between DU symptomatology and BOO or dysfunctional voiding (**Figure 1**). The obvious disadvantages of (invasive) pressure-flow studies have inspired physicians to use non-invasive approaches for estimation of bladder function, varying imaging technique to non-catheter urodynamics, such as the penile cuff test in men. All of these are techniques were developed at first to

diagnose BOO[105]. However, the some techniques such as ultrasound detrusor wall thickness (DWT) measurement, ultrasound decorrelation and the penile cuff test also appear helpful in the diagnostic work-up of patients with DU[106]. The diagnostic potential of one specific technique, DWT measurement, will be discussed in detail in this thesis.

1.6 Treatment options for patients with detrusor underactivity

Treatment of DU involves either improvement of bladder contractility, decrease in bladder outlet resistance, correction of the regulatory pathways, or a combination of these therapies[47]. There is a balance between bladder contractility and bladder outlet resistance. Accordingly, subjects who are able to completely empty their bladders are obviously able to sufficiently overcome bladder outlet resistance, independent on the individual degree of obstruction. This basic rule accounts for men as well as for women, though women seem to present with a widely varying range and origin of BOO. Consequently, two distinct patient groups with DU which different treatment strategic approaches can be identified: 1) DU in patients without BOO and 2) DU in patients with BOO. A second segregation could be made in terms of gender. Treatment options in terms of desobstruction or improvement of contractility may differ from men to women.

1.6.1 Clean Intermittent Catheterisation (CIC)

Clean intermittent catheterisation (CIC) is a symptomatic treatment which can be performed by patients, their partners or other caregivers, regardless of the origin and consequences of incomplete bladder emptying as well as the amount of PVR. CIC can be performed transurethrally or in combination with a continent vesicostomy, with either bladder neck closure or implantation of an obstructive suburethral sling. Catheterisation can be facilitated through Mitrofanoff, Monty or Boari diversion techniques. Catheterisation in general or CIC in particular can sometimes lead to (complicated) recurrent urinary tract infections. However, CIC is well tolerated by the majority of patients and has been shown to result in similar quality of life compared to age-matched control groups[107]. If the patient should be unable to perform CIC, transurethral or suprapubic catheters can be used instead but permanent catheters almost always initiate bacterial colonisation of the lower urinary tract and may cause bladder storage LUTS, bleeding, clogging of the catheter lumen, ulcerations or stenoses of the urethra, or urosepsis. In the long term, deterioration of renal function was seen in a recent study in patients with neurogenic bladder dysfunction with an indwelling catheter[108]. These factors make permanent catheters a less favourable treatment option compared to CIC.

1.6.2 Pelvic floor re-education

Pelvic floor muscle exercises are a non-invasive management option for specific patient groups with DU. It can be considered when the aim is to reduce functional BOO, with or without concomitant bladder inhibition, or to alter psychological inhibition and so provide a non-invasive re-arrangement of the micturition coordination. Relaxation of the pelvic floor/external urethral sphincter combined with straining may help improvement of bladder emptying. Most of the evidence with regard to pelvic physiotherapy as a treatment option for this indication results from paediatric studies. A recent randomised study by Ladi-Seyedian *et al.* showed that animated biofeedback and pelvic floor muscle training[109] are highly effective in non-neurogenic children with voiding dysfunction suspicious of detrusor underactivity. However, the exact mechanism of action of pelvic physiotherapy in adult DU patients is not well understood and needs further research.

1.6.3 Pharmacotherapy

It is warranted to direct therapy towards the underlying pathophysiology of DU and use treatment modalities which have the lowest adverse event profile. Unfortunately, no licensed drug alone has ever shown to effectively increase detrusor contractility or decrease bladder outlet resistance. Therefore, pharmacological treatment of DU is currently impossible. However, it may be possible in the future to specifically increase detrusor contractility with drugs instead of decreasing bladder outlet resistance by an operation, e.g. TURP in men (see section 1.6.5).

Multiple targets with potential effects on contractility and detrusor strength have been identified, of which the adrenergic, cholinergic, prostanoid, purinergic and cannaboid system are the most widely known. Most of the research area covers animal studies or early phase clinical studies. In humans, previous efforts have focused on the cholinergic system, targeting on one of the five muscarinic or the nicotine receptors. Muscarinic receptor agonists (e.g. betanechol) or choline esterase inhibitors (e.g. distigmine) to increase detrusor contractility showed only minor beneficial effects on voiding function and PVR, combined with an unfavourable side effect profile[110,111]; therefore, these two drug classes are no longer recommended for DU. The same accounts for α_1–adrenoceptor antagonists (α-blockers) to decrease bladder outlet resistance[111]. However, a recent study in experimental animals with diabetes mellitus suggested that an α-blocker together with the choline esterase inhibitor distigmine may be able to sufficiently improve voiding function[112]. The study has re-directed attention towards both drug classes for their combined use in DU in humans but clinical studies have not been published.

In the past 10 years, many receptors and transmitters have been identified in the search for new treatment options for the overactive bladder. This knowledge is expected to lead to other counteracting compounds with a favourable effect on DU. Accordingly, pharmacotherapy of DU by modulating the prostanoid system by EP-receptor agonists has

been tested. Stimulation of the EP2 and EP3 receptors appeared to increase contractility and simultaneously induce relaxation of the urethra in *in vitro* studies[113,114]. In addition, a monkey model showed improvement of voided volume per micturition and maximum flow rate when comparing the EP compound to a choline esterase inhibitor[114]. A recent abstract presented at the AUA annual congress in 2015 showed the safety and tolerability trial data of the EP2/EP3 receptor agonist ONO-8055[115]. This compound was well tolerated in a group of healthy volunteers. For further validation of the clinical value of EP-receptor agonists or other compounds, it is first necessary to develop adequate tools for the detection, diagnosis, and judgement of treatment effects.

1.6.4 Sacral Neuromodulation (SNM)

If detrusor underactivity in a patient is not caused by complete denervation of the bladder, voiding dysfunction may be treated by sacral neuromodulation (SNM)[116]. For this procedure, an electrode is placed near the sacral nerves (preferable S3), after which the lead is electrically stimulated during a test-period. If voiding has re-appeared and PVR has reduced, a definite stimulator can be implanted. A recent study of Drossaerts *et al.* showed that patients with DU still had a success rate between 35-67%, depending on the urodynamic technique used for diagnosis[117]. Success has been defined as >50% reduction of the total catheterised volume per 24 hours.

Other neuromodulation techniques, such as percutaneous tibial nerve stimulation (PTNS), have been explored only to a limited extent in patients with DU. With PTNS, the posterior tibial nerve is percutaneously stimulated by needle insertion above the medial malleolus. The needle is connected to a low-voltage stimulator. The correct placement of the needle results in sensory (tickling at the plantar side of the foot) and motor responses (plantar flexion of 1st digit). Treatment effects are tested during 12 sessions, once weekly for 30 minutes. Up to now, the only available study comes from Vandoninck *et al.* reporting the results of 39 patients with chronic voiding dysfunction[118]. Forty-one percent of these patients were successfully treated with PTNS after the treatment period, which is comparable to the SNM outcome in this group of patients[118,119]. These results seem to be promising; however, more evidence is needed to correctly judge and validate these initial results.

It is likely that all neuromodulation techniques are able correct a de-rangement of the central and maybe even local neuro-regulatory systems. SNM is likely to affect sensory pathways and influence specific brain regions such as the periaquaductal gray (PAG) and pontine micturition centre (PMC) through which its regulatory effect is considered to modulate the central reflexes. A potential effect on peripheral motor sensory regulation and efferent effects of SNM are less established and comprise a more hypothetical working mechanism.

1.6.5 Surgical reduction of bladder outlet resistance

In male patients with proven BOO and DU, transurethral resection of the prostate (TURP) to reduce bladder outlet resistance may be considered. However, in the presence of DU in patients with BOO and even more in patients with DU but without BOO is associated with a less favourable outcome and persistence or symptoms or signs of DU[39,120]. Thomas *et al.* presented the results of a retrospective long-term cohort study of 224 men with DU, a condition defined by pressure-flow analysis as BCI <100. Of the total study population, 22 were treated by TURP. Signs and symptoms were re-evaluated after a mean follow-up period of 11.3 years. A comparison of operated patients with 58 age-matched untreated male DU patients showed that TURP was not better than watchful waiting and, therefore, has no long-term benefit[39,120]. Despite the potential complications and treatment failure risks of prostate surgery and due to the lack of alternative treatment options, TURP or similar prostate surgery techniques (e.g. Holmium enucleation of the prostate or GreenLight Laser vaporisation of the prostate) are most probably the most frequently chosen therapies of DU in adult men at present. This treatment, similar to TURP, also reduces bladder outlet resistance, can be used as a last resort. However, prostate surgery In patients with DU represents a trial-and-error approach. An earlier report of van Mastrigt *et al*. already showed that contractility (W_{max}) remains unchanged three months after TURP[121]. However, the follow-up period in this study may be too short to observe post-operative alterations of bladder contractile strength as complete restoration of the operated area may take a longer period of time. At present, long-term data with regard to postoperative contractile strength is missing. Intermediate follow-up results of a prospective trial in non-neurogenic patients with impaired detrusor contractility indicated that Holmium laser enucleation can be a valuable option for patients with BPO and impaired contractility[122].

In women, transurethral incision of the bladder neck has been suggested to improve voiding efficiency by reduction of bladder outlet resistance[123]. This technique has a limited therapeutic utility and seems to be most effective in women with DU and potential bladder neck obstruction. Jhang *et al.* retrospectively analysed the results of 31 female patients with DU[124]. A resectoscope and diathermy electrode was used to incise the bladder neck at the 5 and 7 o'clock lithotomy positions. At three months follow-up, statistically significant improvements of voided volume, maximum urinary flow rate (Q_{max}), PVR, and VE was shown, with a 56% decrease in PVR and VE improvement rangeing from 5 to 52%. Long-term follow-up data (mean 61.8 months) demonstrated consistent improvement in PVR and VE[123]. Though these first results are promising, there are no additional studies confirming these results and no randomised controlled trials have ever been published. It has to be kept in mind that the operation bears a high risk of urinary incontinence and strictures and, therefore, should not be applied in routine clinical practise until additional data has become available.

1.6.6 Reduction cystoplasty

There is only limited support in literature for the value of reduction cystoplasty in patients with DU. The technique has mainly been described in patients with the prune belly syndrome[125,126]. The theoretical basis for the technique is to remove the upper dome of the bladder, which appears most prone to chronic overdistention[127], and herewith (temporarily) improving the bladder emptying capacity by reduction of this flaccid region of the bladder. Additionally, detrusor duplication can be applied. A small case series by Thorner *et al.* presented reduction cystoplasty (in most cases combined with diverticulectomy and/or suprapubic prostatectomy) in a selected group of men with PVR due to DU or bladder acontractility. The application of detrusor duplication was not described in the methods section of this study. The study showed treatment success in 7 out of 8 patients after a follow-up of one year in terms of CIC free rate and improvement of the Patient Global Impression of Improvement (PGII) questionnaire[128]. These preliminary results indicate that reduction cystoplasty may be helpful on the short- or intermediate term for the improvement of voiding efficiency. However, a study in 11 boys with prune belly syndrome treated between 1973 and 1990 presented long-term data with an average follow-up period of 7.7 years (range 1.5-18 years); contrary to the results in adult men, this study showed that reduction cystoplasty is not successful in improvement of voiding dynamics or reduction of bladder capacity[126].

1.6.7 Latissimus dorsi detrusor myoplasty (LDDM)

In selected cases of patients with an acontractile bladder aged 60 years or younger, a latissimus dorsi detrusor myoplasty (LDDM) may be considered. LDDM uses a free pedicled transplant of the latissimus dorsi muscle which is transferred to the bladder during the operation. The vascular pedicle is attached to the epigastric vessels and the thoraco-dorsalis nerve is re-anastomosed to a couple of intercostal nerves normally innervating the rectus abdominis muscle. After follow-up period of approximately 6 months after LDDM, voiding was possible and more efficient by abdominal straining. Approximately 70% of patients in this selected group could stop CIC after the procedure[42]. Although results appear promising, the clinical benefit has to be put into the perspective of an experimental operation with limited patient numbers. Until now, the results of a total amount of only 58 patients treated in four highly specialised centres have been described in the literature. Therefore, LDDM remains experimental surgery and lacks of long-term results[129].

1.8 Outline of the Thesis

This thesis focusses on the evaluation of DU in men or women with incomplete bladder emptying by using clinical data. Chapter 1 introduces ambulatory pressure-flow measurement for patients with impaired bladder emptying. Chapters 2-4 explain the development of a new detrusor contractility-bladder outlet obstruction nomogram, which later has been published as the Maastricht-Hannover nomogram, for the diagnosis of DU in relation to bladder outlet resistance. Chapter 2 focuses on the relationship between detrusor contractility and BOO and clarifies whether it is possible to use threshold values for the diagnosis of DU. The final nomogram and the first pilot validation study will be discussed in Chapters 3 and 4 of this thesis.

In Chapter 5 a non-invasive diagnostic approach of DU in men is described and explored. With development of new diagnostic tools for DU, the preference goes to less invasive options than conventional pressure-flow studies. This chapter presents the results of a pilot study in male patients to distinguish patients with DU from other voiding dysfunctions by the use of ultrasound detrusor wall thickness combined with uroflowmetry. DU as an entity in women and the difficulties in the diagnostic work-up for the female gender will be presented in detail in Chapter 6. Chapter 7 highlights patient management with attention to a specific reconstructive surgical option (latissimus dorsi detrusor myoplasty) to restore voiding function. Chapter 8 explains the pathophysiological background and future perspectives of DU.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. Drake MJ, Kanai A, Bijos DA, Ikeda Y, Zabbarova I, Vahabi B, Fry CH. The potential role of unregulated autonomous bladder micromotions in urinary storage and voiding dysfunction; overactive bladder and detrusor underactivity. *British Journal of Urology International 2016* [Epub ahead of print].
3. Resnick NM, Yalla SV. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. *Journal of the American Medical Association* 1987;257:3076-3081.
4. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, Gravas S. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. *European Urology* 2015;67:1099-1109.
5. Verhamme K, Dieleman J, Bleumink G, Van der Lei J, Sturkenboom M, Panel TP. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care - the Triumph project. *European Urology* 2002;42:323-328.
6. Verhamme K, Dieleman J, van Wijk M, Bosch J, Stricker BC, Sturkenboom M. Low incidence of acute urinary retention in the general male population: the triumph project. *European Urology* 2005;47:494-498.
7. Meigs JB, Barry MJ, Giovannucci E, Rimm EB, Stampfer MJ, Kawachi I. Incidence rates and risk factors for acute urinary retention: the health professionals followup study. *Journal of Urology* 1999;162:376-382.
8. Jacobsen SJ, Jacobson DJ, Girman CJ, Roberts RO, Rhodes T, Guess HA, Liever MM. Natural history of prostatism: risk factors for acute urinary retention. *Journal of Urology* 1997;158:481-487.
9. Temml C, Brössner C, Schatzl G, Ponholzer A, Knoepp L, Madersbacher S. The natural history of lower urinary tract symptoms over five years. *European Urology* 2003;43:374-380.
10. Rodrigues P, Hering F, Meller A, D'Império M. Outline of 3,830 Male Patients Referred to Urodynamic Evaluation for Lower Urinary Tract Symptoms: How Common Is Infravesical Outlet Obstruction? *Urology Internationalis* 2009;83:404-409.
11. Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. *Journal of American Geriatric Society* 2006;54:1920-1932.
12. Di Pierdomenico AA, Radomski SB. Success rates of patients with poor emptying on clean intermittent catheterisation. *The Canadian Journal of Urology* 2014;21:7188-7193.
13. Ruben FL, Dearwater SR, Norden CW, Kuller LH, Gartner K, Shalley A, Amoroso W. Clinical infections in the noninstitutionalised geriatric age group: methods utilised and incidence of infections The Pittsburgh Good Health Study. *American Journal of Epidemiology* 1995;141:145-157.
14. Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. *The American Journal of Geriatric Pharmacotherapy* 2011;9:286-309.
15. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *The American Journal of Medicine* 2002;113:5-13.
16. Turner RM, Wu B, Lawrence K, Hackett J, Karve S, Tunceli O. Assessment of Outpatient and Inpatient Antibiotic Treatment Patterns and Health Care Costs of Patients with Complicated Urinary Tract Infections. *Clinical Therapeutics* 2015;37:2037-2047.

17. Krebs J, Wöllner J, Pannek J. Risk factors for symptomatic urinary tract infections in individuals with chronic neurogenic lower urinary tract dysfunction. *Spinal Cord* 2016;54:682-686.
18. Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, Smith PP. The Underactive Bladder: A New Clinical Concept? *European Urology* 2015;68:351-353.
19. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Wein A. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology* 2014;65:389-398.
20. Gammie A, Kaper M, Dorrepaal C, Kos T, Abrams P. Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies. *European Urology* 2016;69:361-369.
21. Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly persons. *New England Journal of Medicine* 1989;320:1-7.
22. Ameda K, Sullivan MP, Bae RJ, Yalla SV. Urodynamic characterization of nonobstructive voiding dysfunction in symptomatic elderly men. *Journal of Urology* 1999;162:142-146.
23. Abarbanel J, Marcus E-L. Impaired detrusor contractility in community-dwelling elderly presenting with lower urinary tract symptoms. *Urology* 2007;69:436-440.
24. Kuo HC. Videourodynamic analysis of pathophysiology of men with both storage and voiding lower urinary tract symptoms. *Urology* 2007;70:272-276.
25. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Hong SK. Prevalence and clinical features of Detrusor Underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. *Korean Journal of Urology* 2012;53:342-348.
26. Lee JG, Shim KS, Koh SK. Incidence of detrusor underactivity in men with prostatism older than 50 years. *Korean Journal of Urology* 1999;40:347-352.
27. Fusco F, Groutz A, Blaivas JG, Chaikin DC, Weiss JP. Videourodynamic studies in men with lower urinary tract symptoms: a comparison of community based versus referral urological practices. *Journal of Urology* 2001;166:910-913.
28. Nitti VW, Lefkowitz G, Ficazzola M, Dixon CM. Lower urinary tract symptoms in young men: videourodynamic findings and correlation with noninvasive measures. *Journal of Urology* 2002;168:135-138.
29. Wang CC, Dei Yang SS, Chen Y-T, Hsieh J-H. Videourodynamics identifies the causes of young men with lower urinary tract symptoms and low uroflow. *European Urology* 2003;43:386-390.
30. Kaplan SA, Ikeguchi EF, Santarosa RP, D'alisera PM, Hendricks J, Te AE, Miller MI. Aetiology of voiding dysfunction in men less than 50 years of age. *Urology* 1996;47:836-839.
31. Karami H, Valipour R, Lotfi B, Mokhtarpour H, Razi A. Urodynamic findings in young men with chronic lower urinary tract symptoms. *Neurourology and Urodynamics* 2011;30:1580-1585.
32. Jamzadeh A, Xie D, Laudano M, Seklehner S, Elterman D, Shtromvaser L, Chughtai B. Urodynamic characterisation of lower urinary tract symptoms in men less than 40 years of age. *World Journal of Urology* 2014;32:469-473.
33. Resnick NM, Brandeis GH, Baumann MM, DuBeau CE, Yalla SV. Misdiagnosis of urinary incontinence in nursing home women: prevalence and a proposed solution. *Neurourology and Urodynamics* 1996;15:599-618.
34. Choi YS, Kim JC, Lee KS, Seo JT, Kim HJ, Yoo TK, Lee JG, Lee JY. Analysis of female voiding dysfunction: a prospective, multi-centre study. *International Urology and Nephrology* 2013;45:989-994.
35. Groutz A, Gordon D, Lessing JB, Wolman I, Jaffa A, David MP. Prevalence and characteristics of voiding difficulties in women: are subjective symptoms substantiated by objective urodynamic data? *Urology* 1999;54:268-272.
36. Valentini FA, Robain G, Marti BG. Urodynamics in women from menopause to oldest age: what motive? What diagnosis? *International Brazilian Journal of Urology* 2011;37:100-107.

37. Van Koeveringe GA, Rademakers KLJ. Factors impacting bladder underactivity and clinical implications. *Minerva Urologica e Nefrologica* 2015;67:139-148.
38. Seki N, Kai N, Seguchi H, Takei M, Yamaguchi A, Naito S. Predictives regarding outcome after transurethral resection for prostatic adenoma associated with detrusor underactivity. *Urology* 2006;67:306-310.
39. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *British Journal of Urology International* 2004;93:745-750.
40. Ahn C, Bae J, Lee KS, Lee HW. Analysis of voiding dysfunction after transobturator tape procedure for stress urinary incontinence. *Korean Journal of Urology* 2015;56:823-830.
41. Chapple CR, Osman NI. Crystallizing the definition of Underactive Bladder syndrome, a common but under-recognized clinical entity. *Lower Urinary Tract Symptoms* 2015;7:71-76.
42. van Koeveringe GA, Rademakers KLJ, Stenzl A. Latissimus dorsi detrusor myoplasty to restore voiding in patients with an acontractile bladder - fact or fiction? *Current Urology Reports* 2013;14:426-434.
43. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. *Nature Reviews Neuroscience* 2008;9:453-66.
44. Andersson KE, Boedtkjer DB, Forman A. The link between vascular dysfunction, bladder ischaemia, and ageing bladder dysfunction. *Thereapeutic Advances in Urology* 2017;9:11-27.
45. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. II. Ageing detrusor: normal versus impaired contractility. *Journal of Urology* 1993;150:1657-1667.
46. Fry CH, Bayliss M, Young JS, Hussain M. Influence of age and bladder dysfunction on the contractile properties of isolated human detrusor smooth muscle. British Journal of Urology International 2011;108:E91-96.
47. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and W_{max}) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: results from a urodynamic database analysis. *World Journal of Urology* 2014;32:1177-1183.
48. Madersbacher S, Pycha A, Klingler CH, Mian C, Djavan B, Stulnig T, Marberger M. Interrelationships of bladder compliance with age, detrusor instability, and obstruction in elderly men with lower urinary tract symptoms. *Neurourology and Urodynamics* 1999;18:3-13.
49. Smith PP. Aging and the underactive detrusor: a failure of activity or activation? *Neurourology and Urodynamics* 2010;29:408-412.
50. Zhao W, Aboushwareb T, Turner C, Mathis C, Bennett C, Sonntag WE, Andersson KE, Christ G. Impaired bladder function in ageing male rats. *Journal of Urology* 2010;184:378-385.
51. Lai HH, Boone TB, Thompson TC, Smith CP, Somogyi GT. Using caveolin-1 knockout mouse to study impaired detrusor contractility and disrupted muscarinic activity in the ageing bladder. *Urology* 2007;69:407-411.
52. Smith PP, DeAngelis A, Kuchel GA. Detrusor expulsive strength is preserved, but responsiveness to bladder filling and urinary sensitivity is diminished in the ageing mouse. *The American Journal of Physiology; Regulatory, Integrative and Comparative Physiology* 2012;302:R577-586.
53. Smith PP, Chalmers DJ, Feinn RS. Does defective volume sensation contribute to detrusor underactivity? *Neurourology and urodynamics* 2015;*34:*752-756.
54. Kranse R, van Mastrigt R. Relative bladder outlet obstruction. *Journal of Urology* 2002;168: 565-570.

55. van Koeveringe GA, Rademakers KLJ, Birder LA, Korstanje C, Daneshgari F, Ruggieri MR, Igawa Y, Fry CH, Wagg A. Detrusor underactivity: Pathophysiological considerations, models and proposals for future research. ICI-RS 2013. *Neurourology and Urodynamics* 2014;33:591-596.
56. Schroder A, Chichester P, Kogan BA, Longhurst PA, Lieb J, Das AK, Levin RM. Effect of chronic bladder outlet obstruction on blood flow of the rabbit bladder. *Journal of Urology* 2001;165:640-646.
57. Levin RM, Longhurst PA, Barasha B, McGuire EJ, Elbadawi A, Wein A. Studies on experimental bladder outlet obstruction in the cat: long-term functional effects. Journal of Urology 1992;148:939-943.
58. Levin RM, Schuler C, Leggett RE, Callaghan C, Maknuru S. Partial outlet obstruction in rabbits: duration versus severity. *International Journal of Urology* 2013;20:107-114.
59. Levin RM, Haugaard N, O'Connor L, Buttyan R, Das A, Dixon JS, Gosling JA. Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: a direct comparison. *Neurourology and Urodynamics* 2000;19:609-629.
60. Hill SR, Fayyad AM, Jones GR. Diabetes mellitus and female lower urinary tract symptoms: a review. Neurourology and Urodynamics 2008;27:362-367.
61. Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: current translational knowledge. *Journal of Urology* 2009;182:S18-26.
62. Xiao N, Wang Z, Huang Y, Daneshgari F, Liu G. Roles of polyuria and hyperglycaemia in bladder dysfunction in diabetes. *Journal of Urology* 2013;189:1130-1136.
63. Christ GJ, Hsieh Y, Zhao W, Schenk G, Venkateswarlu K, Wang HZ, Tar MT, Melman A. Effects of streptozotocin-induced diabetes on bladder and erectile (dys)function in the same rat in vivo. *British Journal of Urology International* 2006;97:1076-1082.
64. Wang Y, Tar MT, Fu S, Melman A, Davies KP. Diabetes attenuates urothelial modulation of detrusor contractility and spontaneous activity. *International Journal of Urology* 2014;21:1059-1064.
65. Daneshgari F, Moore C. Diabetic uropathy. *Seminars in Nephrology* 2006;26:182-185.
66. Frimodt-Moller C. Diabetic cystopathy. A review of the urodynamic and clinical features of neurogenic bladder dysfunction in diabetes mellitus. *Danish Medical Bulletin* 1978;25:49-60.
67. Frimodt-Moller C. Diabetic cystopathy: epidemiology and related disorders. *Annals of Internal Medicine* 1980;92:318-321.
68. Frimodt-Moller C, Mortensen S. Treatment of diabetic cystopathy. *Annals of Internal Medicine* 1980;92:327-328.
69. Watanabe T, Miyagawa I. Characteristics of detrusor contractility during micturition in diabetics. *Neurourology and Urodynamics* 1999;18:163-171.
70. Kirschner-Hermanns R, Daneshgari F, Vahabi B, Birder L, Oelke M, Chacko S. Does diabetes mellitus-induced bladder remodeling affect lower urinary tract function?: ICI-RS 2011. *Neurourology and Urodynamics* 2012;31:359-364.
71. Changxiao H, Zhengyong Y, Shibing Y, Caiwen W, Yingchuan H, Wei H, Hanhui W, Dong L, Peng H, Jing L, Rui Z, Hong S. Clinical and urodynamic evaluation of women referred with diabetes mellitus. *International Urogynaecology Journal* 2014;25:979-983.
72. de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B, Genulf. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Multiple Sclerosis* 2007;13:915-928.
73. Sakakibara R, Uchiyama T, Yamanishi T, Shirai K, Hattori T. Bladder and bowel dysfunction in Parkinson's disease. *Journal of Neural Transmission* 2008;115:443-460.
74. Kim M, Jung JH, Park J, Son H, Jeong SJ, Oh SJ, Cho SY. Impaired detrusor contractility is the pathognomonic urodynamic finding of multiple system atrophy compared to idiopathic Parkinson's disease. *Parkinsonism Related Disorders* 2015;21:205-210.

75. Bloch F, Pichon B, Bonnet AM, Pichon J, Vidailhet M, Roze E, Perrigot M. Urodynamic analysis in multiple system atrophy: characterisation of detrusor-sphincter dyssynergia. *Journal of Neurology* 2010;257:1986-1991.
76. Young JS, Johnston L, Soubrane C, McCloskey KD, McMurray G, Eccles R, Fry CH. The passive and active contractile properties of the neurogenic, underactive bladder. *British Journal of Urology International* 2013;111:355-361.
77. Ruggieri MR, Braverman AS, D'Andrea L, Betz R, Barbe MF. Functional reinnervation of the canine bladder after spinal root transection and genitofemoral nerve transfer at one and three months after denervation. *Journal of Neurotrauma* 2008;25:401-409.
78. Xiao CG. Reinnervation for neurogenic bladder: historic review and introduction of a somatic-autonomic reflex pathway procedure for patients with spinal cord injury or spina bifida. *European Urology* 2006;49:22-28.
79. Malone L, Schuler C, Leggett RE, Levin RM. The effect of in vitro oxidative stress on the female rabbit bladder contractile response and antioxidant levels. *ISRN Urology* 2013;639685.
80. Radu F, Leggett RE, Schuler C, Levin RM. The effect of antioxidants on the response of the rabbit urinary bladder to in vitro ischemia/reperfusion. *Molecular Cell Biochemistry* 2011;355:65-73.
81. Oka M, Fukui T, Ueda M, Tagaya M, Oyama T, Tanaka M. Suppression of bladder oxidative stress and inflammation by a phytotherapeutic agent in a rat model of partial bladder outlet obstruction. *Journal of Urology* 2009;182:382-390.
82. Boschen MJ. Paruresis (psychogenic inhibition of micturition): cognitive behavioral formulation and treatment. *Depression and Anxiety* 2008;25:903-912.
83. Soifer S, Nicaise G, Chancellor M, Gordon D. Paruresis or shy bladder syndrome: an unknown urologic malady? *Urologic Nursing* 2009;29:87-93.
84. van Koeveringe GA, Rahnama'i MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. *British Journal of Urology International* 2010;105:508-513.
85. Rademakers KLJ, Drossaerts JM, Rahnama'i MS, van Koeveringe GA. Differentiation of lower urinary tract dysfunctions: The role of ambulatory urodynamic monitoring. *International Journal of Urology* 2015;22:503-507.
86. Vrijens D, Drossaerts JMAJ, van Koeveringe GA, Van Kerrebroeck PE, van Os J, Leue C. Affective symptoms and the overactive bladder - A systematic review. *Journal of Psychosomatic Research* 2015;78:95-108.
87. De Wachter SG, Heeringa R, van Koeveringe GA, Gillespie JI. On the nature of bladder sensation: the concept of sensory modulation. *Neurourology and Urodynamics* 2011;30:1220-1226.
88. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, Oelke M, Tikkinen KA, Gravas S. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European Urology* 2015;67:1099-1109.
89. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE, Gonzalez CM, Kaplan SA, Penson DF, Ulchaker JC, Wei JT. Update on AUA guideline on the management of benign prostatic hyperplasia. *Journal of Urology* 2011;185:1793-1803.
90. Clement KD, Burden H, Warren K, Lapitan MC, Omar MI, Drake MJ. Invasive urodynamic studies for the management of lower urinary tract symptoms (LUTS) in men with voiding dysfunction. *The Cochrane database of Systematic Reviews* 2015;4:CD011179.
91. Rademakers KLJ, Constantinou C, Fry C, Kirschner-Hermanns R, Oelke M, Parsons B, Nelson P, Valentini F, Gammie A. Recommendations for Future Development of Contractility and Obstruction Nomograms for Women. ICI-RS 2014. *Neurourology and Urodynamics* 2015;35:307-311.

92. Griffiths DJ. The mechanics of the urethra and of micturition. *British Journal of Urology International* 1973;45:497-507.
93. Griffiths DJ. Assessment of detrusor contraction strength or contractility. *Neurourology and Urodynamics* 1991;10:1-18.
94. Griffiths DJ, Constantinou CE, van Mastrigt R. Urinary bladder function and its control in healthy females. *American Journal of Physiology* 1986;251:225-230.
95. Schafer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. *World Journal of Urology* 1995;13:47-58.
96. Schafer W. Editorial comment to Spangberg et al. *Neurourology and Urodynamics* 1989;8:44-50.
97. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *British Journal of Urology International* 1999;84:14-15.
98. Elliott CS, Comiter CV. Maximum isometric detrusor pressure to measure bladder strength in men with postprostatectomy incontinence. *Urology* 2012;80:1111-1115.
99. Kielb SJ, Clemens JQ. Comprehensive urodynamics evaluation of 146 men with incontinence after radical prostatectomy. *Urology* 2005;66:392-396.
100. Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. *Journal of Urology* 2000;163:1767-1770.
101. Griffiths D, van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. *Neurourology and Urodynamics* 1989;8:17-27.
102. Griffiths D. Detrusor contractility - order out of chaos. *Scandinavian Journal of Urology and Nephrology Supplements* 2004;215:93-100.
103. Tan TL, Bergmann MA, Griffiths D, Resnick NM. Stop test or pressure-flow study? Measuring detrusor contractility in older females. *Neurourology and Urodynamics* 2004;23:184-189.
104. Brown ET, Cohn JA, Kaufman MR, Dmochowski RR, Reynolds WS. Phenotyping women with detrusor underactivity by presumed aetiology: Is it plausible? *Neurourology and Urodynamics* 2016 [Epub ahead of print]
105. Malde S, Nambiar AK, Umbach R, Lam TB, Bach T, Bachmann A, Drake MJ, Gacci M, Gratzke C, Madersbacher S, Mamoulakis C, Tikkinen KA, Gravas S. Systematic review of the performance of noninvasive tests in diagnosing bladder outlet obstruction in men with lower urinary tract symptoms. *European Urology* 2017;71:391-402.
106. Rademakers KLJ, van Koeveringe GA, Oelke M. Detrusor underactivity in men with lower urinary tract symptoms/benign prostatic obstruction: characterisation and potential impact on indications for surgical treatment of the prostate. *Current Opinion in Urology* 2016;26:3-10.
107. Bolinger R, Engberg S. Barriers, complications, adherence, and self-reported quality of life for people using clean intermittent catheterisation. *Journal of Wound Ostomy & Continence Nursing* 2013;40:83-89.
108. Zhang Z, Liao L. Risk factors predicting upper urinary tract deterioration in patients with spinal cord injury: a prospective study. *Spinal Cord* 2014;52:468-471.
109. Ladi-Seyedian S, Kajbafzadeh AM, Sharifi-Rad L, Shadgan B, Fan E. Management of non-neuropathic underactive bladder in children with voiding dysfunction by animated biofeedback: a randomized clinical trial. *Urology* 2015;85:205-210.
110. Barendrecht MM, Oelke M, Laguna MP, Michel MC. Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? *British Journal of Urology International* 2007;99:749-752.

111. Andersson KE, Wein A. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. *Pharmacology Reviews* 2004;56:581-631.
112. Tatemichi S, Tsuchioka K, Yonekubo S, Maruyama K, Kobayashi M. Effects of Silodosin, an alpha-adrenoceptor antagonist, and distigmine, an acetylcholinesterase inhibitor, and their combined effects on impaired voiding function in Zucker diabetic fatty rats. *Pharmacology* 2015;95:285-292.
113. Sekido N, Kida J, Mashimo H, Wakamatsu D, Okada H, Matsuya H. Promising effects of a novel EP2 and EP3 receptor dual agonist, ONO-8055, on neurogenic underactive bladder in a rat lumbar canal stenosis model. *Journal of Urology* 2016;196:609-616.
114. Matsuya H, Otsuki T, Kida J, Wakamatsu D, Okada H, Sekido N. PD7-01 ONO-8055, a novel and potent prostanoid EP2 and EP3 receptor dual agonist, improves voiding dysfunction in a monkey underactive bladder model. *Journal of Urology* 2015;193:e184-185.
115. Chapple C, Bruce M, Ohno T, Kuwayama T, Deacon S. MP21-07 safety, tolerability and pharmacokinetics of single and multiple ascending doses of the EP2/EP3 receptor agonist ONO-8055, a potential new therapy for underactive bladder, in healthy subjects. *Journal of Urology* 2015;4:e235.
116. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama a Nijholt AA, Siegel S, Jonas U, Fowler CJ, Fall M, Gajewski JB, Hassouna MM, Cappellano F, Elhilali MM, Milam DF, Das AK, Dijkema HE, van den Hombergh U. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *Journal of Urology* 2007;178:2029-2034.
117. Drossaerts JM, Rademakers KLJ, van Koeveringe GA, Van Kerrebroeck PE. The value of urodynamic tools to guide patient selection in sacral neuromodulation. *World Journal of Urology* 2015;33:1889-1895.
118. Vandoninck V, van Balken MR, Finazzi Agrò E, Heesakkers JP, Debruyne FM, Kiemeney LA, Bemelmans BL. Posterior tibial nerve stimulation in the treatment of voiding dysfunction: urodynamic data. *Neurourology and Urodynamics* 2004;23:246-251.
119. Wein A. Posterior Tibial Nerve Stimulation in the Treatment of Voiding Dysfunction: Urodynamic Data. *Journal of Urology* 2005;174:1008.
120. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction. *British Journal of Urology International* 2005;96:1301-1306.
121. Van Mastrigt R, Rollema HJ. The prognostic value of bladder contractility in transurethral resection of the prostate. *Journal of Urology* 1992;148:1856-1860.
122. Mitchell CR, Mynderse LA, Lightner DJ, Husmann DA, Krambeck AE. Efficacy of holmium laser enucleation of the prostate in patients with non-neurogenic impaired bladder contractility: results of a prospective trial. *Urology* 2014;83:428-432.
123. Jhang JF, Jiang YH, Lee CL, Kuo HC. Long-term follow up and predictive factors for successful outcome of transurethral incision of the bladder neck in women with detrusor underactivity. *Journal of the Formosan Medical Association* 2016;115:807-813.
124. Jhang JF, Jiang YH, Kuo HC. Transurethral incision of the bladder neck improves voiding efficiency in female patients with detrusor underactivity. *International Urogynaecology Journal* 2014;25:671-676.
125. Perlmutter AD. Reduction cystoplasty in prune belly syndrome. *Journal of Urology* 1976;116:356-362.
126. Bukowski TP, Perlmutter AD. Reduction cystoplasty in the prune belly syndrome: a long-term followup. *Journal of Urology* 1994;152:2113-2116.
127. Kinn AC. The lazy bladder - appraisal of surgical reduction. *Scandinavian Journal of Urology and Nephrology* 1985;19:93-99.

128. Thorner DA, Blaivas JG, Tsui JF, Kashan MY, Weinberger JM, Weiss JP. Outcomes of reduction cystoplasty in men with impaired detrusor contractility. *Urology* 2014;83:882-886.
129. Ginsberg DA. Bladder acontractility: detrusor myoplasty and other options. *Nature Reviews Urology* 2011;8:185-186.

Section II

Research and Publications

Chapter 1

Differentiation of Lower Urinary Tract Dysfunctions: The Role of Ambulatory Urodynamic Monitoring

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Abstract

II.1

Objectives

To determine the value of ambulatory urodynamic monitoring in the assessment of patients with lower urinary tract symptoms.

Methods

This was a cross-sectional study including patients who underwent both conventional urodynamic and ambulatory urodynamic assessment at our centre between December 2002 and February 2013. The ambulatory urodynamic studies were interpreted in a standardised way by a resident experienced with urodynamic measurements, and one staff member who specialised in incontinence and urodynamics.

Results

A total of 239 patients (71 male and 168 female) were included in the present study. The largest subgroup of patients, 79 (33%), underwent ambulatory urodynamic monitoring based on suspicion of an acontractile bladder. However, 66 of these patients (83.5%) still showed contractions on ambulatory urodynamics. Other groups that were analysed were patients with suspected storage dysfunction (47 patients), inconclusive conventional urodynamic studies (68 patients) and incontinence of unclear origin (45 patients). Particularly in this last group, ambulatory urodynamics appeared to be useful for discrimination between different causes of incontinence.

Conclusions

Ambulatory urodynamic monitoring is a valuable discriminating diagnostic tool in patients with lower urinary tract symptoms who have already undergone conventional urodynamics, particularly in the case of patients with suspected bladder acontractility and incontinence of unclear origin during ambulatory urodynamics. Further study is required to determine the clinical implications of the findings and their relationship with treatment outcome.

2.1.1 Introduction

Urodynamic investigations are an important tool in the diagnostic route of patients with lower urinary tract dysfunction. Apart from the generally used conventional urodynamic study (conventional-UDS), certain centres carry out ambulatory-UDS additionally for specific indications.

In contrast to conventional-UDS, in which artificial filling is used, ambulatory urodynamic monitoring is based on diuresis-induced natural filling of the bladder[1]. Natural (orthograde) fill cystometry was described for the first time in 1957 by Comarr[2] and the technique has evolved ever since[1,3,4]. At present, ambulatory-UDS is a reliable and well tolerated cystometry tool overcoming certain arguments that exist against conventional-UDS, such as inadequate representation of normal filling[5]. In addition, ambulatory-UDS is particularly valuable in recording the bladder filling and voiding phase, combined with the amount and timing of UI in a near-normal situation[6-10]. This makes it a useful tool in patients with troublesome urinary tract symptoms[1]. Despite the advantages of ambulatory-UDS, conventional-UDS is the "gold standard" for investigation of lower urinary tract symptoms, as it is a highly standardised and validated measurement tool[11]. Validation of the ambulatory urodynamic monitoring to its gold standard has proven to be difficult, and studies comparing ambulatory urodynamics with patients' treatment outcomes have not been described yet.

Several studies already showed that ambulatory-UDS results in a more frequent detection of storage dysfunctions, such as detrusor overactivity (DO), compared with conventional-UDS[4,12,13]. However, the additional value of ambulatory-UDS with respect to other storage dysfunctions (e.g. mixed urinary incontinence, UI) and voiding dysfunctions (e.g. suspected bladder acontractility) is less clear. Therefore, the primary objective of the present study was to determine the diagnostic value of ambulatory-UDS in different lower urinary tract dysfunctions using a large cohort of patients who underwent both conventional- and ambulatory-UDS.

2.1.2 Methods

The present study was designed as a cross-sectional study. Between December 2002 and February 2013, a total of 239 patients with urinary tract complaints were included consecutively in the ambulatory-UDS database. In all patients, a conventional- and ambulatory-UDS was carried out during diagnostic work-up. Conventional urodynamic studies were carried out in line with the ICS-Good Urodynamic Practices standards[11]. Ambulatory urodynamic monitoring was carried out for different reasons. First, in case of overactive bladder (OAB) complaints without DO on conventional-UDS. Second, in case patients were suspected to suffer from bladder acontractility based on history and conventional-UDS. Third, in case of a history of stress or urge incontinence without additional clinical or urodynamic evidence and in patients, with mixed UI in which the timing

of urine loss and/or the predominant cause of incontinence was not clear. Repeatedly inconclusive or poor quality (as a result of artefacts) conventional-UDS was a fourth reason for carrying out ambulatory-UDS.

Results of the ambulatory-UDS were interpreted by a resident experienced in judging urodynamic measurements, and one staff member who specialised in incontinence and urodynamics from Maastricht University Medical Centre, Maastricht, The Netherlands. Bladder acontractility was defined as a bladder filling and micturition phase without detrusor pressure rise. Patients were only indicated as "suspected for bladder acontractility" in case they were unable to void during free uroflowmetry, or voided with significant post-void residual urine. Hypocontractility was defined as a low detrusor contraction pressure (less than 10 cm H2O) during the voiding phase, relative to the degree of obstruction, not resulting in (efficient) micturition during urodynamic assessment. For the present study, urodynamic results were not solely analysed, but medical history data (i.e. previous surgery, comorbidity and current medication) of these patients were also taken into consideration.

2.1.2.1 Ambulatory urodynamic monitoring

At our urological referral university clinic, ambulatory-UDS is only used as a second-line diagnostic tool. In addition, it is only carried out if indicated based on a previously carried out conventional pressure-flow analysis and clinical necessity. Typically, an ambulatory urodynamic monitoring study takes on average approximately 5-7 hours, during which patients are assumed to take part in normal daily activities[8]. In patients with nocturia, a 12-hour ambulatory-UDS during night-time can be used to determine the underlying condition.

Patients discontinue anticholinergic medication at least 5 days before the urodynamic assessment. Ten days before ambulatory-UDS, the patients' urine is cultured. In case of bacteriuria, focused antibiotic treatment is implemented after which the recovery of the bacteriuria is confirmed before the ambulatory-UDS is started. To start ambulatory urodynamic monitoring, two Uni-sensor micro-tip catheters are inserted (Medical Measurement Systems, Enschede, The Netherlands). One catheter is inserted in the rectum to record abdominal pressure differences. The other catheter containing a double-pressure sensor, combined with a conductance sensor, is inserted through the urethra. The distal pressure sensor lies in the bladder, close to the bladder neck, and the proximal measurement sensor is located in the region with the highest urethral pressure. This way the bladder and urethral pressure are measured accurately, and leakage is registered using a conductance sensor.

The ambulatory recording device contains several event buttons. Patients are instructed to use these buttons at specific events; that is, in case of urgency, a toilet visit, drinking or involuntary leakage of urine. These events are registered at the ambulatory-UDS timeline in parallel. Registration of events, together with the voiding diary and pad test are essential for interpretation of the ambulatory-UDS. If the patient carries out CISC, an additional 8-French catheter is inserted in the urethra during the assessment. Post-voiding residual urine is drained after every voiding attempt in case of incomplete voiding.

2.1.2.2 Statistical analysis

Quantitative data are given as a mean with standard deviation (SD). Other results are presented in frequency tables. The data were collected in an Excel spread sheet, and statistical analyses were performed using IBM SPSS statistics software, version 20 (IBM, Armonk, NY, USA).

2.1.3 Results

The mean age for the 239 patients was 58 years (SD 13.1) in men and 51 years (SD 12.7) in women. Other patient characteristics are shown in Table 1. The mean duration of the ambulatory-UDS was 5.6 hours (SD 2.2). During ambulatory urodynamic monitoring, the mean drinking volume was 1371ml (SD 610). The mean urine production was 827ml (SD 559) with a micturition frequency of 4 (SD 2.9) times during the measurement. The frequency of UI episodes was 2.9, with a mean volume of leakage of 97 gram (SD 254.6), based on the pad test. In the next sections, the specific storage and voiding LUTS indications for ambulatory-UDS are highlighted.

2.1.3.1 Storage dysfunction as an indication for ambulatory-UDS: Suspected detrusor overactivity

A total of 47 patients (19.7%) included in the present study suffered from OAB, as defined by the ICS. To objectify their complaints, they underwent a conventional-UDS and a consecutive ambulatory-UDS. In 29 (61.7%) patients, involuntary detrusor contractions (IDC) during the filling phase were confirmed, where conventional-UDS did not show any IDC, as shown in Table 2. The mean IDC frequency was 7 (6.1), with a mean (SD) maximum contraction amplitude of 129 cm H_2O (66.6 cm H_2O). Seven patients suspected for DO showed mixed UI on ambulatory-UDS, with dominant stress UI in two of these patients. In one patient, solely stress UI was objectified. In 10 (21.2%) patients with OAB, ambulatory-UDS showed a normal micturition without confirmation of IDC.

Table 1. Characteristics of patients undergoing ambulatory urodynamic study.

Patient characteristics	No. patients
Sex (male/female)	71 / 168
Previous history of	
Hysterectomy	49
Urethral suspension operation for UI	42
Prostate operation	24
Hernia nuclei pulposi	14
Diabetes	10
Cerebrovascular accident	1
Medication before conventional-/ambulatory-UDS	
5α-Reductase inhibitors	3
α-Blockage	10
Anticholinergics	26
Para-sympathicomimetics	4
Prostaglandin E_1 inhibitors	7
Antidepressives	15

UI: Urinary incontinence, Conventional-UDS: Conventional urodynamic study, Ambulatory-UDS: Ambulatory urodynamic study

2.1.3.2 Voiding dysfunction as an indication for ambulatory-UDS: Suspected bladder acontractility

In this heterogeneous patient group, the largest subgroup of patients underwent an ambulatory-UDS with the suspicion of bladder acontractility based on conventional urodynamics. In 79 patients (33.0%), an ambulatory-UDS was carried out for this indication. In 13 (16.5%) patients, the diagnosis of acontractile bladder was confirmed (Table 2). The other 66 (83.5%) patients with suspected bladder acontractility showed contractions on ambulatory-UDS. The largest group, 34 (43.0%) patients, had multiple IDC during the filling phase on ambulatory-UDS, with a mean (SD) amplitude of 112 cm H_2O (47.0 cm H_2O) and mean (SD) frequency of 8 (6.8).

Based on the maximum detrusor pressure combined with the initial symptom presentation, a small portion of the patients (12 patients, 15%) was defined as having a hypocontractile rather than acontractile bladder. These patients had a mean (SD) maximum detrusor pressure amplitude of 52 cm H_2O (35.8 cm H_2O). A total of 16 of the 79 patients in this group showed a normal micturition contractile response on ambulatory-UDS without IDC.

In three of the four patients remaining in this group, patients' ambulatory-UDS showed mixed incontinence, of which two patients had predominant stress UI and one had primarily filling phase contractions with subsequent loss of urine. In one young female patient, ambulatory urodynamic monitoring showed high urethral pressures throughout the assessment, with the suspicion of Fowler's syndrome.

2.1.3.3 Incontinence as an indication for ambulatory-UDS

A total of 26 patients with alleged mixed incontinence were included in this database. In 16 of these patients, only IDC were seen on ambulatory-UDS, with a mean (SD) amplitude of 103 cm H_2O (35.1 cm H_2O) and mean (SD) frequency of 9 (5.8). In three patients, only stress UI was objectified. Mixed UI with predominantly IDC was found in two patients, and mixed UI with predominant stress UI in one patient. The remaining four patients showed no IDC or stress-induced UI on ambulatory-UDS.

A total of seven patients with potentially isolated stress UI underwent an ambulatory urodynamic assessment. In four (57.1%) of the patients, stress UI was confirmed in the absence of IDC. In the other three patients, ambulatory-UDS showed a normal filling and micturition phase.

Additional ambulatory-UDS was carried out in 12 patients with urgency, suspicious for urge incontinence. Seven (58.3%) of these patients had IDC during ambulatory urodynamics. The other five (41.7%) patients showed no abnormalities on their ambulatory-UDS recordings.

2.1.3.4 Inconclusive conventional-UDS as an indication for ambulatory-UDS

The second largest group (28.5%) undergoing ambulatory-UDS consisted of patients with an inconclusive conventional-UDS or one of poor quality. In 68 of these cases ambulatory urodynamics was carried out and data were included in the present study. Involuntary detrusor contractions during the filling phase were found in the majority of these patients (63.2%), with a mean (SD) maximum amplitude of 106 cm H_2O (57.6 cm H_2O) and a mean (SD) contraction frequency of 6 (5.1).

In three patients, solely stress UI was found during ambulatory-UDS, and in four patients mixed UI with predominantly stress UI was seen. Two patients appeared to have a hypocontractile bladder during ambulatory urodynamic monitoring, which was not seen on conventional-UDS. In 23.5% of the cases with inconclusive conventional-UDS, ambulatory-UDS showed a normal bladder filling and micturition phase.

Table 2. Diagnosis after ambulatory urodynamic assessment given for each indication.

	Diagnosis after ambulatory-UDS					
	Acontractile bladder	Hypocontractile bladder	IDC	Other	Normal ambulatory-UDS	Total no. pts (% of total)
Indication ambulatory-UDS						
Suspected DO	0	0	29	8	10	47 (19.7)
Suspected acontractile bladder	13	12	34	4	16	79 (33.0)
Inconclusive conventional-UDS	0	2	43	7	16	68 (28.5)
Incontinence	0	0	23	10	12	45 (18.8)
Total no. pts (% of total)	13 (5.4)	14 (5.9)	129 (54.0)	29 (12.1)	54 (22.6)	239 (100)

Bladder acontractility: bladder filling and micturition phase without detrusor pressure rise, Bladder hypocontractility: a low detrusor contraction pressure not resulting efficient micturition during urodynamic assessment.

2.1.4 Discussion

Although relatively elaborate to carry out and to analyse, ambulatory-UDS is thought to be a more accurate tool for diagnosing LUT dysfunctions in both children and adults[14,15]. In case of DO, ambulatory-UDS is reported to have a higher sensitivity compared with conventional-UDS[6]. After conventional-UDS, 47 (19.7%) patients were thought to have involuntary detrusor contractions during the filling phase. However, ambulatory-UDS showed involuntary contractions in 129 (54.0%) patients. Therefore, the results from the present study are in line with the available literature. The difference in observations between both assessment types could be explained by the technique used. The retrograde, rapid bladder filling and the shorter timespan of conventional urodynamics could very well lead to an underestimation of involuntary detrusor contractions. However, it cannot be excluded that the vesical catheter itself is a non-physiological trigger resulting in a higher incidence of detrusor overactivity during ambulatory urodynamics[16]. In addition, a previous study in healthy female volunteers showed IDC on ambulatory-UDS in 68% of the cases, compared with 18% after conventional-UDS[17]. In healthy male volunteers, IDC were also found during ambulatory urodynamics[18].

There still remains a great deal of controversy with regard to the clinical implications of urodynamics in OAB patients[19]. Giarenis *et al.* recently showed that women with OAB and additional DO on conventional- or ambulatory-UDS experience more significant impairment to their quality of life and have a greater degree of bladder dysfunction compared to OAB patients without DO during urodynamic assessment[20]. A study of OAB patients treated

with sacral neuromodulation described a correlation between reduction in IDC and clinical outcome after treatment[21]. Comparable findings were found in neurogenic DO patients after treatment with onabotulinumtoxinA[22]. However, the results after intradetrusor injections of onabotulinumtoxinA appear not to be predicted by the presence of DO during pre-treatment conventional-UDS in idiopathic OAB patients[23].

Ambulatory-UDS is used in our centre in the specific group of treatment refractory OAB patients without DO on conventional-UDS. The fact that the bladder produces involuntary detrusor contractions in response to the small flexible catheters during an ambulatory urodynamic measurement itself might indicate a higher excitability of the bladder sensory function or a decreased central inhibition of the urethra-detrusor facilitative reflex contractions in the filling phase[24]. This might even serve as a biomarker of pathology. To accomplish this, quantification and characterisation of IDC on ambulatory-UDS is necessary. At present, there is an ongoing study from our centre regarding the use of ambulatory-UDS in these patients and the effect of treatment with sacral neuromodulation. In the near future, this might support the use of ambulatory-UDS in differentiation of OAB patients into responders and non-responders to treatment.

Based on the small data sample of patients with incontinence of unclear origin in the present study, we see a slight trend that ambulatory-UDS might be a useful tool in patients with mixed UI and unclear predominant origin of the incontinence. This is a small subgroup of patients, which, at present has not been described in the literature in relation to ambulatory urodynamics. The role of ambulatory-UDS in this subgroup of patients requires further investigation in a prospective setting in which ambulatory-UDS results are related to treatment choice, treatment success rate and patient satisfaction.

The present results show that lower urinary tract dysfunctions that are missed or misdiagnosed in a conventional-UDS could be diagnosed accurately in ambulatory-UDS. However, because of the complexity of the ambulatory-UDS, the time consuming interpretation of the results and the expertise required, ambulatory-UDS is usually not the first choice to diagnose any LUT dysfunctions. Therefore, it should be considered only for certain indications where conventional-UDS has been carried out and has not been able to show the correct diagnosis.

Bladder acontractility is characterised by an inability to empty the bladder completely, without a visible contraction on cystometry. Clinically these patients present themselves with the inability to void to completion and/or with recurrent UTI or urinary retention. Bladder acontractility can be caused by dysfunction at various levels in the brain-bladder axis, from damage to the detrusor muscle itself, its autonomic nerve supply to dysfunction at the spinal level. In addition, the pontine micturition centre can be damaged or even a defect in cortical functions leading to an inability to relax adequately can cause an inhibition of a (persistent) bladder contraction.

Bladder acontractility represents a heterogeneous urological entity and the aetiological variety forces us to search for different therapeutic approaches. However, a first step in this process is finding the most optimal diagnostic tool in diagnosing true bladder acontractility.

The present study, consisting of a cohort of patients undergoing ambulatory-UDS, showed that just 16.5% of the patients with suspected bladder acontractility indeed showed no contraction on ambulatory-UDS. In all other cases, either a minimal or normal micturition contraction was seen, with or without simultaneous storage dysfunction present on ambulatory-UDS (Table 2). The group marked as having a hypocontractile, instead of an acontractile, bladder showed a mean maximum detrusor pressure amplitude of 52 cm H_2O. Although this seems acceptable, in these cases the detrusor pressures appeared to be too low to overcome the urethral resistance, resulting in inefficient voiding in these cases. Possibly, a bladder outlet obstruction component was involved in at least some of these patients. The present study confirms earlier preliminary results from a retrospective study carried out in our centre, pointing out the value of ambulatory-UDS in differentiating LUTS aetiology[8].

Current treatment options for restoring voiding effectiveness in patients with complete ambulatory-UDS confirmed bladder acontractility are limited. Bladder and sphincter reflex modulation techniques, such as sacral neuromodulation, can only be used in case there is little or no damage to the brain-bladder axis in combination with intact function of the detrusor contractile apparatus. Therefore, in the right selection of patients (with at least some contractile function present on ambulatory-UDS), this therapeutic option can be effective[25,26]. Furthermore, a reconstructive surgical procedure, such as latissimus dorsi detrusor myoplasty, is only feasible in a highly selected group of patients with an acontractile bladder[27]. This means that the majority of patients are left with no other options than carrying out life-long CISC[28].

In order to increase the success rate of the invasive, limited and expensive therapeutic options, such as sacral neuromodulation, there is a need for a valid diagnostic tool in patients with suspected bladder acontractility. The present data show that conventional-UDS is not an accurate test in confirming true bladder acontractility. In fact, in over 80% of the cases, ambulatory-UDS led to a different conclusion compared with conventional-UDS. Therefore, in case of no detrusor contractions on conventional-UDS, an ambulatory urodynamic assessment should be carried out to confirm or exclude true bladder acontractility.

In the near future, several novel treatment options are expected, for treatment of either decreased contractile strength or inadequate coordination between urethral relaxation and detrusor contraction[29]. Hence, ambulatory-UDS is expected to gain a more prominent role in the diagnostic algorithm for detrusor underactivity and the differentiation of this entity from true bladder acontractility[30].

2.1.5 Conclusion

The present results show that ambulatory urodynamic monitoring is a valuable discriminating diagnostic tool in patients with various lower urinary tract complaints, particularly in patient with suspected bladder acontractility. In addition, ambulatory-UDS might be a useful tool to distinguish the predominant cause of incontinence in patients with an unclear origin of incontinence. In order to confirm the clinical significance of these findings during the ambulatory urodynamic measurement, a future study is required to relate these results to treatment outcome and to further validate the technique.

References

1. van Waalwijk van Doorn E, Anders K, Khullar V, Kulseng-Hanssen S, Pesce F, Robertson A, Rosario D, Schäfer W. Standardisation of ambulatory urodynamic monitoring: Report of the Standardisation Sub-Committee of the International Continence Society for Ambulatory Urodynamic Studies. *Neurourology and Urodynamics* 2000;19:113–125.
2. Comarr AE. Excretory cystometry: a more physiologic method. *Journal of Urology* 1957;77:622–633.
3. van Waalwijk van Doorn ES, Meier AH, Ambergen AW, Janknegt RA. Ambulatory urodynamics: extramural testing of the lower and upper urinary tract by Holter monitoring of cystometrogram, uroflowmetry, and renal pelvic pressures. *Urologic Clinics of North America* 1996;23:345–371.
4. van Waalwijk van Doorn ES, Remmers A, Janknegt RA. Extramural ambulatory urodynamic monitoring during natural filling and normal daily activities: evaluation of 100 patients. *Journal of Urology* 1991;146:124–131.
5. Oh SJ, Son H, Jeong JY, Ku JH. Patients' experience with ambulatory urodynamics. A prospective study. Scandinavian *Journal of Urology and Nephrology* 2006;40:391–396.
6. Patravali N. Ambulatory urodynamic monitoring: are we wasting our time? *Journal of Obstetrics and Gynaecology* 2007;27:413–415.
7. Pannek J, Pieper P. Clinical usefulness of ambulatory urodynamics in the diagnosis and treatment of lower urinary tract dysfunction. *Scandinavian Journal of Urology and Nephrology* 2008;42:428–432.
8. van Koeveringe GA, Rahnama'i MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. *British Journal of Urology International* 2010;105:508–513.
9. Webb RJ, Ramsden PD, Neal DE. Ambulatory monitoring and electronic measurement of urinary leakage in the diagnosis of detrusor instability and incontinence. *British Journal of Urology International* 1991;68:148–152.
10. Dokmeci F, Seval M, Gok H. Comparison of ambulatory versus conventional urodynamics in females with urinary incontinence. *Neurourology and Urodynamics* 2010;29:518–521.
11. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, Sterling AM, Zinner NR, van Kerrebroeck PE. Good urodynamic practices: uroflowmetry,filling cystometry, and pressure-flow studies. *Neurourology and Urodynamics* 2002;21:261–274.
12. Porru D, Usai E. Standard and extramural ambulatory urodynamic investigation for the diagnosis of detrusor instability-correlated incontinence and micturition disorders. *Neurourology and Urodynamics* 1994;13:237–242.
13. Artibani W. Diagnosis and significance of idiopathic overactive bladder. *Urology* 1997;50:25–32.
14. Deshpande AV, Craig JC, Caldwell PH, Smith GH. Ambulatory urodynamic studies (UDS) in children using a Bluetooth-enabled device. *British Journal of Urology International* 2012;110:38–45.
15. Virseda M, Salinas J, Esteban M, Mendez S. Reliability of ambulatory urodynamics in patients with spinal cord injuries. *Neurourology and Urodynamics* 2013;32:387–392.
16. Sand PK, Hill RC, Ostergard DR. Incontinence history as a predictor of detrusor stability. *Obstetrics and Gynaecology* 1988;71:257–260.
17. Heslington K, Hilton P. Ambulatory monitoring and conventional cystometry in asymptomatic female volunteers. *British Journal of Obstetrics and Gynaecology* 1996;103;434–441.
18. Schmidt F, Jorgensen TM, Djurhuus JC. Twenty-four-hour ambulatory urodynamics in healthy young men. *Scandinavian Journal of Urology and Nephrology* 2004;38:75–83.

19. Chapple C. Overactive bladder and underactive bladder: a symptom syndrome or urodynamic diagnosis? *Neurourology and Urodynamics* 2013;32:305–307.
20. Giarenis I, Mastoroudes H, Srikrishna S, Robinson D, Cardozo L. Is there a difference between women with or without detrusor overactivity complaining of symptoms of overactive bladder? *British Journal of Urology International* 2013;112:501–507.
21. Scheepens WA, van Koeveringe GA, de Bie RA, Weil EH, van Kerrebroeck PE. Urodynamic results of sacral neuromodulation correlate with subjective improvement in patients with an overactive bladder. *European Urology* 2003;43:282–287.
22. Rovner E, Dmochowski R, Chapple C, Thompson C, Lam W, Haag-Molkenteller C. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. *Neurourology and Urodynamics* 2013;32:1109–1115.
23. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourology and Urodynamics* 2011;30:556–562.
24. Bump RC. The urethrodetrusor facilitative reflex in women: results of urethral perfusion studies. *American Journal of Obstetrics and Gynaecology* 2000;182:794–802.
25. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama á Nijholt AA, Siegel S, Jonas U, Fowler CJ, Fall M, Gajewski JB, Hassouna MM, Cappellano F, Elhilali MM, Milam DF, Das AK, Dijkema HE, van den Hombergh U. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *Journal of Urology* 2007;178:2029–2034.
26. White WM, Dobmeyer-Dittrich C, Klein FA, Wallace LS. Sacral nerve stimulation for treatment of refractory urinary retention: long-term efficacy and durability. *Urology* 2008;71:71–74.
27. van Koeveringe GA, Rademakers KLJ, Stenzl A. Latissimus dorsi detrusor myoplasty to restore voiding in patients with an acontractile bladder - fact or fiction? *Current Urology Reports* 2013;14:426–434.
28. Ginsberg DA. Bladder acontractility: detrusor myoplasty and other options. *Nature Reviews Urology* 2011;8:185–186.
29. van Koeveringe GA, Rademakers KLJ, Birder LA, Korstanje C, Daneshgari F, Ruggieri MR, Igawa Y, Fry C, Wagg A. Detrusor underactivity: Pathophysiological considerations, models and proposals for future research. ICI-RS 2013. *Neurourology and Urodynamics* 2014;33:591–596.
30. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Koelbl H, van Kerrebroeck PE, Wein A. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology* 2014;65:389–398.

Chapter 2

Detrusor Contraction Power Parameters (BCI and Wmax) Rise with Increasing Bladder Outlet Obstruction Grade in Men with Lower Urinary Tract Symptoms: Results from a Urodynamic Database Analysis

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Abstract

Purpose

II.2

To investigate to what extent detrusor work during voiding is influenced by bladder outlet obstruction (BOO) in adult men with lower urinary tract symptoms (LUTS).

Materials and methods

We reviewed data of patients with LUTS suggestive of benign prostatic hyperplasia who received computer-urodynamic investigations as part of their baseline clinical assessment. BOO was defined by the Schäfer classification and detrusor work during voiding was quantified by calculation of the bladder contractility index (BCI) and maximum Watt factor (W_{max}) obtained by pressure-flow analysis.

Results

A total of 786 men with medians of 64 years, IPSS 16 and prostate volume of 35 ml, were included in the study. A total of 462 patients (58.8%) had BOO (Schäfer 2–6). Both detrusor contraction power parameters continuously increased with rising BOO grade. Median BCI increased from 73.3 in Schäfer 0 to 188.0 in Schäfer 6, whereas W_{max} increased from 9.6 to 23.4 W/m^2 ($p < 0.001$). Results of BCI and W_{max} correlated well ($p < 0.001$). With increasing BOO grade, there was a significant decrease of voiding efficiency ($p < 0.001$).

Conclusions

In adult male LUTS patients, detrusor contraction power parameters - BCI and W_{max} - continuously increase with rising BOO grade. According to our results, it is impossible to determine a single threshold value for detrusor contraction power to diagnose detrusor underactivity in a group of LUTS patients with different BOO grades. The study is limited to men with non-neurogenic LUTS. Future studies should evaluate exact threshold values for BCI and W_{max} in BOO subgroups to adequately define detrusor underactivity and investigate men with other bladder conditions.

2.2.1 Introduction

Voiding dysfunction in humans and animals may be caused by bladder outlet obstruction (BOO), detrusor underactivity (DU), dysfunctional voiding, or a combination of these conditions[1]. In experimental animals with BOO, bladder wall (smooth muscle cell) hypertrophy and increase of detrusor contraction power develop quickly after partial ligature of the urethra resulting in complete bladder emptying in the initial and compensated stages despite the presence of BOO[2,3]. Bladder wall hypertrophy, diagnosed by ultrasound measurement of bladder or detrusor wall thickness, has been confirmed in adult men with BOO[4,5]. It has been hypothesised that an increase of bladder/detrusor wall thickness (contractile elements) is responsible for increased detrusor contraction power in these men to maintain voiding in the presence of BOO, similar to animal studies[5,6].

In symptomatic men aged ≥50, pressure-flow studies demonstrate BOO in approximately 60%[7,8], whereas DU, alone or in combination with BOO, is detected in up to 40%[9]. With ageing, voided volume and maximum urinary flow rate (Q_{max}) continuously decrease and post-void residual (PVR) increases[10,11]. The prevalence of BOO appears to be rather constant over different age groups[8,10], while DU increases with ageing[10] and approximately two-thirds of incontinent institutionalised elderly are affected[12]. Due to an increasing life expectancy of the Western societies, an increasing amount of patients with voiding dysfunction and especially DU are expected. Therefore, it appears important to adequately diagnose and differentiate the different types of bladder dysfunctions and to understand the relationship between BOO and DU.

Determination and quantification of BOO, DU, or dysfunctional voiding are currently only possible with pressure-flow analysis. Quantification of urethral resistance and determination of BOO are well established by using data derived from the pressure-flow plot and utilising this information in a nomogram (e.g., ICS[13] or Schäfer nomogram[14]). In contrast, quantification of detrusor work during voiding is less verified[15]. The Watt factor[16], detrusor-adjusted mean PURR factor (DAMPF)[15,17], and bladder contractility index (BCI)[18], a numerical expression of categorical DAMPF, have been suggested for quantifying detrusor contraction power[15]. It remains controversial which algorithm and threshold value should be used for the diagnosis of DU. Urodynamic experts have proposed a maximum Watt factor (W_{max}) ≤7-10 W/m^2 or BCI <100[15,18,19] for the diagnosis of DU, but these threshold values have never been thoroughly investigated. Therefore, the aim of our study was to (1) evaluate the relationship between BOO and W_{max} or BCI in a large sample of unselected men with LUTS, (2) compare these results with published data obtained from experimental animals, and (3) propose threshold values of W_{max} and BCI for the diagnosis of DU.

2.2.2 Materials and methods

2.2.2.1 Patient selection

Unselected, treatment naïve men aged ≥40 with uncomplicated lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) who were evaluated in the department of Urology of the Hannover Medical School in Germany between April 1993 and November 2003 were included in this study. In contrast, men with upper or lower urinary tract complications suspicious of BOO (e.g. bladder stones, bladder diverticula, or urinary retention), men with LUTS after lower urinary tract or pelvic surgery, radiotherapy, neurological diseases, urinary tract infection, bladder cancer, urethral strictures, prostate cancer (PSA >10 µg/l or positive biopsies in cases of a PSA concentration between 4 and 10 µg/l or palpable tumour), prostatitis, or distal ureteral stones were excluded from analysis. Furthermore, all men with drugs (α–blockers or antimuscarinics within the last 4 weeks or 5α-reductase inhibitors within the last 6 months before urodynamic investigation) were also eliminated from the analyses.

One to three weeks after initial presentation, patients returned to the hospital, repeated uroflowmetry, and then underwent urodynamics. PVR was measured by bladder catheterisation before the start of the first measurement. Computer-urodynamic investigation was performed by experienced investigators in line with the ICS-Good Urodynamic Practices standards[20]. A transurethral 6-French double-lumen catheter was placed in the bladder to measure the intravesical pressure and fill the bladder and a 10-French single-lumen catheter was inserted into the rectum to measure the intraabdominal pressure. During cystometry, the patient was positioned in the convenient sitting position and the bladder was filled with sterile physiological saline solution of 37°C with a speed between 25 and 50 ml/min until the patient felt a strong desire to void. Afterwards, the patient voided - according to his normal habit - in the sitting or standing position and pressure-flow measurement was taken. Cystometry and pressure-flow analysis were performed at least in duplicate.

2.2.2.2 Parameters for analyses

The free uroflowmetry measurement - after manual artefact correction - with the highest value for maximum urinary flow rate (Q_{max}) was selected for analysis. The lowest amount of PVR determined by either ultrasound or catheterisation was utilised. Voiding efficiency was calculated by using the selected free uroflowmetry recording and applying the formula:

Voiding efficiency (%) = (voided volume/(voided volume + post-void residual)) × 100

As cystometry and pressure-flow recordings were carried out at least twice during one session, the recording with the lowest BOO grade was used for further analyses. Patients were divided into groups based on the Schäfer nomogram[14]. Accordingly, Schäfer grades 0 + 1 resemble unobstructed bladders, Schäfer grade 2 equivocal BOO, and Schäfer grades 3-6 different BOO grades, ranging from minor to severe. Patients with equivocal BOO were positioned in the BOO group because earlier results with ultrasound detrusor wall thickness measurements suggested that these patients have a significantly thicker detrusor compared to patients without BOO or healthy adult volunteers[5,6]. Detrusor contraction power was determined and quantified by calculation of the bladder contractility index (BCI) by using the formula[18]:

$$BCI = P_{det.Qmax} + 5Q_{max}$$

($P_{det.Qmax}$ = detrusor pressure at maximum urinary flow rate; Q_{max} = maximum urinary flow rate) and maximum Watt factor (W_{max}) provided by the urodynamic machine was calculated, after elimination of measurement artefacts, on the basis of the formula[16]:

$$W = (P_{det} \cdot V_{det} + a \cdot V_{det} + b \cdot P_{det})/2\Delta$$
$$[V_{det} = Q/2(3/(4\Delta) \cdot (V_{ves} + Vt))^{-2/3}]$$

(W = detrusor contraction power; P_{det} = detrusor pressure; V_{det} = contraction speed; V = total bladder volume)

Because both detrusor contraction power parameters (BCI and W_{max}) have not been thoroughly investigated or compared with each other, we used them as independent parameters without preference.

2.2.2.3 Statistical analyses

Median values and their 25 and 75 percentiles were calculated for patients' baseline and measurement parameters. Two measurement values were statistically compared by using the Mann–Whitney U test, and more than two measurement values were statistically compared by applying the Kruskal–Wallis test. For correlation analysis, Spearman's correlation coefficient was used. A p-value ≤ 0.05 was considered significant. The Statistical Package for the Social Sciences (SPSS), version 18 (SPSS Inc, Chicago, IL, USA) was used to perform all statistical analyses.

2.2.3 Results

2.2.3.1 Patient characteristics

A total of 786 patients met the inclusion criteria and were evaluated. Median age of the patients was 64 years, median prostate volume 35 ml, and median IPSS 16. Based on the results of pressure-flow analysis, 324 men (41.2%) had no signs of BOO (Schäfer 0 + 1), whereas 462 patients (58.8%) had a variable degree of BOO (Schäfer 2-6). The patient characteristics and measurement results for all participants are shown in Table 1.

2.2.3.2 Differences between parameters in relation to BOO grades

Patient parameters and the statistical comparison of measurement values of patients with different BOO grades (Schäfer 0–6) are also presented in Table 1. BOO grades were unevenly distributed within the study population; either the absence of BOO or mild BOO was seen in a larger amount of patients than moderate or severe BOO. There was no statistical difference with regard to IPSS between the groups ($p = 0.059$). However, significant differences in age and prostate volume (both $p < 0.001$) were found when comparing different BOO grades.

We saw a continuous and significant decrease with increasing BOO grade when evaluating Q_{max} of free uroflowmetry ($p < 0.001$), voided volume of free uroflowmetry ($p < 0.001$), voiding efficiency ($p < 0.001$), and bladder capacity measured during cystometry ($p < 0.001$). In contrast, we observed a continuous and significant increase with rising BOO grade when evaluating PVR ($p = 0.011$), the presence of detrusor overactivity ($p < 0.001$), BCI ($p < 0.001$), and W_{max} ($p < 0.001$).

2.2.3.3 Detrusor contraction power parameters in relation to different BOO grades

Both detrusor contraction power parameters, BCI and W_{max}, showed a similar pattern characterised by a stepwise increase with rising BOO grade (Table 1; Figure 1). Median BCI values ranged from 73.3 in Schäfer 0 to 188.0 in Schäfer 6, whereas W_{max} values increased from 9.6 W/m^2 in Schäfer 0 to 23.4 W/m^2 in Schäfer 6. All median BCI values for patients with Schäfer grades 0–2 were <100, whereas median W_{max} <7 W/m^2 was not seen in any BOO grade.

The Kruskal–Wallis test showed significant differences of median BCI ($p < 0.001$) and W_{max} values ($p < 0.001$) within the entire group of patients. There was also a significant difference in median BCI or W_{max} values when patients without BOO (Schäfer 0 + 1) were compared with those having BOO in pressure-flow analysis (Schäfer 2–6; $p < 0.001$).

Table 1. Patient's characteristics and measurement results for all patients and for the individual BOO (Schäfer) classes. Variables are presented as medians and 25–75 percentiles, unless otherwise indicated.

		Schäfer grade (n)							
	All patients	**0 (n = 144)**	**1 (n = 180)**	**2 (n = 164)**	**3 (n = 137)**	**4 (n = 129)**	**5 (n = 23)**	**6 (n = 9)**	**p-value ***
Age (years)	64 (57-69)	62 (56-69)	61 (56-67)	62 (56-69)	66 (60-71)	64 (58-69)	66 (62-72)	67 (63-75)	< 0.001
IPSS	16 (10-21)	15 (8-20)	15 (10-20)	15 (10-21)	16 (12-21)	18 (12-23)	17 (11-19)	23 (18-23)	0.059
Prostate volume (ml)	35 (26-48)	30 (22-41)	30 (24-40)	35 (25-46)	40 (30-57)	40 (31-52)	49 (36-71)	35 (20-45)	< 0.001
Free uroflowmetry									
Q_{max} (ml/s)	10.8 (7.5-15.0)	13.0 (8.0-18.7)	13.5 (9.8-18.0)	10.7 (7.6-14.2)	9.7 (7.1-12.9)	8.2 (5.8-11.0)	7.0 (4.8-10.1)	8.7 (5.1-12.1)	< 0.001
Voided volume (ml)	228 (166-334)	249 (178-398)	287 (208-374)	242 (170-336)	197 (157-277)	192 (147-277)	146 (121-201)	211 (148-277)	< 0.001
PVR (ml)	65 (23-145)	59 (16-144)	50 (11-142)	58 (20-124)	70 (40-150)	80 (36-149)	60 (20-150)	101 (91-399)	0.011
Voiding efficiency (%)	79.3 (60.1-91.4)	81.8 (62.8-94.1)	86.9 (67.5-96.4)	79.4 (61.8-91.8)	77.3 (60.7-87.8)	73.7 (54.1-85.7)	65.1 (52.0-85.8)	58.5 (37.3-76.1)	< 0.001
Urodynamic Investigation									
Bladder capacity (ml)	392 (286-542)	456 (299-604)	436 (330-592)	402 (285-556)	336 (275-446)	348 (246-460)	299 (220-406)	271 (155-451)	< 0.001
BOOI	35.0 (18.2-55.1)	6 (-3-15)	20 (14-25)	37 (30-42)	51 (47-57)	75 (67-84)	102 (97-111)	149 (128-168)	< 0.001
Bladder Contractility Index	94.0 (74.1-114.2)	73 (54-98)	82 (67-102)	89 (74-109)	100 (85-114)	115 (103-131)	142 (129-175)	188 (157-201)	< 0.001
W_{max} (W/m^2)	12.9 (9.8-17.2)	9.6 (6.0-12.0)	11.4 (9.0-14.7)	12.6 (9.9-16.0)	15.2 (11.8-18.1)	16.9 (13.3-20.3)	22.5 (20.1-28.2)	23.4 (16.1-29.5)	< 0.001

The p value refers to the Kruskal–Wallis test comparing patient parameters in the different Schäfer classes

IPSS: international prostate symptom score, Q_{max}: maximum urinary flow rate, PVR: post-void residual, BOOI: bladder outlet obstruction index, W_{max}: maximum Watt factor

** Kruskal–Wallis test*

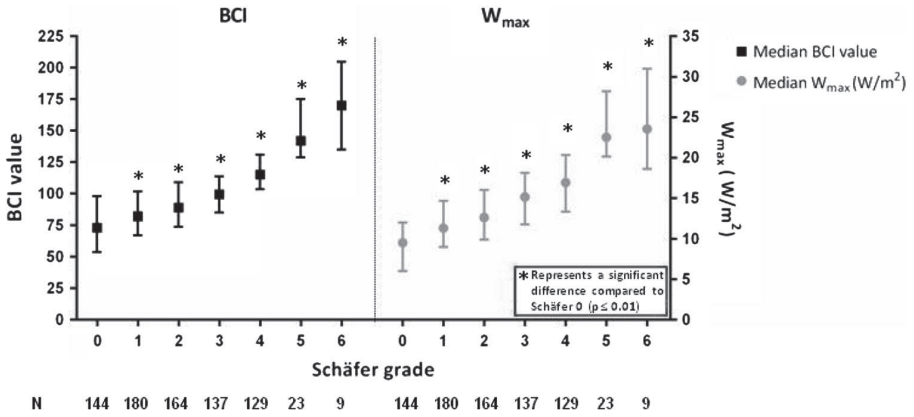

Figure 1. Bladder contractility index (BCI) and maximum Watt factor (W_{max}) in relation to BOO (Schäfer) grades; variables are presented as median and 25–75 percentiles. Asterisk represents a significant difference compared to Schäfer 0 (Mann–Whitney U test; each $p < 0.01$). BCI Bladder Contractility Index, W_{max} maximum Watts factor.

Moreover, median BCI or W_{max} of Schäfer grade 0 was significantly lower compared to the median BCI or W_{max} values of the other Schäfer grades (each $p < 0.01$; Figure 1). Spearman's correlation showed a significant, moderate to strong correlation coefficient between both detrusor contraction power parameters (R^2 of 0.570; $p < 0.001$).

2.2.4 Discussion

Our study shows for the first time in patients with LUTS suggestive of BPH that the commonly used detrusor contraction power parameters BCI and W_{max} continuously and significantly increase with rising BOO grade indicating that threshold values for the determination of DU have to be defined separately for the different BOO grades. Therefore, the commonly used threshold values for the definition of DU (BCI <100 or W_{max} <7 W/m²) should be reconsidered. Moreover, our study demonstrates a continuous and significant decrease of voiding efficiency in men with increasing BOO grade and, for the first time as well, a significant correlation between BCI and W_{max}.

Our results in a large group of unselected men, who were evaluated for LUTS suggestive of BPH during a 10-year period in one hospital with almost identical characteristic compared to those analysed for health seeking behaviour in Europe[21], show a strong correlation between BCI and W_{max} and also a strong correlation between BOO and the two detrusor

contraction power parameters. According to the literature, a BCI value <100 indicates DU ('hypocontractility') in men[18], but this threshold value has never been validated and could refer to patients with BOO only. In order to make a comparison with our data, it would be useful to learn how the BCI threshold value of <100 was determined in the original publication. Of particular interest would be to know whether this BCI threshold value was based on theoretical considerations or measurement data. The same question accounts for the definition of the threshold value of W_{max}[16]. Consequently, studies using a BCI (W_{max}) threshold <100 (<7 W/m²) to define DU have to be used with caution, especially when applied for men or women without BOO[9]. If the BCI threshold value <100 would be applied to our patient population, almost all men with Schäfer grades 0-2 and the majority of patients with Schäfer grade 3 would have been judged with the diagnosis of DU (Table 1; Figure 1). Vice versa, all investigated men of our study population with Schäfer grades 4-6 have a BCI >100, and therefore, no patient would have had DU; these two considerations may be possible but seem unlikely.

Our study was able to confirm results obtained in experimental animals with artificial BOO; these studies showed a significant increase of detrusor contraction power and bladder weight during the initial and compensated stages during which bladder emptying remains complete[2]. Microscopic investigations of the bladder wall in these two stages revealed - besides fibroblast hyperplasia and deposition of collagen fibres - smooth muscle cell hypertrophy. Animal studies suggest that bladder emptying in the presence of BOO persists due to increasing detrusor contraction power as a result of structural changes of the bladder wall[2,22]. Additionally, the results of our present study are in line with conclusions from previous studies showing a significant increase of bladder/detrusor wall thickness in symptomatic male patients with BOO[4,5]; therefore, increased detrusor contraction power in patients seems to be generated by increased mass of smooth muscle cells of the bladder wall (detrusor) as well.

Our study is limited to the analysis of patients with compensated bladders, and hence, we cannot provide information about detrusor contraction power parameters in patients with decompensated bladders or urinary retention. Regardless of this selection bias, patients with increasing BOO grade show a continuous decrease of voiding efficiency which could be caused by BOO and/or DU and may be the first sign of bladder decompensation. Therefore, it remains to be determined whether decreasing voiding efficiency will result in bladder decompensation and urinary retention, without necessarily having increased PVR values before.

Because the calculations of BCI and W_{max} are partially dependent on Q_{max} and abdominal straining during voiding would result in artificially increased BCI or W_{max} values, it is possible that we have calculated too high median values in our sample of patients. Therefore, we have to exclude abdominal straining during voiding by asking patients not to strain during pressure-flow recordings. If straining was still present, manual correction of the pressure-flow plot should be done to determine the precise threshold values for DU of each BOO group in the future. However, the basic principle of increasing BCI or W_{max} with rising Schäfer grade remains unaffected by potential straining during voiding because straining

is likely to appear with similar frequency in all BOO groups. Additionally, it remains to be determined whether our results are only valid for maximum detrusor contraction power or also true for detrusor contraction duration, another component of DU[2,17].

Future (longitudinal) studies should validate our results in an independent group of patients, compare our results with asymptomatic healthy men, determine - after correction for abdominal straining - the exact threshold values for the diagnosis of DU of different BOO grades, reproduce our results in women, evaluate whether differences exist for detrusor contraction duration, and correlate detrusor contraction power parameters with other (non-invasive) measurement data (e.g. detrusor wall thickness).

2.2.5 Conclusions

In patients with LUTS suggestive of BPH, both commonly used detrusor contraction power parameters - BCI and W_{max} - continuously and significantly rise with increasing BOO grade. We could, for the first time, confirm data obtained from animal studies. According to our results, it is impossible to determine a single threshold value for BCI or W_{max} for diagnosing DU in a group of patients with different BOO grades; therefore, future studies have to evaluate individual threshold values for BCI or W_{max} for each BOO subgroup to adequately define DU.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. Levin RM, Haugaard N, O'Connor L, Buttyan R, Das A, Dixon JS, Gosling JA. Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: a direct comparison. *Neurourology and Urodynamics* 2000;19:609–629
3. Gosling JA, Kung LS, Dixon JS, Horan P, Whitbeck C, Levin RM. Correlation between the structure and function of the rabbit urinary bladder following partial outlet obstruction. *Journal of Urology* 2000;163:1349–1356.
4. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A. The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. *Journal of Urology* 1998;159:761–765.
5. Oelke M, Höfner K, Wiese B, Grünewald V, Jonas U. Increase of detrusor wall thickness indicates bladder outlet obstruction (BOO) in men. *World Journal of Urology* 2002;19:443–452.
6. Oelke M, Höfner K, Jonas U, Ubbink D, de la Rosette J, Wijkstra H. Ultrasound measurement of detrusor wall thickness in healthy adults. *Neurourology and Urodynamics* 2006;25:308–317.
7. Reynard JM, Yang Q, Donovan JL, Peters TJ, Schäfer W, de la Rosette JJ, Dabhoiwala NF, Osawa D, Lim AT, Abrams P. The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. *British Journal of Urology International* 1998;82:619–623.
8. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *European Urology* 2008;54:419–426.
9. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. *Korean Journal of Urology* 2012;53:342–348.
10. Madersbacher S, Pycha A, Schatzl G, Mian C, Klingler CH, Marberger M. The ageing lower urinary tract: a comparative urodynamic study of men and women. *Urology* 1998;51:206–212.
11. Berges R, Oelke M. Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling population aged 50 years or older. *World Journal of Urology* 2012;29:171–178.
12. Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalised elderly persons. *New England Journal of Medicine* 1989;320:1–7.
13. Lim CS, Abrams P. The Abrams-Griffiths nomogram. *World Journal of Urology* 1995;13:34–39.
14. Schäfer W. Analysis of bladder-outlet function with the linearised passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. *World Journal of Urology* 1995;13:47–58.
15. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723–728.
16. Griffiths DJ, van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. *Neurourology and Urodynamics* 1989;8:29–52.

17. Schäfer W. Analysis of active detrusor function during voiding with the bladder working function. *Neurourology and Urodynamics* 1991;10:19–35.
18. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *British Journal of Urology International* 1999;84:14–15.
19. Sekido N. Bladder contractility and urethral resistance relation: what does a pressure flow study tell us? *International Journal of Urology* 2012;19:216–228.
20. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg, A, Sterling AM, Zinner NR, van Kerrebroeck PE. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourology and Urodynamics* 2002;21:261–274.
21. Hutchison A, Farmer R, Chapple C, Berges R, Pientka L, Teillac, P, Borkowski A, Dobrinski P. Characteristics of patients presenting with LUTS/BPH in six European countries. *European Urology* 2006;50:555–561.
22. Levin RM, Schuler C, Leggett RE, Callaghan C, Maknuru S. Partial outlet obstruction in rabbits: duration versus severity. *International Journal of Urology* 2013;20:107–114.

Chapter 3

Unravelling Detrusor Underactivity: Development of a Bladder Outlet Resistance - Bladder Contractility Nomogram for Adult Male Patients With Lower Urinary Tract Symptoms

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Abstract

Aims

Voiding dysfunction in adult men may be caused by bladder outlet obstruction (BOO) and/or detrusor underactivity (DU). Until now, it is only possible to classify BOO and DU by pressure-flow analysis. Low values of the maximum Watts factor (W_{max}) indicate DU but thresholds for the diagnosis have not been established. Purpose of this study was to construct a nomogram using bladder outlet resistance and detrusor contractility in order to classify BOO and DU simultaneously.

Methods

Treatment naıve men aged ≥40 years with uncomplicated lower urinary tract symptoms (LUTS) were prospectively evaluated. Patients were assessed with IPSS, prostate volume, uroflowmetry, post-void residual, and pressure-flow measurement. The bladder outlet obstruction index (BOOI) was used to determine BOO-grade and W_{max} to calculate detrusor contractility. Individual BOOI-W_{max} values were plotted in a graph. Linear interpolation was applied to determine the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles.

Results

Retrospective analysis of 822 male patients with means of 64 years, IPSS 16, and prostate volume of 40cc. Patient and clinical parameters of the $<25^{th}$ percentile groups were significantly different compared to the 25^{th} - 50^{th} percentiles: age (66 vs. 63 years, p = 0.006), bladder capacity (503 vs. 442 ml, p = 0.009), post-void residual urine (167 vs. 116 ml, p = 0.001), and voiding efficiency (67% vs. 73%, P = 0.015).

Conclusions

The nomogram quantifies the relationship between detrusor contractility and BOO in men with LUTS. A measurement value $<25^{th}$ percentile correlates with clinical indicators of DU and is proposed as a cut-off value for DU-diagnosis. Higher age, bladder capacity, and PVR as well as lower voiding efficiency indicate DU.

2.3.1 Introduction

Detrusor underactivity (DU) and bladder outlet obstruction (BOO), alone or in combination, are the main causes of voiding dysfunction in adults[1,2]. DU is defined as a detrusor contraction of reduced strength or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span[1,2]. Several symptoms and signs are indicative but not specific for DU; these include increased bladder capacity, post-void residual (PVR) urine, and/or reduced voiding efficiency[3,4]. Up to 40% of men aged >65 years[3], 48% of men aged ≥70 years[5] and approximately two-thirds of incontinent institutionalised elderly men and women are affected by DU,6 whereas approximately 60% of symptomatic, non-neurogenic men aged ≥50 years have BOO[7,8]. The prevalence of BOO and DU increases with aging and, therefore, rising numbers of patients with one or both types of voiding dysfunctions are anticipated in ageing societies.

BOO and DU are diagnosed by pressure-flow measurements[1]. BOO is described by increased detrusor pressure in combination with decreased urinary flow, whereas DU is defined by decreased detrusor pressure in combination with decreased urinary flow[1]. BOO has been well characterized and threshold

values to distinguish between non-obstructed and obstructed bladders have been established. Formula (e.g. bladder outlet obstruction index (BOOI)) or nomograms (e.g. the ICS-, Schäfer or CHESS-nomogram) are used accordingly and help physicians to correctly judge BOO in individual patients[9-12]. Calculation of detrusor contractility (e.g. bladder contractility index (BCI) or maximum Watts factor (W_{max})) is also well established[9,13], but thresholds to distinguish between normal contractility and DU

remain debated. In men, we recently demonstrated that detrusor contractility (BCI, W_{max}) significantly increases with rising BOO-class[14]. Therefore, it is impossible to define a single threshold value for the diagnosis of DU in all patients and necessary to define separate threshold values for different BOO-grades. A nomogram using detrusor contractility and BOO as continuous variables could solve this bi-dimensional problem to correctly classify individual patients. Consequently, the aim of our study was (i) to develop a nomogram using detrusor contraction power (W_{max}) in adult men with lower urinary tract symptoms (LUTS) and different BOO-grades (BOOI) in order to correctly classify individual men as obstructed, underactive, or obstructed and underactive; and (ii) to identify clinical parameters which indicate DU.

2.3.2 Materials and Methods

2.3.2.1 Patient selection

Male patients aged ≥40 years with LUTS evaluated between 4/1993 and 12/2007 in the Hannover Medical School, Germany were included in this study. Patients with serum PSA

concentration 4-10 µg/l needed to have negative prostate biopsies to be enrolled in this study. In contrast, men with complications of BOO (e.g. bladder diverticula, bladder stones) or the inability to void (i.e. urinary retention) were excluded. Additionally, men with LUTS after lower urinary tract or pelvic surgery, radiotherapy of the pelvis, neurological diseases, urinary tract infection, bladder cancer, urethral strictures, prostatitis, known/palpable/biochemical (PSA >10 µg/l) prostate cancer, and patients under LUTS-treatment (α-blockers, 5α-reductase inhibitors, and/or antimuscarinics) were also excluded.

2.3.2.2 General assessment

During the first visit, general, drug and LUTS histories as well as a blood sample for PSA measurement were taken. Physical examination (including digital-rectal examination of the prostate) and ultrasound investigation of the kidneys, bladder, and prostate (by transrectal ultrasound, TRUS) were performed.

After 1995, patients also completed the validated German International Prostate Symptoms Score (IPSS) questionnaire. All patients were asked to void with a full bladder to perform free uroflowmetry; only measurements with a voided volume of ≥125 ml were deemed suitable for further analysis. Immediately after voiding, PVR was measured with a suprapubically positioned ultrasound array.

2.3.2.3 Urodynamic assessment

One to three weeks after initial presentation, patients returned to the office and repeated free uroflowmetry. PVR measurement was done by transurethral catheterisation immediately after voiding and before the start of the urodynamic measurement. Accordingly, a transurethral 6-Fr double-lumen catheter was placed in the bladder to determine PVR volume and, immediately afterwards, to simultaneously fill the bladder and measure the intravesical pressure (P_{ves}). Additionally, a 10-F single-lumen catheter was inserted into the rectum to measure intra-abdominal pressure (P_{abd}). Both water filled catheters were connected with external pressure transducers at the level of the pubic symphysis. Computer-urodynamic investigation was performed by experienced investigators in line with the Good

Urodynamic Practices standards suggested by the International Continence Society[15]. Methods, definitions, and units conform to the standards recommended by the International Continence Society, except where specifically noted[1].

During cystometry, the patient was positioned in the convenient sitting position and the bladder was filled with sterile physiological saline solution with a temperature of 37and a speed between 25-50 ml/min until the patient felt a strong desire to void. Afterwards, the patient voided - according to his normal habit - in the sitting or standing position and pressure-flow measurement was carried out. Cystometry and pressure-flow measurement were performed at least twice during the same urodynamic session.

2.3.2.4 Parameters for analysis

Patient parameters (age, height, weight), total prostate volume, IPSS, parameters of free uroflowmetry (maximum urinary flow rate (Q_{max}), average urinary flow rate (Q_{ave}), and voided volume), PVR, bladder capacity, voiding efficiency, and parameters of pressure-flow recordings (detrusor pressure at maximum flow ($P_{det.Qmax}$), BOOI, BCI [$P_{det.Qmax} + 5Q_{max}$], and W_{max}) were used for analyses. Because free uroflowmetry, PVR, cystometry, and pressure-flow measurements were performed at least in duplicate, representative recordings were used for analyses. The free uroflowmetry measurement, after manual artefact correction, with the highest Q_{max} value was selected. The corresponding measurement of PVR was utilised, assessed either by ultrasound or catheterisation before computer-urodynamic investigation. The pressure-flow measurement without straining and the lowest BOO grad was chosen for analysis after visual control and, if necessary, manual repositioning of the measurement markers. If the patient had more than one computer-urodynamic measurement at different time points, only one trace of the first measurement session was taken for analysis.

Bladder capacity at uroflowmetry was calculated by adding voided volume and PVR. Voiding efficiency (VE) was calculated to determine the percentage of bladder emptying in relation to bladder filling volume by applying the formula

Voiding efficiency (%) = (voided volume/bladder capacity) x 100

For judgment of the BOO grade, BOOI was calculated by the following formula[9]

$$BOOI\ (cm\ H_2O) = P_{det.Qmax} - 2Q_{max}$$

Detrusor contractility was determined by the Watts factor that was calculated by the urodynamic machine based on the following formula[16]

$$W = (P_{det} \cdot V_{det} + a \cdot V_{det} + b \cdot P_{det})/2\Delta$$

In the formula, V_{det} was calculated: $Q/2(3/(4\pi) \cdot (V_{ves} + Vt))^{-⅔}$ (W = detrusor contraction power; P_{det} = detrusor pressure; V_{det} = contraction speed; V = total bladder volume; Q = urinary flow rate, V = total volume of the bladder, reassembled by bladder filling volume (V_{ves}) and volume of the bladder muscle (V_t)). The maximum Watts (W_{max}) factor was used for our analysis.

2.3.2.5 Construction of the BOO-dependent Bladder Contractility Nomogram

An iterative procedure was implemented on the available dataset using the computer program Matlab (The Mathworks). Based on the available W_{max}-BOOI data points, the

best fitting (second order polynomial) curve was defined. Subsequently, the dataset was subdivided into two groups, a group above and a group below this best fitting curve. In these two subgroups, the two best fitting curves were calculated respectively (i.e. the 25th and 75th percentile curves). This process was iterated several times until less than 10 data points were present in one of the subdivided groups.

To determine the specific percentile values (<10th, 25th, 50th, 75th, and >90th) linear interpolation was applied between the calculated curves.

2.3.2.6 Statistical analysis

Mean values and 95% confidence intervals were calculated for baseline and measurement parameters. Two measurement values were statistically compared by using the independent samples t-test. One-way ANOVA was used for the comparison of one variable over more than two percentile groups. A p-value ≤0.05 was considered significant. All statistical analyses were done with SPSS, version 18.

2.3.3 Results

2.3.3.1 Patient characteristics

The database contained a total of 1,155 male patients with LUTS. After exclusion of men with artificially high Q_{max} values at free uroflowmetry, those with urodynamic traces only with straining, artefacts or a second measurement at a different time point, or patients with BOOI <0, the remaining 822 patients were included in the analyses. Mean values and their 95% confidence intervals for the patient and measurement parameters are listed in Table 1. Mean age of the study population was 64 years (range 40-94), mean prostate volume 40 cc (range 10-160), and mean IPSS 16 (range 1-35). Mean voiding efficiency at free uroflowmetry was 73% (range 2-100).

Comparison of the six percentile groups revealed no major differences with regard to height, weight, prostate volume, total IPSS, and IPSS storage, voiding, and quality of life sub-scores (Table 1). However, age was significantly different ($p = 0.004$); patients in the lower percentile groups were older than patients in higher percentile groups. Q_{max} ($p < 0.001$) and Q_{ave} ($p < 0.001$) of free uroflowmetry, VE ($p < 0.001$), and BCI ($p < 0.001$) and W_{max} ($p < 0.001$) evaluated during pressure-flow measurement significantly decreased with decreasing percentile group, whereas PVR significantly increased ($p < 0.001$). In contrast, BOOI ($p = 0.459$) remained stable over the different percentile groups.

2.3.3.2 Comparison of different percentile groups

< 10th Percentile versus 10th–25th percentile groups (Table 2).

The comparison of values between the two lowest percentile groups did not show statistically significant differences for the majority of investigated parameters. Only Q_{max} of free uroflowmetry (8.8 vs. 10.3 ml/sec, p = 0.031) and W_{max} at pressure-flow (6.7 vs. 8.8 W/m², p < 0.001) were significantly lower for patients of the <10th percentile group. Voiding efficiency was also numerically lower for patients of the <10th percentile group (63% vs. 69%) but this difference did not reach statistical significance (p = 0.064). The BOO-grade (BOOI) and BCI values were comparable between the two groups (both p > 0.05).

< 25th Percentile versus 25th–50th percentile groups (Table 3).

Significant differences between patients of <25th percentile groups and those of the 25th–50th percentile groups were seen for age (66 vs. 63 years, p = 0.006), PVR (167 vs. 116 ml, p = 0.001), voiding efficiency (67% vs. 72%, p = 0.015), cystometric bladder capacity (503 vs. 442 ml, p = 0.009), and W_{max} (7.9 vs. 11.7W/m², p < 0.001). In contrast, no significant differences were found when comparing Q_{max}, voided volume, BOOI, and BCI (all p > 0.05).

Table 1. Characteristics and measurement results of all patients and patients in the different percentile groups. Values are presented as mean with 95% confidence intervals (95% CI). Differences between the groups are calculated by using an ANOVA-test.

	All patients	**>90th**	**75th - 90th**	**50th - 75th**	**25th - 50th**	**10th - 25th**	**<10th**	***p*-value**
	n=822	*n=77*	*n=107*	*n=226*	*n=204*	*n=116*	*n=92*	
Age [years]	64 (63-64)	61 (59-63)	63 (61-65)	64 (63-65)	63 (62-64)	66 (64-67)	66 (64-68)	0.004
Height [cm]	175 (175-176)	176 (175-178)	176 (175-178)	175 (173-177)	175 (174-176)	175 (174-177)	175 (173-177)	0.726
Weight [kg]	81 (80-82)	85 (81-89)	81 (79-84)	81 (79-82)	80 (78-82)	80 (78-82)	80 (77-82)	0.125
Prostate volume [cc]	40 (38-42)	41 (35-46)	38 (34-43)	41 (38-44)	40 (37-44)	41 (36-46)	40 (34-46)	0.977
IPSS	16 (15-16)	15 (13-18)	17 (15-19)	16 (15-18)	15 (13-16)	15 (13-17)	15 (13-17)	0.513
IPSS storage sub-score	7 (7-8)	7 (5-9)	8 (7-9)	8 (7-9)	6 (6-7)	7 (6-8)	7 (6-8)	0.133
IPSS voiding sub-score	9 (8-9)	8 (6-10)	9 (8-11)	9 (8-10)	8 (7-9)	8 (7-10)	9 (7-10)	0.885
IPSS QoL score	3 (3-4)	4 (3-4)	3 (3-4)	4 (3-4)	3 (3-4)	4 (3-4)	3 (3-4)	0.548
Free uroflowmetry								
Q_{max} [ml/s]	11.3 (10.9-11.7)	14.9 (13.2-16.5)	13.3 (12.2-14.3)	11.5 (10.6-12.3)	10.2 (9.5-10.9)	10.3 (9.5-11.2)	8.9 (8.0-9.9)	<0.001
Q_{ave} [ml/s]	5.6 (5.4-5.8)	7.0 (5.9-8.2)	6.7 (6.1-7.3)	5.7 (5.2-6.2)	4.8 (4.4-5.2)	5.4 (4.8-6.0)	4.7 (4.2-5.2)	<0.001
Bladder capacity [ml]	377 (359-395)	368 (310-427)	360 (324-396)	349 (325-372)	369 (345-393)	445 (348-543)	411 (369-454)	0.095
Voided volume [ml]	255 (246-264)	279 (241-316)	259 (234-283)	253 (235-270)	254 (236-273)	255 (233-277)	235 (209-261)	0.480
PVR [ml]	119 (108-129)	89 (48-131)	101 (74-128)	96 (80-112)	116 (99-134)	154 (117-192)	184 (150-217)	<0.001
Voiding efficiency [%]	73 (72-75)	82 (77-85)	76 (72-80)	75 (72-78)	72 (69-75)	69 (65-73)	63 (58-68)	<0.001
Multichannel urodynamics								
Cystometric bladder capacity [ml]	437 (421-452)	424 (369-479)	397 (358-435)	395 (369-422)	442 (410-473)	499 (449-549)	507 (464-550)	<0.001
$P_{det.Qmax}$ [cm H2O]	59.5 (57.6-61.4)	69.6 (62.2-77.1)	64.3 (58.9-69.7)	58.5 (55.3-61.8)	57.1 (53.2-61.0)	57.5 (53.0-61.9)	55.6 (50.1-61.2)	0.002
BOOI [cm H2O]	44 (42-46)	46 (38-54)	44 (38-50)	43 (39-47)	45 (41-49)	44 (39-49)	44 (38-50)	0.975
Bladder Contractility Index	98 (96-100)	126 (117-135)	112 (106-118)	99 (95-103)	89 (85-94)	91 (86-95)	86 (81-91)	<0.001
W_{max} [W/m^2]	13.9 (13.4-14.4)	26.4 (24.3-28.6)	18.7 (18.0-19.4)	14.9 (14.5-15.3)	11.7 (11.3-12.1)	8.8 (8.3-9.3)	6.7 (6.1-7.3)	<0.001

Table 2. Comparison of the two lowest percentile groups (<10th versus 10th-25th percentiles). Values are presented as means and 95% confidence intervals (95% CI). p-values are calculated by using an independent samples t-test (considered significant at a level p ≤ 0.05).

	<10th percentile *n=92*	**10th - 25th percentiles** *n=116*	***p*-value**
Age [years]	66 (64-68)	66 (64-67)	0.812
Height [cm]	175 (173-177)	175 (174-177)	0.657
Weight [kg]	80 (77-82)	80 (78-82)	0.785
Prostate volume [cc]	40 (34-46)	41 (36-46)	0.855
IPSS	15 (13-17)	15 (13-17)	0.907
IPSS storage sub-score	7 (6-8)	7 (6-8)	0.647
IPSS voiding sub-score	9 (7-10)	8 (7-10)	0.746
IPSS QoL score	3 (3-4)	4 (3-4)	0.100
Free uroflowmetry			
Q_{max} [ml/s]	8.9 (8.0-9.9)	10.3 (9.5-11.2)	0.031
Q_{ave} [ml/s]	4.7 (4.2-5.2)	5.4 (4.8-6.0)	0.079
Voided volume [ml]	235 (209-261)	255 (233-277)	0.237
Bladder capacity [ml]	411 (369-454)	445 (348-543)	0.788
PVR [ml]	184 (150-217)	154 (117-192)	0.261
Voiding efficiency [%]	63 (58-68)	69 (65-73)	0.064
Multichannel urodynamics			
Cystometric bladder capacity [ml]	507 (464-550)	499 (449-549)	0.821
$P_{det.Qmax}$ [cm H_2O]	55.6 (50.1-61.2)	57.5 (53.0-61.9)	0.606
BOOI [cm H_2O]	44 (38-50)	44 (39-49)	0.868
Bladder Contractility Index	86 (81-91)	91 (86-95)	0.187
W_{max} [W/m^2]	6.7 (6.1-7.3)	8.8 (8.3-9.3)	<0.001

BOOI: bladder outlet obstruction index, IPSS: International Prostate Symptom Score, $P_{det.Qmax}$: detrusor pressure at maximum urinary flow, PVR: post-void residual (urine), Q_{ave}: average urinary flow rate, Q_{max}: maximum urinary flow rate, W_{max}: maximum Watts factor.

Table 3. Comparison of patients below the 25th percentile with patients in the group between 25th-50th percentiles. Values are presented as means and 95% confidence intervals (95% CI). The p-value is calculated by using an independent samples t-test (considered significant at a level p ≤ 0.05).

	<25th percentile	**25th - 50th percentiles**	***p*-value**
	n=208	*n=204*	
Age [years]	66 (65-67)	63 (62-64)	0.006
Prostate volume [cc]	40 (36-45)	40 (37-44)	0.929
Height [cm]	175 (174-176)	175 (174-176)	0.831
Weight [kg]	80 (78-81)	80 (78-82)	0.963
IPSS	15 (14-17)	15 (13-16)	0.639
IPSS storage sub-score	7 (6-8)	6 (6-7)	0.260
IPSS voiding sub-score	8 (7-9)	8 (7-9)	0.917
IPSS QoL score	4 (3-4)	3 (3-4)	0.164
Free uroflowmetry			
Q_{max} [ml/s]	9.7 (9.1-10.4)	10.2 (9.5-10.9)	0.338
Q_{ave} [ml/s]	5.1 (4.7-5.5)	4.8 (4.4-5.2)	0.291
Voided volume [ml]	247 (230-264)	254 (236-273)	0.557
Bladder capacity [ml]	431 (372-490)	369 (345-393)	0.063
PVR [ml]	167 (142-193)	116 (99-134)	0.001
Voiding efficiency [%]	67 (63-70)	72 (69-75)	0.015
Multichannel urodynamics			
Cystometric bladder capacity [ml]	503 (470-536)	442 (410-473)	0.009
$P_{det.Qmax}$ [cm H_2O]	56.7 (53.2-60.1)	57.1 (53.2-61.0)	0.869
BOOI [cm H_2O]	44 (40-48)	45 (41-49)	0.742
Bladder Contractility Index	88.6 (85.1-92.1)	89 (85-94)	0.829
W_{max} [W/m^2]	7.9 (7.5-8.3)	11.7 (11.3-12.1)	<0.001

BOOI: bladder outlet obstruction index, IPSS: International Prostate Symptom Score, $P_{det.Qmax}$: detrusor pressure at maximum urinary flow, PVR: post-void residual (urine), Q_{ave}: average urinary flow rate, Q_{max}: maximum urinary flow rate, W_{max}: maximum Watts factor.

2.3.3.3 Nomogram

The development of the nomogram is shown in Figure 1, including the following steps: plotting of the BOOI-W_{max} data points (Figure 1A), calculation of the percentiles (Figure 1B), and illustration of the area below the 25th percentile (Figure 1C).

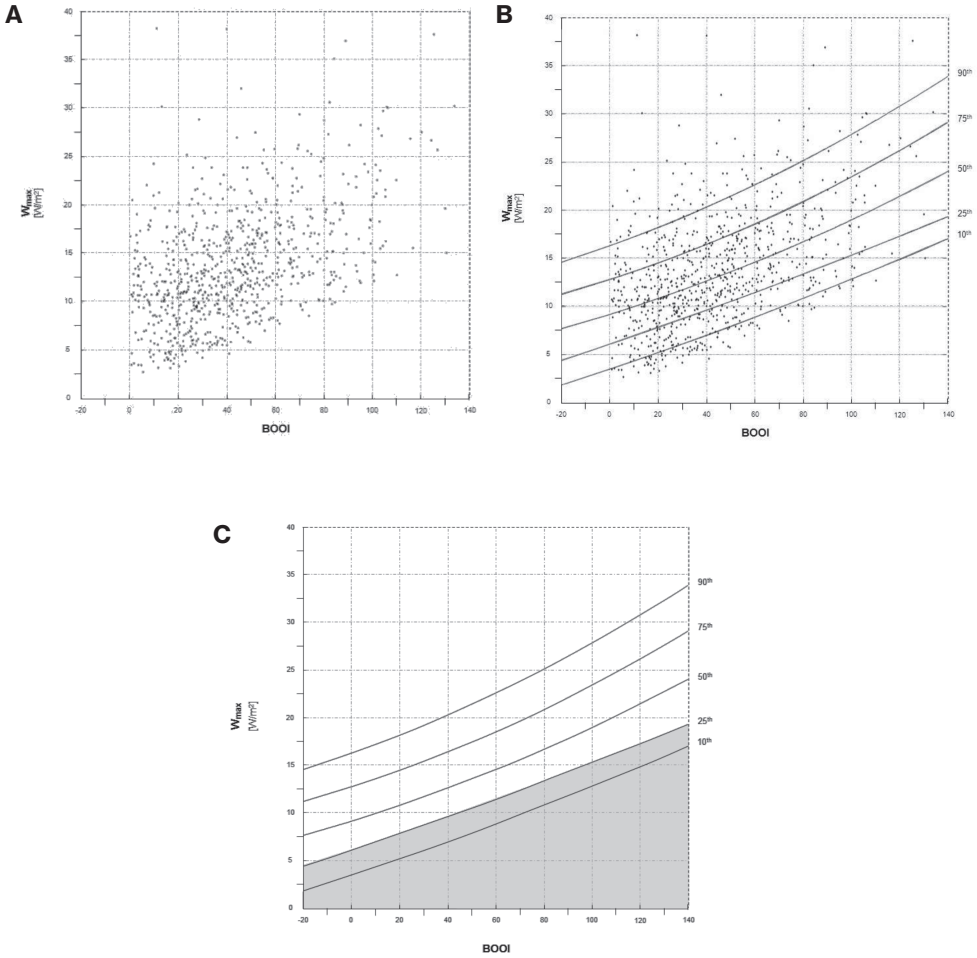

Figure 1. Development of the nomogram depicting bladder outlet obstruction index (BOOI) and maximum Watts factor (W_{max}). A: Measurement values of all men in the study (n = 822). B: Measurement values of all men together with the calculated 10th, 25th, 50th, 75th, and 90th percentiles. C: Nomogram with the five percentiles and illustration of the area for detrusor underactivity (grey field). Note that below approximately 10 x W_{max} = BOOI voiding becomes (mechanically) impossible. BOOI: bladder outlet obstruction index, W_{max}: maximum Watts factor.

2.3.4 Discussion

This is the first analysis of men with LUTS to define threshold values for detrusor contractility (W_{max}) in order to define DU in individual patients with different BOO-grades. Because W_{max} increases with increasing BOO, it is impossible to define a single W_{max} (or BCI) threshold value for the diagnosis of DU in all patient[14]. Therefore, it is necessary to adjust for the compensatory increase in detrusor contractility. Consequently, we have developed a nomogram based on BOOI and W_{max}. By calculating the percentiles for the BOOI-W_{max} values for all patients we could show that men in the <25th percentile groups were significantly different compared to men in higher percentiles with regard to age, PVR, voiding efficiency, and (cystometric) bladder capacity. These clinical parameters were previously thought to be associated with DU[3,4]. We therefore propose the diagnosis of DU for patients below the 25th percentile.

The study population consisted of 822 unselected, treatment naive symptomatic men who appear representative of elderly men who seek help for LUTS in Germany or other European countries[17]. It was the policy of our hospital to separately assess LUTS, prostate size, and bladder outlet obstruction in all patients as a routine procedure, regardless of initial results of patient history, uroflowmetry, or PVR measurement. Therefore, all men aged ≥40 years with LUTS, benign prostatic enlargement, decreased urinary flow rate, and/or PVR were equally assessed and everyone received, besides other tests, prostate volume measurement (TRUS) and computer urodynamic evaluation. Consequently, a database of unselected patients served as the basis for our analysis. We believe that this study population represents the range of untreated patients seen in urology offices and, therefore, are representative for the entire range of German (European) patients with LUTS.

For precise classification of detrusor contractility and BOO, it was necessary to use continuous numbers for both parameters; W_{max} and BOOI were selected accordingly. Other classifications of BOO, such as the ICS-, Schäfer-, or CHESS-nomogram, with categorical groupings of patients were considered less suitable for this purpose[10–12]. Although BOOI was originally described to diagnose obstructed bladders (>40cm H_2O) and not to classify the degree of BOO, it is the only accepted continuous number for BOO-classification. We have chosen W_{max} instead of BCI because the latter parameter is highly dependent on Q_{max} ($BCI = P_{det.Qmax} + 5Q_{max}$)[9]. Therefore, artefacts during Q_{max} measurement or straining during voiding would have resulted in artificially high BCI values. BOOI ($P_{det.Qmax} - 2Q_{max}$) and W_{max} are also dependent on Q_{max}, although less pronounced. To minimise the potential measurement mistake of Q_{max} on these two parameters, we have chosen the recording without straining and artefacts from at least two pressure-flow measurements of the individual patient during one measurement session. Additionally, we have excluded BOOI-value below 0 as they are suspicious for straining or artefacts.

Voiding and voiding efficiency are influenced by detrusor contractility (represented by W_{max}) and bladder outlet resistance (represented by BOOI). The balance between both parameters seems to be important for sufficient bladder emptying[18]. Thus, voiding is still possible in the presence of severe BOO if detrusor contractility is high enough and voiding is also possible in patients with DU if BOO is absent or low. However, voiding and voiding efficiency will become insufficient when there is an imbalance between detrusor contractility and bladder outlet resistance. Patients with low detrusor contractility and high bladder outlet resistance will most likely develop PVR or even retention. It also becomes evident that there are no data points below values of approximately 10 x W_{max} = BOOI as this seems to represent the (mechanical) balance where voiding becomes impossible. Our nomogram informs about contractility and BOO at the same time in order to classify individual patients as obstructed, underactive, or obstructed and underactive. This nomogram is currently only valid for adult male patients with non-neurogenic bladder dysfunction who can still void but the nomogram may be different in younger men, women, patients with neurogenic bladder dysfunction, or other patient groups. The nomogram still has to be validated by independent databases.

Besides diagnosing DU and BOO, the nomogram could be useful for studying effects of drugs or surgical procedures on bladder emptying. It may be possible to predict men who will develop PVR or urinary retention if they receive antimuscarinics[19,20] or botulinum toxin[21] or men who will have insufficient voiding after prostate surgery for BOO[22]. It seems likely that patients with DU (i.e. patients <25th percentiles) are those who develop voiding dysfunction (PVR or urinary retention) when a treatment further reduces detrusor contractility without simultaneously reducing BOO. The location of a measurement value in the nomogram and especially the change of this location in time will help to estimate the compensatory capacity of detrusor contractility and/or the bladder outlet resistance. This will be useful to evaluate drugs targeting these capacities or to predict voiding difficulties related to ageing[23]. Therefore, prospective and longitudinal studies in these patient groups are desirable.

The attempt to classify men with DU with the help of the nomogram has the limitation that pressure-flow measurements are necessary to make the diagnosis. Urodynamic measurements are time consuming, expansive, invasive, and associated with morbidity[24,25]. Additionally, patients in urinary retention are unable to produce pressure-flow recordings and, therefore, it is impossible to classify these people with regard to contractility or BOO. However, the nomogram is currently the best approach for the classification of DU. Future studies should confirm the results of this study and evaluate whether it is possible to replace W_{max} by BCI in order to offer a nomogram to investigators who do not have the W-parameter calculation on their urodynamic machines. Additionally, larger implementation studies should clarify whether it is necessary to replace BOOI against other BOO-parameters (e.g., obstruction coefficient, OCO[26] or Urethral Resistance Algorithm, URA[27]) because the classification of men differs between different BOO-classification systems especially when men have a low detrusor pressure at maximum urinary flow and low maximum flow

rate[28]. Future studies should also evaluate whether it is possible to exchange pressure-flow measurements against non- or minimally-invasive parameters (e.g. PVR, voiding efficiency or ultrasound detrusor wall thickness measurement)[29]. Our nomogram could help evaluating the predictive value of these parameters and combinations accordingly.

2.3.5 Conclusions

The W_{max}-BOOI nomogram combines detrusor contraction power and BOO in order to safely classify patients for both voiding parameters. Men in the <25th percentile groups are significantly older, have a significantly higher cystometric bladder capacity and PVR, and have a significantly lower voiding efficiency compared to patients of higher percentile groups. We propose the 25th percentile as the threshold value for the diagnosis of DU (danger zone).

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, Rizk D, Sand PK, Schaer GN. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourology and Urodynamics* 2010;29:4–20.
3. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. *Korean Journal of Urology* 2012;53:342–348.
4. Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. *Journal of American Geriatrics Society* 2006;54:1920–32.
5. Abarbanel J, Marcus EL. Impaired detrusor contractility in community dwelling elderly presenting with lower urinary tract symptoms. *Urology* 2007;69:436–440.
6. Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly persons. *New England Journal of Medicine* 1989;320:1–7.
7. Reynard JM, Yang Q, Donovan JL, Peters TJ, Schafer W, de la Rosette J, Dabhiowala NF, Osawa D, Limt AT, Abrams P. The ICS-'BPH' Study: Uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. *British Journal of Urology International* 1998;82:619–623.
8. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *European Urology* 2008;54:419–426.
9. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *British Journal of Urology International* 1999;84:14–15.
10. Lim CS, Abrams P. The Abrams-Griffiths nomogram. *World Journal of Urology* 1995;13:34-39.
11. Schäfer W. Analysis of bladder-outlet function with the linearised passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. *World Journal of Urology* 1995;13:47–58.
12. Höfner K, Kramer AE, Tan HK, Krah H, Jonas U. CHESS classification of bladder-outflow obstruction.A consequence in the discussion of current concepts. *World Journal of Urology* 1995;13:59–64.
13. Van Mastrigt R, Griffiths DJ. An evaluation of contractility parameters determined from isometric contractions and micturition studies. *Urology Research* 1986;14:45–52.
14. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and Wmax) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: Results from a urodynamic database analysis. *World Journal of Uroloy* 2014;32:1177–1183.
15. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg, A, Sterling AM, Zinner NR, van Kerrebroeck PE. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourology and Urodynamics* 2002;21:261–274.

16. Griffiths D, van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. *Neurourology and Urodynamics* 1989;8:17–27.
17. Hutchison A, Farmer R, Chapple C, Berges R, Pientka L, Teillac, P, Borkowski A, Dobrinski P. Characteristics of patients presenting with LUTS/BPH in six European countries. *European Urology* 2006;50:555–561.
18. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723–728.
19. van Kerrebroeck PE, Haab F, Angulo JC, Vik V, Katona F, Garcia-Hernandez A, Klaver M, Traudtner K, Oelke M. Efficacy and safety of solifenacin plus tamsulosin OCAS in men with voiding and storage lower urinary tract symptoms: Results from a phase 2, dose-finding study (SATURN). *European Urology* 2013;64:398–407.
20. Drake MJ, Chapple C, Sokol R, Oelke M, Traudtner K, Klaver M, Drogendijk T, van Kerrebroeck PE. Long-term safety and efficacy of single tablet combinations of solifenacin and tamsulosin oral controlled absorption system in men with storage and voiding lower urinary tract symptoms: Results from the NEPTUNE study and NEPTUNE II open-label extension. *European Urology* 2015;67:262–270.
21. Kuo HC, Liao CH, Chung SD. Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: Risk factors and influence on treatment outcome. *European Urology* 2010;58:919–926.
22. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: The influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *British Journal of Urology International* 2004;93:745–750.
23. van Koeveringe GA, Rademakers KLJ, Birder LA, Korstanje C, Daneshgari F, Ruggieri MR, Igawa Y, Fry C, Wagg A. Detrusor underactivity: Pathophysiological considerations, models and proposals for future research. ICI-RS 2013. *Neurourology and Urodynamics* 2014;33:591–596.
24. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP. Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. *Journal of Urology* 1998;159:191–4.
25. Cann KJ, Johnstone D, Skene AI. An outbreak of serratia marcescens infection following urodynamic studies. *Journal of Hospital Infections* 1987;9:291–293.
26. Schäfer W. Basic principles and clinical application of advanced analysis of bladder voiding function. *Urologic Clinics of North America* 1990;17:553–566.
27. Griffiths DJ, van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. *Neurourology and Urodynamics* 1989;8:29–52.
28. Eckhardt MD, van Venrooij GE, Boon TA. Urethral resistance factor (URA) versus Schäfer's obstruction grade and Abrams-Griffiths (AG) number in the diagnosis of obstructive benign prostatic hyperplasia. *Neurourology and Urodynamics* 2001;20:175–185.
29. Oelke M, Rademakers KLJ, van Koeveringe GA. The use of clinical tests for diagnosing detrusor underactivity in adult men - results of a pilot study. *European Urology Supplements* 2014;13:e690.

Chapter 4

Prediction of Sacral Neuromodulation Treatment Success in Men with Impaired Bladder Emptying – Time for a New Diagnostic Approach

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Abstract

Introduction

Detrusor underactivity (DU) is currently a topic of major attention within functional urology. Urologists are often confronted with men who present with voiding dysfunction without bladder outlet obstruction (BOO) or after desobstructive or neuromodulation treatment. Their impaired bladder emptying is suspected to be related to failure of detrusor contractile function. Earlier research indicated that patients with non-obstructive urinary retention (NOR), e.g. detrusor underactivity (DU), have a lower success rate after sacral neuromodulation (SNM) compared to patients treated with SNM for storage dysfunction. However, predicting factors for treatment success in the NOR group have not yet been defined.

Methods and Evidence

The aim of this study was to assess whether the use of the new BOO-contractility (Maastricht-Hannover) nomogram can identify and predict SNM non-responders. Our results in 18 men showed that only 20% of patients below the 10th percentile, but 86% of men between the 10th-25th percentiles of the nomogram can be treated successfully with SNM. All successfully treated patients voided without needing self-catheterisation.

Conclusion

This pilot study showed for the first time that SNM treatment response in male patients with impaired bladder emptying can be predicted with the BOO-contractility (Maastricht-Hannover) nomogram. Men below the 10th percentile are likely to be treatment non-responders, whereas the majority of men above the 10th percentile are responders.

2.4.1 Introduction

Detrusor underactivity (DU) is currently an important research topic within functional urology. However, only a few studies with original scientific data have been published until now. One of the most crucial and urgent gaps to be solved is the diagnostic evaluation of detrusor function[1]. Single pressure-flow parameters have proven to be insufficient to adequately define patients at risk for DU[2]. The main problem with the existing parameters for the evaluation of the contractile function during pressure-flow studies is that they do not take bladder outlet obstruction (BOO) into account[2,3]. Except for Schäfer's detrusor linearised passive urethral resistance relation (linPURR), all of the existing indicators for contractile function have one fixed threshold value, regardless non-BOO, BOO or BOO-grade[4]. The Schäfer nomogram divides BOO and contractility only in rough classes and, therefore, small changes in BOO or contractility cannot adequately be judged. As a result of these disadvantages, our group has recently developed a BOO-dependent contractility (Maastricht-Hannover) nomogram for detection and classification of small changes[5].

This nomogram uses pressure-flow parameters and can distinguish between 'normal' or 'abnormal' contractile function in relation to the bladder outlet resistance. The nomogram was developed on basis of a retrospective analysis of 822 male LUTS patients aged ≥40 years[5]. All patients underwent complete assessment with IPSS, prostate volume, free uroflowmetry, post-void residual (PVR) measurement and pressure-flow analysis. Bladder outlet obstruction index (BOOI) was used to determine the BOO-grade and the maximum Watts factor (W_{max}) to calculate detrusor contractility. The individual BOOI-W_{max} values were plotted in a graph. Linear interpolation was applied to determine the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles. A measurement value $<25^{th}$ percentile correlates well with clinical indicators of DU (higher age, larger bladder capacity and PVR as well as lower voiding efficiency) and, therefore, was proposed as threshold for DU-diagnosis.

This study was designed to validate the nomogram with regard to treatment outcome and simultaneously define whether the nomogram can be used to predict treatment outcome of sacral neuromodulation (SNM) in men with impaired bladder emptying (i.e. post-void residual urine or urinary retention).

2.4.2 Methods and Evidence

A total of 65 male patients received SNM between 2010 and 2015 for impaired bladder emptying. Thirty-seven patients (57%) were screened for inclusion in this study based on availability of pressure-flow studies. The ability to produce urinary flow during pressure-flow recordings was a requirement for inclusion in order to calculate the different urodynamically derived pressure-flow parameters necessary to plot the patients in the Maastricht-Hannover nomogram[5]. Eighteen patients (49%) met these inclusion criteria and were analysed. SNM treatment success is generally defined as a ≥50% reduction of catheterisation frequency

and volume compared to baseline, determined by voiding diaries[6]. Six included patients received sacral neuromodulation for urinary retention and eleven patients for high post-void residuals. Fourteen patients performed clean intermittent catheterisation before SNM treatment. Two of these patients catheterised three times daily, the others four to five times daily. One patient performed 14 times daily intermittent catheterisation with coinciding anxiety problems. Two out of 18 patients had a suprapubic catheter (two patients unknown). The primary causes of voiding dysfunction are presented in Table 1.

Median (interquartile range) age of the included patients was 53 years (48-58). The overall success percentage of SNM test phase was 50% (9/18 patients). All included patients were plotted in the Maastricht-Hannover nomogram (Figure 1) and all were found to be below the 25th percentile, except for one. Both groups were equally distributed in terms of BOO-grade, expressed by bladder outlet obstruction index (BOOI), and all other clinical and pressure-flow parameters. The nine successfully treated patients were all completely cured, meaning there was no need for bladder catheterisation anymore. Patients who were located between the 10th and 25th percentiles had a treatment success rate of 86% (6/7 patients). One patient was positioned above the 25th percentile of the nomogram and was also successfully treated with SNM. In contrast, only 2 of 10 patients (20%) below the 10th percentile met the success criteria for SNM (Figure 1). Two-sided Fisher exact test showed a significant difference between both percentile groups (<10th vs 10th-25th) in terms of SNM treatment success (p = 0.015). In addition, a significant positive correlation was seen when comparing SNM treatment success with the position in the percentile groups (Spearman correlation coefficient of 0.671, p = 0.002). Table 2 displays the differences between SNM patients below and above the 10th percentile, indicating significant differences for voided volume, post-void residual urine, voiding efficiency (VE), maximum urinary flow rate (Q_{max}), bladder contractility index (BCI), and maximum Watts factor (W_{max}). This is in concordance with data previously published by Oelke *et al.*[5]. All patients with a previous episode of urinary retention appeared to be plotted < 10th percentile in the Maastricht-Hannover nomogram which is of additional value for the external validation process of the nomogram.

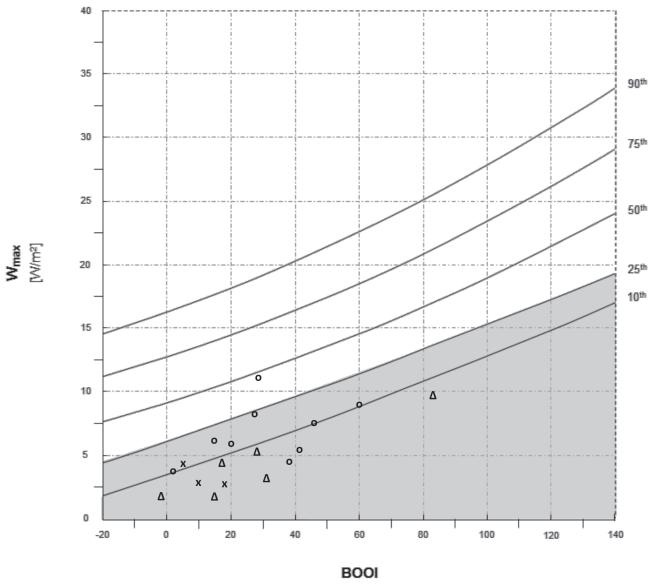

Figure 1. Maastricht-Hannover nomogram and patients with SNM first phase implant. The figure represents patients with first phase SNM implant plotted in the BOOI-Wmax nomogram. O (dots): represent treatment success, X (crosses): represent treatment failure, Δ (triangles): represent treatment failure and complete urinary retention in medical history.

Table 1. Primary causes of impaired bladder emptying.

Cause of impaired bladder emptying	Number of patients (n)
High Energy Trauma	2
Prolapsed intervertebral disc	2
Vertebral surgery	3
Surgery (other than back surgery)	1
After bladder botulin toxin injections	1
Diabetes mellitus	1
Unknown	8

Table 2. Baseline characteristics of patients treated with sacral neuromodulation (SNM), comparing <10th percentile vs. 10th-25th percentiles. All patients received SNM first test phase for incomplete bladder emptying. Only significant p-values are presented. Numbers are presented as median and interquartile range (IQR).

	<10th percentile *(n=10)*	**10th-25th percentiles or greater** *(n=8)*	***p*-value**
Age (yrs)	54 (48-62)	55 (37-64)	
Multichannel urodynamics			
Cystometric capacity (ml)	522 (446-619)	340 (259-611)	
Voided volume (ml)	59 (20-100)	105 (83-450)	0.027
Postvoid residual (ml)	451 (326-591)	192 (124-274)	0.002
Voiding efficiency (%)	11 (4-28)	41 (26-67)	0.004
Voiding time (s)	90 (15-140)	115 (64-145)	
Q_{max} (ml/s)	2.0 (1.0-3.8)	6.0 (4.3-8.8)	0.006
$P_{det.Qmax}$ (cm H_2O)	20.5 (13.8-41.3)	38.0 (19.3-54.0)	
BOOI	23 (13-39)	23 (7-42)	
BCI	35 (21-59)	76 (49-91)	0.034
W_{max} (W/m^2)	3.9 (2.5-5.1)	6.8 (4.9-8.7)	0.021

BCI: Bladder Contractility Index ($P_{det.Qmax}$ + 5Q_{max}), BOOI: bladder outlet obstruction index ($P_{det.Qmax}$ – 2Q_{max}), $P_{det.Qmax}$: detrusor pressure at maximum urinary flow rate (pressure-flow study), Q_{max}: maximum urinary flow rate (free uroflowmetry), W_{max}: maximum Watts factor.

2.4.3 Discussion

Until now, it was difficult to define reliable predictive factors for treatment outcome of patients undergoing SNM because age, gender, history or diagnosis did prognosticate treatment results[7,8]. However, it was suggested that patients with bladder acontractility during ambulatory urodynamics have a lower SNM success rate[6]. In general, predictors for SNM remain rather elusive and difficult to use in clinical practice. Our results indicate that pre-SNM assessment of bladder outlet resistance and bladder contractility by pressure-flow studies and, afterwards, plotting the results in the Maastricht-Hannover nomogram predicts post-SNM treatment success. Therefore, we were able, for the first time, to predict SNS treatment outcome in men with impaired bladder emptying. One acknowledgeable limitation of this study is the sample size and the retrospective nature of the study; nevertheless, the correlation seems so obvious that we are confident that prospective studies are worthwhile to be performed in order to deliver the final proof of our hypothesis.

At present, treatment based validation of the Maastricht-Hannover nomogram using pre- and post-treatment pressure-flow studies is ongoing. This is done by evaluation of different treatment modalities in men with LUTS, such a transurethral resection of the prostate (TURP) or drugs (e.g. α-blockers or antimuscarinics). The aim of these studies is to confirm whether a specific position in the nomogram is predictive for treatment success, as shown for SNS here. In addition, the studies will help to explore whether different treatment modalities in men reduce bladder outlet resistance and/or alter contractile function based on changes in position pre- and post-treatment, bringing theory into practice[9].

2.4.4 Conclusions

Eighty-six percent of patients were successfully treated with SNM for impaired bladder emptying and did not have to perform clean intermittent catheterisation anymore when they were preoperatively positioned above the 10th percentile of the Maastricht-Hannover nomogram, whereas only 20% of men met the success criteria when they were positioned below the 10th percentile. Our study showed for the first time that a nomogram can predict SNM treatment success in patients with impaired bladder emptying. In addition, this study helps validating the nomogram. Our study is the first confirmation that the Maastricht-Hannover nomogram can be useful in clinical practice to predict treatment outcome for voiding dysfunction.

References

1. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Hermanns R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723-728.
2. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and Wmax) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: results from a urodynamic database analysis. *World Journal of Urology* 2014;32:1177-1183.
3. Kranse R, van Mastrigt R. Relative bladder outlet obstruction. *Journal of Urology* 2002;168:565-570.
4. Sekido N. Bladder contractility and urethral resistance relation: what does a pressure flow study tell us? *International Journal of Urology 2012*;19:216-228.
5. Oelke M, Rademakers KLJ, van Koeveringe GA. Unravelling detrusor underactivity: Development of a bladder outlet resistance - bladder contractility nomogram for adult male patients with lower urinary tract symptoms. *Neurourology and Urodynamics* 2016;35:980-986.
6. Drossaerts JM, Rademakers KLJ, van Koeveringe GA, van Kerrebroeck PE. The value of urodynamic tools to guide patient selection in sacral neuromodulation. *World Journal of Urology 2015*;30:1889-1895.
7. Koldewijn EL, Rosier PF, Meuleman EJ, Koster AM, Debruyne FM, van Kerrebroeck PE. Predictors of success with neuromodulation in lower urinary tract dysfunction: results of trial stimulation in 100 patients. *Journal of Urology* 1994;152:2071-2075.
8. Scheepens WA, Jongen MM, Nieman FH, de Bie RA, Weil EH, van Kerrebroeck PE. Predictive factors for sacral neuromodulation in chronic lower urinary tract dysfunction. *Urology* 2002;60:598-602.
9. Rademakers KLJ, van Koeveringe GA, Oelke M. Detrusor underactivity in men with LUTS/BPO: characterisation and potential impact on indications for surgical treatment of the prostate. *Current Opinion in Urology* 2016;26:3-10.

Chapter 5

Ultrasound Detrusor Wall Thickness Measurement in Combination with Bladder Capacity can Safely Detect Detrusor Underactivity in Adult Men

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Abstract

Purpose

Detrusor underactivity (DU) has lately gained increasing interest because this bladder condition is an important cause of post-void residual urine and lower urinary tract symptoms (LUTS) in adult men. Until now, DU can only be diagnosed by pressure-flow measurement. Therefore, the aim of this study was to search for non-invasive tests which can safely predict DU in adult men.

Methods

Unselected, treatment-naïve male patients aged ≥40 years with uncomplicated, non-neurogenic LUTS were prospectively evaluated. All men received - after standard assessment of male LUTS - ultrasound detrusor wall thickness (DWT) measurements at a bladder filling ≥250 ml and computer urodynamic investigation. DU was defined as incomplete bladder emptying (>30 ml) in the absence of bladder outlet obstruction or dysfunctional voiding. Classification and regression tree (CART) analysis was used to determine parameters and threshold values for DU.

Results

The study population consisted of 143 consecutive men with medians of 62 years, IPSS 16, and prostate volume 35 ml. In total, 33 patients (23.1%) had DU. CART analysis showed that all men with DWT ≤1.23 mm plus bladder capacity >445 ml had DU. This multivariate model has a sensitivity of 42%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 85%.

Conclusions

This study showed that all men with ultrasound DWT ≤1.23 mm + bladder capacity >445 ml have DU. Combination of these two tests could help physicians to diagnose DU noninvasively in clinical practice. A prospective independent study should confirm these results.

2.5.1 Introduction

Incomplete bladder emptying can be caused by detrusor underactivity (DU), bladder outlet obstruction (BOO), or dysfunctional voiding[1]. The type of voiding dysfunction can be defined by simultaneous measurement of pressure and flow during voiding[1]. Urodynamic research has much focused on BOO. The two largest urodynamic studies investigating >1000 patients demonstrated BOO in approximately 60% of the symptomatic adult men[2,3]. Little attention has been paid on DU until recently. Preliminary studies showed DU in up to 40% of men aged >65 years and even up to 48% of men aged ≥70 years[4,5]. Therefore, DU - especially in elderly men - appears to be a frequent but also neglected bladder condition.

Reliable diagnoses of DU, BOO, and dysfunctional voiding are currently only possible from pressure-flow data[6-9]. However, urodynamic investigation requires catheter insertion, is bothersome for the patient, time-consuming, expensive, and associated with a considerable morbidity. Complications after urodynamic studies were reported in 19% of men and included urinary tract infections, pyelonephritis, haematuria, and urinary retention[10]. Consequently, it is infeasible and unwarranted to investigate all patients with urodynamic investigation. Therefore, non-invasive tests and clinical parameters for the safe, quick, and cheap determination of the type of voiding dysfunction are desperately needed. Diagnosis of the type of voiding dysfunction by analysis of lower urinary tract symptoms (LUTS) is impossible because LUTS are unspecific for age, gender and the underlying bladder condition[1,11,12]. Clinical parameters such as increased bladder capacity, a palpable bladder, or reduced voiding efficiency are indicative for DU, but threshold values have not been established and most probably also lack specificity[13,14].

Diagnosis of BOO is possible with non-invasive tests, such as ultrasound measurement of detrusor wall thickness (DWT)[15]. Increased DWT is observed in adult men with non-neurogenic LUTS and BOO[16-19]. The more severe BOO becomes, the greater is DWT[16]. A prospective study demonstrated that DWT ≥2 mm in bladders filled ≥250 ml safely indicates BOO (sensitivity 83%, specificity 95%, positive predictive value 94%, negative predictive value 86%, likelihood ratio of a positive test result 17.6)[17]. The aim of this pilot study was to investigate whether ultrasound measurement of DWT, either alone or in combination of other non-invasive tests, can diagnose DU.

2.5.2 Materials and Methods

2.5.2.1 Study design and patients

Adult men with LUTS associated with benign prostatic enlargement, who participated in a prospective trial on the assessment of non-invasive tests for the detection of BOO, were re-evaluated with regard to DU. Study design, patients, methods, and ultrasound measurement of DWT were previously described[17]. In brief, treatment-naïve men aged

≥40 years with uncomplicated LUTS were evaluated by International Prostate Symptom Score (IPSS), ultrasound measurement of DWT, uroflowmetry, measurement of post-void residual (PVR), transrectal ultrasound measurement of prostate volume, and multichannel computer urodynamic studies. Patients were only qualified for the study when they could void, were without previous medical or surgical therapies for LUTS, did not have symptoms or signs for prostate/bladder cancer or neurological diseases, and did not have previous surgery of the lower urinary tract or pelvis. All patients were assessed with a standardised protocol, including DWT and pressure-flow measurements during two visits in the outpatient department. The investigator of the pressure-flow measurement was blinded to the results of the non-invasive tests.

Ultrasound DWT measurements were taken early during the first consultation at the anterior bladder wall with a 7.5-MHz ultrasound array (Figure 1) and bladder filling ≥250 ml (median 407 ml; 25th-75th percentile: 304–540 ml)[17]. A mean of three DWT measurements was used for the analysis.

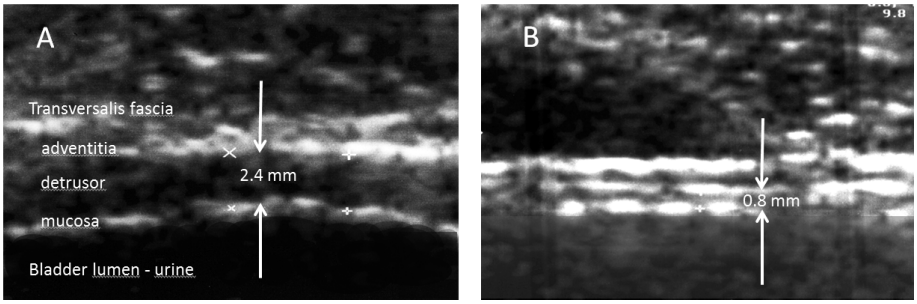

Figure 1. Ultrasound images of the anterior bladder wall with a 7.5 MHz array in two men with lower urinary tract symptoms. Enlargement 9.8 times, bladder filling in both men approx. 350 ml. The detrusor appears hypoechogenic and is sandwiched between the hyperechogenic mucosa and adventitia[19]. Detrusor wall thickness (DWT) is measured from the inner border of the mucosa until the inner border of the adventitia (+). Figure 1A is taken from a patient with mild bladder outlet obstruction (Schäfer grade 3) and normal bladder contractility (W_{max} 11.2 W/m^2); DWT 2.4 mm. Figure 1B is from a patient without bladder outlet obstruction (Schäfer grade 1) but with detrusor underactivity (W_{max} 3.4 W/m^2); DWT 0.8 mm.

2.5.2.2 Definition of detrusor underactivity

Because no universally accepted threshold values for detrusor contraction power parameters (maximum Watts factor [W_{max}] or bladder contractility index [BCI]) exist for the diagnosis of DU, we defined DU by exclusion[8]. Patients with DU are those who had PVR >30 ml but did not have BOO or dysfunctional voiding in pressure-flow measurement. This PVR

threshold was chosen because the German community-based LUTS trial demonstrated median PVR values below this threshold in healthy men aged ≥50 years[20].

2.5.2.3 Data analysis

Patients with DU versus non-DU were analysed and compared by using the following parameters: age, total IPSS, IPSS storage, and voiding sub-scores, uroflowmetry values (maximum urinary flow rate [Q_{max}], average urinary flowrate [Q_{ave}], time to Q_{max}, voiding time, bladder capacity [voided volume + PVR]), PVR, voiding efficiency (voided volume/bladder capacity × 100), prostate volume, and ultrasound DWT.

Multivariate computation with "classification and regression tree" (CART) analysis was performed with the same clinical parameters for the prediction of the clinical diagnosis of DU and establishment of threshold values. CART yields comparable results to logistic regression models. However, CART models capture higher-order interactions and generate a graphical prediction model with specific cutoff values which is easy to interpret and apply in clinical practice[21]. The CART procedure builds a decision tree by selecting locally optimal splits that minimise "impurity" on the outcome measure of the two lower nodes. Low impurity on the outcome measure indicates that the classifier performs well at separating observations with observations with one outcome (DU) from observations with another outcome (no-DU). All possible binary splits are considered for both continuous and categorical variables. The initial split is chosen as the single best classifier on the outcome measure. Then, within each child node, the splitting procedure is repeated until no splits are possible anymore. The optimal tree is defined as the tree with the lowest expected misclassification and is, for this study, selected by using cross-validation.

Statistical analysis was performed with SPSS version 20. Data are presented as median values with interquartile ranges. The Mann-Whitney U test was used to explore differences between two groups, and a p-value ≤0.05 was considered significant.

2.5.3 Results

2.5.3.1 Patient characteristics

The study population consisted of 143 consecutive Caucasian men with medians of 62 years, IPSS 16, and prostate volume 35 ml. Pressure-flow analyses revealed BOO (Schäfer grades 2–6) in 81 patients (56.6%). A total of $^{33}/_{143}$ patients (23.1%) were diagnosed as having DU by applying the study definition (Table 1).

When comparing non-invasive clinical parameters of DU patients with non-DU patients, significant differences between the two groups were seen for DWT (1.3 vs 1.9 mm, $p < 0.001$), maximum bladder capacity (560 vs 385 ml, $p < 0.001$), voided volume (318 vs 212 ml, $p = 0.003$), and PVR (130 vs 71 ml, $p = 0.027$; Table 1). Additionally, several

pressure-flow measurement parameters were also significantly different between the two groups, but these invasive parameters were not used in the multivariate model.

Table 1. Patient characteristics. Variables are presented as medians (with interquartile ranges).

Characteristics	Total Sample	DU *	No-DU	p-value
	n=143	*n=33*	*n=110*	
Age (years)	62 (59-70)	62 (59-73)	62 (57-68)	0.351
Total IPSS	16 (10-21)	14 (10-20)	16 (10-22)	0.295
IPSS storage sub-score	7 (4-10)	6 (3-9)	7 (4-10)	0.141
IPSS voiding sub-score	8 (4-12)	9 (5-11)	13 (8-16)	0.944
Prostate volume	35 (26-67)	34 (26-44)	35 (26-46)	0.606
Detrusor Wall Thickness (mm)	1.70 (1.40-2.20)	1.30 (1.10-1.75)	1.90 (1.50-2.33)	<0.001
Free uroflowmetry				
Q_{max} (ml/s)	10.3 (7.4-14.3)	10.7 (6.4-17.3)	10.3 (7.8-14.0)	0.802
Q_{ave} (ml/s)	5.1 (3.7-7.4)	4.4 (3.6-6.3)	5.3 (3.8-7.4)	0.220
Bladder capacity (ml)	406 (300-541)	560 (390-718)	385 (288-462)	<0.001
PVR (ml)	100 (30-201)	130 (100-250)	71 (30-200)	0.027
Voided volume	224 (153-324)	318 (205-416)	212 (149-292)	0.003
Voiding efficiency (%)	70.7 (51.7-88.4)	63.8 (51.3-84.4)	74.5 (52.1-89.6)	0.260
Pressure-flow study				
$P_{det.Qmax}$ (cm H_2O)	48.7 (34.9-71.3)	27.2 (19.8-39.8)	58.2 (45.6-76.6)	<0.001
W_{max} (W/m^2)	9.8 (6.1-13.1)	4.4 (3.7-6.0)	11.4 (8.2-14.8)	<0.001
BOOI (cm H_2O)	33.5 (18.0-53.2)	15.6 (5.2-27.2)	39.2 (22.9-63.1)	<0.001

*BOOI: bladder outlet obstruction index ($P_{det.Qmax}$ - $2Q_{max}$), DU: detrusor underactivity, IPSS: International Prostate Symptom Score (questionnaire), $P_{det.Qmax}$: detrusor pressure at maximum urinary flow, PVR: post-void residual urine, Q_{max}: maximum urinary flow rate, Q_{ave}: average urinary flow rate, W_{max}: maximum Watts factor. * DU was defined by PVR in the absence of bladder outlet obstruction or dysfunctional voiding.*

2.5.3.2 Multivariate analysis of non-invasive parameters for the diagnosis of DU

CART analysis showed that DWT and bladder capacity were the most predictive non-invasive parameters for DU (Figure 2). All patients with DWT ≤1.23 mm in combination with bladder capacity >445 ml had DU. CART analysis also revealed that DWT ≤1.23 mm alone could already correctly classify DU in 14⁄18 men (78 %). This multivariate model with the chosen threshold values has a sensitivity of 42%, specificity of 100%, positive predictive value of 100%, negative predictive value of 8%, accuracy of 87%, a likelihood ratio of a positive test result (DU) of 42, and a likelihood ratio of a negative test result (no-DU) of

0.58. The odds ratio of having DU compared to no-DU is 164.3 (95% confidence interval 9.4-2870) when using DWT ≤1.23 mm together with bladder capacity >445 ml.

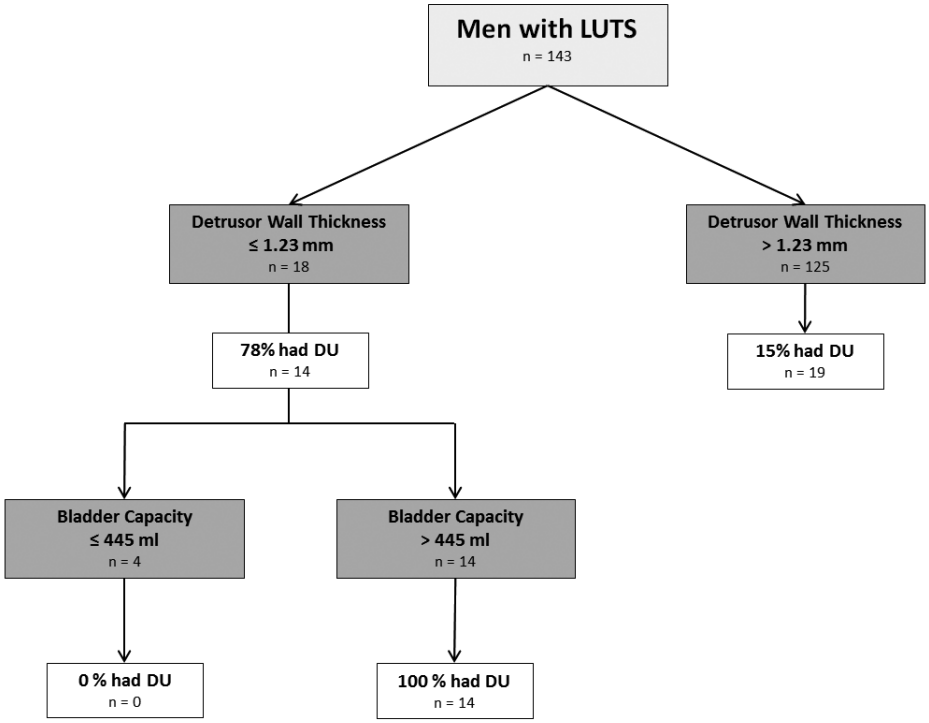

Figure 2. Classification and regression tree (CART) analysis for predicting detrusor underactivity (DU) with non-invasive clinical tests. The following variables were used to generate this model: age; total IPSS, IPSS storage, and voiding sub-scores; maximum flow rate (Q_{max}), average flowrate (Q_{ave}), time to maximum urinary flow, and voiding time of free uroflowmetry; bladder capacity; voiding efficiency; prostate volume; and detrusor wall thickness (DWT). The diagnostic values of non-invasive tests to determine DU were: sensitivity 42%, specificity 100%, positive predictive value 100%, negative predictive value 85%, and likelihood ratio of a positive test result 42.

2.5.3.3 Comparison of correctly identified vs non-identified detrusor underactivity in patients

In total, 33 men had DU based on clinical selection, of which 14 individuals were correctly classified with the CART model. In contrast, 19⁄125 men (15%) had DU if DWT was >1.23 mm (Figure 2). When comparing the 14 DU patients with DWT ≤1.23 mm and bladder capacity >445 ml with the other 19 patients with DWT >1.23 mm (**Table 2**), the most pronounced differences appeared in median DWT (1.1 vs 1.5 mm, p < 0.001), bladder capacity (645 vs 483 ml, p = 0.007), W_{max} (4.1 vs 5.8 W/m2 p = 0.009), and bladder outlet obstruction index (9.3 vs 19.9, p = 0.006).

Table 2. Comparison of the characteristics of correctly classified DU patients (i.e. men with DWT ≤1.23 mm and bladder capacity >445 ml) vs incorrectly classified patients (i.e. men with DWT >1.23 mm). Variables are presented as medians (with interquartile ranges).

Characteristics	**DU** *	**Correctly identified by CART analysis**	**Incorrectly identified by CART analysis**	***p*-value**
	n=33	*n=14*	*n=19*	
Age (years)	62 (59-73)	70 (61-75)	60 (59-72)	0.159
Total IPSS	14 (10-20)	11 (10-19)	16 (12-20)	0.282
IPSS storage sub-score	6 (3-9)	5 (3-9)	10 (6-15)	0.476
IPSS voiding sub-score	9 (5-11)	7 (5-11)	9 (5-13)	0.464
Prostate volume	34 (26-44)	34 (29-47)	34 (19-42)	0.324
Detrusor Wall Thickness (mm)	1.30 (1.10-1.75)	1.10 (0.90-1.20)	1.50 (1.40-2.00)	<0.001
Free uroflowmetry				
Q_{max} (ml/s)	10.7 (6.4-17.3)	12.2 (6.3-18.0)	9.0 (6.3-13.0)	0.332
Q_{ave} (ml/s)	4.4 (3.6-6.3)	5.0 (4.0-6.9)	3.9 (3.3-6.4)	0.333
Bladder capacity (ml)	560 (390-718)	645 (548-790)	483 (300-599)	0.007
PVR (ml)	130 (100-250)	143 (85-302)	125 (100-200)	0.547
Voided volume	318 (205-416)	367 (271-541)	217 (179-348)	0.018
Voiding efficiency (%)	63.8 (51.3-84.4)	67 (54.7-85.5)	60 (50.4-79.4)	0.271
Pressure-flow study				
$P_{det.Qmax}$ (cm H_2O)	27.2 (19.8-39.8)	25.1 (20.0-32.6)	32.0 (18.6-45.8)	0.166
W_{max} (W/m^2)	4.9 (3.7-6.0)	4.1 (3.3-5.0)	5.8 (4.5-6.2)	0.009
BOOI (cm H_2O)	15.6 (5.2-27.2)	9.3 (0.0-16.6)	19.9 (10.9-36.8)	0.006

*BOOI: bladder outlet obstruction index ($P_{det.Qmax}$ - $2Q_{max}$), DU: detrusor underactivity, IPSS: International Prostate Symptom Score (questionnaire), $P_{det.Qmax}$: detrusor pressure at maximum urinary flow rate, PVR: post-void residual urine, Q_{max}: maximum urinary flow rate, W_{max}: maximum Watts factor. * DU was defined by post-void residual urine in the absence of bladder outlet obstruction or dysfunctional voiding.*

2.5.4 Discussion

This is the first study to show that diagnosis of DU is possible with non-invasive tests. We could demonstrate that all men with DWT ≤1.23 mm and bladder capacity >445 ml have DU. Our study also showed that only 42% of men of the total DU study population had these characteristics; therefore, 58% of men with DU and DWT >1.23 mm were not correctly detected in our model. However, patients who were correctly classified with DWT plus bladder capacity had significantly lower detrusor contractility (W_{max}) and DWT values indicating that these men were more severely affected by DU.

Until now, it has only been possible to diagnose DU with pressure-flow measurements after which formulae and calculation of W_{max} are applied to make the diagnosis of DU and differentiate this bladder condition from other[6,7]. However, exact threshold values for W_{max} have yet not been established. To complicate the matter, W_{max} increases with rising BOO grade, and, therefore, DU has to be diagnosed for each BOO-(Schäfer) grade with different threshold values[8]. This indicates that the diagnosis of DU is not even possible with multichannel computer urodynamics in every patient. Consequently, clinical judgment is also necessary to make the diagnosis of DU. Consensus exists among experts that men with DU have specific clinical phenotypes which are incomplete bladder emptying (PVR), high bladder capacity, and low voiding efficiency[6,7,13]. Therefore, the results of this study are in line with expert opinion. The diagnosis of DU can be made in men without BOO or dysfunctional voiding simply by exclusion.

Ultrasound measurement of DWT is a technique that has been developed to non-invasively visualise bladder wall hypertrophy with high accuracy and repeatability in men with BOO[16-19]. The intra- and inter-observer repeatability of DWT measurements was found to be <5 and 4-12%, respectively[19]. It was demonstrated that DWT values ≥2 mm (in bladders filled ≥ 250 ml) indicate BOO in men with high accuracy[16,17,22]. Men without BOO have DWT values <2 mm. Median DWT value of healthy, asymptomatic male volunteers is 1.4 mm (interquartile range 1.33-1.5 mm)[23]. Therefore, the automatically chosen DWT threshold value in the CART analysis of this study for the diagnosis of DU is lower than DWT values measured in patients with BOO or healthy men.

The detrusor is the origin of the bladder contraction force during voiding. It has been hypothesized that DWT reflects the workload of the bladder[23,24]. Contrary to patients with BOO, DWT is decreased in patients with DU, as shown for the first time in this study. Therefore, it can now also be hypothesised that diminished contractile elements due to bladder wall thinning are responsible for incomplete bladder emptying in patients without BOO. It was previously reported in electron microscopy studies of bladder tissue samples that the correlation of impaired bladder contractility in elderly patients is a reduction and widespread degeneration of muscle cells and axons, superimposed by dense band patterns, depleted caveolae, and widened spaces between muscle cells with little collagen content[25,26]. The results seen in ultrastructural studies fit well to the DWT results of this study. However, it is currently impossible to draw the conclusion that detrusor hypotrophy

is the primary reason for PVR; other reasons for incomplete bladder emptying in men without BOO could be altered bladder innervation or a change of the receptor profile of bladder smooth muscle cells with secondary degeneration and thinning of the detrusor.

The results of this study also have clinical implications. If a patient receives transurethral resection of the prostate (TURP) for LUTS or incomplete bladder emptying, the operation is less effective for men with DU than with BOO. In an observational study with a follow-up >10 years, patients with DU did not show any significant improvement in LUTS or other clinical parameters (e.g. Q_{max}, post-void residuals, or voiding efficiency) compared to the preoperative situation or untreated men with DU[27,28]. Therefore, patients with an unfavourable treatment outcome after TURP could already be identified before the operation with the two non-invasive parameters generated of our model and without urodynamic investigation.

Although patient data of this study were prospectively collected in a group of treatment-naïve men representative of the male LUTS population in Germany and the study design fulfilled high-quality standards, the study was not designed to investigate men with DU and, therefore, has some limitations. Our current study is a retrospective analysis of a small group of patients with DU (n = 33, 23.1% of the investigated study population) to detect non-invasive parameters of DU patients. Compared to the original study population of 160 patients, 17 men could not be included in the current analysis due to missing data. The results of this pilot study should therefore be reproduced in a new and specifically designed study for the detection of DU. In such a study, it is necessary to define the threshold values for the diagnosis of DU. Thus, the threshold values generated in this current study should be used accordingly, as recommended by the Standards for Reporting of Diagnostic Accuracy (STARD) initiative[29]. It also needs to be evaluated whether patients with BOO can also have DU, and, therefore, men with the combination of different causes of voiding dysfunction can also be detected with the same non-invasive tests and thresholds. The same research questions are valid for women and children with PVR. Additionally, it remains to be determined whether individuals with DU but without PVR can also be detected with the same parameters and thresholds.

2.5.5 Conclusions

This study demonstrated that ultrasound measurement of DWT ≤1.23 mm in combination of bladder capacity >445 ml can safely detect DU in male patients without BOO or dysfunctional voiding. With these parameters and threshold values, it is possible to diagnose DU in 100% and exclude DU in 85% of patients. The use of the combination of these two non-invasive tests could help physicians to quickly diagnose DU in clinical practice and counsel patients before treatment.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. De la Rosette J, Lim TL. The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. *British Journal of Urology International* 1998;82:619-623.
3. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *European Urology* 2008;54:419–426.
4. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. *Korean Journal of Urology* 2012;53:342–348.
5. Abarbanel J, Marcus EL. Impaired detrusor contractility in community dwelling elderly presenting with lower urinary tract symptoms. *Urology* 2007;69:436–440.
6. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723–728.
7. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Wein A. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology* 2013;65: 389-398.
8. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and Wmax) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: Results from a urodynamic database analysis. *World Journal of Uroloy* 2014;32:1177–1183.
9. Oelke M, Rademakers KLJ, van Koeveringe GA. Unravelling detrusor underactivity: development of a bladder outlet resitance-bladder contractility nomogram for adult male patients with lower urinaruy tract symptoms. *Neurourology and Urodynamics* 2016;35:980-986.
10. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP. Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. *Journal of Urology* 1998;159:191–194.
11. El Din KE, Kiemeney LA, de Wildt MJ, Rosier PF, Debryune F, de la Rosette J. The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the International Prostate Symptom Score. *Journal of Urology* 1996;156:1020-1025.
12. Schäfer W, Rübben H, Noppeney R, Deutz FJ. Obstructed and unobstructed prostatic obstruction. A plea for urodynamic objectivation for bladder outflow obstruction in benign prostatic hyperplasia. *World Journal of Urology* 1989;6:198-203.
13. Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. *Journal of American Geriatrics Society* 2006;54:1920–1932.
14. Gammie A, Kaper M, Dorrepaal C, Kos T, Abrams P. Signs and symptoms of detrusor underactivity: an analysis of clinical presentation and urodynamic tests from a large group of patients undergoing pressure flow studies. *European Urology* 2016;69:361-369.
15. Belal M, Abrams P. Non-invasive methods of diagnosing bladder outlet obstruction in men. Part 1: non-urodynamic approach. *Journal of Urology* 2006;176:22-28.

16. Oelke M, Höfner K, Wiese B, Grünewald V, Jonas U. Increase in detrusor wall thickness indicates bladder outlet obstruction (BOO) in men. *World Journal of Urology* 2002;19:443-452.
17. Oelke M, Höfner K, Jonas U, Jean J, Ubbink DT, Wijkstra H. Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. *European Urology* 2007;52:827-834.
18. Arnolds M, Oelke M. Positioning invasive versus non-invasive urodynamics in the assessment of bladder outlet obstruction. *Current Opinion in Urology* 2009;19:55-62.
19. Oelke M. International Consultation on Incontinence-Research Society (ICI-RS) report on non-invasive urodynamics: the need of standardisation of ultrasound bladder and detrusor wall thickness measurements to quantify bladder wall hypertrophy. *Neurourology and Urodynamics* 2010;29:634-639.
20. Berges R, Oelke M. Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling population aged 50 years or older. *World Journal of Urology* 2011;29:171-178.
21. Muller R, Mockel M. Logistic regression and CART in the analysis of multimarker studies. *Clinica Chimica Acta* 2008;394:1-6.
22. El Saied W, Mosharafa A, ElFayoumy H, ElGhoniemy M, Ziada A, El Ghamrawy H, Ibrahim A, Abdel-Azim M. Detrusor wall thickness compared to other non-invasive methods in diagnosing men with bladder outlet obstruction: a prospective controlled study. *African Journal of Urology* 2013;19:160-164.
23. Oelke M, Höfner K, Jonas U, Jean J, Ubbink DT, Wijkstra H. Ultrasound measurement of detrusor wall thickness in healthy adults. *Neurourology and Urodynamics* 2006;25:308-317.
24. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A. The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. *Journal of Urology* 1998;159:761-765.
25. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility. *Journal of Urology* 1993;150:1657-1667.
26. Brierly RD, Hindley RG, McLarty E, Harding DM, Thomas PJ. A prospective controlled quantitative study of ultrastructural changes in the underactive detrusor. *Journal of Urology* 2003;169:1374-1378.
27. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: The influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *British Journal of Urology International* 2004;93:745–750.
28. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction. *British Journal of Urology International* 2005;96:1301-1306.
29. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *British Medical Journal* 2003;326:41-44.

Chapter 6

Recommendations for Future Development of Contractility and Obstruction Nomograms for Women. ICI-RS 2014

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Abstract

Aims

At present, existing bladder outlet obstruction (BOO) nomograms for women are still not universally accepted. Moreover, only limited information is available regarding bladder contractility in women. The aim is to present the discussions and recommendations from the think tank session ''Can we construct and validate contractility and obstruction nomograms for women?'' held at the 2014 International Consultation on Incontinence-Research Society (ICI-RS) meeting in Bristol, UK.

Methods

An overview of clinical significance, bladder mechanics and modelling, lack of existing nomograms for women, and development of new nomograms were presented and discussed in a multidisciplinary think tank session. This think tank session was based on a collaboration between physicians, engineers, and researchers and consensus was achieved on future research initiatives.

Results and Conclusions

Based on the think tank discussion, the ICI-RS panel put forward the following recommendations: the need to acquire normative age matched data in women to define ''normal'' and ''pathological'' values of urodynamic parameters; the inclusion of additional clinical data in new nomograms and the use of this extra dimension to develop clinically applicable nomograms for female BOO and contractility; and finally, the need to take into account the variability of BOO in women when developing female bladder contractility nomograms.

2.6.1 Introduction

Bladder outlet obstruction (BOO) refers to voiding dysfunction in which there is a pathological increase in bladder outlet resistance, a condition which has been described extensively in males. However, BOO in women still remains difficult to define. BOO in women may be caused by a fixed anatomical obstruction or it may be functional, resulting from a failure of outlet relaxation during detrusor contraction[1,2]. In a retrospective study of 600 women with voiding symptoms, Groutz and colleagues found that almost two third of cases were anatomical in origin[3]. In women, anatomical BOO most commonly arises following anti-incontinence procedures. Non-iatrogenic causes of BOO include pelvic organ prolapse (POP), gynaecological malignancy, extra-urinary vaginal masses, urethral pathology, and pregnancy[4].

The true prevalence of BOO in women is unknown, but estimates from large retrospective studies range from 3 to 8%[5-7]. Part of the difficulty in estimating BOO prevalence rates relate to the fact that, unlike for men, there are no universally accepted or standardised criteria for diagnosing the condition in women. The Blaivas–Groutz nomogram is possibly the most widely used to diagnose female BOO, identifying three degrees of obstruction[3], but has received criticism concerning its sensitivity, particularly in the mild obstruction zone[8,9].

Bladder contractility issues in women have received very little research attention. Voiding symptoms have been shown to have a poor predictive value for diagnosing female voiding dysfunction, rarely exist in isolation, often occur in association with storage-related symptoms[7,10,11], highlighting the importance of additional diagnostic tools in women.

Physicians, engineers, and researchers active in functional urology attended the ICI-RS think tank session on contractility and obstruction nomograms for women, generating a multidisciplinary discussion. The main tasks for this ICI-RS think tank panel were to define existing limitations and suggest ways to improve current and/or create appropriate nomograms and indices for women.

2.6.2 Bladder Mechanics and Modelling

2.6.2.1 Bladder Mechanics - The Concept of Bladder Contractility

The active contraction force (tension) of smooth and cardiac muscle varies according to its resting length or variation of the excitation–contraction pathways during activation. Changes to the latter are regarded as alterations of muscle contractility. When measuring force development in hollow muscular organs such as the bladder, detrusor force (manifest as wall tension, T) is rarely recorded and substituted for by using intravesical pressure, P_{ves}. The relationship between Δp and ΔT upon contractile activation depends on the size of the hollow viscus - Laplace's Law ($P = 2T/r$) - a change of Δp at constant ΔT decreases

as radius (or volume) enlarges. If flow occurs during contraction the bladder is no longer isovolumetric and the Δp will also be a function of this flow rate. Figure 1 represents pressure-flow curves for a hollow viscus at different initial diameters, but developing the same change of wall tension with no change in muscle contractility. There is clearly no unique pressure-flow relationship. Therefore, an estimate of bladder contractility, to compare values between individuals, or how they are influenced by external agents, may only be approximated from changes of detrusor pressure under isovolumetric conditions at a standardised volume. Even this assumes a similar relationship between resting and active tension which may not be the case when bladder compliance alters. Therefore, current and new methods for measuring contractility should factor in the bladder volume.

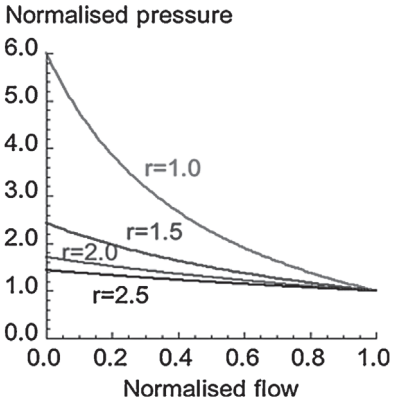

Figure 1. Representing pressure-flow curves for a hollow viscus at different initial diameters.

2.6.2.2 Mathematical Modelling – The VBN System

The main assumption for current nomograms is that the value of $P_{det.Qmax}$ during pressure-flow studies (PFS) and Q_{max} during PFS or free flow are representative of detrusor contractility and urethral obstruction. However, Q_{max} and $P_{det.Qmax}$ are dependent upon the initial bladder volume[12]. VBN allows tabulation of Q_{max} and $P_{det.Qmax}$ against k and U (the variables for contractility and obstruction respectively in the VBN (Valentini, Besson, Nelson) model[13]).

For urethral obstruction, the iso-U curves are almost straight and evenly spaced. This property allows the definition of a parameter, Woman Obstruction Index (WOI = P - 0.5Q), independent of the initial bladder volume, which is a linear function of U. For detrusor contractility, the iso-k curves are not straight and therefore they do not represent a linear correlation of Q_{max} and $P_{det.Qmax}$. In addition, the curves are volume dependent but the volume correction has a simple form[14].

To validate the evaluation of k and U from complete VBN analysis, pressure-flow studies of 125 non-neurological women were analysed[15]. k and U showed a good correlation[14]. Difficulty is encountered when voiding with low pressure and a high flow rate as VBN analysis leads to a negative value for U. It has been assumed that this is due to pelvic floor relaxation allowing low pressure voiding in the female[16], but research to identify the physiology in such conditions is required.

2.6.3 Existing Definitions and Parameters

2.6.3.1 Female Bladder Outlet Obstruction

Several definitions for female BOO have been proposed using various combinations of clinical parameters, pressure flow criteria, and radiographic evidence of BOO, for example by Massey and Abrams in the 80s[17]. Chassange and colleagues compared women with clinically relevant obstruction versus women with stress urinary incontinence and using ROC curve analysis concluded that a Q_{max} ≤15 ml/s and a $P_{det.Qmax}$ ≥20 cm H_2O indicated BOO[18]. These values were amended to Q_{max} ≤11 ml/s and $P_{det.Qmax}$ ≥21 cm H_2O by Lemack and Zimmern using a larger cohort of clinically obstructed women[19]. In 2004, further revisions were made by using asymptomatic controls rather than women with stress urinary incontinence and the highest sensitivity and specificity for predicting BOO were Q_{max} ≤12 ml/s and $P_{det.Qmax}$ ≥25 cm H_2O[20]. Nitti and colleagues defined BOO as fluoroscopic evidence of obstruction between the bladder neck and distal urethra in the presence of a sustained detrusor contraction of any magnitude, usually associated with a reduced or delayed flow[21].

The various approaches to diagnosing female BOO were compared by Akikwala and colleagues by applying the different diagnostic criteria to a cohort of 91 women in whom BOO was clinically suspected in 25[8]. The authors found that the videourodynamic study criteria set out by Nitti and colleagues had the highest concordance with a clinical suspicion of obstruction (87.9%). This points to the fact that absolute pressure and flow values are imprecise and that urodynamic criteria alone should not be used to diagnose BOO in women. Furthermore, a proportion of women will be unable to void during urodynamic testing and concerns have been expressed that the use of certain urethral catheter sizes during PFS may lead to over diagnosis by increasing outlet resistance[22].

Very recently, Solomon and colleagues presented a study (though to date only as a poster) in which they analysed videourodynamic studies of 186 women, divided into four subgroups of obstructed patients and two control groups. They concluded that the criterion $P_{det.Qmax} > 2Q_{max}$ (which actually equals Abrams' BOOI [= $P_{det.Qmax} - 2Q_{max}$] > 0) is the best determinant of urodynamic BOO in women[23]. Dybowski *et al.*[24] propose a similar dividing criterion ($P_{det.Qmax} = 1.5\ Q_{max} + 10$), but only to exclude BOO in women with a low Q_{max}.

Schäfer *et al.* performed a systematic analysis of repeated voiding studies with free flow and PFS in 168 females[25]. They analysed urodynamic data on the basis of P/Q-plots, various

nomograms (provisional ICS, Schäfer, Blaivas–Groutz), and numbers (Abrams' BOOI [= $P_{det.Qmax}$ - $2Q_{max}$], Schäfer's OCO [= $P_{det.Qmax}$ / 40 + $2Q_{max}$]). They concluded that there is agreement between all methods for some women with obstructed bladders. Schäfer and Blaivas–Groutz indicate that 14% and 22% of symptomatic women respectively are mildly obstructed. Using a higher Q_{max} as suggested by Blaivas and Groutz had little influence on BOO grading. BOOI showed the most significant variability with the standard deviation being higher than mean value. This value was strongly dependent on flow.

2.6.3.2 Female Bladder Contractility

Female voiding dynamics differ from those of men and consequently male nomograms and cut-off values are not applicable. Indeed, women normally void with significantly lower detrusor pressures and generate higher flow rates than men. Already in 1986, Griffiths *et al.* published the first and only study aiming to determine contraction strength in healthy women[26]. Detrusor contraction (Watts Factor) was assessed in volunteers aged 28-45 years without urologic complaints. Ideal voidings during these PFS showed a W_{max} between 11 and 24 W/m^2, whereas non-ideal voidings resulted in a W_{max} ranging from 5 to 10 W/m^2. At present, there are no other studies with normative data for women available.

In women, other parameters such as the pressure-flow based Sch- fer nomogram, the projected isovolumetric pressure (PIP) detrusor coefficient (DECO), or bladder contractility index (BCI) have been proposed. However, they greatly overestimate the presumptive value of detrusor contractility in women[27]. These parameters are based on the bladder output relation (BOR) and contain the constant K, which is based mainly on measurements in male patients.

At present, the only reasonably acceptable parameter in women has been published by Tan *et al.* They showed that a modified PIP, PIP_1 ($P_{det.Qmax}$ + Q_{max}) using Q_{max} instead of the constant K, is the only reliable parameter in older women with urgency incontinence compared to the stop-test[27]. This is therefore an area in need of further research.

2.6.4 Limitations of current female nomograms

When bladder volume change due to detrusor contraction equals the flow rate through a relaxed urethra, it can result in low pressure yet effective voiding. Clinically, a raised PVR is of greater concern than the amount of pressure that empties the bladder. Although many women are found to have an asymptomatic post-void residual, data from published studies would appear to support the use of 100 ml as being a clinically significant cut off point[11].

2.6.4.1 Abdominal Straining

Female abdominal straining can be effective in voiding, due to the lower urethral resistance than males. The detrusor pressure measured during a strain is low, but is also inaccurate[30]. Additionally, straining is of clinical concern due to the possibility of pelvic floor damage. Abdominal pressure is therefore an important consideration.

2.6.4.2 Mobile Obstruction

The urethral mobility in the female and thus alterations in outflow obstruction needs to be considered, as the urethral resistance encountered may be posture-, prolapse- , or abdominal pressure-dependent, neither of which is assessed by simple pressure-flow analysis.

These factors imply that assessment of contractility or obstruction in women needs to also consider PVR, voiding efficiency, duration of contraction, initial bladder volume, abdominal straining, and grade of prolapse. This requires more development than the work function[31] or VBN analyses[13], and suggests that a multidimensional nomogram will be required.

2.6.5 Clinical Implications

Contractility indices such as W_{max} and BCI seem to be influenced by the degree of outlet resistance both in males and females[32,33]. Thus, it could be argued that abnormal post-void residuals should be attributed to detrusor insufficiency after BOO has been excluded. Unfortunately, there is no definitive urodynamic definition for female outflow obstruction[33]. The limited articles proposing the use of $P_{det.Qmax}$ and Q_{max} from PFS to define BOO have used quite different cut-off values, as mentioned above[3,20,23,24,35].

Efforts have been made to propose urodynamic parameters for the diagnosis of female BOO and DU using "male" indices with different cut-off values. The Urethral Resistance Factor (URA) of Griffiths *et al.* has been used (women > 20cm H_2O as opposed to > 29cm H_2O in men)[36–38], also in conjunction with the Watts factor (URA/W20) as part of the relative obstruction concept[39]. The equation W80-W20 <0 was found to significantly correlate with Bladder Voiding Efficiency <80% in females and was proposed to identify isotonic DU. Correlations were more obvious in high-grade cystoceles[37].

Thus, the urodynamic diagnoses of female BOO and DU are partially objective and partially dependent on the operating physicians, especially in equivocal cases. Therefore, combination of existing urodynamic indices/nomograms might improve agreement for the more subjective diagnoses reached by physicians when applying the available ICS definitions in conjunction with clinical criteria[40]. Further to pressure-flow analyses, clinical criteria for the distinction between BOO and DU in women with voiding symptoms (reduced flow, hesitancy, sensation of incomplete bladder emptying, difficulty voiding) would need to be produced. For this, the predictive diagnostic value of non-invasive parameters,

including patients' history, demographics, questionnaires, and free flow findings could be investigated in association with established urodynamic criteria of BOO versus DU.

To discriminate between women with postoperative voiding difficulties according to the underlying cause a nomogram to identify and quantify BOO and possibly help to quantify detrusor contractility would be of immense clinical value. At present there is only one study, from Constantinou, comparingcontraction strength both pre- and post-surgery for stress urinary incontinence[41]. In women successfully treated with an endoscopic bladder neck suspension (BNS) no significant difference in W_{max} was seen when comparing pre- and post-surgery urodynamics. Direct pressure measurements of voiding pressure and flow both significantly decreased after BNS.

Besides identifying women after surgical incontinence procedures with iatrogenic BOO, clinicians would like to identify those at risk of postoperative complications. To compare the clinical utility of both W_{max} and direct measurement of voiding pressure in these patients, a comparative study is needed. In such a design, patients successfully treated for stress urinary incontinence should be compared to treatment failures and women with post-surgery complications to determine the predictive value of both parameters. Furthermore, in patients with the overactive bladder syndrome clinicians would like to identify patients who are likely to need intermittent catheterisation after intravesical injection with botulinum toxin-A. More importantly, as current translational research aims at the development of drugs to improve bladder emptying in patients, clinicians will soon be faced with decision-making concerning the appropriate use of such new medication.

In general, the same physical requirements for defining BOO apply to women and men. However, Sch- fer emphasises one of the main differences between women and men: in men with proximal obstruction the flow is driven by P_{det}, whereas in women flow is often driven by P_{ves}, and straining is very effective at enhancing Q_{max}[25,42]. This does raise the question whether we should use P_{det} or P_{ves} when approaching female voiding dysfunction, perhaps using P_{det} in women without straining and P_{ves} when straining is present. Besides this issue, the question how to incorporate the Q_{max} factor in equations in women still remains, as straining leads to an artificially high Q_{max} in most cases. A multidimensional nomogram could potentially limit the influence of straining by stratifying for this based on the clinical data incorporated in such a nomogram.

2.6.6 Future Research

Agreements and Recommendations of the ICI-RS 2014 think tank panel were as follows:

1. Need for normative data

To be able to define a pathological condition we also need to know what is normal. At present, there is only limited normative urodynamic data for women[26]. Moreover, aged-matched normative data is non-existent. However, stress incontinent patients without any urodynamic abnormalities during the voiding phase might also serve for normative aged-matched data. To be able to collect sufficient data, urodynamic data from multiple centres could be pooled, possibly through associations such as the International Continence Society.

2. Pressure-flow studies alone are insufficient for future nomograms in women

The fact that women are capable of voiding off an isotonic contraction, suggests that pressure-flow studies should not be assessed in isolation. Parameters such as bladder capacity, PVR or voiding efficiency and duration of the contraction should be considered as well.

3. Outlet obstruction and bladder contractility

Given that obstruction in women can be either anatomical or functional, it is important to first distinguish both based on a combination of PFS and clinical data/clinical judgement. At present, there is no optimal BOO nomogram that takes into consideration the multi-factorial origin of female obstruction. A next step would be how to relate bladder contractility to the amount of obstruction, as in male patients[43].

4. Development of contractility nomograms

Only one parameter (PIP_1) has been described in the literature as a reliable contractility parameter in older women. Parameters for other groups are needed, either completely new ones, or existing parameters reassessed (e.g. Watts factor) or with different cut-off values. In addition, BCI (instead of the current parameter which should be called detrusor contractility index) might be applicable in women when using P_{ves} instead of P_{det} to limit straining artefacts. When putting contractility parameters in the context of variable obstruction, it is realistic to develop more than one contractility nomogram for different clinical patient groups, example for different grades of outlet obstruction. A feasible option would be to develop contractility nomograms with different threshold values based on, for instance the prolapse grading system (POP-Q). Clinical validation of both obstruction and contractility could be done by comparing preoperative and postoperative changes in pressure-flow and other (clinical) data.

References

1. Goldman HB, Zimmern PE. The treatment of female bladder outlet obstruction. *British Journal of Urology International* 2006;98:17–23.
2. King AB, Goldman HB. Bladder outlet obstruction in women: Functional causes. *Current Urology Reports* 2014;15:436.
3. Blaivas JG, Groutz A. Bladder outlet obstruction nomogram for women with lower urinary tract symptomatology. *Neurourology and Urodynamics* 2000;19:553–564.
4. Dmochowski RR. Bladder outlet obstruction: Etiology and evaluation. *Reviews in Urology* 2005;7:S3–13.
5. Rees DL, Whitfield HN, Islam AK, Doyle PT, Mayo ME, Wickham JE. Urodynamic findings in adult females with frequency and dysuria. *British Journal of Urology International* 1975;47:853–860.
6. Carr LK, Webster GD. Bladder outlet obstruction in women. *Urologic Clinics of North America* 1996;23:385–391.
7. Groutz A, Blaivas JG, Chaikin DC. Bladder outlet obstruction in women: Definition and characteristics. *Neurourology and Urodynamics* 2000;19:213–220.
8. Akikwala TV, Fleischman N, Nitti VW. Comparison of diagnostic criteria for female bladder outlet obstruction. *Journal of Urology* 2006;176:2093–2097.
9. Virseda Chamorro M, Salinas Casado J, Adot JM, Martin GC. May the Blaivas and Groutz nomogram substitute videourodynamic studies in the diagnosis of female lower urinary tract obstruction? *Archives Espanoles de Urologia* 2006;59:601–606.
10. Lowenstein L, Anderson C, Kenton K, et al. Obstructive voiding symptoms are not predictive of elevated postvoid residual urine volumes. International *Urogynaecology Journal and Pelvic Floor Dysfunction* 2008;19:801–804.
11. Robinson D, Staskin D, Laterza RM, Koebl H. Defining female voiding dysfunction: ICI-RS 2011. *Neurourology and Urodynamics* 2012;31:313–316.
12. Griffiths DJ. The mechanics of the urethra and of micturition. *British Journal Urology International* 1973;45:497–507.
13. Valentini FA, Besson GR, Nelson PP, Zimmern PE. Clinically relevant modelling of urodynamics function: The VBN model. *Neurourology and Urodynamics* 2014;33:361–366.
14. Valentini F, Nelson P. Carrying out a nomogram for evaluation of detrusor contractility in women. International Continence Society Annual meeting 2014. *Neurourology and Urodynamics* 2014;33:683–685.
15. Valentini F, Nelson P, Robain G, Zimmern PE. Detrusor force in women: Evaluation from mathematical modelling of pressure-flow studies. Society for Urodynamics and Female Urology: Annual Meeting 2014. *Neurourology and Urodynamics* 2014;33:244.
16. Petros P. An anatomical explanation for "urodynamic features and artefacts": re: Hogan S, Gammie A, Abrams P Urodynamic features and artefacts. Neurourol Urodyn 2012;31:1104–1117. *Neurourology and Urodynamics* 2014;33:153–154.
17. Massey JA, Abrams PH. Obstructed voiding in the female. *British Journal of Urology International* 1988;61:36–39.
18. Chassagne S, Bernier PA, Haab F, Roehrborn CG, Reisch JS, Zimmern PE. Proposed cutoff values to define bladder outlet obstruction in women. *Urology* 1998;51:408–411.
19. Lemack GE, Zimmern PE. Pressure flow analysis may aid in identifying women with outflow obstruction. Journal of *Urology* 2000;163:1823–1828.
20. Defreitas GA, Zimmern PE, Lemack GE. Refining diagnosis of anatomic female bladder outlet obstruction: Comparison of pressure-flow study parameters in clinically obstructed women with those of normal controls. *Urology* 2004;64:675–679. discussion 9-81.

21. Nitti VW, Tu LM, Gitlin J. Diagnosing bladder outlet obstruction in women. *Journal of Urology* 1999;161:1535–1540.
22. Groutz A, Blaivas JG, Sassone AM. Detrusor pressure uroflowmetry studies in women: Effect of a 7Fr transurethral catheter. *Journal of Urology* 2000;164:109–114.
23. Solomon E, Yasmin H, Jenks J, Pakzad M, Hamid R, Ockrim J, Greenwell T. MP76-02 The development and validation of a new nomogram for diagnosing bladder outlet obstruction in women. *Journal of Urology* 2014;191:e882.
24. Dybowski B, Bres-Niewada E, Radziszewski P. Pressure-flow nomogram for women with lower urinary tract symptoms. *Archives of Medical Science* 2014;10:752–756.
25. Sch- fer WCB, Griffiths DJ, Tadic SD, Resnick N. The urodynamics of voiding function in females: Grading of bladder outflow conditions on a continuous scale. *Neurourology and Urodynamics* 2011;30:259–260.
26. Griffiths DJ, Constantinou CE, van Mastrigt R. Urinary bladder function and its control in healthy females. *American Journal of Physiology* 1986;251:R225–230.
27. Tan TL, Bergmann MA, Griffiths D, Resnick NM. Stop test or pressure-flow study? Measuring detrusor contractility in older females. *Neurourology and Urodynamics* 2004;23:184–189.
28. Abrams PH, Griffiths DJ. The assessment of prostatic obstruction from urodynamic measurements and from residual urine. *British Journal of Urology International* 1979;51:129–134.
29. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
30. Hogan S, Gammie A, Abrams P. Urodynamic features and artefacts. *Neurourology and Urodynamics* 2012;31:1104–1117.
31. Griffiths DJ. Assessment of detrusor contraction strength or contractility. *Neurourology and Urodynamics* 1991;10:1–18.
32. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and W_{max}) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: Results from a urodynamic database analysis. *World Journal of Urology* 2014;32:1177–1183.
33. Seki N, Shahab N, Hara R, Takei M, Yamaguchi A, Naito S. Voiding dynamics in women with stress urinary incontinence and high-stage cystocele. *International Journal of Urology* 2011;18: 219–224.
34. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, Rizk D, Sand PK, Schaer GN. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourology and Urodynamics* 2010;29:4–20.
35. Kuo HC. Videourodynamic characteristics and lower urinary tract symptoms of female bladder outlet obstruction. *Urology* 2005;66:1005–1009.
36. Eckhardt MD, van Venrooij GE, Boon TA. Urethral resistance factor (URA) versus Schafer's obstruction grade andAbrams-Griffiths (AG) number in the diagnosis of obstructive benign prostatic hyperplasia. *Neurourology and Urodynamics* 2001;20:175–185.
37. Virseda CM, Teba DPF, Salinas CJ, Fernandez LC, Arredondo MF. Pressure-flow studies in the diagnosis of micturition disorders in the female. *Archivos Espanoles de Urologia* 1998;51:1021–1028.

38. Salinas CJ, Adot ZJM, Dambros M, Virseda CM, Ramirez FJ, Moreno SJ, Silmi MA. Factors for voiding dysfunction and cystocele. *Archivos Espanoles de Urologia* 2005;58:316–323.
39. Kranse R, van Mastrigt R. Relative bladder outlet obstruction. *Journal of Urology* 2002;168:565–570.
40. Mytilekas KV, Sokolakis I, Ioannidou E, Apostolidis A. Defining voiding problems in women: Bladder outlet obstruction versus detrusor underactivity. *European Urology Supplements* 2014;13:e688.
41. Constantinou CE. Contraction strength variance during pressure-flow studies. *Neurourology and Urodynamics* 1991;10:47–52.
42. Sch- fer WCY, Tadic S, Griffiths D, Resnick N. Urodynamic grading of bladder outflow conditions in females. *Neurourology and Urodynamics* 2009;29:861–862.
43. Bosch JL, Kranse R, van Mastrigt R, Schroder FJ. Dependence of male voiding efficiency on age, bladder contractility and urethral resistance: Development of a voiding efficiency nomogram. *Journal of Urology* 1995;154:190–194.

Chapter 7

Latissimus Dorsi Detrusor Myoplasty to Restore Voiding in Patients with an Acontractile Bladder – Fact or Fiction?

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Abstract

Multiple causes at any level between the brain and the bladder can lead to diminished voiding efficiency and bladder acontractility. Treatment options for patients with an acontractile bladder have been limited as most patients were forced to perform lifelong self-catheterization at the moment. The latissimus dorsi detrusor myoplasty (LDDM) is a recent and promising therapeutic surgical option to restore adequate bladder emptying on demand. This article critically reviews the available literature on LDDM and focuses particularly on the preoperative diagnostic evaluation and patient selection, treatment outcome and the postoperative contractility measurement.

2.7.1 Introduction

The two major functions of the urinary bladder are storage of urine and evacuation of urine at a convenient moment. Storage dysfunction may lead to increased voiding frequency, premature sensation of urge with or without urgency incontinence, such as in the overactive bladder (OAB) syndrome. In contrast, disturbances in the evacuation of urine may result in hesitancy, weak stream, the feeling of incomplete bladder emptying, post-micturition dribble or urinary retention. Clinically, complaints such as: a high residual volume after voiding and/or urinary retention are generally considered as possible signs of a failure of the bladder to empty completely, i.e. bladder evacuation dysfunction or underactive bladder.

Adequate bladder emptying requires a coordinated contraction of the bladder and relaxation of the urethra. Failure of this mechanism may occur at any level of the 'brain-bladder' axis, from damage to the detrusor muscle itself, its autonomic nerve supply to dysfunction at the level of the spinal micturition centre or even its subcortical or cortical control mechanisms, can lead to symptoms seen in patients with an acontractile bladder. Possible causes include neurological disease (e.g. multiple sclerosis, Parkinson's disease and spinal cord pathology), congenital anomalies (e.g. myelomeningocele, myelodysplasia), acquired infectious, inflammatory or autoimmune diseases, central or peripheral nerve injury secondary to trauma or degenerative disease (or idiopathic). Data regarding incomplete emptying and retention in relation to neurologic disease, for example in multiple sclerosis (0-40%)[1], Parkinson's disease (53%)[2], Multiple System Atrophy (52-67%)[3,4], and cerebral stroke patients (33-40%)[5] have been published in various articles. The other main group of underlying mechanisms is damage to the detrusor muscle itself, for example due to bladder structural and functional changes associated with benign prostatic hyperplasia (BPH), which may lead to deterioration of intramural ganglia, collagen deposits and fibrosis, and eventually to chronic retention. This second causal group of incomplete bladder emptying and retention is mostly age-related. A study focusing on non-institutionalised elderly reported that in the general population >60 years, 22.1% of the men and 10.8% of the women report difficulties in bladder emptying[6].

Treatment options for restoring voiding effectiveness in these patients are only limited. Bladder stimulation techniques such as sacral neuromodulation (SNM) can only be used in case there is little or no damage to the brain-bladder connections and therefore has only limited possibilities, however, it can be an effective treatment in case the patient has a successful test stimulation[7,8]. Patients not eligible for SNM were forced to perform life-long Clean Intermitting Self-Catheterisation (CISC)[9]. However, in the mid-nineties Stenzl *et al.* reported about a reconstructive surgical procedure, the Latissimus Dorsi Detrusor Myoplasty (LDDM), as a potential treatment for the acontractile bladder[10]. The purpose of this article is to review the available literature on LDDM and focus particularly on the preoperative diagnostic evaluation and patient selection, treatment outcome and postoperative contractility measurement.

2.7.2 History and Development

In the past a variety of studies reported on restoration of bladder contractility and voiding effectiveness. In general, the development of techniques to improve bladder contractility can be subdivided into three groups; detrusor muscle stimulation, neurostimulation, neuromodulation and detrusor myoplasty. In 1975 Katona *et al.* described for the first time the use of intravesical electrotherapy for the paralytic bladder[11]. The goal of this stimulation technique was to reactivate intramural bladder receptors to regain normal bladder function[11-13]. However, this first attempt failed because of lack of long term effectiveness. Eventually, direct detrusor stimulation failed based on feasibility and comprehensiveness of the therapy[14]. Brindley *et al.* developed an intradural spinal neurostimulation technique which was first implanted in 1972, followed by larger case-series of patients with spinal cord injury[15,16]. The stimulation technique activates the sphincter as well as the detrusor muscle at the same time. Due to the slower contraction and relaxation characteristics in the bladder wall (smooth muscle) compared to the urethra (striated muscle), voiding occurs between stimulation pulses. Other neurostimulation and neuromodulation techniques have been developed ever since. One of these developments during the mid-nineties is sacral neuromodulation (SNM). The SNM is proposed to activate or 'reset' somatic afferent inputs that play an important role in the modulation of sensory processing in micturition reflex pathways in the spinal cord and higher brain areas[17]. Sacral neuromodulation (SNM) is now widely used for a variety bladder dysfunctions, including non-obstructive urinary retention[7].

In 1985 Messing *et al.* published the first case of functional bladder augmentation using bilateral pedicled rectus femoris muscle flaps[18]. In addition to this ,several articles described a myoplasty technique using the rectus abdominis muscle as a pedicled flap[19-21]. However, both techniques, did not seem to be capable of building up or sustaining adequate pressure needed for micturition[21]. Bipennate muscles, such as the rectus femoris and rectus abdominis have shorter muscle fibres and a limited capacity for contractility. Secondly, the segmental nerve supply and their course and insertion into the muscle make the rectus abdominis muscle inappropriate for pedicled or free functioning muscle transfer[22]. Therefore, neither of these rectus muscles are a good choice for functional detrusor muscle replacement. In contrast, the configuration of the gracilis muscle makes it suitable for detrusor replacement. However, it is not strong enough and does not contain enough volume for bladder reconstruction[22]. The ability of the latissimus dorsi as a musculocutaneous flap was initially discovered by Tansini in 1906[23]. However, it was not until 1976 that the latissimus dorsi flap became established in reconstructive surgery, as a muscle flap and a musculocutaneous flap[24-26]. In 1994 von Heyden *et al.* described for the first time the use of the latissimus dorsi muscle as a free-muscle flap in dogs. However, the transposed latissimus dorsi flap was only able to evacuate urine less than 50% of the capacity[27]. Stenzl *et al.* published in 1998 their first experience with LDDM in three patients[28], followed by a series of publications with regard to latissimus dorsi myoplasty in more patients with an acontractile bladder[29-31].

2.7.3 Latissimus dorsi muscle

The latissimus dorsi muscle is widely used in reconstructive procedures. The flap has the advantage of being a wide, expandable muscle with a constant and long pedicle. It is utilised for soft-tissue coverage, defect obliteration, tissue augmentation and functional muscle transfer. At its original location, the muscle itself inserts on the humerus for medial rotation, adduction and shoulder extension. This is only possible through synergistic actions of the latissimus dorsi with other muscles[32].

2.7.3.1 Anatomy Latissimus dorsi muscle

The latissimus dorsi is a triangular skeletal muscle originating from the lower thoracic and lumbar vertebrae, sacrum and posterior iliac crest. The latissimus dorsi joins with the teres major muscle at the level of the scapula and wraps around it as it traverses the axillary space, creating the posterior axillary fold[32]. At the cranial side the muscle is inserted into the lower end of the bicipital groove of the humerus, lateral to the teres major muscle. The latissimus is innervated via the thoracodorsal nerve (C6 to C8).

Mathes and Nihai classified in 1981 the vascular anatomy of the latissimus dorsi muscle as being a Type-V variety, which was defined as 'one dominant vascular pedicle and secondary segmental vascular pedicles'[33]. In case of the latissimus dorsi the dominant vascular pedicle is the thoracodorsal artery (TDA) and vein. The thoracodorsal artery originates in most cases from a branch of the subscapular artery, which originates from the axillary artery[34]. An anatomical study showed that outside the latissimus dorsi muscle the TDA branched to the serratus anterior muscle in 99% of the cases and, in addition, a direct cutaneous branch to the skin of the axilla was seen in 47% of the dissections[34]. When perforating the latissimus dorsi muscle, the TDA splits into two main branches, a transverse and descending branch[35,36]. In addition, cadaver dissection studies showed notable similarity in the course of the thoracodorsal nerve, intertwining the TDA and its branches or perforators in 40% of the cases[35].

2.7.4 Preoperative evaluation

2.7.4.1 Patient selections

Currently there are only four studies reporting case series of patients treated with LDDM. Most of the studies regarding LDDM with patient inclusion are published by Stenzl and Ninkovic. Therefore, the criteria used in the different studies reporting about LDDM are highly comparable and current knowledge about the clinical impact of this surgical technique is mainly based on their studies[28-30,31]. Causes of bladder acontractility varied from spinal cord trauma, in the majority of patients, to patients with congenital anomalies. In

a portion of the patients undergoing LDDM, the aetiology of the acontractility was not clear - the idiopathic acontractile group. The percentage of patients with idiopathic bladder acontractility varied from 16.7% to 25.0% among studies in which the aetiology was mentioned[29-31]. One may question whether these patients are indeed eligible for this procedure.

All patients included in the LDDM studies showed bladder acontractility on conventional urodynamics, meaning no detrusor pressure increase was seen during the micturition phase. Furthermore, bladder capacity, urethral sphincter function and overactive detrusor contractions were analysed. In addition to the conventional urodynamic assessment, in some patients an unsuccessful sacral neuromodulation test was performed in the diagnostic phase. To be sure that clean intermittent catheterisation was not a feasible option, most patients performed CISC for at least two years before LDDM was considered. Although age is not an absolute contraindication, age related nerve regeneration capacity is thought to be associated with worse outcome after free flap surgery. In our centre, LDDM is usually not performed preferable in patients older than 60 years because of the increased complication risk, their life expectancy and delayed nervous regeneration. Other relative contraindications for LDDM are surgery in the pelvic region, limited motivation to undergo the treatment and/or a bladder capacity <400 ml. Subsequently, stress urinary incontinence due to reduced or absent sphincter innervation or iatrogenic sphincter damage is also seen as a relative contraindication. Another absolute contraindication is defective innervation of the rectus abdominis muscle. The nerve branch innervating the rectus abdominis muscle is used for reinnervation of the latissimus dorsi flap, which is considered the most important step of the surgical procedure.

The preoperative work-up includes conventional urodynamic assessment and analysing the function of the rectus abdominis muscle, the pudenal nerve and pelvic nerve by using electromyography (EMG). Furthermore, beside the usual preoperative diagnostic evaluation, cystoscopy and upper urinary tract imaging are performed. In some centres a sacral neuromodulation test is also part of the preoperative work-up. Ambulatory urodynamic evaluation is advised as van Koeveringe *et al.* described that more than 80 % of the patients showing an acontractile bladder on conventional urodynamics show detrusor contractions on ambulatory urodynamics (AUM)[37]. So the absence of contractions on conventional urodynamics (CUM) had been seen for other reasons and might be treated differently.

2.7.4.2 Ambulatory urodynamic measurement (AUM) as preoperative diagnostic evaluation

LDDM has a success rate around 71% (Ginsberg 2011), which means that still 29% of the patients have to perform some degree of CISC after undergoing this elaborative surgical procedure[9]. Moreover, a small study from our centre regarding the additional value of ambulatory urodynamics showed that, in patients with the suspicion of an acontractile bladder, alleged bladder acontractility based on the conventional urodynamic measurement (CUM), the diagnosis 'detrusor acontractility' was confirmed by AUM in only 17% (4 out

of 24 cases). The other 83% of the patients had multiple detrusor contractions during voiding attempts on AUM, during their normal daily life activities[37]. These results have also been confirmed in a larger group of patients with alleged bladder acontractility from our centre (unpublished data). So, it can be questioned here to what extent we selected the right patients for the right treatment? These data reflect the need of an additional tool in the diagnostic process of patients with alleged bladder acontractility. Improving patient selection eventually leads to treatment better adjusted to the situation of the patient.

Introduction of ambulatory urodynamics in the evaluation of alleged bladder acontractility is an acceptable step in terms of the tolerability of the assessment[38]. By adding AUM to the diagnostic process, we might even come to the conclusion that the older patients with idiopathic bladder acontractility based on CUM, who do worse after LDDM, have a different diagnosis after AUM. As Gakis mentioned, AUM might reveal detrusor hypocontractility rather than acontractility in some of the patients[39]. However, a portion of these patients might even suffer from detrusor overactivity with impaired contractility (DOIC)[37]. As there is no clear diagnostic algorithm for bladder hypocontractility up to this point, it is too easy to just extend the limits of LDDM based only on this conclusion[40]. To have a more unambivalent view on the treatment outcome it might be considered, according to the algorithm illustrated in Figure 1, to first treat the group of patients clearly having an acontractile detrusor based on both CUM and AUM and, in addition, an unsuccessful SNM test before extending the indication for LDDM.

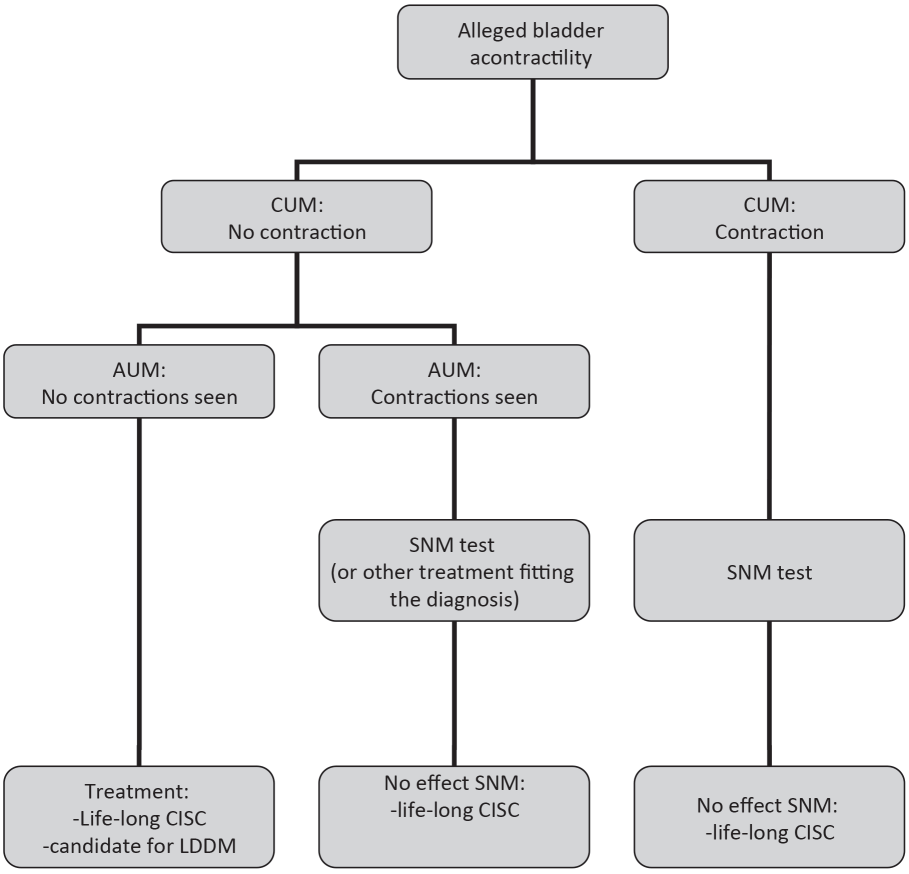

Figure 1. Proposed diagnostic flowchart of patients with alleged bladder acontractility. CUM: Conventional Urodynamic Measurement, AUM: Ambulatory Urodynamic Measurement. SNM: Sacral Neuromodulation. CISC: Clean Intermitting Self-Catheterisation. LDDM: Lattisimus Dorsi Detrusor Myoplasty

2.7.5 Latissimus dorsi detrusor myoplasty (LDDM) procedure

2.7.5.1 Surgical technique

The surgical procedure is performed by a specialised team of urologists and plastic-reconstructive surgeons. First, the team of reconstructive surgeons performs an axillar incision at the anterior border of the latissimus to expose the muscle, preferably of the non-dominant arm. Next, the thoracodorsal vessels and nerve are uncovered. A free muscle flap of at least two-thirds of the muscle is used for the myoplasty. Sutures are used to

mark the resting length of the muscle, which is important when the muscle later is fixated in the pelvis. The neurovascular bundle is now still intact and is not transected until the recipient vessels have been exposed and are ready for microsurgical anastomosis. After the urologist has performed a Pfannenstiel incision, the lowest branches of the intercostal nerve (innervating the rectus abdominis muscle) and the ipsilateral inferior epigastric vein and artery are marked. The bladder is exposed via retroperitoneal approximation and the trigone and both ureters are identified. After exposing the bladder, the sacrospinal ligaments are marked. On the dorsal side of the bladder, a vicryl mesh is positioned underneath the trigone and pulled through underneath one of the bladder pedicles and sutured to coopers ligament (Figure 2). In female patients the mesh is not needed and the vaginal top can be used for dorsal attachment of the muscle.

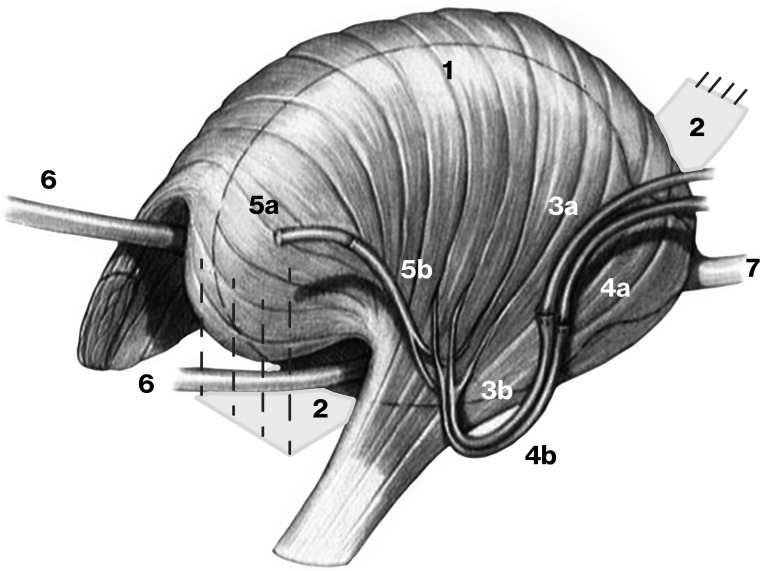

Figure 2. Schematic drawing of lattisimus dorsi detrusor myoplasty in male patient. 1: shape and location of latissimus dorsi muscle at end of procedure. 2: polyglycolic acid mesh (attached to dorsal bladder wall), which is fed through tunnel underneath prostate and attached to Cooper'sligament on either side. 3a: inferior epigastric (donor) artery. 3b: thoracodorsal (recipient) artery. 4a: inferior epigastric (donor) vein. 4b: thoracodorsal (recipient) vein. 5a: motor branch of 12th intercostal (donor) nerve. 5b: thoracodorsal (recipient) nerve. 6: ureters. 7: urethra [41] *(Reprinted from The Journal of Urology with kind permission from Elsevier)*

The thoracodorsal pedicle is now dissected and the latissimus dorsi muscle flap is transferred to the pelvis. The thoracodorsal vessels are microsurgically connected to the epigastric vessels using end-to-end anastomoses. The latissimus tendon is then attached to the right sacrospinal ligament. On the anterior side the latissimus dorsi muscle is connected to Cooper's ligament and the pubic bone, while on the posterior side it is attached to the vicryl mesh. In total, about 75% of the exposed bladder is covered with latissimis dorsi muscle except for the trigonum, both ureteral orifices and the lateral vesical pedicles. The initial resting length of the latissimus dorsi is determined by using the previously positioned sutures. Finally, the microscopic end-to-end coaptation of the thoracodorsal nerve to the earlier identified lower branches of the subcostal nerve is performed by the reconstructive surgeon.

2.7.5.2 Postoperative care

The postoperative care consists of Doppler ultrasound assessment of the vessel anastomosis during the first five days after surgery. In several studies of Ninkovic and Stenzl, perfusion of the transferred latissimus dorsi muscle was monitored using an intramuscular probe measuring the pO_2[30,41]. The bladder is initially drained with an indwelling catheter for four to six weeks, after which the patient starts performing CISC. At twelve weeks after LDDM, patients try to perform bladder emptying by raising abdominal pressure. The CISC frequency can then be reduced depending on the post void residual. A conventional urodynamic assessment is carried out to evaluate the flow, residual volume and detrusor pressure (which are the difference between the vesical and abdominal pressure). The first year this is carried out every three months combined with a Doppler ultrasound assessment. It might also be useful to perform a dynamic MRI-scan to measure the muscle thickness and depict contraction during the follow-up.

2.6.5.3 Outcome

Until recently the latissimus dorsi detrusor myoplasty was only an experimental surgical procedure. Because of this, there are currently only four studies describing small case series of patients treated with LDDM. The mean or median age among the different studies varied from 39 to 42 years, with a postoperative follow-up ranging from 8-89 months. Most of the patients carried out CISC before LDDM was performed (17-319 months).

In three of the four published LDDM studies, outcome of the treatment was defined as 'complete', 'partial' or 'no' response, depending on the post void residual (PVR) and amount of CISC (Table 1). A 'complete' response was defined as spontaneous voiding after LDDM with a post-void residual (PVR) of less than 100 ml. The first article of Stenzl *et al.* described the first three patients successfully treated with LDDM with a PVR ranging from 0-95 ml[28]. Subsequently, the other studies showed a complete response rate varying from 70.8% to 85.0%. The largest of the four studies, a recent multicentre study discussing the long-term

results, showed a success rate after the procedure of 70.8% (17/24 patients), with a partial response in another 12.5% (3/24 patients) of the patients[31]. The same study showed absence of UTIs after LDDM in the group of complete responders. However, as in the other studies the specific decrease in frequency in UTIs is not mentioned.

With the promising success rates, the main question is to what extent these results reflect the long-term outcome after LDDM. Although the mean follow-up period is 46 months there is a wide follow-up range, from eight up to 89 months. When comparing this to the relatively young mean age of the included patients, these results most probably reflect short to midterm outcome rather than the long-term outcome. So although the complete response rate in this study looks promising, it still remains to be seen what are the LDDM results in this relatively young group of patients ten years after surgery.

In two of the articles, both the outcome and the initial, preoperative diagnosis were given per patient[30,41]. In both case series, there was a minority of patients with idiopathic bladder acontractility - in five and two patients - respectively. Remarkably, the outcome after LDDM in this group was worse compared to the other patients. In the first study two of the five idiopathic acontractile bladder patients were non-responders and another patient was a partial responder, making the complete response rate of the idiopathic group in this study only 40%[41]. In the second study one of the two patients with an idiopathic acontractile bladder did not manage to void voluntarily and CISC status was unchanged. In general, these idiopathic patients appear to be much older (mostly ≥60 years) than the other patients selected for LDDM. Therefore, it is suggested to use extra caution in this specific group of patients in which no clear origin of bladder acontractility is found. Furthermore, the use additional diagnostic evaluations should be considered in this group. In the somatic area, an ambulatory urodynamic investigation is advised and, in addition, a proper psychological and psychiatric evaluation should be considered[42].

2.7.5.4 Complications

Complications after LDDM are classified among different studies according the Clavien-Dindo classification of surgical complications and given in Table 2[43]. In general, the complications mentioned in all four studies represent only mild to moderate complications. Gakis *et al.* mentioned for this major surgical procedure a remarkably low complication rate of 33% (8 of 24 patients)[31]. None of the studies report the presence of severe complications and in none did free flap failure occur intraoperative or postoperatively. The overall low complication rate can be explained by the fact that this elaborative surgical technique is only performed in referral centres by a specialised team of urologists and reconstructive surgeons[31].

The donor-site complication rate was moderate to low as well and cases concerned persistent seroma needing puncture or drainage and wound healing problems. In general, extension and adduction ability are compromised after transfer of the latissimus dorsi muscle. These deficits result in a faster rate of fatigue during over-head activities. However, according to Spear *et al.* there is no decrease in the range of shoulder motion when a latissimus dorsi muscle flap is used[32].

Table 1. Outcome after Latissimus Dorsi Detrusor Myoplasty (LDDM).

				Complete Response*			Partial Response+			No Response$		
	Total N	Mean age	FU in months	N (M/F)	Median PVR in ml (range)	CISC/ 24 hrs	N (M/F)	Median PVR in ml (range)	CISC/24 hrs	N (M/F)	Median PVR in ml (range)	CISC/24 hrs
Stenzl *et al.* 1998	3	40	12-20	3	50 (0-95)	-	0	-	-	0	-	-
Stenzl *et al.* 2000	11	42	12-46	8 (-/-)	-	0	2 (-/-)	-	1-3	1 (-/-)	-	4-5
Ninkovic *et al.* 2003	20	39	18-74	17 (11/6)	0 (0-80)	0	1 (0/1)	100	0	2 (1/1)	435 (420-450)	4-5
Gakis *et al.* 2011	24	39	8-89	17 (11/6)	25 (0-100)	0	3 (3/0)	200 (150-250)	2-4	4 (2/2)	575 (400-700)	4-6

*FU: Follow-up period. PVR: post-void residual. CISC: Clean Intermitting Self-Catheterisation. * Spontaneaous postop voiding + PVR less than 100 ml, + Spontaneaous postop voiding + PVR less than 100-250 ml, $ No spontaneous postop voiding*

Table 2. Complications according to Clavien-Dindo classification.

	Stenzl *et al.* 1998	Stenzl *et al.* 2000	Ninkovic *et al.* 2003	Gakis *et al.* 2011
Clavien-Dindo Classification	Complication (N)	Complication (N)	Complication (N)	Complication (N)
I	Urinary tract infection (n=1)	Urinary tract infection (n=2)	Wound healing disorder (n=1) Urinary tract infection (n=2)	Deep venous thrombosis (n=1) Urinary tract infection (n=2)
II	-	-	Bleeding disorder (n=2)	Pulmonary embolism (n=1)
III-a	-	Retroperitoneal hematoma (n=1) Persistent seroma (n=1)	Persistent seroma (n=3)	Wound healing disorder (n=1) Pelvic abscess (n=3)
III-b	-	-	Suspicion flap ischemia (n=2)	Persistent seroma (n=2)
III-(d)	-	-	-	Compartment syndrome of operated arm(n=1)
IV-a	-	-	-	-
IV-b	-	-	-	-
V	-	-	-	-
Total No.	1	4	10	11

2.7.5.5 Postoperative bladder contractility measurement

The studies reporting on LDDM, use different measurement techniques to evaluate the contractility status of the bladder postoperatively. In the first study of Stenzl *et al.* maximum flow rate together with maximum detrusor pressure, bladder compliance and post void residual were evaluated postoperatively[28]. In a subsequent study published in 2000, bladder contractility parameters in the follow-up period were not mentioned[30]. In addition, Ninkovic *et al.* uses the maximal actual detrusor pressure in the follow-up period[41]. In the multicenter study of Gakis *et al.*, the Bladder Contractility Index (BCI) was introduced as the main postoperative contractility parameter[31]. The shift in contractility parameters reflects the continuous search for a reliable parameter for bladder contraction power.

In general, patients eligible for LDDM show no micturition contraction on CUM and a portion of these patients are unable to void. As all contractility parameters (i.e. BCI, $P_{det.Qmax}$, W_{max} etc.) are flow dependent, it is impossible and unnecessary to evaluate the detrusor contractility with these parameters preoperatively in this patient group. Due to this condition urethral parameters such as obstruction and sphincter function are almost impossible to evaluate. In the BCI formula ($P_{det.Qmax} + 5Q_{max}$) detrusor pressure at maximum flow ($P_{det.Qmax}$) and maximum flow (Q_{max}) are included[44]. In addition, after LDDM surgery, BCI change could indicate an improved voiding effectiveness. However,

a good BCI can be caused by increased bladder contractility at maximum flow, less outlet resistance and/or better urinary flow. The latter can originate from increased bladder contractility after LDDM or caused by a more effective transmission of the abdominal pressure to the bladder, both resulting in increased urinary flow. In other words, a good BCI after LDDM does not necessarily indicate the presence of bladder contractility. In the case of a normal pressure transmission on both vesical and abdominal catheters during urodynamics, an increase in detrusor pressure (vesical minus abdominal pressure) would be a simple measurement for bladder contractility supported by the LD flap. Secondly, to measure postoperative bladder contraction power in male and female patients, it might be beneficial to also incorporate W_{max} as a contractility parameter. W_{max} is thought to reflect bladder contractility better and to be less dependent on the obstruction grade compared to BCI[45].

To make it even more complex, if the indications for LDDM would be extended to patients with a hypocontractile bladder, choosing the right contractility parameter is of particular interest[39]. In that case, to justify the choice for LDDM surgery in a specific group of hypocontractile patients, selection should be based on a combination of parameters reflecting bladder contractility and voiding effectiveness initially. Postoperatively these should and also can be re-evaluated and compared to the initial values. With an increasing number of publications regarding LDDM as a therapeutic option in patients with an acontractile (or even hypocontractile) bladder, postoperative contractility measurements should be carried out in similar fashion amongst different studies. This way study results will be comparable.

2.7.6 Conclusions

The latissimus dorsi detrusor myoplasty seem to be a valuable therapy for a distinct group of patients with bladder acontractility unsuccessfully treated with other therapies. For patient selection it is important to consider inclusion of ambulatory urodynamics in the diagnostic process. Current literature only gives limited information about the long-term effects of LDDM treatment. In addition, group size and heterogeneity of the study groups should be taken into account when extrapolating the results to current clinical practice. Therefore, a longer follow-up of the already treated patients in combination with larger prospective studies are desirable to evaluate the long-term outcomes after LDDM.

References

1. de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B, Genulf. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Multiple Sclerosis* 2007;13:915–928.
2. Sakakibara R, Uchiyama T, Yamanishi T, Shirai K, Hattori T. Bladder and bowel dysfunction in Parkinson's disease. *Journal of Neural Transmission* 2008;115:443–460.
3. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. *Journal of Neurology, Neurosurgery and Psychiatry* 2001;71:600–606.
4. Bloch F, Pichon B, Bonnet AM, Pichon J, Vidailhet M, Roze E, Perrigot M. Urodynamic analysis in multiple system atrophy: characterisation of detrusor-sphincter dyssynergia. *Journal of Neurology* 2010;257:1986–1991.
5. Tibaek S, Gard G, Klarskov P, Iversen HK, Dehlendorff C, Jensen R. Prevalence of lower urinary tract symptoms (LUTS) in stroke patients: a cross-sectional, clinical survey. *Neurourology and Urodynamics* 2008;27:763–771.
6. Diokno AC, Brock BM, Brown MB, Herzog AR. Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalised elderly. *Journal of Urology* 1986;136:1022–1025.
7. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Nijholt AA, Siegel S, Jonas U, Cappellano F. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *Journal of Urology* 2007;178:2029–2034.
8. White WM, Dobmeyer-Dittrich C, Klein FA, Wallace LS. Sacral nerve stimulation for treatment of refractory urinary retention: longterm efficacy and durability. *Urology* 2008;71:71–74.
9. Ginsberg DA. Bladder acontractility: detrusor myoplasty and other options. *Nature Reviews Urology* 2011;8:185–186.
10. Stenzl A, Ninkovic M, Willeit J, Hess M, Feichtinger H, Schwabegger A, Bartsch G. Free neurovascular transfer of latissimus dorsi muscle to the bladder. I. Experimental studies. *Journal of Urology* 1997;157:1103–1108.
11. Katona F, Berenyi M. Intravesical transurethral electrotherapy of bladder paralysis. *Orvosi hetilap* 1975;116:854–856.
12. Katona F. Stages of vegatative afferentation in reorganisation of bladder control during intravesical electrotherapy. *Urologia Internationalis* 1975;30:192–203.
13. Katona F, Berenyi M. Intravesical transurethral electrotherapy in meningomyelocele patients. *Acta Paediatrica Academiae Scientiarum Hungaricae* 1975;16:363–374.
14. Cheng EY, Richards I, Balcom A, Steinhardt G, Diamond M, Rich M, Chandra M. Bladder stimulation therapy improves bladder compliance: results from a multi-institutional trial. *Journal of Urology* 1996;156:761–764.
15. Brindley GS. History of the sacral anterior root stimulator, 1969–1982. *Neurourology and Urodynamics* 1993;12:481–483.
16. Brindley GS, Polkey CE, Rushton DN, Cardozo L. Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases. *Journal of Neurology, Neurosurgery and Psychiatry* 1986;49:1104–1114.
17. Leng WW, FO. Bilateral rectus femoris pedicle flaps for detrusor augmentation in the prune belly syndrome. *Journal of Urology* 1985;134:1202–1205.
18. Zhang YH, Shao QA, Wang JM. Enveloping the bladder with displacement of flap of the rectus abdominis muscle for the treatment of neurogenic bladder. *Journal of Urology* 1990;144:1194–1195.

19. Chancellor MB. How sacral nerve stimulation neuromodulation works. *Urologic Clinic of North America* 2005;32:11–18.
20. Messing EM, Dibbell DG, Belzer Chancellor MB, Rivas DA, Salzman SK. Detrusor-myoplasty to restore micturition. *Lancet* 1994;343:669.
21. van Savage JG, Perez-Abadia G, Palanca LG, et al. Comparison of the experience with acute and chronic electrically stimulated detrusor myoplasty. *Neurourology and Urodynamics* 2002;21:516–521.
22. Ninkovic M, Dabernig W. Flap technology for reconstructions of urogenital organs. *Current Opinion in Urology* 2003;13:483–488.
23. Maxwell GP. Iginio Tansini and the origin of the latissimus dorsi musculocutaneous flap. *Plastic Reconstructive Surgery* 1980;65:686–692.
24. Olivari N. The latissimus flap. *British Journal of Plastic Surgery* 1976;29:126–128.
25. McCraw JB, Dibbell DG. Experimental definition of independent myocutaneous vascular territories. *Plastic Reconstructive Surgery* 1977;60:212–220.
26. McCraw JB, Dibbell DG, Carraway JH. Clinical definition of independent myocutaneous vascular territories. *Plastic Reconstructive Surgery* 1977;60:341–352.
27. von Heyden B, Anthony JP, Kaula N, Brock GB, Jakse G, Tanagho EA. The latissimus dorsi muscle for detrusor assistance: functional recovery after nerve division and repair. *Journal of Urology* 1994;151:1081–1087.
28. Stenzl A, Ninkovic M, Kolle D, Knapp R, Anderl H, Bartsch G. Restoration of voluntary emptying of the bladder by transplantation of innervated free skeletal muscle. *Lancet* 1998;351:1483–1485.
29. Ninkovic M, Stenzl A, Schwabegger A, Bartsch G, Prosser R. Free neurovascular transfer of latissimus dorsi muscle for the treatment of bladder acontractility: II. Clinical results. *Journal of Urology* 2003;29:179–180.
30. Stenzl A, Strasser H, Klima G, et al. Reconstruction of the lower urinary tract using autologous muscle transfer and cell seeding: current status and future perspectives. *World Journal of Urology* 2000;18:44–50.
31. Gakis G, Ninkovic M, van Koeveringe GA, Raina S, Sturz G, Rahnama'i MS, Stenzl A. Functional detrusor myoplasty for bladder acontractility: long-term results. *Journal of Urology* 2011;185:593–599.
32. Spear SL, Hess CL. A review of the biomechanical and functional changes in the shoulder following transfer of the latissimus dorsi muscles. *Plastic Reconstructive Surgery* 2005;115:2070–2073.
33. Mathes SJ, Nahai F. Classification of the vascular anatomy of muscles: experimental and clinical correlation. *Plastic Reconstructive Surgery* 1981;67:177–187.
34. Rowsell AR, Davies DM, Eisenberg N, Taylor GI. The anatomy of the subscapular-thoracodorsal arterial system: study of 100 cadaver dissections. *British Journal of Plastic Surgery* 1984;37:574–576.
35. Colohan S, Wong C, Lakhiani C, Cheng A, Maia M, Arbique G, Saint-Cyr M. The free descending branch muscle-sparing latissimus dorsi flap: vascular anatomy and clinical applications. *Plastic Reconstructive Surgery* 2012;130:776e–787e.
36. Rowsell AR, Eisenberg N, Davies DM, Taylor GI. The anatomy of the thoracodorsal artery within the latissimus dorsi muscle. *British Journal of Plastic Surgery* 1986;39:206–209.
37. van Koeveringe GA, Rahnama'i MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. *British Journal of Urology International* 2010;105:508–513.

38. Oh SJ, Son H, Jeong JY, Ku JH. Patients' experience with ambulatory urodynamics. A prospective study. *Scandinavian Journal of Urology and Nephrology* 2006;40:391–396.
39. Gakis G, Ninkovic M, Stenzl A. Bladder hypocontractility–extending the indication for LDDM. *Nature Reviews Urology* 2012;9:231.
40. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723–728.
41. Ninkovic M, Stenzl A, Schwabegger A, Bartsch G, Prosser R, Ninkovic M. Free neurovascular transfer of latissimus dorsi muscle for the treatment of bladder acontractility: II. Clinical results. *Journal of Urology* 2003;169:1379–1383.
42. Cortes E, Sahai A, Pontari M, Kelleher C. The psychology of LUTS: ICI-RS 2011. *Neurourology and Urodynamics* 2012;31:340–343.
43. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004;240:205–213.
44. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *British Journal of Urology International* 1999;84:14–15.
45. Lecamwasam HS, Yalla SV, Cravalho EG, Sullivan MP. The maximum watts factor as a measure of detrusor contractility independent of outlet resistance. *Neurourology and Urodynamics* 1998;17:621–635.

Chapter 8

Detrusor Underactivity: Pathophysiological Considerations, Models and Proposals for Future Research. ICI-RS 2013

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Abstract

Aims

Detrusor underactivity, resulting in either prolonged or inefficient voiding, is a common clinical problem for which treatment options are currently limited. The aim of this report is to summarise current understanding of the clinical observation and its underlying pathophysiological entities.

Methods

This report results from presentations and subsequent discussion at the International Consultation on Incontinence Research Society (ICI-RS) in Bristol, 2013.

Results and Conclusions

The recommendations made by the ICI-RS panel include: Development of study tools based on a system's pathophysiological approach, correlation of in vitro and in vivo data in experimental animals and humans, and development of more comprehensive translational animal models. In addition, there is a need for longitudinal patient data to define risk groups and for the development of screening tools. In the near-future these recommendations should lead to a better understanding of detrusor underactivity and its pathophysiological background.

2.8.1 Introduction

Detrusor underactivity has been defined by the International Continence Society as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal timespan[1]. Successful and complete emptying is necessarily determined by the interplay of several factors including the ability of the bladder to empty, and the resistance offered by the outflow tract (i.e. the capacity of outlet opening). Diminished bladder emptying may occur because of reduced detrusor contractile ability (not equivalent to contractility), an impairment of the outflow tract or a combination of these factors. To a certain extent, both factors may be able to compensate for each other but this compensatory capacity may change in association with disease and ageing.

Anatomical (structural) or physiological (functional) changes may impair either detrusor contractile ability or urethral opening capacity. Efferent nerves may be damaged, the amount of muscle in the bladder wall reduced or replaced by connective tissue, or there may be a reduction in true contractility. In addition, structural bladder outlet obstruction can reduce effective voiding. When both bladder contractile function and the bladder outlet are adequate, an impairment of sensory nerves may also lead to inefficient voiding.

To void efficiently, a feed-forward mechanism by which urinary flow in the urethra helps to enhance and maintain adequate contractile function of the bladder, until the bladder is empty is required. Sensory information is fed back to the motor system at several levels of control between the end organ and brain cortex. These sensors themselves can be damaged, for example through an effect of ageing or ischaemia. In addition, impairment of innervation can lead to decreased information transfer via either the sensory or motor nerves. A functional disruption of higher central nervous regulatory systems can lead to functional abnormal voiding. This can occur as a result of disease induced deregulation (e.g. Parkinson's or Alzheimer's disease), ageing induced defects and psychological or psychiatric pathology. Whether ageing related defects in these systems lead to inefficient emptying depends on the compensatory ability of mechanisms involved in voiding. To manage a dysfunction, the defect itself may be treated, but the compensatory capacity of another mechanism can also be improved. The choice of treatment may depend on the therapeutic effect required and the potential side-effects of the proposed treatment.

The most comprehensive approach to diagnose and treat voiding inefficiency in humans is first to study the pathophysiological alterations leading to impaired bladder emptying in humans. Animal models that mimic elements of derangements, as discussed above may be helpful to identify options that ameliorate these defects, or stimulate compensatory mechanisms and so define potentially treatable options in humans.

Since publication of the ICI-RS article in 2011 the topic of detrusor underactivity (DU) has received increasing research interest[2], with 54 articles retrievable by PubMed using detrusor underactivity/underactive bladder as search terms. However, few of these publications lead to better understanding of the complex pathophysiology underlying

this urological entity[3-7]. There are still many uncertainties with regard to the underactive bladder, particularly the role of ageing, altered sensory function, and the translational value of existing animal models.

2.8.2 Ageing: The primary cause or a condition necessary for development of detrusor underactivity?

The prevalence of impaired bladder emptying is associated with increasing age and occurs in both men and women[8-10]. This is manifest in the frequent finding of a raised post-void residual urinary volume in an otherwise asymptomatic older person[11] and in association with other lower urinary tract diagnoses upon presentation to a clinician[12]. Impaired bladder emptying has most often been described in association with detrusor overactivity, regardless of the presence of bladder outlet obstruction[13]. Urodynamic data revealing impaired emptying function in the elderly are conflicting[14], and also are limited to those with symptoms, perhaps limiting the interpretation of age-associated pathophysiology. Histologically, older bladders differ from those in younger people, in that there is an age-associated accumulation of connective tissue and collagen, resulting in a reduction of the smooth muscle: collagen ratio[15], which may lead to a reduction of transmitted contractile force. At the level of the muscle cell, detrusor contractility is not reduced with ageing in those without detrusor overactivity or obstruction, unlike the diminution reported in older people with these conditions[16]. The reduction of bladder sensory function reported in association with increasing age[17] may also contribute to DU. Functional magnetic resonance imaging in asymptomatic older people found diminished response to bladder filling in the insula, an area of the brain responsible for mapping visceral sensations[18]. The current state of the limited evidence suggests that a number of factors associated with ageing may, per se, predispose to impaired emptying and that it is likely that, for those unaffected older people, their compensatory capacity outweighs the drivers of impaired emptying.

2.8.3 The role of altered sensory function in detrusor underactivity

Impaired bladder contractile ability has been traditionally regarded as a major aetiological factor of DU. However, in the elderly, decreased bladder sensations are associated with DU and suggest a more complex pathology. Because detrusor contraction force and duration are a result of efferent nerve activity in combination with an adequate contractile ability, which in turn is dependent on sensory input, there is the potential for impaired afferent function to cause DU[19]. Structural and functional tissue changes accompanying ageing and particular diseases may result in altered bladder afferent function, with subsequent reflex impairment of voiding function.

The urothelium, detrusor muscle, interposed interstitial cells, and ganglia collectively form a mechano-sensitive sensor transducer system which activates afferent nerve fibres[19]. Abnormalities in each of these components could have an impact on LUT function by altering release of neurotransmitters, as well as the excitability of sensory fibres and the contractility of detrusor muscle in the urinary bladder. Furthermore, because many urothelial functions may be altered with age, defects in urothelial cells may contribute to age-related changes. Moreover, positive sensory feedback from urethral afferents, in response to flow, has been shown to augment detrusor pressure amplitude and duration, and is necessary for efficient voiding[20], thus urethral sensory disturbance could also lead to DU in specific patient categories.

In addition to the positive feedback mechanism described above, a defect in sensory function of the bladder itself may lead to delayed voiding and overdistention, again leading to damage of the sensors, denervation, or impaired muscle function.

2.8.4 What is the value of current animal models of concomitant disease?

The reason for developing animal models is usually to mimic part of a human pathology or a functional problem. Since the clinical problems in DU are in the voiding phase and involve ''prolonged duration'' and/or ''reduced contractile strength'', it is worthwhile to concentrate on creating one or both in an animal. The value of such models is dependent on the question to be addressed: for example, to study the consequence of a lesion or artificial pathology on the voiding phase, or to test a drug intended to reverse a voiding problem. For the latter it is important that the functional parameters in the animal model maybe reversed to warrant testing of a drug. Various models have been constructed and these are discussed with respect to the addition of information to our current knowledge on DU below. Particular attention is given to ageing, age-related comorbidity, obstruction models, and specific neurogenic models for DU.

2.8.4.1 Ageing models

To study ''healthy ageing,'' animal models use the concept of a ''healthspan'' as an age range when an animal is generally healthy[21]. Human lower urinary tract dysfunction, prevalent at an age >65 years should be reflected in laboratory animals. Biomarkers associated with an ageing phenotype appear in mice and rats >18–24 months and guinea-pigs when >30 months[22-24]. In vivo, bladder contractile function may not diminish with age[25] but compliance and/or micturition frequency increase or decrease[25-27]. In vitro, contractility is either diminished or increased with age in both rats and mice[26,28-30]. Muscle loss may[28], but not always increase with age: for example intravesical pressure at micturition actually increased with age in rats[30]. Moreover, motor nerve density is preserved in rabbits[31]. Afferent nerve density declines in ageing animals[32]; however, the age-related increase of urothelial transmitter release in the human bladder[33] has not been reproduced in animal preparations.

Overall, there are conflicting data on bladder function and morphology in ageing animals. It is crucial to characterise individual ageing animal models, using comparable criteria, to determine if their phenotype mirrors that of the ageing human and there is clearly still work to be done in seeking the ideal model which stands up as an adequate specific model for this purpose.

2.8.4.2 Diabetic Bladder Dysfunction (DBD) Models

Recognition of high rates of lower urinary tract symptoms (LUTS) in both type 1 and type 2 diabetic patients led to development of the term diabetic bladder dysfunction (DBD) as an umbrella description for a group of clinical symptoms[34]. DBD includes storage and voiding problems, as well as other less well-defined clinical phenotypes, such as decreased sensation and increased capacity. Portions of this spectrum of changes have been reported in other pathologies that result in LUTS such as bladder outlet obstruction, neurogenic bladder, and geriatric voiding dysfunction[35,36]. Although no single study has yet reported the cumulative effects on patients with type 1 or type 2 diabetes, it has been estimated from multiple studies that DBD is among the most common and costly complications of diabetes mellitus, affecting 87% of patients[34].

In type 1 diabetes models, DBD seems to follow a characteristic progression, resulting in different phenotypes of lower urinary tract dysfunction in early and late phases. Early stage diabetes (<9 weeks in rodents) causes detrusor overactivity in both in vivo (cystometry) and in vitro (organ-bath) studies. In the later stage (>12 weeks in rodents), the detrusor loses its ability to expel urine or respond to in vitro stimuli such as electrical field stimulations. Therefore, it has been hypothesised that the result of end-stage DBD is an atonic or underactive detrusor[37] that is the result of long-term hyperglycaemia related oxidative stress and polyuria[38,39]. There is a growing body of evidence to indicate that oxidative stress and inflammation are independently associated with obesity and diabetes. Furthermore, oxidative stress appears to contribute to complications of these disorders that include detrusor overactivity and geriatric bladder dysfunction[40-42]. It is plausible that the natural history of DBD could be replicated in other chronic conditions affecting the bladder such as obesity and ageing.

2.8.4.3 Obstruction and Bladder Overdistension Models

Bladder outlet obstruction (BOO) is a common precursor of LUTS in the ageing male population, leading to filling and/or voiding phase complaints[43]. However, whether a patient develops a higher post-void residual or eventual urinary retention is not only dependent on the grade of BOO. Numerous in vitro and in vivo animal studies have reported the bladder's response to acute or chronic BOO[44-48]. Several in vitro studies have shown a consistent relationship between increased bladder mass and altered contractile responses in muscle strips in prolonged BOO in rat, rabbit and cat preparations[49-52]. Some studies have even compared findings in animals to the human situation, mainly focusing on structural rather than functional changes[53,54].

Current models mostly induce mechanical obstruction by placing a clip, ring, or suture around the urethra to induce partial BOO. While acute effects are seen in these models, the functional effects in partial BOO (pBOO) for longer times (>6 weeks in rat and rabbit, and >3 months in cats) seem to mimic the effects in human BOO relatively well. In these experimental conditions the bladder mass increases in proportion to the increase of bladder volume and the inability to empty completely. With experimentally-induced BOO in cats, deterioration of bladder function proceeded more slowly than in rats and rabbits and the functional and morphological state of a compensated bladder remain relatively stable[52]; this is also often seen in humans with BOO but occurs at a much slower rate. Thus pBOO models in rodents, rabbits, and cats can mimic some of the aspects of loss of contraction seen in DU. In these models reversibility of function after removal of the obstruction is often not seen. This is not a problem if one is interested in the developmental pathology of DU, but is if the model is to be used for drug-effect studies that might reverse obstruction.

2.8.4.4 Ischaemia/Oxidative Stress Models

The two main animal models to investigate in vitro oxidative damage are: direct bladder damage by hydrogen peroxide; or indirect induction via ischaemia followed by reperfusion[55]. Atherosclerosis-induced chronic bladder ischaemia significantly reduces detrusor contractility of rabbit[56] and rat bladders[57]. A general problem in these models is that the severity of effects is difficult to titrate and establish, leading to large variability of results. In vitro induction of oxidative stress, whether or not caused by artificial obstruction, led to a significant decrease in contractility[55,58]. Overall, in vitro as well as in vivo animal studies clearly show a correlation between oxidative stress and impaired contractility. One of the important remaining questions is to what extent reduction of oxidative stress can be utilised as a potential therapeutic target in humans[59,60].

2.8.4.5 Neurogenic Animal Models

Besides age-related comorbidities, incomplete emptying is also common in patients with bladder dysfunction caused by specific neurological disease, including multiple sclerosis (0-40%)[61], Parkinson's disease (53%)[62], and multiple system atrophy (52-67%)[63]. Several animal models have been designed to mimic specific neurogenic situations and relate these to altered contractility[3]. DU can span a spectrum from slightly decreased ability to generate intravesical pressure (that may in turn be compensated for by increasing outlet-opening capability) to a bladder that cannot generate any pressure for emptying upon neural activation. A canine model of lower motor neuron injury has been developed, resulting in an atonic bladder[64]. This spinal root transection model showed activation of different nerve tracts to the bladder after its reinnervation by transfer of the genitofemoral nerve[65], indicating that there is plasticity in the end organ following bladder reinnervation.

Although the neurogenic models mimic specific situations, experimental results may not be applied to a wider group of DU patients, however, some reinnervation paradigms have already been tested in experimental human studies[66], accentuating their importance and high translational value.

2.8.5 What data do we need and what research questions should be addressed in the future?

1. Development of study tools based on a system's pathophysiological approach

Given that effective voiding is maintained via a complex balance between the compensatory capacity (or contractile reserve) of the bladder and the outlet opening capability of the bladder neck and urethra (Figure 1), improvement of one or both compensatory and correctable mechanisms could potentially be used as a therapeutic target. More insight into the interplay of different mechanisms (Figure 2) such as bladder and urethral sensation, urethral/bladder neck relaxation and detrusor contraction, all under neuro-cognitive control might give additional clues to explain ineffective bladder emptying.

- Which clinical observations determine best detrusor compensatory capacity or infravesical relaxation capacity and might define patients at risk for DU?
- How might the contributions of each factor be isolated and measured?
- What is the role of bladder/urethral sensation and of neurocognitive regulation in DU?

2. Characterisation of morphological and functional properties of isolated bladder wall samples

Research to evaluate structural bladder and urethral changes in humans with DU should lead to better understanding of its aetiology.

In vitro data from isolated human detrusor material should yield invaluable information about cell and tissue pathways that regulate detrusor contractility and urethral relaxation allowing exploration of the relationship between contractility and the clinical observation of impaired contractile function This may be related to confounding factors in in vitro preparations that influence contractile output, but unrelated to muscle contractility per se, including: altered connective tissue content; detrusor denervation and enhanced neurotransmitter secretions from other tissues, such as the mucosa[3,16,67]. Moreover, factors other than changes to bladder wall tension (in principle true detrusor contractility) affect the ability of the bladder to raise intravesical pressure, including: outflow tract resistance; initial bladder volume; and bladder geometry[68].

- What structural bladder and urethral changes in humans are associated with the development of DU?
- What is the relationship between morphological and functional properties of

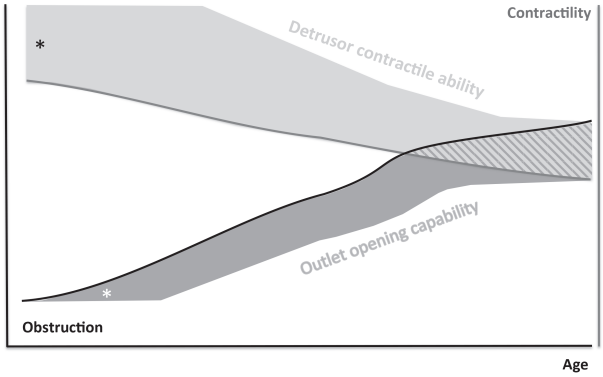

*Figure 1. Schematic hypothetical relationship between obstruction and detrusor contractility as a function of age. The diagram shows an Increase of obstruction and subsequent decrease of detrusor contractility. Whether or not a patient develops detrusor underactivity over time is dependent on the capacity to compensate by increasing detrusor contractility (detrusor contractile ability or ''contractile reserve'') or alter bladder outflow relaxation (outlet opening capability). * Represents the rest compensatory capacity.*

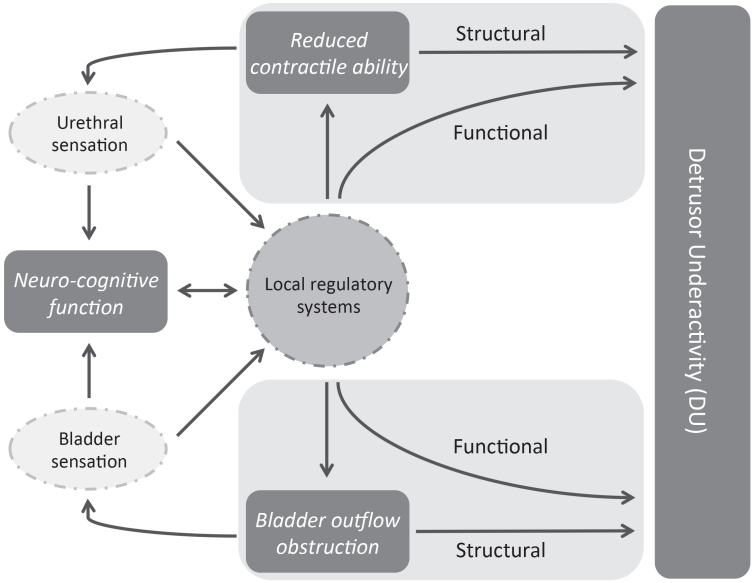

Figure 2. Complexity of the interplay between factors involved in bladder emptying and detrusor underactivity. Structural and/or functional changes may result from reduced ability of the bladder to contract or bladder outflow obstruction (BOO). Changes to sensory pathways and to neuro-cognitive function could affect either of these two major causative pathways.

isolated bladder wall samples and resultant LUT function from bladders yielding those biopsy samples?

3. Correlation of in vitro and in vivo data

Likewise, such exploration of in vitro and in vivo human material should allow additional insight into the translational nature of existing animal models.

- What is the relationship between in vitro data and in vivo function in animal models of DU?

4. Development of more comprehensive models

Currently, most animal models represent a specific disease state to explain DU, for example diabetes or BOO, therefore for every model a translational step to a comparable human conditions should be made.

- Which comprehensive animal models can we develop based on clinical observations and pathophysiological considerations?

5. Longitudinal data; needed for defining risk groups and development of screening tools

In human DU multiple factors are most likely simultaneously involved. This multifactorial nature makes it challenging to define whether a drug, tested in experimental animals, will have a substantial effect in clinical urological practice. Therefore, determination of urodynamic or history based indicators for DU is necessary for detection, diagnosis and follow-up after therapy. In addition, there is a need for longitudinal studies in LUTS patients to define the factors, which place patients at risk for developing DU.

- What are the urodynamic or history-based indicators, associated with DU, which are required for detection, diagnosis and follow-up after therapy?
- Are there specific pathological markers, which could allow definition of at risk groups?
- Is there potential for a non-invasive screening tool to predict at risk patients?

Focus of future DU research	Animal studies	Human studies
Development of study tools based on a system's pathophysiological approach	✓	✓
Characterisation of morphological and functional properties of isolated bladder wall samples	✓	✓
Correlation of in vitro and in vivo data		✓
Development of more comprehensive models	✓	
Longitudinal data; needed for defining risk groups and development of screening tools		✓

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Herrmans R, Oelke M. Detrusor underactivity: A plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723–728.
3. Young JS, Johnston L, Soubrane C, McCloskey KD, McMurray G, Eccles R, Fry CH. The passive and active contractile properties of the neurogenic, underactive bladder. *British Journal of Urology International* 2013;111:355–361.
4. Sekido N, Jyoraku A, Okada H, Wakamatsu D, Matsuya H, Nishiyama H. A novel animal model of underactive bladder: Analysis of lower urinary tract function in a rat lumbar canal stenosis model. *Neurourology and Urodynamics* 2012;31:1190–1196.
5. Everaerts W, De Ridder D. Unravelling the underactive bladder: A role for TRPV4? *British Journal of Urology International* 2013;111:353–354.
6. Jiang HH, Kokiko-Cochran ON, Li K, Balog B, Lin CY, Damaser MS, Lin V, Cheng JY, Lee YS. Bladder dysfunction changes from underactive to overactive after experimental traumatic brain injury. *Experimental Neurology* 2013;240:57–63.
7. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Koelbl H, van Kerrebroeck PE, Wein A. Detrusor underactivity and the underactive bladder: A new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology* 2014;65:389–398.
8. Cucchi A, Quaglini S, Rovereto B. Development of idiopathic detrusor underactivity in women: From isolated decrease in contraction velocity to obvious impairment of voiding function. *Urology* 2008;71:844–888.
9. Madersbacher S, Pycha A, Schatzl G, Mian C, Klingler CH, Marberger M. The ageing lower urinary tract: A comparative urodynamic study of men and women. *Urology* 1998;51:206–212.
10. Malone-Lee J, Wahedna I. Characterisation of detrusor contractile function in relation to old age. *British Journal of Urology International* 1993;72:873–880.
11. Bonde HV, Sejr T, Erdmann L, Meyhoff HH, Lendorf A, Rosenkilde P, Nielsen MB. Residual urine in 75-year-old men and women. A normative population study. *Scandinavian Journal of Urology and Nephrology* 1996;30:89–91.
12. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: A comparison between men and women. *Korean Journal of Urology* 2012;53:342–348.
13. Resnick NM, Elbadawi AE, Yalla SV. Age and the lower urinary tract: What is normal? *Neurourology and Urodynamics* 1995;14:577–79.
14. Ameda K, Sullivan MP, Bae RJ, Yalla SV. Urodynamic characterisation of nonobstructive voiding dysfunction in symptomatic elderly men. *Journal of Urology* 1999;162:142–146.
15. Susset JG, Servot-Viguier D, Lamy F, Madernas P, Black R. Collagen in 155 human bladders. *Investigative Urology* 1978;16:204–206.
16. Fry CH, Bayliss M, Young JS, Hussain M. Influence of age and bladder dysfunction on the contractile properties of isolated human detrusor smooth muscle. *British Journal of Urology International* 2011;108:91–96.

17. Collas DM, Malone-Lee JG. Age-associated changes in detrusor sensory function in women with lower urinary tract symptoms. *International Urogynecology Journal and Pelvic Floor dysfunction* 1996;7:24–29.
18. Griffiths D, Tadic SD, Schaefer W, Resnick NM. Cerebral control of the bladder in normal and urge-incontinent women. *NeuroImage* 2007;37:1–7.
19. Smith PP. Ageing and the underactive detrusor: A failure of activity or activation? *Neurourology and Urodynamics* 2010;29:408–412.
20. Shafik A, Shafik AA, El-Sibai O, Ahmed I. Role of positive urethrovesical feedback in vesical evacuation. The concept of a second micturition reflex: The urethrovesical reflex. *World Journal of Urology* 2003;21:167–170.
21. Sprott RL. Introduction: Animal models of ageing: Something old, something new. *Institute for Laboratory Animal Research Journal* 2011;52:1–3.
22. Hughes BG, Hekimi S. A mild impairment of mitochondrial electron transport has sex-specific effects on lifespan and ageing in mice. *PLoS ONE* 2011;6:e26116.
23. Haynes V, Traaseth NJ, Elfering S, Fujisawa Y, Guilivi C. Nitration of specific tyrosines in FoF1 ATP synthase and activity loss in ageing. *American Journal of Physiology Endocrinology and Metabolism* 2010;298:978–987.
24. Xi M, Chase MH. The impact of age on the hypnotic effects of eszopiclone and zolpidem in the guinea pig. *Psychopharmacology* 2009;205:107–117.
25. Smith PP, DeAngelis A, Kuchel GA. Detrusor expulsive strength is preserved, but responsiveness to bladder filling and urinary sensitivity is diminished in the ageing mouse. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* 2012;302:577–586.
26. Zhao W, Aboushwareb T, Turner C, Mathis C, Bennett C, Sonntag WE, Andersson KE, Christ G. Impaired bladder function in ageing male rats. *Journal of Urology* 2010;184:378–385.
27. Lluel P, Palea S, Barras M, Grandadam F, Heudes D, Bruneval P, Corman B, Martin DJ. Functional and morphological modifications of the urinary bladder in ageing female rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* 2000;278:964–972.
28. Lai HH, Boone TB, Thompson TC, Smith CP, Somogyi GT. Using caveolin-1 knockout mouse to study impaired detrusor contractility and disrupted muscarinic activity in the ageing bladder. *Urology* 2007;69:407–411.
29. Yono M, Latifpour J, Yoshida M, Ueda S. Age-related alterations in the biochemical and functional properties of the bladder in type 2 diabetic GK rats. *Journal of Receptor Signal Transduction Research* 2005;25:147–157.
30. Shenfeld OZ, Meir KS, Yutkin V, Gofrit ON, Landau EH, Pode D. Do atherosclerosis and chronic bladder ischaemia really play a role in detrusor dysfunction of old age? *Urology* 2005;65:181–184.
31. Guven A, Mannikarottu A, Whitbeck C, Chichester P, Leggett RE, Kogan BA, Levin RM. Effect of age on the response to short-term partial bladder outlet obstruction in the rabbit. *British Journal of Urology International* 2007;100:930–934.
32. Mohammed HA, Santer RM. Distribution and changes with age of calcitonin gene-related peptide- and substance P-immunoreactive nerves of the rat urinary bladder and lumbosacral sensory neurons. *European Journal of Morphology* 2002;40:293–301.
33. Yoshida M, Inadome A, Maeda Y, Satoji Y, Masunaga K, Sugiyama Y, Murakami S. Non-neuronal cholinergic system in human bladder urothelium. *Urology* 2006;67:425–430.
34. Gomez CS, Kanagarajah P, Gousse AE. Bladder dysfunction in patients with diabetes. *Current Urology Reports* 2011;12:419–426.
35. Gormley EA. Urologic complications of the neurogenic bladder. *Urology Clinics of North America* 2010;37:601–607.
36. Gammack JK. Lower urinary tract symptoms. *Clinics in Geriatric Medicine* 2010;26:249–260.

37. Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: Current translational knowledge. *Journal of Urology* 2009;182:18–26.
38. Xiao N, Wang Z, Huang Y, Daneshgari F, Liu G. Roles of polyuria and hyperglycaemia in bladder dysfunction in diabetes. *Journal of Urology* 2013;189:1130–1136.
39. Christ GJ, Hsieh Y, Zhao W, Schenk G, Venkateswarlu K, Wang HZ, Tar MT, Melman A. Effects of streptozotocin-induced diabetes on bladder and erectile (dys)function in the same rat in vivo. *British Journal of Urology International* 2006;97:1076–1082.
40. Calabrese V, Cornelius C, Leso V, Trovato-Salinaro A, Ventimiglia B, Cavallaro M, Scuto M, Rizza S, Zanoli L, Neri S, Castellino P. Oxidative stress, glutathione status, sirtuin and cellular stress response in type 2 diabetes. *Biochimica et Biophysica Acta* 2012;1822:729–736.
41. Chang YC, Chuang LM. The role of oxidative stress in the pathogenesis of type 2 diabetes: From molecular mechanism to clinical implication. *American Journal of Translational Research* 2010;2:316–331.
42. Higdon JV, Frei B. Obesity and oxidative stress: A direct link to CVD? *Arteriosclerosis, Thrombosis and Vascular Biology* 2003;23:365–367.
43. Soler R, Andersson KE, Chancellor MB, Chapple CR, de Groat WC, Drake MJ, Gratzke C, Lee R, Cruz F. Future direction in pharmacotherapy for non-neurogenic male lower urinary tract symptoms. *European Urology* 2013;64:610–621.
44. Buttyan R, Chen MW, Levin RM. Animal models of bladder outlet obstruction and molecular insights into the basis for the development of bladder dysfunction. *European Urology* 1997;32:32–39.
45. Nigro DA, Haugaard N, Wein A, Levin RM. Metabolic basis for contractile dysfunction following chronic partial bladder outlet obstruction in rabbits. *Molecular and Cellular Biochemistry* 1999;200:1–6.
46. Rohrmann D, Levin RM, Duckett JW, Zderic SA. The decompensated detrusor I: The effects of bladder outlet obstruction on the use of intracellular calcium stores. *Journal of Urology* 1996;156:578–581.
47. Zderic SA, Rohrmann D, Gong C, Snyder HM, Duckett JW, Wein A, Levin RM. The decompensated detrusor II: Evidence for loss of sarcoplasmic reticulum function after bladder outlet obstruction in the rabbit. *Journal of Urology* 1996;156:587–592.
48. Tong-Long Lin A, Chen KK, Yang CH, Chang LS. Recovery of microvascular blood perfusion and energy metabolism of the obstructed rabbit urinary bladder after relieving outlet obstruction. *European Urology* 1998;34:448–453.
49. Schröder A, Chichester P, Kogan BA, Longhurst PA, Lieb J, Das AK, Levin RM. Effect of chronic bladder outlet obstruction on blood flow of the rabbit bladder. *Journal of Urology* 2001;165:640–646.
50. Zhu Y, Shi B, Xu Z, Liu Y, Zhang K, Li Y, Wang H. Are TGF-beta1 and bFGF correlated with bladder underactivity induced by bladder outlet obstruction? *Urologia Internationalis* 2008;81:222–227.
51. Levin RM, Schuler C, Leggett RE, Callaghan C, Maknuru S. Partial outlet obstruction in rabbits: Duration versus severity. *International Journal of Urology* 2013;20:107–114.
52. Levin RM, Longhurst PA, Barasha B, McGuire EJ, Elbadawi A, Wein A. Studies on experimental bladder outlet obstruction in the cat: Long-term functional effects. *Journal of Urology* 1992;148:939–943.
53. Levin RM, Haugaard N, O'Connor L, Buttyan R, Das A, Dixon JS, Gosling JA. Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: A direct comparison. *Neurourology and Urodynamics* 2000;19:609–629.
54. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. IV. Bladder outlet obstruction. *Journal of Urology* 1993;150:1681–1695.

55. Malone L, Schuler C, Leggett RE, Levin RM. The effect of in vitro oxidative stress on the female rabbit bladder contractile response and antioxidant levels. *ISRN Urology* 2013;2013:639685.
56. Azadzoi KM, Tarcan T, Siroky MB, Krane RJ. Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. *Journal of Urology* 1999;161:1626–1635.
57. Nomiya M, Yamaguchi O, Andersson KE, Sagawa K, Aikawa K, Shishido K, Yanagida T, Kushida N, Yazaki J, Takahashi N. The effect of atherosclerosis induced chronic bladder ischemia on bladder function in the rat. *Neurourology and Urodynamics* 2012;31:195–200.
58. Nomiya M, Yamaguchi O, Akaihata H, Hata J, Sawada N, Kojima Y, Andersson KE. Progressive vascular damage may lead to bladder underactivity in rats. *Journal of Urology* 2014;191:1–8.
59. Oka M, Fukui T, Ueda M, Tagaya M, Oyama T, Tanaka M. Suppression of bladder oxidative stress and inflammation by a phytotherapeutic agent in a rat model of partial bladder outlet obstruction. *Journal of Urology* 2009;182:382–90.
60. Toklu H, Alican I, Ercan F, Sener G. The beneficial effect of resveratrol on rat bladder contractility and oxidant damage following ischemia/reperfusion. *Pharmacology* 2006;78:44–50.
61. de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B. The neurogenic bladder in multiple sclerosis: Review of the literature and proposal of management guidelines. *Multiple Sclerosis* 2007;13:915–928.
62. Sakakibara R, Uchiyama T, Yamanishi T, Shirai K, Hattori T. Bladder and bowel dysfunction in Parkinson's disease. *Journal of Neural Transmission* 2008;115:443–460.
63. Bloch F, Pichon B, Bonnet AM, Pichon J, Vidailhet M, Roze E, Perrigot M. Urodynamic analysis in multiple system atrophy: Characterisation of detrusor-sphincter dyssynergia. *Journal of Neurology* 2010;257:1986–1991.
64. Ruggieri MR, Braverman AS, D'Andrea L, Simpkiss B, Kozin SH, Pontari MA, Betz R, Barbe MF. Functional reinnervation of the canine bladder after spinal root transection and immediate end-on-end repair. *Journal of Neurotrauma* 2006;23:1125–1136.
65. Ruggieri MR, Braverman AS, D'Andrea L, McCarthy J, Barbe MF. Functional reinnervation of the canine bladder after spinal root transection and immediate somatic nerve transfer. *Journal of Neurotrauma* 2008;25:214–224.
66. Xiao CG. Reinnervation for neurogenic bladder: Historic review and introduction of a somatic-autonomic reflex pathway procedure for patients with spinal cord injury or spina bifida. *European Urology* 2006;49:22–8.
67. Kumar V, Chapple CR, Rosario D, Tophill PR, Chess-Williams R. In vitro release of adenosine triphosphate from the urothelium of human bladders with detrusor overactivity, both neurogenic and idiopathic. *European Urology* 2010;57:1087–1092.
68. Bross S, Braun PM, Michel MS, Juenemann KP, Alken P. Bladder wall tension during physiological voiding and in patients with an unstable detrusor or bladder outlet obstruction. *British Journal of Urology International* 2003;92:584–588.

Section III
Discussion

3.1 Aim of the studies

For the last 20-25 years, research interest has primarily focused on bladder storage symptoms (storage LUTS). Although voiding LUTS related to Bladder Outlet Obstruction (BOO) has been explored to a significant extent, the problem of Detrusor Underactivity (DU) and associated post-void residual (PVR) in men and women has been neglected. This may be partially explained by the limited therapeutic options but is also caused by the diagnostic difficulties that have been faced in the past.

DU may be seen as a condition which was developed for research purposes only. However, it is obvious that many patients seek professional help for the treatment of acute urinary retention after stress urinary incontinence treatment or general anaesthesia, or failure to void after desobstructive treatment for Benign Prostatic Obstruction (BPO). Furthermore, recurrent urinary tract infections (UTIs) in elderly women with PVR or young patients with acute urinary retention are part of the spectrum of functional urology seen in physician offices. The presence of these patient groups indicate why research in this field is needed. Therefore, the aim and main body of this thesis focus on novel diagnostic developments to diagnose patients at risk for the development of DU.

3.2 The value of PVR measurement in men and women

PVR is defined as the volume of urine left in the bladder at the end of micturition[1]. PVR may be considered as the most significant sign for inadequate bladder emptying and, therefore, measurement of PVR appears to be the most simple method to diagnose DU. However, the relevance of PVR measurement is still controversial[2]:

3.2.1 Method of measurement

The best method to measure PVR still remains to be determined. A generally accepted option is to measure PVR volume by using transabdominal ultrasound. However, it remains to be determined how comparable suprapubic ultrasound measurements are with transurethral catheterisation after voiding. Simforoosh *et al.* did not find a correlation between both measurement techniques when comparing PVR volume by catheterisation with suprapubic ultrasound measurements of the bladder and applying 11 different formulae in 324 men[3]. The authors emphasised that visualisation of the bladder and PVR measurement is only possible when the bladder is filled with at least 48 ml. In contrast,

Coombes and Millard found no significant differences between ultrasound PVR measurements with two different portable ultrasound scanners and transurethral catheterisation, although the mean differences between the ultrasound measurements and the true values were 41 ml and 25 ml, respectively[4]. Differences amongst the studies may be related to the group of patients, underlying conditions or diseases, gender, and bladder configuration. Furthermore, there also appear to be measurement differences between ultrasound equipment[3,5,6] and different algorithms[7]. In 1996, Griffiths *et al.* published an article on the test variability of PVR in 14 geriatric patients and showed that PVR volume differed during a 24 hour period even in the same patient (SD ± 128 ml), with the largest variation in the morning. Random variability proved to be smaller (SD ± 44 ml)[8]. These results were confirmed by Dunsmuir *et al.*[9]. Measurement variability is suggested to improve by real-time pre-scan imaging (RPI), with good correlation to the actual bladder volume obtained by transurethral catheterisation[10]. It is recommended in national and international guidelines (for men) to repeat PVR measurement at least once if PVR was measured in the first investigation[11-13].

3.2.2 Definition of abnormal PVR

Suggested upper limits for PVR volumes in community-dwelling men are provided in table 1. The *EAU guidelines for the Management of male LUTS* advises ultrasound measurement of PVR in each routine LUTS assessment (level of evidence 3, grade B). In addition, the EAU committee proposes a PVR cut-off value of 300 ml to perform an additional pressure-flow study in symptomatic men with voiding LUTS (level of evidence 3, grade C)[14]. Moreover, interpretation and determination of relevant threshold values for PVR measurement are dependent on the reference population[15]. In the hospitalised elderly population, a PVR volume of 150 ml, which is frequently used as cut-off value in LUTS/BPH studies, is present in up to 24% of this specific population[15]. Rule *et al.* followed 529 community dwelling men over a time interval of 12 years and confirmed the variability of PVR measurements. In addition, these authors also suggest progression of bladder dysfunction with age in terms of decreased voided volume (VV) and increase in PVR over time, with the least variability in VV[16]. A comparable decline over time was found for maximum urinary flowrate[17]. These findings would favour for the use of voiding efficiency (VE) instead of PVR[18].

There is only limited evidence on PVR cut-off values in community dwelling women. Two studies found that a PVR >100ml was present in up to 10% of asymptomatic women[19,20]. In contrast to the male data, this suggests that the normal upper limit should be used as the cut-off value to determine abnormal PVR in symptomatic women (Table 2). This also suggests that there is a rather large overlap between what is defined as 'abnormal' and the 'upper limit of normal' in women.

The parameters maximum urinary flowrate (Q_{max}), PVR and VE may all be indicative for voiding ability of the bladder. Therefore, these parameters should be related to the outlet resistance to create a comprehensive bladder and outlet function assessment; thus, avoiding wrong interpretations of the nature of bladder dysfunction[16].

3.2.3 PVR and UTIs

The relationship between PVR volume and UTIs remains controversial. Multiple studies imply a correlation between PVR and development of UTIs in men (and women). A Brazilian study in 196 men indicated a correlation between PVR and positive culture, with a cut-off value of 180 ml[21]. However, other studies could not confirm this finding[22,23]. Nevertheless, the key finding in this particular Brazilian study might be the fact that VE in men with LUTS is only approximately 30% on average in the group with a positive urine culture.

3.2.4 PVR and AUR

Development of an acute urinary retention (AUR) seems to be the result of the disturbed balance between bladder contractility (detrusor strength and/or contraction duration) and bladder outlet resistance. The incidence of AUR varies with age, ranging from <1 per 1000 person-years in community dwelling males <50 years of age to >15 per 1000 person-years[24]. A review article on AUR found an overall incidence rate in the general population between 2.2 and 8.5 per 1000 person-years in men without risk factors, whereas the incidence varied between 18.3 and 35.9 per 1000 person-years in men with LUTS or other risk factors (e.g. benign prostatic enlargement, increased serum concentration of prostate-specific antigen or previous history of AUR)[25]. The value of PVR itself or the PVR volume for the prediction of the development of AUR remains to be elucidated[24]. A study from Klarskov *et al.* (1987) showed in 228 patients admitted to urology ward because of AUR that the return of spontaneous voiding was significantly more likely in men with a PVR below 500 ml and maximum urinary flowrate >5 ml/s after AUR[26,27]. Since then, multiple studies have been published that reject the relationship between PVR or PVR volume and the development of AUR in male patients (Table 3).

Table 1. Limits of PVR volume in community-dwelling men

Study	Age group (years)	N	PVR volume (ml) Mean (SD) or Median (25^{th}-75^{th} percentile)
Kolman *et al.* 199928	40 – 79	477	9.5 (2.5 – 35.4)
Kok *et al.* 200929	50 – 78	853	20.9 (48)
Berges and Oelke 201130	50 – 80:	684	31.0 (62)
only men without drugs, previous treatments, surgery, radiotherapy diabetes mellitus, elevated PSA or neurological diseases	50 – 54	119	23.8 (14 – 34)
	55 – 59	151	30.7 (19 – 43)
	60 – 64	174	25.8 (18 – 34)
	65 – 69	121	39.4 (29 – 51)
	70 – 74	87	31.4 (22 – 41))
	>75	32	32.2 (9 – 55)

N: amount of patients, PVR: post-void residual, SD: standard deviation.

Table 2. Suggested Threshold values for PVR in women with pelvic floor dysfunction and/or LUTS

	Patient group	N	Threshold (ml)	% above the upper limit
Dwyer *et al.* 1994[31]	Suggestive of VD	165	150	34%
Haylen *et al.* 1999[32]	LUTS	250	30	5 vs 9% (non- vs symptomatic)
Fitzgerald *et al.* 2001[33]	Urgency, frequency	336	100	5%
Constantini *et al.* 2003[34]	LUTS and/or incontinence	348	150	
Milleman *et al.* 2004[35]	OAB	201	100	19%
Lukakc *et al.* 2007[36]	Pelvic floor disorders	1399	100	11%
Gehrich *et al.* 2007[20]	Asymptomatic (mostly) postmenopausal women	96	50 100	15% 5%
Haylen *et al.* 2008[37]	Pelvic floor dysfunction	1140	0-10 11-30 31-50 51-100 >100	76% 5% 5% 8% 6%
Lowenstein *et al.* 2008[38]	LUTS	636	150	Low correlation with obstructive voiding symptoms
Tseng *et al.* 2008[39]	SUI + no previous pelvic surgery or prolapse	902	50 100	36% 16%
Huang *et al.* 2011[19]	Ambulatory women 55-75yrs	987	100	10%
Saaby *et al.* 2012[40]	Urogynaecologic complaints	396	100	T1 14% ; T2-3 1-2%
Khayyami *et al.* 2016[41]	VD based on PF study	205	150	2/20 pts >150 with voiding dysfunction 18/20 pts <150 with voiding dysfunction
Park *et al.* 2016[42]	>65 yrs + OAB	151	100	36%
Lo *et al.* 2016[43]	POP-Q III-IV and reconstruction	1370	>200	OR 2.15 for post-operative VD

N: amount of patients, VD: voiding dysfunction, LUTS: lower urinary tract symptoms, OAB: overactive bladder, SUI: stress urinary incontinence, PF: pressure-flow, T1: timepoint one, Pts: patients, OR: Odds Ratio

Table 3. PVR and relation to development of an AUR in male patients

Study	Study name (if given)	Patient group	Age (years)	PVR cut-off (ml)	N	% AUR	PVR related to development of AUR?
Klarskov *et al.* 1987[26]	-	AUR patients	-	500	228	-	>500ml had 3.6x risk for 2nd AUR
Thomas *et al.* 2005[44]	-	LUTS/BPO	>45	-	141	5%	No
Crawford *et al.* 2006[45]	MTOPS	LUTS, placebo arm	>50	39	737	0.6%	No
Roehrborn *et al.* 2006[46]	ALTESS	LUTS/BPO	>55	350	Placebo (757) Alfuzosin (749)	1.8 % 2.1%	No
Mochtar *et al.* 2006[47]	-	BPH patients	>50	300	914	1.5%	No
Roehrborn *et al.* 2010[48]	CombAT	LUTS/BPO	>50	-	Tamsulosin (1611) Dutasteride (1623) Combination (1610)	6.8% 2.7% 2.2%	No
Cahn *et al.* 2015[49]	-	BPH patients	45-71	100	44	9.1%	No

N: amount of patients, LUTS: lower urinary tract symptoms, BPO: benign prostatic obstruction, PVR: post-void residual, AUR: acute urinary retention.

3.3 Detrusor underactivity versus bladder outlet obstruction in men

DU and BOO may both cause poor urinary stream, PVR and even urinary retention in adult men. DU is characterised by decreased detrusor pressure and decreased urinary flow rate, and the predominant cause is found in the bladder. In contrast, BOO is characterised by increased detrusor pressure and decreased urinary flow rate and the primary problem is found in the bladder outlet or urethra. Any type of obstruction, either of benign or malignant origin, between the bladder neck and the tip of the urethra can cause BOO (e.g. bladder neck stenosis, benign prostatic enlargement, urethral stricture or meatal stenosis). Benign prostatic obstruction (BPO) is a condition and special form of BOO. The term BPO is to be used when the cause of outlet obstruction is known to be benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH)[1]. BOO can also be caused by pelvic floor related functional obstruction where the internal (smooth muscle) or external urethral sphincter (striated muscle) inadequately relaxes during voiding. In general, the prevalence of BPH, BPE and BPO increases with age; however, above a certain age urodynamic BOO incidence stabilises and only the prevalence of DU increases[50,51].

It has been shown that the appearance or severity of LUTS or PVR are not necessarily related to DU or BOO/BPO[52,53]. Therefore, symptoms or signs of DU or BOO/BPO cannot be used to diagnose the condition or estimate the prevalence. This is only possible by multichannel computer-urodynamic measurement until now. Neither a cross-sectional, nor a longitudinal epidemiological study has yet been conducted to determine the prevalence of either condition in general society due to the disadvantages of multichannel computer-urodynamic testing, i.e. high price, time-consuming examination, bother for the patient and some unwanted side effects during or after the assessment, such as bleeding, clot retention, urinary tract infection, urosepsis, or dysuria in up to 19% of men[54]. Therefore, exact numbers of affected men have not been established. Urodynamic studies in large patient cohorts found DU in up to 48% and BOO/BPO in approximately 60% of patients[53,55]. DU can co-exist with BOO/BPO but the prevalence of men affected by both conditions remains to be elucidated.

All efforts to discriminate DU from BOO/BPO are only useful when the condition-specific treatment makes a significant outcome difference. First-line treatments for BOO/BPO consist of behavioural and/or medical treatments which aim to reduce or eliminate LUTS, as comprehensively described in the European Association of Urology (EAU) *Guidelines on the Treatment of Male LUTS*[56]. However, no drug has consistently shown to decrease bladder outlet resistance[57,58] or increase bladder contractility [59]; therefore, behavioural and drug therapies are both symptomatic treatments for LUTS, without major or measurable influence on the underlying condition. Surgical treatment of LUTS or voiding dysfunction is recommended by the EAU *Guidelines on the Treatment of Male LUTS* when the patient has absolute indications (i.e. recurrent urinary retention, recurrent urinary tract infections or bilateral upper urinary tract dilatation due to BOO/BPO) or relative indications for surgery (persistent bothersome LUTS despite behavioural and medical therapy)[56]. Surgical therapy

aims to reduce bladder outlet resistance by removing prostatic tissue, thereby reducing BOO/BPO[56]. However, prostatic tissue removal does not seem to have influence on bladder contractility. TURP in patients with BOO/BPO has success rates which are up to 11-29% higher compared to TURP in patients without BOO/BPO, even in a long-term study with a follow-up of 8 years[60-63]. Although the majority of patients experience sufficient symptom relief after prostate surgery, approximately 20-40% of men remains symptomatic and demand medical treatment within the first 5 years after surgery.

The outcome of men with DU after prostatic surgery (TURP) compared with age-matched untreated men with DU has been investigated[44,64]. After a minimum follow-up of 10 years, patients with TURP did not show significant LUTS improvement compared to the preoperative situation and, additionally, no significant change of Q_{max}, PVR, VE or any other voiding parameter, bladder contractility index (BCI) included. Compared to untreated patients with DU, men with DU who underwent TURP had no significant advantages in the long-term with regard to the type or severity of LUTS, Q_{max}, or post-void residual urine. Although patients after TURP had a significantly lower BOO-grade at follow-up (bladder outlet obstruction index [BOOI] 9 ± 11.9 vs 14 ± 15.3 cm H_2O, p = 0.008), PVR was even significantly higher (80 ± 172 vs 217 ± 336 ml, p = 0.049) and VE significantly lower (82 ± 28 vs 58 ± 29%). These studies demonstrated that prostatic surgery (TURP) and decrease of bladder outlet resistance do not solve voiding dysfunction in men with DU and indicate that men with DU may even do worse in the long-term. Meanwhile, some studies on laser enucleation therapies have suggested that these treatments can be effective for improvement of voiding function in DU patients as well[65-68]. However, these studies do not take long-term longitudinal follow-up and the preoperative bladder contraction parameters (i.e. premature fading of the contraction or low maximum contraction strength) into account[69]. In addition, interpretation of the studies is difficult in absence of a clear reference standard for the diagnoses of DU and patient inclusion in the studies (see section I – General Introduction).

All available information on the treatment of LUTS indicates that the specific therapy of the underlying condition makes a significant and clinically relevant difference on the patient outcome. Therefore, discrimination between DU and BOO/BPO before treatment initiation appears to be important and influences the treatment choice. Consequently, there is a strong need to adequately define, assess and grade DU.

3.4 Characterisation of men with detrusor underactivity and definition of the threshold values for DU

Differentiation between DU, BOO or the combination of DU and BOO appears desirable in order to determine which patient will most likely have a favourable or unfavourable treatment outcome[70]. Treatment indication or patient counselling may be modified accordingly. The ongoing UPSTREAM trial provides data on the preoperative use of pressure-flow studies

in male LUTS patients[71]. However, determination of and differentiation between DU and BOO remains difficult without pressure-flow studies at present[72,73]. Current assessment guidelines recommend investigating LUTS with symptom questionnaires (International Prostate Symptom Score, IPSS) and measuring urinary flow rate as well as PVR. It would be desirable to evaluate all LUTS patients with pressure-flow studies but this in infeasible and too expensive. Consequently, patient pre-selection before urodynamic investigation may be helpful. Earlier in the year 2015, the EAU Guidelines committee on the Assessment of Male LUTS has defined preoperative patient characteristics which should precede pressure-flow studies[14]. Patients defined by these criteria are suspected of having other pathologies than BPO and, therefore, may be poor candidates for prostate surgery for LUTS/BPO. Pressure-flow studies and the evaluation of the underlying pathophysiology of LUTS may be performed in men who cannot void >150 ml during free uroflowmetry, have post-void residual urine >300 ml, are aged <50 or >80 years, or have had previous unsuccessful (invasive) therapy for LUTS.

Regardless the fact whether or not computer-urodynamic investigation should be performed in all or only In a selected group of patients, it remains important to define the condition (DU) and threshold values. Three urodynamic parameters are widely accepted to evaluate the contractile function of the bladder and are usually provided in the results section of pressure-flow analyses on computer-urodynamic machines[74,75]. These parameters are (1) Griffiths' maximum Watt factor (W_{max})[76], (2) Schäfer's detrusor-adjusted mean passive urethral resistance relation (PURR) factor and a gross classification of detrusor contractility into 'strong', 'normal', 'weak' and 'very weak' if the linearised PURR is drawn into the Schäfer nomogram[77] and (3) Abrams' bladder contractility index (BCI) as an equation of Schäfer's linearised PURR[78]. Proposed threshold values for the diagnosis of DU were W_{max} <7 W/m^2 and BCI <100[74]. Single threshold values imply that they are valid for all patients. However, threshold values have not been established for children or women and, moreover, they may also be invalid for men with different grades of BOO/BPO.

Chapter 2 of this thesis summarises the results of a urodynamic study of 786 treatment naïve male LUTS patients aged ≥40 years and demonstrates that W_{max} and BCI continuously rise with increasing BOO grade[79]. Median BCI increased from 73 in Schäfer grade 0 to 188 in Schäfer grade 6 and median W_{max} increased from 9.6 in Schäfer grade 0 to 23 W/m^2 in Schäfer grade 6. The study showed that almost all patients with BCI <100 would have been classified as DU, whereas almost no patient with BOO/BPO (Schäfer grades 4-6) would have DU. When using the threshold of W_{max} <7, almost no patient would have been classified as having the condition DU. This study suggested that the originally described threshold values for the diagnosis of DU do not apply for individual men. The conclusion of this study was to adjust the threshold values for BCI and W_{max} to the individual BOO grade.

Chapter 3 of this thesis presents a nomogram in which each male patient can be classified with regard to bladder outlet resistance (bladder outlet obstruction index, BOOI) and detrusor contractility (W_{max}) at the same time[80]. This nomogram was developed with urodynamic data of 822 treatment naïve, symptomatic men aged ≥40 years who were

suspicious of having BOO/BPO. BOOI-W_{max} data points of the individual patients were first plotted in a diagram and, afterwards, the 10th, 25th, 50th, 75th and 90th percentiles were calculated. This study demonstrated that patients below the 25th percentile significantly differed from patients above the 25th percentile with regard to age, bladder capacity, PVR, and voiding efficiency. Higher age, larger bladder capacity and greater amount of PVR as well as lower voiding efficiency are the parameters which were previously identified to indicate DU[81,82]. Based on the significant differences in these clinical parameters, patients below the 25th percentile should be classified as DU.

Chapter 4 represents the first validation study of the nomogram to evaluate the clinical feasibility. Male patients with DU and PVR, who were candidates for sacral neuromodulation (SNM), underwent a pressure-flow study as part of their normal work-up for surgery. W_{maxx} and BOOI of all of the included 18 patients were plotted in the nomogram. Results showed that only 2 of the 10 patients <10th percentile (20%) were successfully treated with SNM. These men were compared with other patients who were positioned between the 10th and 25th percentile of the nomogram. In total, 7 of these 8 patients (88%) of this group were treatment responders and free of CIC after SNM. Although, this pilot study contained only 18 patients, the results may reflect the clinical utility of the nomogram in evidence-based treatment decision making of patients with DU.

The nomogram may also useful for studying the effects of drugs or other surgical treatments in men with LUTS. If prostatic surgery is done correctly, the operation should decrease bladder outlet resistance (BOOI) but is not expected to have effects on bladder contractility (W_{max}). Therefore, the ability to sufficiently empty the bladder, reduce PVR and to improve voiding efficiency after the operation only depends on the relationship between preoperative (given) bladder contraction power and BOO-grade. According to this hypothesis, a patient with DU but without BOO/BPO will most likely not profit from prostatic surgery (Figure 1A), as previously shown by Thomas *et al.* in their long-term follow-up study of at least 10 years[13]. In contrast, a patient with BOO/BPO but without DU will most likely empty his bladder more sufficiently or completely after the surgery (Figure 1B). A patient with DU and BOO/BPO will only improve his voiding function if he moves above the 25th percentile after surgery (Figure 1C). However, if the patient with DU and BOO remains in the area of the 10th or 25th percentile - due to insufficient prostatic tissue removal or very low detrusor contractility at baseline - he will most likely not improve his voiding function (Figure 1D).

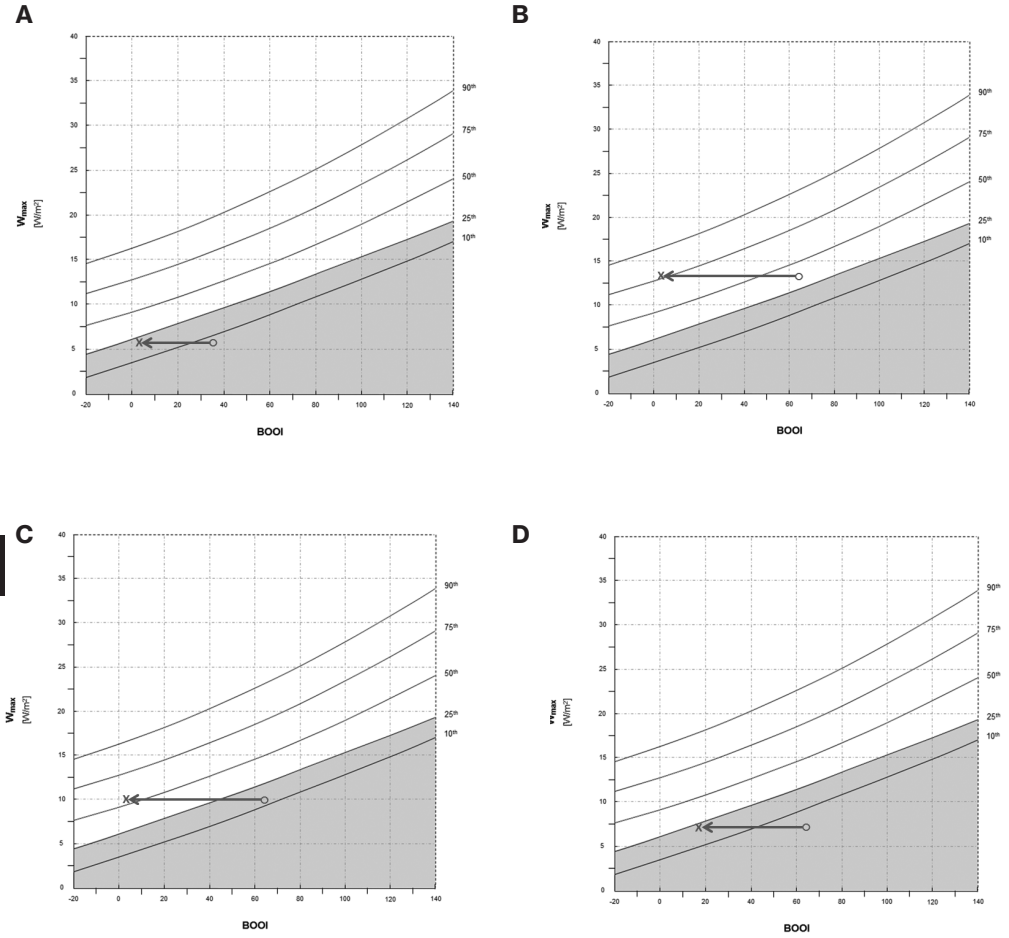

Figure 1. Theoretical effects of prostatic surgery in patients with detrusor underactivity only (A), benign prostatic obstruction only (B), detrusor underactivity together with benign prostatic obstruction and complete removal of prostatic tissue (C), and detrusor underactivity together with benign prostatic obstruction and incomplete removal of prostatic tissue (D). Pre-operative (◦) and post-operative data points (x) are indicated. In the Hannover-Maastricht-nomogram, patients will have improved voiding function, post-void residual urine and voiding efficiency if they are positioned above the 25th percentile line (threshold for DU). If patients stay positioned below the 25th percentile line after the operation (grey zone) they will most probably remain having voiding dysfunction (figures A and D).

3.5 Non-invasive parameters for characterisation of detrusor underactivity in men

Chapple *et al.* have recently suggested a symptomatic definition of the underactive bladder (UAB), similar to the definition of the overactive bladder (OAB): *UAB is a symptom complex suggestive of detrusor underactivity and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling and a slow stream*[83]. The discriminative value of the symptomatic definition (UAB) for the identification of the condition or the prediction of clinical outcome in patients with DU is currently unknown but clinical trials with a new UAB questionnaire have already been started.

Based on the working definition of UAB, several clinical questions can be addressed in order to identify patients with DU only based on symptoms[83]. Gammie *et al.* reported on a higher occurrence of 'decreased and/or interrupted urinary flow', 'hesitancy', 'feeling of incomplete bladder emptying', 'palpable bladder', and 'absent and/or decreased sensation' in patients with DU compared to patients with normal pressure-flow studies[84]. A comparable study by Hoag and Gani in men and women resulted in 'urgency', 'weak stream' and 'straining' as predominant symptoms in the UAB group[85]. Major issue in these studies is used reference standard for DU. Gammie *et al.* used a DU diagnose based on expert opinion as 'gold standard'. The specific parameters were a BCI <100, BOOI <20 and voiding efficiency <90% for DU in men. In patients with a BOOI <20 (no obstruction), BCI is mostly <100, as presented in chapter 4 of this thesis. The inclusion criteria for DU in this study are therefore rather wide which might lead to inappropriate conclusions. Based on the variability of predominant symptoms in both of the studies it remains to be determined whether single symptoms, symptom combinations, or the provisional definition of UAB are useful for the detection of DU in the individual patient and, later, for the prediction of the outcome of prostatic surgery. The results of the IPSS questionnaire seems inadequate to distinguish DU from the presence of BOO[86]. This emphasises the need for additional indicators to stratify patients at risk for DU. Potential parameters could be bladder capacity and sensation extracted from frequency-volume charts. In addition, information on voided volume and PVR (or VE) may be of importance for DU risk assessment.

However, no single parameter is able to differentiate DU from BOO/BPO and, moreover, diagnose DU together with BOO/BPO. Several non-invasive tools have been developed in the past to define BOO/BPO. These non-invasive tests have shown test accuracies between 72 and 88%[87-91]. Until now, non-invasive tests have rarely been investigated for the prediction of DU. Chapter 5 presents the data of the first pilot study on non-invasive parameters and in the diagnostic work-up of DU. The study shows that a thin detrusor at the anterior bladder wall (detrusor wall thickness determined by suprapubic ultrasound ≤1.23 mm) in combination with large bladder capacity (>445 ml) can sufficiently predict DU (positive predictive value 100%, negative predictive value 85%), with or without the presence of BOO/BPO[92]. Limitations of the study include the retrospective

analysis of measurement data, clinical definition of DU, lack of the general availability of ultrasound devices with high frequency ultrasound probes, and the low sensitivity (42%) of the measurement results. Future studies should prospectively investigate the clinical importance of the combined non-invasive test parameters and confirm the threshold values for the diagnosis of DU.

3.6 Diagnostic developments in women

Compared to men, diagnostic developments in the work-up of voiding dysfunction in women has been left untouched and is often overlooked[93,94]. However, failure to fully empty the bladder is also rather common in women, for example in the post-partum period, after stress urinary incontinence surgery or complementary to dysfunctional voiding[95,96]. The question in these patients is the same as in men: can we identify patients at risk of progression to voiding failure in general or DU in particular? Until now, it has been challenging to select these patients sufficiently.

Similar to men, a test should be able to detect and quantify DU in women and should also be able to differentiate DU from BOO. However, tests, parameters and threshold values in women are not available or not generally accepted. Even detection and quantification of anatomical or functional BOO in the female gender remains difficult due to missing assessment criteria and threshold values. This diagnostic dilemma is reflected by using multiple diagnostic criteria only for detection of BOO in women[97,98]. In 1988, Massey and Abrams defined obstruction in women by combining Q_{max} <12ml/s with a $P_{det.Qmax}$ >50 cm H_2O[99]. Whereas other, more recent studies have suggested pressures above 20 - 40 cm H_2O are more indicative for BOO in women[100-102]. Dybowski *et al.* have proposed from a cohort of 67 patients a pressure-flow nomogram that uses the line $P_{det.Qmax}$ >1.5 x Q_{max} + 10 as the separator, in which patients above the line were suspected of BOO[103]. This study, however, did not use data from patients with severe prolapse, urethral stricture or anti-incontinence surgery why the discriminative ability of this formula may be limited[97]. The variability between the diagnostic BOO criteria in women expose that pressure-flow analysis in women is insufficient to define BOO and merely based on assumptions of male database studies. As presented in chapter 6, contractility parameters and nomograms have not been developed to provide proof for these assumptions. Also in women, clinical indicators have been shown to be insufficient in selecting patients at risk. Khayyami *et al.* showed that voiding dysfunction in women with a PVR volume <150 ml cannot be excluded[41]. Therefore, there is a need for a multidimensional approach of the problem. Pressure-flow data should be assessed in combination with clinical data such as PVR, filling sensation, flow parameters and voiding diary parameters. An additional difficulty is that women are able to void without detrusor pressure increase only by straining and relaxation of the urethral sphincters. In order to determine the contractile reserve, for example during the work-up for an anti-incontinence procedure, estimation of the bladder

contraction power during voiding would be beneficial. The development of contractility measurements in women should therefore focus on application of a fixed or adjustable induced obstruction component comparable to the penile cuff principle in male patients in contrast to only pressure-flow characterisation[91].

3.7 The advantages of specialised urodynamics: ambulatory measurement

Conventional pressure-flow studies are the gold standard in LUTS evaluation[1]. However, recently the International Continence Society revised and discussed the potential role of ambulatory urodynamic monitoring as a third line diagnostic tool in patients with lower urinary tract dysfunction, as discussed in chapter 1 of this thesis[104]. The use of ambulatory urodynamics seems to overestimate detrusor contractions during the filling phase because results are comparable in patients as well as healthy volunteers[105-107]. The bladder filling technique by drinking, however, may be used in patients with potential bladder acontractility[108]. The use of ambulatory storage and voiding phase pressure measurements in patients with suspected voiding dysfunction, amongst other lower urinary tract dysfunctions, could also be considered if it has treatment implications. Drossaerts *et al.* previously showed that patients without detrusor contractions during ambulatory urodynamics have a significantly lower success rate when sacral neuromodulation (SNM) treatment was performed[109].

3.8 Latissimus dorsi detrusor myoplasty as a last resort

More elaborate surgical procedures such as the reduction cystoplasty or lattisimus dorsi detrusor myoplasty (LDDM) may only be considered in highly selected patients with severe DU. Overall, there is currently no convincing evidence for the effectivity of a reduction cystoplasty, as the evidence only consists of one case series in adults (see section I – General Introduction). In contrast, several studies have been published on the results of LDDM in adults with bladder acontractility. As discussed in chapter 7, mean age of the patients eligible for LDDM is 39-42 years. LDDM outcome across the various studies ranges between 70.8 and 85.0% complete response (meaning PVR <100 ml). Although these results seem promising, the longest published follow-up period is 89 months. Long-term treatment effects, for example after 10 - 20 years, are still unavailable. Specifically in case of elaborate surgical procedures, optimal preoperative diagnostic evaluation and patient selection are essential. An ambulatory urodynamic assessment may already provide information in addition to bladder diaries, uroflowmetry and conventional pressure flow study. However, measurement of the bladder's sensory input or measurement of the detrusor's capability at maximum stimulation have not yet been published (chapter 8). In the future, these measurements may provide the missing information needed to define the bladder status from afferent to efferent function.

3.9 Future perspectives

Research on the physiology and pathophysiology of voiding, specifically on DU/UAB, has just started. With the increase of the understanding of the condition and increasing study data on the topic, even more scientific questions have arisen. Research perspectives with regard to DU/UAB may begin with basic knowledge about health and disease. The lack of studies in male and female LUTS with regard to age-matched data comparing healthy individuals and patients with the condition indicates the fine line between health and a functional urologic condition. This raises several questions such as: Where should be started, with individual subjective symptoms or objective (pressure-flow) parameters? Are there gender related differences with regard to voiding? In addition to this, it would open up a pathophysiological matter on the process of voiding. A phase III study combining pressure-flow measurements during voiding and functional Magnetic Resonance Imaging (fMRI) of Onuf's nucleus or the brain may provide further information on the central processing pathways of voiding. A first pilot study should focus on healthy individuals and gender differences in central processing of voiding. In a second study, data of healthy individuals should be compared to those of patients with impaired voiding. An interventional study could be used as last in the sequence of this study model to evaluate the effect for example in a group of patients with impared bladder emptying and sacral neuromodulation treatment.

As mentioned in this thesis, the process of voiding is influenced by multiple factors and may be altered by highly prevalent conditions such as diabetes mellitus or cardiovascular diseases. However, data has only been obtained in animal studies. A translational approach on the topic could give a deeper insight into the relationship between DU and concomitant conditions. These relationships might not be explained by clinical studies. Structural studies and investigations of the role of epigenitics and the urinary microbiome may very well be necessary to explain correlations from different angles.

Parallel to the pathophysiological approach of DU, improvement of assessment techniques to determine impaired contractility is currently an important issue. Previously published pressure-flow parameters do not take into account that there is an existing balance between urethral or pelvic resistance and bladder contractility. In addition, measurement of contractility in women needs to be redefined and reanalysed. Moreover, in contrast to conventional parameters which mostly decribe a feature at one timepoint during the voiding phase, voiding time, inititiation and termination of flow should be incorporated. All of these adjustments may improve the capability to diagnose detrusor underactivity correctly to make sure eventually the right patients receive the correct treatment.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
2. Griebling TL. Re: Measurement of Post-Void Residual Bladder Volumes in Hospitalised Older Adults. *Journal of Urology* 2015;194:1054-1055.
3. Simforoosh N, Dadkah F, Hosseini SY, Asgari MA, Nasseri A, Safarinejad MR. Accuracy of residual urine measurement in men: comparison between real-time ultrasonography and catheterisation. *Journal of Urology* 1997;158:59-61.
4. Coombes G, Millard RJ. The accuracy of portable ultrasound scanning in the measurement of residual urine volume. *Journal of Urology* 1994;152:2083-2085.
5. Small D, Watson A, McConnachie A. A quantitative comparison of four current portable ultrasound bladder scanners. *British Journal of Medical and Surgical Urology* 2008;1:35-40.
6. Byun SS, Kim HH, Lee E, Paick JS, Kamg W, Oh SJ. Accuracy of bladder volume determinations by ultrasonography: are they accurate over entire bladder volume range? *Urology* 2003;6:656-660.
7. Hwang JY, Byun SS, Oh SJ, Kim HC. Novel algorithm for improving accuracy of ultrasound measurement of residual urine volume according to bladder shape. *Urology* 2004;64:887-891.
8. Griffiths D, Harrison G, Moore K, McCracken P. Variability of post-void residual urine volume in the elderly. *Urological Research* 1996;24:23-26.
9. Dunsmuir W, Feneley M, Corry DA, Bryan J, Kirby R. The day-to-day variation (test-retest reliability) of residual urine measurement. *British Journal of Urology International* 1996;77:192-193.
10. Park YH, Ku JH, Oh SJ. Accuracy of post-void residual urine volume measurement using a portable ultrasound bladder scanner with real-time pre-scan imaging. *Neurourology and Urodynamics* 2011;30:335-338.
11. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE, Gonzalez CM, Kaplan SA, Penson DF, Ulchaker JC, Wei JT. Update on AUA guideline on the management of benign prostatic hyperplasia. *Journal of Urology* 2011;185:1793-1803.
12. Koyanagi T, Artibani W, Correa R, Desgrandchamps F, de Reijke TM, Govier F, Kurth KH. Initial diagnostic evaluation of men with lower urinary tract symptoms. In: Denis L, Griffiths K, Khoury S, Cockett ATK, McConnell J, Chatelain C, Murphy G, Yoshida O, eds. 4th Consultation on Benign Prostatic Hyperplasia (BPH). Plymbridge Distributors Ltd, Plymouth 1998:179-257.
13. Abrams P, Chapple C, Khoury S, Roehrborn C, de la Rosette J. Evaluation and treatment of lower urinary tract symptoms in older men. *Journal of Urology* 2009;181: 1779-1787.
14. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, Oelke M, Tikkinen KA, Gravas S. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European Urology* 2015;67:1099-1109.
15. Shimoni Z, Fruger E, Froom P. Measurement of Post-void Residual Bladder Volumes in Hospitalised Older Adults. *American Journal of Medicine* 2015;128:77-81.
16. Rule AD, Jacobson DJ, McGree ME, Girman CJ, Lieber MM, Jacobsen SJ. Longitudinal changes in post-void residual and voided volume among community dwelling men. *Journal of Urology* 2005;174:1317-1322.

17. Roberts RO, Jacbobsen SJ, Jacobsen DJ, Rhodes T, Girman CJ, Lieber MM. Longitudinal changes in peak urinary flow rates in a community based cohort. *Journal of Urology* 2000;163:107-113.
18. Bosch JL, Kranse R, van Mastrigt R, Schröder FH. Dependence of male voiding efficiency on age, bladder contractility and urethral resistance: development of a voiding efficiency nomogram. *Journal of Urology* 1995;154:190-194.
19. Huang AJ, Brown JS, Boyko EJ, Morre EE, Scholes D, Walter LC, Lin F, Vittinghoff E, Fihn SD. Clinical significance of post-void residual volume in older ambulatory women. *Journal of the American Geriatrics Society* 2011;59:1452-1458.
20. Gehrich A, Stany MP, Fischer JR, Buller J, Zahn CM. Establishing a mean post-void residual volume in asymptomatic perimenopausal and postmenopausal women. *Obstetrics and Gynaecology* 2007;110:827-832.
21. Truzzi JC, Almeida FM, Nunes EC, Sadi MV. Residual urinary volume and urinary tract infection - when are they linked? *Journal of Urology* 2008;180:182-185.
22. Hampson S, Noble JG, Rickards D, Milroy EJ. Does residual urine predispose to urinary tract infection? *British journal of Urology International* 1992;70:506-508.
23. May M, Brookman-Amissah S, Hoschke B, Gilfrich C, Braun KP, Kendel F. Post-void residual urine as a predictor of urinary tract infection - is there a cut-off value in asymptomatic men? *Journal of Urology* 2009;181:2540-2544.
24. Kaplan SA, Wein A, Staskin DR, Roehrborn CG, Steers WD. Urinary retention and post-void residual urine in men: separating truth from tradition. *Journal of Urology* 2008;180:47-54.
25. Oelke M, Speakman MJ, Desgrandchamps F, Mamoulakis C. Acute Urinary Retention Rates in the General Male Population and in Adult Men With Lower Urinary Tract Symptoms Participating in Pharmacotherapy Trials: A Literature Review. *Urology* 2015;86:654-665.
26. Klarskov P, Andersen JT, Asmussen CF, Brenoe J, Jensen SK, Jensen IL, Lund P, Schultz A, Vedel T. Symptoms and signs predictive of the voiding pattern after acute urinary retention in men. *Scandinavian Journal of Urology and Nephrology* 1987;21:23-28.
27. Emberton M. Definition of at-risk patients: dynamic variables. *British Journal of Urology International* 2006;97:12-15.
28. Kolman C, Girman CJ, Jacobsen Sj, Lieber MM. Distribution of post-void residual urine volume in randomly selected men. *Journal of Urology* 1999;161:122-127.
29. Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, Bosch JL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy ageing men: the Krimpen Study. *Journal of Urology* 2009;181:710-716.
30. Berges R, Oelke M. Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling population aged 50 years or older. *World Journal of Urology* 2011;29:171-1178.
31. Dwyer P, Desmedt E. Impaired bladder emptying in women. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1994;34:73-78.
32. Haylen B, Law MG. Frazer M, Schulz S. Urine flow rates and residual urine volumes in urogynecology patients. *International Urogynaecology Journal* 1999;10:378-383.
33. Fitzgerald M, Jaffar J, Brubaker L. Risk factors for an elevated postvoid residual urine volume in women with symptoms of urinary urgency, frequency and urge incontinence. *International Urogynaecology Journal* 2001;12:237-240.
34. Costantini E, Mearini E, Pajoncini C, Biscotto S, Bini V, Porena M. Uroflowmetry in female voiding disturbances. *Neurourology and Urodynamics* 2003;22:569-573.
35. Milleman M, Langenstroer P, Guralnick ML. Post-void residual urine volume in women with overactive bladder symptoms. *Journal of Urology* 2004;172:1911-1914.

36. Lukacz ES, DuHamel E, Menefee SA, Luber KM. Elevated post-void residual in women with pelvic floor disorders: prevalence and associated risk factors. *International Urogynaecology Journal* 2007;18:397-400.
37. Haylen BT, Lee J, Logan V, Husselbee S, Zhou J, Law M. Immediate postvoid residual volumes in women with symptoms of pelvic floor dysfunction. *Obstetrics and Gynaecology* 2008;111:1305-1312.
38. Lowenstein L, Anderson C, Kenton K, Dooley Y, Brubaker L. Obstructive voiding symptoms are not predictive of elevated post-void residual urine volumes. *International Urogynaecology Journal and Pelvic Floor Dysfunction* 2008;19:801-804.
39. Tseng LH, Liang CC, Chang YL, Lee SJ, Lloyd LK Chen CK. Post-void residual urine in women with stress incontinence. *Neurourology and Urodynamics* 2008;27:48-51.
40. Saaby ML, Lose G. Repeatability of post-void residual urine ≥100 ml in urogynaecologic patients. *International Urogynaecology Journal* 2012;23:207-209.
41. Khayyami Y, Klarskov N, Lose G. Post-void residual urine under 150 ml does not exclude voiding dysfunction in women. *International Urogynaecology Journal* 2016;27:467-473.
42. Park J, Lavelle JP, Palmer MH. Voiding dysfunction in older women with overactive bladder symptoms: A comparison of urodynamic parameters between women with normal and elevated post-void residual urine. *Neurourology and Urodynamics* 2016;35:95-99.
43. Lo TS, Shailaja N, Hsieh WC, Uy-Patrimonio MC, Yusoff FM, Ibrahim R. Predictors of voiding dysfunction following extensive vaginal pelvic reconstructive surgery. *International Urogynaecology Journal* 2016 [Epub ahead of print]
44. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction. *British Journal of Urology International* 2005;96:1301-1306.
45. Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, Meehan AG, Bautista OM, Noble WR, Kusek JW, Nyberg LM, Roehrborn CG. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *Journal of Urology* 2006;175:1422-1426.
46. Roehrborn CG. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. *British Journal of Urology International* 2006;97:734-741.
47. Mochtar CA, Kiemeney LA, van Riemsdijk MM, Laguna MP, Debruyne FM, de la Rosette JJ. Post-void residual urine volume is not a good predictor of the need for invasive therapy among patients with benign prostatic hyperplasia. *Journal of Urology* 2006;175:213-216.
48. Roehrborn CG, Siami P, Barkin J, Damiao R, Major-Walker K, Nandy I, Morrill BB, Gagnier RP, Montorsi F. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *European Urology* 2010.;57:123-131.
49. Cahn DB, Ross CP, Dubowitch EP, Persun ML, Ginsber PC, Harkaway RC. Predicting Acute Urinary Retention in Patients with Elevated Post-Void Residuals. *Current Urology* 2015;8:79-83.
50. Rodrigues P, Hering F, Meller A, D'Imperio M. Outline of 3,830 Male Patients Referred to Urodynamic Evaluation for Lower Urinary Tract Symptoms: How Common Is Infravesical Outlet Obstruction? *Urologia Internationalis* 2009;83:404-409.
51. Verhamme K, Dieleman JP, van Wijk MA, Bosch JL, Stricker BH, Sturkenboom MC. Low incidence of acute urinary retention in the general male population: the triumph project. *European Urology* 2005;47:494-498.
52. Botker-Rasmussen I, Bagi P, Jorgensen JB. Is bladder outlet obstruction normal in elderly men without lower urinary tract symptoms? *Neurourology and Urodynamics* 1999;18:545-551.

53. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *European Urology* 2008;54:419-426.
54. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP. Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. *Journal of Urology* 1998;159:191-194.
55. Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette J, Porru D, Thüroff JW. The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. *Journal of Urology* 1997;157:885-889.
56. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, N'dow J, Nordling J, de la Rosette JJ. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European Urology* 2013;64:118-140.
57. Barendrecht MM, Abrams P, Schumacher H, de la Rosette JJ, Michel MC. Do alpha1-adrenoceptor antagonists improve lower urinary tract symptoms by reducing bladder outlet resistance? *Neurourology and Urodynamics* 2008;27:226-230.
58. Schäfer W, Tammela TL, Barrett DM, Abrams P, Hedlund H, Rollema HJ, Nordling J, Andersen JT, Hald T, Matos-Ferriera A, Bruskewitz R, Miller P, Mustonen S, Cannon A, Malice Mp, Jacobsen CA, Bach MA. Continued improvement in pressure-flow parameters in men receiving finasteride for 2 years. Finasteride Urodynamics Study Group. *Urology* 1999;54:278-283.
59. Barendrecht MM, Oelke M, Laguna MP, Michel MC. Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? *British Journal of Urology International* 2007;99:749-752.
60. Jensen K, Jørgensen J, Mogensen P. Urodynamics in prostatism. II. Prognostic value of pressure-flow study combined with stop-flow test. *Scandinavian Journal of Urology and Nephrology* 1987;114:72-77.
61. Neal DE, Ramsden PD, Sharples L, Smith A, Powell PH, Styles RA, Webb RJ. Outcome of elective prostatectomy. *British Medical Journal* 1989;299:762-767.
62. Robertson AS, Griffiths C, Neal DE. Conventional urodynamics and ambulatory monitoring in the definition and management of bladder outflow obstruction. *Journal of Urology* 1996;155: 506-11.
63. Jensen KM, Jorgensen TB, Mogensen P. Long-term predictive role of urodynamics: an 8-year follow-up of prostatic surgery for lower urinary tract symptoms. *British Journal of Urology International* 1996;78:213-218.
64. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *British Journal of Urology International* 2004;93:745-750.
65. Yu Z, Li J, Li Z, Hou R. Photoselective vaporization of the prostate and simultaneous suprapubic cystostomy for the treatment of benign prostatic hyperplasia in patients with mild to severe detrusor underactivity. *Urologia Internationalis* 2015;95:269-275.
66. Choi SW, Choi YS, Bae WJ, Kim SJ, Cho HJ, Hong SH, Lee JY, Hwang TK, Kim SW. 120 W Greenlight HPS laser photoselective vaporization of the prostate for treatment of benign prostatic hyperplasia in men with detrusor underactivity. *Korean Journal of Urology* 2011;52:824-828.
67. Mitchell CR, Mynderse LA, Lightner DJ, Husmann DA, Krambeck AE. Efficacy of holmium laser enucleation of the prostate in patients with non-neurogenic impaired bladder contractility: results of a prospective trial. *Urology* 2014;83:428-432.

68. Cho KJ, Kim HS, Koh JS, Han SB, Kim SH, Kim HW, Cho SY, Kim JC. Preoperative factors affecting postoperative early quality of life during the learning curve of holmium laser enucleation of the prostate. *International Neurourology Journal* 2013;17:83-89.
69. van Mastrigt R, Rollema HJ. The prognostic value of bladder contractility in transurethral resection of the prostate. *Journal of Urology* 1992;148:1856-1860.
70. Biardeau X, Elkoushy MA, Aharony S, Elhilali M, Corcos J. Is multichannel urodynamic assessment necessary before considering a surgical treatment of BPH? Pros and cons. *World Journal of Urology* 2016;34:463-469.
71. Bailey K, Abrams P, Blair PS, Chapple C, Glazener C, Horwood J, Lane JA, McGrath J, Noble S, Pickard R, Taylor G, Young GJ, Drake MJ, Lewis AL. Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men: study protocol for a randomised controlled trial. *Trials* 2015;16:567.
72. Clement KD, Burden H, Warren K, Lapitan MC, Omar MI, Drake MJ. Invasive urodynamic studies for the management of lower urinary tract symptoms (LUTS) in men with voiding dysfunction. *Cochrane Database Systematic Reviews* 2015;4:CD011179.
73. Parsons BA, Bright E, Shaban AM, Whitehouse A, Drake MJ. The role of invasive and non-invasive urodynamics in male voiding lower urinary tract symptoms. *World Journal of Urology* 2011;29:191-197.
74. van Koeveringe GA, Vahabi B, Andersson KE, Kirschner-Hermans R, Oelke M. Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. *Neurourology and Urodynamics* 2011;30:723-728.
75. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Koelbl H, van Kerrebroeck PE, Wein A. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology* 2014;65:389-398.
76. Griffiths D, van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. *Neurourology and Urodynamics* 1989;8:17-27.
77. Schafer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. *World Journal of Urology* 1995;13:47-58.
78. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *British Journal of Urology International* 1999;84:14-15.
79. Oelke M, Rademakers KLJ, van Koeveringe GA. Detrusor contraction power parameters (BCI and W max) rise with increasing bladder outlet obstruction grade in men with lower urinary tract symptoms: results from a urodynamic database analysis. *World Journal of Urology* 2014;32:1177-1183.
80. Oelke M, Rademakers KLJ, van Koeveringe GA. Unravelling detrusor underactivity: Development of a bladder outlet resistance-bladder contractility nomogram for adult male patients with lower urinary tract symptoms. *Neurourology and Urodynamics* 2016;35:980-986.
81. Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. *Journal of the American Geriatrics Society* 2006;54:1920-1932.

82. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon Cy, Hong SK, Byun SS, Lee SE. Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. *Korean Journal of Urology* 2012;53:342-348.
83. Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, Drake MJ, Yamaguchi O, Abrams P, Smith PP. The Underactive Bladder: A New Clinical Concept? *European Urology* 2015;68:351-353.
84. Gammie A, Kaper M, Dorrepaal C, Kos T, Abrams P. Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies. *European Urology* 2016;69:361-369.
85. Hoag N, Gani J. Underactive bladder: clinical features, urodynamic parameters, and treatment. *International Neurourology Journal* 2015;19:185.
86. Rademakers KLJ, van Koeveringe GA, Oelke M. Symptomatic differences in non-obstructive patients with poor detrusor function versus normal detrusor function. International Continence Society Annual Meeting 2015. *Neurourology and Urodynamics* 2015;34:S1-461.
87. Kessler TM, Gerber R, Burkhard FC, Studer UE, Danuser H. Ultrasound assessment of detrusor thickness in men-can it predict bladder outlet obstruction and replace pressure flow study? *Journal of Urology* 2006;175:2170-2173.
88. De Nunzio C, Lombardo R, Gacci M, Milanesi M, Cancrni F, Tema G, Cocci A, Giordano G, Leonardo C, Carini M, Tubaro A. The diagnosis of benign prostatic obstruction: validation of the Young Academic Urologist clinical nomogram. *Urology* 2015;86:1032-1036.
89. Kuo TL, Teo JS, Foo K. The role of intravesical prostatic protrusion (IPP) in the evaluation and treatment of bladder outlet obstruction (BOO). *Neurourology and Urodynamics* 2016;35:535-537.
90. Ochiai A, Kojima M. Correlation of ultrasound-estimated bladder weight with ultrasound appearance of the prostate and post-void residual urine in men with lower urinary tract symptoms. *Urology* 1998;51:722-729.
91. Griffiths C, Rix D, MacDonald AM, Drinnan MJ, Pickard RS, Ramsden PD. Non-invasive measurement of bladder pressure by controlled inflation of a penile cuff. *Journal of Urology* 2002;167:1344-1347.
92. Oelke M, Rademakers KLJ, van Koeveringe GA. Non-invasive clinical indicators of detrusor underactivity in adult men - results of a pilot study. *Journal of Urology* 2014;191:E887.
93. Cho KJ, Kim HS, Koh JS, Kim JC. Evaluation of female overactive bladder using urodynamics: relationship with female voiding dysfunction. *International Brazilian Journal of Urology* 2015;41:722-728.
94. Choi YS, Kim JC, Lee KS, Seo JT, Kim HJ, Yoo TK, Lee JB, Choo MS, Lee JG, Lee JY. Analysis of female voiding dysfunction: a prospective, multi-center study. *International Urology and Nephrology* 2013;45:989-994.
95. Yip SK, Brieger G, Hin LY, Chung T. Urinary retention in the post-partum period: The relationship between obstetric factors and the post-partum post-void residual bladder volume. *Acta Obstetricia et Gynecologica Scandinavica* 1997;76:667-672.
96. Ford A, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Systematic Reviews* 2015;7:CD006375.
97. Gammie A, Kirschner-Hermanns R, Rademakers KLJ. Evaluation of obstructed voiding in the female: how close are we to a definition? *Current Opinion in Urology* 2015;25:292-295.
98. Akikwala TV, Fleischman N, Nitti VW. Comparison of diagnostic criteria for female bladder outlet obstruction. *Journal of Urology* 2006;176:2093-2097.

99. Massey J, Abrams P. Obstructed voiding in the female. *British Journal of Urology International* 1988;61:36-39.
100. Defreitas GA, Zimmern PE, Lemack GE, Shariat SF. Refining diagnosis of anatomic female bladder outlet obstruction: comparison of pressure-flow study parameters in clinically obstructed women with those of normal controls. *Urology* 2004;64:675-679.
101. Chassagne S, Bernier PA, Haab F, Roehrborn CG, Reisch JS, Zimmern PE. Proposed cut-off values to define bladder outlet obstruction in women. *Urology* 1998;51:408-411.
102. King AB, Goldman HB. Bladder outlet obstruction in women: functional causes. *Current Urology Reports* 2014;15:1-9.
103. Dybowski B, Bres-Niewada E, Radziszewski P. Pressure-flow nomogram for women with lower urinary tract symptoms. *Archives of Medical Science* 2014;10:752-756.
104. Digesu GA, Gargasole C, Hendricken C, Gore M, Kocjancic E, Khullar V, Rosier PF. ICS teaching module: Ambulatory urodynamic monitoring. *Neurourology and Urodynamics* 2015 [Epub ahead of print]
105. van Waalwijk van Doorn ES, Anders K, Khullar V, Kulseng-Hanssen S, Pesce F, Robertson A, Rosario D, Schäfer W. Standardisation of ambulatory urodynamic monitoring: Report of the Standardisation Sub-Committee of the International Continence Society for Ambulatory Urodynamic Studies. *Neurourology and Urodynamics* 2000;19:113-125.
106. van Waalwijk van Doorn ES, Remmers A, Janknegt RA. Conventional and extramural ambulatory urodynamic testing of the lower urinary tract in female volunteers. *Journal of Urology* 1992;147:1319-1325.
107. van Waalwijk van Doorn ES, Remmers A, Janknegt RA. Extramural ambulatory urodynamic monitoring during natural filling and normal daily activities: evaluation of 100 patients. *Journal of Urology* 1991;146:124-131.
108. van Koeveringe GA, Rahnama'I MS, Berghmans BC. The additional value of ambulatory urodynamic measurements compared with conventional urodynamic measurements. *British Journal of Urology International* 2010;105:508-513.
109. Drossaerts JM, Rademakers KLJ, van Koeveringe GA, van Kerrebroeck PE. The value of urodynamic tools to guide patient selection in sacral neuromodulation. *World Journal of Urology* 2015;33:1889-1895.

Summary

Detrusor Underactivity (DU) is a functional urological entity in disguise without consensus on diagnostic evaluation or established treatment. Symtoms related to impaired bladder emptying caused by either DU, bladder outlet obstruction (BOO) or both are a frequent reason for outpatient consultation. However, for a long time research has not been focused on the background related to these symptoms. It is only at the International Consultation on Incontinence research society (ICI-RS) meeting of 2011 that the topic regained interest. The content of this thesis has kickstarted research in the field of DU, with specific attention towards pathophysiology of voiding function, measurement techniques for DU, and therapeutic options and margins.

Chapter 1 discusses the role of alternative pressure-flow measurement tools to differentiate various lower urinary tract dysfunctions. In this chapter specific attention is directed towards the role of ambulatory urodynamic monitoring (AUM) in impaired bladder emptying. Contractile dysfunction of the detrusor may vary from DU/hypocontractility to an acontractile bladder. AUM is shown to better differentiate between patients with bladder acontractility and hypocontractility. This knowledge is necessary in treatment of DU patients, for example with sacral neuromodulation (SNM). Patients with AUM based acontractility may be prone to a significantly reduced SNM treatment outcome compared to AUM based hypocontractile patients.

Chapter 2 is the first of three publications highlighting the relationship between BOO and detrusor contractile function in men during voiding. In the urological practice both bladder contractility index (BCI) and maximum Watts factor (W_{max}) are used to calculate detrusor strength in men with lower urinary tract symptoms (LUTS) using fixed threshold values for all men. This retrospective cohort study shows that detrusor contraction power parameters - BCI and W_{max} - continuously increase with rising BOO grade. According to these results, it has been shown impossible to determine a single threshold value for detrusor contraction power to diagnose detrusor underactivity in a group of LUTS patients with different BOO grades.

Chapter 3 describes the development of a pressure-flow based, BOO related, bladder contractility nomogram in men with LUTS, the Maastricht-Hannover nomogram. The nomogram quantifies the relationship between detrusor contractility and BOO in men with LUTS by the use of W_{max} (as contractility parameter) and bladder outlet obstruction index (BOOI, as obstruction parameter). Our results show that a measurement value <25th percentile correlates with clinical indicators of DU (higher age, higher bladder capacity, larger post-void residual volume and lower voiding efficiency and is proposed as a cut-off value for DU-diagnosis.

Chapter 4 is a first clinical validation study of the Maastricht-Hannover nomogram. Purpose of the study was to assess whether the use of the new BOO-contractility (Maastricht-Hannover) nomogram can identify and predict SNM non-responders. For the first time, SNM treatment response in male patients with impaired bladder emptying can

be predicted with the BOO-contractility (Maastricht-Hannover) nomogram. Men below the 10th percentile are likely to be treatment non-responders, whereas the majority of men above the 10th percentile are responders.

Chapter 5 focuses on non-invasive diagnostic techniques to assess detrusor underactivity. Pressure-flow studies are expensive, time consuming and may cause complications. Therefore, a non-invasive assessment may be valuable in the work-up of male patients with voiding dysfunction and a suspicion of DU. Classification And Regression Tree (CART) analysis shows that ultrasound detrusor wall thickness (DWT ≤1.23 mm) combined with relatively high bladder capacity (>445 ml) may predict DU in males with LUTS. The combination of these two tests could help physicians to diagnose DU noninvasively in clinical practice.

Chapter 6 is a think tank panel publication by the International Consultation on Incontinence (ICI-RS). In the past there has not been an extensive focus on the terms 'BOO' and 'bladder contractility' in women. At present, only limited women-specific BOO and bladder contractility indices are available. Therefore, the ICI-RS panel has put forward the following recommendations: the need to acquire normative age matched data in women to define ''normal'' and ''pathological'' values of urodynamic parameters; the inclusion of additional clinical data in new nomograms and the use of this extra dimension to develop clinically applicable nomograms for female BOO and contractility; and finally, the need to take into account the variability of BOO in women when developing female bladder contractility nomograms.

Chapter 7 gives an overview of the available evidence for a surgical treatment modality in patients with bladder acontractility. The history, anatomy, technique, results and complications of the latissimus dorsi detrusor myoplasty (LDDM) are described. LDDM outcome across the various studies ranges between 70.8 and 85.0% complete response (meaning PVR<100 ml). However, the current literature only gives limited information about the long-term effects of LDDM treatment.

Chapter 8 is a second think tank panel publication by the International Consultation on Incontinence (ICI-RS) on the pathophysiological background of DU and proposals for future research. The recommendations made by the ICI-RS panel include: Development of study tools based on a system's pathophysiological approach, correlation of in vitro and in vivo data in experimental animals and humans, and development of more comprehensive translational animal models. In addition, there is a need for longitudinal patient data to define risk groups and for the development of screening tools.

In summary, research with regard to DU and impaired bladder emptying in men and women has received increasing attention in recent years. However, only limited new data on pathophysiology, assessment of contractile function and treatment targets have been published. This thesis is the first of its kind, focussing on new developments in the assessment of DU and giving recommendations for (near-)future research opportunities.

Nederlandse Samenvatting (Dutch Summary)

Symptomen passend bij incomplete blaaslediging kunnen worden veroorzaakt door een te weinig actieve blaasspier (detrusor): ook wel genoemd Detrusor onderactiviteit (DU), blaas uitgangs obstructie (BOO) of beiden en zijn frequent een reden voor bezoek aan de polikliniek urologie. Detrusor onderactiviteit (DU) is een functioneel urologische entiteit welke vaak verscholen is achter andere oorzaken van blaasledigingsdisfunctie en waarvoor er geen consensus is met betrekking tot diagnostische evaluatie of behandeling. Gedurende lange tijd is er echter nauwelijks tot geen aandacht geweest voor het onderscheid tussen deze entiteiten, DU en BOO, gerelateerd aan de symptomatologie. Pas vanaf de International Consultation on Incontinence research society (ICI-RS) bijeenkomst in 2011 heeft onderzoek op dit gebied een nieuwe impuls gekregen. De inhoud van deze thesis heeft de aanzet gegeven tot verder onderzoek op het gebied van DU, met specifieke aandacht voor de pathofysiologie van de ledigingsfunctie van de blaas, technieken om DU te vast te stellen en te kwantificeren, en therapeutische opties en kaders voor DU.

Hoofdstuk 1 bespreekt de rol van alternatieve urodynamica methoden en instrumenten om verschillende disfuncties van de lagere urinewegen (LUTS) te onderscheiden. In dit hoofdstuk is er specifieke aandacht voor het gebruik van ambulante urodynamica (AUM) bij blaasledigingsproblematiek. Bij standaard urodynamica wordt de blaas artificieel gevuld via een katheter en wordt de (blaas)druk geregistreerd tijdens de vul- en ledigingsfase van de blaas. AUM is een meerdere uren durende meting van o.a. de blaasdruk in een alledaagse situatie waarbij de blaas zich ook op de natuurlijke manier vult. De contractiele disfunctie van de detrusor spier die kan worden vastgesteld middels AUM kan variëren van DU/hypocontractiliteit tot een volledig acontractiele blaas. Resultaten van deze studie laten zien dat AUM beter is in het onderscheiden van patiënten met blaas acontractiliteit en hypocontractiliteit dan conventionele blaasdrukmeting. Deze kennis is nodig bij de behandeling van DU patiënten, bijvoorbeeld bij patiënten die behandeld worden met sacrale neuromodulatie (SNM). Patiënten met op AUM gebaseerde acontractiliteit van de blaas hebben minder kans op een succesvolle SNM behandeling vergeleken met patiënten met op AUM gebaseerde hypocontractiliteit.

Hoofdstuk 2 is het eerste in een drieluik van publicaties waarin de aandacht is gevestigd op de relatie tussen BOO en de contractiele functie van de detrusor spier bij mannen tijdens de mictie. In de urologische praktijk worden zowel de bladder contractility index (BCI) als maximum Watts factor (W_{max}) gebruikt om detrusor kracht bij mannen met LUTS te kwantificeren. Hierbij worden vaste afkapwaarden gebruikt voor alle mannen. Deze retrospectieve cohort studie laat zien dat deze detrusor contractiekracht parameters - BCI en W_{max} - continu toe nemen bij een stijgende obstructie graad. Deze resultaten laten zien dat het onmogelijk is om middels één enkele afkapwaarde voor detrusor contractiekracht de detrusor onderactiviteit te kwantificeren bij mannelijke LUTS patiënten met verschillende BOO gradaties. Er moet dus worden gezocht naar alternatieve meetmethodes om bij de verdenking op DU, de contractiekracht van de detrusor spier te kwantificeren.

Hoofdstuk 3 beschrijft de ontwikkeling van een op urodynamica gebaseerd nomogram waarin blaas contractiliteit wordt uitgezet tegen BOO bij mannen met LUTS, het zogenaamde Maastricht-Hannover nomogram. Het nomogram kwantificeert de relatie tussen detrusor contractiliteit en BOO bij mannen met LUTS door gebruik van W_{max} (als contractiliteitsparameter) en bladder outlet obstruction index (BOOI, als obstructie parameter). Onze resultaten laten zien dat een meetwaarde <25^{e} percentiel op het nomogram correleert met klinische indicatoren van DU (hogere leeftijd, grotere blaas capaciteit, groter residuaal volume na mictie en lagere mictie efficiëntie. Derhalve wordt deze afkapwaarde voorgesteld om DU te diagnosticeren.

Hoofdstuk 4 is een eerste klinische validatie studie van het Maastricht-Hannover nomogram. Het doel van de studie was om te kijken of dit nieuwe BOO-contractiliteits (Maastricht-Hannover) nomogram gebruikt kan worden om het falen van een behandeling met SNM vast te stellen en te voorspellen. Voor het eerst kan nu de SNM behandelingsrespons bij mannen met incomplete blaaslediging worden voorspeld door het gebruik van het Maastricht-Hannover nomogram. Van de mannen onder het 10^{e} percentiel op het nomogram reageert slechts 20% op behandeling met SNM. In tegenstelling tot de groep boven het 10^{e} percentiel, waarvan het grootste deel van de mannen respondeert op behandeling met SNM.

Hoofdstuk 5 richt zich op niet-invasieve diagnostische technieken om DU te identificeren. Urodynamica is een dure, invasieve methode welke tijdrovend is en mogelijk leidt tot complicaties van de interventie. Om deze redenen zou een niet-invasieve techniek van waarde kunnen zijn in de analyse van mannelijke patiënten met een blaasledigingsstoornis en de verdenking op DU. Een classificatie en regressie analyse (genaamd CART) laat zien dat echografische weergave van de detrusor wanddikte (DWT ≤1.23 mm) gecombineerd met een relatief grote blaascapaciteit (>445 ml) mogelijk voorspellend is voor DU bij mannen met LUTS. De combinatie van deze twee technieken kan clinici helpen om DU op een niet-invasieve manier, door gebruik van een echo, vast te stellen in de dagelijkse praktijk.

Hoofdstuk 6 is een denktank panel publicatie door de International Consultation on Incontinence (ICI-RS). In het verleden is er weinig onderzoeksinteresse geweest voor de termen 'BOO' en 'blaascontractiliteit' bij vrouwen. Dit heeft tot gevolg dat momenteel slechts enkele, voor vrouwen specifieke, BOO en blaascontractiliteit parameters beschikbaar zijn. Derhalve heeft het ICI-RS panel de volgende aanbevelingen gegeven: de noodzaak van normatieve, met leeftijd geassocieerde data voor vrouwen om te bepalen welke urodynamica waarden als 'normaal' en 'pathologisch' worden gezien; de toevoeging van additionele klinische data aan nieuwe nomogrammen en het gebruik van deze klinische informatie moeten zorgen voor klinisch toepasbare nomogrammen voor BOO en contractiliteit bij vrouwen. Tot slot moet de variabiliteit van BOO, door het wisselend aanspannen van de bekkenbodemspieren, bij vrouwen in acht worden genomen wanneer dergelijke blaascontractiliteit nomogrammen worden ontwikkeld.

Hoofdstuk 7 geeft een overzicht van de beschikbare literatuur met betrekking tot de chirurgische behandeling van patiënten met blaas acontractiliteit. De geschiedenis, anatomie, techniek, resultaten en complicaties van de latissimus dorsi detrusor myoplastiek (LDDM) worden beschreven in deze publicatie. LDDM is een procedure waarbij een spierflap (latissimus dorsi spier) om de blaas wordt gewikkeld als alternatief voor de niet goed functionerende blaasspier. De LDDM resultaten in de verschillende studies variëren in een complete behandelingsrespons (dit betekent een residuaal volume na mictie <100ml) tussen 70.8 en 85.0%. Echter, de huidige literatuur geeft slechts weinig inzicht in de langetermijneffecten van behandeling middels LDDM bij patiënten met blaas acontractiliteit.

Hoofdstuk 8 is een tweede denktank panel publicatie door de International Consultation on Incontinence (ICI-RS) met betrekking tot de pathofysiologische achtergrond van DU en voorstellen voor toekomstig onderzoek op dit gebied. Aanbevelingen door het ICI-RS panel luiden als volgt: ontwikkeling van studie technieken gebaseerd op de pathofysiologische benadering van een system; correlatie van in vitro en in vivo data bij proefdieren en mensen; en de ontwikkeling van diermodellen die te vertalen zijn naar de menselijke situatie. Additioneel aan deze aanbevelingen is er de noodzaak tot longitudinale verzameling van patiënten data om zo risicogroepen te definiëren en hiermee screeningstechnieken te ontwikkelen.

Samenvattend is er sinds enkele jaren een evidente toename in onderzoek met betrekking tot het onderwerp DU en blaasledigingsproblematiek bij zowel mannen als vrouwen. Er is echter nog weinig bewijskracht voor de pathofysiologische mechanismen, het meten van contractiele functie en behandelstrategieën bij DU. Dit proefschrift is het eerste proefschrift dat zich richt op dit onderwerp binnen de functionele urologie en waarin de aandacht is gevestigd op nieuwe ontwikkelingen in de diagnostiek van DU en aanbevelingen worden gegeven voor toekomstige onderzoeksmogelijkheden.

Valorisation

Lower urinary tract symptoms (LUTS), including urinary incontinence, are major and important quality of life issues within urology. It has been estimated that approximately 1 million people in the Netherlands suffer from LUTS in general and urinary incontinence in particular, and both LUTS and incontinence are responsible for health care seeking behaviour and health care expenditure. With an increasingly ageing population, LUTS, particularly voiding LUTS, become more prominent in society and are responsible for substantial morbidity and quality of life deterioration. The presence of voiding LUTS may precipitate urinary retention and can cause urinary tract infections (UTIs), overflow incontinence, and renal failure. It is estimated that voiding dysfunction occurs in up to two-thirds of the institutionalised elderly and is related to high rates of catheter use[1]. For the last decades, research with regard to voiding dysfunction in both men and women has focused on bladder outlet resistance as the main source of voiding LUTS, increased post-void residual urine, urinary retention, overflow incontinence, and UTIs. However, the role of the bladder as the major cause of voiding dysfunction has become increasingly apparent during the recent years, mainly by decreasing bladder outlet obstruction (BOO) in patients with benign prostatic hyperplasia (e.g. by transurethral resection of the prostate) or increasing obstruction in patients with stress urinary incontinence (e.g. by with slings or tapes) has resulted in a number of treatment failures.

Voiding dysfunction caused by a bladder unable to produce sufficient contraction strength and/or adequate duration resulting in incomplete bladder emptying is termed 'detrusor underactivity' (DU) by the International Continence Society[2]. DU may be related to a number of other voiding LUTS and development of UTIs in specific populations. As antibiotic resistance increases rapidly and has become a serious threat, UTIs could even be lethal, as pointed out by the WHO in February 2017[3]. This health alert on antibiotic treatment, with particular attention to UTIs, emphasises the importance of adequate analysis of potential aetiological factors such as DU in order to diagnose and treat the underlying cause correctly. However, in an era when humans even develop artificial intelligence only little is known about something seemingly simple such as voiding physiology and pathophysiology.

This PhD thesis investigates and discusses DU in broad perspective. DU reflects the result of failure of multiple regulatory systems of the bladder. As the bladder is not only the 'mirror of the soul' but also a reflection of function of different organ systems, failure of these systems and systemic diseases should be taken into account. For example, the presence of DU is related to highly prevalent diseases such as diabetes mellitus or atherosclerosis. Knowledge on the interaction between the bladder (voiding function) and systemic diseases is of major importance and, therefore, reflects an emerging basic research area within urology.

A major part of this thesis covers assessment tools and algorithms to screen and diagnose DU patients among other causes of voiding dysfunction. Diagnosis of DU is highly challenging because all types of voiding dysfunction (i.e. DU, BOO, and detrusor-sphincter dysfunction) often result in the same symptoms and signs. As DU prevalence rate is estimated as high as 45% in the LUTS outpatient department, identifying and categorising these patients is of key importance. Until recently, there has not been a non-invasive or invasive tool available to adequately assess DU and separate it from other types of voiding dysfunctions. The publications included in this thesis have opened a new field of research within functional urology. Several articles form the basis for new research with regard to diagnostic challenges and possibilities to assess voiding function. In addition, this thesis emphasises the importance of differences in voiding function between men and women, something that has been ignored in the past. The output of my research and content of this thesis may help a large group of urological patients and urologists to (1) protect a group of patients to be assessed and treated in the wrong way (e.g. women who receive a transvaginal tape but are unable to void after surgery), (2) raise awareness to urologists to adequately assess a patient with a large post-void residual or urinary retention, and (3) stimulate new treatment options for DU. At present, there are only limited treatment options for DU. Consequently, this PhD thesis on DU aims to initiate research with regard to new pharmacological compounds or smart devices such as neuro-modulators to improve voiding function at various levels.

1. Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. *Journal of American Geriatric Society 2006*;54:1920-1932.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck PE, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;21:167–178.
3. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. *World Health Organization*, February 2017.

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List of Publications

Articles

1. van Koeveringe GA, ***Rademakers KLJ***, Stenzl A. Latissimus Dorsi Detrusor Myoplasty to restore voiding in patients with an acontractile bladder: fact or fiction? *Current Urology Report* 2013;14:426-434.

2. ***Rademakers KLJ****, van Koeveringe GA*, L. Birder, F. Daneshgari, M. Ruggieri, Y. Igawa, C. Fry, A. Wagg. Detrusor Underactivity, pathophysiological considerations, models and proposals for future research: ICI-RS 2013. *Neurourology and Urodynamics* 2014;33:591-596.

3. ***Rademakers KLJ****, Oelke M*, van Koeveringe GA. Detrusor Contraction Power Parameters (BCI and Wmax) Rise with Increasing Bladder Outlet Obstruction Grade in Men with Lower Urinary Tract Symptoms - Results from a Urodynamic Database Analysis to Define Detrusor Underactivity. *World Journal o*f Urology 2014;32:1177-1183.

4. Den Hollander PP, ***Rademakers KLJ***, van Roermund JGA. Is periprostatic adipose tissue associated with aggressive tumor biology in prostate cancer? *World Journal of Clinical Urology* 2014;3.

5. ***Rademakers KLJ***, Drossaerts JMAJ, Rahnama'i MS, van Koeveringe GA. Differentiation of Lower Urinary Tract Dysfunctions: The role of ambulatory urodynamic monitoring. *International Journal of Urology* 2015;22:503-507.

6. Drossaerts JMAJ, ***Rademakers KLJ***, van Kerrebroeck PE, van Koeveringe GA. The value of urodynamic tools to guide patient selection in sacral neuromodulation. *World Journal of Urology* 2015;33:1889-1895.

7. van Koeveringe GA, ***Rademakers KLJ***. Factors impacting bladder underactivity and clinical implications. *Minerva Urologica e Nefrologica* 2015;67:139-148.

8. Drossaerts JMAJ, ***Rademakers KLJ***, van Kerrebroeck PE, van Koeveringe GA. De rol van urodynamische onderzoeken bij de selectie van patiënten voor sacrale neurmodulatie. *Tijdschrift voor Urologie* 2015;5:112-118.

9. Gammie A, Kirschner-Hermanns R, ***Rademakers KLJ***. Evaluation of obstructed voiding in the female: how close are we to a definition? *Current Opinion in Urology* 2015;25:292-295.

10. ***Rademakers KLJ***, van de Beek C. Case Report. Urinary Tract Aspergilloma. *Tijdschrift voor Urologie* 2015;5:131-134.

11. ***Rademakers KLJ***, Apostolidis AA, Constantinou C, Fry C, Kirschner-Hermanns R, Oelke M, Parsons B, Nelson P, Valentini F, Gammie A. Development of Contractility and Obstruction Nomograms for Women: Bladder mechanics, Considerations and Clinical Implication. ICI-RS 2014. *Neurourology and Urodynamics* 2016;35:307-311.

12. ***Rademakers KLJ***, van Koeveringe GA, Oelke M. Detrusor Underactivity in men with lower urinary tract symptoms/benign prostatic obstruction: characterization and potential impact on indications for surgical treatment of the prostate. *Current Opinion in Urology* 2016;26:3-10.

13. Vrijens DMJ, Drossaerts JMAFL, ***Rademakers KLJ***, Smits MAC, de Wachter SG, Leue C, van Koeveringe GA. Associations of psychometric affective parameters with urodynamic investigation for urinary frequency. *Lower Urinary Tract Symptoms* 2016 June [Epub ahead of print].

14. ***Rademakers KLJ****, Oelke M*, van Koeveringe GA. Unravelling detrusor underactivity: development of a bladder outlet resistance - bladder contractility nomogram for adult male patients with lower urinary tract symptoms. *Neurourology and Urodynamics* 2016;35:980-986.

15. ***Rademakers KLJ***, van Koeveringe GA, Oelke M. Ultrasound detrusor wall thickness measurement in combination with bladder capacity can safely detect detrusor underactivity in adult men. *World Journal of Urology* 2017;35:153-159.

16. ***Rademakers KLJ***, Drossaerts JM, van Kerrebroeck PE, Oelke M, van Koeveringe GA. Prediction of sacral neuromodulation treatment success in men with impaired bladder emptying – Time for a new diagnostic apporoach. *Neurourology and Urodynamics* 2017;36:808-810.

17. Vahabi B, Wagg A, Rosier P, ***Rademakers KLJ***, Denys MA, Pontari M, Lovick T, Valentini F, Nelson P, Andersson KE, Fry CH. Can we define and characterise the ageing lower urinary tract? – ICI-RS 2015. *Neurourology and Urodynamics* 2017;36:854-858.

18. ***Rademakers KLJ***, Drake MJ, Gammie A, Djurhuus J, Rosier P, Abrams P, Harding C. Male bladder outlet obstruction: Time to re-evaluate the definition and reconsider our diagnostic pathway? ICI-RS 2015. *Neurourology and Urodynamics* 2017;36:894-901.

19. Andersson KE, Fry CH, Panicker J, ***Rademakers KLJ***. Which molecular target do we need to focus on to restore voiding function? ICI-RS 2017. *Neurourology and Urodynamics* 2017 [In preparation].

20. Tarcan T, ***Rademakers KLJ***, Arlandis S, van Koeveringe GA, von Gontard A, Abrams P. Do the definitions of Underactive Bladder and Detrusor Underactivity help in managing patients? ICI-RS Tink Tank 2017. *Neurourology and Urodynamics* 2017 [In preparation].

**Shared first authorship*

Book Chapters and Educational Projects

1. ***Rademakers KLJ***, van Koeveringe GA. Managing Detrusor Underactivity. BJUI Knowledge, *British Journal of Urology International* 2016.

2. ***Rademakers KLJ***, van Koeveringe GA. Special Urodynamics: Ambulatory Urodynamic Study. Editors: Cardozo and Staskin, *Textbook of Female Urology & Urogynaecology* 2017.

3. ***Rademakers KLJ***, van Koeveringe GA. Non-invasive diagnostics for Detrusor Underactivity / Underactive Bladder. Editors: Chapple, Osman and Wein. *Underactive Bladder* 2017.

4. ***Rademakers KLJ***, van Koeveringe GA. Bladder wrap procedures. Editors: Chapple, Osman and Wein. *Underactive Bladder* 2017.

5. ***Rademakers KLJ***, Igawa Y, Lowry A, Sievert KD, Laterza R, Serati M, DeLancey J, Koebl H, Sultan A, Salvatore S. Pathophysiology of urinary incontinence, faecal incontinence and pelvic organ prolapse. Editors: Abrams, Cardozo, Wagg and Wein. *Incontinence* 2017.

List of Presentations

1. Dutch Surgical Association meeting (Chirurgendagen) 2011: invited speaker working group on surgical endoscopy. ***Rademakers KLJ***, Leijtens JWA, Maas M, Doornebosch PG, Karsten TM, Derksen EJ, Stassen LPS, Rosman C, Beets GL, Heemkerk J, E. de Graaf. Oncologische grenzen van transanale endoscopische microchirurgie bij het rectumcarcinoom: Een retrospectieve analyse uit Zuid-West Nederland.

2. Dutch Gasteroenterology meeting (NVGE) 2012: Student Award. ***Rademakers KLJ,*** Leijtens JWA, Maas M, Doornebosch PG, Karsten TM, Derksen EJ, Stassen LPS, Rosman C, Beets GL, Heemkerk J, E. de Graaf. Transanal Endoscopic Microsurgery; a multicenter retrospective analysis of patients with a pT2/T3N0M0 rectal carcinoma.

3. United European Gastroenterology Week (UEG Week) 2012. ***Rademakers KLJ***, Leijtens JWA, Maas M, Doornebosch PG, Karsten TM, Derksen EJ, Stassen LPS, Rosman C, Beets GL, Heemkerk J, E. de Graaf. Transanal Endoscopic Microsurgery; a multicenter retrospective analysis of patients with a pT2/T3N0M0 rectal carcinoma.

4. Dutch Urological Association (NVU) spring meeting 2013: prime-time session. ***Rademakers KLJ***, Rahnama'i S, GA van Koeveringe. De rol van ambulante urodynamica bij patiënten met ogenschijnlijk acontractiele blaas.

5. Young Urology meeting 2013. ***Rademakers KLJ***, Oelke M, van Koeveringe GA. Increase in detrusor wall thickness (DWT) is significantly associated with increase in bladder outlet obstruction (BOO) grade and detrusor contraction power (W_{max}) in adult men with LUTS.

6. European Association of Urology (EAU) annual meeting 2014. Oelke M**,** ***Rademakers KLJ***, van Koeveringe GA. The use of clinical tests for diagnosing detrusor underactivity in adult men – results of a pilot study.

7. European Association of Urology (EAU) annual meeting 2014. ***Rademakers KLJ***, Oelke M, van Koeveringe GA. Bladder contractility rises with increasing bladder outlet obstruction (BOO) in men with lower urinary tract symptoms (LUTS) - results from a large urodynamic cross-sectional study.

8. International Consultation on Incontinence Research Society (ICI-RS) meeting 2014. **Think Tank 6** "Development of Contractility and Obstruction Nomograms for Women: Bladder mechanics, Considerations and Clinical Implication". Chairmen Rademakers KLJ, Gammie A. ***Rademakers KLJ***. Contractility and obstruction nomograms for women.

9. State Of The Art (SOTA) Urology 2014: invited speaker. ***Rademakers KLJ***. Detrusor onderactiviteit: een nieuwe entiteit?

10. International Continence Society (ICS) annual meeting 2014. **Workshop** "Detrusor underactivity: detection and diagnosis" Presentations by: prof. dr. Gommert van Koeveringe, ***Kevin Rademakers***, prof dr. Matthias Oelke en prof. dr. Chris Chapple.

11. International Continence Society (ICS) annual meeting 2014. ***Rademakers KLJ***, Drossaerts JMAJ, Rahnama'I MS, van Koeveringe GA. Absent bladder sensation during conventional urodynamics is associated with bladder acontractility confirmed by ambulatory urodynamics.

12. International Continence Society (ICS) annual meeting 2014. ***Rademakers KLJ***, Oelke M, van Koeveringe GA. Detrusor underactivity in females: Significant correlation between standardized medical history assessment and urodynamic findings.

13. Scholarship UNICAMP, Campinas Brasil 2014. ***Rademakers KLJ***. Special Urodynamic testing: Ambulatory Urodynamics.

14. Scholarship UNICAMP, Campinas Brasil 2014. ***Rademakers KLJ***. Detrusor Underactivity: A new urological entity?

15. European Association of Urology (EAU) annual meeting 2015. ***Rademakers KLJ***, van Koeveringe GA, Oelke M. Development of a nomogram for the classification of detrusor underactivity (DU) in adult men with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO).

16. Dutch Urological Association (NVU) spring meeting 2015. ***Rademakers KLJ***, M Oelke, GA van Koeveringe. Ontwikkeling van een nomogram voor de classificatie van detrusor onderactiviteit bij mannen met luts en verdenking op obstructie (BOO).

17. International Neuro-Urology meeting 2015. Session: Young Talents in Neuro-Urology. ***Rademakers KLJ***. Non-invasive clinical indicators of Detrusor Underactivity in adult men: Results of a pilot study.

18. International Consultation on Incontinence Research Society (ICI-RS) meeting 2015. **Think Tank 4** "Male BOO diagnosis and diagnostics". Chairmen Rademakers KLJ, Harding CH. ***Rademakers KLJ***. Current diagnosis and clinical utility.

19. International Continence Society (ICS) annual meeting 2015. **Workshop** "Detrusor underactivity: detection and diagnosis". Presentations by: prof. dr. Gommert van Koeveringe, ***Kevin Rademakers***, prof. dr. Matthias Oelke and prof. dr. Chris Chapple.

20. Dutch Brazilian connection (DBC) meeting 2016. ***Rademakers KLJ***. How to treat UAB.

21. Global Congress on Lower Urinary Tract Dysfunctions 2016. ***Rademakers KLJ***. PVR and urinary retention: How much PVR can we tolerate?

22. Österreichische Gesellschaft für Urologie und Andrologie AUO/AK prostata meeting 2017: invited speaker. ***Rademakers KLJ***. Detrusor underactivity: From theory to clinical practice.

23. European Association of Urology (EAU) annual meeting 2017: invited speaker. ***Rademakers KLJ***. OAB: what matters about OAB outcomes.

24. International Consultation on Incontinence Research Society (ICI-RS) meeting 2017. **Think Tank 6** “Are our definitions of underactive bladder and detrusor underactivity useful in managing patients”. Chairman: Tarcan T. ***Rademakers KLJ***. Do we need to have different definitions of UAB/DU based on gender and aetiology?

25. International Consultation on Incontinence Research Society (ICI-RS) meeting 2017. **Think Tank 5 “**What is utility of urodynamic including Ambulatory and 24 hr, in predicting upper urinary tract damage in neuro-urological patients and other LUTD?”. Chairmen: Castro-Diaz D, Djurhuus JC. ***Rademakers KLJ***. The role of ambulatory urodynamics in complex voiding dysfunction.

26. International Continence Society (ICS) annual meeting 2017. **Workshop** “Detrusor underactivity: detection and diagnosis”. Presentations by: prof. dr. Gommert van Koeveringe, ***Kevin Rademakers***, prof. dr. Matthias Oelke and prof. dr. Chris Chapple.

27. International Continence Society (ICS) annual meeting 2017. **Workshop** “Wiki what? – Be a part of the future of ICS and urology terms”. Presentations by: Elizabeth Shelly, Sajjad Rahnama’I, ***Kevin Rademakers***, Luis Miguel Abranches-Monteiro, prof. dr. Roger Dmochowski, Melanie Morin.

Curriculum Vitae

Kevin Leon Johannes Rademakers was born on November 30th 1987 in Weert, the Netherlands. After finishing secondary school (Atheneum, Nature and Health track) at Bisschoppelijk College in Weert he entered medical school at Maastricht University in 2006. Kevin obtained his bachelor degree (BSc) in Medicine in 2009. During his last year of medical training Kevin started his research project on Detrusor Underactivity, supervised by prof. dr. Gommert van Koeveringe and prof. dr. Matthias Oelke. After obtaining his Master degree (medicine, MSc) in 2012 he continued his work on this project as a PhD candidate at the department of urology, Maastricht University Medical Center (MUMC+). During this 2 ½ year period as a researcher he was responsible for over a dozen of publications and over 20 (inter)national oral presentations in the field of functional urology. Kevin worked as a resident in the MUMC+ in 2015 and was accepted to the Dutch urology resident training program in that year. He started his training in 2016 with the aim to finish his urology training in July 2021.

Aside from his work as a resident, Kevin is currently an active member of several societies: the International Continence Society (ICS), being involved in a standardisation subcommittee, ICS wiki committee and reviewer of Neurourology and Urodynamics; the International Consultation on Incontinence Research (ICI-RS); and the EAU, as an invited speaker at the EAU annual congress London 2017 and reviewer for European Urology.