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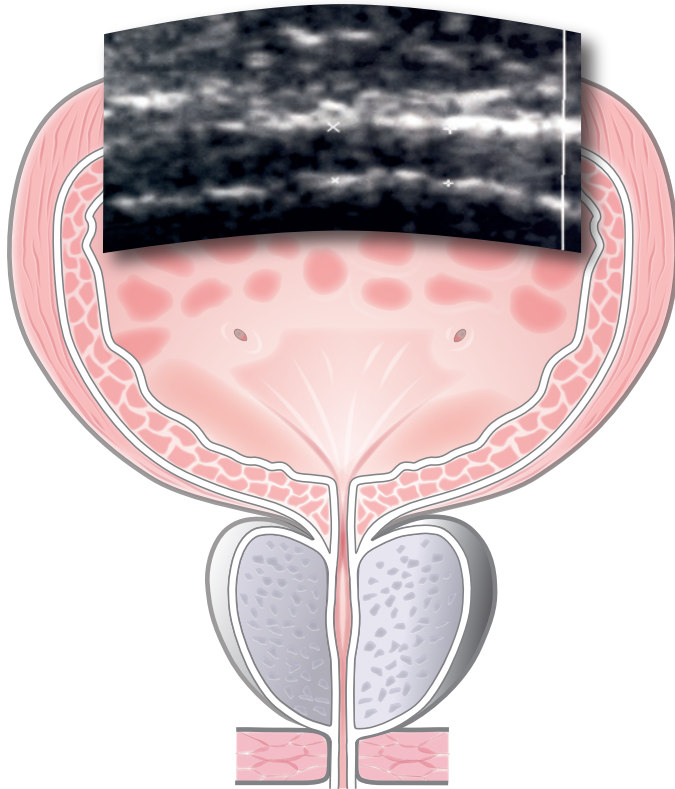
Non-invasive Diagnosis
of Bladder Outlet Obstruction (BOO)
in Male Patients with Lower Urinary
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- Matthias Oelke -

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Non-invasive Diagnosis of Bladder Outlet Obstruction (BOO) in Male Patients with Lower Urinary Tract Symptoms (LUTS)

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

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Matthias Oelke

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General Introduction

CHAPTER 1

Scope and Outline of the Thesis

1.1   DEFINITIONS

Bladder outlet obstruction (BOO) is a urodynamic observation which has been defined by the International Continence Society (ICS) as obstruction during voiding and is characterized by increased detrusor pressure and decreased urinary flow rate; BOO is diagnosed by studying the synchronous values of flowrate and detrusor pressure [1]. BOO has been defined for adult men but not for women or children until now [1]. Any type of obstruction between the bladder neck and the tip of the urethra, either of benign or malignant origin, can cause BOO (e.g. bladder neck stenosis, sclerosis of the external urethral sphincter, urethral stricture, urothelial cancer of the urethra, foreign body or stone in the urethra, 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].

The term BPH is only used to describe the microscopic changes in the prostate which are characterized by benign growth of epithelial, muscular and/or fibrotic cells in the prostate. The cause of BPH remains largely unknown but the prevalence increases with ageing [2]. BPH can cause growth of the transition zone of the prostate, an area on the dorsal side of the prostatic urethra between the central and peripheral zone and proximal of the veromontanum [3,4]. The transition zone volume, which is approximately 5% of the glandular prostatic volume in young adults (peripheral zone 75%, central zone 20%), continuously increases with increasing severity of BPH [4]. As a result of transition zone enlargement, total prostate volume increases and may be measurable and/or palpable (**figure 1**). The volume of the prostate in young adults and men without BPH is approximately 20–25 cm^3 on average [2, 5]. Therefore, the term BPE can be applied when the prostate has a volume >25 cm^3 [5,6].
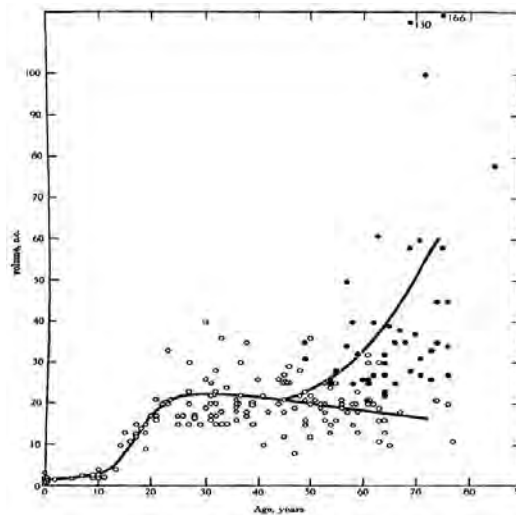
Figure 1: Prostate volume (y-axis, cm^3) in relation to age (x-axis, years) in an autopsy study of men without (○) or with (•) the histologic signs of benign prostatic hyperplasia [5]. In boys before puberty, prostate volume is low and varies between 1 and 4 cm^3. The prostate grows in puberty and reaches an average volume of approx. 20-25 cm^3 in adult men without benign prostatic hyperplasia, whereas men with benign prostatic hyperplasia have an increasing prostate volume with aging.

Lower urinary tract symptoms (LUTS) are the subjective indicator of a disease or change in condition as perceived by the patient, carer or partner and may lead him to seek help from health care professionals [1]. LUTS may either be volunteered or described during the patient interview and are usually qualitative [1]. LUTS can also be quantified by using validated questionnaires such as the American Urological Association-Symptom Index (AUA-SI) or, if a quality of life question is added, International Prostate Symptom Score (IPSS) [7, 8]. These questionnaires evaluate seven symptoms for a recall period of 4 weeks (feeling of incomplete emptying, urinary frequency, intermittency of urinary flow, urgency, weak urinary stream, straining, and nocturnal voiding frequency); the result ranges from 0-35 and divides symptomatology into no (0), mild (1-7), moderate (8-19), and severe LUTS (20-35). LUTS can be divided into storage, voiding or post-micturition symptoms when they appear during bladder filling, micturition or after voiding [1, 9]. Although voiding LUTS (e.g. hesitancy, weak urinary stream, straining, or feeling of incomplete bladder emptying) are more frequently reported, storage LUTS (e.g. urgency, daytime or nighttime frequency/nocturia, urgency incontinence) are usually more bothersome for men and decrease health-related quality of life more substantially [10-12]. LUTS are unspecific for age, gender or the underlying disease [13-15]. Therefore, LUTS in general or the type or severity of LUTS do not necessarily indicate BPE or BOO/BPO in adult men. Besides the prostate, the origin of LUTS may also be the urinary bladder, urethra, pelvic floor, central or peripheral nervous system, intestine, or even the ureter in case of distal ureteral stones.

1.2   EPIDEMIOLOGY OF BPH-COMPONENTS – DIMENSION AND BURDEN OF THE DISEASE

Microscopic BPH, as determined in autopsy studies, affects approx. 40, 70, 80, and 90% of men in their 6th, 7th, 8th, and 9th decade, respectively [2]. Therefore, microscopic BPH is rather the rule than the exception in elderly people. It is estimated that approx. one third to one half of men with the histologic signs of BPH also has a prostate volume of more than 25 cm^3 (BPE), and up to 42% have moderate to severe LUTS [2, 16]. In urodynamic case studies of patients with clinical BPH (i.e. signs and symptoms of BPH), the chance of BOO/BPO was highly variable. BOO/BPO was detected in 32–83% of men even in studies of the same author group [17, 18], indicating that patient selection is responsible for different results. Larger series of unselected patients with BPH reported about BPO in approx. 60% of the symptomatic and 52% of the asymptomatic men [19, 20]. However, cross-sectional or longitudinal studies on BOO/BPO in community-dwelling men have yet not been conducted due to the necessity to perform pressure-flow studies to determine BOO/BPO. Damage of the lower urinary tract (e.g., bladder diverticula, bladder stones, or urinary retention) and upper urinary tract (e.g., vesical-ureteral reflux, bilateral hydronephrosis, or impairment or loss of renal function) is thought to be associated with BOO/BPO [21]. Exact numbers of men with and knowledge about the pathophysiology of lower or upper urinary tract damage do not exist. Clinical BPH represents the most frequent benign tumor in adult men, is the seventh most commonly treated disease in industrial countries in men aged ≥50 years, positioned among the ten most costly diseases in men, and associated with the highest socio-economic burden in urology [22].

The characteristics of men with clinical BPH (i.e. sign or symptoms of BPH) were evaluated in 4979 individuals in six European countries (France, Germany, Italy, Poland, Spain, and United Kingdom) [23]. The majority of men requested medical advice for bothersome LUTS (approx. 77%); other reasons were fear for prostate cancer (approx. 11%) or participation at a screening program (approx. 10%). The median age of men visiting doctor offices was 65 years (interquartile range 58-71), median value on the IPSS questionnaire was 12 (scale 0-35), mean quality of life value was 3.3 (scale 0-6), median prostate volume was between 37 (Germany) and 62 cm^3 (UK), and median post-void residual urine volume varied between 39 (Spain) and 86 ml (UK). Approx. 62% of men had co-morbidities (27% multiple co-morbidities). Arterial hypertension (37%), coronary heart disease (13%), diabetes mellitus (10%), chronic respiratory failure (8%), chronic gastrointestinal diseases (7%), cerebrovascular accidents or transient ischemic attack (4%), and other neurological diseases (4%) were most frequently reported.

In the year 2011, the total population in Germany was approx. 80.2 million, the male population approx. 39.1 million (48.8%), and men aged 50 years or older approx. 13 million [24]. An epidemiological study in Germany (2000) investigating a representative sample of men aged ≥50 years in the district of Herne estimated that the prevalence of BPE is approx. 26.9% (3.2 million), LUTS approx. 40.5% (5 million), and BPO approx. 17.3% (2.1 million) [25]. Based on the demographics of the German population, average annual treatment costs of BPH of € 900 per patient [26], and considering prevalence data from Berges et al. [25] approx. 2.5 million German men with symptoms or signs of BPH are under treatment and responsible for more than € 2.2 billion treatment costs per year.

1.3   PATHOPHYSIOLOGY – INTERRELATIONSHIPS BETWEEN BOO/BPO, BPE AND LUTS

The chance of BOO/BPO rises with increasing prostate volume [27]. However, there are only weak and inconsistent relationships between LUTS and BOO/BPO [27-29], LUTS and the severity of BOO/BPO [27, 30-32], as well as LUTS and prostate volume [33-35]. Taken together all information, there are no clear relationships between BOO/BPO, BPE and LUTS which are sufficient enough for use in clinical practice and individual patients. Therefore, the existence or severity of one component (LUTS, BPE, BOO/BPO) does not necessarily predict the existence or severity of other components of the BPH disease. The relationships between BOO/BPO, BPE and LUTS can be illustrated as a diagram (**figure 2**) [36]. The exact proportions between the three individual components of the BPH-disease in community-dwelling men or males with LUTS/BPH have yet not been investigated and remain unknown.
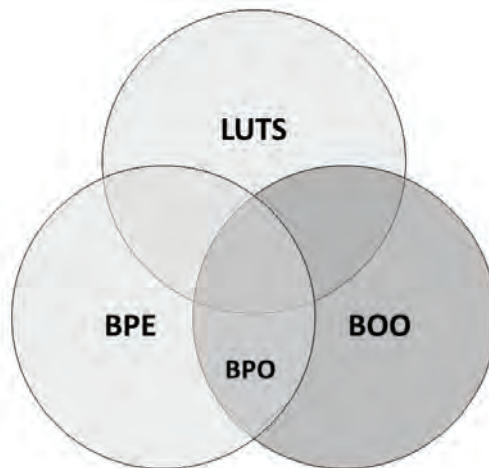
Figure 2: Diagram to illustrate the relationships between lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE), bladder outlet obstruction (BOO) and benign prostatic obstruction (BPO) [36]. All individual components of the BPH-disease can appear separately but may also be combined. In clinical practice, the three components need to be evaluated and quantified separately in order to correctly judge the individual patient.

1.4   CHANGES OF THE BLADDER FOLLOWING BOO/BPO IN EXPERIMENTAL ANIMALS

Basic knowledge of bladder changes as a result of BOO was obtained from experimental animals in which a suture was placed around the catheterized urethra. Decrease of the urethral lumen increased urethral resistance after catheter removal and caused BOO. Changes of the obstructed bladder are time-dependent and can be divided in animals into three distinct stages which are characterized by typical morphological, functional, and biochemical alterations [37]:

- Initial stadium: a progressive increase of bladder weight due to thickening of the bladder wall can be found within two weeks after induction of artificial BOO (**figure 3**). Compared to sham operated animals, bladder weight increases 3-5fold in rats and 5-6fold in rabbits [38].

- Compensation stadium: bladder weight remains stable, detrusor contraction strength (contractility) is unchanged or even increased, and bladder emptying is complete (i.e. no post-void residual urine). Microscopic investigations of the bladder wall in these animals show characteristic changes predominantly in the detrusor which consist of hypertrophy of smooth muscle cells, hyperplasia of fibroblasts, and deposition of collagen fibers between muscle cell bundles of the detrusor (**figure 4**) [39].

- Decompensation stadium: three weeks to six months (rabbits) after induction of artificial BOO a further increase of bladder weight develops, detrusor contraction strength decreases, post-void residual urine progressively increases, urinary retention occurs, and the animal dies in renal insufficiency. Microscopic studies of the bladder wall in this stadium showed widened

spaces between smooth muscle cells due to additional deposition of collagen and elastic fibers. Urodynamic studies revealed low bladder compliance [40]. The more pronounced the deposition of the connective tissue becomes the more the bladder compliance decreases.
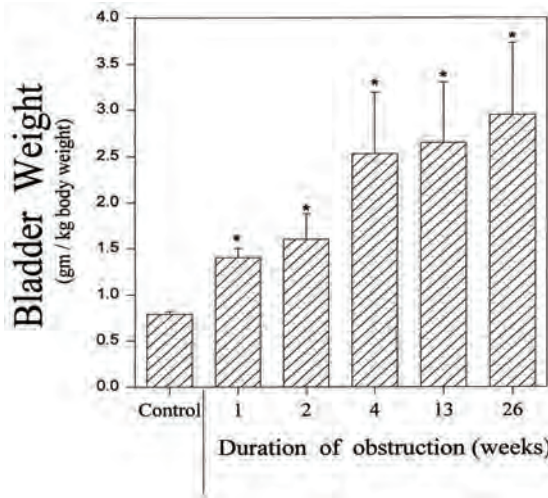
Figure 3: Bladder weight after induction of artificial bladder outlet obstruction by suturing the urethra of rabbits compared to sham-operated animals [37]. Bladder weight significantly (*) increases already 1 week after suturing the urethra and further increases thereafter.
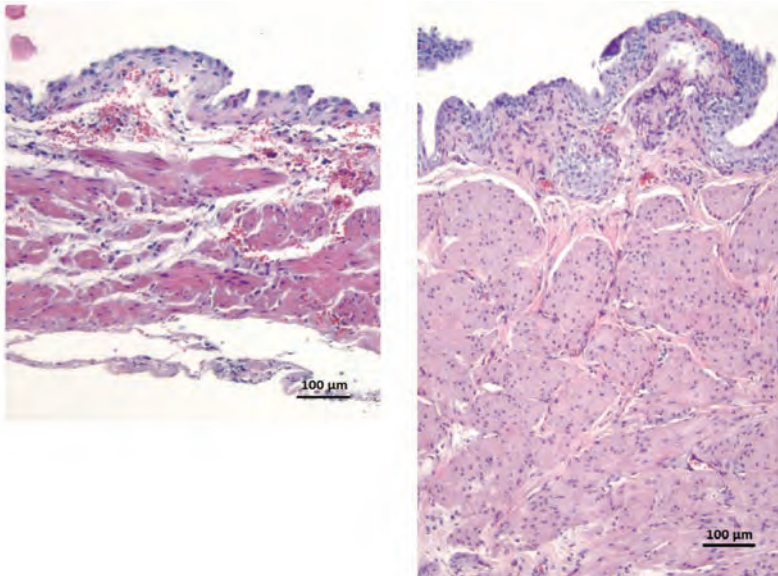
Figure 4: Hematoxylin-eosin staining of transverse sections of rat bladder walls 1 (left image) and 7 days (right image) after induction of artificial bladder outlet obstruction by suturing the urethra. Bladder weight increased up to 90% due to the increase and hypertrophy of detrusor muscle cells [41].

In contrast to experimental animals, BPO in men develops slowly during years or even decades and, consequently, strict differentiation between three distinct stages is impossible [37]. Compensation mechanisms in human bladders could therefore be more effective than after sudden induction of artificial BOO in animals. Nevertheless, similar morphological, functional, and biochemical changes of the bladder wall have been observed in men with BOO/BPO. Hypertrophy of smooth muscle cells, hyperplasia of fibroblasts, and infiltration of collagen and elastic fibers between muscle cells of the detrusor were also documented in humans [42, 43]. Bladder weight in men with BOO/BPO increases 2-4fold as a result of bladder wall hypertrophy [44, 45]. Urodynamic studies in men with BOO/BPO confirmed decreasing bladder compliance with increasing urodynamic obstruction grade [46]. Low-compliance of the bladder seems to be responsible for upper urinary tract dilatation and renal insufficiency in men with BPO [47].

All data indicate that human bladders of patients with BOO/BPO behave similar compared to those of animals with artificial BOO. Bladder wall hypertrophy due to thickening of the detrusor as a result of BOO/BPO is the most prominent visible change. Increased detrusor or bladder wall thickness seems to be similar to visible changes in the heart in which the muscular wall thickens due to a valve stenosis or arterial hypertension [48]. Consequently, it was hypothesized that detrusor or bladder wall thickness reflects the workload of the bladder and provides information about the degree of BOO/BPO [48, 49]. Thickening of the detrusor or bladder wall seems to be a compensation mechanism of the bladder to maintain voiding in the presence of BOO/BPO [50].

1.5   TESTS TO DIAGNOSE BOO/BPO

Because of the inconsistent and unreliable relationships between LUTS, BPE and BOO/BPO, each parameter of the BPH disease has to be evaluated separately. Quantification of prostate volume by digito-rectal examination or (transrectal) ultrasound measurement and evaluation of LUTS by history or the IPSS questionnaire are quick and simple. Evaluation of BOO/BPO is more difficult. Until now, only pressure-flow studies (urodynamic investigation) are able to determine BOO/BPO accurately and, therefore, are considered to be the reference standard. However, pressure-flow studies are invasive, expensive, and time consuming. Urodynamic studies are associated with adverse events which are as frequent as 19% in men and consist of urinary tract infections, pyelonephritis, hematuria, or urinary retention [51]. Longitudinal or epidemiological studies on BOO/BPO have not been carried out due to the invasive character of pressure-flow studies. Several tests have been investigated for the ability to alternatively and non-invasievely diagnose BOO/BPO. Ultrasound - as a harmless and non-invasive imaging technique with widespread availability - has gained increasing popularity for the non-invasive diagnosis of BOO/BPO. The following tests are frequently carried out in clinical routine practice or in scientific investigations in order to judge BOO/BPO.

1.5.1   Urethro-cystoscopy

Visual judgment of the occlusion grade of the prostatic urethra or trabeculation grade of the bladder

The endoscopic assessment of the lower urinary tract with a cystoscope aims to visualize the degree of occlusion of the prostatic urethra by the lateral prostate lobes or a median lobe as well as the degree of trabeculation of the bladder mucosa. The degree of occlusion of the prostatic urethra can be divided into 3 grades and degree of trabeculation of the bladder mucosa into 4 grades (**figure 5**) [52, 53].
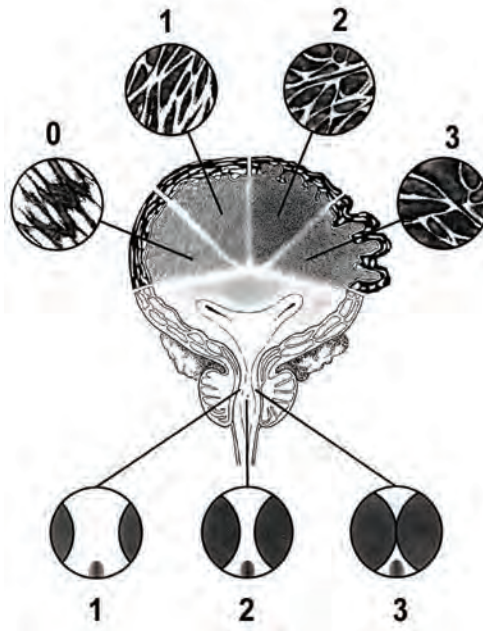
Figure 5: Illustration of the grade of trabeculation of the bladder (0-3, upper part of image) and grade of occlusion of the prostatic urethra (1-3, lower part of image) evaluated during urethro-cystoscopy [52, 53].

Grade 0:	smooth surface of the bladder mucosa, no signs of trabeculation
Grade 1:	uneven surface of the bladder mucosa, little trabeculation
Grade 2:	strong trabeculation without pseudo diverticula
Grade 3:	strong trabeculation with pseudo diverticula

Grade 1:	prostatic lateral lobes not existing or little prominent, free passage into the urinary bladder (prostatic urethra non-obstructed)
Grade 2:	prostatic lateral lobes prominent but they do not touch each other in the midline (prostatic urethra moderately obstructed)
Grade 3:	prostatic lateral lobes prominent and touch each other in the midline (prostatic urethra severely obstructed)

The diagnostic value of urethro-cystoscopy and visualization of the prostatic urethra as well as the bladder mucosa for the prediction of BOO/BPO was tested in 492 adult men with LUTS [53]. The authors could demonstrate a significant relationship between the occlusion or trabeculation grades and BOO/BPO. Approx. 40% without prostatic lateral or median lobes (occlusion grade I) but 90% of bladders in men with prominent prostatic lateral lobes (occlusion grade III) were obstructed in pressure-flow analysis. In men without bladder trabeculation (trabeculation grade 0), 50%, 32% and 18% had no, equivocal/mild and severe BOO/BPO in pressure-flow analysis, respectively. In contrast, 6%, 24% and 69% of patients with severe bladder trabeculation (trabeculation grade 3) had no, equivocal/mild and severe BOO/BPO, respectively. The authors concluded that despite the significant statistical differences the degree of occlusion or trabeculation is not helpful for the individual patient and, therefore, not clinically relevant. Bladder trabeculation seems to be a sign of detrusor overactivity rather than BOO/BPO [54] but, however, BOO/BPO and detrusor overactivity could also be linked to each other. Additionally, the diagnostic value of endoscopy for the diagnosis of BOO/BPO has to be balanced against potential adverse events during or after this invasive investigation (e.g. pain, discomfort, urethral trauma, hematuria, infection).

1.5.2 Non-invasive urodynamic tests

1.5.2.1 Uroflowmetry

For this investigation, the patient voids with a full bladder in a funnel that is connected with an uroflowmeter where the excreted urine volume is measured per time (i.e. urinary flow rate). Important parameters of free uroflowmetry are, besides the shape of the flow curve, maximum (Q_{max}) and average urinary flow rate (Q_{ave}) [1]. It is recommended that the patient voids at least 150 ml to obtain representative measurements [55]; however, approx. 30% of elderly men are not able to void the recommended ≥150 ml [56]. There is a linear rise of Q_{max} with voided volume between 125 and 525 ml but, thereafter, a decrease of Q_{max} due to overdistension of the bladder [57-59]. However, the exact volumes for increasing and then decreasing Q_{max} may be different in individual men [59]. For the interpretation of measurement values it also is important to know that Q_{max} und voided volume significantly increase in patients with LUTS when repeating the uroflowmetry in offices or hospitals [60]. The mean difference of Q_{max} between the first and second void was 2.3 m/s (95% confidence interval 1.9-2.7) and the mean difference between voids 1-3 and 1-4 was 1.5 ml/s (95% confidence interval 1.2-1.8); the corresponding mean voided volumes increased by 12 and 25 ml, respectively. Whereas office uroflowmetry values significantly increase with the number of voids, home uroflowmetry values are considered highly reproducible [61, 62]. However, the variability of Q_{max} in men with clinical BPH is higher than in healthy individuals and varies up to ± 4.1 ml/s [63, 64]. It is therefore recommended to repeat uroflowmetry in cases of insufficient voiding volumes and abnormal voiding values [55].

Q_{max} values ≥15 ml/s are considered normal and, consequently, values <15 ml/s abnormal in men with voided volumes ≥150 ml. Urinary flow rate is the product of the contractile function of the

detrusor (contractility) and bladder outlet resistance (BOO) [65]. A decrease in detrusor contractility or an increase in bladder outlet resistance decreases urinary flow rate. Therefore, a Q_{max} value <15 ml/s can only indicate a pathological flow rate and cannot distinguish between BOO/BPO and detrusor underactivity. To complicate matter, up to 25% of patients with BOO/BPO still have a Q_{max} ≥15 ml/s due to increased contractility, a condition described as 'high-flow obstruction' [66-68]. Consequently, uroflowmetry values (and the shape of the uroflow curve) are unreliable indicators of BOO/BPO. Nevertheless, all epidemiological trials on BPH used (different threshold values of) Q_{max} to estimate BOO/BPO [25].

1.5.2.2 Measurement of isovolumetric bladder pressure

Measurement of isovolumetric bladder pressure ($P_{ves.iso}$) provides information about the bladder pressure during voiding and, when urinary flow is synchronously measured, can also distinguish between BOO/BPO and detrusor underactivity (hypocontractility). The condom catheter method and penile cuff test are able to measure $P_{ves.iso}$. Both tests are based on the postulate that a continuous fluid column exists between the bladder and the tip of the urethra during micturition [69]. Thus, the external pressure on the urethra which is needed to interrupt the urinary flow during micturition is equal to the bladder pressure at the time the flow stops [70, 71].

Condom catheter method

A modified incontinence condom catheter is used for the measurement of $P_{ves.iso}$ [72]. The self-adhesive condom is placed on the penis and connected to tubes, valves and a pressure transducer; the tubes drain into a flowmeter. During micturition, the outflow resistance is gradually increased in the valve until urinary flow ceases. The pressure in the condom at that moment is equal to $P_{ves.iso}$ [73, 74]. The patient continues to void after reducing the resistance of the valve and, afterwards, measurements of $P_{ves.iso}$ can be repeated several times during one void. For adequate measurements, Q_{max} of at least 5.4 ml/s is necessary, urinary flow has to be continuous, and straining has to be avoided [75]. $P_{ves.iso}$ is also dependent on bladder filling volume and ~250 ml seems to be ideal [73, 76]. Reproducibility and reliability of $P_{ves.iso}$ measurements were confirmed in 754 volunteers [77].

Measurements of $P_{ves.iso}$ were correlated with pressure-flow results of 56 patients to determine the ability to assess BOO/BPO correctly [78]. Patients with confirmed or equivocal BOO/BPO were combined to one group and compared with patients with non-obstructed bladders. The authors could correctly judge 82% of the obstructed and 59% of the unobstructed bladders. Good reproducibility of the test was demonstrated in men who participated in an epidemiological study [79]. Measurements of $P_{ves.iso}$ with the condom catheter were successful once in 94% and twice in 84% of the 659 volunteers. Although two consecutive measurements of $P_{ves.iso}$ of the same patient differed significantly, this difference was judged as clinically irrelevant.

Penile cuff test

A pneumatic cuff is placed around the penis which automatically inflates in a stepwise increment of 10 cm H_2O per second when voiding commences [80, 81]. The pressure during complete interruption of urinary flow is determined ($P_{cuff.int}$) which is a reproducible estimate of $P_{ves.iso}$ [82-84]. Mean cuff pressure is slightly higher than bladder pressure (mean difference ~16 cm H_2O) due to the difference of height between the pubic symphysis and the cuff [84]. Immediately after flow interruption, the cuff is rapidly deflated again allowing flow to resume. Release of cuff pressure results in a flow surge (Q_{surge}) that quickly passes on to a steady state flow (Q_{ss}; **figure 6**). The cycle can be repeated several (typically three to five) times until voiding is complete. For the valid interpretation of the results, the voided volume should be >150 ml. Good reliability and reproducibility was documented [83]. Maximum values of $P_{cuff.int}$ and Q_{max} at cuff occlusion can be plotted in a nomogram to categorize bladders as obstructed, non-obstructed or uncertain [85-87]. Only patients in the uncertain group would require invasive pressure-flow studies to safely assess BOO/BPO or other forms of lower urinary tract dysfunction. Morbidity of the penile cuff test was documented in 179 patients, affected 2% of subjects and included discomfort and urethral bleeding [87].
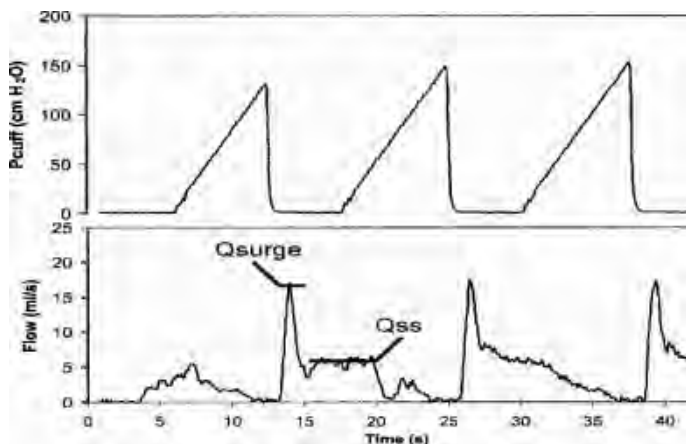
Figure 6: Penile compression-release maneuver [88]. A cuff was placed around the penis which inflates rapidly after voiding has started und squeezes the urethra (upper graph) until urinary flow commences (lower graph). The pressure at complete interruption is a reliable estimate of isovolumetric bladder pressure ($P_{ves.iso}$). After pressure release in the cuff, a flow surge appears (Q_{surge}) which is followed by a steady-state flow (Q_{ss}). Q_{surge} is expressed as a percent of Q_{ss}. This PCR index (%) is significantly higher in men with BOO/BPO compared to those individuals without BOO/BPO.

In 144 men with clinical BPH, Griffiths and colleagues evaluated the diagnostic accuracy of the nomogram which was able to correctly identify 68% of the patients' bladders as obstructed and 78% as non-obstructed [85]. However, 31% of patients were judged as 'uncertain'. Sullivan and Yalla investigated the usefulness of Q_{sure} and Q_{ss} in 124 patients, expressed Q_{sure} as the percentage of Q_{ss} and termed this test "Penile Compression-Release (PCR) Index" [89]. The authors showed that PCR is

significantly higher in patients with BOO/BPO. PCR index >100% had the ability to diagnose 74% of patients with BOO/BPO correctly. These results were confirmed in 150 patients later [88]. Nevertheless, the combination of PCR, Q_{max} <10 ml/s during the cuff test, and the nomogram classification had the highest diagnostic accuracy [85, 90].

The Griffiths nomogram was also tested with regard to its ability to predict the outcome after TURP in 179 patients [87]. Improvement was defined as a reduction of 50% on the IPSS questionnaire four months after surgery. Patients in the BOO/BPO group reported about improvement in 87% but improvement was only verified in 56% in men without BOO/BPO (p<0.01). 40% of patients were judged as 'uncertain'. Comparison of the penile cuff test with Q_{max} of free uroflowmetry in terms of symptomatic improvement and prediction of good treatment outcome demonstrated that the penile cuff test was superior to Q_{max} (likelihood ratios 6.7 vs. 4.0). $P_{cuff.int}$ was measured again four months after TURP in a subgroup of 143 patients [91]. The authors showed in these patients that $P_{cuff.int}$ decreased by 45 cm H_2O in the obstructed group and 85% of patients who were originally classified as obstructed moved to the unobstructed group.

1.5.3 Ultrasound-derived tests

1.5.3.1 Ultrasound measurement of post-void residual urine

Post-void residual (PVR) urine is defined as the volume of urine left in the bladder at the end of micturition [1]. PVR can be measured invasively by transurethral catheterization, endoscopy, radiological methods (after intravenous excretion urography, voiding cystography, or renal radioisotope examination), or non-invasively by ultrasonography (**figure 7**). Due to the non-invasive and harmless character ultrasound PVR measurement by suprapubic positioning of the ultrasound array has become the preferred and most widely used method [92].
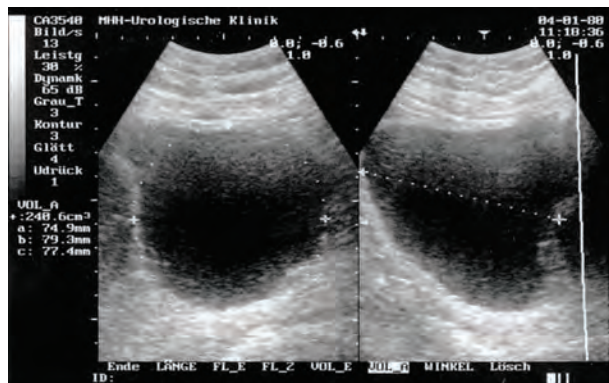
Figure 7: Ultrasound imaging of the urinary bladder after voiding to demonstrate and measure post-void residual urine (left image: transverse section; right image: longitudinal section). The bladder is imaged in three dimensions by positioning of a low frequency ultrasound array suprapubically (in this patient 3.5 MHz). The example of this individual patient shows a post-void residual volume of 240.6 cm^3.

Healthy adult young men have PVR values between 0.09 and 2.24 ml with a mean of 0.53 ml [93]. Another study demonstrated PVR values <5 ml in 78% and <12 ml in 100% of young healthy males [94]. In 477 randomly selected men aged 40–79 years of the community-based Olmsted County study, median PVR volume was 9.5 ml [95]. In a community-based study in Rotterdam in 326 men aged 55–74 years, mean PVR volume was 23 ± 3 ml [96]. PVR volume significantly increased with aging. In the Rotterdam cohort, 88% of men aged 55–59 years and 70% of men aged 70–74 years had PVR ≤ 50 ml. Similar values were obtained in the German epidemiological trial in the district of Herne in 1763 men aged ≥50 years after exclusion of co-morbidities or co-medications with possible influence on the bladder or prostate [97]. Median PVR volumes were 23.8 ml for men aged 50–54 years and 32.2 ml for those aged ≥75 years. In clinical routine, PVR values ≤50 ml are considered normal and values >50 ml abnormal [92]. Men with PVR values >50 ml have a 3-fold increased risk of acute urinary retention during a follow-up period of 3–4 years compared to men with lower PVR values [95].

PVR and voiding efficiency are, similar to urinary flow rate, a result of the contractile function of the detrusor and bladder outlet resistance [65]. A decrease in contractility or an increase in bladder outlet resistance will result in PVR or even acute urinary retention without the possibility to distinguish between detrusor underactivity and BOO/BPO. Patients with clinical BPH have significantly higher and varying PVR values during repeated measurements compared to healthy individuals [98-100]. The highest PVR values were found in the early morning [100]. Urodynamic studies in adult male patients with clinical BPH demonstrated that approx. 30% of men with PVR ≥50 ml do not have BOO/BPO, independent on the magnitude of PVR [101] and, vice versa, 24% of men with urodynamically confirmed BOO/BPO have PVR <50 ml [102]. Another study demonstrated that 60% of patients with PVR <100 ml and 86.1% of patients with PVR ≥100 ml had BOO/BPO [103]. Taken together these information, PVR or the amount of PVR is a poor predictor of BOO/BPO and seems to be associated with decreased detrusor contractility (detrusor underactivity with or without BOO/BPO) [104].

1.5.3.2 Prostate volume, transition zone volume and transition zone index

Ultrasound imaging of the prostate by positioning of a high frequency ultrasound probe in the rectum (transrectal ultrasound of the prostate, TRUS) can visualize the borders of the prostate and the texture of the prostatic parenchyma with high quality. The transition zone appears hypoechogenic and, therefore, can be differentiated well from the more hyperechogenic central or peripheral zones (**figure 8**) [105]. Histologic BPH develops predominantly in the transition zone of the prostate and the volume of this zone continuously increases with BPH disease progression, whereas the volume of the residual prostate remains nearly unchanged at about 20–22 cm^3 [105, 106]. Initial studies in 205 adult men confirmed that transition zone volume is greater in men with clinical BPH (24.8 ± 14.4 cm^3) than in men without symptoms or signs of BPH (6.1 ± 3.2 cm^3) [105]. Reduction of transition zone volume is possible by using 5α-reductase inhibitors (dutasteride, finasteride), a group of drugs inhibiting the conversion of the active metabolite of testosterone (dihydrotesterone) in the prostate, thereby inducing apoptosis of prostate cells [107, 108]. Transition zone volume was reduced by 26.5% after dutasteride therapy for 4 years [108].
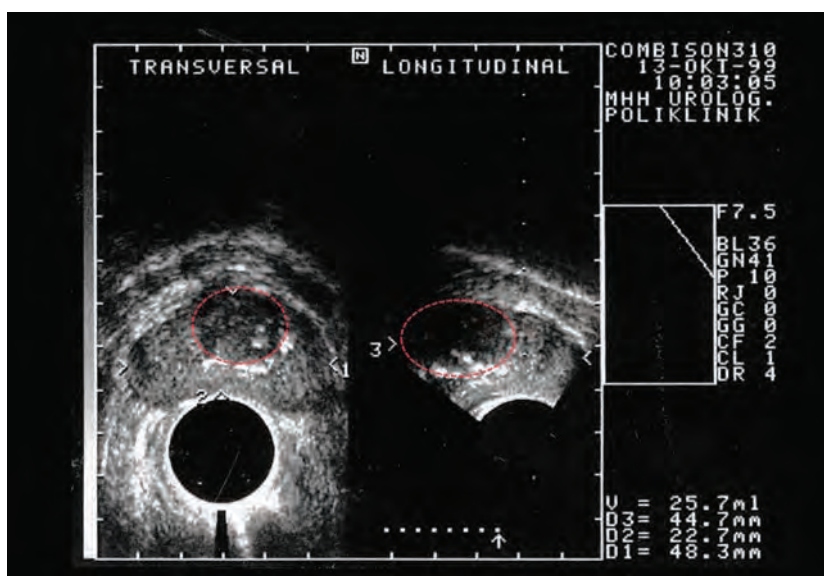
Figure 8: Transrectal ultrasound imaging of the prostate (TRUS) with a 7.5 MHz ultrasound array to measure total prostate and transition zone volume (left image: transverse section; right image: longitudinal section). The prostate appears as a hyperechogenic organ. The transition zone of the prostate (encircled) appears hypoechogenic compared to the central and peripheral zone. The border between the transition zone and other zone often contains hyperechogenic areas (stones). The patient of this example has a total prostate volume von 25.7 cm³.

The volumes of the entire prostate and transition zone, as well as the volume of the transition zone in relation to total prostate volume, a parameter known as transition zone index (TZI), have been investigated to predict BOO/BPO. In a retrospective case series of 521 men, approx. 90% patients with prostate volumes >80 cm³ had BOO/BPO, although more than half of patients with BOO/BPO were only mildly obstructed. In contrast, 68% of patients with a prostate volume <40 cm³ had BOO/BPO, of those approx. 25% had severely obstructed bladders [27]. The authors concluded that, although there is a statistically significant correlation of prostate volume and BOO/BPO, this correlation was poor so that pressure-flow studies are still necessary to evaluate the patient in order to determine BOO.

Kaplan et al. first described statistically significant correlations between transition zone volume and LUTS or Q_{max} of free uroflowmetry as well as TZI and LUTS, Q_{max} or detrusor pressure at maximum urinary flow ($P_{det.qmax}$) [109]. These correlations were later confirmed by other study groups, although the correlations between transition zone volume or TZI and LUTS or Q_{max} were only low or modest and, therefore, unsuitable for use in clinical practice [110, 111]. TZI >0.5 best indicated patients with severe LUTS, abnormal Q_{max}, and pathological $P_{det.qmax}$ [109]. Mean TZI was significantly higher in symptomatic African-American or Korean men (0.44 ± 0.05 and 0.45 ± 0.08) compared to age-matched Caucasian or

Hispanic men (0.39 ± 0.03 and 0.38 ± 0.02) [112, 113]. Other authors compared total prostate volume, transition zone volume and TZI with clinical and urodynamic parameters [114]. Although they saw significant correlations of all three prostate parameters with LUTS (IPSS) or pressure-flow values there was no additional benefit of the measurements of transition zone volume or TZI compared to the measurement of total prostate volume alone (all correlation coefficients 0.37 - 0.44). A prospective urodynamic study could not find any independent effect of TZI for the prediction of BOO/BPO compared to total prostate volume or transition zone volume [115].

It was shown in the Olmsted County study that increased total prostate volume, a parameter thought to be associated with BOO/BPO, is one of the risk factors for acute urinary retention [116]. Men with a total prostate volume (>30 cm^3) had a 3fold risk of acute urinary retention (95% confidence interval 1.0–9.0, p=0.04) compared with men with a smaller prostate volume. In a case series of 331 Japanese men with clinical BPH, 64 men (19.3%) developed acute urinary retention [117]. Transition zone index, transition zone volume and prostate volume were significantly greater in men with than without retention. TZI was the most precise test to predict acute urinary retention.

1.5.3.3 Ultrasound measurement of intravesical prostatic protrusion

Growth of the transition zone due to BPH can be directed towards the prostatic urethra (see chapter 1.5.1, urethro-cystoscopy) and/or into the urinary bladder. The parts of the prostate which grow from the bladder base into the bladder lumen can be visualized and measured by ultrasound, a term known as intravesical prostatic protrusion (IPP) [118]. For IPP measurement, the ultrasound array is positioned suprapubically and in longitudinal direction, thereby measuring the distance between the bladder base (bladder neck) and the tip of the prostate inside the bladder lumen in the mid-sagittal plane (**figure 9**). It is recommended to fill the bladder with 100-200 ml of fluid in order to receive representative measurements; particularly bladder fillings >400 ml will result in lower IPP values [119]. The IPP measurement distances can be divided into three grades: grade I = 0–4.9 mm, grade II = 5–10 mm, and grade III = more than 10 mm [118].

It has been hypothesized that the prominent lateral and/or median prostate lobe(s) can cause a 'valve ball' type obstruction caused by incomplete opening and disruption of the funneling effect of the bladder neck [120]. Based on the fact that only enlarged prostate lobes which protrude into the bladder lumen are measured with this technique, IPP measurements are only able to demonstrate BPO but cannot prove or disprove other types of BOO (e.g. bladder neck stenosis, sphincter sclerosis, or urethral stricture). Chia and colleagues originally described IPP measurements as a diagnostic tool to detect BPO [118]. The authors investigated 200 men with LUTS and demonstrated with pressure-flow analyses that 94% of patients with IPP-grade III had obstructed bladders, whereas 70% of patients with IPP-grades I and II were not obstructed. In the logistic regression model, the odds-ratio of IPP-grade III for detecting BPO was 6.2 and better parameter for the prediction of BPO than age, IPSS, Q_{max}, post-void residual urine and total prostate volume [118]. Lim and colleagues demonstrated in 95 men with clinical BPH that only IPP was independently associated with BPO when comparing total prostate

volume, serum PSA-concentration, and IPP with the results of the pressure-flow measurements (odds-ratio 1.21, p=0.02) [121]. Keqin et al. described that men with an IPP-grade III have a significantly higher total prostate volume, serum-PSA concentration, post-void residual urine, detrusor pressure at maximum urinary flow ($P_{det.qmax}$) and BOO-Index as well as higher incidence rates of bladder trabeculation, detrusor overactivity, low bladder compliance, and acute urinary retention [122]. Furthermore, the authors showed a significantly lower Q_{max} in patients with IPP-grade III. Patients with trilobar prostate adenomas (enlargement the two lateral lobes and the median lobe) are significantly more obstructed and have significantly larger total prostate volumes than patients with bilobar prostate adenomas (enlargement only of the lateral lobes) [123, 124]. Several other study groups have confirmed that IPP-grade III is significantly associated with BPO [125-127]. However, the original threshold value for determination of BPO (IPP >10 mm) has lately been questioned because many patients with IPP ≤10 mm also have an obstructed bladder; Keqin et al. [122] proposed a threshold of >8.5 mm and Shin et al. [127] >5.5 mm for the diagnosis of BPO.
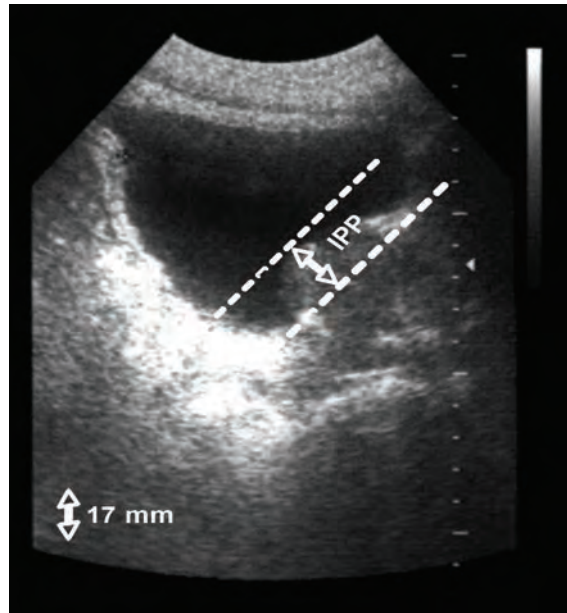
Figure 9: Transabdominal ultrasound imaging of the urinary bladder in longitudinal direction to visualize a prostate median lobe growing inside the bladder lumen. The distance between bladder neck and the tip of the prostate median lobe is known as intravesical prostatic protrusion (IPP). The IPP distance of this individual patient is 17 mm (IPP-grade 3).

IPP has also been described as a prognostic tool in patients with clinical BPH. Compared with IPP-grade I (≤5.0 mm), the odds ratio for clinical BPH disease progression, as defined as development of post-void residual urine >100 ml, acute urinary retention or IPSS worsening ≥4 points, was 5.1 for IPP-grade II (5.1–10 mm) and 10.1 for IPP-grade III (>10 mm) [128]. Community-dwelling men of the Olmsted County study with IPP-grade III (10% of the study population) had a greater chance of using BPH drugs compared to men with IPP-grades I (60% of the study population) or II (30% of the study population) [129]; the odds-ratio for using α-blockers, 5α-reductase inhibitors and/or herbal drugs was 2.95 (95% confidence interval 1.23–7.06). Men with bladder stones had a significantly greater median IPP (11.5 mm) than men without bladder without bladder stones (3.4 mm) [130]; only older age, longer IPP, and lower Q_{max} predicted bladder stones. Treatment of LUTS with the α–blocker tamsulosin was more efficacious in men with lower IPP-grades (grade I > grade II > grade III) [131]. In contrast to medical treatment, surgical treatment of LUTS/BPO with transurethral resection of the prostate (TURP) was significantly more efficacious in men with IPP-grades II and III compared to IPP-grade I [132].

1.5.3.4 Ultrasound-estimated bladder weight and ultrasound measurement of bladder wall thickness

Bladder wall hypertrophy and increased bladder weight are the physiologic responses of the urinary bladder to BOO/BPO, as demonstrated in experimental animals [37]. The longer BOO/BPO exists the thicker the bladder wall and heavier the bladder becomes in both animals and humans [37, 40]. Kojima and coworkers were the first to measure bladder wall thickness with a suprapubically positioned ultrasound array in order to calculate 'ultrasound-estimated bladder weight (UEBW)' as an indicator for and the degree of BOO/BPO in men with clinical BPH [44, 45, 133, 134]. Initial investigations of these authors focused on the ultrasound appearance of the bladder wall and demonstrated that the detrusor appears as a hypoechogenic (black) area that is sandwiched between the hyperechogenic (white) mucosa and adventitia (**figure 10**) [44]. For the ultrasound measurement of bladder wall thickness (BWT) it is necessary to position the calipers of the ultrasound machine at the outer borders of the mucosa and adventitia and measure the distance in between these two calipers. The authors also demonstrated that the thicknesses of the lateral, ventral and dorsal bladder walls as well as trigone and dome were comparable and not significantly different in individual men at the same bladder filling volume [44]. Therefore, ultrasound measurement of the thickness of the anterior bladder wall is identical to the thickness of all other parts of the bladder. Consequently, the authors suggested using the thickness of the anterior bladder wall as a representative location for BWT measurement.
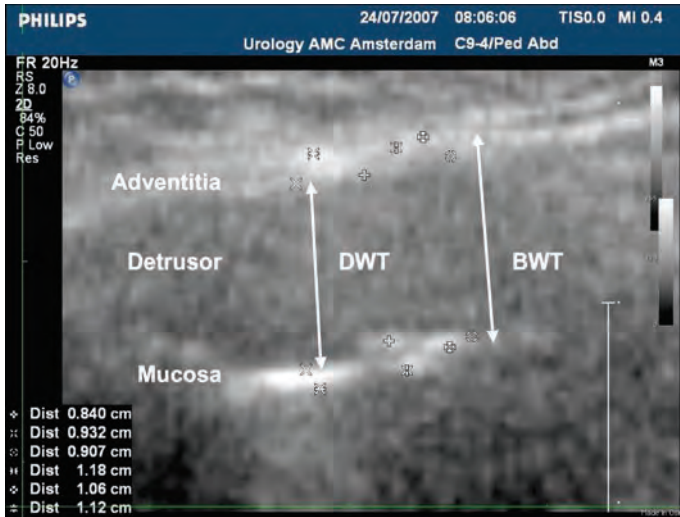
Figure 10: Ultrasound imaging of the anterior bladder wall by suprapubic positioning of a high frequency ultrasound array. The mucosa and adventitia of the bladder appear as hyperechogenic (white) thin lines, whereas the detrusor appears as a hypoechogenic (grey) bar between the hyperechogenic mucosa and adventitia. The measurement distance from the outside border of the mucosa until the outside border of the adventitia represents bladder wall thickness (BWT), whereas the distance from the inner border of the mucosa until the inner border of the adventitia represents detrusor wall thickness (DWT).

Kojima and coworkers used a 7.5 MHz ultrasound array to measure the thickness of the anterior bladder wall and a 3.5 MHz ultrasound array to measure bladder volume in order to determine UEBW by calculating the inner and outer diameters of the bladder, thereby assuming the bladder is a ball or ellipsoid [44]. Bladder weight is then calculated by the subtraction of the inner from the total bladder volume and multiplication of the specific weight of the bladder wall tissue (**figure 11**). Because bladder weight is constant in individual men during the entire storage period measurement and calculation of UEBW is independent of the actual state of bladder filling. UEBW in men with urodynamically proven BOO/BPO was up to 4fold higher than in men without BOO/BPO [44, 45 1997]. A threshold value of 35 g best distinguished between obstructed and non-obstructed bladders in Asian men [44]. Kojima and coworkers confirmed that the human bladder reacts similar compared to the bladder of experimental animals with artificial BOO. Measurement and calculation of UEBW was reproducible between different investigators and at different time points; the intra- and inter-observer variability was less than 5% [135].
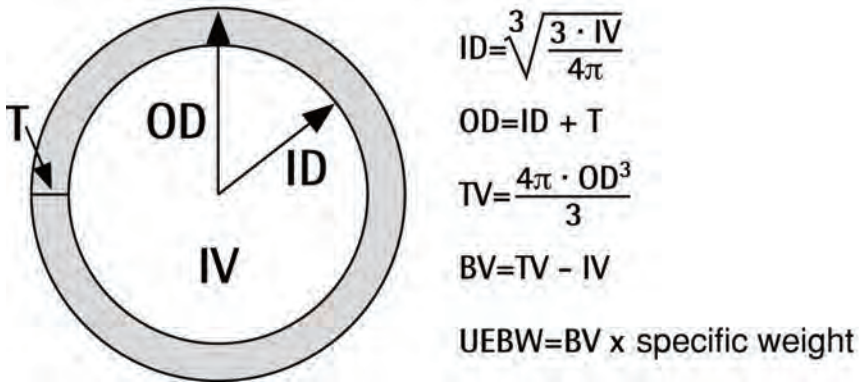
Figure 11: Calculation of ultrasound-estimated bladder weight (UEBW) after ultrasound measurement of bladder wall thickness (T) and bladder filling (IV), assuming the bladder is a ball [44]. After calculation of the inner diameter (ID), the outer diameter (OD) and total volume (TV) of the bladder are calculated. Bladder volume (BV) is determined by subtracting the total volume from the inner volume. UEBW is finally calculated by multiplying the bladder volume with the specific weight of bladder wall tissue.

Manieri and coworkers were able to demonstrate that BOO/BPO evaluation can be simplified by measuring only BWT at the anterior bladder wall with ultrasound [49]. In 174 symptomatic men with the clinical features of BPH, the authors filled the bladder with 150 ml of physiologic saline solution by transurethral bladder catheterization and measured the thickness of the anterior bladder wall with a 3.5 MHz ultrasound array, similar to the technique of Kojima et al. [44, 133]. Mean BWT was significantly greater in men with compared to men without BOO/BPO (5.0 vs. 3.6 mm). The greater the BOO/BPO grade was in pressure-flow analysis the greater ultrasound BWT measurement of the anterior bladder wall became. A threshold value of 5.0 mm best distinguished between obstructed and unobstructed bladders. The authors could also show that ultrasound measurement of BWT was superior to the measurement of Q_{max} (uroflowmetry) for diagnosing BOO/BPO. The intra-observer variability was ± 0.2 mm (4.6–5.1%) and the inter-observer variability ± 0.57 mm (12.3%). Isikay and colleagues measured BWT at the anterior bladder wall in 155 symptomatic men with clinical BPH at a bladder filling volume of 150–200 ml and used Q_{max} <10 ml/s (free uroflowmetry) for classification of BOO/BPO [136]. The authors demonstrated that patients with Q_{max} <10 ml/s (BOO/BPO) had a significantly greater mean BWT compared to patients with Q_{max} ≥10 ml/s (BWT 4.44 ± 1.18 vs. 3.85 ± 0.76 mm, p<0.01).

Ultrasound BWT is not only dependent on the degree of BOO/BPO but also on the state of bladder filling. Preliminary results came from a study investigating ultrasound BWT in healthy children aged between day 1 and 19 years as well as 10 healthy adults [137]. The authors measured BWT at the lateral bladder walls with 5.0 or 7.5 MHz ultrasound arrays and described decreasing BWT with increasing bladder filling volume. BWT was 2.76 ± 0.58 mm in children with an empty bladder (<10% of capacity), whereas BWT was 1.55 ± 0.56 mm on average in children with a full

bladder (≤90% of capacity). Boys had thicker bladder walls than girls but this numerical difference was not statistically significant. Age did not have a significant impact on bladder wall thickness.

UEBW or ultrasound BWT measurements are also useful to investigate BPH disease progression or response to medical or surgical treatment of LUTS/BPO. Patients with UEBW >35 g have a 13.4-fold greater chance of developing acute urinary retention than patients with UEBW ≤35 g [138]. A recently published study by Ho and colleagues confirmed these initial findings [139]. The only significant predictors of acute urinary retention were high IPSS values and UEBW ≥35 g (sensitivity 63.3%, specificity 87.5%). Egilmez and colleagues measured BWT and calculated UEWB before and three months after treatment with the α-blockers alfuzosin or tamsulosin in 41 patients with clinical BPH [140]. The authors observed a significant reduction of UEBW only in patients treated with α-blockers and found that reduction of UEBW was significantly associated with a decrease of LUTS (IPSS) and post-void residual urine as well as an increase of Q_{max}. It was previously shown in patients with BOO/BPO that the α_1-blocker tamsulosin reduced BWT by 23% one month after treatment initiation and this reduction correlated well with Q_{max} improvement [141]. Kojima and colleagues demonstrated in 33 men with BPO that UEBW significantly decreases within the first 12 weeks after prostate operations (subcapsular prostatectomy or TURP), from 52.9 ± 22.6 to 31.6 ± 15.8 g [134]. Tubaro and colleagues measured BWT at the anterior bladder wall in 32 patients before and after transvesical prostatectomy in bladders filled with 150 ml [142]. BWT was significantly reduced already one week after the operation, reached a nadir at six weeks, and remained stable until the end of follow-up period of 12 months (mean BWT before vs. one year after surgery: 5.2 ± 0.7 mm vs. 2.9 ± 0.9 mm, p<0.01). Lee et al. recently confirmed in 51 symptomatic patients with BPE that BWT is reduced already one month after TURP [143].

1.6   DIAGNOSTIC VALUES OF NON- OR MINIMALLY-INVASIVE TESTS TO IDENTIFY BOO

Pressure-flow studies, in which the pressures with synchronous flow rates are recorded during micturition, are the reference standard for BOO diagnosis [1]. For retrospective calculation of the diagnostic values for this thesis it was taken for granted that pressure-flow studies presented in the literature were carried out with the highest diagnostic standards and without artifacts because validation or correction of published urodynamic data is impossible. The diagnosis of BPO cannot be made retrospectively because it is based on BPE, a diagnosis that requires a thorough clinical investigation of the patient [1]. The results of the pressure-flow studies were dichotomized into 'BOO' and 'no BOO', independent on the BOO-classification system used. 'Equivocal' results were positioned into the group of 'no BOO' [1, 144]. Publications using proxy parameters for BOO were not utilized. The results of the reference standard were then compared with the results of the non- or minimally-invasive tests which pretend to diagnose BOO alternatively. The definitions of the diagnostic values are listed in **table 1** [145-147].

Table 1: Definitions and explanations of test indicators to judge the diagnostic test for the ability to determine bladder outlet obstruction (BOO).

Test indicator	Definition
positive predictive value (ppv)	proportion of diseased among subjects with a positive test result = proportion of patients with a test result indicating BOO who also have BOO in pressure-flow analysis
negative predictive value (npv)	proportion of healthy among subjects with a negative test result = proportion of patients with a test result indicating no BOO who also have no BOO in pressure-flow analysis
sensitivity	proportion of a positive test result among diseased = proportion of patients who were correctly diagnosed by the test as having BOO divided by the total number of patients with BOO, as defined by pressure-flow studies
specificity	proportion of a negative test result among healthy = proportion of patients who were correctly diagnosed by the test as having no BOO divided by the total number of patients without BOO, as defined by pressure-flow studies
accuracy	proportion of correctly identified subjects
likelihood ratio of a positive test result (LR[+])	ratio of a positive test result among diseased to the same result in the healthy, sensitivity/(1-specificity)
likelihood ratio of a negative test result (LR[-])	ratio of a negative test result among diseased to the same result in the healthy, (1-sensitivity)/specificity

The positive and negative predictive values are influenced by the occurrence of BOO in the study population. It was mentioned earlier that patient selection is responsible for the different prevalence of BOO in investigated cohorts [17, 18]. It is easier to determine BOO in a study population with a high proportion of patients with BOO and, vice versa, it is easier to exclude BOO in a study population with a low proportion of BOO [146, 147]. The likelihood ratios seem to be more suitable to judge the ability of the non- or minimally-invasive test to diagnose or exclude BOO [145-147]. The likelihood ratio of a positive test result (LR[+]) expresses the chance that the result of the non- or minimally-invasive test would be expected in a patient with BOO compared to the chance that the same result would be expected in a patient without BOO. In contrast, the likelihood ratio of

a negative test result (LR⁻) provides the chance that the non- or minimally-invasive test result would be expected in a patient without BOO compared to the chance that the same result would be expected in a patient with BOO. Therefore, the likelihood ratios determine how much a diagnostic test result would increase or decrease the pre-test probability of BOO. The effect of LR^+ on changes in pre- to post-test probabilities may be minimal (LR^+ = 1 – 2), small (LR^+ = 2.1 – 5), moderate (LR^+ = 5.1 – 10) or large (LR^+ >10) [145-147]. LR^+ >10 indicates that the non- or minimally-invasive test (i.e. index test) has an excellent ability to diagnose BOO and would be suitable to replace pressure-flow studies (i.e. reference test).

The diagnostic values of non- or minimally-invasive tests to determine BOO are listed in **table 2**. Wherever the diagnostic values were not mentioned in the article, the positive or negative predictive values, sensitivity, specificity, accuracy, and likelihood ratios of a positive or negative test result have been re-calculated based on numbers of patients provided in the publication; these re-calculated values are indicated in the table (*). It was impossible to retrospectively re-calculate the diagnostic values for several studies. The minimal amount of information necessary for re-calculation of the diagnostic values are (1) two x two table with listing of the results of the reference standard (BOO determined by pressure-flow analysis) and the index test, (2) number of patients with BOO, total number of investigated patients, sensitivity, and specificity and (3) total number of investigated patients, prevalence of BOO in the study population, sensitivity, and specificity.

Table 2 demonstrates a 'good' (LR^+ 5.1 – 10) or 'excellent" (LR^+ >10) ability to predict BOO for the occlusion grade 3 during urethro-cystoscopy (LR^+ 6.7), in one study of Q_{max} (free uroflowmetry) for threshold values <8, <10, and <12 ml/s (LR^+ 5.6 – 7.3), in one study of prostate volume with a threshold ≥30 cm³ (LR^+ 5.2), combination of non-invasive measurements (Q_{max} ≤10 ml/s + prostate volume ≥40 cm³ + ≥IPSS 20; LR^+ >50), in one study of BWT with a threshold ≥5 mm (LR^+ 6.8), in studies of detrusor wall thickness with thresholds ≥2 mm (LR^+ 5.8 – 43), in one study of IPP with a threshold >10 mm (LR^+ 9.5), and in a study of the penile compression-release test in combination with Q_{max} <10 ml/s (LR^+ 6.6). All other non-invasive tests had a LR+ below 5. No information regarding the diagnostic ability to detect BOO is available for the trabeculation grade during cystoscopy, transition zone volume of the prostate, and transition zone index.

Table 2: Diagnostic values of non- or minimally-invasive tests to detect or exclude bladder outlet obstruction (BOO) in patients with clinical benign prostatic hyperplasia. Only the presented studies were sufficient to re-calculate parameters of test indicators. The likelihood ratio of a positive test result indicates the pre-test to post-test probability to detect BOO. The higher the likelihood ratio of a positive test result the better the ability of the test to detect BOO (likelihood ratio 1–2 = minimal, 2.1–5 = moderate, 5.1–10 = good, and >10 = excellent) [145-147].

Test	References	Patients [n]	Threshold values (BOO vs no BOO)	Positive Predictive Value [%]	Negative Predictive Value [%]	Sensitivity [%]	Specificity [%]	Accuracy [%]	Likelihood ratio of pos. test result (LR+)	Likelihood ratio of neg. test result (LR-)
Urethro-cystoscopy Occlusion grade	Homma et al. 1998 [148]	232	grade 3 vs grades 1 and 2	98 *	27 *	60	91	64 *	6.7 *	0.44 *
Q_{max} (free uroflowmetry)	Reynard et al. 1996 [60]	157	<8 vs ≥8 ml/s	91	43	14	98	48 *	7.0 *	0.88 *
			<10 vs ≥10 ml/s	92	47	29	96	56 *	7.3 *	0.74 *
			<12 vs ≥12 ml/s	89	55	50	91	66 *	5.6 *	0.55 *
			<15 vs ≥15 ml/s	78	65	76	67	72 *	2.3 *	0.36 *
	Schacterle et al. 1996 [149]	134	<10 vs ≥10 ml/s	76	69	62	81	72 *	3.3 *	0.47 *
			<15 vs ≥15 ml/s	60	81	89	44	66 *	1.6 *	0.25 *
	Reynard et al. 1998 [19]	933	<10 vs ≥10 ml/s	70 *	47 *	47	70	56 *	1.6 *	0.44 *
			<15 vs ≥15 ml/s	66 *	58 *	82	38	64 *	1.3 *	0.47 *
	Homma et al. 1998 [148]	232	<15 vs ≥15 ml/s	64 *	79 *	97	17	65 *	1.2 *	0.18 *
	Kuo 1999 [103]	324	≤10 vs >10 ml/s	79 *	58 *	75	64	71 *	2.1 *	0.39 *
	Steele et al. 2000 [150]	204	≤10 vs >10 ml/s	85 *	43 *	73	60	70 *	1.8 *	0.45 *
	ElSaied et al. 2013 [151]	50	<10 vs ≥10 ml/s	58	100	100	37	66	1.6	<0.01
Q_{ave} (free uroflowmetry)	ElSaied et al. 2013 [151]	50	<7 vs ≥7 ml/s	57	80	87	44	64	1.6	0.29
Post-void residual	Abrams & Griffiths 1979 [152]	117	≥50 vs <50 ml	80 *	48 *	88	35	75 *	1.4 *	0.34 *
	ElSaied et al. 2013 [151]	50	>50 vs ≤50 ml	53	67	74	44	58	1.3	0.59
Prostate volume (total gland size)	Rosier & de la Rosette 1995 [27]	521	≥40 vs <40 cm³	54 *	28 *	49	32	43 *	0.7 *	1.59 *
	Homma et al. 1998 [148]	232	≥30 vs <30 cm³	89 *	56 *	52	90	67 *	5.2 *	0.53 *
	Lim et al. 2006 [121]	95	>40 vs ≤40 cm³	58	32	51	38	46 *	0.8 *	1.29 *
	Steele et al. 2000 [150]	204	≥40 vs <40 cm³	85 *	39 *	66	64	66 *	1.8 *	0.53 *
	Franco et al. 2010 [153]	100	≥38 vs ≤38 cm³	84	44	72	61	70	2.0	0.55
	ElSaied et al. 2013 [151]	50	>25 vs ≤25 cm³	51	73	87	30	56	1.3	0.44
Composite measures of clinical data	Steele et al. 2000 [150]	204	BOO: Q_{max} ≤10 ml/s + Pvol ≥40 ml + IPSS ≥20	100 *	31 *	26	100	45 *	>50 *	0.76 *

	Study	n	Threshold							
BWT	Manieri et al. 1998 [49]	174	≥5.0 vs <5.0 mm	90 *	60 *	54	92	70 *	6.8 *	0.50 *
	Franco et al. 2010 [153]	100	≥6.0 vs <6.0 mm	90	50	73	82	84	4.1	0.37
DWT	Kessler et al. 2006 [154]	102	≥2.0 vs <2.0 mm	81	85	92	68	82 *	2.9 *	0.12 *
			≥2.5 vs <2.5 mm	90	65	69	88	77 *	5.8 *	0.35 *
			≥2.9 vs <2.9 mm	100	54	43	100	66 *	43 *	0.57 *
	ElSaied et al. 2013 [151]	50	≥2.0 vs <2.0 mm	91	86	83	93	88	11.2	0.19
UEBW	Kojima et al. 1997 [45]	65	>35 vs ≤35 g	88 *	84 *	85	87	86 *	6.5 *	0.17 *
	Han et al. 2011 [155]	193	<24 vs ≥24 g/m^2	29	87	91	21	39 *	1.2 *	0.43 *
			<28 vs ≥28 g/m^2	35	82	62	60	61 *	1.6 *	0.63 *
			<33 vs ≥33 g/m^2	25	75	10	91	70 *	1.1 *	0.99 *
			<42 vs ≥42 g/m^2	26 *	75 *	0	100	74 *	1.0 *	1.0 *
IPP	Chia et al. 2003 [118]	200	>10 vs ≤10 mm	94	70	76	92	82 *	9.5 *	0.26 *
	Nose et al. 2005 [156]	30	>10 vs ≤10 mm	67 *	75 *	90	40	69 *	1.5 *	0.25 *
	Lim et al. 2006 [121]	95	>10 vs ≤10 mm	72	42	46	65	53 *	1.3 *	0.83 *
	Reis et al. 2008 [125]	42	>10 vs ≤10 mm	70	79	80	68	74	2.5	0.29
	Franco et al. 2010 [153]	100	≥12 vs <12 mm	88	47	65	77	83	2.1	0.45
	Shin et al. 2013 [127]	239	>5.5 vs ≤5.5 mm	45 *	91 *	67	81	78 *	3.5 *	0.41 *
Condom + Q$_{max}$	Pel et al. 2002 [78]	56	n.a.	66	77	64	79	73 *	3.1 *	0.46
PCR index	Sullivan & Yalla 2000 [89]	90	100%	74	89	91	70	80 *	3.0 *	0.13 *
	Harding et al. 2004 [88]	101	160%	65	91	78	84	82 *	4.9 *	0.26 *
PCR - nomogram	Griffiths et al. 2005 [85]	116	n.a.	68	78	73	75	74 *	2.9 *	0.36 *
PCR + nomogram Q$_{max}$ < 10 ml/s	Griffiths et al. 2005 [85]	116	n.a.	88	86	77	89	84 *	7.0 *	0.26 *

* recalculated based upon published data

BOO = bladder outlet obstruction; BWT = bladder wall thickness; DWT = detrusor wall thickness; IPP = intravesical prostatic protrusion; PCR = penile compression-release test; Q$_{ave}$ = average urinary flow rate; Q$_{max}$ = maximum urinary flow rate; UEBW = ultrasound-estimated bladder weight; n.a. = not applicable.

1.7   OUTLINE OF THE PROBLEMS AND AIMS OF THE THESIS

LUTS are the most frequent urological reason for physician consultations in adult men in the Western world [22]. LUTS are unspecific for the underlying disease and may also be bothersome [14, 15]. The relationships between LUTS, BPE, and BOO/BPO are inconsistent and weak. Therefore, it is impossible to predict the existence or magnitude of one component based on the existence or magnitude of another component. Consequently, the constellation of the individual components has to be determined individually. Detection and quantification of LUTS, by taking the patient history or using validated symptom questionnaires, and determination of prostate size, by judgment of the borders of the prostate during digital rectal examination or transrectal or suprapubic ultrasound measurement, are quick, easy and a routine procedure in physician offices. In contrast, detection and quantification of BOO/BPO requires a multichannel computer-urodynamic study which is invasive, bothersome for the patient, expensive, and time consuming; therefore, pressure-flow studies are rarely performed in clinical routine and scientific investigations. Consequently, only little information is available on the existence and consequences of BOO/BPO in men with LUTS/BPH. It is generally believed in men with clinical BPH that damage of the lower and/or upper urinary tract is caused by BOO/BPO (e.g. bladder diverticula, bladder stones, urinary retention, vesical-ureteral reflux, hydronephrosis, or impairment or loss of renal function) [21]. The aim was to determine first whether the existent literature can proof that damage of the urinary tract in patients with LUTS/BPH is really related to BOO/BPO, highlight the prevalence and pathophysiology of urinary tract complications, suggest trials to clarify the incidence and pathophysiology of these complications, and specify men who will most likely develop urinary tract complications as a result of BOO/BPO (**Chapter 2**).

Enlarged prostate lobes due to BPH or other pathologies of the lower urinary tract (e.g. bladder neck stenosis or urethral stricture) can result in BOO/BPO. Although these pathologies with increase of bladder outlet resistance are located between the bladder neck and tip of the urethra [1], they may also have consequences on the morphology and/or function of the urinary bladder, as suggested in animal studies [37]. Involuntary detrusor contractions during the bladder storage phase, a urodynamic observation known as detrusor overactivity [1], may therefore be related to BOO/BPO as well. Retrospective case studies with limited patient numbers have suggested that BOO/BPO may induce detrusor overactivity [157-160]. The aim was to clarify the relationship between detrusor overactivity and clinical as well as urodynamic parameters by investigating a large cohort of unselected, treatment naïve, adult male patients who underwent multichannel computer-urodynamic investigation as part of their routine investigation of LUTS, BPE and/or post-void residual urine (**Chapter 3**).

In clinical routine and epidemiological studies, measurements of free uroflowmetry (Q_{max} and Q_{ave}), post-void residual urine, and prostate volume are used to estimate BOO/BPO in men with LUTS/BPH. It was previously shown that these non- or minimally-invasive tests have only a low accuracy and reliability for the determination of BOO/BPO [146, 147]. Therefore, it would be desirable to develop a test that non-invasively, quickly, and accurately assesses BOO/BPO at low cost and without morbidity or bother for the patient. Ultrasound-derived tests appear ideal for this purpose. It was shown previously that ultrasound-estimated bladder weight (UEBW) or ultrasound

measurement of bladder wall thickness (BWT) were able to detect BOO/BPO with high accuracy [44, 49]. However, bladder wall hypertrophy as a result of BOO/BPO originates in the detrusor where hypertrophy of smooth muscle cells was seen in both experimental animals and humans [37, 43]. Therefore, it appears plausible to measure only detrusor walls thickness (DWT) with ultrasound. The aims were to prospectively investigate the relationships between DWT and bladder filling, gender, age, and body-mass index in young and healthy adult volunteers in order to establish DWT reference values first (**Chapter 4**). Afterwards, DWT was prospectively measured in unselected adult male patients with LUTS, BPE and/or post-void residual urine. The aims of this study were to evaluate DWT at different bladder fillings in order to determine the adequate bladder filling volume for DWT measurements, find out whether patients with BOO/BPO have significantly increased DWT values compared to patients without BOO/BPO, whether constrictive or compressive BOO/BPO is responsible for DWT increase, and what the best threshold value for BOO/BPO diagnosis is (**Chapter 5**). Non- or minimally-invasive tests, which are widely used in clinical routine to estimate BOO/BPO (uroflowmetry and measurements of prostate volume or post-void residual urine), have never been prospectively tested against each other in order to compare the accuracy for BOO/BPO diagnosis. Therefore, it was the aim to prospectively evaluate the diagnostic values of these non- or minimally-invasive tests (index tests) to detect BOO/BPO - as defined by pressure-flow analysis (reference standard) - in unselected adult men with LUTS/BPH and compare results to those of ultrasound DWT measurements of the same cohort of men (**Chapter 6**). In the year 2005, a machine for automatic measurement of BWT and UEBW was introduced to the market (BVM 6500, Verathon®). It was the aim to determine whether this new device really measures BWT, compare repeatability and agreement of conventional ultrasound BWT measurements with automatically obtained BWT measurements by the BVM 6500 device, and evaluate whether automatic measurements can replace manual measurements for determination of BOO/BPO (**Chapter 7**). Another report aimed to compare the various ultrasound techniques for quantification of bladder wall hypertrophy, clarify agreements and disagreements of the various techniques and research groups, and propose future research and standardization of the techniques (**Chapter 8**).

Current standards of a medical society are summarized in guidelines which aim to steer physicians to correctly use diagnostic tests and apply targeted therapy in order to reduce morbidity, quickly restore the quality of life of patients, and effectively use the financial resources of health care systems. The European Association of Urology (EAU) is the supervisory organization of the urological communities in Europe which have established and published the guidelines on male LUTS and BPO. It was the aim to describe and balance the standard non- or minimally-invasive tests to determine BOO/BPO as well as the new tests described in chapter 1.5 with regard to applicability for the urological community as well as to determine in which patient groups pressure-flow measurements should still be used (**Chapter 9**). The various drugs and surgical techniques for the treatment of Male LUTS have a different effect on BOO/BPO. The last article aimed to summarize which drugs or surgical techniques are suitable for which symptomatic patient by analyzing the published literature between 1966 and October 2012 for the EAU guidelines on the treatment of male LUTS (**Chapter 10**).

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Part II:

Relevance of Bladder Outlet Obstruction in Adult Men

CHAPTER 2

Can We Identify Men Who Will Have Complications From Benign Prostatic Obstruction (BPO)?

Matthias Oelke, Ruth Kirschner-Hermanns, Nikesh Thiruchelvam, John Heesakkers

ABSTRACT

Aims: This ICI-RS report aims to analyse morphological or functional complications of the lower or upper urinary tract in elderly men, clarify the association between complications and benign prostatic obstruction (BPO) and define men who will develop these complications. Research proposals to further enlighten these associations were to be defined.

Methods: A think-tank discussion was held on the annual ICI-RS meeting in 2011. The published literature between 1966 and 2011 was reviewed and research proposals were defined with all congress participants.

Results: Post-void residual, bladder diverticula or calculi, vesico-ureteral reflux, hydronephrosis, renal insufficiency, and urinary retention appear with greater prevalence in patients with symptoms or signs of benign prostatic hyperplasia. BPO may directly or indirectly be responsible for these complications but conclusive evidence for BPO as the primary cause does not exist. Many of the complications have a multifactorial aetiology and BPO is only partially responsible. It is currently impossible to define men who will develop complications.

Conclusions: In contrast to the widespread belief of urologist, there is only rudimentary data available showing no convincing association between urinary tract complications and BPO. The ICI-RS proposes that prospective trials are conducted to demonstrate the association between complications and BPO by using cystometry, pressure-flow studies, and other commonly used BPO-parameters in men with complications and comparing those with a cohort of age-matched men without complications. Non-invasive proxy parameters of BPO, e.g. ultrasonic measurement of detrusor wall thickness, can be used instead of pressure-flow studies especially in longitudinal trials.

INTRODUCTION

Benign prostatic obstruction (BPO) has been defined by the International Continence Society as bladder outlet obstruction (BOO) in the presence of benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH). In this paradigm, BPH is the term reserved for the characteristic histological changes, and does not imply either BPE or BPO [1]. BOO is an urodynamic observation characterized by increased detrusor pressure and reduced urinary flow rate during voiding [1]. Therefore, the diagnosis of BPO requires pressure-flow (P/F) studies and, as a particular form of BOO, discrimination from other BOO types, e.g. bladder neck stenosis, urethral stricture, or meatal stenosis.

Only loose associations have been found between BPO and the presence, quality, or quantity of lower urinary tract symptoms (LUTS) [2,3]; BPO was detected in approximately 58% of unselected patients with LUTS suggestive of BPO [4] and 52% of age-comparable male volunteers without LUTS [5]. Similar inconsistent associations have been found between BPO and prostate size [6]. The relationships between the three major components of the BPH-disease (BPE-BOO/BPO-LUTS) are best characterized by the overlapping rings first described by Tage Hald (**Figure 1**) [7]. Consequently, the presence or magnitude of one component does not necessarily enlighten other components, and all three components have to be evaluated and quantified individually.
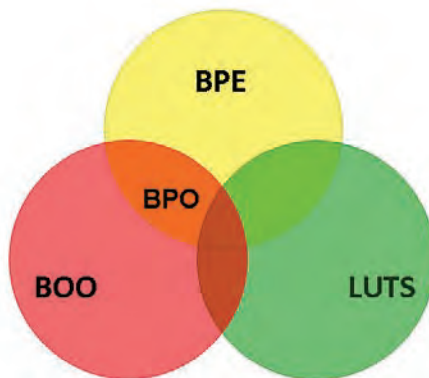
Figure 1: Associations between bladder outlet obstruction (BOO), benign prostatic obstruction (BPO), benign prostatic enlargement (BPE), and lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH) (modified according to [7]). Note that the exact quantitative distribution of and the overlap between the components are currently unknown.

P/F studies as the basis for the assessment of BPO are time-consuming, expensive, bothersome for patients, and associated with complications in up to 19% of investigated men, including macroscopic hematuria, urinary tract infections, sepsis, or urinary retention [8]. Additionally, investigators' experience seems crucial with regard to the execution of urodynamic measurements, artefact analyses, and interpretation of measurement results. Therefore, P/F studies

in patients with LUTS/BPO remain difficult and unpopular and only limited P/F data, mostly as retrospective single centre trials, are available in men with suspected BOO/BPO. Likewise, only few longitudinal urodynamic studies in selected patients with unsuccessful treatment and no epidemiological trials have been conducted on BPO due to the above mentioned reasons.

There has been paucity on P/F studies investigating men with suspected BPO since the late 1990s but efforts have been made to establish non-invasive techniques for determination of BPO, e.g. quantification of bladder mass using ultrasound devices and measuring bladder or detrusor wall thickness (BWT or DWT) or calculating ultrasound-estimated bladder weight (UEBW) as proxy parameters for BOO/BPO [9-11]. The positive predictive values for the detection of BOO/BPO are as high as 88% for BWT (threshold value 5 mm at bladder filling of 150 ml), 94% for DWT (threshold value 2 mm at bladder filling >250 ml), and 92% for UEWB (threshold value 35g at bladder filling between 100-300 ml) making these non-invasive techniques attractive alternatives to invasive P/F measurements [12-14].

Urologists often believe that the following complications in the lower or upper urinary tract appear in patients with BPO and are directly or indirectly linked to this condition: urinary tract infections, bladder stones (**Figure 2a**), bladder diverticula, vesico-ureteral reflux, hydronephrosis (**Figure 2b**), renal insufficiency, and urinary retention [16]. Therefore, these complications are regarded as absolute or relative indications for the surgical removal of the prostatic transition zone, for example by transurethral resection of the prostate (TURP), which results in BPO relief (deobstruction) and disappearance of the aforementioned complications if treated early enough.
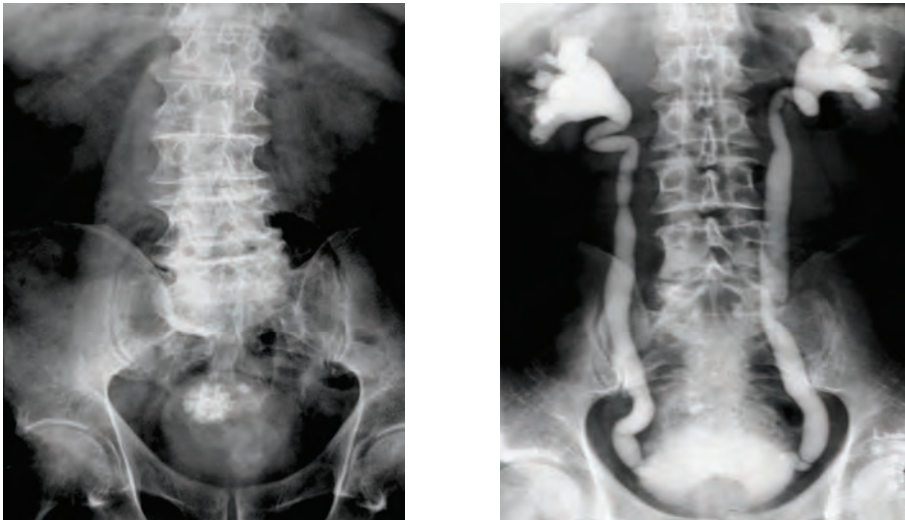
Figure 2: X-ray imaging of the urinary tract in men with urodynamically-confirmed benign prostatic obstruction. **A:** plain X-ray of the abdomen (K.U.B.) of a 64-year old man with bladder stones. **B:** Intravenous urography 30 min after infusion of contrast media of a 68-year old man with bilateral dilation of the upper urinary tract, fish-hook configuration of the distal ureters [15], intravesical prostatic protrusion, and postvoid residual urine.

This ICI-RS report aims to (1) validate whether urologists' assumptions on urinary tract complications and the association to BPO are evidence-based, (2) highlight the prevalence and pathophysiology of urinary tract complications, (3) suggest trials to clarify the incidence and pathophysiology of these associations, and (4) specify men who will most likely develop urinary tract complications as a result of BPO.

MATERIAL AND METHODS

This ICI-RS report was developed, discussed and summarized in 2011 following a sequence of defined steps:

- Step 1: The topic "*can we predict men who will have complications from BPO?*" was proposed for presentation and discussion on the 3rd annual meeting of the ICI-RS and sent to the scientific office of the society in January 2011 (M.O.). Of over 50 submitted applications, this proposal, next to 19 others, was chosen for presentation by the ICI-RS members in March 2011 using an email-based voting system.

- Step 2: The think-tank discussion was prepared by the two chairmen of the session (M.O. and J.H.) who reviewed and summarized the literature published in PubMed/Medline between January 1966 and June 2011. Any European language was deemed suitable for this purpose. The search terms "benign prostatic obstruction", "bladder outlet obstruction" or "benign prostatic hyperplasia" were combined with the search terms "postvoid residual", "urinary tract infection", "bladder stone", "bladder calculi", "bladder diverticulum", "vesico-ureteral reflux", "hydronephrosis", "renal insufficiency", "renal failure", "dialysis", or "urinary retention". The internet search was supplemented by hand searches of selected books and review articles.

- Step 3: The results of the literature search, together with a list of research proposals, were presented by the two chairmen, discussed with the congress participants, and audio-recorded on the ICI-RS meeting in Bristol on 14th June 2011. Finally, the five most important and urgent research proposals were defined together with the congress participants.

- Step 4: The results of the literature search and think tank discussion were summarized by the authors of this article. Proposed future research activities are highlighted in boxes.

RESULTS

Definition of urinary tract complications due to BPO

Identification of men who will have complications from BPO necessitates the information what kind of changes in the urinary tract are expected in these subjects. Alterations of the urinary tract in men with BPO should appear with greater frequency than in men without BPO. The literature search identified ten changes of the urinary tract which emerge with greater prevalence in men with "BPH" or BPO (**Table 1**). Of these morphological or functional urinary tract alterations, only

- post-void residual (PVR) urine,
- bladder diverticulum,
- bladder stone,
- vesico-ureteral reflux,
- hydronephrosis,
- renal insufficiency, and
- urinary retention

were considered complications, whereas bladder wall hypertrophy, bladder trabeculation, and the fish-hook configuration of the distal ureters were deemed physiological compensation mechanisms of the lower urinary tract in response to BPO and, therefore, are without clinical significance and without relevance for this article. Therefore, only the listed seven complications were analysed in greater detail.

Table 1: Prevalence of morphological or functional changes of the urinary tract in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction (LUTS/BPO) or urodynamically-confirmed BPO compared to asymptomatic individuals or men without BPO.

Changes Urinary Tract	Prevalence in men with LUTS/BPO - X-ray or ultrasound - [%]	Prevalence in men without LUTS/BPO - X-ray or ultrasound - [%]
Bladder trabeculation [17]	32.1 – 33.7	0.3
Bladder diverticulum [17]	3.2 – 3.4	0.3
Bladder stone [17]	3.2 – 3.4	0.2
Vesico-ureteral reflux [18]	14	5.1
Hydronephrosis [17]	5.8 – 6.9	0.6
Renal insufficiency [17, 18]	8.3 – 13.6	1.7
Urinary retention [19]	0.5 – 2% per year	

	Prevalence in men with BPO - pressure-flow studies - [%]	Prevalence in men without BPO - pressure-flow studies - [%]
Bladder trabeculation – diagnosed by cystoscopy [20]	92	77
Bladder wall hypertrophy [13, 14]	83 – 85	4.7 – 13
Fish-hook configuration of the distal ureters [15]	53	24.2
Post-void residual >50 ml [13, 21]	72 – 87.5	57.6 – 65

> **Recommendations:** The ICI-RS proposes to confirm that the aforementioned seven complications are really caused by BPO and not by other factors, such as aging, BPE, or detrusor underactivity. Patients with these complications should be urodynamically evaluated (P/F) and compared to cohorts of age-matched men without these complications to assess severity of BOO. Alternatively and most probably more feasible, proxy parameters of BPO (e.g. DWT, BWT, or UEBW) could be used in these cohorts or in epidemiological, longitudinal studies.

Associations between urinary tract complications and BPO

Post-void residual (PVR) urine

PVR <5 ml was measured in 78% and <12 ml in 100% of healthy males [22]. However, PVR >50 ml is considered clinically relevant. 24% of men with BPO have PVR <50 ml [23], whereas 30% of patients without BPO have PVR >50 ml [24]. PVR volume ≥50 ml for the prediction of BPO has a sensitivity of 69-72% and specificity of 42-48% [13, 21]. PVR is seen as a sign of deteriorated detrusor function rather than BPO [7, 23]. However, studies in experimental animals suggest that long-lasting and untreated BPO can also result in deteriorated detrusor function. Vesico-ureteral reflux, bladder diverticula, and circadian rhythms (highest amount in the early morning) can cause or increase PVR as well [25]. Therefore, PVR seems to be multifactorial and BPO is not the only cause.

There are known associations between urinary tract infections and aging but no scientific proof exists that BPO or PVR triggers bacteriuria or urinary tract infections [26-28]. Additionally, PVR in patients with LUTS/BPO does not gradually increase and results in urinary retention; 107 untreated patients with a varying volume of PVR have been followed for 5 years and only two men developed urinary retention, whereas mean PVR maintain unchanged in the rest [29]. This myth is perpetuated by studies examining the role of antimuscarinic agents in men with BPO-type symptoms where men are excluded if the PVR is >200 ml.

Bladder diverticulum

Data on the pathophysiology of bladder diverticula in BPO patients are scarce. Only one retrospective trial has been published in which 24 patients with LUTS/BPO and bladder diverticula were compared with 67 patients with LUTS/BPO but without diverticula. Significant differences between the two groups were noted for the prevalence of acute urinary retention (25 vs. 6.1%), urinary tract infections (21.7 vs. 3.1%), PVR (221 vs. 46 ml), bladder capacity (351 vs. 211 ml), and BPO grade (urethral resistance algorithm 48.5 vs. 36.5 cm H_2O) [30]. This trial has shown for the first time that diverticula are associated with higher voiding pressures but, however, does not proof that BPO is the origin of diverticula.

Bladder stone

Limited data on the incidence or pathophysiology of bladder stones are available despite the fact that bladder calculi were once endemic in many places [31] and still account for approximately

5% of urinary tract stones [32]. Men are affected in the vast majority of cases [33]. Two series of patients have been published; only one contained urodynamic data and both were without a control group. One trial in 100 patients with bladder stones not necessarily associated with LUTS/BPO or BPE reported about "obstruction" in 88%, a diagnosis based on symptoms and clinical judgement rather than P/F measurements [31]. The other trial in 50 consecutive men with bladder stones due to various underlying diseases, including BPE, showed in P/F studies BPO in 51%, detrusor underactivity in 10%, and detrusor overactivity in 68% of patients [34]. Both trials indicate a possible association between bladder stone formation and BOO/BPO; however, detrusor underactivity or overactivity [34] or other types of BOO, such as urethral stricture, neurogenic bladder dysfunction, or prostate cancer [31], may also play a role. Data suggest that calculi remain lying in the bladder due to incomplete bladder emptying; therefore, any voiding disorder associated with PVR seems to be associated with bladder stones.

Vesico-ureteral reflux

No report was identified on the incidence or pathophysiology of vesico-ureteral reflux in adult men. The lack of information seems partially attributable to the fact that voiding cystography is no longer recommended for the assessment of patients with LUTS/BPO [35].

Hydronephrosis

It has been postulated that anatomic obstruction of the uretero-vesical junction due to bladder muscle hypertrophy as a result of BPO or functional compression of the uretero-vesical junction due to bladder overdistension, via an increase of ureteral resistance through the ureteral tunnel, causes bilateral hydronephrosis [36]. However, there are multiple other possible causes for bilateral hydronephrosis [36], which all have not been rigorously studied. One trial in 27 patients with bilateral hydronephrosis found in 52% of patients bladder storage pressures (P_{det}) >40 cm H_2O at maximum bladder capacity; however, increased storage pressures in patients with hydronephrosis were not necessarily sustained during the entire storage phase [37]. Interestingly, higher and sustained storage pressures were related to renal insufficiency in patients with hydronephrosis indicating that vesical pressure during the filling phase may play an important role for upper urinary tract complications.

Renal insufficiency

Deterioration of renal function was found in the Olmsted community in symptomatic men (IPSS >7, odds ratio 2.91) with low maximum urinary flow rate (Q_{max} <15 ml/s, odds ratio 2.96) and PVR >100 ml (odds ratio 2.28) [38]. As mentioned in the previous section, patients with renal insufficiency had higher intravesical pressures compared to men without renal insufficiency [37]. Furthermore, men with decreased bladder compliance were likely to develop renal insufficiency (78%) compared to men with normal bladder compliance (36%) [39], and low bladder compliance was directly related to BPO (compliance 23 ml/cm H_2O in men with and 39 ml/cm H_2O in men without BPO) [40]. It remains to be evaluated why men with BPO develop low bladder compliance and whether more severe BPO increases the risk for renal insufficiency and/or time plays a role.

Recommendations: The ICI-RS suggests clarifying the pathophysiology of urinary tract complications by investigating men with these signs using cystometry, P/F studies, imaging techniques (ultrasound of the bladder wall, prostate volume, renal collecting system, and PVR) together with assessment of renal function (creatinine level) and compare these patients with a cohort of men without these complications. Multivariate analysis should clarify the primary factor for these complications.

Urinary retention

Prospective epidemiological studies or post-hoc analyses of drug trials have determined the risk factors for (acute) urinary retention in elderly men [19, 41]; age, prostate volume, PSA concentration, Q_{max}, symptoms, and PVR were contributing factors. As all factors are also significantly associated with BPO, it is possible that BPO is the major cause for urinary retention. It has been shown that men with bladder wall hypertrophy (UEBW >35 g) have a 13.4 times increased risk for the development of acute urinary retention compared to men with a normal bladder mass [42].

Recommendations: The ICI-RS proposes that longitudinal studies are conducted with repeated measurements of BPO and other common BPO-parameters over time (P/F studies or DWT/BWT/UEBW), to identify those men who are most likely to develop acute urinary retention or other urinary tract complications. It appears useful to focus on men with increased risk of disease progression (BPE or elevated PSA concentration). Multivariate analysis should be conducted to evaluate the primary cause(s) of urinary tract complications.

CONCLUSIONS

In contrast to the widespread belief of urologists and common clinical practice, little evidence exists on the incidence or pathophysiology of lower or upper urinary tract complications in elderly men and associations between urinary tract complications and BPO. Although these complications appear with greater prevalence in men with LUTS/BPO or BPE, the exact origin and pathophysiology remain to be elucidated. At present, it is impossible to predict who will have urinary tract complications and to state the precise origin. BPO may directly or indirectly cause these complications but other factors - such as aging, detrusor overactivity, detrusor underactivity, and low bladder compliance - may also cause or contribute to urinary tract complications (**Table 2**). The knowledge about the primary factors causing urinary tract complications would allow physicians to determine the most adequate therapy or follow-up sequence according to the individual risk or progression profile.

Table 2: Summary of the literature with regard to the associations between benign prostatic obstruction (BPO) and urinary tract complications

Complications Urinary Tract	Scientific Evidence for BPO as Trigger for Complications
Post-void residual urine	**Partially** → cause of PVR most likely multifactorial and BPO only one origin besides detrusor underactivity, vesico-ureteral reflux, bladder diverticula, or others.
Bladder diverticulum	**Possible** → development most likely due to BPO / increased voiding pressures but only one published trial with small amount of patients.
Bladder stone	**Partially** → bladder stone formation most likely multifactorial and linked to incomplete bladder emptying, foreign bodies, and recurrent urinary tract infections. → BPO only one origin beside other types of BOO (bladder neck stenosis, urethral stricture), detrusor underactivity, or neurogenic bladder dysfunction.
Vesico-ureteral reflux	**No / Unknown** → no study available on reflux
Hydronephrosis	**Possible** → indirect via increased bladder storage pressure / low-compliance bladder
Renal insufficiency	**Possible** → indirect due to increased bladder storage pressure / low-compliance
Urinary retention	**Possible** → one trial indicated a direct link between retention and BPO (bladder wall hypertrophy).

BOO and BPO are still the least investigated components of the BPH-disease (**Figure 1**), and problems with invasive, expensive, and time-consuming P/F studies have certainly contributed to this deficit. New non-invasive and reliable techniques for the assessment of BOO/BPO have lately become available which can overcome these unfavourable issues of urodynamics. Ultrasonic quantification of bladder hypertrophy - either with BWT, DWT or UEBW - can be used as proxy parameters for the quick determination of BOO/BPO in studies in the future. Other non-invasive techniques for the assessment of BPO – ultrasonic measurement of intravesical prostatic protrusion [43] or measurement of isovolumetric bladder pressure by the penile cuff test [44] or condom catheter method [45] - may be applied alternatively.

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CHAPTER 3

Age and Bladder Outlet Obstruction are Independently Associated with Detrusor Overactivity in Patients with Benign Prostatic Hyperplasia

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ABSTRACT

Purpose: To determine clinical and urodynamic parameters associated with detrusor overactivity (DO) in patients with clinical benign prostatic hyperplasia (BPH).

Material & Methods: During 1993–2003, urodynamic investigations were systematically performed in patients with clinical BPH which was defined by lower urinary tract symptoms and/or benign prostatic enlargement in men aged 40 years or older. DO was defined according to the new International Continence Society classification (2002) as involuntary detrusor contractions together with urgency during cystometry. The Schäfer algorithm was used to determine BOO.

Results: 1,418 men were investigated (median age 63 years) of whom 864 men (60.9%) had DO. In univariate analysis, men with DO were significantly older, more obstructed, had larger prostates, higher irritative IPSS sub-scores, a lower voiding volume at free uroflowmetry, and a lower bladder capacity at cystometry (each parameter $p<0.05$). The prevalence of DO rose continuously with increasing BOO-grade ($p<0.01$). Multivariate analysis showed that only age ($p<0.01$) and BOO grade ($p<0.01$) were independently associated with DO. After age-adjustment, the odds ratio of DO compared to Schäfer class 0 was 1.2 for Schäfer class I ($p=0.282$), 1.4 for Schäfer class II ($p=0.044$), 1.9 for Schäfer class III ($p<0.01$), 2.5 for Schäfer class IV ($p<0.01$), 3.4 for Schäfer class V ($p=0.002$), and 4.7 for Schäfer class VI ($p=0.016$).

Conclusions: This study demonstrates in patients with clinical BPH that DO is independently associated with age and BOO. The probability of DO rises with increasing age and BOO-grade.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common condition in the aging male. Men with BPH can have benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), lower urinary tract symptoms (LUTS), or a combination of these components [1]. The severity of all components of the BPH disease increases with aging. Detrusor overactivity (DO) is one known cause of LUTS and is linked to bladder storage symptoms (urgency, frequency, or urge incontinence). In men with BPH the prevalence of DO increases with age as well [2–4]. DO can only be diagnosed by urodynamic investigation during which involuntary detrusor contractions, either spontaneously or provoked, occur during filling cystometry [5]. Cystometric studies in men with BPH revealed DO in 50–75%, and a meta-analysis demonstrated DO with a mean prevalence of 60.2% (95% CI: 52–68%) [6].

It remains controversial whether DO is only caused by age or is also related to BOO or BPE [3, 7]. In experimental animals, DO develops after partial ligature of the urethra and, therefore, obstructed bladders are used as a model to study DO [8]. In men, urodynamic studies showed heterogeneous results. Some studies found a significant relationship between DO and BOO [9–13], whereas other studies failed to demonstrate this relationship [7, 14]. Indirect information with regard to BOO and BPE derives from studies with symptomatic BPH patients who had proven DO before transurethral resection of the prostate; approximately two-thirds of these men were without DO after transurethral resection [6]. It was concluded that BOO or BPE were originally responsible for DO in cured patients. A more recent study supported these results and demonstrated that 60% of men with DO and equivocal BOO before transurethral resection of the prostate had persistent postoperative DO, compared with 27% who had DO and more severe BOO preoperatively [15]. Furthermore, some studies showed that men have a higher prevalence of DO compared to age-matched women (55% vs 11%) indicating once more that BOO or BPE might be responsible for DO as well [14, 16]. Our study aims to clarify the relationship between DO and clinical as well as urodynamic parameters in men with symptoms or signs most likely attributable to BPH.

PATIENTS and METHODS

Patient selection

Between April 1993 and November 2003, all men with clinical BPH who came to the urological outpatient department of the Medical School Hannover, Germany were included in this study. Clinical BPH was defined by LUTS and/or BPE in men with an age of 40 years or older in absence of other diseases that most likely cause these symptoms. Therefore, men with LUTS after lower urinary tract or pelvic surgery, radiotherapy, urinary tract infection, bladder cancer, interstitial cystitis, neurological diseases, prostatitis, prostate cancer, urethral strictures, or ureteral stones were excluded from this study. Furthermore, all men with BPH-related complications (urinary retention, bladder stones, or bladder diverticula) were also excluded.

Patient assessment

At initial presentation, patient history and a blood sample for PSA measurement were taken and the IPSS-questionnaire was filled in by the patient. Afterwards, physical examination including digito-rectal palpation of the prostate, ultrasound imaging of the bladder and kidneys, and free uroflowmetry were performed. A suprapubically positioned 3.5 MHz ultrasound array was used to measure postvoid residual urine and a transrectal 7.5 MHz ultrasound array was used to measure the prostate volume. One to three weeks after initial assessment and after exclusion of prostate cancer by prostate biopsies in cases of palpable tumors or elevated PSA concentrations (>4 µg/l) experienced residents performed urodynamic investigations which were in line with the suggested "good urodynamics practice standards" of the International Continence Society [14]. Urine cultures were sterile at the time of the initial presentation of the patient and urine dipsticks were without signs of infection on the day of urodynamic investigation. All patients were measured in the sitting position. Urodynamic examinations were performed with external pressure transducers, a 6 French double-lumen transurethral and a 10 French single-lumen rectal catheter. Sterile physiological saline solution with a temperature of 37° C was infused through the transurethral catheter with an infusion speed of 25 - 50 ml/min. Cystometry and pressure-flow recordings were repeated in each patient 2-4 times during the same urodynamic appointment. DO was defined according to the 2002 classification of the International Continence Society as spontaneous or provoked (coughing) involuntary detrusor contractions during the bladder filling phase associated with urgency but regardless of the amplitude [8]. In cases of involuntary detrusor contractions, patients were asked to inhibit DO and urinary leakage by urethral sphincter contraction. BOO was assessed with the Schäfer algorithm [15]. The pressure-flow measurement with the lowest BOO-grade was used for further analysis.

Directly after the urodynamic measurement and elimination of measurement artifacts, the urodynamic traces were judged by the resident together with the responsible staff member (K.H.) and a diagnosis with regard to DO, DO-incontinence, and BOO-grade was documented in a protocol. In 2005, all urodynamic measurements were evaluated again (M.O.) without knowing the results of the original judgment. In cases of different results compared to the original report, the urodynamic traces were judged independently by a third person (U.J.), and this result was digitally stored for further evaluation. Additionally, the following information was documented in the database: details of patient history (age and body-mass index), total IPSS (sum of the answers of questions 1-7), irritative (sum of the answers of questions 2, 4, and 7) and obstructive IPSS sub-scores (sum of the answers of questions 1, 3, 5, and 6), prostate volume determined by transrectal ultrasound, parameters of free uroflowmetry (maximum urinary flow rate, voided volume), postvoid residual urine volume after free uroflowmetry, and details of the urodynamic investigation (involuntary detrusor contractions, bladder volume at first involuntary detrusor contraction, maximum amplitude of involuntary detrusor contractions, and cystometric bladder capacity).

Statistical evaluation

Non-parametric tests were necessary to compare the groups with or without DO because the data was unevenly distributed; the Mann-Whitney or Kruskal-Wallis test was used to compare numerical data. Correlation analysis and the Spearman rank test was applied to demonstrate the

relationship between BOO and bladder volume at first involuntary detrusor contraction or maximum amplitude of involuntary detrusor contraction. Binary stepwise logistic regression analysis was used for multivariate exploration. The odds-ratio was calculated to demonstrate the probability of DO in men with different grades of BOO (Schäfer classes I-VI) compared to men without BOO (Schäfer class 0). A p-value equal or below 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS version 12.0.2, Chicago, Ill., USA) was used for statistical analyses.

RESULTS

Urodynamic investigations were performed in 1,460 men. Forty-two men (2.9%) could not void during urodynamic assessment and were excluded from further analysis. The patient characteristics and measurement results after initial assessment of the remaining 1,418 patients are listed in **table 1**.

Table 1: Clinical and urodynamic parameters of all patients investigated in this study (n=1,418).

Parameter	Range	Median (25th – 75th percentiles)
Age [years]	40 – 89	63 (57 – 69)
Body-mass index [kg/m^2]	16.1 – 45.8	25.8 (23.9 – 28.3)
IPSS (questions 1-7)	0 – 35	16 (10 – 21)
IPSS irritative sub-score (questions 2, 4, and 7)	0 – 15	7 (4 – 10)
IPSS obstructive sub-score (questions 1, 3, 5, and 6)	0 – 20	9 (4 – 13)
Prostate volume [ml]	11 – 160	35 (26 – 47)
Q_{max} [ml/s]	1.5 – 58.6	11.0 (7.4 – 15.5)
Voided volume (free uroflowmetry) [ml]	60 – 1110	230 (170 – 332)
Postvoid residual urine [ml]	0 – 600	60 (20 – 134)
Cystometric bladder capacity [ml]	45 – 1812	381 (281 – 532)
Bladder volume at 1st involuntary detrusor contraction [ml]	1 - 1178	124 (45 – 260)
Maximum amplitude of involuntary detrusor contraction [cm H$_2$O]	5 – 330	35 (18 – 70)

During filling cystometry, 864 patients (60.9%) had involuntary detrusor contractions. Men with DO were significantly older and more obstructed, had a higher irritative IPSS sub-score, greater prostate volume, lower voiding volume at free uroflowmetry, and a lower maximum cystometric bladder capacity (each parameter <0.05, Mann-Whitney test, **table 2**). The relationship between DO and different age groups is shown in **figure 1**.

In pressure-flow analysis, BOO-grades were unevenly distributed with more men located in lower Schäfer classes. Patients with DO were significantly more obstructed than patients without DO (median Schäfer class III vs. I, p<0.01, Mann-Whitney test). The prevalence of DO rose continuously with increasing BOO-grade, reaching from 51.4% in Schäfer class 0 to 83.3% in Schäfer class VI (p<0.01, Kruskal-Wallis test; **figure 2**). There was weak but significant negative correlation between

BOO (expressed as detrusor pressure at maximum flow, $Pdet_{qmax}$) and bladder volume at first involuntary detrusor contraction (Spearman rank test -0.082, p=0.017; **figure 3**) and a weak positive correlation between BOO and maximum amplitude of involuntary detrusor contractions (Spearman rank test 0.097, p=0.006; **figure 4**).

Table 2: Median values and 25th – 75th percentiles of clinical and urodynamic parameters divided by the absence or presence of detrusor overactivity. IPSS = International Prostate Symptom Score, Q_{max} = maximum urinary flow rate of free uroflowmetry.

Detrusor overactivity / Parameter	Absent — Median (25th - 75th percentile)	Present — Median (25th - 75th percentile)	P-value *
Age [years]	61 (56 - 68)	64 (59 - 70)	<0.01
Body-mass index [kg/m^2]	25.9 (23.8 - 28.4)	25.8 (23.9 - 28.1)	0.606
IPSS (questions 1-7)	15 (9 - 21)	17 (11 - 21)	0.08
IPSS irritative sub-score (questions 2+4+7)	6 (3 - 9)	8 (5 - 11)	<0.01
IPSS obstructive sub-score (questions 1+3+5+6)	9 (4 - 13)	9 (5 - 12)	0.311
Prostate volume [ml]	33 (25 - 45)	36 (27 - 49)	0.014
Q_{max} [ml/s]	11.2 (7.4 - 16.3)	11.0 (7.4 - 15.2)	0.588
Voided volume (free uroflowmetry) [ml]	263 (181 - 376)	217 (166 - 307)	<0.01
Postvoid residual urine [ml]	64 (20 - 150)	60 (20 - 124)	0.574
Cystometric bladder capacity [ml]	409 (299 - 574)	357 (268 - 493)	<0.01

* Mann-Whitney test

Logistic regression analysis revealed that only age (p<0.01) and BOO-grade (p<0.01) were independently associated with DO. To further elucidate the relationship between DO and BOO-grade we compared Schäfer class 0 (no BOO) with Schäfer classes I-VI (different BOO-grades) and corrected the data for patient age. Compared to Schäfer class 0, the prevalence of DO was significantly different in Schäfer classes II-VI (**table 3**). The estimated odds ratio for the appearance of DO rose with increasing BOO-grade, reaching from 1.2 in Schäfer class I to 4.7 in Schäfer class VI.
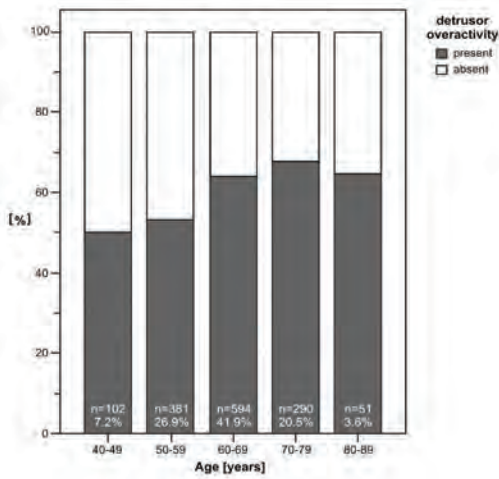
Figure 1: Prevalence of detrusor overactivity in relation to different age-groups. Patients in the older age-groups had a significantly higher chance to have detrusor overactivity. The number of men (%) in each age-group is listed at the base of the column.
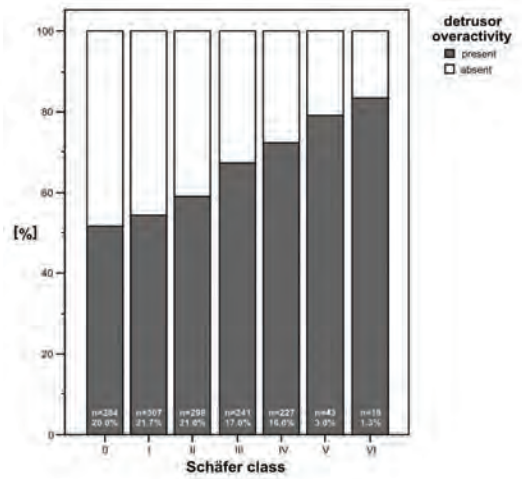
Figure 2: Prevalence of detrusor overactivity in relation to the obstruction grade (Schäfer class). The prevalence of detrusor overactivity increases continuously from 51.4% in Schäfer class 0 to 83.3% in Schäfer class VI. The number of men (%) in each Schäfer class is listed at the base of the column.
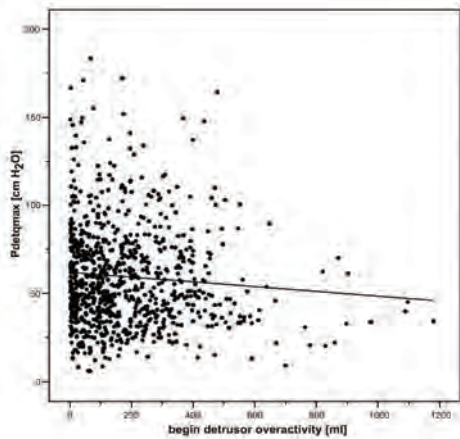
Figure 3: Relationship between detrusor pressure at maximum flow (Pdet$_{qmax}$) and bladder filling volume at begin of involuntary detrusor contractions. With increasing bladder outlet obstruction involuntary detrusor contractions appeared at lower bladder volumes.
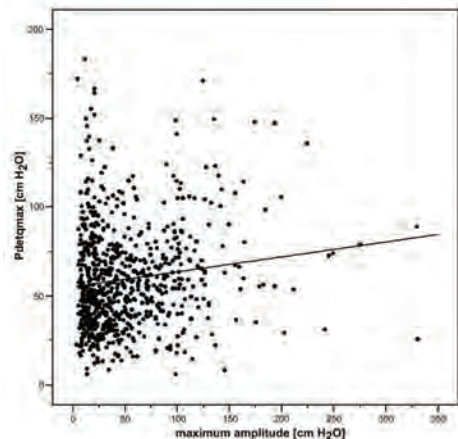
Figure 4: Relationship between detrusor pressure at maximum flow (Pdet$_{qmax}$) and maximum amplitude of involuntary detrusor contractions. With increasing bladder outlet obstruction the maximum amplitude of involuntary detrusor contractions increased as well.

Table 3: Logistic regression analysis for evaluation of clinical and urodynamic parameters associated with detrusor overactivity (data age corrected). Schäfer classes I-VI (different grades of bladder outlet obstruction) were calculated against Schäfer class 0 (no bladder outlet obstruction). Only the age of the patients and Schäfer classes (II-VI) were independently associated with detrusor overactivity. The odds ratio of detrusor overactivity increases with increasing obstruction grade (Schäfer class).

	P-value	Odds ratio	95% confidence interval of odds ratio	
			Lower limit	Upper limit
Schäfer 0				
Schäfer I	0.282	1.2	0.86	1.66
Schäfer II	0.044	1.4	1.01	1.95
Schäfer III	<0.01	1.9	1.33	2.71
Schäfer IV	<0.01	2.5	1.74	3.67
Schäfer V	0.002	3.4	1.58	7.44
Schäfer VI	0.016	4.7	1.33	16.8
Age	<0.01	1.03	1.01	1.04

DISCUSSION

Our study demonstrated that the appearance of DO in filling cystometry in men with clinical BPH is independently associated only with age and BOO. The probability of DO rises with increasing BOO-grade. There was a tendency that with increasing BOO-grade DO appeared at a lower bladder filling and with higher amplitude.

This study included all men with clinical BPH who were evaluated in the urological department of the Medical School Hannover during a 10½ year time period. It is the policy of this department to evaluate each component of the BPH disease separately in order to quantify LUTS, BPE, and BOO before therapy. Our study group consists of men with symptoms most likely attributable to BPH. Even though other diseases than BPH were not evident at the time of assessment other causes of LUTS still might had been latently present. Prostate biopsies to exclude prostate cancer or prostatitis were only taken in men with a PSA concentration of more than 4 µg/l or palpable tumors and, therefore, latent prostate diseases might have been overseen. The majority of men investigated in our study sought help for moderate to severe LUTS. All baseline characteristics of patients in our study are nearly identical with those of 4,979 European men with clinical BPH who were investigated to determine health seeking behavior [16]. Therefore, our patients seem to represent typical men with clinical BPH who visit their doctor because of this condition. However, our results cannot simply be extrapolated to the normal male population or to men with LUTS who do not seek medical help because the characteristics of these men are mainly unknown.

Urodynamic studies with a large number of BPH patients are sparse. Therefore, our study also provides information about the distribution of BOO-grades within a group of clinical BPH patients. Pressure-flow studies of our patients revealed that 58.3% had BOO. Even though patients were not selected after initial assessment to undergo urodynamic investigation, younger patients (≥40 years) were also investigated, pressure-flow measurements were repeatedly performed and the lowest BOO-grade was used for analysis, the probability of BOO was almost identical to the one of the ICS-BPH study. This until now largest urodynamic study included a total of 1,271 patients with clinical BPH and demonstrated BOO in 60% [17]. However, no large scale urodynamic study has investigated the distribution of BOO-grades so far. Our results indicate that BOO-grades are not normally distributed within the group of clinical BPH patients and that more men have no BOO (Schäfer classes 0-I; 41.7%) or mild to moderate BOO (Schäfer classes II-IV; 54%) than severe BOO (Schäfer classes V-VI; 4.3 %).

In the aging male, LUTS suggestive of BPH belong to the most common urological conditions that affect quality of life. Even though voiding symptoms (e.g. hesitancy, slow urinary stream, or extended micturition time) are reported more frequently by men with clinical BPH, storage symptoms (urgency, pollakisuria, nocturia, or urge incontinence) are more bothersome and reduce the quality of life more substantially [18, 19]. Storage symptoms can be caused by DO but might also be related to other myogenic, neurogenic, hormonal, or behavioral abnormalities (e.g. postvoid residual urine due to BOO or detrusor underactivity, increased fluid intake, or insufficiency of vasopressin production) [20]. The incidence of DO in our group of clinical BPH patients was 60.9% and, therefore, almost identical with the prevalence of DO reported in the metaanalysis of urodynamic studies (60.2%) [9].

In univariate analysis, we found several parameters in patients with DO that were significantly different compared to those in men without DO (age, prostate volume, voiding frequency, urinary incontinence, voided volume in free uroflowmetry and maximal cystometric bladder capacity). Even though the individual relationships between DO and most of these clinical or urodynamic parameters have been reported before, especially the relationship between DO and age, no study has investigated all parameters in one patient group so far. The central finding of our study is the significant and independent relationship between DO and age as well as DO and BOO-grade. Compared to Schäfer class 0 the prevalence of DO in Schäfer classes II-VI was significantly higher. Only patients with a Schäfer class I did not have an increased prevalence of DO; this mild BOO-grade, however, is clinically considered as non-obstruction as well. We could demonstrate for the first time that the prevalence of DO continuously rises with increasing BOO-grade. Information in terms of DO and BOO have been controversial so far. Some authors did not find a significant relationship between DO and BOO [10, 12], whereas others authors demonstrated that the appearance of DO in filling cystometry is increased in men with BOO [21-25]. Our study, therefore, confirmed the findings of the latter studies which, however, used the old DO definition of the International Continence Society (involuntary detrusor contractions with an amplitude >15 cm H_2O), used other BOO assessment algorithms (e.g. opening contraction power, maximum urinary flow rate, or the urethral resistance algorithm), investigated small groups of highly selected patients, or did not examine the relationship between DO, different BOO-grades and age in one group of patients. In contrast to previous studies, our investigation analyzed all men with symptoms suggestive of BPH and/or BPE

without further patient selection, used a well-accepted urodynamic BOO assessment algorithm and applied the new DO definition of the International Continence Society (2002). Furthermore, the odds-ratio of DO of different BOO-grades was calculated in our study for the first time and demonstrated that the prevalence of DO continuously increases with rising BOO-grade.

The exact etiology of DO in men with or without DO remains unclear. Theories explaining DO in men with BOO focus on myogenic, neurogenic or combined origins. Increased bladder outlet resistance leads to bladder wall thickening, partial denervation, supersensitivity of muscarinic receptors to acetylcholine, increased collagen content in the detrusor, ischemia, changes in electrical properties of detrusor smooth muscle cells, or reorganization of the spinal micturition reflex [6, 11, 26]. Microscopic investigations of the detrusor in patients with DO revealed abnormal intercellular connections (protrusion junctions or ultra-close abutments) which seem to be responsible for the propagation of spontaneous depolarisation of detrusor cells leading to synchronous involuntary contractions of detrusor regions [27, 28]. These alterations are believed to be a response of the smooth muscle to a reduction in its normal excitatory neuronal input caused by denervation. Because the detrusor wall thickens continuously with increasing BOO-grade it is likely that the probability of DO increases as well and, vice versa, thinning of the detrusor wall after surgical relief of BOO decreases the probability of DO [29].

CONCLUSIONS

We demonstrated that age and BOO are independently associated with DO in men with clinical BPH. The odds-ratio of DO rises with age and increasing BOO-grade. In contrast to this, prostate volume or other patient characteristics were not independently associated with DO in these men. With increasing BOO-grade DO appears at a significantly lower bladder filling and with higher amplitude. The pathophysiological mechanisms that lead to DO in men with BPH remain unknown.

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Part III:

Ultrasound Detrusor Wall Thickness Measurement as a Non-Invasive Test to Evaluate Bladder Outlet Obstruction

CHAPTER 4

Ultrasound Measurement of Detrusor Wall Thickness in Healthy Adults

Matthias Oelke, Klaus Höfner, Udo Jonas, Dirk Ubbink, Jean J. de la Rosette, Hessel Wijkstra

ABSTRACT

Aims: Measurements of detrusor wall thickness (DWT) are used to diagnose bladder outlet obstruction (BOO). No values of DWT exist in healthy adults so far. These values, however, are necessary to judge DWT in patients with suspected BOO correctly. The aim of this study was to determine DWT in healthy adults and to investigate if bladder filling, gender, age or body-mass index (BMI) influences DWT.

Material and methods: In 55 healthy adult volunteers between 15-40 years of age, DWT was measured at the anterior bladder wall with a 7.5 MHz ultrasound probe and with a full bladder. In 9 of those volunteers, an urodynamic investigation was performed additionally during which DWT was measured in steps of 50 ml until 300 ml and in steps of 100 ml until the maximum bladder volume.

Results: DWT decreases rapidly during the first 250 ml of bladder filling but, thereafter, remains almost stable until maximal bladder capacity. No statistical difference was found between DWT at 250 ml and DWT at a higher bladder filling. Men had a greater DWT compared to women (1.4 vs. 1.2 mm, $p < 0.001$). The age and BMI did not have a significant impact on DWT.

Conclusions: DWT remains stable at a bladder filling of ≥ 250 ml. At this state of bladder filling, DWT between different groups are comparable. Men have to be evaluated separately from women.

INTRODUCTION

Measurements of the bladder or detrusor wall thickness have received increasing interest as a non-invasive test to diagnose bladder outlet obstruction (BOO). In experimental animals with BOO, detrusor wall thickness (DWT) and bladder weight increase due to smooth muscle hypertrophy and deposition of connective tissue [1, 2]. These histological changes of the detrusor as a result of BOO have been confirmed in humans [3, 4]. Thickening of the detrusor occurs as a result of increased workload similar to the heart in which the muscular wall thickens due to a valve stenosis or arterial hypertension [5]. Consequently, it is hypothesized that DWT reflects the workload of the bladder and gives information about urethral resistance.

The bladder wall as well as the different layers of the bladder (mucosa, detrusor and adventitia) can be imaged with ultrasound technology. Sonographic measurements of the bladder wall have shown a low intra- and interobserver variability which makes this technique suitable for the routine use in patients [6-8]. Before using DWT for determination of BOO, it is essential to know DWT of healthy individuals. Values of healthy individuals have to serve as a reference to judge measurements in patients correctly. All information about the normal DWT is from ultrasound studies of BPH-patients without BOO [6, 9] or women with urinary incontinence [10]. However, it is unclear if these values reflect DWT in healthy individuals correctly. Furthermore, it is unknown at what bladder filling DWT should be measured and if other factors might also influence DWT. Therefore, the aim of this study was to determine DWT in healthy adults and to investigate if the parameters bladder filling, gender, age or body-mass-index (BMI) might also influence DWT.

MATERIAL and METHODS

Volunteers

Fifty-five healthy adult volunteers (30 women, 25 men) between 15-40 years of age were included in this study. All volunteers were investigated to show the relationship between DWT and age, gender or BMI. 9 of these volunteers (5 women, 4 men) were also studied to evaluate the relationship between DWT and bladder filling. All examinations were performed in accordance to the regulations of the local ethics committee. All individuals were employees of the hospital (female and male doctors, scientists, nurses and probationers). The age of the male volunteers varied between 16-40 years (mean 28.2 years) and the age of the female volunteers between 15-40 years (mean 26.5 years; p=0.394, T-Test). None of the volunteers had lower urinary tract symptoms, previous operations at the urinary tract or small pelvis, a neurological deficit or diabetes mellitus. Before including the volunteers in the study, normal bladder emptying was assessed by uroflowmetry and sonographic measurements of postvoid residual urine. All volunteers had a maximum urinary flow (Q_{max}) of >15 ml/s and postvoid residual volume of ≤10 ml (1-10 ml, mean 4 ml). The average Q_{max} was 26.2 ± 6.6 ml/s in men and 31.1 ± 10 ml/s in women (p=0.038, T-Test). The characteristics of volunteers are shown in the **table I**.

Table I: Characteristics of the volunteers who participated in this study. No significant differences with regard to height, weight or BMI were seen between the different age groups of one gender (p>0.05). SD = standard deviation, BMI = body-mass-index (weight [kg]/height x height [m^2])

Gender	Age [years]	Number of volunteers	Height [cm] mean ± SD	Weight [kg] mean ± SD	BMI [kg/m^2] mean ± SD
Males	16 - 20	5	179 ± 6.5	80.0 ± 13.6	24.9 ± 3.0
	21 - 30	10	185 ± 6.9	78.4 ± 7.2	22.9 ± 1.4
	31 - 40	10	182 ± 6.2	83.4 ± 14.1	25.1 ± 4.5
Females	15 - 20	10	169 ± 4.8	65.7 ± 8.1	23.2 ± 3.0
	21 - 30	10	167 ± 4.8	61.1 ± 3.7	21.9 ± 2.1
	31 - 40	10	166 ± 6.4	65.2 ± 6.4	23.7 ± 2.9

Urodynamic investigation

A computer-urodynamic investigation (Ellipse, ANDROMEDA, Taufkirchen, Germany) was performed in 9 volunteers to show the relationship between DWT and bladder filling. Under sterile conditions, a 6 French H_2O-catheter was inserted through the urethra in the bladder and a 10 French H_2O-catheter was placed in the rectum. Before starting the measurement, the bladder was emptied completely through the transurethral catheter. Afterwards, the bladder was filled with physiologic saline solution of 37° C at a filling rate of 25 ml per minute. During filling and voiding phases, intravesical and intrarectal pressures were simultaneously recorded; detrusor pressure was calculated by subtracting the intrarectal from the intravesical pressure. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [11]. For sonographic determination of DWT, the urodynamic measurement was interrupted. Immediately after the last DWT measurement, pressure-flow-measurement was performed and the degree of BOO was calculated using the algorithm of the Schäfer-classification [12, 13]. No volunteer showed any signs of BOO (all Schäfer class 0); all volunteers had "normal" detrusor strength (DAMPF).

Measurement of detrusor wall thickness

Sonographic measurement of DWT was performed at the anterior bladder wall using a 7.5 MHz linear array (SonoDIAGNOST 360, Philips Medical Systems, Eindhoven, The Netherlands) positioned suprapubically in horizontal direction. At low magnification, anatomical structures of the anterior abdominal wall and the bladder wall were identified (**figure 1**). The digital picture was enlarged to factor 9.8, and the detrusor wall was measured at least at 3 different sites with the integral equipment of the ultrasound system (**figure 2**). Perivesical tissue, mucosa and submucosal tissue appear hyperechogenic; the detrusor appears hypoechogenic [14, 15]. The mean value of those measurements was used for further calculations.
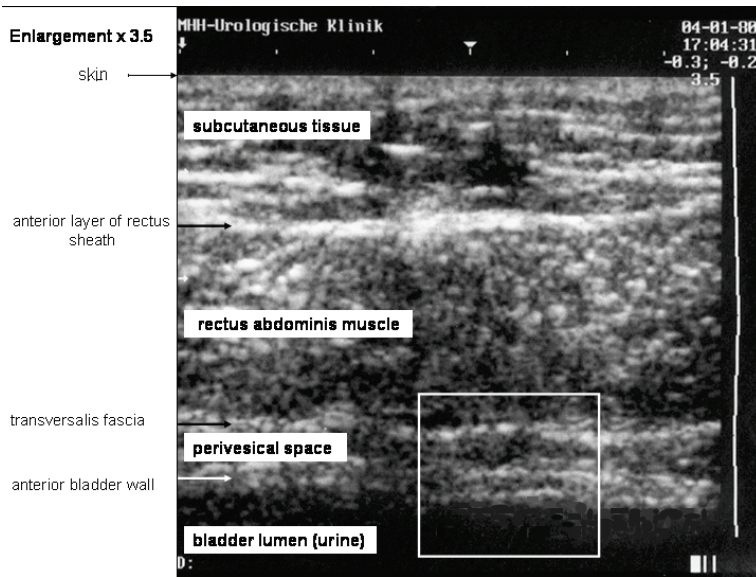
Figure 1: Ultrasound image of the anterior abdominal wall and anterior bladder wall with a 7.5 MHz linear array positioned suprapubically. At low magnification of the ultrasound picture (3.5 x), the anterior bladder wall can be identified.
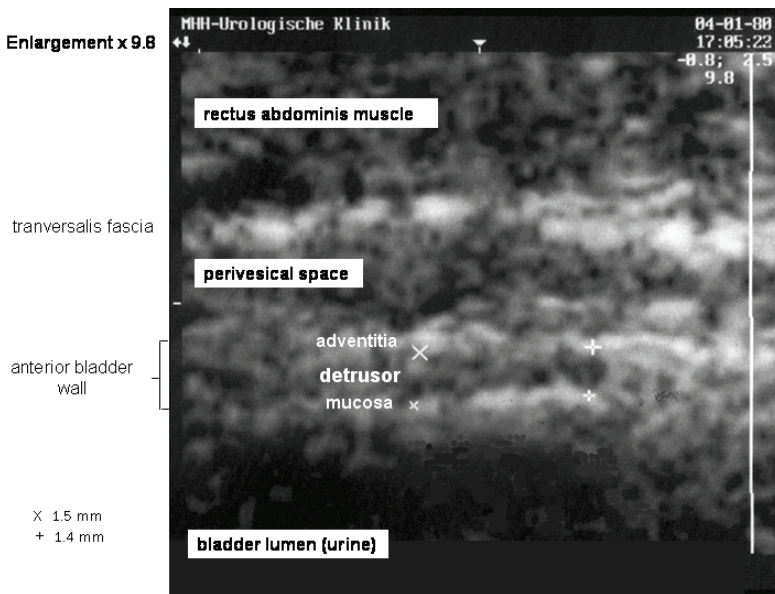
Figure 2: After enlargement of the digital ultrasound image (9.8x), the structures of the anterior bladder wall can be further analysed. Mucosa and adventitia appear hyperechogenic, the detrusor appears hypoechogenic. The distance between the two hyperechogenic lines represents the detrusor wall thickness (DWT) that can be measured with the integrated measuring function of the ultrasound device (in this example 1.4 and 1.5 mm).

In all volunteers with an urodynamic investigation, DWT measurements were performed during cystometry in steps of 50 ml up to a bladder filling of 300 ml and every 100 ml up to the maximum bladder filling. In those volunteers without an urodynamic investigation, DWT was measured at the time when they felt the strong desire to void and would usually empty the bladder.

Statistical evaluation

Non-linear regression analysis was used for evaluation of DWT at different bladder filling volumes. Non-parametric tests were used to show the relationship between DWT and bladder filling, gender or age (Kruskal-Wallis or Mann-Whitney Test). Non-parametric correlation analysis and the Spearman coefficient were used to demonstrate any relationship between DWT and BMI. Differences of means of continuous variables were evaluated with the Student's T-Test and differences of categories were evaluated with the ANOVA-Test. A p-value of 0.05 or less was considered to be significant. The Statistical Package for Social Sciences (SPSS, Version 12.0.2; Chicago, Illinois, USA), and S-PLUS (Version 2000; Seattle, Washington, USA) were used for statistical analyses.

RESULTS

DWT and bladder filling

In all 9 volunteers, DWT decreased rapidly during the first 250 ml of bladder filling. This feature was similar in men (**figure 3a**) and women (**figure 3b**). At a bladder filling of 50 ml, DWT varied between 2.2–4.4 mm in men and 2.5–4.4 mm in women. At a bladder filling of 250 ml, DWT was 1.4 mm in men and between 1.4-1.5 mm in women. After 250 ml of bladder filling, DWT decreased only slightly until the maximum bladder filling. DWT at maximum bladder filling was between 1.3-1.4 mm in men and between 0.9-1.4 mm in women. Comparisons of DWT between different bladder fillings revealed that there were no significant differences of DWT between bladder fillings of ≥ 250 ml (p>0.05, Mann-Whitney Test). DWT between 200 and 250 ml of bladder filling was still significantly different (p=0.008, Mann-Whitney Test), whereas DWT between 250 and 300 ml of bladder filling did not show a statistical difference anymore (p=0.139, Mann-Whitney Test).

If bladder filling volume was converted to percentage of bladder capacity, DWT decreased rapidly during the first 40-50% of bladder capacity. Thereafter, DWT decreases only slightly until maximal bladder capacity. The characteristic of DWT with increasing bladder capacity was similar in both men (**figure 4a**) and women (**figure 4b**).
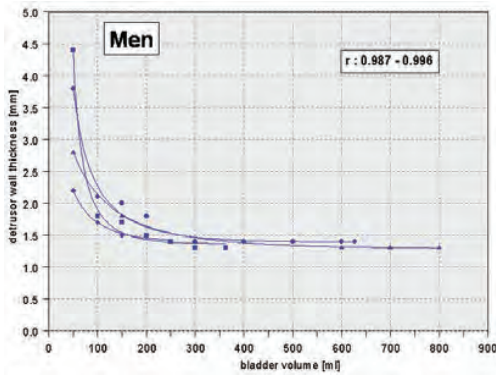
Figure 3a: DWT in relation to bladder filling in healthy adult men. Each line represents the measurements of one man. During the first 250 ml of bladder filling, DWT decreases continuously but, thereafter, remains almost stable until maximum bladder filling. No significant differences of DWT were found at a bladder filling volume ≥ 250 ml.
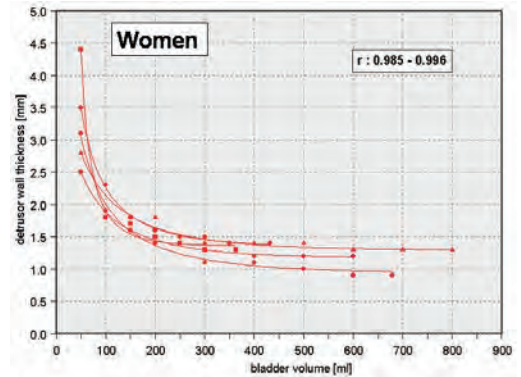
Figure 3b: DWT in relation to bladder filling in healthy adult women. Each line represents the measurements of one woman. Similar to men, DWT decreases during the first 250 ml. After 250 ml of bladder filling, DWT stays almost stable and does not show significant differences compared to DWTs at higher bladder fillings.
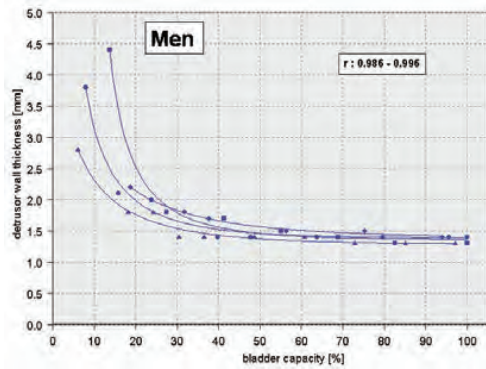
Figure 4a: DWT in relation to bladder capacity in healthy adult men. Each bladder filling volume of men was converted to percentage of bladder capacity. DWT decreases quickly at low bladder capacity but, thereafter, remains almost stable until maximum bladder capacity.
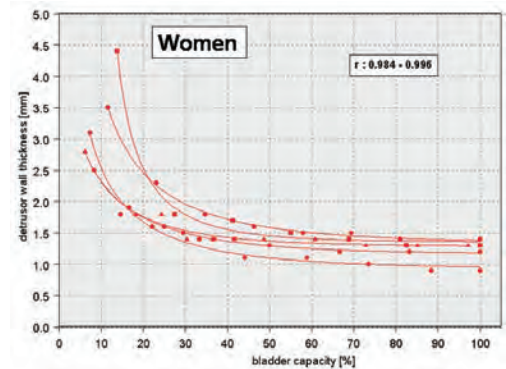
Figure 4b: DWT in relation to bladder capacity in healthy adult women. Similar to men, DWT decreases at low bladder capacity quickly but, thereafter, stays almost stable until maximum bladder capacity.

DWT and gender

DWT was measured in 25 male and 30 female volunteers with a full bladder only. Men were measured with a bladder filling volume of 400 ± 131 ml and women with a bladder filling volume of 423 ± 137 ml (p=0,361, T-Test). DWT varied between 1.2–1.6 mm in men and 1.1–1.6 mm in women. Median DWT in males (1.4 mm; 25-75% percentiles 1.33-1.5 mm) was significantly thicker than in females (1.2 mm; 25-75% percentiles 1.2-1.31 mm; p<0.001, Mann-Whitney Test; **figure 5**).

DWT and age

Male and female volunteers were evaluated separately in order to avoid the influence of the gender on DWT. Both men and women were divided into 3 different age groups comparing volunteers between 15-20, 21-30 and 31–40 years of age. Bladder filling at the time of DWT measurement was not significantly different between the age groups (389–436 ml; p=0.547, ANOVA). DWT between the different age groups of men (p=0.421, Kruskal-Wallis Test) or women (p=0.98, Kruskal-Wallis Test) did not show any significant differences (**figure 6**).
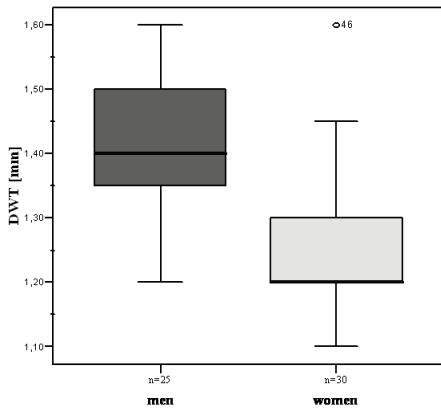
Figure 5: DWT in men and women. DWT was significantly greater in healthy male volunteers than in female volunteers (p<0.001). Each box shows 50% of the measurements of one group; the black line in the box represents the median value of the measurements. The distances from the median value to the upper or lower edges of the box represent the 25% or 75% percentiles. The line at the top of the box reaches to the maximum measurement and the line at the bottom of the box to the minimum measurement.
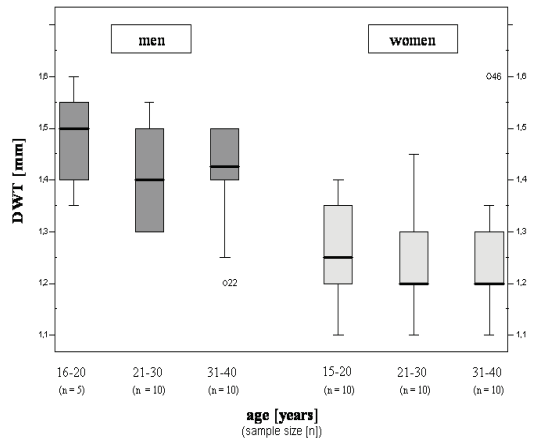
Figure 6: DWT of male and female volunteers of different ages. Each gender group was divided in 3 different age group (15-20, 21-30, and 31-40 years). No significant differences were found between the different life intervals (p>0.05).

DISCUSSION

The bladder wall and the different layers of the bladder can be imaged very well using ultrasound technology. Schoor et al. first demonstrated in rabbits that bladder wall thickness can be measured with an ultrasound device accurately [16]. Later, other study groups used ultrasound technology in men with BPH [6, 9, 15, 17, 18] and in children with non-neurogenic bladder dysfunction [19] to prove thickening of the bladder wall due to BOO as well as in women to discriminate between stress and urge urinary incontinence [10, 20]. Until now, only 5 studies have investigated bladder or detrusor wall thickness in healthy children [14, 21-23] or healthy adults [18]. DWT of non-obstructed BPH-patients or women with urinary incontinence might not reflect DWT in healthy adults accurately and, therefore, should be measured in group of healthy individuals. Because only the detrusor adapts to the increased workload in patients with BOO, Oelke et al. proposed to measure DWT only in order to receive more detailed information about the bladder muscle and the state of muscle decompensation [9]. This was the reason why we measured detrusor instead of bladder wall thickness of healthy adults in this study. Similar approaches were made in children [7, 19, 21, 22].

Measurements of DWT were performed at the anterior bladder wall using a 7.5 MHz linear array. It has been reported that all parts of the bladder (anterior, posterior and lateral walls as well as the trigone and dome) have the same thickness in one individual [15, 21]. Therefore, the anterior bladder wall is a reliable location to receive information about DWT. The depth of penetration of the ultrasound waves as well as the resolution of the ultrasound image is frequency dependent: the higher the ultrasound frequency, the better the resolution but, however, the lower the penetration of the ultrasound waves in the tissue [24]. 2.5 or 3.5 MHz ultrasound probes penetrate deeper into the tissue than a 7.5 MHz probe but give less resolution and image quality at the anterior bladder wall. The anterior bladder wall of a full bladder in adults is located approximately 4-8 cm below the skin and, thus, can be imaged with a 7.5 MHz ultrasound probe excellently. The distance between the skin and the anterior bladder wall depends on the thickness of the subcutaneous fatty tissue and abdominal muscles as well as on the bladder filling. DWT measurements of very thick or muscular individuals might be difficult but, however, was not a problem with any volunteer in this study. Structures deeper than the anterior bladder wall (such as the dorsal parts of the lateral wall or the posterior bladder wall) appear with less resolution and quality. These structures are difficult to image with a suprapubically positioned 7.5 MHz ultrasound array good enough for measurements of DWT. This might be the reason why the measurements of DWT at a low bladder capacity and, therefore, at a higher distance from the ultrasound probe vary so much. The closer the anterior bladder wall moves to the skin and ultrasound probe, the better the quality of the images and the more precise the measurements of DWT become. At a full bladder, the difference between the 3 measurements of one individual was only 0.1 mm which corresponds to the measurement error of the ultrasound device (which is <0.13 mm for a 7.5 MHz ultrasound probe).

This study demonstrated that DWT is dependent on the bladder filling but only at a bladder filling volume of < 250 ml. At a bladder filling of ≥ 250 ml, DWT remains almost stable

maximum bladder filling. No statistical differences between DWT of 250 ml and DWT of 300-800 ml were found. 250 ml of bladder filling corresponded to 31-94 % of the individual bladder capacity. If DWT was measured at a time that the volunteer had a full bladder (100% bladder capacity), bladder filling was always > 250 ml. Therefore, DWT should be determined at a full bladder or bladder filling volume of at least 250 ml. At this state of bladder filling, DWT is not volume dependent anymore and measurements of different volunteers or patient groups become comparable. To our best knowledge, this feature of DWT with increasing bladder filling is the first report in healthy adults. Inadequate bladder filling (< 250 ml) might occur in patients with an overactive bladder. In such cases, there needs to be a different reference value for DWT which, however, can be estimated with the help of the DWT-bladder volume graphs (**figure 3**).

In accordance with our findings, Hakenberg et al. described a significant negative correlation between bladder volume and bladder wall thickness in healthy men and women as well as in symptomatic patients with BPH [18]. However, this result was obtained in a group analysis of 488 individuals in whom bladder wall thickness was measured in each individual at a single but varying bladder filling volume. In newborns and children up to 13 years of age, measurements of DWT with varying bladder volumes demonstrated a similar characteristic to that of our study [22, 23]. Because of the increasing bladder size with increasing age of children, DWT was correlated with bladder capacity. The feature of detrusor wall thinning with increasing bladder capacity was very similar in children from 0-1.9, 2-6.9 and 7-13 years of age and also similar to the findings of our study [22].

Our study also proved a significant difference of DWT between healthy men and women. The difference of DWT between the genders was 0.2 mm. Hakenberg et al. also found a significant difference between men and women but did not correct the measurements for bladder filling volume [18]. Yamazaki et al. investigated 238 neonates and found a bladder wall thickness of 1.38 mm in females and 1.63 mm in males [23]. Müller et al. also found a significant difference of DWT at the anterior bladder wall between the sexes [22]. This study evaluated 79 boys and 71 girls between 0.04 and 13.1 years of age and found a gender difference of 0.2 mm. According to the available data, it seems to be necessary to evaluate DWT in men and women separately. A thicker detrusor wall in males might reflect the greater voiding resistance of the male urethra which is longer and passes through the prostate.

In order to evaluate the influence of the age on DWT, we divided men and women in 3 different age groups each (15-20, 21-30 and 31-40 years). No individual older than 40 years was included in this study because no employee of our department was older than this age. Calculation of DWT was performed in men and women separately in order to exclude gender differences. No significant differences of DWT were found between the different age groups of one gender. With regard to DWT, ageing does not play a significant role in young adults. However, DWT remains to be investigated in healthy and asymptomatic individuals older than 40 years of age. With ageing, the histological components of the detrusor might change which may also result in changes of DWT. In healthy children, DWT increased significantly with increasing age [21, 22]. Even though

boys and girls were not calculated separately in these studies, DWT increased from 1.1 mm in children of 2 years to 1.4 mm in children of 16 years [21]. Differences of DWT between different age groups of children might reflect the growth of the urethra and development of the prostate in young men. In young adults however, this growth is completed and no physiological changes should appear after puberty.

BMI does not have an influence on DWT. No analysis of this factor has been done so far. BMI was used to investigate the influence of the body constitution and to make the higher weight as well as height in men comparable with women. This study included volunteers of all body constitutions and BMI (18.4 – 37.1 kg/m^2). The average values for BMI of different age and gender groups as well as the correlation between BMI and DWT were not significantly different. Therefore, weight, height, BMI or body constitutions do not have a significant impact on DWT and can be ignored during DWT measurement.

This study aimed to determine the normal DWT in healthy adults. According to our results, DWT at the anterior bladder wall has to be evaluated in men and women separately and with a full bladder or at least with a bladder filling of 250 ml. Under these conditions, measurements are comparable and can be used as reference values for patients. DWT was 1.4 mm in healthy men and 1.2 mm in healthy women. The results of our study are in line with those that were published earlier: In healthy children between 0 and 19 years of age, DWT varied between 1.2 mm [21], 1.3 mm [21], 1.55 mm [14], and 1.38-1.63 mm [23]. In our study, all measurements of DWT in healthy individuals were ≤ 1.6 mm. In a former study of 70 symptomatic BPH-patients, a regression tree analysis showed that a DWT of < 2 mm indicated men without BOO and ≥ 2 mm men with BOO the best [9]. Unobstructed patients of this study had an average DWT of 1.3 mm and patients with equivocal obstruction one of 1.62 mm. Therefore, symptomatic but unobstructed men with BPH do not seem to have a different DWT compared to healthy young adults.

Another study investigated 174 BPH-patients of which 24 patients were urodynamically unobstructed [6]. The mean bladder wall thickness of these unobstructed patients (Schäfer grade 0+1) varied between 3-4 mm and, thus, was thicker than the DWT of healthy volunteers in our study. 3 reasons might be responsible for these differences which underline the necessity to standardize ultrasound measurements of the bladder wall in the future: differences of bladder filling, measurement of bladder or detrusor wall thickness and different ultrasound probes. Manieri et al. inserted a transurethral catheter, filled the bladder with 150 ml and measured the thickness of the anterior bladder wall with a 3.5 MHz ultrasound probe afterwards. Due to the fact that measurements were performed at a lower bladder filling than in our study but bladder wall thickness decreases with increasing bladder filling, it becomes obvious that the values of this study have to be greater than those of our study. Bladder wall thickness should be thicker than DWT because the lengths of the mucosa and adventitia have to be added to the detrusor. On ultrasound images of the bladder wall, the mucosa and adventitia appear hyperechogenic. However, the adventitia cannot always be discriminated from the perivesical tissue which is hyperechogenic as well, especially when using an ultrasound probe with a frequency of 3.5 MHz (which has a resolution of approximately 0.3 mm). Placement of the

measurement marker in the perivesical tissue would indicate a thicker bladder wall. In contrast, the detrusor appears hypoechogenic and, thus, can be discriminated from the inner and outer hyperechogenic layers of the bladder wall accurately [15]. Furthermore, the thickness of the mucosa or adventitia could be affected by other factors (such as infection or cancer) which would make the measurement unreliable for determination of the BOO or incontinence. Therefore, measurements of DWT with a 7.5 MHz ultrasound array seem to be more accurate and reliable than measurements of bladder wall thickness with a 3.5 MHz array.

With catheterization and retrograde filling of the bladder with a certain amount of fluid, the ultrasound measurement of DWT becomes invasive [6]. With measurements at a full bladder, catheterization and filling of the bladder are not necessary anymore. Our technique, therefore, provides a rationale for a non-invasive measurement which appears to be one of the major advantages compared to an (invasive) urodynamic evaluation.

CONCLUSIONS

Our study, for the first time, demonstrated the relationship between DWT and bladder filling, gender, age and BMI in healthy adults. DWT decreases with increasing bladder filling volume only during the first 250 ml but remains stable at a higher bladder filling. According to our results, it is crucial to compare measurements at the same state of bladder filling and, therefore, the degree of bladder filling should be indicated in all studies in the future. Measurements of DWT at ≥ 250 ml of bladder filling should be used to show the influence of a disease on the detrusor. Healthy men have a significantly greater DWT than women and, thus, have to be evaluated separately. The age and BMI of the volunteer have no significant influence on DWT. In order to judge DWT in patients correctly, measurements should be compared with DWT values of healthy individuals.

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Chapter 5

Increase in Detrusor Wall Thickness Indicates Bladder Outlet Obstruction (BOO) in Men

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ABSTRACT

Introduction: Bladder outlet obstruction (BOO) leads to enlargement of the detrusor due to hypertrophy of smooth muscle cells and intercellular deposition of connective tissue. The aims of our study were to evaluate detrusor wall thickness at different stages of bladder filling to find the adequate volume for ultrasound measurements, to investigate sonographically detrusor wall thickness in men with BOO and to compare the diagnostic value of detrusor wall measurement with other clinically used predictors of BOO (Q_{max}, Q_{ave}, residual urine, prostate volume).

Methods: Sonographic measurements of detrusor wall thickness were performed at the anterior bladder wall using a 7.5 MHz linear array. Detrusor wall thickness in relation to different filling volumes was measured in healthy adult volunteers. Additionally, 70 patients with LUTS and/or prostate enlargement were investigated by routine work-up, urodynamic investigation and detrusor wall measurement. CHESS-classification was used to determine BOO.

Results: Detrusor wall thickness decreases continuously during filling up to 50% of bladder capacity and then remains constant until 100%. Therefore, detrusor wall measurements were performed in patients at maximum capacity only. Mean detrusor wall thickness for unobstructed (n=14), equivocal (n=23) and obstructed patients (n=33) were 1.33, 1.62 and 2.4 mm, respectively (p<0.001). With increasing CHESS-letters and CHESS-numbers detrusor wall thickness increased likewise (p<0.001). The positive predictive value of detrusor wall measurement (95.5% for a cut-off value of ≥2 mm) was superior to all other predictors investigated.

Conclusions: Detrusor wall thickness increases dependent on the extent of BOO. Both, constrictive and compressive BOO lead to increase of detrusor wall thickness. 95.5% of men with a detrusor wall thickness ≥2 mm have BOO. Measurement of detrusor wall thickness can be used as a screening test to detect BOO.

INTRODUCTION

Benign prostatic hyperplasia (BPH), bladder neck sclerosis, urethral valves or urethral strictures can cause mechanical bladder outlet obstruction (BOO). In experimental animals, bladder weight increases after partial ligation of the urethra due to increase of detrusor wall thickness. Bladder weight increases 3- to 5-fold in rats [22] and 5- to 6-fold in rabbits [19] within 2 weeks after partial ligation of the urethra (initial stage). Afterwards, bladder mass as well as detrusor pressure remain almost constant, and the bladder is able to empty completely or at least up to 80% of volume compared to untreated animals (compensated stage). After a variable time (in rabbits 2 weeks to 6 months) bladder weight increases, additionally, bladder emptying becomes incomplete and detrusor contractility decreases (decompensated stage). Because of the clear onset of BOO, strict differentiation between initial, compensated and decompensated stage is only possible in experimental animals. In contrast, in men BPH and BOO develop slowly. Despite this difference morphological and functional changes of the detrusor are similar in men with BOO. Microscopic investigations of detrusor specimen in men and animals with urodynamically proven BOO showed hypertrophy of smooth muscle cells and increased intercellular deposition of collagen and elastic fibers [8,9]. The more severe the level of decompensation, the greater is the increase of bladder mass [14]. With decompensation of the detrusor, bladder compliance decreases progressively [14,20].

Kojima et al. [16-18] were the first authors who used ultrasound devices to calculate bladder weight as an indicator for BOO. The bladder weight estimated by ultrasound was up to 4-fold higher in males with BOO than in males without BOO [17]. Since bladder weight is a constant factor in each man at the time of investigation, evaluation of ultrasound estimated bladder weight works independently from filling volume. Manieri et al. [21] measured bladder wall thickness only. The authors demonstrated a significant enhancement of bladder wall thickness with increasing BOO in patients with BPH. With a static filling volume of 150 ml in every patient, a bladder wall thickness of 5 mm or more identified 87.5% of the obstructed and a bladder wall thickness of less than 5 mm 63.3% of the non-obstructed males. However, it remains unknown at what filling volume bladder wall thickness should be measured. Furthermore, all current studies used bladder wall thickness instead of detrusor wall thickness. Since the detrusor is the only part of the bladder, which shows adaptive enlargement due to BOO, detrusor wall thickness is more adequate to investigate. The aims of our study were to:

1.   evaluate sonographically detrusor wall thickness at different filling volumes of the bladder

2.   find out the adequate filling volume for detrusor wall measurement

3.   investigate sonographically detrusor wall thickness in men with different grades of BOO

4.   compare the diagnostic value of detrusor wall measurement with other clinical predictors of BOO (uroflowmetry, residual urine, prostate volume).

PATIENTS, MATERIAL and METHODS

Four healthy adult male volunteers aged between 16 and 72 years (mean: 45.5 years) were studied for evaluation of detrusor wall thickness at different filling volumes of the bladder. These males had no urinary symptoms, no history of urinary tract surgery and physical as well as neurological examinations were inconspicuous. Normal bladder emptying was proven by uroflowmetry; sonographically none of the volunteers had residual urine. During urodynamic investigation sonographic measurement of the detrusor was performed at the anterior bladder wall with a 7.5 MHz linear array (SonoDIAGNOST 360, Philips™) positioned suprapubically in horizontal direction. At low magnification anatomical structures of the anterior abdominal wall and bladder wall were identified. The digital picture was enlarged to factor 9.8, and the detrusor wall was measured at least at two different sites with the integral equipment of the ultrasound system. Perivesical tissue, mucosa and submucosal tissue appear hyperechogenic; the detrusor appears hypoechogenic [17]. The mean value of those measurements was used for further calculation. Detrusor wall thickness was measured in steps of 50 ml up to a filling volume of 300 ml and in steps of 100 ml up to maximum filling volume. Pressure-flow-analysis did not indicate obstruction in any volunteer.

Between February and September 1999 every male patient (n=70) with LUTS and/or prostate enlargement all suspicious of BOO was recruited from our outpatient department for evaluation of detrusor wall thickness in men with different grades of BOO. The age of the patients varied between 42 and 82 years (mean: 63 years). All patients with prior urinary tract or pelvic surgery, prostate carcinoma, diabetes mellitus, neurological history or neurological deficit were excluded from the study. At their first visit all participants completed the International Prostate Symptom Score (IPSS) questionnaire. Body weight as well as height was documented and the body-mass-index (weight [kg]/height [m]^2) was calculated. Afterwards, prostate volume was measured by transrectal ultrasound. Free uroflowmetry and residual urine were recorded at least twice, all patients had a voiding volume of more than 100 ml (mean: 216 ml). The measurement with the higher value of Q_{max} and Q_{ave} was used for further calculation. The patient characteristics at baseline are listed in **Table 1**. Free uroflowmetry was performed at least twice; the measurement with the higher value of Q_{max} and Q_{ave} was used for further calculation.

Computer-urodynamic investigation (Ellipse, Andromeda™) was performed in all volunteers and patients. After insertion of 6 F transurethral and 10 F transrectal H_2O-catheters under sterile condition, the bladder was filled with physiologic saline solution of 37°C at a filling rate of 25 ml per minute. During cystometry and pressure-flow-analysis intravesical and intrarectal pressures as well as pelvic floor EMG were recorded simultaneously, detrusor pressure was calculated by subtracting intrarectal from intravesical pressure. Methods, definitions and units conform to the standards recommended by the International Continence Society [2,10]. Detrusor wall thickness was measured at the end of the first cystometry, the obstruction grade of the patient was unknown so far. The ultrasound system and the method of detrusor wall measurement were the same as described earlier. Immediately after detrusor wall measurement, pressure-flow-analysis was performed. CHESS-classification was used to determine BOO [11]. Field A1 was considered as non-obstruction, fields A2 and B1 as equivocal and all other fields as different grades of obstruction. Cystometry and pressure-flow-measurements were recorded at least twice. All data of the measurement with the lowest degree of obstruction were digitally stored and used for further statistical calculation.

Table 1: Characteristics of all patients (n=70) participating in this study. All patients received an IPSS-questionnaire, the amount of all symptoms (questions 1-7), of obstructive (questions 1+3+5+6) and of irritative symptoms (questions 2+4+7) are listed. Prostate volume was measured by transrectal ultrasound.

	Minimum	Maximum	Mean ± SD
Age [years]	42	82	63 ± 10.4
Height [cm]	160	190	174.6 ± 6.2
Weight [kg]	54	120	77.3 ± 12.6
Body-Mass-Index [kg/m^2]	18.7	37.9	25.3 ± 3.7
Prostate volume [ml]	12	120	38.6 ± 21.4
IPSS-total score	2	29	14.4 ± 7.2
IPSS-obstructive symptoms	0	20	7.7 ± 5.1
IPSS-irritative symptoms	0	15	6.7 ± 3.9
Q_{max} (uroflowmetry) [ml/s]	2.7	32.2	10.8 ± 6.3
Q_{ave} (uroflowmetry) [ml/s]	1.5	20.7	5.9 ± 3.9
Voided volume (uroflowmetry) [ml]	104	591	216 ± 107
Residual urine [ml]	0	650	147 ± 140

In order to evaluate detrusor wall thickness at different filling volumes of the bladder non-linear regression analysis using a 3-parameter logistic model was performed. The data of the sonographic detrusor wall measurement at maximum bladder filling, uroflowmetry, residual urine, prostate volume and of the urodynamic investigation in patients with suspected BOO were calculated statistically by correlation analysis (Spearman), analysis of variance (ANOVA) and T-Test. A p-value of 0.05 or less was considered as significant. Sensitivity, specificity, negative and positive predictive values for detection of BOO (determined by pressure-flow-analysis) were calculated for detrusor wall thickness, maximum and average urinary flow of free uroflowmetry, residual urine as well as for prostate volume. Receiver Operating Characteristic (ROC) curves were used to visualize the association between urodynamically proven BOO and measured predictors. Afterwards, the Area Under the Curve (AUC) for each predictor was calculated to determine the strength of association. An AUC of 0.5 was considered as no association and an AUC of 1.0 as strong association. The Statistical Package for Social Sciences (SPSS, Version 9.0), Number Cruncher Statistical System (NCSS, Version 2000) and S-PLUS (Version 2000) were used for statistical analyses.

RESULTS

In volunteers, detrusor wall thickness decreases continuously during the first 200 - 300 ml of bladder filling. Thereafter, detrusor wall thickness remains constant up to maximum bladder filling. Because maximum bladder filling was reached at different filling volumes (246 - 800 ml), graphs for detrusor wall thickness at different percentages of bladder capacity were drawn for the same volunteers afterwards. Detrusor wall thickness decreases continuously during the first 50% of bladder capacity. Between 60 - 100% of bladder capacity detrusor wall thickness remains stable. In patients with suspected BOO, detrusor wall thickness was therefore measured at maximum bladder capacity, regardless of filling volume.

In pressure-flow-analyses, 14 patients (20%) were unobstructed, 23 patients (32.9%) were equivocal and 33 patients (47.1%) obstructed. Detrusor wall thickness for the 3 groups is shown in **figure 1**. Mean detrusor wall thickness for unobstructed, equivocal and obstructed patients was 1.33 mm (95%-CI: 1.17 - 1.48), 1.62 mm (95%-CI: 1.48 - 1.76) and 2.4 mm (95%-CI: 2.12 - 2.68), respectively. Six patients with severe obstruction (B4 or D2-4 according to CHESS-classification) had a detrusor wall thickness of more than 3 mm (**figure 2**). Maximum enhancement of detrusor wall thickness was 4.7 mm in a patient with D4 obstruction. Mean detrusor wall thickness varied significantly between unobstructed and obstructed patients as well as equivocal and obstructed patients ($p<0.001$). However, there was no significant difference of detrusor wall thickness between unobstructed and equivocal patients ($p=0.349$). With increasing CHESS-letter (**figure 3**) and increasing CHESS-number (**figure 4**) detrusor wall thickness increased in the same manner ($p<0.001$). Mean detrusor wall thickness between each CHESS-letter and each CHESS-number also varied significantly ($p<0.05$). Dividing the CHESS-board into 4 squares, there was a significant difference of detrusor wall thickness between the squares (**figure 5**, $p<0.001$). Direct comparison of squares revealed a significant difference of mean detrusor wall thickness between all squares ($p<0.05$) except squares 3 and 4 ($p=0.998$).
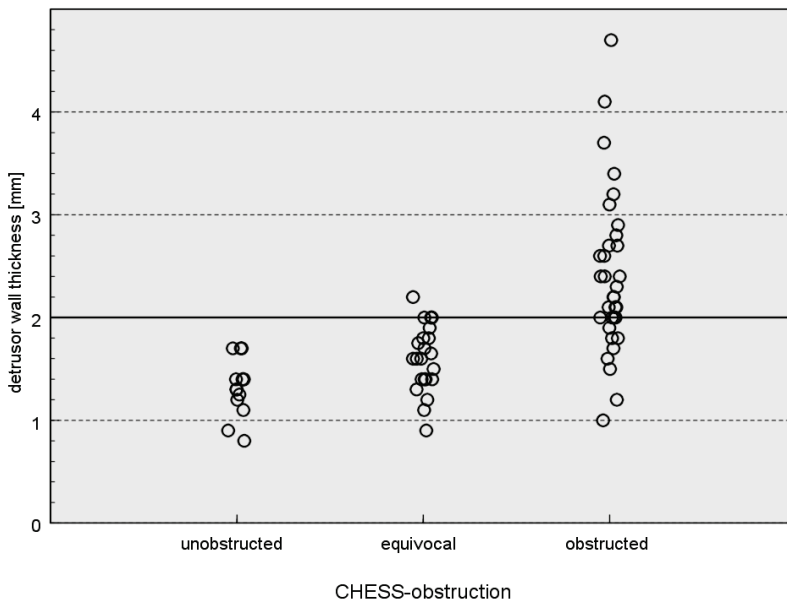
Figure 1: Detrusor wall thickness of patients without obstruction (n=14), equivocal obstruction (n=23) and obstruction (n=33) according to CHESS-classification. The mean detrusor wall thickness varied significantly between unobstructed and obstructed as well as equivocal and obstructed patients ($p<0.001$).
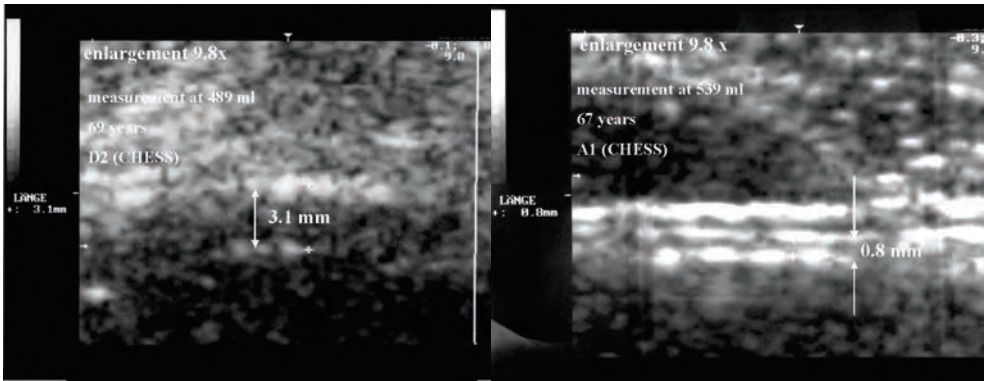
Figure 2: Sonographic measurement of detrusor wall thickness in a patient with severe obstruction (D2 according CHESS-classification, left image) compared to a patient without obstruction but detrusor hypocontractility (A1 according CHESS-classification, W_{max} 2.7 W/m^2, right image). Both patients experienced recurrent urinary retention and were clinically classified as obstructed previously.
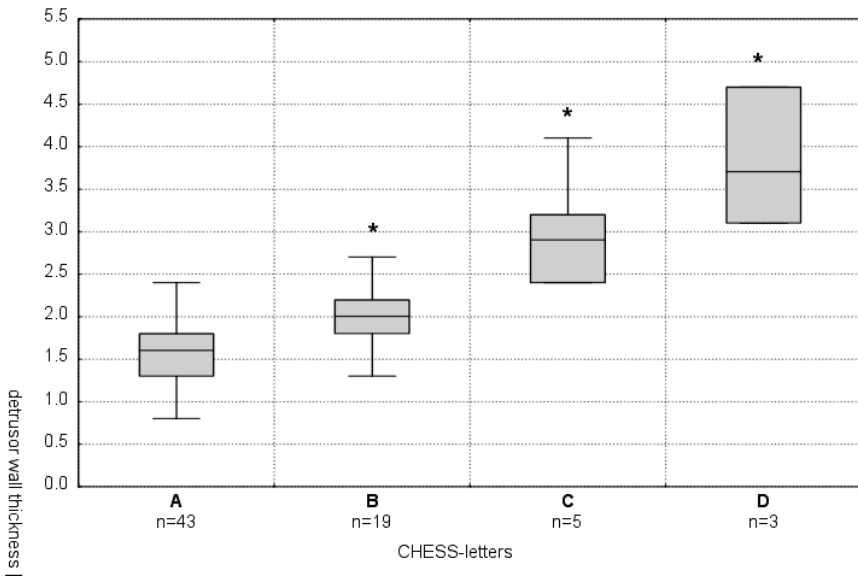
Figure 3: Relationship between detrusor wall thickness and different CHESS-letters. In box-plot-imaging, each box represents 50% of the measurements. The black line in the box represents the median value of measurements. The lines beginning at the top and bottom of the box are drawn to the maximum or minimum measurements. The edges of each box mark the 25th and 75th percentiles. With increasing CHESS-letter detrusor wall thickness increased likewise (p<0.001). Comparing letter A with all others, the mean detrusor wall thickness between CHESS-letters was significantly different (p<0.05, *).
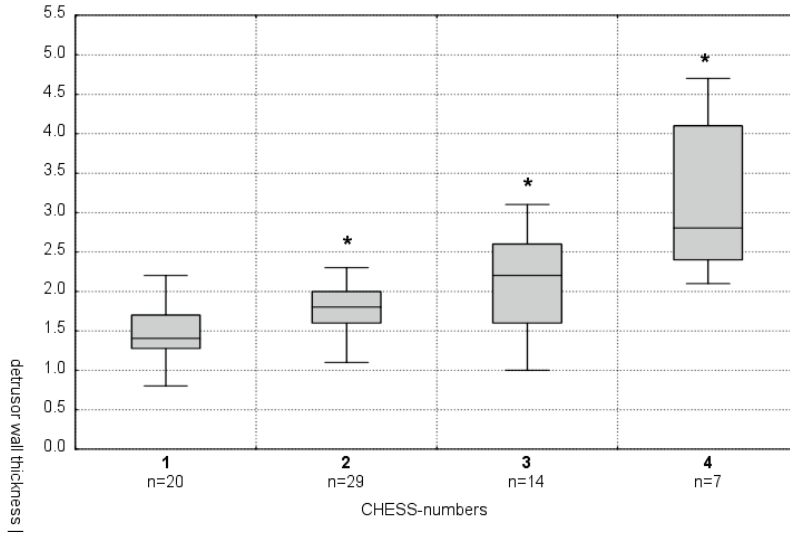
Figure 4: Relationship between detrusor wall thickness and different CHESS-numbers. With increasing CHESS-number the detrusor wall thickness increased in the same manner (p<0.001). Comparing CHESS-number 1 with all others, the mean detrusor wall thickness between CHESS-numbers was significantly different (p<0.05, *).
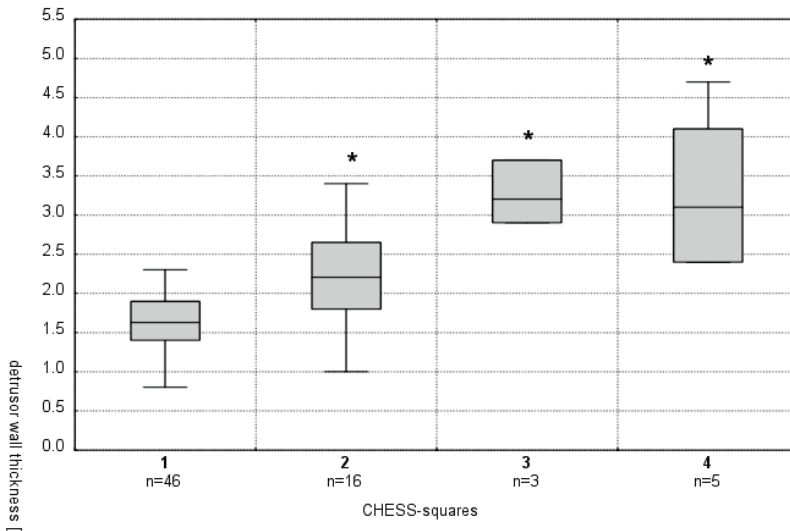
Figure 5: Relationship between detrusor wall thickness and CHESS-squares. Square 1 (A1, A2, B1, B2) represents unobstructed men, square 2 (A3, A4, B3, B4) constrictive obstruction, square 3 (C1, C2, D1, D2) compressive obstruction and square 4 (C3, C4, D3, D4) the combination of constrictive and compressive obstruction. Detrusor wall thickness between the squares varied significantly (p<0.001). Comparison of square 1 with other squares revealed that the mean detrusor wall thickness of squares 2 to 4 was significantly different (p<0.05*). However, no statistical difference was found between squares 3 and 4 (p=0.998).

No significant difference for any parameter was found between unobstructed and equivocal patients. Therefore, patients without and with equivocal obstruction were combined in one group. This group (n=37) was compared with the obstructed patients (n=33, **table 2**). Significant differences between the groups were found for the IPSS-score, maximum urinary flow (Q_{max}), average urinary flow (Q_{ave}) and voided volume at uroflowmetry, residual urine and detrusor wall thickness (p<0.05). Maximum bladder capacity and prostate volume did not vary significantly between patients with and without obstruction. Furthermore, there was no significant correlation between detrusor wall thickness and age, height, weight and body-mass-index of the patients.

Table 2: Characteristics of patients without (n=37) and with obstruction (n=33). Of all clinical parameters and measurements (beside pressure-flow-data) only IPSS-score, Q_{max}, Q_{ave} and voided volume, residual urine as well as detrusor wall thickness varied significantly between the groups. Bladder capacity was not statistically different between unobstructed and obstructed patients.

	Bladder Outlet Obstruction		p-value
	NO (mean ± SD)	**YES** (mean ± SD)	
Age [years]	61.2 ± 11.9	65.1 ± 8.2	0.122
Height [cm]	175.2 ± 6.2	173.9 ± 6.1	0.379
Weight [kg]	77.2 ± 13.8	77.4 ± 11.4	0.954
Body-Mass-Index [kg/m^2]	25.1 ± 3.9	25.6 ± 3.5	0.579
Prostate volume [ml]	32.3 ± 12.8	44.5 ± 26.1	0.07
IPSS-symptomscore	11.8 ± 6.9	17.1 ± 6.7	**0.003**
IPSS-obstructive symptoms	6.0 ± 4.7	9.4 ± 5.1	**0.01**
IPSS-irritative symptoms	5.7 ± 3.8	7.7 ± 3.8	**0.046**
Q_{max} (uroflowmetry) [ml/s]	13.6 ± 7.1	7.7 ± 3.4	**<0.001**
Q_{ave} (uroflowmetry) [ml/s]	7.5 ± 4.7	4.3 ± 2.1	**<0.001**
Voided volume (uroflowmetry) [ml]	250 ± 126	179 ± 95	**0.01**
Residual urine [ml]	109 ± 119	190 ± 152	**0.016**
First sense (cystometry) [ml]	185 ± 110	192 ± 113	0.768
Bladder capacity (cystometry) [ml]	451 ± 199	407 ± 198	0.354
Pdet open [cm H$_2$O]	35.0 ± 17.1	76.9 ± 45.4	**<0.001**
Pdet qmax [cm H$_2$O]	40.9 ± 12.8	77.7 ± 38.1	**<0.001**
Pdet max [cm H$_2$O]	55.9 ± 17.5	94.0 ± 41.6	**<0.001**
Pdet close [cm H$_2$O]	29.3 ± 13.0	50.8 ± 30.6	**0.001**
W_{max} [W/m^2]	11.2 ± 6.5	12.1 ± 5.4	0.511
Detrusor wall thickness [mm]	1.51 ± 0.34	2.4 ± 0.8	**<0.001**

Evaluation of the diagnostic values of detrusor wall thickness and other clinically used predictors of BOO (Q_{max}, Q_{ave}, residual urine, prostate volume) indicated that detrusor wall thickness was the only parameter, which could detect BOO adequately (**table 3**). A detrusor wall thickness of ≥2 mm at maximum bladder filling has a high positive predictive value for the detection of BOO (95.5%), whereas the positive predictive values of the other predictors were low (52.5 - 55.9%). On the other hand, the negative predictive values of Q_{max} (100%) and Q_{ave} (80%) were superior to those of detrusor wall thickness, residual urine and prostate volume (71.4 - 75%). ROC-analysis revealed that detrusor wall thickness is the best parameter to detect BOO, having an

area under the curve (AUC) of 0.882 (**figure 6**). Q_{max} (AUC 0.779), Q_{ave} (AUC 0.765), residual urine (AUC 0.699) and prostate volume (AUC 0.626) had a minor impact of association.

Table 3: Predictive values of detrusor wall thickness and other clinically used predictors of BOO. Detrusor wall thickness ≥ 2 mm at maximum bladder filling has the highest positive predictive value for detection of BOO.

	Obstructed/ unobstructed	Positive predictive value	Negative predictive value	Sensitivity	Specificity
Detrusor wall thickness	≥2 / <2 mm	95.5%	75%	63.6%	97.3%
Q_{max}	<15 / ≥15 ml/s	55%	100%	100%	25%
Q_{ave}	<8 / ≥8 ml/s	52.5%	80%	93.6%	22.2%
Residual urine	>50 / ≤50 ml	55.3%	72.7%	81.3%	43.2%
Prostate volume	>20 / ≤20 ml	55.9%	71.4%	90.5%	25%
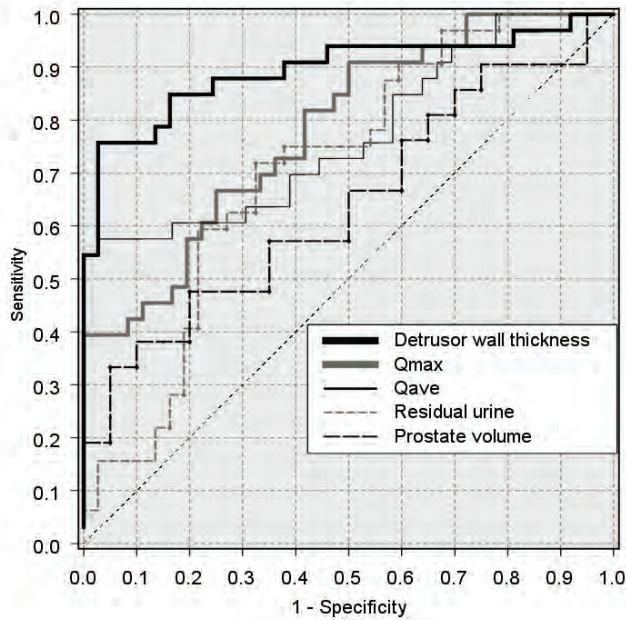
Figure 6: ROC-analysis for detrusor wall thickness and other clinically used predictors of BOO. The area under the curve (AUC) of detrusor wall thickness (0.882), Q_{max} (0.779), Q_{ave}e (0.765), residual urine (0.669) and prostate volume (0.626) indicates that detrusor wall thickness is the best predictor for BOO.

DISCUSSION

Clinical BPH is characterized by prostate enlargement (BPE), lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO). Patients with bladder neck sclerosis or urethral strictures often complain about the same symptoms. LUTS are often bothersome and will guide men to seek professional care. In the Olmsted-Country-Study, 13% of men aged between 40 and 49 years and 28% of men 70 years or older complained about moderate to severe urinary symptoms [7]. Among symptomatic males, BOO was determined urodynamically in up to 83% [23]. In the ICS-BPH-Study, 60% of investigated males had urodynamically proven BOO [26]. In our series of patients each elderly symptomatic male with or without BPE and suspected BOO was recruited between February and September 1999. To our knowledge, this is the only study in which, without exception, each male was investigated by urodynamic work-up during a defined period. BOO was confirmed by pressure-flow-analysis in only 47% of these males and seems to be less frequent than reported in other studies. However, no data exist on BOO in asymptomatic elderly men. Men without LUTS can still have BOO (silent obstruction) which may alter bladder or kidney function and lead to renal failure. The prostate volume is approximately 20 ml after puberty and remains stable until the 5th decade [5]. Even though the prostate volume increases in most men afterwards due to development of BPH, no clear correlation has been found between prostate size and BOO in other studies [6, 27]. In our series of patients, we also found no significant correlation between prostate volumes of obstructed and unobstructed patients. Because of the inconsistent relations between prostate size and obstruction [6, 27], LUTS and obstruction [3, 4] as well as LUTS and prostate size [4, 13] each parameter of the BPH-complex should be evaluated separately.

Detection and quantification of prostate enlargement by digito-rectal examination or (transrectal) ultrasound measurement, and of LUTS by history or IPSS-questionnaire are quick and simple. However, evaluation of BOO is more difficult. Currently, only pressure-flow-analysis of urodynamic investigation can determine obstruction in an adequate way. Thus, all other methods to determine BOO have to be compared with pressure-flow-data. In clinical routine, uroflowmetry (Q_{max} and Q_{ave}), postvoid residual urine and prostate volume are used to detect BOO. All tests have repeatedly shown to be poor predictors of obstruction (**table 4**). The data of our current study confirm these results. Basic urodynamic knowledge indicates that uroflowmetry and residual urine can only diagnose the existence, but not the cause of voiding dysfunction. Therefore, urodynamic investigation remains the gold standard for detection of voiding dysfunction and BOO. However, urodynamic investigation is time consuming, expensive and invasive. Severe complications during or after urodynamic investigation were reported in up to 19% including urinary retention, gross haematuria, urinary tract infection and fever [15]. Even though we cannot confirm this high morbidity, some side effects may still occur. Therefore, we looked for an alternative test to detect BOO. The test should be quick, simple, cheap and without morbidity.

Table 4: Diagnostic values of Q_{max}, Q_{ave}, residual urine and prostate volume for predicting BOO, literature review.

	obstructed/ unobstructed	Positive predictive value	Negative predictive value	Sensitivity	Specificity
Q_{max}	≤10 / >10 ml/s [25]	75%	50%	69%	57%
	<10 / ≥10 ml/s [26]	70%	54%	47%	70%
	≤15 / <15 ml/s [25]	71%	63%	90%	31%
	<15 / ≥15 ml/s [12]	88%	42%	97%	17%
	<15 / ≥15 ml/s [26]	67%	42%	82%	38%
	<15 / ≥15 ml/s [24]	71%	62%	90%	30%
Q_{ave}	<10 / ≥10 ml/s [24]	69%	75%	97%	16%
Residual urine	≥50 / <50 ml [1]	86%	25%	69%	48%
Prostate volume	>50 / ≤50 ml [25]	78%	36%	34%	80%
	≥30 / <30 ml [12]	77%	23%	52%	90%

Sonographic evaluation of bladder wall thickness in order to calculate bladder weight was first performed by Kojima et al. [16-18]. The authors resembled the bladder as a sphere or ellipsoid, measured bladder wall thickness as well as diameters of the bladder sonographically and subtracted the inner volume ($V_{inner} = \frac{4}{3} \times \pi \times r^3$) from the outer volume of the bladder ($V_{outer} = \frac{4}{3} \times \pi \times r'^3$), r´ being inner radius + bladder wall thickness. Initial experiments with cadaverous bladders revealed no statistical differences between bladder wall thickness of the anterior or lateral bladder walls, trigone or dome [17]. Calculation of bladder weight is an elegant method as it works independently from bladder filling. Kojima et al. demonstrated that in men the bladder weight increases with BOO in the same manner as shown previously in experimental studies with animals. Ultrasound estimated bladder weight was up to 4-fold higher in men with BOO than men without BOO [17]. Using a cut-off value of 35 grams for calculated bladder weight, 88-94% of obstructed males were diagnosed correctly [16, 17]. To calculate the bladder weight it was necessary to resemble the bladder as a sphere or ellipsoid, which, in fact, is a simplification of the true situation. As the bladder fills with urine, the bladder wall expands in that direction where the lowest pressure exists, whereas it is impressed at places where other organs (e.g. bowel) have contact with the bladder. Therefore, ultrasound imaging of the bladder rarely shows a sphere or ellipsoid. Furthermore, little deviations in measuring the radius or bladder wall thickness will make great differences in calculation of bladder weight as distances in the volume formula are used in the third potency. For these reasons calculated bladder weight has an erroneous factor of up to 22.5% compared to actual bladder weight [17]. In addition, calculation of bladder weight is too complicated for routine use. Manieri et al. [21] measured bladder wall thickness only after catheterisation and filling the bladder with 150 ml of fluid. With a static filling volume of 150 ml, 87.5% of men with BOO had a bladder wall thickness ≥5 mm (positive predictive value) and 63.3%

of men without BOO had a bladder wall thickness <5 mm (negative predictive value). The reasons for filling the bladder with 150 ml are unclear. Additionally, as the detrusor is the only part, which shows enlargement due to BOO, it remains unclear, why the entire bladder wall was measured. The detrusor wall can be visualized and measured excellently during sonographic investigation. In contrast, discrimination between subserosal tissue of the bladder wall and fatty tissue of the perivesical space is often difficult. Furthermore, mucosa thickness could be influenced by other factors (e.g. infection, carcinoma). These were the reasons why we measured detrusor wall thickness only. By using a 7.5 MHz linear array the entire anterior bladder wall was visualized without refraction and falsification at the lateral sides, the picture was enlarged to maximum magnification (9.8x), and detrusor wall thickness was measured exactly with the integral equipment of the ultrasound device (accuracy in measurement 0.1 mm). The detrusor wall thickness was measured at least at two different sites of the anterior bladder wall, and the mean value was used for further calculation. The greatest differences between the measurements of one volunteer/patient were 0.2 mm. Each measurement took less than 1 minute of time.

Inspired by the methods of both study groups we first investigated detrusor wall thickness in relation to various bladder fillings in healthy adult volunteers. Our initial experiments showed that detrusor wall thickness decreases continuously during the first 200 - 300 ml of bladder filling. Thereafter, the detrusor wall thickness remains constant up to maximum bladder filling. As every male has his own physiologic bladder capacity, the plateau of detrusor wall thickness is reached dependent on the individual filling volume. By measuring with a static filling volume of 150 ml, the bladder is almost empty in one man, but almost full in another. If filling volume is related to bladder capacity each volunteer reaches the plateau at approximately 50% regardless of actual bladder filling. Therefore, measurements of detrusor wall thickness at 60 to 100% of bladder capacity will be identical. For this reason we measured detrusor wall thickness at full bladder in patients with suspected BOO. With this strategy we were able to compare the effect of BOO on detrusor wall thickness between different patients. Retrospective comparison of bladder filling between patients with and without BOO revealed no statistical difference at the time of measurement (407 vs. 451 ml, p=0.354).

For determination of bladder-outflow obstruction CHESS-classification was used. This classification is a two-dimensional model using footpoint and curvature of passive urethral resistance relation (PURR) of the pressure-flow-plot [11]. Both parameters of PURR have shown to be independent predictors of BOO [11, 28, 29]. According to CHESS-classification, CHESS-letters increase with increasing PURR-footpoint and CHESS-numbers with increasing PURR-curvature. Every combination of footpoint and curvature is possible. For practical reasons, footpoint boundaries of 35, 55 and 80 cm H_2O and curvature boundaries of 0.15, 0.5 and 1.25 cm $H_2O/(ml/s)^2$ were established [11]. Of the 16 fields, only A1 was considered as non-obstruction, A2 and B1 as equivocal obstruction and all other fields (n=13) as different grades of obstruction. Measurements of the detrusor revealed a significant increase in detrusor wall thickness with increasing CHESS-letters as well as CHESS-numbers (p<0.001, ANOVA). Mean detrusor wall thickness between each

CHESS-letter and each CHESS-number varied significantly (p<0.05, T-Test). According to the classification system used, high CHESS-letters with low -numbers represent compressive obstruction and low CHESS-letters with high -numbers constrictive obstruction. By dividing the CHESS-board into 4 squares, square 1 (A1, A2, B1, B2) represents unobstructed men, square 2 (A3, A4, B3, B4) constrictive obstruction, square 3 (C1, C2, D1, D2) compressive obstruction and square 4 (C3, C4, D3, D4) the combination of constrictive and compressive obstruction. Mean detrusor wall thickness for the squares were significantly different (p<0.001, ANOVA) indicating that both compressive as well as constrictive obstruction lead to enhancement of detrusor mass.

For simplicity, we divided men in unobstructed, equivocal and obstructed only (similar to ICS-classification). The mean detrusor wall thickness was significantly greater in obstructed (2,4 mm) compared to unobstructed (1.33 mm) or equivocal males (1.62 mm). Using a threshold of ≥ 2 mm for obstruction, 95.5% of males were diagnosed correctly as obstructed. Only 3 patients with equivocal obstruction - 2 of them with a detrusor wall thickness of 2 mm and a third patient with 2.2 mm - were misdiagnosed as obstructed (false-positive). These patients were among the first males in the series of 70 and were misdiagnosed because of lack of experience with the new technique. We believe that with increasing experience measurements of detrusor wall thickness becomes more precise. On the other hand, 8 patients with urodynamically proven BOO had a detrusor wall thickness <2 mm. All of those patients had a minor degree of obstruction (A3 or B2 according to CHESS-classification) and were misdiagnosed as unobstructed (false-negative). Significant sphincter activity of patients during pressure-flow-studies or increased resistance due to the indwelling catheter may have led to the urodynamic diagnosis of obstruction. However, none of the unobstructed men and none of the patients with severe obstruction were misdiagnosed by detrusor wall measurement. Assessment of the diagnostic values of detrusor wall thickness, uroflowmetry, residual urine and prostate volume showed that only measurements of detrusor wall thickness could detect BOO adequately. Using a threshold of ≥ 2 mm for obstruction, measurements of detrusor wall thickness have a positive predictive value of 95.5%. All other tests for detection of BOO are less reliable (positive predictive values 52.5 - 55.9%). On the other hand, detrusor wall thickness <2 mm can only detect 75% of the unobstructed males. Using a threshold ≥ 15 ml/s, Qmax is the best parameter for exclusion of BOO. Q_{max} has a negative predictive value of 100% in this current study. High-flow obstruction is a rare condition, which was not seen in any of our patients, but could reduce the negative predictive value of Q_{max}. In the ICS-BPH-Study, high-flow obstruction was even diagnosed in 18% of the patients [26]! Comparison of sensitivity and specificity revealed that detrusor wall measurement is the best test to distinguish between obstructed and unobstructed patients. The area under the (ROC) curves was high for detrusor wall measurement (AUC 0.882), but lower for Q_{max}, Q_{ave}, residual urine and prostate volume (AUC 0.779-0.626). Similar results for bladder wall thickness, Q_{max} and Q_{ave} were described earlier [21, 24].

Up to now, no screening test for the detection of BOO is available. Measurements of detrusor wall thickness can detect BOO adequately. Catheterisation of the patient is no longer necessary, as measurements of detrusor wall thickness are always performed with a full bladder. If there is any doubt about a full bladder, conventional ultrasound investigation can clarify the situation. If a man has detrusor-hyperactivity or urge-incontinence, the bladder should contain at least 50% of the maximum bladder capacity for detrusor wall measurement. Even if a man does not complain of LUTS, detrusor wall measurement is a useful tool to detect silent obstruction. In patients with urinary retention, pressure-flow recordings are impossible. Measurement of detrusor wall thickness could clarify whether retention is caused by BOO or detrusor-hypocontractility. History and physical examination are important in order to exclude patients with neurogenic disorders, because increase of detrusor wall thickness was also seen in males and females with myelomeningocele in combination with low-compliance bladders. If detrusor wall thickness is <2 mm in symptomatic men with BPH, urodynamic investigation is still useful to determine the cause of voiding dysfunction. Once BOO is diagnosed, further examinations are necessary to evaluate the origin of obstruction (prostate enlargement, bladder neck sclerosis or urethral strictures). Additional studies have to be performed in children with urethral valves to determine if the young detrusor wall reacts likewise.

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Chapter 6

Diagnostic Accuracy of Non-invasive Tests to Evaluate Bladder Outlet Obstruction in Men: Detrusor Wall Thickness, Uroflowmetry, Post-void residual urine, and Prostate volume

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ABSTRACT

Objectives: The aim of this prospective study was to compare the diagnostic accuracy of detrusor wall thickness (DWT), free uroflowmetry, post-void residual urine, and prostate volume (index tests) with pressure-flow studies (reference standard) to detect bladder outlet obstruction (BOO) in men.

Methods: During a two-year period, men above 40 years of age, with lower urinary tract symptoms and/or prostatic enlargement had the following tests: ultrasound measurements of DWT, free uroflowmetry (Q_{max}, Q_{ave}), post-void residual urine, and prostate volume. Pressure-flow studies were used to divide obstructed from non-obstructed bladders.

Results: 160 men between 40-89 years of age (median: 62 years) were included in the study. 75 patients (46.9%) had BOO according to pressure-flow studies. The results of all investigated index tests were significantly different between obstructed and non-obstructed men. DWT was the most accurate test to determine BOO: the positive predictive value was 94%, specificity 95%, and the area under the curve of ROC-analysis 0.93. There was an agreement of 89% between the results of DWT measurement and pressure-flow studies.

Conclusions: Measurements of DWT can detect BOO better than free uroflowmetry, post-void residual urine or prostate volume. In clinical routine, DWT measurements can be used to judge BOO non-invasively.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common benign diseases in men that can lead to benign prostatic enlargement (BPE), lower urinary tract symptoms (LUTS) and/or bladder outlet obstruction (BOO). One third to one half of men with histological signs of BPH also has a prostate volume of more than 25 ml (BPE), and up to 28% have moderate to severe LUTS [1,2]. The majority of men seek medical help because of bothersome LUTS [3]. BOO was detected in about 60% of the symptomatic and 52% of the asymptomatic men with BPH [4,5]. No clear association between LUTS, BPE and BOO has been found so far [6,7]. Therefore, each parameter of this disease has to be evaluated separately. Quantification of prostate size by digito-rectal examination or (transrectal) ultrasound measurement, and LUTS by history or IPSS-questionnaire is quick and simple. Evaluation of BOO is more difficult. Until now, only pressure-flow studies are able to determine BOO accurately. However, pressure-flow studies are invasive, expensive, and time consuming. In clinical routine, measurements of free uroflowmetry, post-void residual urine, and prostate volume are used to estimate BOO in men with BPH.

Studies in artificially obstructed animal bladders revealed a significant enlargement of the bladder wall due to smooth muscle cell hypertrophy, fibrocyte hyperplasia, and collagen deposition in the detrusor [8]. These experimental findings were confirmed in humans with BOO [8,9]. The detrusor wall can be visualized with ultrasound technology very well and, as a consequence, measurements of detrusor wall thickness (DWT) have been used lately to diagnose BOO in men with BPH [10-12]. In a recently published meta-analysis of all available non-invasive tests for BOO evaluation, ultrasound measurements of DWT or bladder weight were the only promising methods with a good evidence base to support their use in entering clinical practice after further evaluation [13]. Until now, no study has prospectively investigated the diagnostic accuracy of DWT measurements together with other clinical routine tests in one group of patients and no study has been conducted according to the recommendations of the STARD initiative (Standards for Reporting of Diagnostic Accuracy) [14]. Therefore, the aim of our study was to prospectively evaluate the diagnostic accuracy of DWT measurements, free uroflowmetry, post-void residual urine, and prostate volume (index tests) in one group of patients with clinical BPH in order to diagnose BOO defined by pressure-flow analysis (reference standard).

METHODS

Patients and study design

From January 1st 2000 until December 31st 2001, each new patient with clinical BPH, an age of 40 years or older, LUTS and/or a prostate volume over 25 ml, was recruited from the urological outpatient department of the University Hospital Hannover. All men with α–blockers, 5α-reductase inhibitors, urinary retention, prior lower urinary tract or pelvic surgery, evident prostate carcinoma or a neurological deficit were excluded from the study. Everyone who met the inclusion criteria was willing to participate in the prospective study, which was conducted according to the regulations of the local ethics committee. Study design, terminology and presentation of the results followed the

recommendations of the STARD initiative (**figure 1**) [14]. All tests were performed at the urological outpatient department of the University Hospital Hannover during two visits.
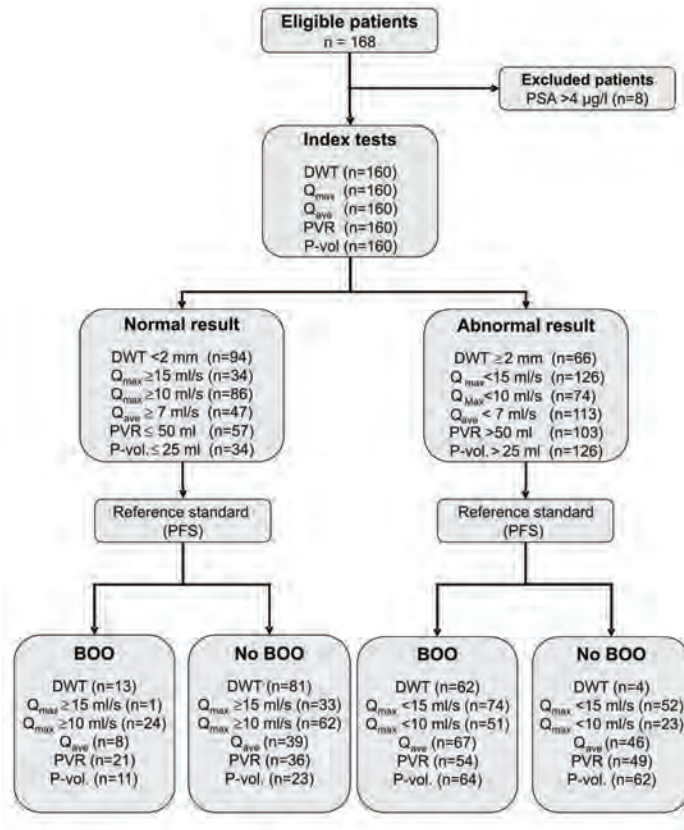
Figure 1: Study design and distribution of test results. DWT = detrusor wall thickness, Q_{max} = maximum urinary flow, Q_{ave} = average urinary flow, PVR = post-void residual urine, P-vol. = prostate volume, PFS = pressure-flow study, BOO = bladder outlet obstruction

Index tests

At the first visit, a comprehensive patient history was taken and the International Prostate Symptom Score (IPSS) questionnaire was used to quantify LUTS. Digito-rectal examination was performed to exclude men with palpable prostate cancer and to judge the prostate size for study inclusion in asymptomatic men (IPSS ≤7). All men with a PSA-concentration of more than 4 µg/l were excluded from the study (n=8). Participants who met the inclusion criteria were asked to drink water until they felt the strong desire to void. With a full bladder, DWT was measured at the anterior bladder wall using a 7.5 MHz linear ultrasound array [9]. The technique of DWT measurement has been described earlier [9, 11, 15]. With a magnification factor of the ultrasound picture of 9.8, the

adventitia, detrusor and mucosa were identified (**figure 2**). Afterwards, all men performed a free uroflowmetry and the maximal (Q_{max}) as well as average urinary flow (Q_{ave}) was quantified. Post-void residual urine was measured immediately after voiding with a 3.5 MHz curved ultrasound array, and prostate volume was determined with a 7.5 MHz transrectal ultrasound probe (all ultrasound measurements were done by M. O. with SonoDIAGNOST360, Philips Medical Systems, Eindhoven, The Netherlands). The baseline characteristics and results after initial evaluation of the patients are listed in t**able 1**.
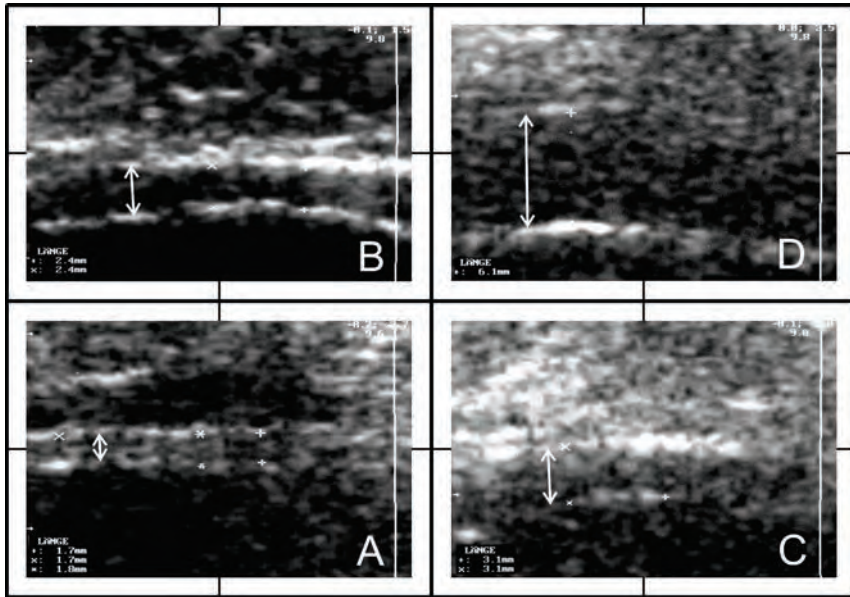
Figure 2: Ultrasound measurements of DWT. The mucosa (lower line) and adventitia of the bladder (upper line) appear hyperechogenic; the hypoechogenic area between those lines represents the detrusor and DWT (↕). The figure shows DWT measurements of 4 BPH patients (all 9.8 enlarged). **A:** No BOO (A1, DWT 1.7-1.8 mm), **B - D:** Varying degrees of BOO (B: B3 obstruction with a DWT of 2.4 mm; C: C1 obstruction with a DWT of 3.1 mm; D: D4 obstruction with a DWT of 6.1 mm).

Reference test

At the second visit one to three weeks after initial presentation, all patients had a computer-urodynamic investigation (Ellipse, ANDROMEDA Medical Systems, Taufkirchen, Germany) which was performed by experienced residents according to the "good urodynamic practice" standard of the International Continence Society [16]. The investigators of the urodynamic studies were blinded to the results of the index tests. BOO was determined by pressure-flow analysis using the CHESS classification [17]. The fields A1, A2 and B1 were considered as non-obstruction and all other fields as obstruction. Men with obstructed and non-obstructed bladders were divided on the basis of the pressure-flow analysis, which served as the reference standard for BOO.

Table 1: Baseline data of the patients and test results after initial evaluation with non- or minimally-invasive tests

Parameter [unit]	Range	Median (25th – 75th percentile)
Age [years]	40 - 89	62 (59 - 70)
IPSS	2 - 30	15 (10 - 21)
DWT [mm]	0.8 – 8.4	1.7 (1.4 - 2.2)
Bladder filling at DWT measurement [ml]	250 - 1086	407 (304 - 540)
Q_{max} [ml/s]	2.7 – 35.4	10.2 (7.2 - 14.4)
Q_{ave} [ml/s]	1.5 – 20.7	5.1 (3.7 - 7.4)
Post-void residual urine [ml]	0 - 670	100 (30 - 200)
Prostate volume [ml]	12 - 130	35 (28 - 48.5)

IPSS = International Prostate Symptom Score, DWT = detrusor wall thickness, Q_{max} = maximum urinary flow, Q_{ave} = average urinary flow

Statistical analysis

Because the data were unevenly distributed, median values including their 25th and 75th percentiles were calculated for the baseline data of the patients and results of the index tests. The differences in results between index tests and reference test were analyzed with the Mann-Whitney Test. A p-value equal or below 0.05 was considered significant. Positive and negative predictive values, sensitivity, specificity, accuracy, and the likelihood ratios of a positive or negative test result (**table 2**) were calculated for DWT, Q_{max}, Q_{ave}, post-void residual urine, and prostate volume. For the index tests, clinical cut-off values for BOO determination were used and defined before the start of the study [18]. The diagnostic accuracy was also calculated for a cut-off value of Q_{max} <10 ml/s [19]. DWT ≥2 mm served as a cut-off value to detect BOO because a previous study demonstrated that this value most accurately distinguishes between obstructed and unobstructed bladders [11]. Receiver operator characteristic (ROC) curves were produced to visualize, and calculation of the area under the curve (AUC) was used to describe the diagnostic characteristics of the index tests to diagnose BOO. The Statistical Package for Social Sciences (SPSS, Version 12.0.2; Chicago, Ill., USA) was used for the statistical analysis.

Table 2: Definitions of the test indicators used in this study

Test indicator	Definition
positive predictive value (ppv)	proportion of diseased among subjects with a positive test result
negative predictive value (npv)	proportion of healthy among subjects with a negative test result
sensitivity	proportion of a positive test result among diseased
specificity	proportion of a negative test result among healthy
accuracy	proportion of correctly identified subjects
likelihood ratio of a positive test result (LR$^+$)	ratio of a positive test result among diseased to the same result in the healthy, sensitivity/(1-specificity)
likelihood ratio of a negative test result (LR$^-$)	ratio of a negative test result among diseased to the same result in the healthy, (1-sensitivity)/specificity

RESULTS

One hundred sixty men between 40-89 years of age (median: 62 years) participated in this study. 13 men (8.1%) had BPE (>25 ml) without LUTS (IPSS ≤7), 34 men (21.3%) had LUTS (IPSS >7) without BPE, and 113 men (70.6%) had both BPE and LUTS. Based on the pressure-flow analysis, the prevalence of BOO in this study population was 46.9% (75 out of 160). DWT, Q_{max}, Q_{ave}, post-void residual urine, and prostate volume were all significantly different between non-obstructed and obstructed bladders (**table 3**). However, there were no significant differences between age, IPSS value or bladder filling at the time of DWT measurement.

Patient inclusion and distribution of the tests results are shown in **figure 1**. Diagnostic accuracy data are shown in **table 4**. Calculation of the positive predictive values demonstrated that 94% of patients with DWT ≥2 mm had BOO, whereas the other index tests varied between 52-69%. Q_{max} ≥15 ml/s at free uroflowmetry showed the highest negative predictive value which was 97%. Q_{max} with a cut-off value of 15 ml/s had the highest sensitivity (99%) and DWT measurements had the highest specificity (95%). The likelihood ratio of BOO was the best with DWT ≥2 mm and the likelihood ratio of non-obstruction was the best with Q_{max} ≥15 ml/s. There was an 89% agreement between the results of pressure-flow studies and DWT whereas the agreement between pressure-flow studies and all other index tests was maximally 70%.

Table 3: Comparison of men with obstructed or non-obstructed bladders. All parameters but bladder filling at the time of DWT measurement, age and IPSS were significantly different between the two groups.

Parameter [unit]	BOO		p-value
	No Median (25th-75th percentiles)	**Yes** Median (25th-75th percentiles)	
Age [years]	62 (56 - 70)	63 (60 - 70)	0.051
IPSS	14 (10 - 20)	17 (11 - 22)	0.053
DWT [mm]	1.4 (1.3 – 1.7)	2.2 (2.0 – 2.7)	<0.001
Bladder filling at DWT measurement [ml]	414 (301 - 566)	400 (310 - 480)	0.588
Q_{max} [ml/s]	13.1 (9.8 – 17.8)	8.0 (5.3 – 10.3)	<0.001
Q_{ave} [ml/s]	6.4 (4.6 – 9.0)	3.8 (2.8 – 5.6)	<0.001
Post-void residual urine [ml]	70 (20-142)	145 (50-240)	0.001
Prostate volume [ml]	32.9 (22 - 44)	40 (29 - 58)	0.014

IPSS = International Prostate Symptom Score, DWT = detrusor wall thickness, Q_{max} = maximum urinary flow, Q_{ave} = average urinary flow

ROC-analyses of all tests are shown in **figure 3**. The AUC of ROC demonstrated that the measurement of DWT was the best test to detect BOO, with an AUC of 0.93 (95% confidence interval 0.88–0.98). In contrast, measurements of Q_{max} (AUC: 0.84; 95% confidence interval 0.78–0.91), Q_{ave} (AUC: 0.82; 95% confidence interval 0.75–0.89), post-void residual urine (AUC: 0.64; 95% confidence interval 0.55–0.74) and prostate volume (AUC: 0.62; 95% confidence interval 0.52–0.71) were less accurate to detect BOO.
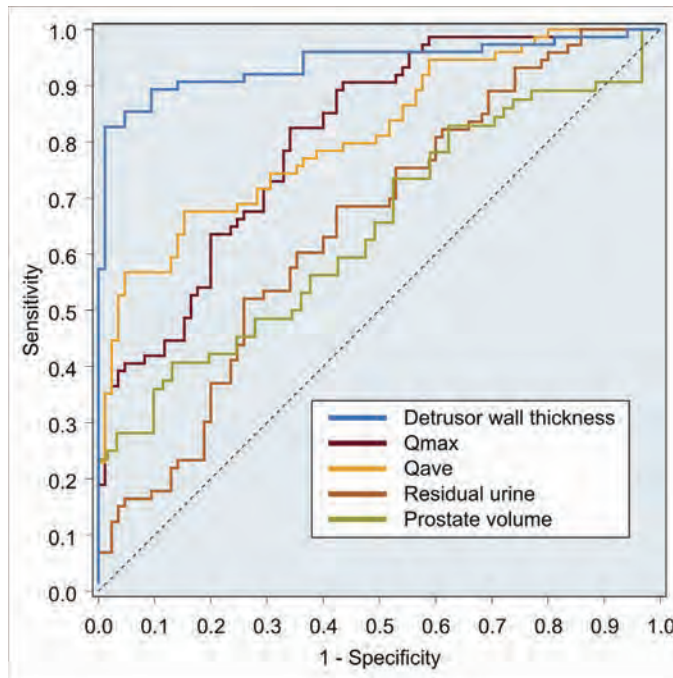
Figure 3: ROC curves of investigated non- or minimally invasive tests commonly used to predict BOO

DISCUSSION

This study showed that the diagnostic accuracy of BOO assessment is better with DWT measurements than with measurements of Q_{max}, Q_{ave}, post-void residual urine, or prostate volume. BOO can be detected with DWT measurements almost as accurately as with pressure-flow studies.

The characteristics of the patients of this study were very similar to those published before [3]. Patients of our study therefore appear to be representative for patients who visit their doctors because of BPH. In patients with BPH, no strict relationship between LUTS, BPE and BOO has been found so far. A recently published article reviewed the morphological and functional changes of the bladder wall in response to BOO, describes comprehensively how mechanical stretch induces gene expression and protein synthesis in the epithelium and smooth muscle cells, and explains how BOO could cause LUTS [20]. It is the policy of the Hannover University Hospital to investigate all men with BPH according to a work-up protocol prior to therapy to clarify the relationship between LUTS, BPE, and BOO. Uroflowmetry, measurements of post-void residual urine and prostate volume as well pressure-flow studies are performed in all patients accordingly. For this study, only DWT measurements were added to the investigational protocol. To avoid evaluation bias, DWT was measured at the beginning of the patient evaluation and pressure-flow studies, the reference standard of BOO evaluation, was performed as the last test, without knowing the results of the previous tests. The time between the index tests and the pressure-flow study appears to be too short to develop BOO in the meantime.

Table 4: Diagnostic parameters of non- or minimally-invasive tests to diagnose BOO in men with BPH. The 95%-confidence interval of the result is listed in brackets.

Parameter	non-obstructive/ obstructive	ppv [%]	npv [%]	sensitivity [%]	specificity [%]	accuracy [%]	LR^+	LR^-
DWT	<2 / ≥2 mm	94 (88 - 100)	86 (79 - 93)	83 (74 - 91)	95 (91 - 100)	89	17.57 (6.71 – 45.98)	0.18 (0.11 – 20.02)
Q_{max}	≥15 / <15 ml/s	59 (50 - 67)	97 (91 - 103)	99 (96 - 101)	39 (28-49)	67	1.61 (1.36 – 1.91)	0.03 (0 – 4.42)
	≥10 / <10 ml/s	69 (58 - 79)	72 (63 - 82)	68 (57 - 78)	73 (63 - 82)	70	2.5 (1.7 – 3.68)	0.44 (0.31 – 3.2)
Q_{ave}	≥7 / <7 ml/s	59 (50 - 68)	83 (72 - 94)	89 (82 - 96)	46 (35 - 56)	66	1.65 (1.34 – 2.04)	0.23 (0.12 – 1.98)
Post-void residual urine	≤50 / >50 ml	52 (43 - 62)	63 (51 - 76)	72 (62 - 82)	42 (32 - 53)	56	1.25 (0.99 – 1.57)	0.66 (0.43 – 1.33)
Prostate volume	≤25 / >25 ml	51 (42 - 60)	67 (51 - 83)	85 (77 - 93)	27 (18 - 36)	54	1.16 (0.99 – 1.37)	0.56 (0.29 – 0.98)

DWT = detrusor wall thickness, Q_{max} = maximum urinary flow, Q_{ave} = average urinary flow, ppv = positive predictive value, npv = negative predictive value, LR^+ = likelihood ratio of positive test result, LR^- = likelihood ratio of negative test result

The reference standard (pressure-flow studies) is considered to be the best available test for the assessment of BOO [14]. Several classification systems were established using varying amounts of information of the pressure-flow plot. The CHESS-classification uses footpoint and curvature of the passive urethral resistance relation because both parameters have shown to be independent predictors of BOO [17,21,22]. In contrast to CHESS, the ICS-classification uses only one point ($P_{detqmax}$) and the Schäfer-classification only two points of the pressure-flow plot ($P_{detminvoid}$ and $P_{detqmax}$) [21]. If a classification system uses only few classes, small changes in urethral resistance may not be detected. Therefore, CHESS appears to be the most precise method to assess BOO. CHESS is an established BOO assessment algorithm that was recommended by the International Continence Society [22].

All tests that aim to measure BOO as well (index tests) have to be compared with the reference standard. The index test that has the highest amount of agreement with the reference test should be preferably used to evaluate BOO non-invasively. Of all investigated index tests of our study, ultrasound measurement of DWT showed the highest accuracy to detect BOO. The results of the current investigation are in line with those of previous studies in which DWT was investigated retrospectively and was not blinded to the results of pressure-flow studies. Our study, however, investigated the diagnostic accuracy of DWT, Q_{max}, Q_{ave}, post-void residual urine, and prostate volume prospectively in one group of patients with clinical BPH. A previous study in which 70 men with BPH were evaluated with the same technique and cut-off values found a positive predictive value of DWT measurements of 95.5% [11]. A recently published study of 102 men with clinical BPH found a positive predictive value of DWT measurements of 89% using a cut-off value of ≥2.5 mm and 100% using a cut-off value of ≥2.9 mm [12]. Both studies demonstrated that the diagnostic accuracy of BOO detection is higher with DWT measurements than with free uroflowmetry, post-void residual urine, or prostate volume. A third study in which bladder wall thickness (instead of DWT) at a bladder filling volume of 150 ml was measured in 174 men with LUTS found a positive predictive value of 88% [10]. Again, sonographic measurement of bladder wall thickness detected BOO more accurately than Q_{max} of free uroflowmetry. However, other parameters than bladder wall thickness and Q_{max} were not evaluated in this study. The diagnostic accuracy of DWT or bladder wall thickness measurements is remarkable in all studies. Despite differences in study design and BOO evaluation algorithms, the AUC of ROC analysis varied between 0.88 and 0.93. The results come close to the reference standard indicating that sonographic measurements of DWT or bladder wall thickness are accurate enough to detect BOO in clinical routine.

All other tests that are used in clinical routine to diagnose BOO minimally- or non-invasively were less accurate to detect BOO. It has been repeatedly demonstrated for these tests that they are poor predictors of BOO [23]. The results of the current study confirm these findings. Abnormal measurements of free uroflowmetry or post-void residual urine can only detect voiding dysfunction without indicating BOO specifically. Post-void residual urine or reduced values of Q_{max} or Q_{ave} can be caused by BOO, detrusor underactivity or a combination of both. Changing the cut-off value of Q_{max} from 15 to 10 ml/s helps to identify more men with BOO. However, the detection rate of BOO increased from 58% to 69% only which is clearly lower than with DWT measurements.

Ultrasound measurement of DWT is a new method to diagnose BOO. This technique is based on the results of studies with experimental animals in which the detrusor thickened and bladder weight increased after induction of BOO [8]. Bladder wall hypertrophy can be visualized and measured with an

ultrasound device in animals and humans [10, 11]. For precise measurements of DWT it is necessary to use high frequency ultrasound arrays (7.5 MHz or higher) and ultrasound devices with an enlargement function of the ultrasound picture [15]. Even small differences of DWT can be evaluated and patients can be classified correctly with this technical support. A study with human cadaverous bladders revealed no significant differences between the anterior, posterior or lateral bladder walls, trigone or bladder dome [9]. Therefore, evaluation of DWT is possible at any part of the bladder but, however, resolution of the ultrasound picture with a suprapubically positioned 7.5 MHz ultrasound array is usually only sufficient at the anterior bladder wall. Increase of DWT correlates very well with BOO and the grade of BOO [9-12]. After BOO relief, bladder hypertrophy is reversible within 4-12 weeks [24]. All studies indicate that bladder wall thickening is associated with BOO. Although the performance of sonographic DWT measurements is operator-dependent, it has been shown that these measurements are accurate, reliable, quick, and simple. Though not investigated in our study, intraobserver variability is ≤5.1% and interobserver variability between 4-12.3% [10, 12]. Measurements of the bladder or detrusor wall are usually done in less than 2 minutes and can be performed by either urologists or radiologists.

A standardized technique of DWT measurement is essential to judge BOO. The technique used in our study is non-invasive and, therefore, without morbidity. It was demonstrated earlier that DWT depends only on gender, bladder filling, and BOO grade [11, 15]. DWT decreases continuously with increasing bladder filling only up to 250 ml but, thereafter, remains stable until maximum bladder capacity. DWT was measured in our study when the participant reported to have a full bladder. Determination of bladder volume showed that all men had a bladder filling of ≥250 ml at the time of DWT measurement. A bladder filling less than the required volume could appear in patients with detrusor overactivity. In these patients, a DWT cut-off value of ≥2 mm cannot be used to diagnose BOO. Therefore, bladder volume should be determined before DWT measurement. Furthermore, DWT measurements can only diagnose BOO, but are not able to detect other abnormalities during bladder filling or voiding. It remains unknown in men with BPH if DWT is also influenced by detrusor overactivity, incontinence, low-compliance, dysfunctional voiding, or detrusor underactivity. Urodynamic studies are therefore still indicated to clarify LUTS in BPH patients without increased DWT or those in whom bladder filling of ≥250 ml cannot be achieved.

CONCLUSIONS

This study showed that sonographic measurements of DWT are an accurate alternative for pressure-flow measurements to assess the presence of BOO. DWT measurements show a higher diagnostic power than measurements of Q_{max}, Q_{ave}, post-void residual urine, or prostate volume. DWT measurements appear to be suitable for the routine use in patients with clinical BPH and suspicion of BOO. The results of this study could help to assess BOO non-invasively in all men and could be useful to evaluate the value of BOO at assessment and during treatment of BPH patients in the future.

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Chapter 7

Manual versus Automatic Bladder Wall Thickness Measurements:

A Method Comparison Study

Matthias Oelke, Charalampos Mamoulakis, Dirk T. Ubbink, Jean J. de la Rosette, Hessel Wijkstra

ABSTRACT

Aims: To compare the accuracy and repeatability of conventional ultrasound bladder wall thickness (BWT) measurements with automatically obtained BWT measurements by the BVM 6500 device.

Methods: Adult patients with lower urinary tract symptoms, urinary incontinence, or postvoid residual urine were urodynamically assessed. During two subsequent cystometry sessions the infusion pump was temporarily stopped at 150 and 250 ml bladder filling to measure BWT with conventional ultrasound and the BVM 6500 device. For each method and each bladder filling repeatability and variation was assessed by the method of Bland and Altman.

Results: Fifty unselected patients (30 men, 20 women) aged 21-86 years (median 62.5 years) were prospectively evaluated. Invalid BWT measurements were encountered in 2.1-14% of patients when using the BVM 6500 vs. 0% with conventional ultrasound (significant only during the second measurement at 150 ml bladder filling). Mean difference in BWT values between the measurements of one technique was minus 0.1 to 0.01 mm. Measurement variation between replicate measurements was smaller for conventional ultrasound and the smallest for 250 ml bladder filling. Mean difference between the two techniques was 0.11-0.23 mm and did not differ significantly. The BVM 6500 device was not able to correctly measure BWTs above 4 mm.

Conclusions: Both BWT measurements are repeatable and agree with each other at 150 ml and 250 ml bladder filling. However, conventional ultrasound measurements have a smaller measurement variance, which is the smallest for 250 ml bladder filling, can measure BWT in all patients and are also able to measure greater BWTs.

INTRODUCTION

Ultrasound bladder wall thickness (BWT) measurements became popular for measuring, quantifying, and monitoring bladder outlet obstruction in men [1-5], for detecting detrusor overactivity in women [6-8], and for assessing urethral valves or abnormal urethral function in children [9,10]. Bladder outlet obstruction due to benign prostatic hyperplasia or urethral valves, detrusor overactivity, or dysfunctional voiding/detrusor-sphincter-dyssynergia is associated with an increased BWT, which can be quickly detected by ultrasound technology. Ultrasound BWT measurements offer the advantage of detecting non-invasively the bladder wall response to lower urinary dysfunction; thus, avoiding expensive, potentially harmful, time- and material-consuming urodynamic investigations in these particular patient groups. Additionally, ultrasound BWT measurements might be used for epidemiological or clinical studies, in which large numbers of healthy volunteers or patients can be repeatedly screened and classified without being submitted to invasive urodynamic investigations.

Experienced centers have demonstrated small intra- and interobserver variabilities of conventional ultrasound BWT measurements in the range of ≤5% and 4-12%, respectively [1,4]. However, this experience originates from single centers and remains limited to a small group of investigators. This, together with the fact that the learning curve is not negligible, might hinder new investigators in employing this technique and limit its widespread use [11]. Therefore, a machine for automatic measurements of BWT is desirable. Such a machine was introduced by Verathon® (formerly Diagnostic Ultrasound®; Bothell, WA, USA). BVM 6500 device is a small, light, battery-powered, portable ultrasound machine that aims to measure BWT and bladder volume automatically and accurately at bladder filling volumes between 100 and 400 ml [12]. The suprapubically positioned 3.7 MHz scanner of BVM 6500 produces three-dimensional V-mode® images of the bladder (patented multiple aligned B-mode images of a 120-degree cone) within approximately 10 seconds. The scanned image data has to be transmitted to a server computer in the USA via an internet connection, where the bladder is delineated, the bladder surface area calculated and the distance from the outer layer of the anterior bladder wall to the bladder surface (which is BWT) measured. The scanned images and results (thickness of the anterior wall, bladder volume, and ultrasound-estimated bladder weight) are returned to the sender after approximately two minutes.

It remains to be seen if automatic BWT measurements are accurate and repeatable and, therefore, might replace conventional BWT measurements in the future. We initiated this study to investigate whether automatic BWT measurements with the BVM 6500 device are repeatable, if repeatability depends on bladder filling volume, and if they are comparable with hand-measured values of an experienced investigator using conventional ultrasound machines.

MATERIAL AND METHODS

Patients and study design

Adult male and female patients with an indication for urodynamic investigation in terms of their workup for lower urinary tract symptoms, urinary incontinence, or postvoid residual urine were

asked to participate in this prospective study between April and October 2007. The trial was conducted according to the regulations of the local ethics committee. All patients were fully informed about the study protocol and gave their consent before initiation of the measurements.

Examination protocol

Each patient was placed in the lithotomy position and the bladder was emptied with a 12 F lubricated transurethral catheter by the investigator. A 6 F transurethral, double-lumen catheter was inserted into the bladder and a 10 F single-lumen catheter into the rectum. The empty bladder was confirmed by a suprapubically positioned dynamic 9-4 MHz ultrasound array (iU22; Philips®, Eindhoven, The Netherlands). Afterwards, all patients were transferred to a more convenient sitting position. The bladder was filled with sterile saline solution of 37° C at a bladder filling rate of 25-30 ml/min. Urodynamic investigations (Ellipse, Andromeda, Taufkirchen, Germany) were performed according to the "good urodynamic practice" standards recommended by the International Continence Society [13].

Figure 1: Conventional ultrasound image of the anterior bladder wall using a dynamic 9-4 MHz scanner and an enlargement factor of 8. For bladder wall thickness measurements (↕), the distance from the outer border of the hyperechogenic distal line (mucosa and submucosal tissue) to the outer border of the hyperechogenic proximal line (adventitia) was measured. The hypoechogenic area between the two hyperechogenic lines represents the detrusor.

At 150 ml of bladder filling the infusion pump was temporarily stopped to measure anterior BWT, first with the bladder scan (BS) BVM 6500 (BS_{150A}) and immediately afterwards with the conventional dynamic 9-4 MHz ultrasound (US) scanner (US_{150A}), as previously described (**figure 1**)

[3,14]. The average value of three US measurements at the anterior bladder wall was used for further calculation. BS data were sent to the Verathon[*] central server via a specific internet homepage using a personal login code. In the meantime, the bladder was filled until 250 ml and BWT measurements were repeated (BS_{250A} and US_{250A}). Afterwards the bladder was filled until the patient reported a strong desire to void and a pressure-flow study followed. After the voiding phase, postvoid residual urine volume was measured via the transurethral catheter and the bladder was once more checked for emptiness with the conventional ultrasound array.

The urodynamic investigation was repeated immediately afterwards exactly as described above and ultrasound BWT measurements were performed during the second cystometry at 150 ml and 250 ml again (BS_{150B} and US_{150B}; BS_{250B} and US_{250B}). All measurements were performed by a single experienced urologist (M.O.).

Statistical evaluation

Repeatability of each BWT measurement method from replicated measurements at both bladder filling volumes separately was assessed based on the methodology described by Bland and Altman [15]. For each method and at each specific bladder filling volume the distribution of differences between replicate measurements was plotted against their average. The existence of any systematic difference between replicates, their variation (indicated by mean ± 2 SD), and any possible trend of the distribution of differences across the range of BWT measurements was assessed graphically. Only patients with two valid measurements were included in the analysis. In order to compare the two different methods of BWT measurement at each bladder filling volume separately, and to determine the agreement between them, the same methodology was applied based on valid measurements by both modalities during the first urodynamic investigation only. The one-sample t-test was applied to test whether mean differences between replicates differed from zero. McNemar's test was used to compare the proportions of patients with valid measurements by the same modality at the different bladder filling volumes as well as the proportions of patients with valid measurements by different modalities at the same bladder filling volume. A probability of 0.05 or less (two-tailed) was considered to indicate statistical significance. Variables were generated in Excel for Windows (Microsoft Corporation; Redmond, WA, USA). The data were further processed and analyzed with the Statistical Package for Social Sciences (SPSS, version 15.0 for Windows; Chicago, IL, USA).

RESULTS

Fifty unselected adult patients aged between 21 and 86 years (median age: 62.5 years; male/female: 30/20) submitted to urodynamic investigation were included in the study. Patient characteristics are summarized in **table 1**. All patients reached the bladder filling volume of 150 ml during cystometry. In contrast, three patients did not reach the bladder filling volume of 250 ml.

Table 1: Characteristics of patients who participated in the prospective study. The patients sought help for lower urinary tract symptoms, urinary incontinence, or postvoid residual urine and were randomly selected regardless of age, body-mass index, or urodynamic diagnosis. PVR=postvoid residual urine

		All patients (n=50)	Men (n=30)	Women (n=20)
Age [years] Median (range)		62.5 (21 - 86)	65.0 (32 - 86)	54.5 (21 - 78)
Body-mass index [kg/m^2] Median (range)		26.0 (19.1 - 40.3)	26.0 (19.1 - 36.1)	26.1 (19.5 - 40.3)
Primary Urodynamic Diagnosis	Detrusor overactivity ± incontinence	10	6	4
	Stress urinary incontinence	9	0	9
	Increased bladder sensation	4	1	3
	Bladder outlet obstruction	17	17	0
	Detrusor underactivity	8	6	2
	Dysfunctional voiding and PVR	2	0	2

Valid BWT measurements with conventional ultrasound could be performed during both urodynamic investigations in all 50 patients at 150 ml and in all 47 patients who reached the bladder filling volume of 250 ml. In contrast, the BVM 6500 device failed to deliver a valid measurement after central server evaluation in four patients (8%) during the first measurement at 150 ml and seven patients (14%) during the second measurement at 150 ml. The same happened at 250 ml in one (2.1%) and three patients (6.4%) during the first and second cystometry, respectively. The proportion of patients with valid measurements by each modality at 150 ml did not differ significantly in the first urodynamic investigation (P=0.125), but was significantly higher for conventional ultrasound in the second urodynamic investigation (P=0.016). The respective proportions did not differ significantly at 250 ml (first urodynamic investigation: P=1.0; second urodynamic investigation: P=0.25). No significant differences in patients with valid measurements were detected between 150 ml and 250 ml bladder filling volumes for BS in either urodynamic investigation (first urodynamic investigation: P=0.375, second urodynamic investigation: P=0.125).

Comparison between ultrasound measurements as obtained by the same method

BWT measurement values using conventional ultrasound ranged from 1.1 to 13.5 mm at 150 ml and from 1.2 to 12.6 mm at 250 ml bladder filling, whereas with the BVM 6500 device BWT measurement values ranged from 1.8 to 6.1 mm at 150 ml and from 1.5 to 3.9 mm at 250 ml. There was no statistical difference between mean BWT values when the same ultrasound method was compared during the first or second measurement either at 150 ml or at 250 ml. All differences between repeated measurements were distributed evenly around their mean without any evident trend across the respective ranges of BWT measurements (**figure 2**). Mean differences of replicate measurements were subtle (-0.1 to 0.01 mm). Both modalities were repeatable at both bladder filling

volumes since no systematic differences were observed between replicates. The variation of differences between replicates (mean ± 2 SD) was higher at 150 ml than 250 ml bladder filling with both modalities. However, the variation was generally higher with the BVM 6500 device at both bladder filling volumes compared to the corresponding variation with conventional ultrasound.
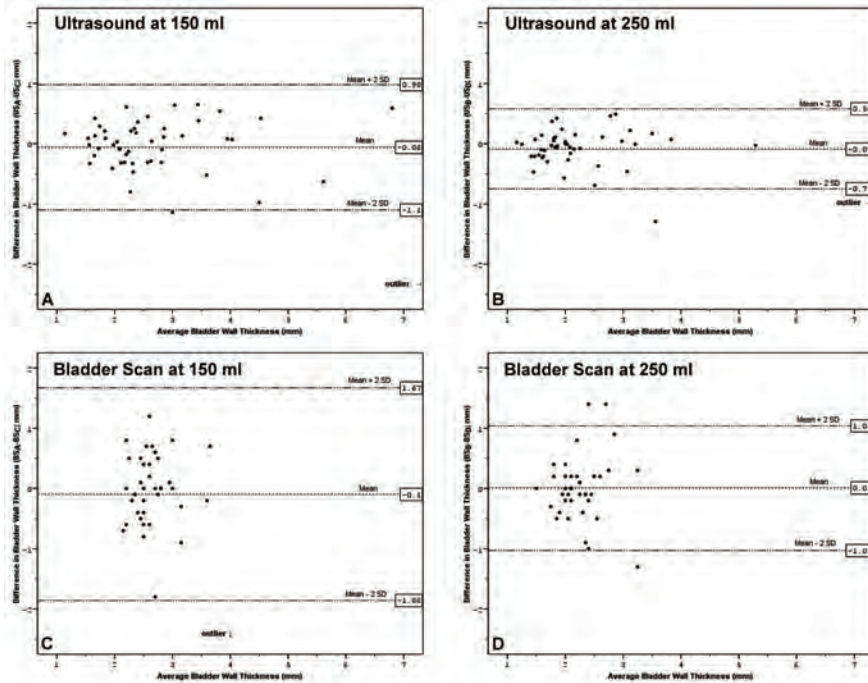
Figure 2: Repeatability of bladder wall thickness measurements: Ultrasound at 150 ml; n=50 replicates **(A)** and 250 ml; n=47 replicates **(B)**, Bladder Scan at 150 ml; n=40 replicates **(C)** and 250 ml; n=43 replicates **(D)**. The mean difference between replicates and their variation (mean ± 2 SD) are indicated by respective lines. 95% CI of the mean (not shown) are -0.21mm to +0.09mm (A), -0.18mm to +0.01mm (B), -0.38mm to +0.18mm (C) and -0.15mm to +0.17mm (D). The presence of one outlier is indicated in A (patient 17), B (patient 17) and C (patient 16). The exact position of each outlier in relation to x, y axes (not shown) is (12.37mm, -2.33mm) in A, (12.08mm, -0.97mm) in B and (4mm, -4.20mm) in C. There is no obvious trend of the distribution of differences across the range of BWT measurements. Both modalities are repeatable at both bladder filling volumes since no systematic differences are observed between replicates; mean differences do not differ significantly from zero (P>0.05). However, repeatability is improved at the bladder filling volume of 250 ml for both modalities (reduced variation).

Abbreviations: US_{150A} = Conventional ultrasound measurement during first urodynamic investigation at 150 ml bladder filling; US_{250A} = Conventional ultrasound measurement during first urodynamic investigation at 250 ml bladder filling; US_{150B} = Conventional ultrasound measurement during second urodynamic investigation at 150 ml bladder filling; US_{250B} = Conventional ultrasound measurement during second urodynamic investigation at 250 ml bladder filling; BS_{150A} = Bladder Scan measurement during first urodynamic investigation at 150 ml bladder filling; BS_{250A} = Bladder Scan measurement during first urodynamic investigation at 250 ml bladder filling; BS_{150B} = Bladder Scan measurement during second urodynamic investigation at 150 ml bladder filling; BS_{250B} = Bladder Scan measurement during second urodynamic investigation at 250 ml bladder filling

Comparison between ultrasound measurements obtained by different methods

Comparison of conventional ultrasound measurements with bladder scan measurements showed that the mean difference (US minus BS) was 0.23 mm at 150 ml and 0.11 mm at 250 ml bladder filling (**figure 3**). Mean differences did not differ significantly from zero (P=0.362 and P=0.662 for bladder filling volumes of 150 and 250 ml, respectively). However, there was a trend towards a higher difference of BWT at higher BWT values which was as high as 11.7 mm and 11.0 mm at 150 ml and 250 ml, respectively (concerning a patient with severe bladder outlet obstruction). Direct comparison of the conventional ultrasound images with automatically obtained images in patients with thicker anterior bladder walls showed that the BVM 6500 device did not capture the entire anterior bladder wall and measured the inner part of the anterior bladder wall only (**figure 4**).
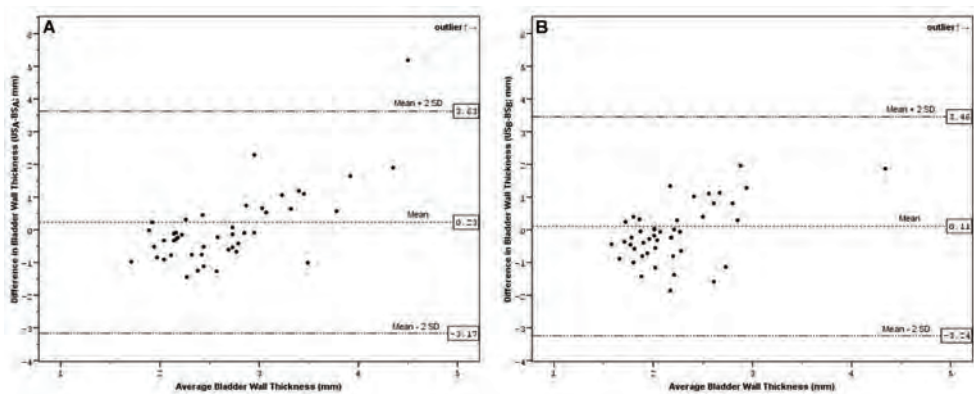
Figure 3: Comparison of bladder wall thickness measurements with conventional ultrasound and bladder scan based on first urodynamic investigation measurements at 150 ml **(A)** and 250 ml **(B)**; n=46 pairs of measurements. Mean difference between paired measurements and their variation (mean ± 2 SD) are indicated by respective lines. 95% CI of the mean (not shown) are -0.27mm to +0.74mm (A), -0.39mm to +0.61mm (B). The presence of one outlier is indicated in A and B (patient 17). The exact position of the outlier in relation to x-y axes (not shown) is (6.90mm, +8.60mm) in A and (6.80mm, +9.60mm) in B. There is an obvious positive trend of the distribution of differences across the range of BWT measurements (differences increase for higher BWT values). There is evidence of agreement between the two modalities at both bladder filling volumes since no systematic differences are observed between paired measurements; mean differences do not differ significantly from zero (P>0.05).

Abbreviations: US_{150A} = Conventional ultrasound measurement during first urodynamic investigation at 150 ml bladder filling; BS_{150A} = Bladder Scan measurement during first urodynamic investigation at 150 ml bladder filling; US_{250A} = Conventional ultrasound measurement during first urodynamic investigation at 250 ml bladder filling; BS_{250A} = Bladder Scan measurement during first urodynamic investigation at 250 ml bladder filling
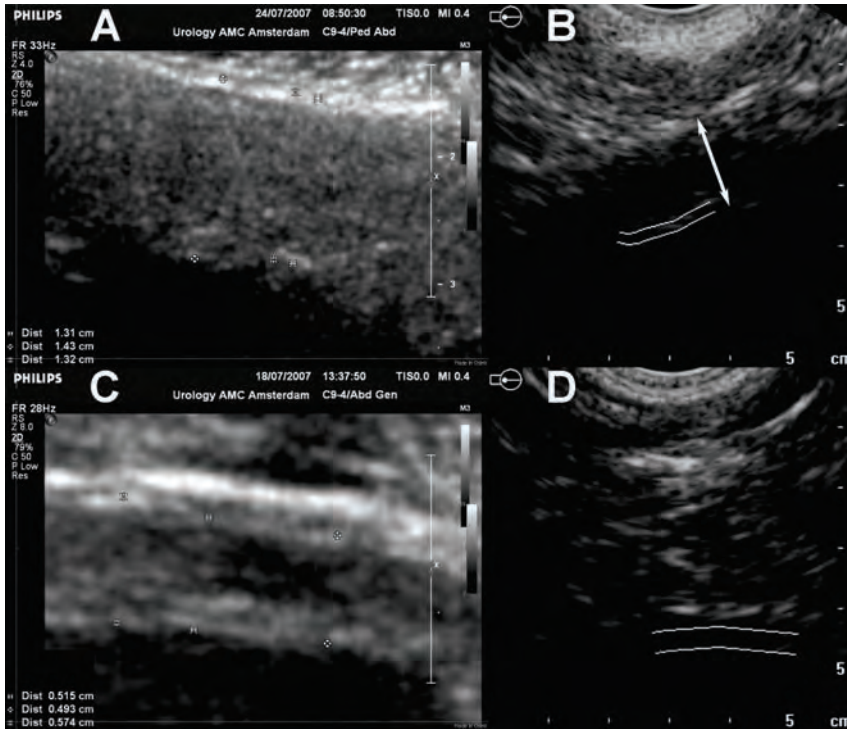
Figure 4: Bladder wall thickness measurements of a patient with conventional ultrasound (A) in comparison to the corresponding image of the BVM 6500 device (B). Note that the enlargement factor of figure 4A is half compared to figure 1. The patient had a thick bladder wall due to urodynamically confirmed severe bladder outlet obstruction (patient 17, first measurement at 250 ml). Bladder wall thickness measured with conventional ultrasound was greater in comparison to the measurement with the BVM 6500 device which measured only the inner part of the anterior bladder wall (≈). The double arrow (↕) in figure 4B indicates the true bladder wall thickness which is comparable with the measurement value of conventional ultrasound.

DISCUSSION

This is the first study on repeatability and agreement of automatic and conventional ultrasound BWT measurements. Our study of 50 unselected male and female patients with different types of bladder dysfunction provided evidence of good repeatability for both modalities and agreement between them at both bladder filling volumes tested (150 and 250 ml). Repeatability was shown to be improved at higher bladder filling volumes for both modalities. However, the BVM 6500 device could not deliver a valid measurement in up to 14% of patients, thicker anterior bladder walls could not be measured correctly, and the variation of repeated measurements was higher than with conventional ultrasound.

The BVM 6500 device has to be positioned on the skin of the lower abdomen and is able to identify and measure the volume of the urinary bladder as well as the thickness of the anterior bladder wall. The correct position of the device on the lower abdomen and a measurement of good quality are

immediately indicated on the display of the BVM 6500 device. If the device is improperly positioned, arrows on the display indicate the direction towards which the device has to be moved in order to receive images and measurements of good quality. Although these suggestions were followed meticulously in all patients and the BVM 6500 device indicated measurements with good quality, invalid measurements were still delivered in 2-14% of patients after sending the data to the central sever computer. Since we proceeded with the bladder filling of the patients during the central computer evaluation time span of approximately two min, invalid measurements could not be repeated. An integrated evaluation function inside the measurement device of the BVM 6500 without data transfer to the central server computer could have delivered the measurement results faster and might solve this problem in the future. Invalid measurements at both bladder filling volumes appeared in different men and women indicating that gender or tissue properties patients were not responsible for these missing values.

Chalana and colleagues [12] suggested measuring BWT with the BVM 6500 device between 100 to 400 ml of bladder filling. However, BWT should be measured according to the official Verathon® handbook for the BVM 6500 device at a bladder filling volume between 100 and 300 ml. We evaluated BWT at a bladder filling of 150 and 250 ml in order to ensure measuring within the recommended volume range of 100 to 300 ml. Automatic BWT measurements at 100 or 400 ml might have provided different results. In contrast to these recommendations, conventional ultrasound measurements of the anterior bladder wall are possible at every state of bladder filling [14].

Thicker anterior bladder walls appeared in patients with bladder outlet obstruction due to benign prostatic hyperplasia. This result is in line with previous findings [1-5]. Although mean BWT of all patients in our study did not differ significantly when conventional ultrasound was compared with automatic evaluation, BWT values of obstructed patients were lower with the BVM 6500 device. There was no patient with bladder outlet obstruction with an automatic BWT measurement above 4 mm, whereas 5 patients with bladder outlet obstruction had a BWT between 4.1 and 13.5 mm with conventional ultrasound BWT measurement. Direct comparison of the ultrasound images of both techniques in these obstructed patients showed that the BVM 6500 measured only the inner part of the anterior bladder wall without including the outer part. If the investigator could manually change the measurement lines on the BVM 6500 images to indicate the true inner and outer border of the anterior bladder wall, these erroneous measurements could be avoided. However, measurement lines provided by the current version of the BVM 6500 device cannot be changed after central server computer evaluation. Although BWT values of severely obstructed patients obtained by conventional ultrasound and BVM 6500 were not directly comparable, automatic BWT measurements still indicated a thicker anterior bladder wall which might be sufficient enough to classify these specific patients as obstructed. A study based exclusively on obstructed patients could clarify this matter in the future.

Differences between conventional ultrasound and bladder scan measurements could have also been attributed to different ultrasound frequencies of the two techniques or to an operator dependent bias. We used a dynamic 9 to 4 MHz ultrasound scanner for conventional ultrasound measurements, whereas the BVM 6500 device uses a 3.7 MHz scanner. Because the conventional ultrasound scanner was located on the skin of the lower abdomen with a distance to the bladder of only a few centimeters, ultrasound frequencies close to 9 MHz were used to image the anterior bladder wall. The resolution of ultrasound images is frequency dependent. Ultrasound scanners of 7.5 and 3.5 MHz have a resolution in

the order of 0.13 mm and 0.3 mm, respectively [14]. Hand measurements with conventional ultrasound during the second urodynamic investigation might have unconsciously been influenced by the results of the first measurement. Furthermore, intraobserver variability of BWT measurements might partially be responsible for measurement variations between results of one measurement technique and between results of the different techniques.

Our study also demonstrated that both ultrasound techniques produce repeatable results at both 150 and 250 ml of bladder filling. The variance of measurements was lower at 250 ml bladder filling with both ultrasound techniques compared to 150 ml bladder filling. Therefore, a higher bladder filling seems to be more suitable for BWT measurements. However, we investigated measurement variations only at 150 and 250 ml bladder filling; thus, the variance of measurement results might further decrease at bladder fillings above 250 ml. The variance of BWT measurements at the same patient and bladder filling was lower with conventional ultrasound at 250 ml; therefore, determination of BWT with conventional ultrasound at 250 ml appears to be the most precise technique and volume of all tested.

CONCLUSIONS

BWT measurements at the anterior bladder wall both manually with conventional ultrasound and automatically with the BVM 6500 device are repeatable and agree with each other. Conventional ultrasound measurements provide a smaller measurement variance during repeated investigations. BWT can be measured with conventional ultrasound technique in all patients, which is not the case for the BVM 6500 device. Thicker bladder walls cannot be measured automatically with precision. Even though the performance of BVM 6500 device is encouraging, automatic BWT measurements cannot replace hand measurements with conventional ultrasound at this point of development.

Acknowledgement

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CHAPTER 8

International Consultation on Incontinence-Research Society (ICI-RS) Report on Non-invasive Urodynamics: The Need of Standardization of Ultrasound Bladder and Detrusor Wall Thickness Measurements to Quantify Bladder Wall Hypertrophy

Matthias Oelke

ABSTRACT

Introduction: Ultrasonic measurements of urinary bladders are suitable to quantify bladder wall hypertrophy due to bladder outlet obstruction, detrusor overactivity, or neurogenic bladder dysfunction in adult men or women and in children. Quantification of bladder wall hypertrophy seems to be useful for the assessment of diseases, prediction of treatment outcomes, and longitudinal studies investigating disease development and progression.

Measurement techniques: Four distinct measurement techniques have been published using bladder wall thickness (BWT), detrusor wall thickness (DWT), or ultrasound-estimated bladder weight (UEBW) assessed by suprapubic or transvaginal positioning of ultrasound probes and different bladder filling volumes. As a result, different threshold and reference values were established causing confusion. This ICI-RS report summarizes the agreements of different research groups in terms of ultrasonic BWT or DWT measurements, critically discusses the four ultrasonic measurement techniques, suggests criteria for quality control, and proposes future research activities to unify measurement strategies

Proposed standardization and research: For quality control, all future reports should provide information about frequency of the ultrasound probe, bladder filling volume at measurement, if BWT, DWT, or UEBW was measured, enlargement factor of the ultrasound image, and one ultrasound image with marker positioning. The ICI-RS intends to found a standardization committee that will initiate and judge studies on ultrasonic bladder wall measurements to clarify the most suitable, most accurate, and least invasive measurement technique.

INTRODUCTION

Bladder wall hypertrophy has been documented in men with bladder outlet obstruction (BOO) [1-7], women with detrusor overactivity [8-12], and children with urethral valves, dysfunctional voiding, or neurogenic bladder dysfunction (e.g. detrusor-sphincter-dyssynergia, low-compliance bladders) [13-17]. Bladder wall hypertrophy is caused by thickening of the detrusor [18]. It was hypothesized that detrusor wall thickness (DWT) or bladder wall thickness (BWT) reflects the workload of the bladder similar to the heart, in which the cardiac wall thickens in patients affected by arterial hypertension or cardiac valve stenosis [19]. Bladder wall hypertrophy can be imaged with ultrasound technology in experimental animals with partial BOO [20] and humans with neurogenic or non-neurogenic bladder dysfunction.

Imaging of the bladder wall provides information about the state of hypertrophy and grade of decompensation of the urinary bladder that can be used to assess diseases (e.g. BOO or detrusor overactivity) avoiding invasive, expensive, and time-consuming urodynamic investigations. Ultrasonic investigations of bladders in patients with benign prostatic obstruction (BPO) demonstrated that the bladder wall thickens with increasing obstruction grade [3,5]. Under standardized conditions and with defined threshold values it is possible to quickly diagnose BOO with ultrasound technique; sensitivity, specificity, and predictive values of ultrasound BWT/DWT measurements are similar to those of urodynamic investigation [3,5-7] and superior to other non-invasive tests usually performed in clinical routine (uroflowmetry, measurements of postvoid residual urine or prostate volume, and symptoms assessed by the International Prostate Symptom Score) [3,5,6]. In a meta-analysis of non- and minimally-invasive tests to diagnose BOO it was concluded that ultrasound BWT/DWT measurements are one of the promising techniques that have the potential to replace urodynamic investigations in the future [21]. A detailed description and comparison of all promising techniques (measurements of the bladder wall, intravesical prostatic protrusion, and isovolumetric bladder pressure by the condom catheter method or penile cuff test) has been published recently [22].

Furthermore, bladder wall imaging might be helpful to understand disease development or predict treatment outcome. It was shown in patients with BOO that bladder wall hypertrophy is quickly reversible after BOO relief [23-25]. Ultrasonic investigations of bladders in patients after transurethral resection of the prostate or open prostatectomy showed a significant decrease of BWT as early as one week after the operation and reached the nadir at about 56% of the original thickness six weeks later [24]. Patients with persistent bladder wall hypertrophy after treatment remained symptomatic and had a poor treatment outcome [23]. Ultrasound studies in men with lower urinary tract symptoms (LUTS) due to BPH showed during α–blocker treatment a decrease of symptoms and postvoid residual urine as well as increase of maximum urinary flow rate which correlated well with decrease of bladder wall hypertrophy [26,27]. Studies on women with detrusor overactivity showed that antimuscarinic drugs can also reduce bladder wall thickness quickly [28,29]. Children with myelomeningoceles and an unfavourable urodynamic pattern have increased BWT [17]; however, children with sufficient treatment and regular follow-up investigations have DWTs similar to healthy controls [30]. This information might be useful to understand the pathophysiology of the disease, identify treatment responders or non-responders even before treatment begin, or monitor treatment.

Last but not least, BWT/DWT measurements could be useful for epidemiological studies investigating disease development and progression over a long period of time in large groups of people, thereby avoiding bothersome urodynamic investigations, study withdrawals, or proxy parameters during follow-up visits. Longitudinal studies in men investigating the development and progression of BOO have not yet been performed due to the above mentioned reasons. Ultrasonic investigations of BWT/DWT seem to be ideal tool for this purpose. However, it has already been demonstrated that symptomatic men with BPO and bladder wall hypertrophy have an approximately 13 times increased risk of developing acute urinary retention [31].

Without doubt, research on ultrasound measurements of the bladder wall has led to a massive increase of knowledge and further understanding of bladder pathophysiology. Despite several agreements on ultrasonic investigations of the bladder wall the measurement technique has not yet been standardized. Techniques differ in terms of positioning of the ultrasound probe, bladder filling, and measuring of different parts of the bladder wall. As a result, different reference and threshold values have been established causing confusion and non-acceptance of the concept in general. Correction factors to directly translate measurement values obtained by different techniques have not been described. The lack of standardization inhibits further scientific development of ultrasound bladder wall measurements. This report aims to list the agreements and disagreements of various research groups and suggest future research and standardization.

AGREEMENTS BETWEEN RESEARCH GROUPS

Experts agree on the following facts during ultrasonic measurements of BWT and DWT:

- Use of high frequency ultrasound probes: The resolution of the ultrasound image is frequency dependent: The higher the ultrasound frequency the better the resolution. High frequency ultrasound probes (e.g. 7.5 MHz) have a resolution of less than 0.13 mm, whereas ultrasound probes with a frequency of 3.5 MHz have a resolution of approximately 0.3 mm [32]. Considering DWTs between 1.1-1.8 mm in filled bladders of healthy male volunteers or non-obstructed bladders [5,32] and DWTs of 2 mm or higher in patients with obstructed bladders [5,7] it is important to use frequencies high enough to capture small differences.

- Use of digital ultrasound machines for adequate image enlargement: For precise marker positioning and bladder wall measurements it is necessary to enlarge ultrasound images. Digital ultrasound machines for clinical use can enlarge the image 5 to 15fold. If the image has not been adequately enlarged imprecise placement of the markers would result in great measurement differences and might suggest bladder wall hypertrophy.

- Ultrasonic appearance of the bladder wall: The outer and inner layers of the bladder wall appear hyperechogenic (white) and represent the adventitia and mucosa/submucosal tissue, respectively. The detrusor appears hypoechogenic (black) and is sandwiched between the hyperechogenic lines of the adventitia and mucosa (**figure 1a**) [1,33]. Measurement of all three layers represents bladder wall thickness (BWT) and measurement of the detrusor only represents detrusor wall thickness (DWT). Therefore, BWT values are always greater than DWT values in the same patient and direct comparison of both values is not possible (**figure 1b**).
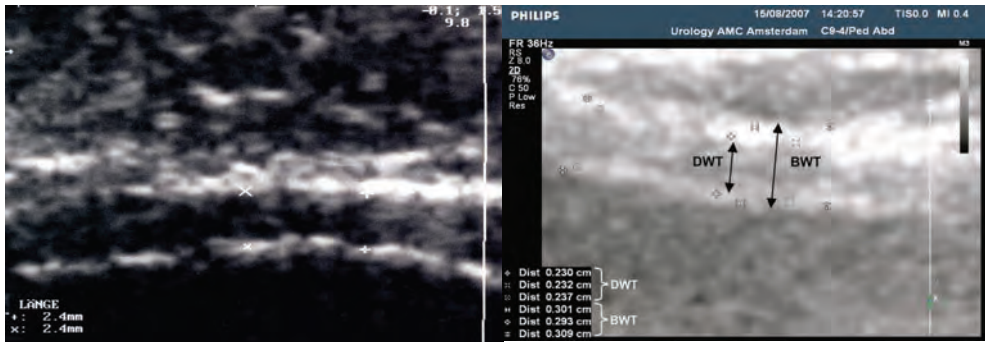
Figure 1: (a) Imaging of the anterior bladder wall with a linear 7.5 MHz ultrasound array, enlargement factor of the image 9.8fold. The outer and inner hyperechogenic (white) lines represent the adventitia and mucosa/submucosal tissue, respectively. The hypoechogenic (black) bar in between the hyperechogenic lines represents the detrusor. The measurement markers are positioned at the outer and inner border of the detrusor and indicate detrusor wall thickness (2.4 mm). **(b)** Measurement of detrusor wall thickness (DWT) and bladder wall thickness (BWT) in the same patient, enlargement factor of the ultrasound image 8fold. For DWT measurement it is necessary to measure the full distance of the hypoechogenic detrusor and for BWT measurement it is necessary to measure distance from the outer border of the hyperechogenic mucosa until the outer border of the hyperechogenic adventitia. BWT values in the same patient and bladder filling are always greater than DWT values; see measurement values on the left bottom.

- Perpendicular imaging of the bladder wall: If the bladder wall has been tangentially imaged measurements might suggest bladder wall hypertrophy. Perpendicular imaging is achieved when the hyperechogenic adventitia and mucosa appear as thin and sharp lines [32].

- Decrease of thickness with increasing bladder filling: BWT and DWT depend on bladder filling in the range of 50 to 250 ml. It was first demonstrated by Khullar et al. that no significant differences of BWT exist in almost empty bladders and those filled until 50 ml [8]. Oelke et al. showed in healthy adult male and female volunteers that DWT decreases rapidly between 50 and 250 ml of bladder filling (or until 50% of bladder capacity) but reaches a plateau thereafter with only minor and insignificant differences between 250 ml and maximum bladder capacity (**figures 2a and 2b**) [32]. The difference of measurements at 50 and 100% bladder capacity is in the order of image resolution of a 7.5 MHz ultrasound array. This hyperbolic detrusor wall characteristic is identical in both healthy men and women and in line with results obtained in healthy children [34, 35] and women with overactive bladder/detrusor overactivity with or without urinary incontinence [12].
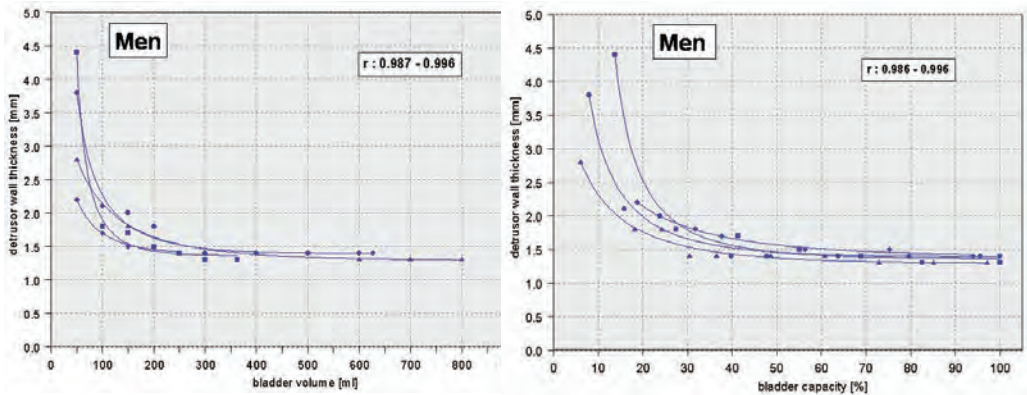
Figure 2: Relationship between detrusor wall thickness and bladder filling volume **(a)** or bladder capacity **(b)** in healthy adult males [32]. The measurements of one volunteer are connected with lines. Detrusor wall thickness decreases rapidly until 250 ml (50% bladder capacity) and reaches a plateau thereafter.

- Similar thicknesses at different parts of the bladder: All parts of the bladder (dome, anterior, posterior, or lateral walls) have the same thickness in the same patient and in the same state of bladder filling [1, 34, 36]. Therefore, any part of the bladder can be imaged to measure BWT or DWT and diagnose bladder wall hypertrophy.

- Gender specificity of measurement values: It was shown in children and adults that females have a significantly lower BWT and DWT than males [4, 32, 34]. Higher BWT and DWT values in males might reflect greater voiding pressures due to the prostate and longer urethra. Therefore, measurement values of females cannot be directly compared to those obtained in males.

- Low intra- and interobserver variabilities: Experienced centres have demonstrated that repeated measurements of BWT or DWT have an intraobserver variability of less than 5% and an interobserver variability of 4-12% [3, 6, 37, 38].

DISAGREEMENTS BETWEEN RESEARCH GROUPS

Different techniques have been established to determine bladder wall hypertrophy; suprapubic measurement techniques can be distinguished from the transvaginal technique (**figure 3**).
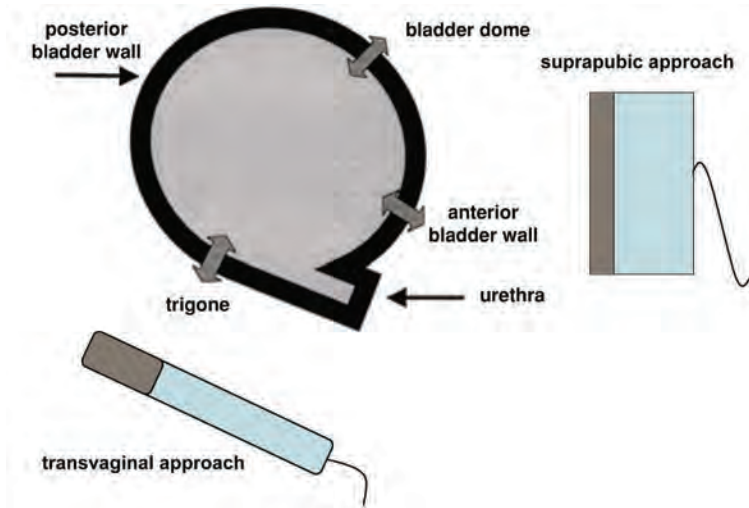
Figure 3: Different approaches for measurements of the bladder wall [adapted and modified from 10]. All parts of the bladder have the same thickness in one person at the same bladder filling. Because high frequency ultrasound probes have to be positioned close to the site the investigator wishes to investigate, suprapubically positioned ultrasound probes can image the anterior bladder wall and vaginally positioned ultrasound probes can image the anterior and posterior bladder walls as well as the trigone.

Suprapubic measurement approaches

Supporters of the suprapubic approaches are mainly urologists who aim to assess BOO in patients with BPH or urethral valves or dysfunctional voiding in children. Because of the low tissue penetration of high frequency ultrasound devices only the anterior bladder wall can be imaged with good quality and resolution. Three distinct measurement techniques have been published which are linked to certain study groups:

- Tubaro technique: Andrea Tubaro and co-workers from Italy filled bladders with 150 ml in every patient by catheterization and measured BWT at the anterior bladder wall [3, 24]. BWT in male patients with BOO was significantly thicker than BWT in patients without BOO. A threshold value of 5 mm discriminated well between obstructed or non-obstructed bladders.

- Oelke technique: Matthias Oelke and co-workers from Germany and the Netherlands measured DWT in bladders filled with 250 ml or more, hereby using the observation that DWT reaches a plateau at this bladder filling volume (**figures 2a and 2b**) [32]. Therefore, the exact volume in bladders filled with 250 ml or more is not important anymore. The patients are asked to fill their bladders by drinking until they feel a strong desire to void. This technique has the advantage that catheterization is not necessary anymore. Arguments to measure only DWT (instead of BWT) were (1) bladder wall hypertrophy is a product of muscle cell hypertrophy due to the increased workload of the bladder which only happens in the detrusor, whereas the adventitia and mucosa are not involved in hypertrophy, (2) adventitia or mucosa could be affected by other diseases (e.g. inflammation or cancer) and measurement of these layers

could cause a false positive increase of BWT, (3) the hyperechogenic adventitia is sometimes difficult to distinguish from the perivesical fatty tissue making the marker placement for BWT measurements difficult (**figure 4**). DWT in male patients with BOO is significantly thicker than in patients without BOO [5, 7]. A threshold value of 2 mm best distinguished between obstructed or non-obstructed bladders [5, 7, 39]. The technique has been lately confirmed by Kessler et al. from Switzerland although a threshold value of 2.5 mm seemed more appropriate to distinguish obstructed from non-obstructed bladders in order to achieve similar sensitivity and specificity [6]. Compared to the Tubaro approach, measurement and threshold values are smaller with the Oelke technique because bladders are filled with higher volumes and only DWT (instead of BWT) is measured.
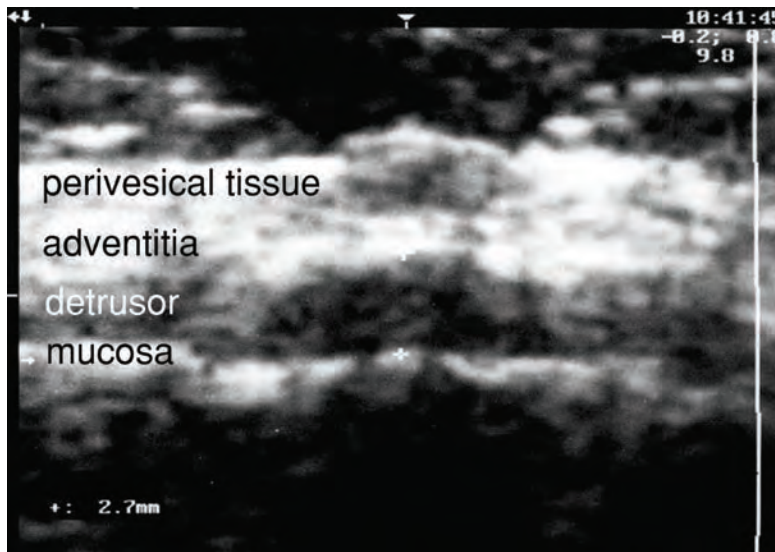
Figure 4: Ultrasound image of the anterior bladder wall in a patient with hyperechogenic (fatty) tissue around the bladder which makes measurements of bladder wall thickness but not detrusor wall thickness difficult. Enlargement factor of the ultrasound image 9.8fold.

- Kojima technique: Munekado Kojima and co-workers from Japan measure BWT and bladder filling volume, calculate the outer and inner diameter of the bladder wall by volume formulas, subtract the inner from the outer volume, and multiply the result with the specific gravity of bladder wall tissue (**figure 5**) [1]. The measurements and calculations result in ultrasound estimated bladder weight (UEBW) which can be independently calculated from actual bladder filling volume. Initial experiments in cadaver bladders confirmed that UEBW in the same cadaver is more or less identical in bladders filled between 100 and 300 ml [1]. A threshold value of 35 g distinguished the best between obstructed and non-obstructed bladders in Japanese patients [1, 2]. The technique has the advantage that measurement results of humans can directly be compared with those obtained in experimental animals in

which the bladder is excised and weighted. However, the technique has the disadvantage that small measurement mistakes, either at volume or BWT measurements, have a great impact on UEBW because measurement values are used in the third potency in volume formulae [5]. Furthermore, it is doubtful if Caucasians have the same bladder weight compared to Asians.
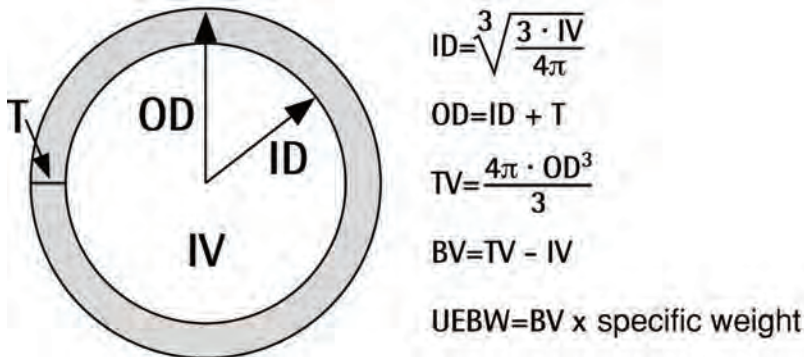
Figure 5: Schematic drawing and formulas for calculation of ultrasound-estimated bladder weight (UEBW) [adapted and modified from 1]. IV = intravesical volume (measured by ultrasound); T = thickness of the bladder wall (measured by ultrasound); ID = inner diameter (calculated); OD = outer diameter (calculated); TV = total vesical volume (calculated).

Transvaginal measurement approach

Supporters of the transvaginal measurement technique are gynaecologists who aim to assess detrusor overactivity and urinary incontinence. The ultrasound probe is positioned in the vagina close to the bladder and enables the investigator to measure the trigone, anterior bladder wall, and dome with good quality and resolution. The transvaginal approach originates from Vikram Khullar and colleagues from England [8, 9]. Patients are asked to empty their bladders in order to measure at bladder fillings less than 50 ml. The exact bladder filling volume in empty bladders and those filled until 50 ml is not important because BWT is constant in this volume range; therefore, catheterization is not necessary. After vaginal positioning of the ultrasound probe, BWT is measured at the anterior bladder wall, trigone, and dome. All three measurement values are added and, afterwards, divided by three to achieve mean BWT [8]. A threshold value of 5 mm best discriminated between detrusor overactivity and other bladder conditions (normal, stress urinary incontinence, or mixed incontinence) [9]. The technique has been confirmed by Dudley Robinson and co-workers although a threshold value of 6 mm might be more appropriate to diagnose detrusor overactivity [10]. Criticism has appeared lately because the trigone might not been the correct measurement location, it might be volume independent, have a different thickness compared to other bladder sites at the same bladder filling, and is likely not to be involved in bladder contractions. The Khullar technique has the disadvantage that the ultrasound probe has to be inserted into the vagina which makes the technique invasive and, obviously, unsuitable for men.

In conclusion, all techniques are capable of detecting bladder wall hypertrophy but differ in terms of bladder filling volume at measurement and evaluation of BWT or DWT. Table 1 summarizes the results obtained by different techniques. For quality control in the future, the following information about ultrasonic measurements of the bladder wall should be provided in all reports:

- Names of the ultrasound company and machine

- Frequency of the ultrasound probe

- Bladder filling volume/state of bladder filling at measurement

- Information whether BWT, DWT, or UEBW was measured

- Enlargement factor of the ultrasound image during measurement

- At least one ultrasound image with maximum enlargement and positioning of the measurement markers

- Information whether patients received treatment with α–blockers or muscarinic receptor antagonists.

Measurements that are not in line with measurement recommendations might result in insignificant differences between different patients groups, as demonstrated by Blatt et al. [42].

FUTURE RESEARCH

It is desirable to establish one technique and one threshold value in men or women in order to bundle resources and unify research activities in diseased patients in the future. It remains to be investigated which of the described methods is most suitable to measure bladder wall hypertrophy or if a new method should be established that combines advantages of previously described techniques ("best out of all"). For standardization of the measurement technique it is necessary to evaluate:

1. ideal bladder filling for measurement

2. whether BWT, DWT, or UEBW is most suitable for exact quantification of bladder wall hypertrophy

3. whether the suprapubic approach delivers similar measurement values compared to the transvaginal approach

4. correction factor to directly translate measurement values of one technique to another

5. whether the trigone has the same thickness compared to other parts of the bladder wall

6. which measurement technique has the highest patient acceptance and the lowest bother

These questions could be answered by conducting a study in one group of volunteers or patients measuring both BWT and DWT at different bladder fillings and by using suprapubic as well as vaginal (rectal) ultrasound devices; repeatability, accuracy, and measurement variation should be evaluated for BWT, DWT, and UEBW in this group. A recently published article indicates that measurement variation of BWTs is lower at 250 ml compared to 150 ml [43]. A multicenter study seems to be superior to a single centre approach.

7. If ultrasound measurement values can be reproduced by other imaging techniques: Although the resolution of MRI in clinical setting is only approximately 1 mm this imaging technique seems to be suitable for this purpose due to the lack of radiation and advantages of post-imaging data processing. Ultrasound values should be compared with MRI values in the same group of patients and the same bladder filling in order to reproduce measurement and threshold values.

8. Learning curve for each technique: A study should evaluate the number of measurements that are necessary to receive similar measurements compared to experienced investigators or MRI values.

9. Whether different bladder dysfunctions need different measurement techniques: It has to be demonstrated that bladder hypertrophy due to detrusor overactivity can also be assessed by suprapubic measurement of BWT or DWT and at higher bladder filling volumes than 50 ml. Vice versa, it should be evaluated if bladder hypertrophy due to BPE-BOO can also be assessed by transrectal ultrasound and with bladder filling volumes less than 250 ml.

After evaluation of all aspects of bladder wall hypertrophy measurements and before further evaluation of disease specific questions a standardization committee hosted by the ICI-RS should discuss and decide which technique should be used in the future. This decision should be based on objective data and results of measurement accuracy, repeatability, variation, practicality, morbidity, availability of ultrasound probes, and patients' quality of life during measurement.

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Part IV:

Benign Prostatic Obstruction within the Perspective of the Guidelines of the European Association of Urology

CHAPTER 9

EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction (BPO)

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ABSTRACT

Context: Lower urinary tract symptoms (LUTS) represent one of the most common clinical complaints in adult men and have multifactorial aetiology. Objective: To develop European Association of Urology (EAU) guidelines on the assessment of men with non-neurogenic LUTS.

Evidence acquisition: A structured literature search on the assessment of non-neurogenic male LUTS was conducted. Articles with the highest available level of evidence were selected. The Delphi technique consensus approach was used to develop the recommendations.

Evidence synthesis: As a routine part of the initial assessment of male LUTS, a medical history must be taken, a validated symptom score questionnaire with quality-of-life question(s) should be completed, a physical examination including digital rectal examination should be performed, urinalysis must be ordered, post-void residual urine (PVR) should be measured, and uroflowmetry may be performed. Micturition frequency-volume charts or bladder diaries should be used to assess male LUTS with a prominent storage component or nocturia. Prostate-specific antigen (PSA) should be measured only if a diagnosis of prostate cancer will change the management or if PSA can assist in decision-making for patients at risk of symptom progression and complications. Renal function must be assessed if renal impairment is suspected from the history and clinical examination, if the patient has hydronephrosis, or when considering surgical treatment for male LUTS. Uroflowmetry should be performed before any treatment. Imaging of the upper urinary tract in men with LUTS should be

performed in patients with large PVR, haematuria, or a history of urolithiasis. Imaging of the prostate should be performed if this assists in choosing the appropriate drug and when considering surgical treatment. Urethro-cystoscopy should only be performed in men with LUTS to exclude suspected bladder or urethral pathology and/or before minimally invasive/surgical therapies if the findings may change treatment. Pressure-flow studies should be performed only in individual patients for specific indications before surgery or when evaluation of the pathophysiology underlying LUTS is warranted.

Conclusions: These guidelines provide evidence-based practical guidance for assessment of non-neurogenic male LUTS. An extended version is available online (www.uroweb.org/guidelines).

Patient summary: This article presents a short version of European Association of Urology guidelines for non-neurogenic male lower urinary tract symptoms (LUTS). The recommended tests should be able to distinguish between uncomplicated male LUTS and possible differential diagnoses and to evaluate baseline parameters for treatment. The guidelines also define the clinical profile of patients to provide the best evidence-based care. An algorithm was developed to guide physicians in using appropriate diagnostic tests.

1.   INTRODUCTION

Lower urinary tract symptoms (LUTS) represent one of the most common clinical complaints in adult men [1]. The prevalence of LUTS increases with age, and estimates vary widely depending on definitions and cohorts studied [1,2]. LUTS have a major impact on health-related quality of life (QoL) [2] and are associated with substantial personal and societal costs [3]. LUTS can be divided into storage, voiding, and post-micturition symptoms, and have traditionally been related to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction (BPO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition benign prostatic hyperplasia (BPH) [4]. Several recent studies have shown, however, that LUTS are not necessarily related to pathologies of the prostate. For instance, various types of bladder dysfunction may also be involved in the pathogenesis of LUTS, which is sometimes urodynamically manifest as detrusor overactivity (during the storage phase) or underactivity (during the voiding phase). In addition, many other conditions, both urological and non-urological, may also contribute to LUTS (**Figure 1**).
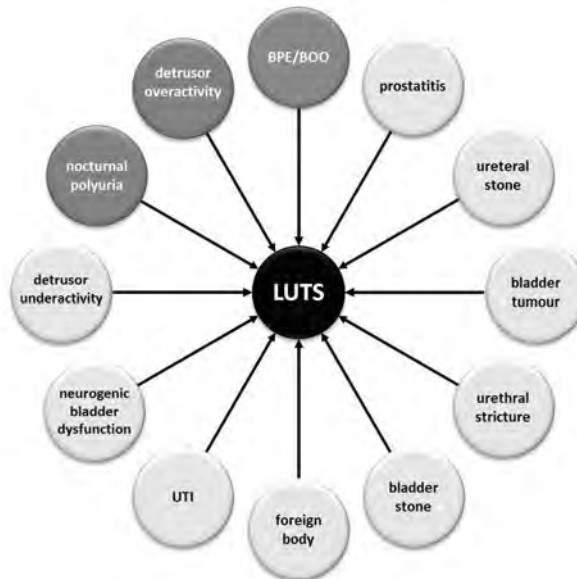
Figure 1: Causes of male lower urinary tract symptoms (LUTS)

1.1.   Scope and purpose of the guidelines

Owing to the high prevalence of LUTS and the underlying multifactorial pathophysiology, accurate assessment of male LUTS is crucial to establish a differential diagnosis among possible causes and to define the clinical profile of men with LUTS to provide the best evidence-based care (overall objectives). The assessment should be able to identify patients for whom watchful waiting (WW) or medical or surgical treatment can be recommended, as well as men at risk of disease progression, and to assess patients' values and preferences. The guidelines aim to answer the clinical question as to which tests are recommended in the assessment of non-neurogenic LUTS in men aged ≥40 yrs. and when these tests should be performed.

2.   EVIDENCE ACQUISITION

The recommendations in these guidelines are based on a structured literature search for articles published in English according to the PubMed/Medline, Web of Science, and Cochrane databases between 1966 and October 1, 2013, including the search terms "*lower urinary tract symptoms*", "*benign prostatic hyperplasia*", "*detrusor overactivity*", "*overactive bladder*", "*nocturia*", and "*nocturnal polyuria*" in combination with the pre-specified diagnostic tests and the search limits "*humans*", "*adult men*", "*review*", "*randomised clinical trials*", "*clinical trials*", and "*metaanalysis*". Each extracted article was separately analysed, classified, and labelled with a level of evidence (LE) according to a classification system modified from the Oxford Centre for Evidence-based Medicine, ranging from systematic reviews of randomised trials (LE 1a, highest evidence level) to expert opinion (LE 4, lowest evidence level) (modified from [5]). The working panel used the Delphi technique consensus approach, which is based on the rationale that decisions captured systematically from a structured group of individuals (the working panel) are more valid than those from unstructured groups. When published information is scarce, experts can make inferences using other data from comparable contexts. Using bespoke software (www.acord.it), propositions were put to experts, who voted for their preference. The results from the group were then sent back anonymously to all participants, who were able to review their responses in the context of group-wide results. This practice conferred anonymity and allowed opinions to be expressed free from peer-group pressure. The web-based system offered participants the option to comment and justify their decisions anonymously. After consideration of the view of the group and a review of the comments, a second round of anonymous voting took place. Experts were encouraged to revise their earlier answers in light of the replies of other working panel members. Three iterations of the process were used, during which the range of the answers decreased and the group converged towards a consensus answer. The working panel predetermined the consensus level at 77% (7 out of 9) using the Delphi process, such that consensus on and recommendation for any test required support from at least 77% of the panel members. The panel has classified diagnostic tests into three categories: must, should, and may, which represents the highest, intermediate, and lowest levels of obligation, respectively. Each recommendation is based on the strongest clinically relevant data as far as possible. However, it should be noted that when recommendations are graded, there is no automatic relationship between LE and grade of recommendation (GR). The availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation if there are methodological limitations, disparity in published results, uncertainty about the balance between desirable and undesirable effects, uncertainty or variability in patients' values and preferences, or uncertainty about whether the intervention represents wise use of resources. Alternatively, an absence of high-level evidence does not necessarily preclude a grade A recommendation; if there is considerable clinical experience and consensus to support a high-level recommendation, a grade A recommendation can be made. Such decisions are clearly indicated in **Table 1** with an asterisk to denote ''upgraded based on panel consensus''. The working panel for the non-neurogenic male LUTS guidelines consists of experts with a urological and epidemiological background. Although the guidelines are written primarily for urologists, they can also be used by general practitioners, patients, and other stakeholders. The working panel intends to regularly update the content and recommendations according to the structure and classification systems given.

Table 1: Evidence levels and grades of recommendation on the assessment of non-neurogenic male LUTS

Assessment Tool	LE	GR
A medical history *must* always be taken from men with LUTS	4	A*
A validated symptom score questionnaire with QoL question(s) *should* be used for the routine assessment of male LUTS in all patients and should be applied for re-evaluation of LUTS during treatment	3	B
Micturition frequency/volume charts (FVC) or bladder diaries *should* be used to assess male LUTS with a prominent storage component or nocturia	3	B
FVC's should have a duration of at least 3 days	2b	B
Physical examination including DRE *should* be a routine part of the assessment of male LUTS	3	B
Urinalysis (by dipstick or urinary sediment) *must* be used in the assessment of male LUTS	3	A*
PSA measurement *should* be performed only if a diagnosis of prostate cancer will change the management or if PSA can assist in decision making in patients at risk of progression of BPE	1b	A
Renal function assessment *must* be performed if renal impairment is suspected based on history and clinical examination or in presence of hydronephrosis or when considering surgical treatment for male LUTS	3	A*
Measurement of post-void residuals (PVR) in male LUTS *should* be a routine part of the assessment	3	B
Uroflowmetry in the initial assessment of male LUTS *may* be performed and *should* be performed prior to any treatment	2b	B
Imaging of the upper urinary tract (with ultrasound) in men with LUTS *should* be performed in patients with a large PVR, hematuria or a history of urolithiasis	3	B
When considering medical treatment for male LUTS, imaging of the prostate (either by TRUS or transabdominal ultrasound) *should* be performed if it assists the choice of the appropriate drug	3	B
When considering surgical treatment, imaging of the prostate (either by TRUS or abdominal US) *should* be performed	3	B
Urethro-cystoscopy *should* be performed in men with LUTS to exclude suspected bladder or urethral pathology and/or prior to minimally invasive/surgical therapies if the findings may change treatment	3	B
PFS *should* be performed only in individual patients for specific indications prior to surgery or when evaluation of the underlying pathophysiology of LUTS is warranted	3	B
PFS *should* be performed in men who have had previous unsuccessful (invasive) treatment for LUTS	3	B
When considering surgery, PFS *may* be used for patients who cannot void > 150 ml	3	C
When considering surgery in men with bothersome predominantly voiding LUTS, PFS *may* be performed in men with a PVR > 300 ml	3	C
When considering surgery in men with bothersome predominantly voiding LUTS,, PFS *may* be performed in men aged > 80 years	3	C
When considering surgery in men with bothersome predominantly voiding LUTS, PFS *should* be performed in men aged < 50 years	3	B

* upgraded based on panel consensus

3. DIAGNOSTIC TESTS

Recommendations apply to men aged ≥40 yrs. who seek professional help for various non-neurogenic benign forms of LUTS. Men with LUTS not falling into this category (e.g., concomitant neurological diseases, young age, prior lower urinary tract disease or surgery) usually require a more extensive work-up that is not covered by these guidelines but may include several of the tests mentioned in the following section. All recommendations for diagnostic tests, along with LE and GR, are summarised in **Table 1.**

3.1. Medical history

Earlier guidelines on male LUTS and/or BPH emphasise the importance of assessing the patient's history [6–9]. The aim of obtaining a medical history is to identify potential causes of LUTS and relevant comorbidities, such as medical (e.g., diabetes mellitus or insipidus, renal disease, heart failure, sleep apnoea) and neurological diseases (e.g., Parkinson's disease, multiple sclerosis, cerebrovascular disease, spinal cord injury, or prolapsed intervertebral disc impinging on the spinal cord). It is further recommended to review current medication, and assess lifestyle habits, as well as emotional and psychological factors. The panel highlights the need to discuss the patient's perspectives regarding LUTS and possible treatment options. The patient should be reassured that the presence of LUTS does not indicate a higher prevalence of prostate cancer (PCa) compared with asymptomatic men [10, 11]. As part of the urological/surgical history, a self-completed validated symptom questionnaire (Section 3.2) should be delivered to objectively identify and quantify LUTS. The same symptom questionnaire should subsequently be discussed with the patient during follow-up to assess therapeutic efficacy. Potential erectile and other forms of sexual dysfunction should be investigated (preferably with validated symptom questionnaires).

3.2. Symptom score questionnaires

During the past two decades, symptom scores have become a standard tool in the assessment of male LUTS. Existing guidelines on male LUTS and/or BPH recommend the use of validated symptom score questionnaires [6–9]. Several questionnaires are available, all of which are sensitive to symptom changes and treatment monitoring [12–18]. The International Prostate Symptom Score (IPSS) is an eight-item (seven symptom questions and one global QoL question) questionnaire, initially created as the American Urological Association Symptom Index [14]. The International Consultation on Incontinence Questionnaire ICIQ-MLUTS was created from the ICS male questionnaire (which resulted from an outcome of the ICS BPH study) and is another widely used and validated patient-completed questionnaire for evaluating male LUTS [15]. A third questionnaire is the Danish Prostate Symptom Score (DAN-PSS) [13], which is mainly used in Denmark and Finland. The IPSS includes only one overall QoL question, whereas the DAN-PSS and ICIQ-MLUTS assess the bother of individual LUTS. Symptom scores are recommended for all patients during initial assessment as they are helpful in quantifying individual LUTS and identifying which type of symptoms (storage or voiding) are predominant, yet they are not disease-, age-, or gender-specific. Symptom scores can also be used to monitor response to therapy.

3.3. Frequency-volume charts and bladder diaries

Recording of the volume and time of each void by the patient is referred to as a frequency-volume chart (FVC). The record is known as a bladder diary if additional information is captured, such as fluid intake, use of pads, activities during recording, or symptom scores [4]. Parameters that can be derived from the FVC include: voiding frequency per 24 h; total voided volume per 24 h, including the fraction of urine produced during the night, known as the nocturnal polyuria index; and the volume of individual voids (mean and range). FVCs are beneficial when assessing patients with bothersome storage LUTS, particularly nocturia, as they can underpin categorisation of the underlying mechanism(s) [19–21]. FVCs are typically more accurate than patient recall [22,23], particularly for nocturia. However, FVC use may lead to a bladder training effect, and nights during FVC recording may be atypical since substantial variations in the frequency of nocturnal voids have been observed [24]. Hence, there is no agreement on standardizing the approach to deriving the above information in LUTS evaluation [25]. The observation duration should be long enough to avoid sampling errors, but short enough to avoid noncompliance [25]. Several studies have compared shorter (3–5 d) with longer (7 d) diary durations [26–31]. A 2009 systematic review of the literature recommended the use of ≥3 d [32]. A recent phase 1 study on the development and validation of a urinary diary suggested that the FVC duration should be ≥4 d [33].

3.4. Physical examination and digital rectal examination (DRE)

A physical examination should be performed on the suprapubic area to rule out bladder distention, on the external genitalia to identify conditions that may cause or contribute to LUTS (e.g., urethral discharge, phimosis, meatal stenosis, penile cancer), and on the perineum/lower limbs to evaluate motor/sensory function. Therefore, a physical examination is especially useful for differential diagnosis of LUTS. DRE is an important examination in men with LUTS and may help to determine the coexistence of PCa, despite its low diagnostic value, and abnormalities of anal sphincter tone. DRE overestimates prostate volume (PV) in smaller prostates and underestimates PV in larger prostates, but is a sufficient method to discriminate whether PV is greater or less than 50 ml [34]. The capacity of DRE to estimate PV is helpful for choosing treatment options, as these depend on PV (e.g., 5a-reductase inhibitors [5-ARIs], transurethral incision of the prostate, transurethral resection of the prostate, and others; see EAU Guidelines on the treatment of non-neurogenic male LUTS [35]).

3.5. Urinalysis

Urinalysis (dipstick or sediment) is an inexpensive test that does not require sophisticated technical equipment, and it must be incorporated in the primary evaluation of any patient presenting with LUTS to determine conditions such as urinary tract infection and diabetes mellitus on the basis of abnormal findings (haematuria, proteinuria, pyuria, glycosuria, ketonuria, positive nitrite test). Therefore, urinalysis is helpful for the differential diagnosis of LUTS. Once abnormal findings have been diagnosed, further evaluation is recommended according to the standards provided in other EAU guidelines, such as those on non–muscle-invasive bladder cancer, muscle-invasive and metastatic

bladder cancer, upper urinary tract urothelial cell carcinoma, primary urethral carcinoma, and urological infections [36–39]. Urinalysis is traditionally recommended in most guidelines for the primary management of patients with LUTS [40, 41]. Even in the absence of controlled studies, there is general expert consensus that the benefits clearly outweigh the costs, although the use of urinalysis should always be associated with prognostic significance [42]. Nevertheless, despite official guidelines and the widespread use of urinalysis among urologists [43], the value of urinary dipstick/microscopy for diagnosing urinary tract infection in patients with painless LUTS has recently been questioned [44].

3.6. Prostate-specific antigen (PSA)

3.6.1. PSA and PV prediction

Several reports have demonstrated the reliability of serum PSA for predicting PV [45–47]. However, determination of exact PV for an individual from PSA does not seem to be possible because of the relatively large standard deviation for the estimation curve [48].

3.6.2. PSA and PCa probability

The role of serum PSA in the diagnosis of PCa is described in the EAU guidelines on prostate cancer [49]. The benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient, including the possibilities of false-positive and false-negative results, complications of subsequent transrectal ultrasound (TRUS)-guided biopsy, false-negative biopsies, and overdiagnosis and overtreatment of PCa [49].

3.6.3. PSA and prediction of BPO-related outcomes

Serum PSA appears to be a stronger predictor of prostate growth than PV [50]. In addition, the PLESS study showed that PSA also predicted changes in LUTS, QoL/bother, and the maximum urinary flow rate (Q_{max}) [51]. In a longitudinal study of men managed conservatively, serum PSA was a highly significant predictor of clinical progression [52]. More importantly, in the placebo arms of large double-blind controlled studies, baseline serum PSA consistently predicted the risk of acute urinary retention (AUR) and BPE-related surgery [53, 54]. Patients with BPO appear to have higher serum PSA and greater PV compared to men without BPO [55]. The positive predictive value (PPV) of PSA for detection of BPO was recently shown to be 68% [56].

3.7. Renal function measurement

Renal function may be assessed by measurement of serum creatinine or calculation or determination of the estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency, and urinary retention appear with greater prevalence in patients with symptoms or signs of BPO [57]. Even though BPO may be partly responsible for these complications, there is no conclusive evidence that BPO is the primary cause [57]. One study evaluated 246 men presenting with LUTS and found that 11% had renal insufficiency [58]. The same study also noted that it was rather rare to find patients with high creatinine levels due to BPO alone [58]. Comiter et al. [59] reported that voiding

dysfunction of a non-neurogenic aetiology did not appear to be a risk factor for elevated creatinine levels. In addition, in the MTOPS study, less than 1% of men with LUTS presented with renal insufficiency during the observational period of at least 4 yrs. [54]. In 2741 consecutive patients who presented with LUTS, a decrease in Q_{max} and a history of hypertension and/or diabetes were significantly associated with chronic kidney disease [60]. A recent study demonstrated that Q_{max} correlated significantly with GFR in middle-aged men with moderate to severe LUTS [61, 62]. In addition, patients with renal insufficiency have a higher risk of developing postoperative complications compared to those with normal renal function [63].

3.8. Post-void residual urine

Post-void residual urine (PVR) can be measured by transabdominal ultrasonography, a bladder scan, or catheterisation. The interval between voiding and PVR measurement should be short [64]. Ultrasound (US) bladder volume measurement is generally the preferred approach for measuring PVR [64], which is not necessarily associated with BOO, since high PVR can be a consequence of BOO and/or poor detrusor function (underactivity) [65,66]. It has been shown that for volumes >50 ml, the diagnostic accuracy of PVR measurement has PPV of 63% and a negative predictive value (NPV) of 52% in determining BOO [62]. A large PVR is not a contraindication for watchful waiting or medical therapy, although PVR indicates bladder dysfunction and predict a poor response to treatment, especially to WW. In both the MTOPS and ALTESS studies, high baseline PVR was associated with an increased risk of symptom deterioration [53, 54]. In addition, monitoring of PVR changes over time could predict AUR occurrence; patients who subsequently developed AUR showed a steady increase in PVR [53]. This is of particular importance for the treatment of patients using antimuscarinic medication. By contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α_1-blocker therapy or WW [67]. However, owing to large test-retest variability and a lack of outcome studies, it is currently impossible to establish a PVR threshold for treatment decisions.

3.9. Uroflowmetry

Urinary flow rate assessment is a basic non-invasive urodynamic test that is widely used to evaluate the joint functioning of the lower urinary tract components (bladder and outlet). Key parameters are Q_{max}, voided volume, and flow pattern. Uroflowmetry parameters should ideally be evaluated when the voided volume is >150 ml. Q_{max} can be subject to within-subject variation on the same or different days [68,69]; therefore, it is advisable to repeat uroflowmetry measurements when the voided volume is <150 ml or Q_{max} or the flow pattern is abnormal. The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by diagnostic threshold values. A Q_{max} threshold of 10 ml/s had specificity of 70%, PPV of 70%, and sensitivity of 47% for BOO. For a Q_{max} threshold of 15 ml/s, specificity was 38%, PPV was 67%, and sensitivity was 82% [70]; thus, uroflowmetry alone is unsuitable for detection and quantification of BOO. Low Q_{max} can arise as a consequence of BOO [71], detrusor underactivity, or an underfilled bladder [72]. Thus,

uroflowmetry is limited as a diagnostic test as a consequence of the inability to discriminate underlying mechanisms in men with low Q_{max}. Specificity can be improved by repeated flow-rate testing in individual patients. Uroflowmetry can be used to monitor treatment outcomes [73] and correlate symptoms with objective findings.

3.10. Imaging

3.10.1. Upper urinary tract

Routine imaging of the upper urinary tract in men with LUTS is not recommended as these patients are not generally at higher risk of upper tract malignancy or other abnormalities (including hydronephrosis, measurable degrees of renal insufficiency, renal cysts) compared to the general population (see above) [74–77]. Several arguments support the use of renal US in preference to intravenous urography (IVU). US allows better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum at the same time, and evaluation of the bladder, PVR and prostate compared to IVU, at lower cost and without radiation exposure and side effects [75].

3.10.2. Prostate

Imaging of the prostate can be performed using several imaging techniques including transabdominal US, TRUS, computed tomography (CT), and magnetic resonance (MR) imaging. In daily practice, however, imaging of the prostate by TRUS or transabdominal US is mainly used [75]. PV measurement is important before treatment with 5-ARIs and for selection of an appropriate interventional treatment [35]. Recent data suggest that PV may predict which patients with LUTS will develop symptom progression and complications [54]. A large body of evidence documents the accuracy of TRUS in calculating PV. TRUS is superior to suprapubic (transabdominal) PV measurement because all three distances for the prostate can be measured more accurately via the transrectal approach [78,79]. The presence of a middle lobe protruding into the bladder may guide the treatment choice in patients scheduled for a minimally invasive approach. US measurement of intravesical prostatic protrusion (IPP) has also been introduced. The concept is that a prostate median lobe protruding into the bladder can cause a valve ball type of BPO with incomplete opening and disruption of the funnelling effect of the bladder neck [80]. IPP correlated well with BPO, with PPV of 94% and NPV of 79% [80], and also seems to predict successful outcome of trial without catheter after AUR [81,82]. Therefore, IPP may be a feasible option for diagnosing BPO in men with LUTS, but its role as a non-invasive alternative to pressure-flow studies (PFS) in the assessment of male LUTS is under evaluation, and currently no specific recommendations can be made.

3.10.3. Bladder/detrusor wall thickness and US-estimated bladder weight (UEBW)

For bladder wall thickness (BWT) assessment, the entire diameter of the bladder wall is measured, which represents the distance between the hyperechogenic mucosa and the hyperechogenic adventitia. For detrusor wall thickness (DWT) assessment, only the hypoechogenic

detrusor sandwiched between the hyperechogenic mucosa and adventitia is measured [83]. It has been shown that BWT and DWT measurements have higher diagnostic accuracy in detecting BOO than Q_{max} in free uroflowmetry or measurements of PVR, PV, or symptom severity [62]. Disadvantages of the method include the lack of standardisation in terms of threshold values and bladder filling so far, with varying results for different bladder filling levels, and a lack of evidence of whether BWT or DWT is more clinically relevant [84]. The concept of bladder weight (BW) as a measure of bladder wall hypertrophy has also been introduced [85]. Comparison of UEBW and PFS revealed that UEBW could identify BOO with a diagnostic accuracy of 86.2% using a cut-off value of 35 g [86]. Measurement of BWT or DWT and UEBW may be a feasible option for diagnosing BOO in men with LUTS. The role of BWT, DWT, and UEBW as a non-invasive alternative to PFS in the assessment of male LUTS or BOO is under evaluation, and currently no specific recommendations can be made.

3.11. Urethro-cystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture (or relevant risk factors, such as history of urethritis, urethral injury, urethral instrumentation, or previous urethral surgery), or bladder cancer who present with LUTS should undergo urethro-cystoscopy during diagnostic evaluation. Several studies have addressed whether urethro-cystoscopy findings correlate with functional data [87–89]. In the largest study, urethroscopic findings were correlated to urodynamic studies in 492 elderly men with LUTS [89]. Correlation between cystoscopic appearance (grade of bladder trabeculation and grade of urethral occlusion) and urodynamic indices, detrusor overactivity, and low compliance was observed. It should be noted, however, that BOO was present in approximately 15% of patients with normal cystoscopic findings, while approximately 8% of patients had no BOO even in the presence of severe trabeculation [89]. Evaluation of a prostatic middle lobe in urethro-cystoscopic findings is necessary to determine the indication for certain interventional treatments, such as transurethral needle ablation and transurethral microwave therapy.

3.12. Urodynamics (computer urodynamic investigation)

In male LUTS, the most widespread urodynamic techniques used are filling cystometry (to assess the bladder storage phase) and PFS (to assess the voiding phase). The major aims of urodynamics are to explore the functional mechanisms of LUTS and identify potential risk factors for adverse outcomes (for informed/shared decision-making). Most parameters and diseases or conditions (e.g., detrusor overactivity, low compliance, BOO/BPO, detrusor underactivity) are identified by urodynamic investigation.

3.12.1. Diagnosing BOO

PFS are the basis for identifying BOO and are the primary objective in ascertaining its presence. BOO involves increased detrusor pressure and decreased urinary flow during voiding. BOO/BPO has to be differentiated from detrusor underactivity, which is defined as decreased detrusor pressure during

voiding in combination with a decreased urinary flow rate. During the storage phase, urodynamic testing of overactive bladder (OAB) patients may identify detrusor overactivity (DO), which is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. OAB is diagnosed from the patient's symptoms, based on the presence of urgency, usually with increased daytime frequency, nocturia, and/or urgency incontinence [4]. Thus, the terms OAB and DO are not interchangeable. For instance, in one study, 21% of men with urinary urgency did not have DO [90], and DO can be asymptomatic; several studies have described an association between BOO and DO [91,92]. In men with LUTS attributed to BPE, DO was present in 61% of patients (n = 1418) and independently associated with BOO grade and ageing. As BOO grade and patient age increased, DO prevalence increased, ranging from 50% in men without BOO to 83% in men with the most severe BOO [93]. Prevalence estimates of detrusor underactivity in men with LUTS vary between 11% and 40% [93,94]. Detrusor contractility does not appear to decline in long-term BOO, and surgical relief of BOO does not improve contractility [95,96]. No randomised studies were identified regarding the usefulness of cystometry in guiding clinical management for patients with LUTS. Furthermore, there are no published RCTs comparing standard investigation (uroflowmetry and PVR measurement) with PFS in men with LUTS and possible BPO.

Owing to the invasive nature of urodynamic testing because of catheter placement, computer urodynamic investigation is generally only offered once conservative treatment has failed. The panel attempted to suggest specific indications for PFS based on age, findings from other diagnostic tests, and previous treatments. These include situations in which the diagnosis of BPO is uncertain and the patient has a significant chance of additional problems such as detrusor overactivity or underactivity. The panel allocated different degrees of obligation for PFS in men >80 yrs. and men <50 yrs., and this may reflect the lack of clear evidence (**Table 1**). In addition, there was no consensus on whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} >10 ml/s, although the panel recognised that BOO is likely for Q_{max} <10 ml/s and PFS are not necessarily needed. It should be underlined that patients with neurological disease, including those with previous radical pelvic surgery, should be assessed according to the EAU guidelines on neurogenic lower urinary tract dysfunction [97].

3.12.2. Videourodynamics

Inclusion of intermittent synchronous x-ray imaging and filling of the bladder with contrast medium for cystometry and PFS is termed videourodynamics. The test provides additional anatomical information. During filling, imaging is usually undertaken in the postero-anterior axis and can show bladder configuration (bladder trabeculation and diverticula), vesico-ureteral reflux, or pelvic floor activity. During voiding, a 45° lateral projection is typically used and can show the exact location of BOO. Videourodynamics may be used when there is uncertainty regarding the mechanisms of voiding LUTS.
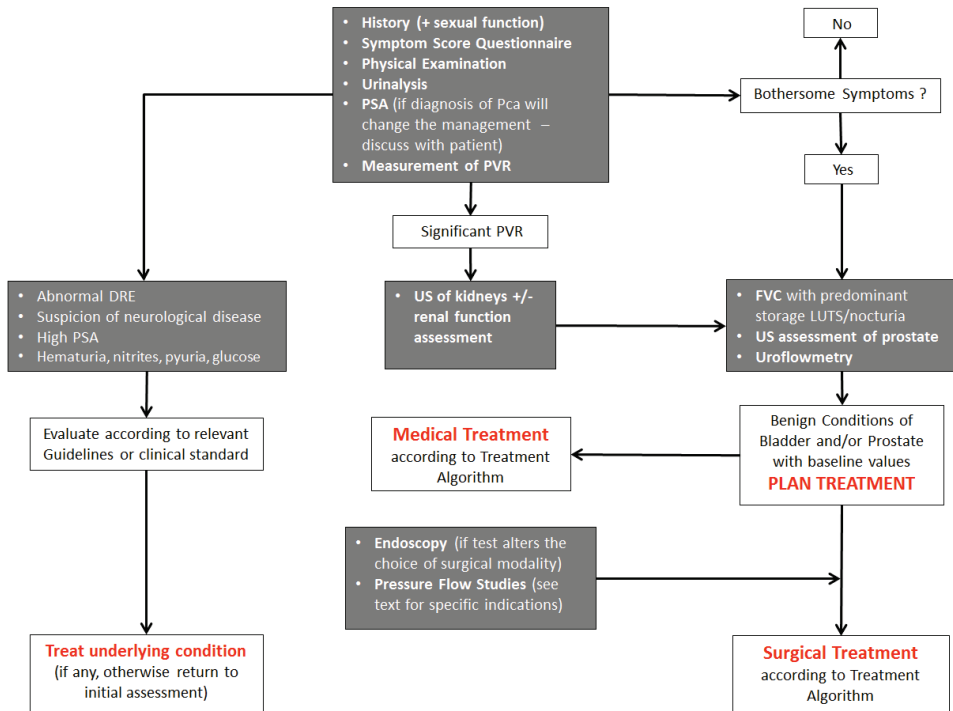
Figure 2: Algorithm for assessment of lower urinary tract symptoms (LUTS) in men aged ≥40 yr. DRE = digital rectal examination; PCa = prostate cancer; PSA = prostate-specific antigen; PVR = post-void residual urine; US = ultrasound.

4.   CONCLUSIONS

Tests are useful for diagnosis, monitoring, assessment of the prognosis for disease progression, treatment planning, prediction of treatment outcome, and ascertainment of patient values and preferences. Standardisation of LUTS assessment in men represents a significant challenge because of the low LE of existing studies. The guidelines presented here are not an update of the BPH guidelines published in 2004. The multifactorial view of the aetiology of LUTS has been adopted and a broader approach to the assessment of men suffering from LUTS has been introduced. In addition, for the first time in the male LUTS guidelines, the panel used the Delphi consensus method to strengthen the value of its recommendations. A practical algorithm based on the recommendations has been developed (**Figure 2**). It should also be noted that the low LE for the majority of diagnostic tests emphasises the need for high-LE studies to determine the value of each diagnostic tool.

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CHAPTER 10

EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms, including Benign Prostatic Obstruction

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ABSTRACT

Objective: To present a summary of the 2013 version of the EAU Guidelines on the treatment and follow-up of male lower urinary tract symptoms (LUTS).

Evidence acquisition: Literature search in computer databases for relevant articles published between 1966 and 31st October 2012. The Oxford classification system (2001) was used to determine the level of evidence for each article and to assign the grade of recommendation for each treatment modality.

Evidence synthesis: Men with mild symptoms are suitable for watchful waiting. All men with bothersome LUTS should be offered lifestyle advice prior to or concurrent with any treatment. Men with bothersome moderate-to-severe LUTS quickly benefit from α_1-blockers. Men with enlarged prostates, especially those >40 ml, profit from 5α-reductase inhibitors which slowly reduce LUTS and the probability of urinary retention or need for surgery. Antimuscarinics might be considered in patients who have predominant bladder storage symptoms. The phosphodiesterase 5 inhibitor tadalafil can quickly reduce LUTS to a similar extent to α_1-blockers and, additionally, improves erectile dysfunction. Desmopressin can be used in men with nocturia due to nocturnal polyuria. Combination treatment with α_1-blocker and 5α-reductase inhibitor (in men with enlarged prostates) or antimuscarinics (with persistent storage symptoms) combines positive effects of either drug class to achieve greater efficacy. Prostate surgery is indicated in men with absolute operation indications or drug treatment-resistant LUTS due to BPO. Transurethral resection of the prostate (TURP) is the current standard operation for men with prostates 30-80 ml, whereas open surgery or transurethral Holmium laser enucleation is for men with prostates >80 ml. Alternatives for monopolar TURP

include bipolar TURP, and transurethral incision of the prostate (for glands <30 ml) and laser treatments. Transurethral microwave therapy and transurethral needle ablation are effective minimally invasive treatments with higher re-treatment rates compared to TURP. Prostate stents are an alternative to catheterisation for men unfit for surgery. Ethanol or botulinum toxin injections into the prostate are still experimental.

Conclusions: These symptom-oriented guidelines provide practical guidance for the management of men suffering of LUTS. The full version is available online at www.uroweb.org/gls/pdf/12_Male_LUTS.pdf.

1. INTRODUCTION

Lower urinary tract symptoms (LUTS) in elderly men were traditionally attributed to the enlarging prostate. The mechanisms invoked were one or all of the following: histologic benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), or benign prostatic obstruction (BPO). However, during the last decade the causal link between the prostate and the pathogenesis of LUTS has come into question [1]. Although the enlarged prostate can contribute to the onset of LUTS in a proportion of men >40 yrs. of age, other factors are of equal importance. **Figure 1** illustrates the many causes of LUTS. In any single person complaining of LUTS, it is common for more than one of these factors to be present. This multifactorial view of the aetiology of LUTS has led most experts to regard the whole urinary tract as a single functional unit. This broader, more complex approach to the pathogenesis of LUTS meant that this guidelines panel modified the title (to reflect the change in perspective) from the former ''EAU [European Association of Urology] Guidelines on LUTS Suggestive of BPO (BPH)'' [2] to the more contemporary and precise ''EAU Guidelines on Non-neurogenic Male LUTS Including BPO.'' Because patients seek help for LUTS and not an underlying attribute of the prostate such as BPH or BPE, these updated guidelines have been written from the perspective of men who complain about a variety of bladder storage, voiding, and/or post-micturition symptoms. The recommendations made within the guidelines are based on the best available evidence. These recommendations apply to men ≥40 yrs. of age who seek professional help for various forms of non-neurogenic benign forms of LUTS, for example, LUTS/BPO, detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. EAU guidelines on LUTS due to neurologic diseases [3], urinary incontinence [4], urogenital infections [5], ureteral stones [6], or malignant diseases of the lower urinary tract [7] have been published elsewhere.
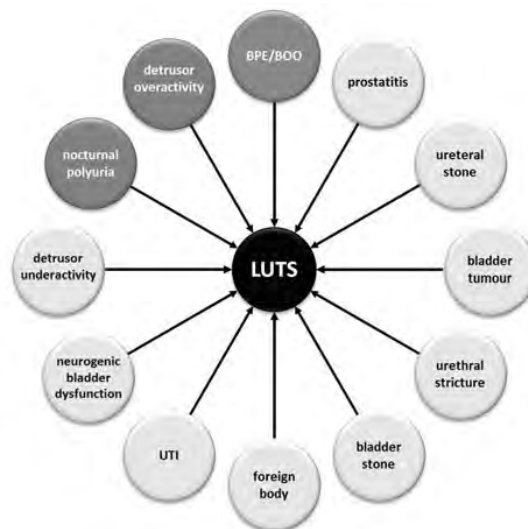
Figure 1: Multifactorial aetiology of lower urinary tract symptoms (LUTS). The EAU Guidelines on Non-Neurogenic Male LUTS mainly covers LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder (OAB), and nocturia due to nocturnal polyuria. Other causes of male LUTS are covered by separate EAU Guidelines [3-7].

2.   EVIDENCE ACQUISITION

The recommendations of these guidelines are based on a literature search using articles in the English language published in the PubMed/Medline, Web of Science, and Cochrane databases between 1966 and 31 October 2012, including the search terms lower urinary tract symptoms, benign prostatic hyperplasia, detrusor overactivity, overactive bladder, nocturia, and nocturnal polyuria in combination with the various treatment modalities and the search limits humans, adult men, review, randomised clinical trials, clinical trials, and meta-analysis (**Table 1**). Each extracted article was separately analysed, classified, and labelled with a level of evidence (LE) according to a classification system modified from the Oxford Centre for Evidence-based Medicine in 2001 (**Table 2a**) [8]. Subsections for the various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing (1) mechanism of action, (2) available drugs with a table of key pharmacokinetic profiles (for this article summarised in **Table 3**), (3) efficacy with a table of trials with the highest LE, (4) tolerability and safety, (5) practical considerations, and (6) recommendations drawn from the relevant articles using a grade of recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine (**Table 2b**) [8]. The full analysis of the literature with all tables, recommendations, and conclusions is available online on the EAU home page (www.uroweb.org/gls/pdf/12_Male_LUTS.pdf); this article summarises these analyses and lists all Les and GRs of analysed treatment modalities in one table (**Table 4**). The guidelines panel consisted of urologists, a pharmacologist, and an epidemiologist and statistician who have been working on the topic for the last 6 yr. The guidelines are primarily written for urologists but can also be used by general practitioners, patients, or other stakeholders. The guidelines panel intends to update the content and recommendations according to the given structure and classification systems every 2 yr.

Table 1: Literature search methodology

Databases: PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/)		
Web of Science (http://apps.webofknowledge.com)		
Cochrane (http://www.cochrane.org/)		
Language: English		
Literature Search: conducted 1st February - October 2012		
Search Period: 1966 – October 2012		
Search limits …	For group search terms … (AND)	In combination with investigated drugs, operations, or synonyms (AND)
humans **AND** adult men **AND** review **OR** randomised clinical trials **OR** clinical trials **OR** meta-analysis	- lower urinary tract symptoms - benign prostatic hyperplasia - detrusor overactivity - overactive bladder - nocturia - nocturnal polyuria	-alpha-adrenoceptor antagonist -adrenergic alpha-1 receptor antagonists - alpha-blocker - alfuzosin - doxazosin

		- tamsulosin
		- terazosin
		- 5α-reductase inhibitor
		- dutasteride
		- finasteride
		-PDE5
		-tadalafil
		-sildenafil
		-vardenafil
		-Prostatectomy
		-open
		-monopolar transurethral
		-bipolar transurethral
		- laser
		-ablation
		-resection
		-vaporisation
		-enucleation
		- microwave thermotherapy
		- transurethral needle ablation
		-ethanol injections
		- botulinum injections

Table 2a: Level of Evidence (LE), modified from the Oxford Centre for Evidence Based Medicine [8]

Level	Type of Evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative or correlation studies and case reports
4	Evidence obtained from expert committee reports or options or clinical experience of respected authorities

Table 2b: Grade of Recommendation (GR), modified from the Oxford Centre for Evidence Based Medicine [8]

Grade	Recommendation
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

3. EVIDENCE SYNTHESIS

3.1. Conservative treatment

Many men with LUTS are not bothered enough by their symptoms to need drug treatment or surgical intervention. Most of these men can be managed conservatively by a process known as watchful waiting (WW). All men with LUTS should be formally assessed prior to any allocation of treatment. The aim of this assessment is to establish the severity of LUTS and to discriminate the vast majority of men with so-called uncomplicated LUTS that pose no threat to life expectancy from the more unusual presentation of complicated LUTS that might do. Men with mild-to-moderate uncomplicated LUTS, who are not too bothered by their symptoms, are suitable for WW. It is customary for this type of management to include the following components: education, reassurance, lifestyle advice, and periodic monitoring [9–12] that include:

- Reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g., at night or going out in public).
- Avoidance or moderation of caffeine or alcohol that may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency, and nocturia.
- Use of relaxed and double-voiding techniques.
- Urethral milking to prevent post-micturition dribble.
- Distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms.
- Bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids.
- Reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects. These recommendations apply especially to diuretics.
- Providing necessary assistance when there is impairment of dexterity, mobility, or mental state.
- Treatment of constipation.

Table 3: Key pharmacokinetic properties and standard doses of drug therapy licensed in Europe for treating LUTS

Drug (class)	t_{max} [hours]	t½ [hours]	Recommended daily dose
α_1-adrenoceptor antagonists (for treating 'signs or symptoms of BPH')			
Alfuzosin IR	1.5	4-6	3 x 2.5 mg
Alfuzosin SR	3	8	2 x 5 mg
Alfuzosin XL	9	11	1 x 10 mg
Doxazosin IR	2-3	20	1 x 2-8 mg
Doxazosin GITS	8-12	20	1 x 4-8 mg
Silodosin	2.5	11-18	1 x 4-8 mg
Tamsulosin MR	6	10-13	1 x 0.4 mg
Tamsulosin OCAS	4-6	14-15	1 x 0.4 mg
Terazosin	1-2	8-14	1 x 5-10 mg
5α-reductase inhibitors (for treating 'benign prostatic enlargement due to BPH')			
Dutasteride	1-3	3-5 weeks	1 x 0.5 mg
Finasteride	2	6-8	1 x 5 mg
Antimuscarinic drugs (for treating 'OAB/storage symptoms')			
Darifenacin	7	12	1 x 7.5-15 mg
Fesoterodine	5	7	1 x 4-8 mg
Oxybutynin IR	0.5 - 1	2 - 4	3-4 x 2.5-5 mg
Oxybutynin ER	5	16	2-3 x 5 mg
Propiverine	2.5	13	2-3 x 15 mg
Propiverine ER	10	20	1 x 30 mg
Solifenacin	3 - 8	45 - 68	1 x 5-10 mg
Tolterodine IR	1 - 3	2-10	2 x 1-2 mg
Tolterodine ER	4	6 - 10	1 x 4 mg
Trospium IR	5	18	2 x 20 mg
Trospium ER	5	36	1 x 60 mg
Vasopressin analogue (for treating 'nocturnal polyuria')			
Desmopressin tbl.	1 - 2	3	1 x 0.1-0.4 mg orally before sleeping
Desmopressin oral lyophilisate (MELT)	0.5 - 2	2.8	1 x 60-240 µg * sublingually before sleeping
Phosphodiesterase 5 Inhibitors (for treating 'signs or symptoms of benign prostatic hyperplasia with or without erectile dysfunction')			
Tadalafil	2 (0.5-12)	17.5	1 x 5 mg

LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia; ER: extended release; GITS: gastrointestinal therapeutic system; IR: immediate release; MR: modified release; OAB: overactive bladder; OCAS: oral controlled absorption system; SR: sustained release; t_{max}: time to maximum plasma concentration; t½: elimination half-life; * equivalent to tablet doses of 0.1 - 0.4 mg

Table 4: Level of Evidence (LE) and Grade of Recommendation (GR) for the various treatments of male LUTS and follow-up

		LE	GR
CONSERVATIVE TREATMENT – WATCHFUL WAITING			
	Men with mild symptoms are suitable for watchful waiting.	1b	A
	Men with LUTS should be offered lifestyle advice prior to or concurrent with treatment.	1b	A
DRUG TREATMENT			
1.	α_1-Blockers should be offered to men with moderate-to-severe LUTS, especially to those with prostate volumes <40 ml.	1a	A
2.	5α-reductase inhibitors should be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 ml). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A
3.	Muscarinic receptor antagonists might be considered in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.	1b	B
	Caution is advised in men with BOO.	4	C
4.	Tadalafil 5 mg once daily reduces moderate-to-severe male (storage and voiding) LUTS, with or without erectile dysfunction.	1a	A
	Sildenafil or vardenafil are currently restricted to men with erectile dysfunction or pulmonary arterial hypertension. Treatment of male LUTS with these (or other) PDE5 inhibitors should only be performed in clinical trials.	1b	A
	Insufficient information is available on the combination treatment of tadalafil + α_1-blocker (or other drugs) and, therefore, combination treatment should only be used in clinical trials.	1b	A
5.	Desmopressin can be used for the treatment of nocturia due to nocturnal polyuria.	1b	A
6.	Combination treatment with an α_1-blocker together with a 5α-reductase inhibitor should be offered to men with bothersome moderate-to-severe LUTS, enlarged prostates, and reduced Q_{max} (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (<1 year).	1b	A
7.	Combination treatment with an α_1-blocker together with a muscarinic receptor antagonists might be considered in patients with bothersome moderate-to-severe LUTS if symptom relief has been insufficient with the monotherapy of either drug. Combination treatment should cautiously be prescribed in men who are suspicious of having BOO.	1b	B
		2b	B
SURGICAL TREATMENT			
1.	Monopolar TURP is the current surgical standard procedure for men with prostate sizes of 30-80 ml and bothersome moderate-to-severe LUTS secondary of BPO. Monopolar TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
	Bipolar TURP achieves short-term results comparable to monopolar TURP.	1a	A
	TUIP is the surgical therapy of choice for men with prostate sizes <30 ml, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A
2.	Open prostatectomy is the first choice of surgical treatment in men with prostate sizes >80 ml, bothersome moderate-to-severe LUTS secondary to BPO, and LUTS refractory to drugs in the absence of a Holmium laser.	1b	A

	Open prostatectomy is the most invasive surgical method with significant morbidity.	1b	A
3.	TUMT achieves symptom improvement comparable to TURP, but is associated with decreased morbidity and lower flow improvements.	1a	A
	Durability is in favour of TURP with lower re-treatment rates compared to TUMT.	1a	A
4.	TUNA™ is an alternative to TURP for patients who wish to defer/avoid (complications of) TURP, but patients should be aware of significant re-treatment rates and less improvement in symptoms and quality of life.	1a	A
5.	HoLEP and 532 nm laser vaporization of the prostate are minimally-invasive alternatives to TURP in men with moderate-to-sever LUTS due to BPO. Laser operations lead to immediate, objective and subjective improvements comparable to TURP.	1b	A
	With regard to intra-operative safety, 532 nm laser vaporization is superior to TURP and should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B
	With regard to long-term complication rates, results are only available for HoLEP, and are comparable to TURP.	1b	A
6.	Prostatic stents are an alternative to catheterisation for men unfit for surgery. Stents may have a role in the temporary relief of LUTS/BPO after minimally invasive treatment.	3	C
7.	Intra-prostatic ethanol injections for men with moderate-to-severe LUTS secondary to BPO are still experimental and should be performed only in clinical trials.	3	C
8.	Intra-prostatic BTX injections for men with bothersome moderate-to-severe LUTS secondary to BPO or men in urinary retention are still experimental and should be performed only in clinical trials.	3	C
FOLLOW-UP			
	Follow-up for all conservative, medical or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence based studies.	3-4	C

BOO: bladder outlet obstruction; BPH: benign prostatic hyperplasia; BPO: benign prostatic obstruction; BTX: botulinum toxin; HoLEP: holmium laser enucleation; LUTS: lower urinary tract symptoms; PDE5 inhibitor: phosphodiesterase 5 inhibitor; TUMT: transurethral microwave therapy; TUNA™: transurethral needle ablation; TURP: transurethral resection of the prostate

3.2. Drug treatment

3.2.1. α_1-Adrenoceptor antagonists (α_1-blockers)

3.2.1.1. Mechanisms of action

Contraction of the human prostate is mediated predominantly, if not exclusively, by α_{1A}-adrenoceptors [13]. α_1-Adrenoceptors in blood vessels, other nonprostatic smooth muscle cells, and the central nervous system are considered mediators of adverse events during α_1-blocker treatment, and all three receptor subtypes (α_{1A}, α_{1B}, and α_{1D}) seem to be involved. This concept has favoured the use of α_{1A}-selective blockers.

3.2.1.2. Available drugs.

Five types of α_1-blockers are currently in mainstream use: alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin (**Table 3**). Indoramin and naftopidil are also available in a few countries but not discussed in these guidelines.

3.2.1.3. Efficacy

Indirect comparisons between α_1-blockers and limited direct comparisons demonstrate that all α_1-blockers have a similar efficacy in appropriate doses [14]. Although these improvements take a few weeks to develop fully, significant efficacy over placebo was demonstrated within hours to days. α_1-Blockers have a similar efficacy, expressed as a percentage improvement in International Prostate Symptom Score (IPSS) in patients with mild, moderate, or severe LUTS [15]. Controlled studies have shown that α_1-blockers typically reduce IPSS, after a placebo run-in period, by approximately 30 - 40% and increase the maximum flow rate (Q_{max}) by approximately 20 - 25%. In open-label studies (without a run-in period), an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented. α_1-Blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect α_1-blocker efficacy in studies with follow-up periods of ≤1 yrs., but patients with smaller prostates (<40 ml) seem to have better efficacy compared with those with larger glands in longer-term studies [16–19]. α_1-Blocker efficacy is similar across age groups [15]. α_1-Blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies [16–18,20]; therefore, some patients must be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during α_1-blocker treatment appears to be maintained over at least 4 yr.

3.2.1.4. Tolerability and safety

Distribution into lower urinary tract tissues, subtype selectivity, and the pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α_1-blockers are asthenia, dizziness, and (orthostatic) hypotension. In particular, patients with cardiovascular comorbidity and/or vasoactive co-medication may be susceptible to α_1-blocker–induced vasodilatation [21]. In contrast, the frequency of hypotension with the α_{1A}-selective blocker silodosin is comparable with placebo. The intraoperative floppy iris

syndrome was only discovered in 2005 in the context of cataract surgery [22], and tamsulosin has the greatest risk. A systematic review concluded that a1-blockers do not adversely affect libido. They have a small beneficial effect on erectile function but sometimes cause abnormal ejaculation (i.e., decrease or absence of seminal fluid during orgasm) [23]. Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation [24].

3.2.1.5. Practical considerations

α_1-Blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, as well as the low rate and severity of adverse events. Ophthalmologists should be informed about α_1-blocker use prior to cataract surgery.

3.2.2. 5α-reductase inhibitors

3.2.2.1. Mechanism of action

5α-reductase inhibitors (5-ARIs) block the conversion of testosterone to dihydrotestosterone in prostatic stroma cells by blocking the enzyme 5α-reductase and inducing apoptosis of prostate epithelial cells leading to a 18 - 28% prostate size reduction and about a 50% reduction in circulating prostate-specific antigen (PSA) levels after 6 - 12 mo of treatment [25,26].

3.2.2.2. Available drugs

Dutasteride and finasteride are available for clinical use (**Table 3**). Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5a-reductase types 1 and 2 with similar potency (dual 5-ARI). However, the clinical benefit of dual inhibition remains unclear.

3.2.2.3. Efficacy

Clinical effects relative to placebo are seen after minimum treatment duration of ≥6 - 12 mo. After 2 - 4 yrs. of treatment, 5-ARIs reduce LUTS (IPSS) by 15 - 30%, decrease prostate volume by 18 - 28%, and increase Q_{max} by 1.5 - 2.0 ml/s in patients with LUTS due to BPE. Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [26,27]. Symptom reduction depends on initial prostate size and may not be more efficacious than placebo in patients with prostates <40 ml [28]. Comparative studies with α_1-blockers and a recent meta-analysis have demonstrated that 5-ARIs reduce LUTS more slowly and that finasteride is less effective than either doxazosin or terazosin but equally effective compared with tamsulosin [20,29–31]. A long-term trial with dutasteride in symptomatic men with prostate volumes >30 ml and increased risk for disease progression showed that dutasteride reduced LUTS in these patients at least as much or even more effectively than the α_1-blocker tamsulosin [17,18,32]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride. 5-ARIs, but

not α_1-blockers, reduce the long-term (>1 yr) risk of acute urinary retention or need for surgery [20,33,34]. In the Proscar Long-Term Efficacy and Safety Study after 4 yr, finasteride treatment reduced the relative risk of acute urinary retention (AUR) by 57% and surgery by 55% compared with placebo [34]. In the Medical Therapy of Prostatic Symptoms (MTOPS) study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [20]. A pooled analysis of randomised trials with 2-yr follow-up data reported that treatment with finasteride significantly decreased the occurrence of AUR by 57% and surgical intervention by 34% relative to placebo in patients with moderately symptomatic BPH [35]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Pooled phase 3 studies have shown a reduced relative risk of AUR (57%) and a surgical intervention (48%) compared with placebo at 2 yr [36]. In addition, this reduction was maintained to 4 yr during the open-label phase of the study [37].

3.2.2.4. Tolerability and safety

The most relevant adverse effects are related to sexual function and include reduced libido, erectile dysfunction, and, less frequently, ejaculation disorders [18,20]. The incidence of sexual dysfunction and other adverse events is low and decreased with trial duration. Gynecomastia (breast enlargement with breast or nipple tenderness) develops in approximately 1 - 2% of patients. Data from two important trials on Prostate Cancer chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARI arms compared with placebo arms [38,39]. Although no causal relationship between 5-ARIs and high-grade prostate cancer has been proven, men taking a 5-ARI should be followed up regularly using serial PSA testing. Any confirmed increase in PSA while on a 5-ARI should be evaluated.

3.2.2.5. Practical considerations

Treatment with 5-ARIs should only be recommended in men with bothersome moderate-to-severe LUTS and enlarged prostates (prostate volume >40 ml) or elevated PSA concentrations (>1.4 ng/ml). Due to the slow onset of action, 5-ARIs are only suitable for long-term treatment.

3.2.3. Muscarinic receptor antagonists

3.2.3.1. Mechanism of action

Muscarinic receptors are densely expressed on detrusor smooth muscle cells and other cell types, such as epithelial cells of the salivary glands and the prostate, urothelial cells of the urinary bladder, or nerve cells of the peripheral or central nervous system. Inhibition of muscarinic receptors reduces smooth muscle cell contractions and the sensory threshold of the bladder. Antimuscarinic effects might also be induced or modulated by the urothelium and/or by the central nervous system.

3.2.3.2. Available drugs

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms in both men and women: darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride (**Table 3**).

3.2.3.3. Efficacy

Muscarinic receptor antagonists have been tested predominantly in women in the past because it was believed that LUTS in women are caused by the bladder and, therefore, have to be treated with bladder-specific drugs. Four *post hoc* analyses (two analyses with tolterodine extended release, one with solifenacin 5 mg, and one with fesoterodine 4 and 8 mg) of data from large randomized controlled trials (RCTs) on the treatment of OAB in women and men without presumed bladder outlet obstruction (BOO) were performed focusing only on the group of men [40–43]. It was demonstrated that tolterodine can significantly reduce urgency incontinence, daytime or 24-h frequency, and urgency-related voiding and improve patient perception of treatment benefit compared with placebo. Solifenacin significantly improved mean Patient Perception of Bladder Condition scores, mean scores on the OAB-q and overall perception of bladder problems, and fesoterodine had significantly greater median percentage improvements in micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes whereas significantly greater percentages reported a treatment response versus placebo. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS were significantly reduced compared with baseline values after 12–25 wks [44, 45].

Few studies have investigated the efficacy of monotherapy with antimuscarinics for male patients with BOO and OAB symptoms with unsatisfactory findings. In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety Study, patients who received tolterodine as monotherapy were significantly improved only in urge incontinence, but they did not show any significant improvement in urgency, IPSS (either total or storage sub-score), and the overall percentages of patients reporting treatment benefit compared with placebo [46]. A further analysis showed that men with PSA levels <1.3 ng/ ml (smaller prostates) might profit more from antimuscarinic drugs [47]. Two other studies [44,48] found a positive effect of antimuscarinics in patients with OAB and concomitant BOO. In a small RCT without placebo, patients in the propiverine hydrochloride arm experienced improvement in urinary frequency and urgency episodes compared with baseline [48]. In an open-label study, tolterodine decreased the mean 24-h micturition and nocturia, and mean American Urological Association Symptom Index scores significantly improved [44].

3.2.3.4. Tolerability and safety

Muscarinic receptor antagonists are generally well tolerated. Compared with placebo, drug-related adverse events appear with higher frequencies for dry mouth (≤16%), constipation (≤4%), micturition difficulties (≤2%), nasopharyngitis (≤3%), and dizziness (≤5%). Increase of postvoid residual (PVR) urine in men without BOO is minimal and not significantly different compared with placebo (0 - 5 ml vs -3.6 to 0 ml). The incidence of urinary retention in men without BPO was comparable with placebo in trials with tolterodine (0 - 1.3% vs. 0 - 1.4%). Short-term treatment with antimuscarinic drugs (tolterodine) in men with BOO appears safe [49].

3.2.3.5. Practical considerations

Although not all antimuscarinic agents have been tested in elderly men with LUTS and OAB symptoms, they likely present similar efficacy and adverse events. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are not yet available; therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised.

3.2.4. Phosphodiesterase type 5 inhibitors

3.2.4.1. Mechanism of action

PDE type 5 inhibitors (PDE5-Is) increase the concentration and prolong the activity of intracellular cyclic guanosine monophosphate, thereby reducing smooth muscle tone of the detrusor, prostate, and urethra. PDE4 and PDE5 are the predominant isoenzymes in the lower urinary tract [50]. Nitric oxide and PDEs might also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [51]. It has also been proposed that PDE-Is increase blood perfusion and oxygenation of the lower urinary tract, but the exact mechanism of action of PDE-Is remains to be determined.

3.2.4.2. Available drugs

Although three selective oral PDE5-Is (sildenafil, tadalafil, and vardenafil) have been licensed in Europe for the treatment of erectile dysfunction and clinical trials have been conducted in patients with male LUTS with all of them, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe (**table 3**).

3.2.4.3. Efficacy

RCTs on the efficacy of all three available oral PDE5-Is have been published during the last few years. A recent meta-analysis (3214 men with a median follow-up of 12 wks.) reported that monotherapy with a PDE5-I achieved a significant improvement in the International Index of Erectile Function (IIEF) score (+5.5) and IPSS (-2.8), but no significant improvement in Q_{max} was found (0.00) compared with placebo [52]. With regard to tadalafil 5 mg, it was found that it significantly reduces IPSS after a run-in period by 22–37% (4.7 - 6.6 IPSS points; IPSS points relative to placebo: 2.1 - 4.4) [53,54]. Significant LUTS (IPSS) reduction has been documented with tadalafil as early as 1 wk. of treatment. In the latter RCT not included in the meta-analysis just cited, a statistically significant increase in Q_{max} with tadalafil compared with placebo (+2.4 ml/s) was reported for the first time [54]. Tadalafil had no significant impact on PVR. The combination of α_1-blockers with PDE5-Is has also been evaluated. A meta-analysis of five RCTs with a limited number of patients and short-term follow-up on the combination of a-blockers with PDE5-Is (two studies with tadalafil 20 mg, two studies with sildenafil 25 mg, and one with vardenafil 20 mg) versus a1-adrenergic blockers alone showed that the combination significantly improved Q_{max} (+1.5 ml/s), IPSS (-1.8), and IIEF score (+3.6) when compared with the use of α_1-blockers alone [52]. However, because only tadalafil 5 mg has been licensed, data on combinations of PDE5-Is and other LUTS medications are considered insufficient.

3.2.4.4. Tolerability and safety

PDE5-Is most frequently cause headache, back pain, dizziness, and dyspepsia. PDE5-Is are contraindicated in patients who use nitrates, potassium channel openers, nicorandil, or the α_1-blockers doxazosin or terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (<3 mo) or stroke (<6 mo), myocardial insufficiency (New York Heart Association stage >2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5-Is.

3.2.4.5. Practical considerations

To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS, with or without erectile dysfunction. Therefore, only tadalafil should be used clinically for the treatment of male LUTS. The meta-analysis on PDE5-Is suggested that younger men with a low body mass index and more severe LUTS profit the most from PDE5-I treatment [52]. Long-term experience with tadalafil in patients with LUTS is limited to one trial, and therefore judgement of efficacy or tolerability >1 yr is not possible. There is limited information at present about the reduction of prostate size and no information on slowing of disease progression.

3.2.5. Plant extracts: phytotherapy

Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (mono-preparations); others combine the extracts of two or more plants into one pill (combination preparations). The most widely used plants are *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. *Sabal serrulata*; berries of the American dwarf palm, saw palmetto), and *Urtica dioica* (roots of the stinging nettle). Various producers use different extraction techniques, distribute active ingredients with different qualitative and quantitative properties, or combine two or more herbal compounds into one pill. The extracts of the same plant produced by different companies do not necessarily have the same biologic or clinical effects; therefore, the effects of one brand cannot be extrapolated to others [55]. To complicate matters further, even two different batches of the same producer might contain different concentrations of active ingredients and cause different biologic effects [56]. Thus the pharmacokinetic properties can differ significantly between different plant extracts.

Available Cochrane meta-analyses suggest that (1) men treated with *Pygeum africanum* were twice as likely to report symptom improvement (although analysed trials did not use validated questionnaires, e.g., the IPSS), (2) men treated with *Secale cereale* were twice as likely to benefit from therapy compared with placebo, and (3) *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [57–59].

The guidelines committee has not made any specific recommendations on phytotherapy for the treatment of male LUTS because of the heterogeneity of the products, lack of regulatory framework, and the considerable methodological problems associated with the published trials and meta-analyses.

3.2.6. Vasopressin analogue: desmopressin

3.2.6.1. Mechanism of action

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and the control of urine production by binding to the V2 receptor in the renal collecting ducts. AVP increases water reabsorption as well as urinary osmolality and decreases water excretion as well as total urine volume. AVP might be used therapeutically to manipulate the amount of urine excretion; however, AVP also has V1 receptor-mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for the treatment of nocturia/nocturnal polyuria.

3.2.6.2. Available drugs

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties but has no relevant V1 receptor affinity and hypertensive effects. Desmopressin has been approved in most European countries for the treatment of nocturia secondary to nocturnal polyuria in adult patients (**Table 3**). The clinical effects, in terms of urine volume decrease and an increase in urine osmolality, last for approximately 8 - 12 h [60].

3.2.6.3. Efficacy

In pivotal clinical trials, desmopressin significantly reduced nocturnal diuresis by approximately 0.6 - 0.8 ml/min (-40%), decreased the number of nocturnal voids by approximately 0.8–1.3 (-40%), and extended the time until the first nocturnal void by approximately 1.6 - 2.1 h. Desmopressin significantly reduced night-time urine volume and the percentage of urine volume excreted at night [61–63]. A meta-analysis of the available RCTs found that desmopressin reduced significantly the overall number of nocturnal voids and increased significantly the hours of undisturbed sleep in comparison with placebo. However, these RCTs were conducted in extremely heterogeneous populations with variable dosages [64].

3.2.6.4. Tolerability and safety

The most frequent adverse events in short-term (≤3 wks.) and long-term studies (12 mo) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth, and hyponatremia (serum sodium concentration <130 mmol/l). Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial [63]. Hyponatremia of all degrees, not necessarily associated with symptoms, occurs in 5 - 7.6% of patients early after treatment initiation [65, 66]. The risk of

developing hyponatremia is significantly lower in men and significantly increases with age, lower serum sodium concentration at baseline, and higher basal 24-h urine volume per bodyweight [65]. The risk of hyponatremia in patients <65 yr of age is <1%, whereas the risk for older patients increases to 8%with normal sodium concentrations and up to 75% in patients with low sodium concentrations at baseline [65]. A recently published sub-analysis suggests that oral doses of 50 - 100 mg desmopressin (Melt) are safe in men [67].

3.2.6.5. Practical considerations

Desmopressin is indicated in patients with nocturia secondary to nocturnal polyuria and should be taken once daily before sleeping. Because the optimal dose differs between patients, desmopressin treatment should be initiated at a low oral dose (0.1 mg/d) and may be gradually increased every week until maximum efficacy is reached. The maximum oral daily dose recommended is 0.4 mg/d. Patients should avoid drinking fluids at least 1 h before using desmopressin and for 8 h after dosing. Serum sodium concentrations should be monitored at days 3 and 7 after starting therapy and regularly thereafter.

3.2.7. Combination therapies

3.2.7.1. α_1-Blockers plus 5α-reductase inhibitors

An α_1-blocker together with a 5-ARI aims to combine the differential effects of both drug classes with regard to symptom improvement and prevention of disease progression. Four year data analysis from MTOPS, as well as the 2- and 4-yr results from the Combination of Avodart and Tamsulosin (CombAT) trials, have been reported [17, 18, 20]. The latter trial included older men with larger prostates and higher serum PSA concentrations and therefore appears to represent men at greater risk of disease progression. In contrast to earlier studies with only 6 - 12 mo of follow-up, long-term data have demonstrated that combination treatment is superior to monotherapy with regard to symptom reduction and improvement in Q_{max} [17, 18, 20]. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy (vs placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [20]. In addition, finasteride, alone or in combination, but not doxazosin significantly reduced both risks of AUR and the need for BPH-related surgery over the 4-yr study. In the CombAT study, combination therapy reduced the relative risks of AUR by 67.8%, BPH-related surgery by 70.6%, and symptom deterioration by 41.3% compared with tamsulosin, after 4 yr [18].

Discontinuation of the α_1-blocker after 6 - 9 mo of combination therapy was investigated by an RCT and open-label multicentre trial [68, 69]. However, the main limitations of those studies include the short duration of the combination therapy and the short follow-up period after discontinuation. Adverse events of both drug classes are reported with combination treatment [17, 18 ,20]. α_1-Blockers together with 5-ARIs should be prescribed primarily in men with moderate-to-severe LUTS who are at risk of disease progression (e.g., higher prostate volume, higher PSA concentration, advanced age) and when the patient accepts long-term treatment (>12 mo).

3.2.7.2. α_1-Blockers plus muscarinic receptor antagonists

An α_1-blocker together with a muscarinic receptor antagonist aims to antagonise both α_1-adrenoceptors and M_2- and M_3-receptors in the lower urinary tract, thereby using the efficacy of both drug classes to achieve synergistic effects. Several RCTs [70–75] and prospective studies have evaluated the efficacy of the combination of α_1-blockers and muscarinic receptor antagonists either as initial treatment in men with OAB and presumed BPO or as sequential treatment in men with persistent storage symptoms despite treatment with an α_1-blocker. Combination treatment was more efficacious in reducing voiding frequency, nocturia, or IPSS compared with α_1-blockers or placebo alone. Combination treatment significantly reduced UUI episodes as well as urgency and significantly increased quality of life (QoL) [75]. Persistent LUTS during α_1-blocker treatment can be significantly reduced by the additional use of a muscarinic receptor antagonist, especially when detrusor overactivity had been demonstrated. Two systematic reviews (no statistical analyses were provided) of studies on the efficacy and safety of antimuscarinic agents (including tolterodine, oxybutynin, propiverine, solifenacin, trospium, and fesoterodine) for the treatment of LUTS, including OAB in men, supported that combination treatment provides significant benefit to those men [76, 77].

Adverse events of both drug classes are reported with combination treatment with α_1-blockers and muscarinic receptor antagonists. Some side effects (e.g., xerostomia or ejaculation failure) may appear with increased frequency and cannot simply be explained by adding the frequencies of adverse events of either drug. Combination studies of α_1-blockers and antimuscarinics that measured PVR volume showed an increase (but not clinically significant) in PVR, and the risk of AUR seems to be low [76,77]. A recent RCT investigated the safety in terms of maximum detrusor pressure and Q_{max} of the combination of solifenacin (6 and 9 mg) and tamsulosin in men with LUTS and BOO compared with placebo [78]. At the end of treatment the combination therapy was non-inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [78]. Class effects are likely to be responsible for increased efficacy and QoL in patients treated with an α_1-blocker and muscarinic receptor antagonist. Trials used mainly storage symptom end points, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR urine is recommended during combination treatment to assess increased PVR or urinary retention.

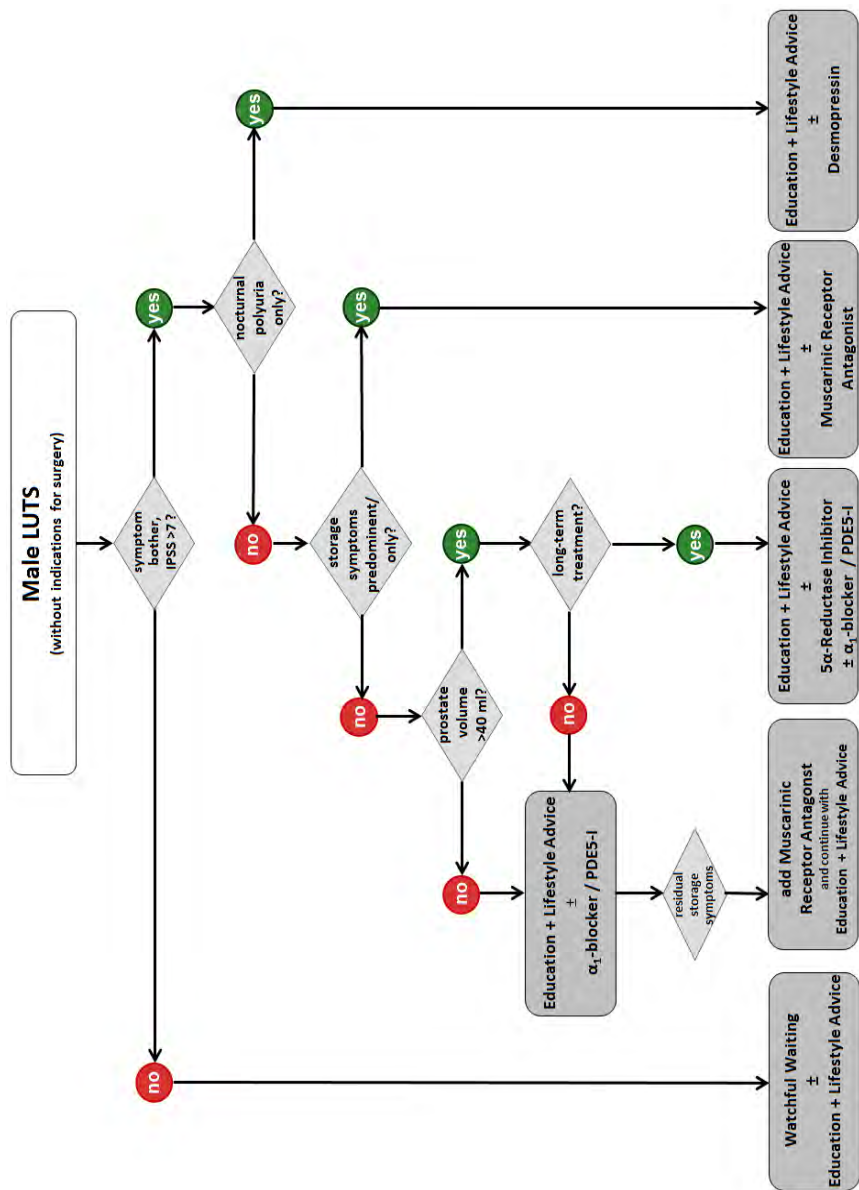**Figure 2:** Treatment algorithm of male lower urinary tract symptoms (LUTS) using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation (o).The absence ("No") or presence of the condition ("Yes") are indicated in circles (o). Note that patients' preferences may result in different treatment decisions. PDE5-I = phosphodiesterase type 5 inhibitor.

3.3. Surgical treatment

3.3.1. Transurethral resection and transurethral incision of the prostate

3.3.1.1. Mechanism of action

Transurethral resection of the prostate (TURP) aims to resect tissue from the transition zone of the prostate to treat LUTS secondary to BPO. TURP is still regarded as the standard surgical procedure for the treatment of LUTS secondary to BPO in prostates ≤80 ml. Transurethral incision of the prostate (TUIP) reduces BPO by splitting the bladder outlet without tissue removal.

3.3.1.2. Efficacy

In 1999, a meta-analysis of 29 RCTs found a mean decrease in LUTS of 70.6% and a mean increase in Q_{max} by 125% after TURP [79]. In a recent analysis of 20 contemporary RCTs published between 2005 and 2009 and a maximum follow-up of 5 yr, TURP resulted in a substantial improvement of mean Q_{max} (+162%) and a significant reduction of mean IPSS (-70%), mean QoL scores (-69%), and mean PVR urine (-77%) [80]. TURP also delivers durable clinical outcomes. One study with a mean follow-up of 13 yrs. reported a significant and sustained decrease in most symptoms and an improvement of urodynamic parameters following TURP; subjective and objective failures were associated with detrusor underactivity rather than redevelopment of BPO [81]. A meta-analysis of short- and long-term data from 10 RCTs comparing TUIP with TURP found similar LUTS improvements and lower but not significant improvements in Q_{max} for TUIP patients with small prostates but without enlarged prostate median lobes [82]. Meta-analysis of six trials showed that the need for reoperation was more common after TUIP (18.4%) than after TURP (7.2%) (relative risk: 2.40) [82].

3.3.1.3. Tolerability and safety

Perioperative complications include mortality during the first 30 d (0.1% after TURP), TUR-syndrome (<1.1% after TURP and 0% after TUIP), and blood transfusion (8.6% after TURP and negligible for TUIP) [79]. Similar results on TURP complications were reported by the analysis of the contemporary RCTs having TURP as comparator: bleeding requiring blood transfusion 2% (range: 0 - 9%), TUR-syndrome 0.8% (range: 0 - 5%), AUR 4.5% (range: 0 - 3.3%), clot retention 4.9% (range: 0 - 39%), and urinary tract infection (UTI) 4.1% (range: 0 - 22%) [80]. Long-term complications comprise urinary incontinence (1.8% following TUIP to 2.2% following TURP), urinary retention and UTIs, bladder neck stenosis (4.7% after TURP), urethral stricture (3.8% after TURP and 4.1% after TUIP), retrograde ejaculation (65.4% after TURP and 18.2% after TUIP), and erectile dysfunction (6.5% after TURP) [79].

3.3.1.4. Practical considerations

TURP and TUIP are both effective primary treatments for men with moderate-to-severe LUTS secondary to BPO. The choice between TURP and TUIP should be based primarily on prostate volume, with prostates <30 ml suitable for TUIP and prostates 30 - 80 ml for TURP. UTIs should be treated prior to TURP or TUIP [83]. No studies on the optimal cut-off value are available, but the rate

of complications increases with size [84]. The upper limit depends on the experience of the surgeon and is mostly suggested as 80 ml.

3.3.2. Modifications of transurethral resection of the prostate: bipolar resection of the prostate

3.3.2.1. Mechanism of action

Bipolar TURP (B-TURP) addresses the fundamental flaw of monopolar TURP (M-TURP) by allowing performance in normal saline (NaCl 0.9%) irrigation. Contrary to M-TURP systems, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed at the resection site between an active and a return pole attached to a single support on the resectoscope [85].

3.3.2.2. Efficacy and safety

B-TURP is the most widely and thoroughly investigated alternative to M-TURP. A metaanalysis based on 17 RCTs [86] concluded that no clinically relevant differences exist in short-term (up to 12 mo) efficacy, urethral stricture, and bladder neck contracture rates but that B-TURP is preferable due to a more favourable perioperative safety profile (elimination of TUR-syndrome; less bleeding, i.e., lower clot retention and blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [86]. Two subsequent RCT-based meta-analyses supported these conclusions [80,87], which despite the relatively low trial quality appear reliable and currently reflect the best available evidence. A contemporary update [88] of a meta-analysis detected 16 additional RCTs published during the last 3 yr (33 RCTs; 3601 randomised patients in total). Updated pooled results are still awaited, but no individual RCT favours M-TURP in any aspect [88]. Midterm, short-term, and perioperative complication rates did not differ significantly between arms [89–91]. The effect on overall sexual function, efficacy, and all other secondary outcomes were comparable throughout follow-up [89–91]. Seven RCTs published to date have follow-up durations >12 mo (range: 18 - 60 mo) showing no differences in terms of IPSS and Qmax between B-TURP and M-TURP at midterm [90, 92–97].

3.3.2.3. Practical considerations

B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO with similar efficacy but lower perioperative morbidity [86]. The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up >12 mo. Midterm results (up to 5 yr) of B-TURP safety/efficacy are comparable with those of M-TURP. The choice of B-TURP should currently be based on the availability of the bipolar armamentarium, the surgeon's experience, and the patient's preference.

3.3.3. Open prostatectomy

3.3.3.1. Mechanism of action

Open prostatectomy is the oldest surgical treatment modality for moderate-to-severe LUTS secondary to BPO. Removal of prostatic tissue resolves BPO and, secondarily, LUTS.

3.3.3.2. Efficacy

Open prostatectomy results in reduction of LUTS by 63 - 86% (12.5 - 23.3 IPSS points), improvement of the IPSS-QoL score by 60 - 87%, mean increase of Q_{max} by 375% (range: 88 - 677%; in absolute terms +16.5 - 20.2 ml/s), and reduction of PVR by 86 - 98% [98,99]. Efficacy is maintained after long-term observations >5 yr.

3.3.3.3. Tolerability and safety

Perioperative complications include mortality (<0.25% in contemporary series) and blood transfusion (7 - 14%) [98, 99]. Long-term complications are urinary incontinence (≤10%) and bladder neck stenosis or urethral stricture (approximately 6%) [98,100].

3.3.3.4. Practical considerations

Open prostatectomy is the most invasive but also the most effective and durable procedure for the treatment of LUTS/BPO. Only holmium enucleation delivers similar results but with less morbidity [98,100]. In the absence of endourologic armamentarium and a holmium laser, open prostatectomy is the surgical treatment of choice for men with prostates >80 ml who have absolute indications for surgery or experience moderate-to-severe LUTS secondary to BPO who have been treated insufficiently by drugs.

3.3.4. Transurethral microwave therapy

3.3.4.1. Mechanism of action

Microwave thermotherapy works by emitting microwave radiation through an intraurethral antenna to deliver heat into the prostate, which leads to tissue destruction, apoptosis, and denervation of a-receptors and thus reduces BPO and LUTS.

3.3.4.2. Efficacy

Although one RCT obtained comparable clinical results 5 yr after transurethral microwave therapy (TUMT) or TURP [101], a systematic review found TUMT somewhat less effective than TURP in reducing LUTS [102]. The pooled mean symptom score for TUMT decreased by 65% in 12 mo compared with 77% in TURP, which results in a weighted mean difference of -1.0 in favour of TURP. TURP achieved a greater Q_{max} improvement (119%) than TUMT (70%), with a weighted mean difference of

5.1 ml/s in favour of TURP [102]. In addition, TUMT was associated with increased risks for retreatment for BPH symptoms. TUMT also improved IPSS symptom scores (weighted mean difference [WMD]: -4.20) and peak urinary flow (WMD: 2.30 ml/s) in the one comparison with α_1-blockers [102].

3.3.4.3. Tolerability and safety

Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. In the Cochrane systematic review of RCTs comparing TURP with TUMT, it was shown that catheterization time, incidence of dysuria/urgency, and urinary retention were significantly less with TURP, whereas the incidence of hospitalisation, haematuria, clot retention, transfusions, TUR-syndrome, and urethral strictures were significantly less for TUMT [102]. Sexual dysfunction and retreatment rates for strictures of the meatus, urethra, or bladder neck were higher after TURP than after TUMT.

3.3.4.4. Practical considerations

Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Because of the low peri- and postoperative morbidity and no need for anaesthesia, TUMT is a true outpatient procedure and an alternative for older patients with comorbidities and those at risk for anaesthesia otherwise unsuitable for invasive treatment [103]. Independent baseline parameters predicting an unfavourable outcome include small prostates, mild-to-moderate BOO, and low energy delivered during treatment [104]. Predictive factors for particular devices cannot necessarily be applied to systems of other producers.

3.3.5. Transurethral needle ablation of the prostate

3.3.5.1. Mechanism of action

The transurethral needle ablation (TUNA) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. The energy induces coagulation necroses in the prostatic transition zone resulting in prostate volume reduction and BPO reduction/resolution.

3.3.5.2. Efficacy

A meta-analysis of two randomised trials, two nonrandomised protocols, and 10 single-arm studies conducted on TUNA showed that it achieved a 50% decrease of the mean IPSS and a 70% improvement in Q_{max} from baseline at 1 yr after treatment [105]. A more recent metaanalysis of 35 studies (9 comparative, 26 non-comparative) confirmed these results [106]. TUNA significantly improved IPSS and Q_{max} with respect to baseline values, but in comparison with TURP this improvement was significantly lower at 12 mo. TURP versus TUNA differences in means were -4.72 and 5.9 ml/s for the IPSS and Q_{max}, respectively [106]. TUNA has a significant higher retreatment rate compared with TURP (odds ratio [OR]: 7.44 (2.47 - 22.43). The overall retreatment rate after TUNA was 19.1% (95% confidence interval [CI], 18.7 - 39.7) as calculated from 17 non-comparative studies [106].

3.3.5.3. Tolerability and safety

Postoperative urinary retention with a mean duration of 1 - 3 d is seen in 13 - 42% of patients; within 1 wk., 90 - 95% of patients are catheter free [107]. Bladder storage symptoms are common for the first 4 - 6 wks. after the operation [108]. TUNA is associated with fewer adverse events compared with TURP including mild haematuria, urinary infections, strictures, incontinence, erectile dysfunction, and ejaculation disorders (OR: 0.14; 95% CI, 0.05 - 0.41) [106].

3.3.5.4. Practical considerations

TUNA can be performed as a day-case procedure under local anaesthesia or sedation. TUNA is unsuitable for prostates >75 ml or isolated bladder neck obstruction. Because TUNA cannot effectively treat prostatic middle lobes, it remains unclear whether men with large middle lobes will benefit from this treatment.

3.3.6. Laser treatments of the prostate

3.3.6.1. Holmium laser enucleation or holmium resection of the prostate

3.3.6.1.1. Mechanism of action

The holmium: yttrium-aluminium-garnet (Ho:YAG) laser with a wavelength of 2140 nm is a pulsed solid-state laser that is promptly absorbed by water and water-containing tissues. Holmiumlaser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) results in BPO relief and, secondarily, in LUTS reduction.

3.3.6.1.2. Efficacy

In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at 6 or 12 mo postoperatively, but HoLRP achieved a significantly greater increase in Q_{max} compared with TURP with a WMD of 4.8 ml/s [109]. One RCT comparing TURP with HoLRP with a minimum follow-up of 4 yr showed no difference in urodynamic parameters between the two techniques after 48 mo [110]. Three meta-analyses that analysed RCTs comparing HoLEP and TURP [111–113] reported a significantly longer operation time for the laser operation. Symptom improvement was comparable or superior with HoLEP. Furthermore, Q_{max} at 12 mo was significantly better with HoLEP [111–113]. One RCT comparing photoselective vaporisation of the prostate (PVP) and HoLEP in patients with prostates >60 ml showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [114]. Available RCTs indicated that in large prostates HoLEP was as effective as open prostatectomy for improving micturition [98,100], with equally low reoperation rates after 5 yr (5% vs 6.7%, respectively) [98]. One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-yr follow-up found that the functional long-term results of HoLEP were comparable with TURP; no HoLEP patient required reoperation for recurrent BPH [115]. A retrospective study of 949 treated with HoLEP with the longest follow-up (up to 10 yr; mean follow-up: 62 mo) reported durable functional results; bladder neck contracture, urethral stricture, and reoperation due to residual adenoma developed in 0.8%, 1.6%, and 0.7% of patients, respectively [116].

3.3.6.1.3. Tolerability and safety

No major intraoperative complications have been described; in a meta-analysis, no statistically significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress incontinence (1.5% vs. 1.5%; p=0.980), and re-intervention (4.3% vs. 8.8%; p=0.059) [112]. Pooled data from large case series (total of 1847 patients) showed low complication rates including perioperative mortality (0.05%), transfusion (1%), UTI (2.3%), urethral stricture/bladder neck contracture (3.2%), and reoperation (2.8%) [117]. Patients using anticoagulant medication and those with urinary retention can be treated safely [118,119]. Three meta-analyses found that HoLEP resulted in a significantly shorter catheterization time and hospital stay, reduced blood loss [111–113], and fewer blood transfusions compared with TURP [112,113]. Similarly available RCTs indicated that HoLEP was better than open prostatectomy for blood loss, catheterisation, and hospitalisation time [98,100].

3.3.6.1.4. Practical considerations

The holmium operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [120,121].

3.3.6.2. Greenlight 532-nm laser vaporisation of prostate

3.3.6.2.1. Mechanism of action

The kalium-titanyl-phosphate (KTP) and the lithium triborate (LBO) lasers are both derived from the neodymium:YAG (Nd:YAG) laser. The addition of a KTP or LBO crystal to the laser resonator converts the Nd:YAG wavelength from 1064 nm to 532 nm, and laser energy is absorbed within the tissue by haemoglobin, which acts as an intracellular chromophore, and not by the water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and, secondarily, reduction of LUTS. In 2013, three different Greenlight lasers are in use: the 80-W (KTP), 120-W HPS (LBO), and the 180-W XPS (LBO) laser systems. They differ in maximum power output, fibre design, and maximum energy application.

3.3.6.2.2. Efficacy

A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 [122]. No differences were found in Q_{max} and IPSS between PVP and TURP, but only three RCTs [123–125] provided sufficient 12-mo data to be included in the meta-analysis. The longest RCT using the 80-W KTP laser has a follow-up of only 12 months [123]. A case series of 246 patients who completed the 5-yr follow-up showed that functional outcomes after the 80-W KTP laser were durable with an overall retreatment rate of 8.9% at 5 yr due to recurrent adenoma (7.7%) and bladder neck contracture (1.2%) [126]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 mo (5.2 - 60.6 mo) reported a retreatment rate of 14.8% due to recurrent or persisting adenoma (6.8%), bladder neck strictures (3.6%), or urethral strictures (4.4%) [127]. The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 mo and showed a comparable improvement in IPSS, Q_{max}, and PVR, whereas

the percentage reductions in PSA level and prostate volume were significantly higher in the TURP group.

Reoperation rate was significantly higher after PVP (11% vs 1.8%; p=0.04) [128]. Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 mo [124,129]. No RCTs had been published on the 180-W Greenlight laser until the end of the literature search. A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former Greenlight laser systems [130]. Interestingly, transurethral enucleation of the prostate using a 120-W 532-nm HPS Greenlight laser in combination with a 600-µm side-fire laser fibre has been described [131].

3.3.6.2.3. Tolerability and safety

The meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but significantly shorter catheterisation time and length of hospital stay after PVP [122]. Postoperative blood transfusions and clot retention were significantly less with PVP. No difference was noted in the occurrence of postoperative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck contracture [122]. Safety in patients with oral anticoagulation, urinary retention, or prostates >80 ml was shown in various prospective nonrandomised trials [131–137].

3.3.6.2.4. Practical considerations

The evolution of the Green-Light laser from 80-W to 120-W and then to 180-W resulted in a wide variation in the degree of maturity of each laser therapy. Long-term results on 120-W and RCTs on 180-W are still pending.

3.3.6.3. Diode laser vaporisation of the prostate

3.3.6.3.1. Mechanism of action

In diode lasers, a semiconductor is used to generate the laser light. The wavelength of the laser beam depends on the semiconductor material used. For the application in prostate surgery, diode lasers with a wavelength of 940 nm, 980 nm, 1318 nm, and 1470 nm are available, and they are absorbed by both water and haemoglobin [138]. Depending on wavelength, power output, and fibre design, diode lasers can be used for vaporization in noncontact and contact mode and enucleation.

3.3.6.3.2. Efficacy

A major drawback of all studies on diode laser vaporisation is the lack of RCTs in comparison with TURP or open prostatectomy and the short follow-up period (up to 12 mo). Case series as well as two comparative studies of a 980-nm diode laser to the 120-W HPS laser are available [139–148]. IPSS, QoL, Q_{max}, and PVR improved significantly in all diode laser studies compared with the baseline value. Compared with the 120-W HPS laser, the improvement of IPSS, QoL, Q_{max}, and PVR was similar at 6 mo and 12 mo [139,142]. A small RCT with a 6-mo follow-up comparing laser enucleation using a

1318-nm diode laser with B-TURP reported similar efficacy and safety results [149]. Operative time, blood loss, catheterisation, and hospitalisation time were in favour of laser enucleation.

3.3.6.3.3. Tolerability and safety

Studies on diode lasers indicate a high level of intraoperative safety. The application of the 980-nm diode laser showed no intraoperative bleeding, whereas with the 120-W HPS laser, bleeding was reported in 11% and 13% of the cases [139,142]. Notably, in these two studies, anticoagulants or platelet aggregation inhibitors were taken in 23.6% and 52% of the diode laser cases compared with 25% and 43% of the cases in the 120-W HPS group [139,142]. Comparable haemostatic properties are also reported for the 1470-nm diode laser [145]. During the postoperative course, a significantly higher rate of dysuria with sloughing tissues occurs after the 980-nm diode laser compared with the 120-W HPS laser [139,142]. The modification of the 980-nm diode laser fibre with a quartz head led to a significant reduction of dysuria lasting >1 mo from 42% to 17% [146]. Reoperation due to bladder neck stricture and obstructive necrotic tissue (33% vs. 4%) and persistence of stress urinary incontinence (9.1% vs. 0%) were significant higher after 980-nm diode laser compared with 120-W HPS laser [139,142]. In contrast, two cohort studies of the 980-nm diode laser reported no reoperations but only after 3 and 6 mo [143,148]. After treatment with the 1470-nm diode laser, reoperation in 2 of 10 patients was necessary during the 12 mo after surgery [145].

3.3.6.3.4. Practical considerations

Diode lasers lead to immediate, subjective, and objective improvements of LUTS due to BPO and appear to be safe due their haemostatic properties. Based on the short follow-up, the lack of RCTs in comparison with TURP or open prostatectomy, and controversial data on retreatment rate, diode lasers cannot be recommended as a standard treatment option for BPO.

3.3.6.4. Thulium:yttrium-aluminium-garnet laser

3.3.6.4.1. Mechanism of action

In thulium:YAG (Tm:YAG) lasers, a wavelength of approximately 2000 nm is emitted in continuous-wave mode. The target chromophore is water. The laser is primarily used in front-fire applications; the continuous-wave output of the Tm:YAG allows smooth incision of tissue [138]. Four different techniques have been described: Tm:YAG vaporisation of the prostate (ThuVaP), Tm:YAG vaporesection (ThuVaRP), Tm:YAG vapoenucleation (ThuVEP), and Tm:YAG laser enucleation of the prostate (ThuLEP). ThuVEP follows a HoLEP-like approach, and ThuLEP consists mainly of blunt dissection of the tissue.

3.3.6.4.2. Efficacy

A major drawback of all studies on thulium lasers is the limited number of RCTs in comparison with TURP and the lack of RCTs in comparison with open prostatectomy. No data beyond a follow-up of 18 mo are available yet. One RCT and one non-RCT compared ThuVaRP with M-TURP

[150,151]; one RCT comparing ThuVaRP and B-TURP was published recently [152]. In summary, all studies show a comparable improvement of symptoms and voiding parameters. There are only few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [153–156]. Interestingly, a comparative study showed that both 120-W and 200-W ThuVEP had an equivalent efficacy and safety at 12-mo follow-up [155]. ThuLEP and HoLEP were compared in one RCT with 18-mo follow-up [157]. Symptom improvement, increase of Q_{max}, and reduction of PVR volume sustained and were comparable between ThuLEP and HoLEP [157].

3.3.6.4.3. Tolerability and safety

Thulium laser prostatectomy shows high intraoperative safety in RCTs [150,152,157] as well as in case series in patients with large prostates [153] and for anticoagulation therapy or bleeding disorders [154]. Catheterisation time, hospital stay, and blood loss were significantly shorter in comparison with TURP [150–152]. In one RCT, operation time was longer with ThuLEP compared with HoLEP, whereas blood loss was reduced with ThuLEP [157]. The rate of postoperative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and the reported reoperation rate was 0 - 7.1% during the 9- to 12-mo follow-up [150, 151,158]. Urethral stricture after ThuVEP occurred in 1.6% of the patients, and the overall retreatment rate was 3.4% after a mean follow-up of 16.5 mo [159]. No urethral and bladder neck strictures after ThuLEP were reported during the 18-mo follow-up [157].

3.3.6.4.4. Practical considerations

The limited number of RCTs evaluating thulium laser applications for the surgical management of BPO and the limited follow-up (up to 18 mo) do not permit final conclusions regarding the long-term efficacy of thulium laser prostatectomy.

3.3.7. Prostate stents

3.3.7.1. Mechanism of action

Stents are tubes that can be placed temporarily or permanently in the prostatic urethra to compress prostatic tissue and open the bladder outlet. Immediate BPO relief occurs after stent placement. A prostatic stent requires a functioning detrusor.

3.3.7.2. Efficacy

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series, with a total of 990 patients who received the UroLume stent [160]. These trials with a varying follow-up reported relevant symptom improvement; IPSS decreased by 10 - 12.4 points [160]. Additionally, mean Q_{max} increased by 4.2 - 13.1 ml/s following stent insertion. The best data on non-epithelising prostatic stents are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent [161]. A total of 14 case series with 839 patients were reviewed. The Memokath stent reduced IPSS by 11–19 points. However, assessments were

made at different times after stent placement; similarly, stent insertion resulted in a Q_{max} increase of 3 - 11 ml/s [161].

3.3.7.3. Tolerability and safety

Stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [162]. The main adverse events immediately following stent placement include perineal pain or bladder storage symptoms. It can be difficult to remove permanent stents in cases of stent migration, stent encrustation, or epithelial ingrowth, and general anaesthesia is usually needed in these cases. Removal of a temporary stent is achieved by pulling the retrieval suture until the stent is completely retracted or by using graspers under endoscopic guidance.

3.3.7.4. Practical considerations

Because of the side effects and high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS secondary to BPO. Prostatic stents remain an alternative to transurethral catheterisation for men who have (recurrent) urinary retention and are at high risk for surgery. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [162].

3.3.8. Emerging operations

3.3.8.1. Intraprostatic ethanol injections

3.3.8.1.1. Mechanism of action

Absolute (dehydrated, 95 - 98%) ethanol is injected into the prostatic parenchyma. Ethanol causes inflammation, coagulation necrosis with protein denaturation and cell membrane lysis, and, finally, atrophy and ablation of prostatic tissue resulting in cavity formation and BPO relief. However, the precise mechanism of action remains unclear.

3.3.8.1.2. Efficacy

Open trials with a mean follow-up of 3 - 54 mo demonstrated a significant reduction in symptoms (decrease of IPSS 40 - 71%, or 6.7 - 16.5 score points) and PVR (up to 99%, or 286 ml) as well as a significant improvement in Q_{max} (35 - 155%, or 3.2 - 11 ml/s) and QoL (IPSS-QoL) [163–165]. However, no predictive efficacy parameters and dose-response relationships have been found. Several trials demonstrated a considerable number or retreatments within the first year, and one trial reported a retreatment rate of 41% after 3 yr [166].

3.3.8.1.3. Tolerability and safety

Local anaesthesia supplemented by conscious sedation may be considered, although most patients choose regional or general anaesthesia. Frequently reported adverse events included perineal or abdominal discomfort/pain, bladder storage symptoms (≤40%), haematuria (≤40%), UTI

or epididymitis, and urinary retention. Two cases of severe complications have been reported; bladder necrosis required cystectomy and urinary diversion [163].

3.3.8.1.4. Practical considerations

Ethanol injections are considered a minimally invasive treatment option for patients with moderate-to-severe LUTS secondary to BPO. However, the mechanism of action, patient selection, and application of ethanol (number of injection sites and injection volume) have not been well investigated, severe adverse events occurred in some patients [163], and long-term results are sparse. Intraprostatic ethanol injections are therefore regarded as experimental procedures and should only be used in trials. RCTs with long-term follow-up comparing ethanol injections with TURP, other minimally invasive procedures, or drugs are needed to judge adequately the value of this treatment modality.

3.3.8.2. Intraprostatic botulinum toxin injections

3.3.8.2.1. Mechanism of action

Botulinum toxin (BTX) is the most potent neurotoxin known in humans. Botulinum toxin A (BoNTA) directly or indirectly reduces LUTS by induction of apoptosis of prostatic (epithelial) cells leading to tissue atrophy and prostate size reduction, inhibition of sensory neurons in the prostate and reduction of afferent signals to the central nervous system, and/or relaxation of smooth muscle cells in the prostatic parenchyma and reduction of BPO [167]. Downregulation of α_{1A}-adrenergic receptors in the prostate may contribute to smooth muscle cell relaxation [167]. The latter two mechanisms are summarized as chemical denervation that possibly has a negative influence on prostate growth.

3.3.8.2.2. Efficacy

A review of the available RCTs or prospective observational studies (until 2010) on the use of intraprostatic injection of BoNTA for LUTS/BPH showed an improvement in IPSS in 20 studies; this reduction was statistically significant in 13 studies [168]. Similarly, Q_{max} increased in all series, reaching statistical significance in 14 studies. The reduction in prostate volume varied between the different series and was statistically significant in 18 studies. Duration of the effects of treatment was also variable, ranging from 3 to 30 mo [168]. In patients with urinary retention before BoNTA injections, most men could void spontaneously within 1 mo [168]. In two recent RCTs comparing several BoNTA doses, no differences were observed between groups in term of efficacy [169,170]. In addition, the results from the largest placebo-controlled study on the efficacy of different doses of BoNTA (100 U, 200 U, and 300 U) in men with LUTS/BPH have been published [171]. No significant difference between BoNTA and placebo arm was observed in terms of IPSS, QoL, and Q_{max} at week 12 [171].

3.3.8.2.3. Tolerability and safety

BoNTA injections were well tolerated in all studies. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis, and grade 2-3 events (unspecified) among 35% of patients in the series [168]. In addition, patients may receive a transurethral catheter or perform clean intermittent catheterisation during the early postoperative period (1 wk. to 1 mo) [171, 172]. Intraprostatic injections of BoNTA in patients with BPE seem to have no impact on sexual function [168, 173].

3.3.8.2.4. Practical considerations

BoNTA injections into the prostatic parenchyma are a promising and quick minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. Trials with a larger number of patients, randomisation against saline injections, drugs, TURP, or other minimally invasive treatments, systematic evaluation of doses and dilutions, and long-term follow-up are necessary to judge adequately the value of intraprostatic BoNTA injections in the context of other available medical or surgical treatments of LUTS/BPO.

3.4.   Patient selection

The choice of treatment depends on findings assessed during evaluation, ability of the treatment to change assessed findings, treatment preferences of the individual patient, as well as expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression (**table 5**). Note that treatment modalities may be combined leading to different effects. Behavioural modifications with or without medical treatments are usually the first choice of therapy.

Figure 2 provides a flowchart illustrating treatment choice according to evidence-based medicine and patient profiles. Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery). Additionally, surgery is usually needed when patients have had insufficient relief of LUTS or PVR after conservative or medical treatments (relative operation indications). The choice of the surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches to care is provided in **figure 3**.
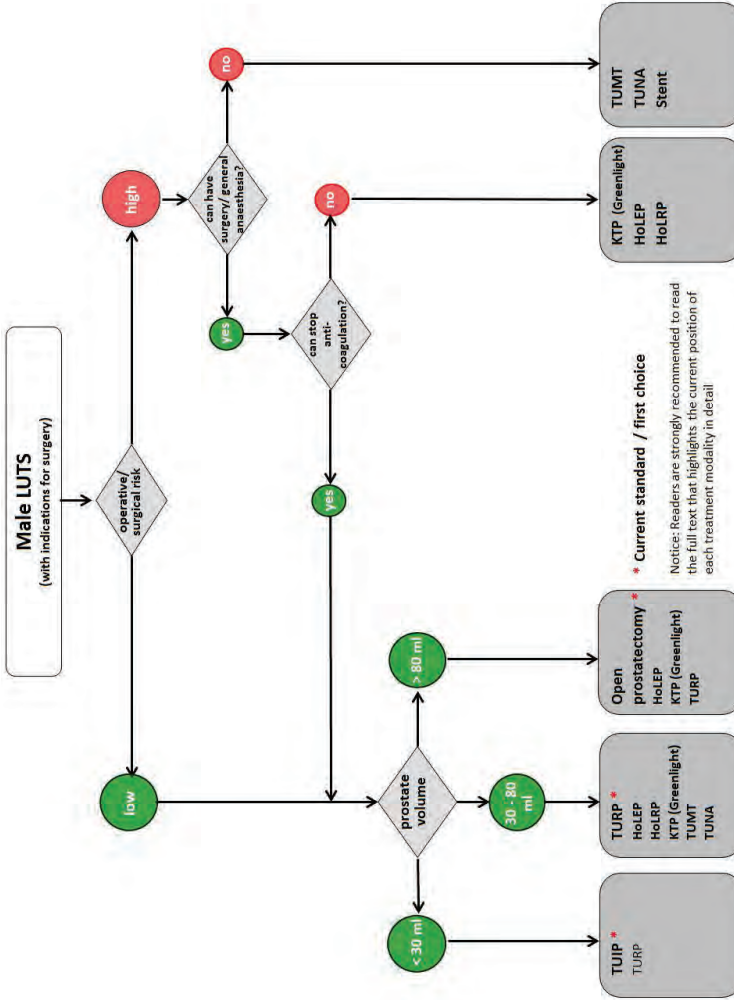
Figure 3: Treatment algorithm of bothersome lower urinary tract symptoms (LUTS) refractory to conservative/medical treatment or in cases of absolute operation indications (e.g. urinary retention, recurrent urinary tract infections, bladder stones or diverticula, treatment-resistant macroscopic hematuria, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency). Note that this flowchart has been stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size; however, the choice of the surgical techniques also depends on patients' preferences, willingness to accept surgery-associated side effects, availability of the armamentarium, and surgeon's experience with the operation technique. *Notice:* Readers are strongly recommended to read the full text that highlights the current position of each treatment modality in detail.

HoLEP = Holmium Laser Enucleation of the Prostate; HoLRP = Holmium Laser Resection of the Prostate; KTP = K⁺-titanyl-phosphate laser ("greenlight"); TUIP = Transurethral Incision of the Prostate; TUMT = Transurethral Microwave Therapy; TUNA = Transurethral Needle Ablation of the prostate; TURP = Transurethral Resection of the Prostate

Table 5: Speed of onset and influence on basic parameters with conservative, medical, or surgical treatment modalities for the management of male LUTS. Note that the drug treatment studies have typically used data after a run-in phase as baseline, whereas those of interventional treatments did not.

Treatment	Speed of Onset	LUTS (IPSS)	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative and drug treatments						
Watchful waiting, behavioural treatment	months	+ (-1.3 to -5.7 points)	-	-	-	?
α1-adrenoceptor antagonists	days	++ (-31 to -48.2%)	++ (+1.4 to +3.2 ml/s)	-	- / + (-17 to -39%)	+++ (symptoms)
5α-reductase inhibitors	months	+ (-13.3 to -38.6%)	++ (+1.4 to +2.2 ml/s)	+ - ++ (-15 to -28%)	-	+++ (retention)
Muscarinic receptor antagonists	Weeks	++ (storage symptoms) (-35.3 to -54%)	-	-	+ (0 to +49ml)	?
PDE5 inhibitors (tadalafil)	Days	++ (-17 to -37%)	- / +	-	- / + (+9 to -19 ml)	?
α1-adrenoceptor antagonists + 5α-reductase inhibitors	Days	++ (-38 to -49.7%)	++ (+2.3 to 3.8 ml/s)	+ -++ (-11.9 to -27.3%)	- / +	+++ (symptoms + retention)
α1-adrenoceptor antagonists + muscarinic receptor antagonists	Days	++ (-31.8 to -66.4%)	++	-		?
Surgical treatments			*After catheter removal*			
TURP–TUIP	Hours	++++ (-63 to -88%)	++++ (+6.9 to 22.9 ml/s)	+++	++++	++++
Open prostatectomy	Hours	++++ (-62 to -86%)	++++ (+7.0 to +21.4 ml/s)	++++ (-88%)	++++ (-86 to -98%)	++++
TUMT	Weeks	+++ (-40 to -87%)	+++ (+2.4 to 8.4 ml/s)	++ (-8.1 to 33.0%)	++ (-34 to -84.1%)	+++

TUNA™	Weeks	+++ (-45 to -56%)	+++ (+4.7 to 6.5 ml/s)	++	+ (-20 ml or -22%)	++
HoLEP/HoLRP	Hours	++++ (-66 to -92%)	++++ (+10.9 to 23.0 ml/s)	++++ (-34 to -54%)	++++ (-68 to -98%)	++++
KTP/Greenlight	Days	+++ (-31 to -75%)	+++ (+4.7 to 14.9 ml/s)	+++ (-44 to -63%)	+++ (-57 to -91%)	+++
Diode laser	hours	+++ (-55 to -84.3%)	+++ (+5.1 to 13.7 ml/s)	+++ (-30.3 to -58.1%) PSA-based reduction	+++ (-58.1 to -87.7%)	+++
Thulium Laser ThuVaP, ThuVaRP, and ThuVEP	hours	+++ (-63 to 85.4%)	+++ (=12.8 to 18.7 ml/s)	+++ (-35.7 to -88%) PSA-based reduction	+++ (-72.4 to -94.4%)	+++
Prostate stents	hours	++ (-10 to -19 points)	++ (+3 to 13.1 ml/s)	-	+++	?

- no influence; + mild influence; ++ moderate influence; +++ strong influence; ++++ very strong influence; ? unknown

BTX: Botulinum Toxin; HoLEP: Holmium Laser Enucleation of the Prostate; HoLRP: Holmium Laser Resection of the Prostate; IPSS: International Prostate Symptom Score; KTP: K^+-titanyl-phosphate, "greenlight" laser vaporization; LUTS: Lower Urinary Tract Symptoms; PDE5 inhibitor: phosphodiesterase 5 inhibitor; PVR: Post-Void Residual urine; ThuVaP: Tm:YAG vaporisation of the prostate; ThuVaRP: Tm:YAG vaporesection ThuVEP: Tm:YAG vapoenucleation; TUMT: Transurethral Microwave Therapy; TUNA™: Transurethral Needle Ablation; TUIP: Transurethral Incision of the Prostate; TURP: **T**ransurethral Resection of the Prostate; Q_{max}: maximum urinary flow rate

3.5.   Follow-up

Patients who elect to pursue a WW policy should be reviewed at 6 mo and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment.

Patients receiving α_1-blockers, muscarinic receptor antagonists, or the combination of α_1-blockers plus 5-ARIs or muscarinic receptor antagonists should be reviewed 4 - 6 wks. after drug initiation to determine treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 mo and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment.

Patients receiving 5-ARIs should be reviewed after 12 wks. and 6 mo to determine their response and adverse events. Men taking a 5-ARI should be followed up regularly using serial PSA testing if life expectancy is >10 yr and if diagnosis of prostate cancer could alter management. A new baseline PSA should be determined at month 6, and any confirmed increase in PSA while on a 5-ARI should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 mo, and, if serum sodium concentration has remained normal, every 3 mo subsequently. The follow-up sequence should be restarted after dose escalation.

Patients after prostate surgery should be reviewed 4 – 6 wks. after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further reassessment is necessary.

4.   CONCLUSIONS

These symptom-oriented guidelines provide practical guidance for the management of men experiencing LUTS. The full version is available online (www.uroweb.org/gls/pdf/12_Male_LUTS.pdf).

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Part V:

General Discussion

CHAPTER 11

Reflections and Future Perspectives

11.1   IMPORTANCE OF BLADDER OUTLET OBSTRUCTION IN ADULT MEN

Microscopic BPH develops in aging men and affects as many as 70% of individuals aged 61–70 years, 80% of those aged 71–80 years, and 90% of individuals aged 81–90 years [1]. Based on this data, almost every man at a certain age will have BPH which, therefore, seems to be a normal aging process of the prostate. Elderly men with BPH may also develop BPE, LUTS and/or BOO/BPO, and the prevalence all BPH-disease components increase with aging. However, the presence or magnitude of BPE or LUTS does not reliably predict the presence or magnitude of BOO/BPO [2-4]; therefore, it is impossible to anticipate BOO/BPO only from the existence of LUTS or BPE. Consequently, each component of the BPH-disease has to be evaluated separately in the individual man.

LUTS/BPH affects approx. 40% of the adult male population [5, 6], is the primary reason for consultations of adult men in physican offices across Europe [7], the most frequently diagnosed and treated urological disease, and the 7th most common and costly disease in men aged ≥50 years in Western countries, only outnumbered by cardiac arrthymia, arthritis, cataract, coronary artery disease, bursitis, and diabetes mellitus type II [8]. The estimated treatment costs for LUTS only in German are approx. € 2.2 billion per year [6, 9]. The median age of European men seeking professional help for LUTS/BPH is approx. 65 years (interquartile range: 59–74) [7]. The estimated life expectancy of German men aged 65 years is currently 17.5 years [10], continuously increasing and, therefore, expected to further rise in the future, thereby increasing the number of patients with LUTS/BPH and the disease-related costs for the health care system. Similar numbers exist for most of the Western countries. Because life expectancy will also rise in many of the developing countries worldwide, LUTS/BPH will progress to a global problem and cause major challenges for health care systems. Consequently, knowledge of the epidemiology, pathophysiology, and natural history of BPH, BPE, LUTS, and BOO/BPO are essential for the understanding, assessment, and treatment of the BPH-disease today and even more in the future.

Information about the prevalence and natural history of the BPH-disease originate from cross-sectional and longitudinal epidemiological studies, such as the Olmsted County study in the USA [11], Krimpen study in the Netherlands [12], and Herne study in Germany [6] as well as from patients treated with placebo in LUTS/BPH trials, such as the MTOPS study [13]. It was shown in the German epidemiological study that more than 40% of German men older than 50 years of age have LUTS (approx. 5 million), almost 27% have BPE (approx. 3.2 million), and more than 17% have BOO/BPO (approx. 2.1 million) [6]. However, it is still speculative how many men really have BOO/BPO and how this component of the BPH-disease develops over time because invasive pressure-flow measurements to accurately diagnose BOO/BPO have yet not been performed in cross-sectional or longitudinal studies. Instead, proxy parameters for BOO/BPO were used, most frequently measurements of urinary flow rate with a Q_{max} threshold value of 10 ml/s [6].

There are some arguments why assessment of BOO/BPO could be useful in adult men, with or without LUTS or BPE. If the human bladder with BOO/BPO behaves similar compared to the bladder of experimental animals with artificial BOO most untreated men will develop urinary retention, upper urinary tract dilatation, and renal insufficiency over time [14]. Damage of the urinary bladder as a result of BOO/BPO could be irreversible [15]. Immediate treatment of BPO by

transurethral resection of the prostate (TURP) in patients with moderate LUTS at baseline results in a significantly better symptomatic outcome, higher Q_{max}, and less post-void residual urine compared to patients who were initially treated with watchful waiting and later received TURP, as determined in a prospective study of 556 patients [16]. TURP in patients with BPO results in success rates which are up to 11–29% higher compared to TURP in patients without BPO, even in long-term studies with a follow-up of 8 years [17-20]. Up to 40% of men aged >65 years [21] and approx. 48% of men aged ≥70 years [22] have detrusor underactivity as the primary cause of bladder dysfunction and LUTS. If those patients with detrusor underactivity are treated with TURP the symptomatic outcome and Q_{max} remain unchanged even after mean a follow-up period of 11.3 years [23]. In this longitudinal study in men with detrusor underactivity, IPSS and Q_{max} values in men treated with TURP were similar to untreated men. In line with these findings, detrusor underactivity is associated with a significant amount of post-void residual urine [24] and persistent voiding LUTS after the prostate operation [25].

Morphological or functional changes of the lower and/or upper urinary tract (e.g. post-void residual urine, bladder diverticula, bladder stones, vesico-ureteral reflux, hydronephrosis, renal insufficiency, urinary retention) are also thought to be associated with BOO/BPO. The evidence behind these assumptions has been reviewed in **chapter 2** of this PhD-thesis [26]. Published literature between 1966 and 2011 was systematically reviewed accordingly. The published evidence demonstrated that, although post-void residual urine, bladder diverticula, bladder stones, vesico-ureteral reflux, hydronephrosis, renal insufficiency, and urinary retention appear with greater prevalence in men with clinical BPH, there was no conclusive proof that BPO is really the primary cause for these alterations. Aging, BPE or detrusor underactivity may alternatively or additionally be responsible for lower and/or upper urinary tract damage. It was concluded that lower and upper urinary tract complications have a multifactorial etiology and BPO is only partially responsible for these changes. Therefore, it is currently impossible to predict which men will have urinary tract complications. The literature search also revealed that pressure-flow studies have rarely been conducted to elucidate the relationship between the urinary tract complications and BPO or other forms of lower urinary tract dysfunction.

While investigations with pressure-flow data are still pending, studies with non-invasive tests have meanwhile been conducted and provided further insight into the pathophysiology of morphological or functional urinary tract changes. Men with bladder wall hypertrophy, determined by ultrasound-estimated bladder weight (UEBW) >35 g (indicating BOO/BPO), have a 13.4 times increased risk for developing acute urinary retention compared to men without bladder wall hypertrophy (i.e. UEBW ≤35 g) [27]. Similar results were obtained from a cross-sectional study investigating men aged ≥50 years with LUTS or acute urinary retention [28]. In multivariate analysis, only severe LUTS and UEBW were found to be significant predictors of acute urinary retention, the latter with the highest area under the curve. Acute urinary retention is also significantly and more frequently found in patients with intravesical prostatic protrusion (IPP) >10 mm (indicating BPO) compared to men with IPP ≤10 mm [29]. Additionally, untreated men with IPP >10 mm (9/14 patients, 64.3%) developed significantly more frequently acute urinary retention during a follow-up period of 6 months compared to men with IPP ≤10 mm (4/17 patients, 23.5%) [29]. A retrospective analysis of 271 consecutive patients undergoing elective TURP demonstrated that men with bladder stones have a significantly higher IPP distance compared to men without bladder

stones (11.5 ± 10 mm vs 3.4 ± 5.5 mm, p<0.001) [30]. In multivariate analysis, the odds ratio for bladder stone formation for a greater IPP distance was 1.15 (95% confidence interval 1.072–1.223) and independent of older age and lower Q_{max}. Another study investigated the value of IPP for BPH-disease progression, defined as development of post-void residual urine >100 ml, acute urinary retention or deterioration of LUTS ≥4 IPSS points [31]. During a mean follow-up interval of 32 months, 6% of patients with IPP grade 1 (≤5 mm), 20% of patients with IPP grade 2 (5.1–10 mm) and 44% of patients with IPP grade 3 (>10 mm) developed clinical disease progression. Compared to IPP grade 1, the odds ratio for clinical disease progression was 5.1 for IPP grade 2 (95% confidence interval 1.6-16.2) and 10.4 for IPP grade 3 (95% confidence interval 3.3-33.4). All cited studies with non-invasive tests (UEBW, IPP) strengthen the assumption that changes of the urinary tract (acute urinary retention, BPH-disease progression, or bladder stones) are caused by BOO/BPO. However, future studies have to confirm these initial results and, additionally, should investigate morphological and functional changes other than urinary retention, disease progression, or bladder stones.

Bladder storage symptoms are perceived by the patient during the bladder storage phase, include urgency, daytime frequency, nocturia and urgency incontinence, and are usually more bothersome than voiding symptoms [32-35]. The overactive bladder syndrome (OAB; synonyms: urge syndrome, urgency-frequency syndrome) is a clinical diagnosis, belong to the symptom syndromes suggestive of lower urinary tract dysfunction, and are defined as urgency, with or without incontinence, usually associated with frequency and nocturia [32]. This symptom combination is suggestive of detrusor overactivity which is a urodynamic observation characterized by involuntary detrusor contractions during the bladder filling phase [32]. Especially men with urgency or urgency incontinence have shown to have a high chance of detrusor overactivity [36] which may be of primary (idiopathic) or secondary origin [32]. Patients with clinical BPH also have a high prevalence of detrusor overactivity; a meta-analysis indicated detrusor overactivity in 60.2% of patients (95% confidence interval 52–68%) [37]. The association between detrusor overactivity and BOO/BPO as well as the degree of BOO/BPO was investigated in **chapter 3** of this PhD-thesis [38]. A treatment naïve, unselected sample of patients who received computer-urodynamic investigation as part of their routine check-up was retrospectively evaluated. In total, 1418 men with clinical BPH were investigated. This is until now the largest series of patients with clinical BPH who received computer-urodynamic investigation for clarification of BOO/BPO and detrusor overactivity. In this study, 864 patients (60.9%) had detrusor overactivity during cystometry which is almost identical to the prevalence of detrusor overactivity shown in the previously published meta-analysis (60.2%). In multivariate analysis, detrusor overactivity was independently associated with BOO/BPO (p<0.001) and age (p=0.047). The more obstructed the bladder and the older the patients were the more likely was detrusor overactivity. The prevalence of detrusor overactivity continuously rose with increasing BOO/BPO grade. Detrusor overactivity appeared in 51.4% of patients without BOO/BPO (Schäfer class 0), in 67.8% in patients with mild BOO/BPO (Schäfer class 3), and in 83.3% of patients with severe BOO/BPO (Schäfer class 6). Therefore, BOO/BPO was responsible for detrusor overactivity in approx. 30% of all investigated men (secondary detrusor overactivity), whereas aging was responsible for detrusor overactivity in approx. 50% of men (primary or idiopathic detrusor overactivity). Compared to Schäfer class 0, the odds ratio for detrusor overactivity rose with each Schäfer class (1.2 → 4.7) and was statistically significant in all classes greater than Schäfer class 1.

Controversial results regarding the association between detrusor overactivity and BOO/BPO were previously published. Whereas some authors previously found an association between detrusor overactivity and BOO/BPO [39-43], others did not [44, 45]. Therefore, the study shown in **chapter 3** confirmed the association between detrusor overactivity and BOO/BPO and, additionally, could show for the first time that with increasing BOO/BPO-grade detrusor overactivity stepwise increased as well. Small sample size and pre-selection of patients who had undergone urodynamic investigation seem to be responsible for the failure to demonstrate the association between detrusor overactivity and BOO/BPO in previous studies [44, 45]. Furthermore, detrusor overactivity appeared at lower bladder filling volumes (p=0.017) and with higher amplitude (p=0.006) the more obstructed the bladder of the patient was. This association was previously unknown. All results of the study shown in **chapter 3** were later fully confirmed by a prospective Korean study in 193 patients [46].

The retrospective study of 1418 unselected, treatment naïve patients with clinical BPH originally intended to investigate the relationship between BOO/BPO and detrusor overactivity but could also demonstrate the prevalence of BOO/BPO and the distribution of patients within the individual BOO/BPO (Schäfer) classes. The study demonstrated BOO/BPO (Schäfer classes 2-6) in 58.3% of patients which is nearly identical to the prevalence seen in the so far largest urodynamic study, the 'International Continence Society BPH study', in which 1271 patients were urodynamically investigated and BOO/BPO was found in 60% [47]. Our study could also show that patients are unevenly distributed within the BOO/BPO-grades, with more men having only a minor degree of BOO/BPO (21.0% in Schäfer class 2 and 17% in Schäfer class 3) than a higher degree (16% in Schäfer class 4, 3.0% in Schäfer class 5, and 1.3% in Schäfer class 6). Therefore, the majority of men with clinical BPH have no or only a minor degree of BOO/BPO (approx. 80%). If the hypothesis is correct that BOO/BPO is really be responsible for lower and/or upper urinary tract damage (**chapter 2**) the low prevalence of severe BOO/BPO could be the reason why only a few patients develop these complications in real life. This suggests that the relationship between BOO/BPO and urinary tract damage has to be investigated in a large cohort of men with clinical BPH. Pressure-flow measurements in so many men over time are infeasible and, consequently, other tests to determine BOO/BPO at baseline and during follow-up are needed to avoid the disadvantages of pressure-flow measurements. Therefore, there is a strong need for non- or minimally-invasive tests to detect and quantify BOO/BPO alternatively and in order to answer clinically-relevant research questions.

11.2 ULTRASOUND DETRUSOR WALL THICKNESS MEASUREMENT AS A NON-INVASIVE TEST TO EVALUATE BLADDER OUTLET OBSTRUCTION

Although BOO is defined by pressure-flow analysis [32] and computer-urodynamic investigation is currently the only accepted test to diagnose BOO, there are several reasons for rejecting this examination. Arguments against computer-urodynamic investigations are the invasive, time consuming and costly procedure which is also frequently bothersome for patients. Multichannel computer-urodynamic investigation causes serious morbidity in approx. 19% of men [48], and people even died after the invasive investigation due to urosepsis as a result of using infected catheters (*serratia marcescens*) [49]. Computer-urodynamic investigation of patients with suspected BOO/BPO

lasts approx. 60 - 90 minutes (dependent on the filling speed of the bladder, bladder capacity of the patient, and number of replications) and currently costs approx. € 250 - 300 (dependent on the used catheters and number of participating health care professionals). Additionally, pressure-flow studies require special knowledge of the measurement technique and interpretation of the measurement results, incl. artifact analysis. Consequently, pressure-flow studies have seldom been performed in scientific investigations of patients with clinical BPH. BOO/BPO is the least investigated BPH-disease component and, therefore, the relevance of BOO/BPO still remains largely unknown. Thus, there is a strong scientific need to evaluate BOO/BPO in elderly men with clinical BPH and to establish a test without the disadvantages of computer-urodynamics.

In order to avoid the problems with pressure-flow measurements, non- or minimally invasive tests to quickly diagnose BOO/BPO were established. Based on the results of animal studies with detection of bladder wall hypertrophy as a physiological response to BOO/BPO, ultrasound measurements of bladder wall thickness (BWT) and ultrasound-estimated bladder weight (UEBW) were originally examined by other study groups [50-52]. The detection of enlarged bladder walls consistently proved to be a reliable indicator of BOO/BPO. The higher the BOO/BPO-grade became the thicker BWT or ultrasound-estimated bladder weight (UEBW) was. However, calculation of UEBW is complicated and assumes that the bladder is a ball or sphere which, however, has never been proven and may actually be untrue. Additionally, small deviations during the ultrasound measurement of BWT or the radius of the bladder results in great differences when calculating UEBW because distances in the volume formula are used in third potency; therefore, calculated bladder weight (UEBW) had a difference up to 22.5% compared to the actual bladder weight [50]. Ultrasound measurement of BWT requires transurethral catheterization and bladder filling with 150 ml; therefore, BWT measurement is invasive as well. Additionally, the mucosa or adventitia of the bladder, which sandwich the detrusor and is included in the BWT measurement, could be affected by infection, tumor, edema or other diseases, thereby increasing the BWT measurement values and pretending BOO/BPO (false-positive results). It is also sometimes difficult to discriminate the hyperechogenic adventitia from the hyperechogenic perivesical tissue. Animal studies indicated that only the thickness of the detrusor is increased as a result of BOO [14, 53-55]; therefore, it appears plausible to measure only detrusor wall thickness (DWT) to evaluate the response to BOO/BPO. A series of studies was conducted to investigate ultrasound DWT measurements as a truly non-invasive test to diagnose BOO/BPO in humans. Results of previous studies on the ultrasound appearance of the bladder wall and identical thicknesses of different parts of the bladder in the individual man in the same state of bladder filling were taken for granted [50]. Studies on ultrasound DWT measurements of the anterior bladder wall represent the center of this PhD-thesis.

At the very beginning, ultrasound DWT measurements were performed in female or male nurses or hospital physician colleagues who were healthy, without LUTS or post-void residual urine, with normal uroflowmetry values, and aged between 18 and 40 years (**chapter 4**) [56]. Five female and four male volunteers agreed to have their bladders catheterized. The bladders were filled with sterile saline solution, DWT was measured at the anterior bladder wall at three different locations and mean DWT was used. DWT was measured every 50 ml until 300 ml of bladder filling and, thereafter, in steps of 100 ml until maximum bladder capacity. DWT measurements showed similar DWT characteristics in

both men and women. In these 9 volunteers, the anterior detrusor wall was thick when the bladder was filled with only 50 ml (2.2 – 4.4 mm) but continuously decreased with increasing filling until approx. 250 ml. Afterwards, decrease of DWT was only minimal and remained nearly unchanged until maximum capacity was reached (0.9 – 1.4 mm). The ultrasound DWT measurement difference of bladders filled between 250 ml and maximum bladder capacity was only 0.1 to 0.2 mm in each individual, statistically and clinically insignificant, and within the measurement mistake given by the ultrasound frequency (≤1.3 mm with ultrasound probe of 7.5 MHz) [57]. The influence of bladder filling volume was also seen for men and women in another study of 166 women and 172 men when BWT was measured with ultrasound [58]. Later, identical characteristics of DWT with increasing bladder filling volume were described for adult women with OAB when using transvaginal or transabdominal ultrasound probes [59]. It appeared problematic to determine the exact turning point from the precipitous to the more or less horizontal line of DWT because volunteers had different maximum bladder capacities (strong desire to void), ranging from 260 to 800 ml. Therefore, the bladder filling (ml) at ultrasound DWT measurement was converted to percentage of bladder capacity. This conversion resulted in nearly identical lines in both women and men. DWT rapidly decreased during the first 50% of bladder capacity but, thereafter, remained almost constant until maximum bladder capacity. The DWT measurement difference between 50% and 100% of bladder capacity was statistically and clinically insignificant (0.1–0.2 mm). DWT measurement values and the DWT behavior during bladder filling of the healthy adult volunteers were also remarkably similar to measurement values and DWT characteristics obtained in healthy children aged ≤13 years [60]. In these children, DWT was <1.5 mm in bladders filled with 50% of capacity and <1.3 mm at maximum capacity. No additional studies have been published after these experiments. Taken together all information from these basic experiments, DWT measurement values in healthy children or young adults are almost identical when the bladder is filled ≥250 ml or ≥50% of capacity. This behavior of the detrusor has not been well understood but was reported in several studies now. Therefore, transurethral catheterization is not necessary anymore above these threshold values and at this stage of bladder filling. Therefore, all further experiments were performed without transurethral catheterization and when the volunteers or patients had a bladder filling ≥250 ml or a subjectively full bladder (when reaching a strong desire void, i.e. ≥60% of capacity [61]).

In healthy female and male adult volunteers, additional ultrasound DWT measurements of the anterior bladder wall in bladders filled by drinking until a strong desire to void was reached demonstrated that age, height, weight, and body-mass index had no significant impact on DWT (**chapter 4**). However, male volunteers had significantly greater DWT values than female volunteers at bladder capacity (1.4 vs 1.2 mm, p<0.0001). It was hypothesized that significantly greater DWT values in men reflect the greater voiding resistance due to the longer urethra and the existence of the prostate [56]. Therefore, men and women have to be evaluated separately when investigating the effect of diseases on DWT. Ultrasound DWT investigations of another study group in children aged ≤13 years also found a significantly greater DWT in boys (0.2 mm) which was identical to the measurement difference in adult men found in our investigation [60]. Likewise, BWT was numerically greater in adult men compared to adult women in another study, with a mean measurement difference of 0.29 mm [58]. In contrast to our investigation, ultrasound DWT measurements in children could detect an effect of aging on DWT in boys; there was an increasing DWT with age, most probably related to the growth

of the prostate during puberty [60, 62]. However, only healthy adult women and men aged 18 to 40 years were investigated in our study; therefore, it may still be possible that DWT changes as a result of aging in individuals aged >40 years.

Ultrasound DWT measurements at the anterior bladder wall were then performed in 70 male patients aged 42 - 80 years (mean age 63 years) with LUTS and BPE in whom BOO/BPO was clinically suspected (**chapter 5**) [63]. All patients had computer-urodynamic investigations as part of their routine check-up. During cystometry, the bladder was filled with the transurethral measurement catheter and DWT was measured when the patient had a strong desire to void (full bladder, before pressure-flow measurement for determination of bladder outlet resistance). DWT was 1.33 mm (95% confidence interval 1.17 - 1.48) in patients without BOO/BPO, 1.62 mm (95% confidence interval 1.48 - 1.76) in patients with equivocal BOO/BPO, and 2.4 mm (95% confidence interval 2.12 - 2.68) in patients with BOO/BPO. The differences of mean DWT between the three groups were statistically highly significant ($p < 0.001$). DWT in all patients with severe BOO/BPO was >3 mm. Both constrictive and compressive BOO/BPO resulted in significantly increased DWT measurement values ($p < 0.05$); however, DWT in patients with the combination of constrictive and compressive BOO/BPO did not have significantly increased DWT values compared to constrictive or compressive BOO/BPO alone. A threshold value of 2 mm best discriminated between BOO/BPO and equivocal/no BOO/BPO. Comparison of the diagnostic values of DWT, Q_{max}, Q_{ave}, prostate volume, and post-void residual urine for the prediction of BOO/BPO (pressure-flow analysis) demonstrated that ultrasound DWT measurement had the highest positive predictive value (95.5%), specificity (97.3%), and area under the curve in ROC-analysis (0.882). Therefore, ultrasound DWT measurement was the most precise examination for the prediction of BOO/BPO of all evaluated non- or minimally-invasive tests.

This was the first study that used ultrasound DWT measurements in male patients with clinical BPH to demonstrate significantly increased DWT in men with BOO/BPO. Later, other studies with patients with clinical BPH confirmed the results of this pilot study. Kessler et al. used the same DWT measurement technique in 102 male patients with a median age of 67 years and compared DWT results with those of pressure-flow measurements [64]. Median DWT for men without BOO/BPO was 1.7 mm (interquartile range 1.5 - 2.0), with equivocal BOO/BPO 1.8 mm (interquartile range 1.5 - 2.2), and with BOO/BPO 2.7 mm (interquartile range 2.4 - 3.3). The highest DWT measurement value for men without or equivocal BOO/BPO was 2.8 mm. Therefore, DWT ≥2.9 mm could detect all patients with BOO/BPO (positive predictive value and specificity 100%). In a study published by Franco et al., DWT was measured with a bladder filling of approx. 200 ml [65]. The description of the measurement technique suggests that BWT was actually measured. Although the absolute values are not comparable with those of the previous two studies due to the different measurement technique, the authors also found a statistically significant difference in mean 'DWT' between patients with or without BOO/BPO (5.0 ± 1.0 vs 7.1 ± 2.2 mm; $p = 0.001$). Significantly higher DWT measurement values were also described in other patient populations. Children with BOO due to urethral valves or dysfunctional voiding also have a significantly greater DWT compared to those without these diseases [66]. The studies on ultrasound DWT measurement are fully in line with results obtained with ultrasound BWT or UEBW measurements in men with or without BPO [50-52], children with urethral values [67, 68], or women with BOO [69-71]. Taken together all information of published studies, DWT or BWT is significantly

increased in patients with BOO, no matter of the origin (prostate, urethral values, urinary sphincter, etc.). Therefore, bladder wall hypertrophy (increased DWT or BWT) seems to be a physiologic response to increased bladder outlet resistance, unrelated to the origin of BOO, and a compensatory mechanism of the bladder as a result of BOO.

Studies in women with detrusor overactivity or OAB using high-frequency transvaginal ultrasound probes in bladders filled <50 ml demonstrated a significantly increased BWT compared to patients with stress urinary incontinence or healthy individuals [69-75]. Due to the different measurement technique BWT results of women are not directly comparable with those obtained in men with transabdominal positioning of the ultrasound probe. However, suprapubic DWT or BWT measurements (at different bladder filling volumes) were later performed in women with detrusor overactivity or OAB and confirmed initial results of transvaginal BWT measurements [59, 76]. Therefore, increased BWT or DWT is also detected in women with detrusor overactivity. It was hypothesized that involuntary detrusor contractions (against the closed bladder outlet) causes bladder wall hypertrophy [69, 73]. Ultrasound BWT or DWT measurements in men with detrusor overactivity or OAB have never been conducted. However, a large proportion of men with clinical BPH also have detrusor overactivity, as shown in **chapter 3** of this thesis. This implies that patients with BOO/BPO and detrusor overactivity could have greater DWT or BWT values compared to those with BOO/BPO but without detrusor overactivity. Subgroup analyses of men with or without detrusor overactivity and with or without BOO/BPO could clarify the influence of involuntary detrusor contractions in male bladders.

In order to investigate the diagnostic value of ultrasound DWT measurements compared to other non- or minimally-invasive tests, which are commonly used in clinical routine to estimate BOO/BPO, a prospective study was conducted in 160 treatment naïve patients with LUTS and/or BPE aged ≥40 years (**chapter 6**) [77]. Ultrasound DWT measurements at the anterior bladder wall with a subjectively full bladder were performed at the initial presentation of the patient and the very beginning of patient assessment; accordingly, DWT measurements were done after taking the patient history and before uroflowmetry and measurements of post-void residual urine as well as prostate volume. Additionally, the investigator of the non- or minimally-invasive tests was different from the investigator of the pressure-flow studies in order to avoid bias. This was the first study to prospectively investigate values of uroflowmetry (Q_{max}, Q_{ave}), post-void residual urine, prostate volume, and ultrasound DWT (index tests) to detect BOO defined by pressure-flow analysis (reference standard). The study fully complied with the recommendations of the STARD initiative (Standards for Reporting of Diagnostic Accuracy). Established threshold values for each parameter were pre-defined before the start of the study, and DWT ≥2 mm was used for the diagnosis of BOO/BPO. Significant differences between men with or without BOO/BPO were found for all investigated index tests. The calculation of the diagnostic values for the index tests showed that ultrasound DWT measurement was the most precise test to detect BOO/BPO, providing a positive predictive value of 94%, negative predictive value of 86%, sensitivity of 83%, specificity of 96%, a likelihood ratio of a positive test results (BOO/BPO) of 17.57, and an area under the curve (AUC) of receiver-operating characteristics (ROC) of 0.93. Only Q_{max} of free uroflowmetry had a better negative predictive value of 97%, sensitivity of 99% and likelihood ratio of a negative test result of 0.03. It was concluded from this study that DWT was the best test to detect and Q_{max} the best test to exclude BOO/BPO. The diagnostic values and the conclusion that

ultrasound DWT measurements are superior to commonly used tests of clinical routine have been reproduced in several studies, although most of the other studies did not follow the same quality standards of reporting of diagnostic accuracy (STARD recommendations) [63-65, 78].

A study by ElSaied et al. also followed the STARD recommendations and used the same threshold values for classification of BOO/BPO for all index tests [78]. The likelihood ratio of a positive test result (BOO/BPO) was the best for DWT (11.2) and the likelihood ratio of a negative test result (no BOO/BPO) was the best for Q_{max} of free uroflowmetry (0). Another study compared the diagnostic values of ultrasound DWT measurements with intravesical prostatic protrusion (IPP) [65]. The diagnostic value was higher for DWT compared to IPP measurements: positive predictive value (90 vs 88%), specificity (82 vs 77%), and likelihood ratio of a positive test result (4.05 vs 2.08). The combination of DWT and IPP measurement results in improved sensitivity (90%) without adding specificity (63.1%). All studies on ultrasound DWT measurements are also in line with a study investigating the diagnostic value of BWT for the detection of BOO/BPO [52]. Although the measurement technique was different, ultrasound BWT measurement was better for the prediction of BOO/BPO than Q_{max} of free uroflowmetry (AUC 0.860 vs 0.688). In summary, all studies which have investigated non- or minimally-invasive tests commonly used in clinical routine demonstrated that ultrasound DWT or BWT measurements are superior to other tests for the detection of BOO/BPO.

With the exception of one study, which directly compared ultrasound DWT with IPP measurements [65], no other study directly compared experimental non-invasive tests with each other. The comparison of the diagnostic values between the tests of different authors and study groups appears difficult because different patient populations with different in- and exclusion criteria were investigated. However, differences in the diagnostic ability of a test to detect or exclude BOO/BPO can be estimated by calculation and comparison of sensitivity, specificity, positive and negative predictive values, as well as likelihood ratios of a positive or negative test result (see introduction, chapter 1.6). Of all tests analyzed, only ultrasound measurements of DWT, ultrasound-estimated bladder weight (UEBW), composite measures of Q_{max} ≤10 ml/s + prostate volume ≥40 cm^3 + ≥IPSS 20, and the penile compression-release test in combination with Q_{max} <10 ml/s have a good or excellent ability to detect BOO/BPO (likelihood ratio of positive test results >5). The diagnostic values of non-invasive tests evaluated in two articles of this thesis (chapters 5 and 6) compared to the published literature are shown in **table 1**. The advantages and disadvantages of tests with a good or excellent ability to detect BOO non-invasively are listed in **table 2**. Although it may look easier to measure IPP with a suprapubically-positioned ultrasound array, this test has the disadvantage that it can only detect BPO and, therefore, is limited to the assessment of men with clinical BPH. Other types of BOO (e.g. bladder neck stenosis, urethral stricture, urethral valves, meatal stenosis) cannot be detected with IPP measurements. The assessment of women or children with IPP measurements regarding the presence or absence of BOO is also impossible. The evaluation with IPP in other patient groups would deliver false-negative results. Furthermore, the intra- and inter-observer variability as well as the learning curve have not been investigated for ultrasound IPP measurements until today. IPP measurements have shown only in one study that this non-invasive test can predict BPO well; other studies could not confirm the initial results.

Table 1: Diagnostic values of non- or minimally-invasive tests to detect or exclude bladder outlet obstruction (BOO) in patients with clinical benign prostatic hyperplasia. Studies of this thesis are highlighted in bold letters. References are listed in table 2 of the introduction section (pages 30 and 31). The higher the likelihood ratio of a positive test result the better the ability of the test to detect BOO (likelihood ratio 1 – 2 = minimal, 2.1 – 5 = moderate, 5.1 – 10 = good, and >10 = excellent).

Test	References	Patients [n]	Threshold values (BOO vs no BOO)	Positive Predictive Value [%]	Negative Predictive Value [%]	Sensitivity [%]	Specificity [%]	Accuracy [%]	Likelihood ratio of pos. test result (LR+)	Likelihood ratio of neg. test result (LR-)
Urethro-cystoscopy Occlusion grade	Homma et al. 1998	232	grade 3 vs grades 1 and 2	98 *	27 *	60	91	64 *	6.7 *	0.44 *
Q$_{max}$ (free uroflowmetry)	Reynard et al. 1996	157	<8 vs ≥8 ml/s	91	43	14	98	48 *	7.0 *	0.88 *
			<10 vs ≥10 ml/s	92	47	29	96	56 *	7.3 *	0.74 *
			<12 vs ≥12 ml/s	89	55	50	91	66 *	5.6 *	0.55 *
			<15 vs ≥15 ml/s	78	65	76	67	72 *	2.3 *	0.36 *
	Schacterle et al. 1996	134	<10 vs ≥10 ml/s	76	69	62	81	72 *	3.3 *	0.47 *
			<15 vs ≥15 ml/s	60	81	89	44	66 *	1.6 *	0.25 *
	Reynard et al. 1998	933	<10 vs ≥10 ml/s	70 *	47 *	47	70	56 *	1.6 *	0.44 *
			<15 vs ≥15 ml/s	66 *	58 *	82	38	64 *	1.3 *	0.47 *
	Homma et al. 1998	232	<15 vs ≥15 ml/s	64 *	79 *	97	17	65 *	1.2 *	0.18 *
	Kuo 1999	324	≤10 vs >10 ml/s	79 *	58 *	75	64	71 *	2.1 *	0.39 *
	Steele et al. 2000	204	≤10 vs >10 ml/s	85 *	43 *	73	60	70 *	1.8 *	0.45 *
	Oelke et al. 2002 [63]	**70**	**<15 vs ≥15 ml/s**	**54**	**100**	**100**	**25**	**60 ***	**1.3 ***	**0 ***
	Oelke et al. 2007 [77]	**160**	**<10 vs ≥10 ml/s**	**69**	**72**	**68**	**73**	**70**	**2.5**	**0.44**
			<15 vs ≥15 ml/s	**59**	**97**	**99**	**39**	**67**	**1.6**	**0.03**
	ElSaied et al. 2013	50	<10 vs ≥10 ml/s	58	100	100	37	66	1.6	<0.01
Q$_{ave}$ (free uroflowmetry)	**Oelke et al. 2002 [63]**	**70**	**<8 vs ≥8 ml/s**	**52**	**81**	**94**	**22**	**56 ***	**1.2 ***	**0.27 ***
	Oelke et al. 2007 [77]	**160**	**<7 vs ≥7 ml/s**	**59**	**83**	**89**	**46**	**66**	**1.7**	**0.23**
	ElSaied et al. 2013	50	<7 vs ≥7 ml/s	57	80	87	44	64	1.6	0.29
Post-void residual	Abrams & Griffiths 1979	117	≥50 vs <50 ml	80 *	48 *	88	35	75 *	1.4 *	0.34 *
	Oelke et al. 2002 [63]	**70**	**>50 vs ≤50 ml**	**56**	**72**	**81**	**43**	**61 ***	**1.4 ***	**0.44 ***
	Oelke et al. 2007 [77]	**160**	**>50 vs ≤50 ml**	**52**	**63**	**72**	**42**	**56**	**1.3**	**0.66**
	ElSaied et al. 2013	50	>50 vs ≤50 ml	53	67	74	44	58	1.3	0.59
Prostate volume (total gland size)	Rosier & de la Rosette 1995	521	≥40 vs <40 cm³	54 *	28 *	49	32	43 *	0.7 *	1.59 *
	Homma et al. 1998	232	≥30 vs <30 cm³	89 *	56 *	52	90	67 *	5.2 *	0.53 *
	Steele et al. 2000	204	≥40 vs <40 cm³	85 *	39 *	66	64	66 *	1.8 *	0.53 *
	Oelke et al. 2002 [63]	**70**	**>20 vs ≤20 cm³**	**52**	**76**	**91**	**25**	**56 ***	**1.2 ***	**0.36 ***
	Lim et al. 2006	95	>40 vs ≤40 cm³	58	32	51	38	46 *	0.8 *	1.29 *

		160	>25 vs ≤25 cm³	51	67	85	27	54	1.2	0.56
	Oelke et al. 2007 [77]	100	≥38 vs <38 cm³	84	44	72	61	70	2.0	0.55
	Franco et al. 2010	50	>25 vs ≤25 cm³	51	73	87	30	56	1.3	0.44
	ElSaied et al. 2013									
Composite measures of clinical data	Steele et al. 2000	204	BOO: Qmax ≤10 ml/s + Pvol ≥40 ml + IPSS ≥20	100*	31*	26	100	45*	>50*	0.76*
BWT	Manieri et al. 1998	174	≥5.0 vs <5.0 mm	90*	60*	54	92	70*	6.8*	0.50*
	Franco et al. 2010	100	≥6.0 vs <6.0 mm	90	50	73	82	84	4.1	0.37
DWT	**Oelke et al. 2002 [63]**	70	≥2.0 vs <2.0 mm	95	75	64	97	81*	21.3*	0.37*
	Kessler et al. 2006	102	≥2.0 vs <2.0 mm	81	85	92	68	82*	2.9*	0.12*
			≥2.5 vs <2.5 mm	90	65	69	88	77*	5.8*	0.35*
			≥2.9 vs <2.9 mm	100	54	43	100	66*	43*	0.57*
	Oelke et al. 2007 [77]	160	≥2.0 vs <2.0 mm	94	86	83	95	89	17.6	0.18
	ElSaied et al. 2013	50	≥2.0 vs <2.0 mm	91	86	83	93	88	11.2	0.19
UEBW	Kojima et al. 1997	65	>35 vs ≤35 g	88*	84*	85	87	86*	6.5*	0.17*
	Han et al. 2011	193	<24 vs ≥24 g/m²	29	87	91	21	39*	1.2*	0.43*
			<28 vs ≥28 g/m²	35	82	62	60	61*	1.6*	0.63*
			<33 vs ≥33 g/m²	25	75	10	91	70*	1.1*	0.99*
			<42 vs ≥42 g/m²	26*	75*	0	100	74*	1.0*	1.0*
IPP	Chia et al. 2003	200	>10 vs ≤10 mm	94	70	76	92	82*	9.5*	0.26*
	Nose et al. 2005	30	>10 vs ≤10 mm	67*	75*	90	40	69*	1.5*	0.25*
	Lim et al. 2006	95	>10 vs ≤10 mm	72	42	46	65	53*	1.3*	0.83*
	Reis et al. 2008	42	>10 vs ≤10 mm	70	79	80	68	74	2.5	0.29
	Franco et al. 2010	100	≥12 vs <12 mm	88	47	65	77	83	2.1	0.45
	Shin et al. 2013	239	>5.5 vs ≤5.5 mm	45*	91*	67	81	78*	3.5*	0.41*
Condom + Qmax	Pel et al. 2002	56	n.a.	66	77	64	79	73*	3.1*	0.46
PCR index	Sullivan & Yalla 2000	90	100%	74	89	91	70	80*	3.0*	0.13*
	Harding et al. 2004	101	160%	65	91	78	84	82*	4.9*	0.26*
PCR - nomogram	Griffiths et al. 2005	116	n.a.	68	78	73	75	74*	2.9*	0.36*
PCR + nomogram Qmax < 10 ml/s	Griffiths et al. 2005	116	n.a.	88	86	77	89	84*	7.0*	0.26*

* recalculated based upon published data

BOO = bladder outlet obstruction; BWT = bladder wall thickness; DWT = detrusor wall thickness; IPP = intravesical prostatic protrusion; PCR = penile compression-release test; Qave = average urinary flow rate; Qmax = maximum urinary flow rate; UEBW = ultrasound-estimated bladder weight; n.a. = not applicable

Table 2: Advantages and disadvantages of emerging tests to noninvasively diagnose bladder outlet obstruction

Test	Advantages	Disadvantages
DWT, BWT or UEBW	• BOO assessment possible in men and women • BOO assessment also possible in patients with other types of BOO than BPO • BOO assessment possible without voiding, also in patients with urinary retention • Ultrasound equipment widely available • Small learning curve • Low intra- (≤5%) and inter-observer variability (4 - 12%) • Highest likelihood ratios of all non-invasive tests • No morbidity • Prognostic value: predicts favorable outcome of α-blocker treatment	• No consensus about threshold values and bladder filling at measurement so far • Varying results with different bladder fillings • Unclear if BWT or DWT should be measured • Relationship between BWT and DWT remains to be investigated
IPP	• Ultrasound equipment widely available • No morbidity • Prognostic value: predicts patients who are likely to develop acute urinary retention or bladder stones • Prognostic value for successful TWOC	• Limited to men • Limited to diagnosis of BPO and assessment of patients with BPH-BPE • Results almost exclusively obtained in Asian patients • Threshold values under discussion • No information with regard to intra- or inter-observer variability and learning curve • Likelihood ratio to predict BPO is high in only one study
Penile Cuff Test **or** **Condom Catheter Test**	• Well investigated in a large number of volunteers and patients • Similarities to pressure-flow studies • Discrimination between BOO and detrusor underactivity possible • BOO assessment also possible in patients with other types of BOO than BPO • Prognostic value: predicts favorable outcome of TURP	• Limited to men • Special equipment and uroflowmetry device necessary • Results predominantly from one study group • High percentage of undefined results • Likelihood ratios to predict BOO/BPO low

DWT=detrusor wall thickness; BWT=bladder wall thickness; IPP=intravesical prostatic protrusion; BOO=bladder outlet obstruction; BPH=benign prostatic hyperplasia; BPE=benign prostatic enlargement; TWOC=trial without catheter; TURP=transurethral resection of the prostate; Q_{max}=maximum urinary flow rate at free uroflowmetry

The repeatability and agreement of conventional ultrasound BWT measurement results were compared with those of automatically generated BWT measurement results by using the commercially available Bladder Scan® BVM 6500 device (**chapter 7**) [79]. This hand-held device (Verathon Inc., Washington, USA) can measure the bladder filling volume and BWT by a patented ultrasound technology via suprapubic positioning of the 3.7 MHz scanner and, based on these measurements, can calculate UEBW by computer submission of the measurement data to a central computer in the USA. In total, 20 unselected women and 30 unselected men with a median age of 62.5 years were prospectively enrolled. Hand measurements of BWT with a high-frequency ultrasound array and automatic measurements of BWT were both obtained twice in the same patients at a bladder filling volume of 150 and 250 ml during routine computer-urodynamic measurement for evaluation of lower urinary tract dysfunction. UEBW was not analysed. Invalid automatic BWT measurements occurred in up to 14% of patients after submission of the measurement data to the central US computer, although the local scanner indicated sufficient measurement quality. Furthermore, BWT >4 mm could only be detected by hand measurements using conventional ultrasound arrays. In these patients, the Bladder Scan® BVM 6500 indicated much smaller measurement distances and measured erroneously only the inner part of the bladder wall. There was a trend towards a higher BWT difference with increasing BWT values. The measurement variance between repeated BWT measurements was smaller for the conventional ultrasound device. It was concluded from this prospective pilot study that both ultrasound BWT measurement techniques are repeatable and agree with each other but automatic BWT measurements cannot replace hand BWT measurements because of invalid data in up to 14% of measurements, higher variance, and the inability to detect BWT >4 mm. This is the first and only study which has ever compared both BWT measurements techniques.

The automatic evaluation of BWT appears attractive because this non-invasive test to measure the anterior bladder wall can be performed without previous ultrasound experience or an expensive ultrasound device. However, this device is useless for the application in routine patients because it intends to diagnose BOO/BPO but cannot measure BWT >4 mm. The BWT threshold value for BOO/BPO with conventional ultrasound was previously determined with 5 mm [Manieri 1998]). A cross-sectional study of 95 healthy male or female Turkish individuals aged 18–56 years demonstrated with the Bladder Scan® BVM 6500 device a mean BWT of 2.0 ± 0.4 mm and a mean UEBW of 44.6 ± 9.3 g [80]. Both BWT and UEWB were negatively correlated with bladder filling volume. The threshold value of UEBW for the detection of BOO/BPO in men was previously determined with 35 g [50, 51]; therefore, UEBW values determined with the Bladder Scan® BVM 6500 device appear to be greater than expected and pretend BOO/BPO even in healthy individuals. In another study, the Bladder Scan® BVM 6500 device was used in 187 Greek women with lower urinary tract dysfunction [81]. Automatically-measured BWT (1.9 ± 0.3 mm) and UEBW values (39.3 ± 3.0 g) were significantly lower in women with detrusor underactivity compared to healthy women (BWT 2.1 ± 0.3 mm; UEBW 45.7 ± 3.1 g). Additionally, BWT (2.4 ± 0.4 mm) and UEBW (52.3 ± 6.2 g) were significantly higher in women with BOO compared to normal women. In this study, UEBW was also above the threshold value for BOO/BPO in men which was previously determined for Asian men. There are two possible explanations

for the greater UEBW values; (1) either the Bladder Scan® BVM 6500 device does not measure or calculate correctly or (2) the threshold values of Asian men for determination of BOO cannot be transferred to Caucasians. Despite the promising technology, the Bladder Scan® BVM 6500 device has been withdrawn from the market. Reasons for the withdrawal of the automatic measurement device are unknown but the results of the article presented in **chapter 7** could have contributed to this decision. Therefore, additional studies will most probably not appear in the literature anymore.

The last article of the second section of the PhD-thesis summarized published data on ultrasound DWT and BWT measurements as well as for UEBW and proposed standardization as well as research for these ultrasound techniques to detect and quantify bladder wall hypertrophy (**chapter 8**) [82]. The article condensed the results of a think tank discussion held on the annual congress of the International Consultation on Incontinence-Research Society (ICI-RS) in Bristol in June 2009. It was concluded that the research groups, who apply different measurement techniques, all agree on certain facts: use of high frequency ultrasound probes, use of digital ultrasound machines for adequate image enlargement, ultrasound appearance of the bladder wall, perpendicular imaging of the bladder wall, decrease of the thickness of the bladder wall with increasing bladder filling, similar thicknesses at different parts of the bladder wall in the same state of bladder filling, gender specificity of measurement values, and low intra- and inter-observer variability. Disagreements between the research groups still exist for the placement of the ultrasound device (suprapubic vs transvaginal placement only for women), exact bladder filling volume for measurement of BWT or DWT, and whether DWT, BWT or UEBW is most suitable for quantification of bladder wall hypertrophy. In total, nine research questions were proposed to investigate and standardize the measurement techniques. The research proposals dealing with the comparison of suprapubic vs transvaginal BWT measurements and whether the trigone has the same thickness compared to other parts of the bladder have meanwhile been elucidated [83]. Other research questions remain to be answered. The ICI-RS article also proposed quality parameters for reporting on DWT, BWT or UEBW measurements: names of the ultrasound company and machine, frequency of the ultrasound probe, bladder filling volume at measurement, information whether DWT, BWT or UEBW was measured, one ultrasound image with maximum enlargement and positioning of the calipers, and information on drug treatment (especially with α-blockers or muscarinic receptor antagonists because these drugs could decrease DWT/BWT). Most of these recommendations have been implemented in subsequent articles [78, 84, 85].

11.3 BENIGN PROSTATIC OBSTRUCTION WITHIN THE PERSPECTIVE OF THE GUIDELINES OF THE EUROPEAN ASSOCIATION OF UROLOGY

Guidelines intend to summarize the published literature of a disease or symptom complex and deliver state-of-the-art information of accepted knowledge to physicians, health care providers, patients, or other stakeholders. Guidelines need to be updated on a regular base to catch up with the latest published evidence. In the years 2013 and 2015, the European Association of Urology (EAU) has

published evidence-based guidelines on the assessment and treatment of non-neurogenic male LUTS which originated from systematic reviews of the published literature. The EAU guidelines on the assessment and treatment of LUTS apply for men aged ≥40 years without symptoms or signs of a manifest neurological disease. These guidelines have replaced the guidelines on benign prostatic hyperplasia because BPH is considered to be a histological diagnosis but not a disease itself [86]. LUTS have a multifactorial etiology and do not only appear in patients with BPE or BPO. The bladder, pelvic floor, ureters, the central or peripheral nervous system, or even excessive urine production of the kidneys may also be responsible for or contribute to LUTS in adult men. Because patients seek professional help for LUTS [7] symptom-centered guidelines from the perspective of the patient have been published; nevertheless, the pathophysiology behind LUTS still has to be evaluated. Therefore, not only LUTS but also prostate size and BOO/BPO needs to be investigated in the individual patient.

The EAU guidelines on the assessment of non-neurogenic male LUTS, including BPO specifically mentioned and described the tests which are able to diagnose BPO (**chapter 9**) [87]. Each test was provided with the level of evidence (LE) and grade of recommendation (GR). Measurement of the serum concentration of prostate-specific antigen (PSA) a proxy parameter for prostate volume (and exclusion of prostate cancer) *should* be done (LE 1b, GR A). Uroflowmetry and determination of Q_{max} *may* be performed during the initial assessment of the patient but *should* be done before any treatment (LE 2b, GR B). Measurement of post-void residual urine *should* be a routine part of the assessment of every patient with male LUTS (LE 3, GR B). Imaging of the prostate and determination of prostate size by transrectal or transabdominal ultrasound *should* be performed if the information assists the choice of the appropriate drug (LE 3, GR B). Invasive pressure-flow studies *should* be performed in men with bothersome, predominantly voiding LUTS before surgery or when evaluation of the underlying pathophysiology of LUTS is warranted, who previously had unsuccessful (invasive) treatment of LUTS, or are younger than 50 years of age (LE 3, GR B). Invasive pressure-flow studies *may* be performed in men who cannot void >150 ml, have post-void residuals >300 ml, and are older than 80 years of age (LE 3, GR C). For the first time in international guidelines, ultrasound measurements of IPP, DWT, BWT, and UEBW were mentioned as feasible tests to diagnose BPO. Because these ultrasound tests for the assessment of BPO in patients with male LUTS are currently under investigation, no specific recommendations were made. Other non- or minimally invasive tests for the determination of BPO were considered too experimental or unsuitable for doctors of the urological society. The adherence of urologists to the recommendations of EAU guidelines on the assessment of male LUTS seems crucial for the evidence-based evaluation of patients.

The adherence has not been evaluated for these recently published guidelines (June 2015). However, adherence analysis was done for the AUA guidelines on the management of BPH (version 2003) which recommended the testing of serum PSA (as a proxy parameter for prostate volume) in all patients, next to the assessment of LUTS by history and questionnaires, physical examination, serum creatinine, and urinalysis [88]. Optional tests in the AUA guidelines were uroflowmetry, measurement of post-void residual urine, imaging of the prostate with ultrasound, imaging of the upper urinary tract, and pressure-flow studies. The adherence to the guidelines was analysed in a 5% sample of patients of

the US Medicare Claims database, investigating the files of 10,248 men aged >65 years [89]. Urologists with poor compliance to the guidelines performed prostate surgery (TURP) in 11% of patients within the first year of diagnosis, whereas doctors with a good compliance only operated 2% of their patients, which translates into a 91% decrease in the adjusted odds of receiving surgery with good vs poor guidelines compliance.

The EAU guidelines on the treatment and follow-up of non-neurogenic male LUTS, including BPO provide evidence-based recommendations on watchful waiting, various drugs, and different surgical treatments (**chapter 10**) [90]. Symptom relief is the primary goal for all treatments. The absence or presence of BPO is of minor importance for watchful waiting and the majority of drug therapies. The majority of drugs used to treat LUTS in adult men does not or only has a minor influence on BPO and, vice versa, BPO does not negatively impact efficacy, tolerability and adverse events in patients treated with these drugs. However, BPO may be relevant during treatment with muscarinic receptor antagonists which inhibit muscarinic receptors on smooth muscle cells of the bladder (and on other organs) and can inhibit detrusor smooth muscle contractions. In patients with BPO, inhibition of detrusor muscle cells can decrease detrusor contractility which could result in increase of post-void residual urine, decrease of voiding efficiency, and may eventually end in urinary retention. These adverse events during treatment with muscarinic receptor antagonists have rarely been seen in randomized, placebo-controlled or observational trials with muscarinic receptor antagonists as mono- or combination therapy with α-blockers but, however, patients with severe BPO or post-void residuals >150 ml were previously excluded from trial participation [91]. At the time of the literature search only one study had a follow-up period of 25 weeks when using the muscarinic receptor antagonist tolterodine 4 mg once daily as monotherapy [92], whereas all other mono- or combination therapy studies with muscarinic receptor antagonists had a follow-up of ≤12 weeks. Therefore, long-term effects of muscarinic receptor antagonists on voiding efficiency, post-void residual urine, and urinary retention remain unknown. It was recommended in the EAU guidelines that caution is advised in patients who are treated with muscarinic receptor antagonists and have BPO; these men should have regular re-evaluation of LUTS (IPSS) and measurements of post-void residual urine (LE 2b, GR B). In contrast to medical therapy of LUTS, all surgical therapies aim to reduce BPO by prostatic tissue ablation (e.g. TURP, open prostatectomy, TUNA, Laser treatments) or incision of the prostate (TUIP). Urodynamic studies have shown that all treatment modalities can effectively reduce BPO. Therefore, the indication for surgery is, beside absolute indications, bothersome moderate to severe LUTS secondary of BPO.

11.4   FUTURE PERSPECTIVES

The answer to one research question opens questions to others. Relevant research questions arising from this thesis are mentioned above.

To clarify the relationships between BOO/BPO and lower or upper urinary tract damage it is necessary to investigate patients with these urinary tract complications with pressure-flow studies to

uncover the pathophysiology behind these changes and compare patients with urinary tract complications with age-matched men without these complications. Alternatively, validated proxy parameters of BOO/BPO (e.g. ultrasound measurement of DWT, UEBW, or IPP or measurement of isovolumetric bladder pressure by the penile cuff test or condom catheter method) could be used to clarify the pathophysiology, thereby avoiding the disadvantages of pressure-flow studies.

It was shown that BOO/BPO is responsible for detrusor overactivity in a subset of patients. It seems interesting to know what will happen to patients with or without BOO/BPO if they would all receive transurethral resection of the prostate or any other treatment with prostatic tissue ablation. It is likely that detrusor overactivity will disappear in patients with BOO/BPO and remain in those without BOO/BPO. A longitudinal study with pressure-flow studies could clarify this question and could show whether patients without BOO/BPO have a higher chance to become incontinent after the operation (detrusor overactivity incontinence). This would be another argument to perform BOO/BPO assessment before treatment.

Future studies on ultrasound DWT measurements in healthy individuals should further elucidate the relationship to bladder filling. Although the thinning of the detrusor in the first 50% of bladder capacity and an almost constant DWT until maximum capacity was described by several independent study groups, this behavior of the detrusor needs to be confirmed. This could be done in healthy individuals by using high resolution magnetic resonance tomography (MRT) of the bladder at different bladder fillings. This investigation could also be used to confirm identical DWT measurements at different bladder locations (anterior, posterior and lateral walls, bladder dome, and trigone). Healthy volunteers should also be investigated to determine the effect of aging on DWT, especially in those aged >40 years.

Because women with detrusor overactivity or OAB have significantly increased BWT or DWT values compared to female patients without detrusor overactivity or OAB it would be interesting to evaluate men with or without BOO/BPO and subgroups with or without detrusor overactivity. This study could easily be done by sub-analysis of men with clinical BPH who were investigated for this thesis. Furthermore, the detrusor behavior in healthy adult women and men with thinning until 50% of bladder capacity and an almost constant thickness thereafter should also be investigated in men with clinical BPH. This could be done during routine computer-urodynamic investigation in the target group with ultrasound measurement of DWT every 50 ml of bladder filling.

The diagnostic ability to detect BOO/BPO was good or excellent for ultrasound DWT or BWT measurements. In order to directly compare these measurement results with other new non- or minimally-invasive tests (e.g. IPP, penile cuff test) it is necessary to conduct a prospective study with several of those new promising tests in the same cohort of patients. This study has to be conducted according to the recommendations of the STARD initiative and could be done as a mono- or multicenter study.

Future studies with the Bladder Scan® BVM 6500 are not possible because the device has meanwhile been withdrawn from the market. However, it appears useful to invent and establish a new automatic and portable device for the automatic evaluation of BWT and UEBW. This new device should use a high frequency scanner (≥7.5 MHz) instead of a 3.7 MHz ultrasound array, should have the ability

for manual correction of the automatically generated BWT measurement lines, should avoid filters for the measurement of BWT >4 mm and should use a local computer for evaluation of the measurement values. Automatic BWT and UEBW measurements would stimulate the widespread use of ultrasound technology to diagnose BOO/BPO or other forms of lower urinary tract dysfunctions in clinical routine and scientific investigations (e.g. cross-sectional or longitudinal epidemiological trials).

Standardization of the ultrasound measurement technique appears crucial in order to homogenize measurements and bundle time as well as research capacities in the future. Therefore, the implementation of standards is crucial. This should be done by asking reviewers of medical journals to remind the authors of reporting about pre-defined quality criteria of DWT, BWT and UEBW measurements. Future studies should focus on the research questions listed in the standardization report of the ICI-RS, most importantly the evaluation of the ideal bladder filling for DWT or BWT measurement, evaluation of the learning curve, determination of a conversion factor between DWT and BWT measurement values, and whether different forms of lower urinary tract dysfunction need different measurement techniques.

The EAU guidelines on the assessment of non-neurogenic male LUTS have recently been published (June 2015). Future studies should evaluate the acceptance of and adherence to these guidelines by a questionnaire based internet evaluation of urologists in which these EAU members are asked about the implementation of the various tests in their daily clinical practice. Additionally, national databases of health care systems of the EAU membership countries should be analyzed for tests and treatments during a defined period in order to evaluate whether doctors with poor compliance to the guidelines perform prostate surgery more frequently than doctors with good compliance to the guidelines. EAU data could then be compared to AUA data.

The EAU guidelines on the treatment of non-neurogenic male LUTS recommend using muscarinic receptor antagonists with caution in patients with BPO. Limited data are available for long-term treatment. Evaluation of BPO and the BPO-grade before treatment and subsequent treatment with muscarinic receptor antagonists for a longer period of time (≥1 year) should clarify whether patients with BPO develop post-void residual urine or retention. Pressure-flow studies or reliable non-invasive tests could be used to determine BPO at baseline and long-term follow-up.

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Summary

This thesis is divided into three sections. The first section focuses on the relevance of bladder outlet obstruction (BOO) or benign prostatic obstruction (BPO) in adult men. Two articles added knowledge to this topic. The first article (**chapter 2**) investigated whether BOO/BPO is responsible for functional or structural damage of the lower or upper urinary tract. The systematic literature search showed that post-void residual urine, bladder diverticula, bladder stones, vesico-ureteral reflux, hydronephrosis, renal insufficiency, and urinary retention appear with higher prevalence in patients with clinical BPH but there is no scientific proof that BOO/BPO is really responsible for these alterations. The second article of the first section (**chapter 3**) investigated whether BOO/BPO causes detrusor overactivity. It was shown that BOO/BPO and age are independently associated with detrusor overactivity. With increasing BOO/BPO-grade, the chance of detrusor overactivity increases likewise. Furthermore, earlier appearance and higher amplitude of involuntary detrusor contractions are significantly associated with BOO/BPO.

The second section deals with ultrasound detrusor wall thickness (DWT) measurements. Basic principles of this measurement technique were described in 55 healthy adult female and male volunteers (**chapter 4**). The influence of bladder filling on DWT was evaluated first. DWT decreases with increasing bladder filling volume until approx. 250 ml (50% of capacity) but, thereafter, remains almost constant until the bladder is completely full (100% capacity). It was concluded that ultrasound DWT measurements are possible without bladder catheterization when measuring at a bladder filling volume ≥250 ml or ≥50% of capacity. On this understanding, all additional investigations on DWT were performed with a full bladder. The initial study in healthy individuals also demonstrated that men have a significantly thicker DWT compared to women; therefore, DWT needs to be separately evaluated in both genders. Age, height, weight, or body-mass index did not have a significant influence on DWT and, therefore, these parameters were considered irrelevant for the additional studies. A prospective study evaluated the effect of BOO/BPO on DWT in 70 adult men with LUTS and/or BPE by using the measurement technique described above (**chapter 5**). Mean DWT is significantly higher in men with urodynamically-confirmed BOO/BPO than in men with equivocal or without BOO/BPO. The greater the BOO/BPO-grade is the greater DWT becomes. A DWT threshold value ≥2 mm best detects BOO/BPO. Both constrictive and compressive BOO/BPO result in significantly increased DWT measurements. The diagnostic value of ultrasound DWT measurement with a pre-defined threshold value of 2 mm was compared with the diagnostic values of commonly used routine clinical tests in order to detect BOO/BPO, as defined by pressure-flow measurement (**chapter 6**). In total, 160 symptomatic, treatment naïve patients with or without BPE were prospectively evaluated. Of all investigated index tests, only ultrasound DWT measurement showed an excellent ability to detect BOO/BPO (likelihood ratio of a positive test result of 17.6). The ability to detect BOO/BPO was minimal or moderate at best for all other tests (Q_{max}, Q_{ave}, post-void residual urine, prostate volume). However, Q_{max} of free uroflowmetry was the best test to confirm non-obstruction (likelihood ratio of a negative test result 0.03). Repeatability and agreement of manual and automatic BWT measurements with the Bladder Scan® BVM 6500 device were evaluated in 50 unselected women and men at a bladder filling volume of 150 and 250 ml (**chapter 7**). This prospective pilot study demonstrated that both ultrasound BWT measurement techniques are repeatable and agree with each other but automatic BWT measurements delivered invalid data in up to 14% of measurements.

had a higher measurement variance and were not able to detect BWT >4 mm. It was concluded that automatic BWT measurements cannot replace conventional BWT measurements. The last article of the second section is a standardization report of the International Consultation on Incontinence-Research Society (ICI-RS) which summarizes the similarities and differences between the various research groups dealing with detection and quantification of bladder wall hypertrophy (**chapter 8**). In this standardization report, it was presumed that all research groups agree with the majority of basic facts for the measurements of DWT, BWT and UEBW (i.e. use of high frequency ultrasound scanners, use of digital ultrasound machines, ultrasound appearance and perpendicular imaging of the bladder wall, decrease of BWT/DWT with increasing bladder filling, similar thickness of the different parts of the bladder, gender specificity, and low intra- and inter-observer variability). Nevertheless, the various measurement techniques are currently not interchangeable and several research questions still have to be answered for further standardization, especially clarification of the bladder filling volume at measurement and determination of a conversion factor to translate DWT into BWT values.

The last part of the thesis investigates the relevance of BPO in the guidelines of the European Association of Urology (EAU) for the assessment and treatment of male LUTS. The recently published, evidence-based EAU guidelines on the assessment of non-neurogenic male LUTS, including benign prostatic obstruction specifically mention the tests to evaluate BPO (**chapter 9**). Suitable tests are measurement of serum prostate-specific antigen (PSA) concentration as a proxy parameter for prostate volume (Level of Evidence [LE] 1b, Grade of Recommendation [GR] A), uroflowmetry before any treatment (LE 2b, GR B), ultrasound measurement of post-void residual urine (LE 3, GR B), and ultrasound measurement of prostate size if the information assists the choice of the appropriate drug (LE 3, GR B). Pressure-flow studies for the assessment of BPO (and exclusion of other forms of lower urinary tract dysfunction) are indicated in men with bothersome, predominantly voiding LUTS before surgery, when evaluation of the underlying pathophysiology of LUTS is warranted, in men who previously had unsuccessful (invasive) treatment of LUTS, are younger than 50 or older than 80 years of age, cannot void >150 ml, and have post-void residuals >300 ml (LE 3, GR B/C). For the first time in international guidelines, ultrasound measurements of IPP, DWT, BWT, and UEBW were mentioned as feasible tests to diagnose BPO but recommendations regarding LE and GR have not been provided because these non-invasive tests are still under investigation. The EAU guidelines on the treatment of non-neurogenic male LUTS, including benign prostatic obstruction have clarified the effect of drugs and surgical treatment modalities on BPO (**chapter 10**). The majority of drugs does not have any or only has a minor impact on BPO and, vice versa, BPO does not have a relevant effect on the efficacy, tolerability or adverse events of these drugs. Only muscarinic receptor antagonists should be used with caution because inhibition of detrusor muscle contractions could induce post-void residual urine or urinary retention. Therefore, patients treated with muscarinic receptor antagonists should be regularly monitored with re-assessment of LUTS (IPSS) and measurement of post-void residual urine. In contrast to drugs, all surgical treatments of the prostate reduce BPO. Therefore, prostate surgery is indicated when patients have bothersome moderate to severe LUTS secondary to BPO and when they have absolute indications for surgery such as urinary retention, bladder stones, or upper urinary tract dilatation with or without renal insufficiency due to BPO.

Samenvatting

Dit proefschrift bestaat uit drie delen. Het eerste gedeelte richt zich op blaas uitgang obstructie ('Bladder Outlet Obstruction': BOO) of ook wel genoemd benigne prostaat obstructie ('Benign Prostatic Obstruction': BPO) bij volwassen mannen. Twee artikelen dragen bij aan de kennis over dit onderwerp. Het eerste artikel (**hoofdstuk 2**) onderzoekt of BOO/BPO verantwoordelijk is voor functionele of structurele beschadiging van de urinewegen. Een systematisch literatuuronderzoek laat zien dat urine residu, blaas divertikels, blaasstenen, vesico-ureterale reflux, hydronefrose, nier insufficiëntie en urine retentie vaker voorkomen bij patiënten met klinische BOO/BPO maar er is geen wetenschappelijk bewijs dat BOO/BPO verantwoordelijk is voor deze aandoeningen. Het tweede artikel (**hoofdstuk 3**) onderzoekt of BOO/BPO overactiviteit van de detrusor veroorzaakt. Er werd aangetoond dat BOO/BPO en leeftijd onafhankelijk geassocieerd zijn met detrusor overactiviteit. Met de toename van de BOO/BPO-graad, neemt de kans op detrusor overactiviteit in dezelfde mate toe. Bovendien zijn een vroeg optreden en een hoge amplitude van onvrijwillige detrusor contracties significant geassocieerd met BOO/BPO.

Het tweede gedeelte behandelt de detrusor wanddikte ('Detrusor Wall Thickness': DWT) metingen met echografie. De basisprincipes van deze meettechniek worden beschreven in 55 gezonde volwassen mannelijke en vrouwelijke vrijwilligers (**hoofdstuk 4**). Als eerste werd de invloed van de blaas vulling op DWT geëvalueerd. DWT neemt af bij een toegenomen blaasvolume tot ongeveer 250 ml (50% van de capaciteit) maar blijft daarna bijna constant totdat de blaas compleet vol is (100% van de blaas capaciteit). De conclusie is dat ultrageluid DWT metingen mogelijk zijn zonder blaas katheterisatie wanneer er gemeten wordt met een blaas vulvolume van ≥250 ml of ≥50 % van de blaas capaciteit. Met dit inzicht werden alle aanvullende onderzoeken naar DWT uitgevoerd met een volle blaas. De eerste studie bij gezonde individuen toonde eveneens aan dat mannen een aanzienlijk dikkere DWT hebben dan vrouwen; daarom moet de DWT afzonderlijk worden geëvalueerd in beide geslachten. Leeftijd, lengte, gewicht of Body-Mass Index (BMI) hebben geen significante invloed op de DWT en daarom werden deze parameters als niet relevant beschouwd voor de aanvullende studies. In een prospectieve studie werd het effect van BOO/BPO op DWT in 70 volwassen met LUTS en/of "Benign Prostate Enlargement" (BPE) met gebruik van de bovenstaande meettechniek onderzocht (**hoofdstuk 5**). De gemiddelde DWT was significant hoger in mannen met urodynamisch bevestigde BOO/BPO dan in mannen met "equivocal" of zonder BOO/BPO. Hoe hoger de BOO/BPO-graad was, des te hoger de DWT werd. Een DWT drempelwaarde van ≥2 mm kon het beste BOO/BPO detecteren. Zowel constrictieve als compressieve BOO/BPO resulteerde in een aanzienlijk toegenomen DWT. De diagnostische waarde van een ultrageluid DWT meting met de vooraf bepaalde drempelwaarde van 2 mm werd vergeleken met de normaal gebruikte klinische testen om BOO/BPO vast te stellen: de blaasdruk-flowmeting (**hoofdstuk 6**). In totaal werden 160 symptomatische onbehandelde patiënten met of zonder BPE prospectief onderzocht. Van alle onderzochte index testen, liet alleen de echografie DWT meting een uitstekende mogelijkheid zien om BOO/BPO vast te stellen (waarschijnlijkheidsratio van een positief test resultaat van 17,6). De mogelijkheid om BOO/BPO te detecteren was minimaal of matig voor alle andere testen (maximale flow (Q_{max}), gemiddelde flow (Q_{ave}), urine residu, prostaat volume). Echter, Q_{max} van de vrije uroflowmetrie was de beste manier om geen obstructie te bevestigen (waarschijnlijkheidsratio van een negatief test resultaat 0,03). Herhaalbaarheid en

overeenstemming van handmatige en automatische BWT metingen met het Bladder Scan® BVM 6500 apparaat werden geëvalueerd in 50 niet-geselecteerde vrouwen en mannen bij een blaas vulvolume tussen 150 en 250 ml (**hoofdstuk 7**). Deze prospectieve pilot-studie toonde aan dat zowel echografie BWT meettechnieken herhaalbaar en overeenkomstig zijn, maar dat automatische BWT metingen in tot 14 % van de metingen niet valide gegevens produceren, een hogere meting variantie hadden en niet in staat waren om BWT >4 mm te detecteren. Er werd geconcludeerd dat automatische BWT metingen conventionele BWT metingen niet kunnen vervangen. Het laatste artikel van het tweede deel betreft een standaardisatie rapport van de International Consultation on Incontinence Research Society (ICI-RS) dat de overeenkomsten en verschillen tussen de verschillende onderzoeksgroepen samenvat met betrekking tot de detectie en kwantificering van blaaswand hypertrofie (**hoofdstuk 8**). In dit standaardisatie rapport werd aangenomen dat alle onderzoeksgroepen het eens zijn met de meerderheid van de basis factoren voor de metingen van de DWT, blaas wand dikte ("Bladder Wall Thickness": BWT) en blaas gewicht (Utrasound Estimated Bladder Weight": UEBW) (d.w.z. het gebruik van hoge frequentie en digitale ultrasound scanners, loodrechte ultrasound meting van de blaaswand, afname van BWT/DWT bij toenemende blaasvulling, vergelijkbaar dikte van de verschillende delen van de blaas, geslacht specificiteit en lage intra- en inter-observer variabiliteit). Toch zijn de verschillende meettechnieken momenteel niet uitwisselbaar en een aantal onderzoeksvragen moeten nog beantwoord worden voor verdere standaardisatie, met name verduidelijking van het blaasvul volume bij het meten en het bepalen van een conversie factor om DWT te vertalen naar BWT waarden.

Het laatste deel van dit proefschrift onderzoekt de relevantie van BPO in de richtlijnen van de European Association of Urology (EAU) voor de beoordeling en behandeling van mannelijke LUTS. De recent gepubliceerde, evidence-based EAU richtlijn voor de beoordeling van niet-neurogene mannelijke LUTS, waaronder benigne prostaatobstructie, noemen specifiek de tests om BPO te onderzoeken (**hoofdstuk 9**). Geschikte tests zijn het meten van serum Prostaat-Specifiek Antigen (PSA) concentratie als parameter voor prostaat volume (Level of Evidence [LE] 1b, Grade of Recommendation [GR] A) , uroflowmetrie voor iedere soort behandeling (LE 2b, GR B) , echografie meting van het urineresidu (LE 3, GR B) en echografie meting van prostaatgrootte als de informatie gebruikt wordt voor het meest geschikte geneesmiddel (LE 3, GR B). Druk-flow studies voor de beoordeling van BPO (en uitsluiting van andere vormen van lagere urinewegen dysfunctie) zijn geïndiceerd in mannen met hinderlijke, overwegend "lediging-mictieklachten" voor de operatie, wanneer de evaluatie van de onderliggende pathofysiologie van LUTS noodzakelijk is, bij mannen die eerder een mislukte (invasieve) behandeling van LUTS hebben gehad, jonger zijn dan 50 of ouder dan 80 jaar, niet >150 ml kunnen urineren, en een residu hebben na het urineren van >300 ml (LE 3 , GR B/C) . Voor het eerst in de internationale richtlijnen, werden echografie metingen van IPP ("Intravesical Prostate Protrusion"), DWT, BWT en UEBW genoemd als mogelijk tests voor de diagnose van BPO, maar aanbevelingen met betrekking tot LE en GR werden niet verstrekt, omdat deze niet-invasieve tests nog steeds onderzocht worden. De EAU richtlijnen voor de behandeling van niet-neurogene mannelijke LUTS, waaronder benigne prostaat obstructie, hebben het effect van geneesmiddelen en chirurgische behandelingen vastgesteld (**hoofdstuk 10**). De meerderheid van de geneesmiddelen heeft geen of een gering effect op BPO, en vice versa, heeft BPO geen relevant effect op de werkzaamheid, verdraagbaarheid en bijwerkingen van

deze medicijnen. Alleen muscarine receptor antagonisten moeten met zorgvuldigheid worden gebruikt, omdat remming van de detrusor spiercontracties een urine residu of urineretentie kan veroorzaken. Daarom moeten patiënten behandeld met muscarine receptor antagonisten regelmatig worden gecontroleerd met een herbeoordeling van LUTS (IPSS) en meting van het urine residu. In tegenstelling tot geneesmiddelen, verminderen alle chirurgische behandelingen van de prostaat BPO. Daarom is een prostaatoperatie geïndiceerd bij patiënten met matige tot ernstige LUTS secundair aan BPO en in het geval van absolute indicaties voor een operatie zoals urineretentie, blaasstenen, of hogere urinewegen dilatatie met of zonder nierinsufficiëntie als gevolg van BPO.

Brief Curriculum Vitae

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Matthias Oelke studied medicine in Munich and Hannover, Germany. After his final examination in Hannover, he trained in general surgery at the Marienhospital in Osnabrück, Germany from 1994 to 1996. Afterwards, he conducted his residency in urology at the Hannover Medical School from 1996 to 2001. He passed his German Urology Board examination in 2001 and the Examination of the European Board of Urology (Part I) in 2003. In 2004, Matthias Oelke completed his German doctoral thesis with *summa cum laude* and, in the same year, he joined the Department of Urology at the Academic Medical Centre in Amsterdam, where he worked as Section Head of Functional & Reconstructive Urology. In 2005, Matthias Oelke completed the Examination of the European Board of Urology (Part II) and was appointed as Fellow of the European Board of Urology, F.E.B.U. Matthias Oelke returned to the Hanover Medical School in Germany in 2008 where he became Vice-Chairman and Associate Professor in 2010.

Matthias Oelke is an active member in many societies including the European Association of Urology, International Continence Society, International Consultation on Incontinence-Research Society, Dutch Society of Urology, the German Society of Urology, German Urodynamic Society, German League of Urologists, and the German Society of University Teachers. He was chairman of the EAU Guidelines on Male LUTS from 2004 to 2012 and panel member until 2014. He participates in the German Expert Group on Benign Prostatic Hyperplasia, German Expert Group on Functional Urology, and European Section of Female Functional Urology (ESFFU). He has recently been elected as chairman of the German Expert group on Benign Prostatic Hyperplasia and member of the detrusor underactivity commission of the International Continence Society. He is a member of the editorial boards of the World Journal of Urology, Der Urologe, International Brazilian Journal of Urology, Urologia Essencial, BioMed Research International and UroVirt, regular reviewer of 22 medical/urological journals, and medical advisor of several companies.

Matthias Oelke received 16 national or international awards and received four research grants, one of them the *Astellas European Foundation Grant 2012.* He is an active investigator in drug trials in which he has been co-investigator in 6 and principle investigator in 16 studies.

PUBLICATION LIST

Original Scientific Articles

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