BLADDER OUTFLOW OBSTRUCTION: TOWARDS MORE ADVANCED ANALYSIS

Thesis for the degree of Master of Science in Technical Medicine

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Preface

This thesis is a product of my graduating internship completing the Technical Medicine masters program. In the research performed during this internship, I created a comparison between several decades-old measures which exist within the field of urodynamics, based on almost twenty years of measured data. During an earlier internship at the urology department of the university medical center Utrecht, my interest in the field of urodynamics aroused. It is an area within (technical) medicine in which a lot of research is done, but still includes a lot of questions which could not easily be answered earlier. As the tools of big data analysis become more and more available, advanced analysis methods could be created, thereby extending the clinical impact of a diagnostic tool. Besides the interesting field of urodynamics, the enthusiastic supervision by dr. Rosier was a key factor in this internship. He ensured me beforehand that I could research anything I liked within the field of urodynamics (which resulted in me doing research in field of interest). Our hours-long discussion over every small detail sharpened my critical thinking. Besides dr. Rosier, prof. Geurts and drs. Van Steenbergen had a substantial impact on my development within the practice of research in general and urodynamics in particular. Besides the research done, drs. De Witte mentored me in my personal development, by questioning events that occured during the internship and providing background information about social interactions.

In this thesis, the urodynamic subject is first introduced, by giving a brief overview of the anatomy and physiology of the lower urinary tract. This is followed by an overview of the normal urodynamic procedure and the history of the urodynamic quantification and classification of the urethral resistance, concluded with the overall aim to this thesis. Next, two articles will be included, the first one discussing several existing measures for the quantification of urethral resistance and the second one clarifying the clinical relevance of subclassification of bladder outflow obstruction. Those articles will be followed by three abstracts which are accepted for a short oral at the International Continence Society annual congress in September. The first two consist of a short summary of the two articles included in this thesis. The last one considers the use of unsupervised machine learning for distinguishing several types of bladder outflow obstruction. The thesis will conclude with a further outlook on research in the field of urodynamics.

Contents

1. Introduction

1.1 The bladder and outflow tract in men: anatomy and physiology

This part is mainly based on Clinical Oriented Anatomy[1] and Medical Physiology[2], Other sources will be referenced if applicable.

The urinary organs can be divided into two main parts. The upper urinary tract, including the kidneys and the ureters, and the lower urinary tract (LUT). The LUT is different in men and women, mostly due to the longer urethra and the presence of a prostate by men. The LUT also includes the bladder, which will be discussed later on. During voiding, in men, the urine will pass through four distinguished parts of the urethra. Starting with the intramural part, which is surrounded by the internal urinary sphincter, which is normally tonically contracted during filling and relaxed during voiding. Next is the urethra prostatica, where the urethra passes through the prostate. After the urethra prostatica, the intermediate part is found, which includes the external urinary sphincter, followed by the spongy urethra which courses through the corpus spongiosum until the meatus is reached.

The bladder consists of three layers of smooth muscle, which are together called the detrusor. During the filling of the bladder, the detrusor is normally in a relaxed state, resulting in a small compliance (which is equal to $\Delta V/\Delta p$) and thereby a small increase in pressure. The innervation of the bladder and urinary sphincters is a combination of sympathetic, parasympathetic - both part of the autonomic nerve system -, and somatic nerves. During the storage phase, the sympathetic nervous system is activated. Those fibers convey from the spinal cord between T10 and L2 and pass through several nervous plexi. Activation will result in a relaxation of the detrusor, while the internal sphincter is activated. The parasympathetic fibers originate from the segments S2 to S4 of the spinal cord and are activated during voiding, resulting in an excitation of the detrusor and an inhibition of the internal sphincter. The somatic pudendal nerve originates also from the segments S2 to S4 of the spinal cord and innervates the skeletal muscle which forms the external sphincter. The sensory, afferent fibers of most of the bladder follow the course of the parasympathetic fibers, while pain fibers from the superior part of the bladder follow the sympathetic fibers. The control of voiding is based on the pontine micturition center, which acts as a switch between urine storage and voiding. In healthy adults, higher cerebral functions have full control over this micturition center, so voiding is only initiated at voluntary will by relaxing the external sphincter.

During voiding, the detrusor will deliver energy to the bladder content, which will result in an increase in pressure.[3] As a result of this pressure, the collapsed outflow tract is distended, so urine can be expelled. The urine flow rate is determined by the flow controlling zone, which is a physiological feature that can be represented by many anatomical points. In young men, the lumen of the external sphincter is expected to be the anatomical limiting factor, as this lumen is the most narrow part of the urethra. In the elderly male population, the anatomical limiting factor is most likely caused by the enlarged prostate.

1.2 General urodynamics

This part is based on the 2023 ICS-SUFU standard for urodynamic pressure-flow studies (ICS-PFS23)[3,4] and the 2016 Good Urodynamic Practices.[5]

The urodynamic study (UDS) is used to assess the function of the lower urinary tract (LUT) in terms of pressures and flow. During an invasive urodynamic measurement, a small catheter is inserted in the bladder through the urethra, measuring the intravesical pressure (p_{ves}). An additional rectal catheter is used, measuring the abdominal pressure (p_{abd}). As an increase in abdominal pressure caused by e.g. movement, coughing, or talking will result in an increase in both p_{abd} and p_{ves}, calculating the difference between those pressures will result in the pressure which is the result of the compliance or contraction of the detrusor muscle (p_{det}). The flow leaving the meatus can be measured using a weight or rotating disc measurement device.

The patient is asked to come with a filled bladder, so a non-invasive uroflowmetry can be performed before the invasive urodynamic tests. Based on the uroflowmetry and the bladder diary including all voided volumes for 24 hours, the filling rate can be determined. This is estimated in such a way that the bladder will be filled in approximately 10 minutes with NaCl 0.9%, using a secondary lumen included in the vesical catheter . For a normal physiological bladder volume of 450-500ml, a filling rate of 50ml/min is used.

After the insertion of the catheters, the measurement equipment is normalized to the atmospheric pressure, and the pressure transmission is checked, which could be performed by asking the patient to cough. The urodynamic measurement can be divided into 2 main parts: the measurement of the filling of the bladder, called cystometry, normally directly followed by the pressure-flow study (PFS). The transition between those phases is marked with the permission to void, given by the urodynamicist.

Cystometry

From the cystometry, several measures can be deducted: First, the total bladder capacity can be deduced, which is normally limited by a strong but not uncomfortable need to void. Next, the sensations during the filling are reported at three moments: First sensation, the moment that the patient perceives that the bladder is not empty anymore; normal desire, the moment that the patient will go to the toilet at the next convenient moment; and strong desire, the moment that the patient will not postpone a visit to the nearest restroom without loss of urine or pain. If patients are not able to adequately report their sensations, the clinical impression of the urodynamicist and the direct interpretation of the measurement is relevant in the determination of the amount of filling.

Third, the pressure pattern during the filling of the bladder will be analyzed. For a normal healthy detrusor, only a minor pressure increase due to the compliance of the bladder is expected during filling. Due to amongst others fibrosis, this compliance can be larger, resulting in a higher pressure at the same volume. Besides compliance, the presence of detrusor overactivity (DO) is analyzed, which is stated to be present if there is a detrusor contraction visible before the permission to void is given to the patient. When DO is present, the amplitude has to be reported and any urine leakage has to be denoted.

Moreover, some additional tests can be performed during cystometry. Anamnestic stress incontinence can be simulated by asking the patient to cough, perform a vasalva, or stand up during the measurement. Leakage or pressure differences due to these tests must be denoted.

Pressure-Flow study

The PFS begins directly after the permission to void is given by the urodynamicist and ends when the detrusor pressure has returned to the baseline, the flow rate becomes zero, and/or the patient considers the voiding to be completed. During the PFS, it is recommended that the urodynamicist leaves the room, to allow some privacy for the patient which could also result in a more representative voiding. The patient is instructed to void without abdominal straining if possible, to ensure optimal analysis of the results. Representativity of the voiding must always be checked after the patient has finished voiding.

Based on the PFS, the urethral resistance (UR) and the detrusor voiding contraction (DVC) can be analyzed. The delay between the fluid leaving the meatus and hitting the flowmeter has to be taken into account and should be reduced as much as possible by adjusting the flowmeter as close as possible to the meatus. For analyzing the UR and the DVC, it is recommended to use a plot with the pressure on the X-axis and the time delay corrected flow on the Y-axis.

For analyzing the UR, several measures are proposed over time, which will be discussed in paragraph 1.3 and article 1. The currently in-use measures are based on a (simplified) expected relation, based on distensible–collapsible tube dynamics, between the maximal flow with the corresponding pressure and the minimal urethral opening pressure, which is the pressure measured at the end of voiding. The bladder outflow obstruction (BOO) is defined as a specific UR value considered clinically relevant, which is slightly different within the currently existing measures.

The DVC can be classified as an underactive, normal, or strong contraction, which should only be based on both pressure and flow. The currently mostly used measure for DVC is the detrusor contraction index (DCI), a continuous measure for which several cut-off values are defined and based on the maximal flow rate and the corresponding detrusor pressure. Continuous measures of the DVC during voiding are the bladder working function or the bladder watts factor, but cut-offs for patterns visible in these continuous measures are not formulated.

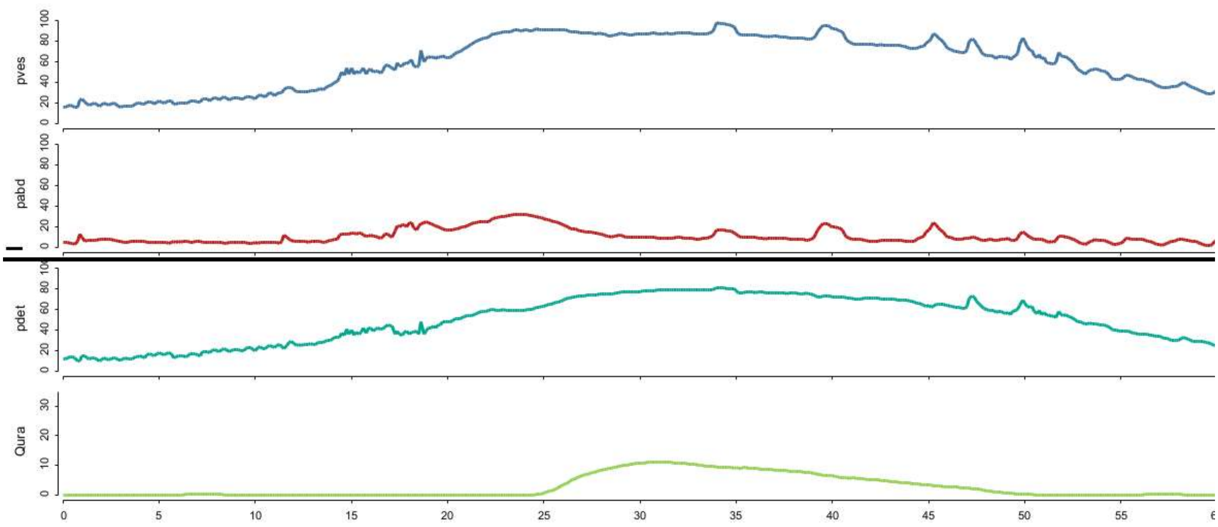

Figure 1: Overview of a PFS. The blue upper line represents the intravesical pressure, and the red line the abdominal pressure. The difference between those pressure is the detrusor pressure shown. The lower green line represents the flow rate.

1.3 History of bladder outflow obstruction measures

Table 1: Overview of proposed methods for describing and classifying urethral resistance. Adapted from Griffiths et al.[6]

Method	Year	Quantification	Number of P/Q points	Used PURR relation	Number of parameters	Number of classes
URA *Griffith* [7]	1989	Formula	1	Quadratic	1	Continuous
BOOI *Lim* [8]	1995	Formula	1	Linear	1	Continuous
A/G nomogram *Abrams* [9]	1979	Nomogram	1	Linear	1	3
ICS nomogram [10]	2002	Nomogram	1	Linear	1	3
linPURR nomogram *Schäfer* [11]	1995	Nomogram	1 (or 2)	Linear	1	Continuous + 7 classes
DAMPF *Schäfer* [11]	1995	Nomogram	2	Linear	1	Continuous
OBI *van Mastrigt* [12]	1995	Formula	Many	Polynomial $2/3 \leq n \leq 2$	1	Continuous
PURR *Schäfer* [13]	1983	Other	Many	Quadratic	1 (2)	Continuous
3PM *Spangberg* [14]	1991	Formula	Many	Polynomial $2/3 \leq n \leq 2$	3	Continuous + 4 classes
CHESS *Höfner* [15]	1995	Other	Many	Linear or Quadratic	2	16

Over the years, several mathematical models for the urinary outflow tract were proposed, which were used for the quantification of the UR. Initially, the urethra was modeled as a rigid tube, eventually including turbulent flow to improve the correlation between the model and the measurements.[16] Later, the rigid tube was replaced by a model including a distensible and collapsible tube, which is still in use.[17,18] In this model, the relation between the pressure and flow after maximal flow was stated to be quadratic. This part was called the passive urethral resistance relation (PURR).[13] Although later, based on theoretical explorations, the type of relationship between pressure and flow was found to be not always quadratic but could have any exponent between 2/3 and 2,[14] this is not implemented in most of the quantification methods currently in use.

Within the PURR, several moments can be marked which include information about the UR. The mostly used moments are the maximal flow rate (Q_{max}) with the corresponding pressure ($p_{detQmax}$, together $p_{detQmax}$-Q_{max}) and p_{muo}, the minimal urethral opening pressure. P_{muo} can be found at the end of the voiding and represents the minimal pressure needed to have some distension which makes flow possible. As influences of the bladder contractility for p_{muo} are minimal, p_{muo} is seen as the best representative parameter describing BOO.

The currently used classification methods for the UR can be divided into two main categories. The first category includes methods that estimate p_{muo}, and thereby BOO, only based on $p_{detQmax}$-Q_{max}. The Urethral Resistance Factor A (URA) is calculated with a formula, describing the expected PURR relation, based on the voidings of 292 male adults.[7] The original proposed quadratic PURR formula was slightly altered by including an additional relation between p_{muo} and the curvature of the UR. In addition, average values for the constants included in the PURR formula were calculated, and cut-off values for BOO were established. The A/G nomogram used a simple graphical nomogram for the classification of the UR.[9] This nomogram was further simplified into the ICS nomogram[10], with the bladder outflow obstruction index (BOOI)[8] being a formula describing the same relations included in the ICS nomogram, but with a continuous scale. The linPURR nomogram was originally based on a two-point classification system, including both $p_{detqmax}$-Q_{max} and p_{muo}, but the classification system for BOO was reduced to only $p_{detqmax}$-Q_{max}.[11] Cut-off values for BOO are slightly different when compared to the ICS nomogram, and additional classes are formulated. Differences in the classification of BOO between those methods were found minimal.[19]

The second category is more extended and multiple points of the pressure-flow graph are used for the classification of the UR. The Detrusor Adjusted Mean PURR Factor (DAMPF) uses the intersection of a linear line between $p_{detQmax}$-Q_{max} and p_{muo} with a line in the nomogram which represents the normalized linearized detrusor power, resulting in a theoretical minor influence of the actual detrusor pressure on the quantification of the UR.[11] The Obstructed Bladder Index (OBI) combines several parameters deducted from the PURR into one parameter using Fisher's linear discriminant.[12]

The other methods in the second category do not only classify the UR in terms of obstruction but include subtyping of this obstruction. The PURR (not to be confused with the PURR: the measurement after maximal flow) used the best (manual) fit of a quadratic relation on the low-pressure flank of the PURR.[13] Besides a quantification method of BOO, a distinction between compressive and constrictive BOO, based on the curvature of the PURR was also proposed, but cut-off values were not established. The three-parameter method (3PM) uses the best fit of a formula with three degrees of freedom to the whole PURR measurement.[14] One parameter represents the existence of BOO, the other two include some additional subtyping. Finally, the CHESS classification combines a four-class grading of p_{muo} with a four-class grading of the curvature of the PURR or the slope of the linPURR, resulting in sixteen UR classes.[15]

1.4 Aim

The overall aim of this thesis is to compare existing methods for the quantification of BOO and to investigate the possibility of further classification of the UR besides the amount of BOO, based on a large amount of UDS performed in the past years.

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Quantifying Bladder Outflow Obstruction in Men: A Comparison of Four Quantification Methods Exploiting Large Data Samples

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Neurourology and Urodynamics, *In review*

Abstract

Introduction

A pressure flow study (PFS), part of the ICS standard urodynamic test, is regarded gold standard for the classification and quantification of the urethral resistance (UR), expressed in the BOO. For men with BPH, the minimum urethral opening pressure (p_{muo}), found at the end of the passive urethral resistance relation (PURR) is considered the most objective parameter describing BOO. However, in clinical practice, direct measurements of p_{muo} are easily confounded by terminal dribbling. For that reason, alternative methods were developed to derive p_{muo}, and thereby assess BOO, using the maximum urine flow rate (Q_{max}) and the corresponding pressure ($p_{detQmax}$) instead. These methods were never directly compared against a large dataset. The current study compares four well-known methods quantifying p_{muo} and examines the relation between p_{muo} and $p_{detQmax}$-Q_{max}.

Methods

In total 1717 high-quality PFS of men referred with LUTS between 2003 and 2020 without earlier LUT surgery were included. From these recordings, p_{muo} was calculated according to three one-parameter methods: In addition, a three-parameter approach (3PM) was used, based on a fit through the lowest pressure flank of the pressure-flow plot. The estimated p_{muo}'s were compared with a precisely assessed p_{muo}. A difference of less than 10 cmH$_2$O between an estimate and the actual p_{muo} was considered accurate. A comparison between the four quantification methods and the actual p_{muo} was visualized using a Bland-Altman plot. The differences between the actual and the estimated slope were assessed and dependency on p_{muo} was analyzed.

Results

1717 studies were analyzed. In 55 (3.2%) PFS, 3PM analysis was impossible because all pressures after Q_{max} were higher than $p_{detQmax}$. The 3PM model was superior in predicting p_{muo}, with 75.9% of the quantifications within a range of +10 or -10 cmH$_2$O of the actual p_{muo}. Moreover, p_{muo} according to URA and linPURR appear equally reliable. BOOI was significantly less accurate when compared to all others. Bland-Altman analysis showed a tendency of BOOI to overestimate p_{muo} in men with higher grades of UR, while URA tended to underestimate p_{muo} in those cases. The slope between p_{muo} and $p_{detQmax}$-Q_{max} increased with larger p_{muo}, as opposed to the constant relation proposed within BOOI.

Conclusion

Of the four methods to estimate p_{muo} and quantify BOO, 3PM was found the most accurate and BOOI the least accurate. As 3PM is not generally available and performance in lower quality PFS is unknown, linPURR is (for now) the most accurate in clinical practice.

Introduction

Bladder outflow obstruction (BOO) in males is a common lower urinary tract (LUT) dysfunction that may lead to LUT symptoms (LUTS). Although BOO in male patients can have several causes, including urethral strictures and bladder neck obstruction, most commonly it is caused by prostate enlargement.[1] Larger prostate size is significantly associated with an increase in the likelihood of BOO in men with LUTS.[2,3] Urethral resistance (UR) during voiding is defined by the ratio of detrusor pressure during voiding (p_{det}) and urine flow rate (Q). BOO is diagnosed when the UR is elevated to a limit that is considered clinically relevant.[4] UR can be graded using a pressure-flow study (PFS), which is part of the International Continence Society (ICS) standard urodynamic test to evaluate the voiding function.[4]

To interpret the PFS, several physical models for the urethra, i.e. the outflow tract, were proposed, which were used for the quantification of BOO. The currently accepted model is based on distensible and collapsible tube hydrodynamics. [5,6] Based on this model, it was proposed that for quantification of BOO, the ideal and most representative relation between p_{det} and Q occurs following the point of maximum flow (Q_{max}) during PFS, which was called the Passive Urethral Resistance Relation (PURR).[7] Deviations from this ideal PURR were called the Dynamic Urethral Resistance Relation (DURR).[7] In addition, the PFS was presented with a PFS-plot, initially with the uroflow rate on the X-axis and pressure on the Y-axis, which were later flipped.[8,9]

There was agreement that the shape of the PURR as visualized within the pressure-flow plot, showed a polynomial relation between Q and p_{det}, with an offset of p_{det} on the pressure axis. This offset was called the minimum urethral opening pressure (p_{muo}), representing 'the minimum pressure during measurable flow'. Conceptually, within the distensible and collapsible tube hydrodynamics, p_{muo} is the least dependent on detrusor voiding contraction strength, and would therefore be an independent quantifier of BOO in men with LUTS caused by BPH. However, in clinical practice, p_{muo} is often not unambiguously (automatically) detectable because of dribbling and varying pressure – flow delay. For that reason, several methods were developed to estimate p_{muo}, and thereby BOO, mostly based on Q_{max} and the corresponding pressure ($p_{detQmax}$) (combined: $p_{detQmax}$-Q_{max}). These methods are based on the assumption that the relation between p_{muo} and $p_{detQmax}$-Q_{max}, which could be expressed in the slope of the linearized PURR, can be defined by a constant or are only dependent on $p_{detQmax}$-Q_{max}.

Although formulated decades ago, a direct assessment of UR quantification methods on their accuracy in quantifying p_{muo}, and thereby BOO, is not performed. One study used manual fitting of the PURR graph against the so-called lower pressure border of the PFS plot and compared this with

URA[10], but comparisons with other methods were never published. The current study compares four PURR evaluations (See fig. 1 and below.) on their capability of quantifying p_{muo}, and examines the relations between p_{muo} and the slope of the linearized PURR, proposed in these methods.

Methods

All 5657 urodynamic studies including PFS of men, performed between 2003 and 2020 were initially included. Data selection and analysis steps were performed in Matlab R2022b (The Mathworks Inc., Natick, USA), and statistical analysis was performed in SPSS, version 27 (IBM, Armonk, USA). The urodynamic studies were performed in accordance with the ICS Good Urodynamic Practices.[4,11] Intravesical and abdominal pressures were recorded with a 7F water-filled catheter, using the Ellipse urodynamics machine with AUDACT software (Andromeda Medizinische Systeme GmbH, Taufkirchen, Germany). The urine flow rate (UFR) was measured using a weight-transducer measurement device. Voiding was typically allowed after strong desire of the patient and was performed in their preferred position, usually standing, when possible. The urine flow meter was adjusted to the length of the patient, thereby minimizing the lag induced by the distance between the flowmeter and the meatus. The pressures were digitally recorded with a sampling frequency of 20 Hz, while the UFR was sampled at 8 Hz.

Data selection

PFS of urodynamic studies with missing data (3.1%) and studies of patients with relevant interventions in the past (57.1%) were excluded. In addition, PFS with Q_{max} >35 ml/s or <2 ml/s (1.8%), a voided volume <100 ml (4.0%), and maximum detrusor pressure during voiding <20 cmH_2O or >200 cmH_2O (0.3%) were excluded from further analysis, as those values are considered not physiological in men with LUTS.[11] Studies were automatically analyzed on catheter dislocation during voiding(5.4%), using an algorithm further explained in Appendix A. The otherwise randomly selected studies were visually checked on remaining large artifacts, resulting in a set of 1717 high-quality PFS, without clinical or technical artifacts, applicable for further analysis. After correction for the lag time between the UFR and the pressure signal with 0.75 seconds, all signals were filtered with a 2-second moving average filter.[11]

A complementary analysis criterion was established, only including curves following an (almost) pure PURR relation, called the PFS-PURR. PFS-PURR includes all studies for which the p_{det} or UFR at any point after Q_{max} is lower than all pressures or UFRs before. A variation of the UFR of a maximum of 1 ml/s was accepted, while for p_{det}, a variation of a maximum of 5 cmH_2O was accepted. This resulted in a subselection of PFS with a near-perfect PURR, closely following the theoretical PURR, with minimum 'accessory bladder outflow tract dynamics' or DURR. The representativity of this subset was analyzed, by comparing the age, voided volume, Q_{max}, $p_{detQmax}$, and UR between all PFS and PFS-PURR.

Table 1: Overview of the four methods to estimate p_{muo} based on $p_{detQmax}$-Q_{max}, including the formula used for calculation and the motivation of that formula.

Method	Abbreviation	Formula	Motivation
Three-parameter method[12,13]	3PM	$p = p_{muo} + A * Q^k$, $2/3 \le k \le 2$	Theoretical study
Linearized passive urethral resistance relation[14]	linPURR	$p_{detQmax} = p_{muo} + A * Q_{max}$, $0 \le A \le 5$	Observational study
Urethral resistance A[15]	URA	$p_{detQmax} = p_{muo} + (p_{muo}^2 * d) * Q_{max}^2$, $d = 3.8*10^{-4}$	Observational study
Bladder outflow obstruction index[16,17,18]	BOOI	$p_{detQmax} = p_{muo} + 2 * Q_{max}$	Provisional ICS recommendation

Data analysis

The minimal detrusor opening pressure p_{muo} was quantified using four methods, see Table 1 and Figure 1. p_{muo} estimated by the linPURR (PmuolinPURR)[13], p_{muo} estimated by URA (PmuoURA)[14], and p_{muo} estimated with BOOI (PmuoBOOI)[16] were used.

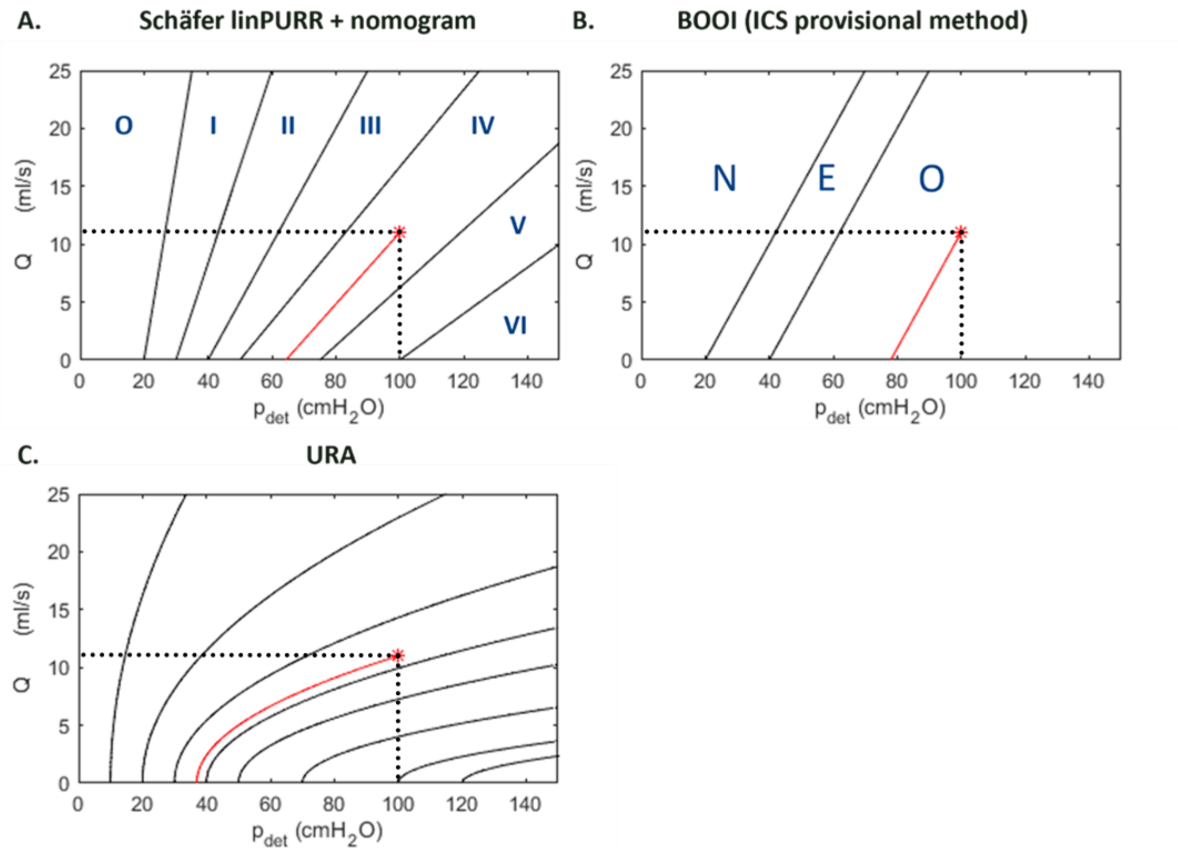

Figure 1: Overview of the three one-parameter methods compared in this study. The value of $p_{detQmax}$-Q_{max} (identical in each of the graphs) is given with the asterisk. The red line represents the relation between $p_{detQmax}$-Q_{max} as proposed in the particular method, while the estimated p_{muo} can be found at the red line for Q = 0. A substantial difference in estimated p_{muo} is seen between those three methods, as those estimated p_{muo}'s differ substantially (A: 64; B: 79; C: 38). As 3PM includes multiple parameters, it is not possible to visualize this method using a simple nomogram.

The p_{muo} according to the 3PM (Pmuo3PM) method was calculated using the following steps. First, the low-pressure flank of the p_{det}-Q relation (the URR) was determined.[19] This implements the rule that only the flow points with the lowest pressure were included, see Figure 2. Next, the PURR was fitted using the Matlab *fit* function, implementing the formula given in Table 1, with the least squares method and high weight for Q_{max} (1000000 vs 1 for all other points), so the PURR was forced to pass through this point. Pmuo3PM was found at Q=0. If all pressure points after $p_{detQmax}$ were higher than $P_{detQmax}$, the fit could not be performed and the corresponding PFS were excluded from the analysis.

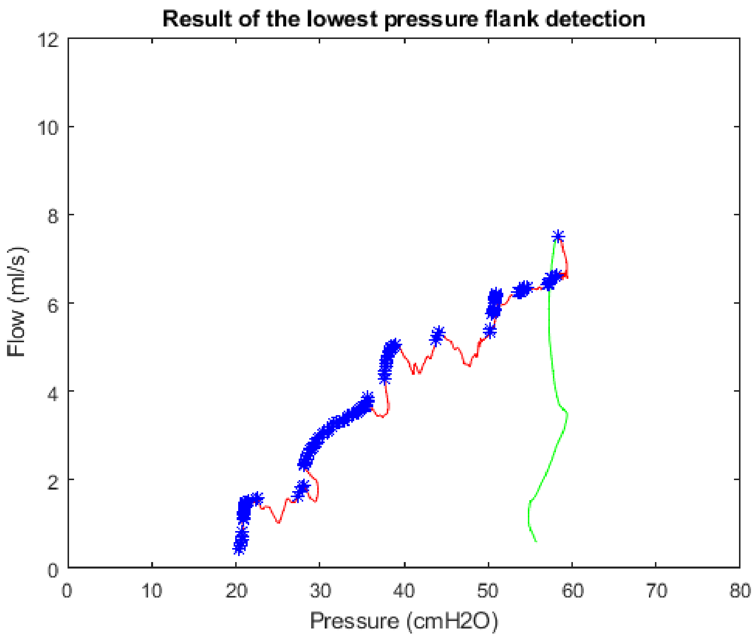

Figure 2: Low-pressure flank detection algorithm as described by *Kranse*. The green line indicates the pressure-flow relation before Q_{max}, while the red line represents the URR. Only the blue dots serve as input for the 3PM quantification method. A point is included if no lower pressures can be found for a larger flow.

As the observed p_{muo} could be erroneous because of the terminal dribbling, the average p_{det} between 1 and 0.5 ml/s at the end of the voiding was used in this study to represent the actual p_{muo} (PmuoAct), resulting in the mean pressure at a flow of 0.75 ml/s. PmuolinPURR, PmuoURA, PmuoBOOI, and Pmuo3PM were corrected to the estimated pressure at a flow of 0.75 ml/s, to enable a comparison with PmuoAct.

To study the accuracy of a quantification method, the proportion of estimated p_{muo}'s which were within a range up to 20 cmH_2O of PmuoAct were calculated. Moreover, the percentages of estimated p_{muo} within 10 cmH_2O of PmuoAct were evaluated using the N-1 Chi-squared test for all four methods, as a difference of less than 10 cmH_2O was considered to be not clinically significant.[20] In addition, Bland-Altman plots were created, including a linear regression for the differences between the real p_{muo} and the estimated p_{muo}'s by the four methods, so systemic deviations could be noticed.

Finally, as the one-parameter methods define different relations between $p_{detQmax}$-Q_{max} and p_{muo} and expect them to be constant or only dependent on $p_{detQmax}$-Q_{max}, the slope of the straight connection line between $p_{detQmax}$-Q_{max} and p_{muo} (slope) was further analyzed on the dependency of p_{muo}. Therefore, we divided PmuoAct into 6 bins of approximately similar widths. The mean slope, according to PmuoAct and the four quantification methods, was given for each bin, including the 95% confidence interval. Differences between the real slope and the slope based on the estimated p_{muo}'s were investigated.

Results

A total of 1717 PFSs were included in this study. In 55 studies, all pressure points after $p_{detQmax}$ were higher than $p_{detQmax}$, preventing the calculation of Pmuo3PM. Consequently, 1662 PFS are included. The mean age of the patients was 59 years (17-93), with 89% of the patients >40 years. The Q_{max}, $p_{detQmax}$, voided volume, URA, BOOI, and Schäfer grade for all PFS and PURR-PFS are displayed in Table 2. No significant differences in mean UR, according to URA, BOOI, or Schäfer grade were observed between all PFS and PURR-PFS. Age was significantly different, but voided volume was smaller in the PURR-PFS -subgroup.

Table 2: Basic patient and urodynamic descriptives. As there is only minimal difference between all the studies and the PURR-PFS subselection, results are expected to be generally applicable.

	All (n=1662) **Mean (min-max)**	**PURR-PFS (n=376)** **Mean (min-max)**	**Mann-Whitney U test for differences** **p-value**
Age (years)	58.8 (17-93)	60.8 (18-88)	0.012
Q_{max} (ml/s)	10.1 (2.1-31.7)	9.6 (2.3-30.1)	0.112
$p_{detQmax}$ (cmH2O)	59 (11-164)	61 (12-151)	0.192
Voided volume (ml)	310 (100-1290)	260 (100-670)	<0.001
URA	31.1 (6.3-108.0	33.0 (8.9-108.0)	0.158
BOOI	39.0 (-39.7-155.9)	42.2 (-23.4-143.4)	0.108
Schäfer grade	2.4 (0-6)	2.5 (0-6)	0.141

Pmuo3PM was found to be the most accurate, as the proportion of estimated p_{muo} according to Pmuo3PM is the highest for all investigated deviations, see Figure 3. URA and linPURR performed similarly, while BOOI showed a lower fraction of estimated p_{muo} within an analyzed range.

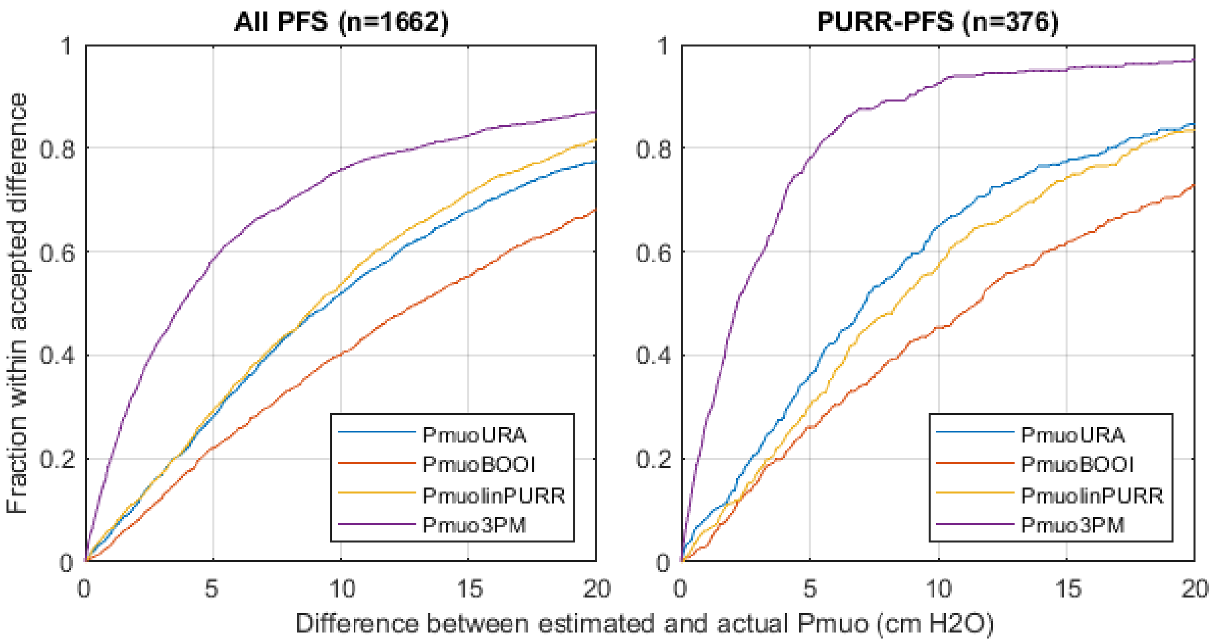

Figure 3: Proportion of estimated p_{muo} within an accepted difference with the actual p_{muo} as a fraction of the total number of PFS, plotted against the accepted difference between the estimated and actual p_{muo}. Abbreviations: see Table 1.

The proportions of estimated p_{muo} which differ no more than 10 cmH_2O from PmuoAct can be found in Table 3. All proportions for the investigated methods at this range were significantly different from each other (N-1 Chi-squared test $p<0.025$), except for URA and linPURR for all PFS ($p=0.291$). All the quantification methods performed significantly better for the PURR-PFS ($p<0.05$), except for the Schäfer method ($p=0.204$).

Table 3: Values for the proportion of the estimated p_{muo} within a range of 10 cmH_2O of PmuoAct as a fraction of the total number of studies. Abbreviations: see Table 1.

Quantification method	All PFS	PURR-PFS
3PM	0.75	0.93
linPURR	0.53	0.57
URA	0.52	0.65
BOOI	0.40	0.45

The linear regression within the Bland-Altman plots showed a significant correlation for the BOOI and URA method between the average of the estimated and actual p_{muo} and the average of those values, see the regression lines in Figure 4. This correlation was not significant for PmuoURA within the PURR-PFS, see Figure 5. All other regressions were found non-significant. Overall, Pmuo3PM showed the most narrow confidence interval range, especially within the PURR-PFS. Some outliers are seen for all methods, with some obvious outliers for Pmuo3PM, predominantly caused by a substantial increase of pressure during voiding, visible as a large positive difference in the plot.

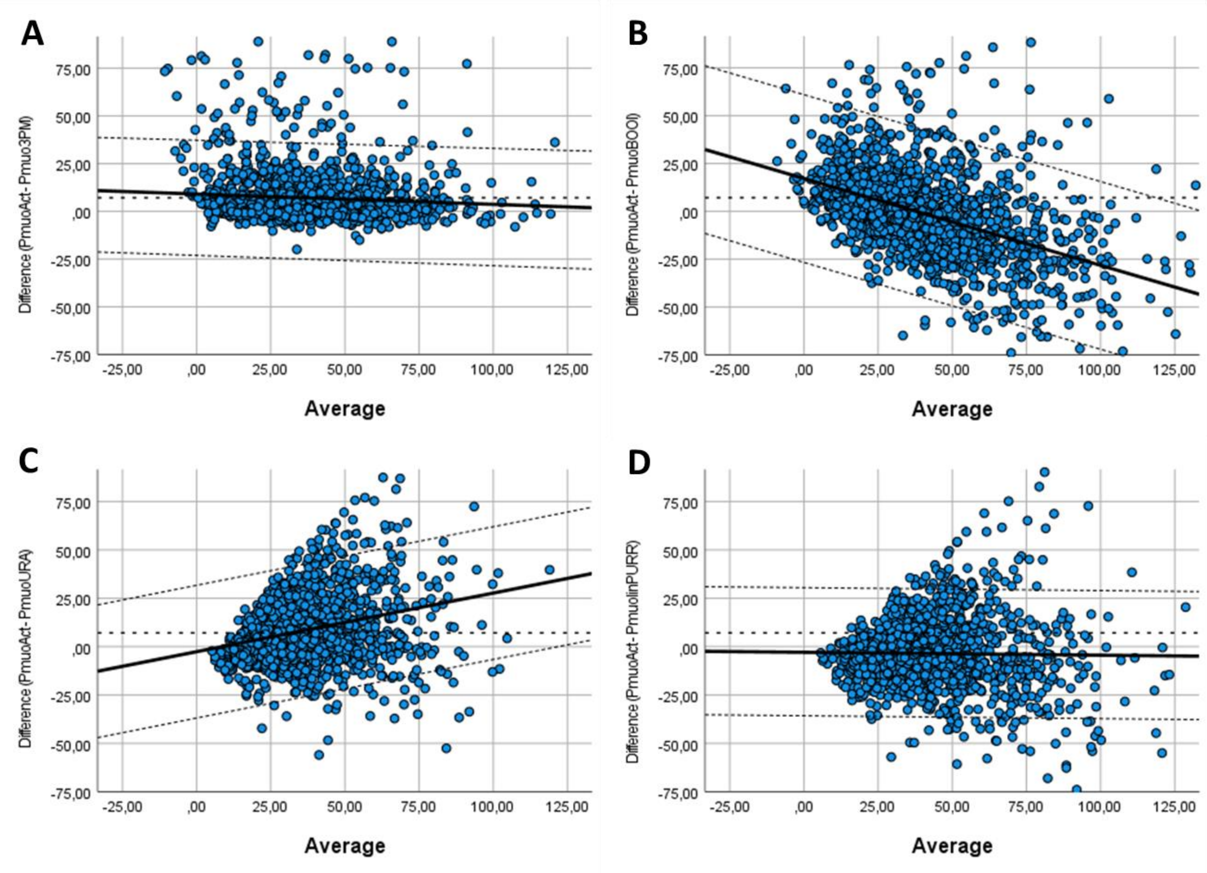

Figure 4: Bland-Altman plots for the difference between PmuoAct and Pmuo3PM (A), PmuoBOOI (B), PmuoURA (C), PmuolinPURR (D) for all measurements. The average of PmuoAct and p_{muo} according to the particular method is shown on the x-axis. Linear regression is shown (thick line) including the 95% confidence limits (dashed line). Abbreviations: see Table 1.

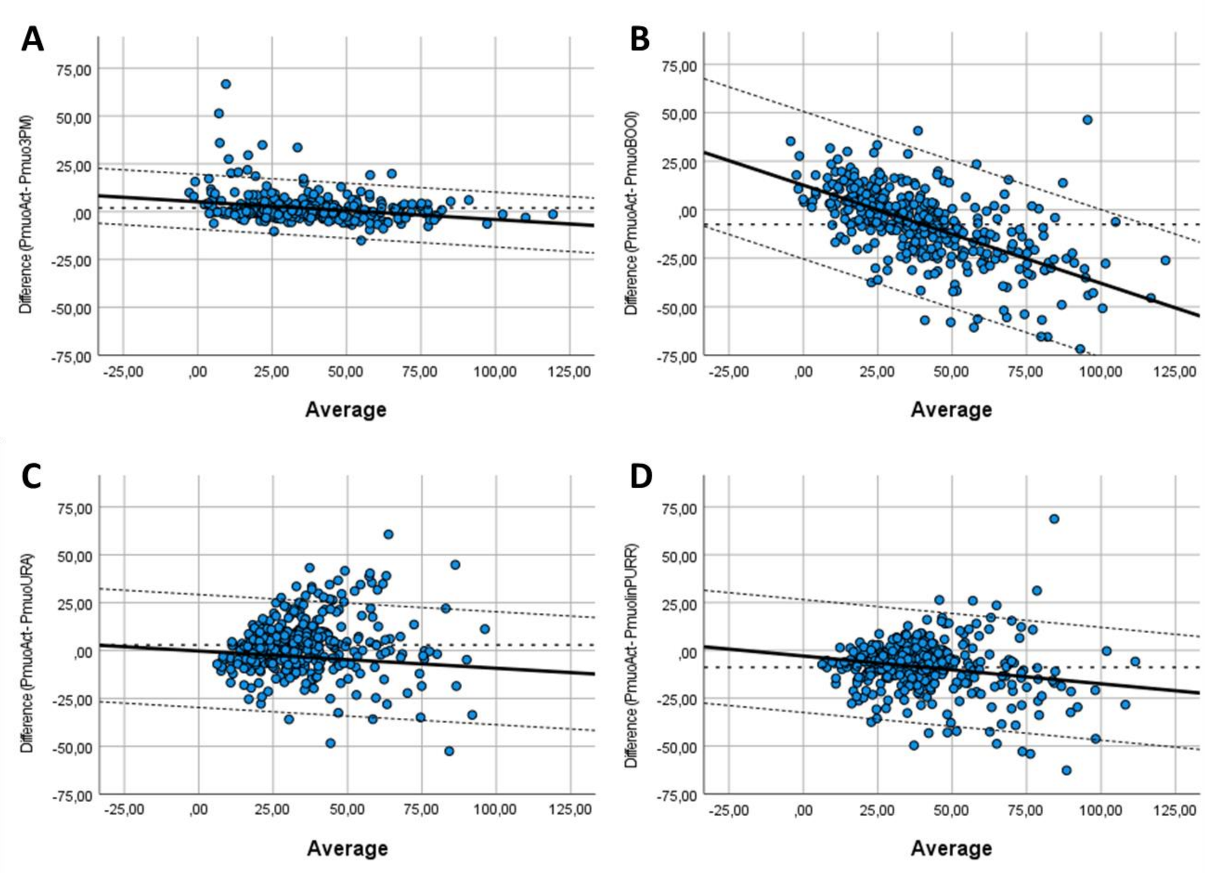

Figure 5: Bland-Altman plots for the difference between PmuoAct and Pmuo3PM (A), PmuoBOOI (B), PmuoURA (C), PmuolinPURR (D) for the PURR-PFS. The average of PmuoAct and p_{muo} according to the particular method is shown on the x-axis. Linear regression is shown (thick line) including the 95% confidence limits (dashed line). Abbreviations: see Table 1.

PmuoAct was divided into 6 bins with similar pressure widths and a similar number of observations to allow an analysis of the associations between the slope and PmuoAct, see Table 4. Figure 6 illustrates that for every method, except BOOI, a positive relationship exists between the slope and p_{muo}, which was stronger within the PURR-PFS. The inherently fixed slope within BOOI was found significantly incorrect, as the actual slope was found larger in the higher p_{muo} pressure -bins and statistically significantly different with PmuoBOOI (Wilcoxon $p<0.05$) for bin 21-29 and higher. The URA and 3PM methods did not result in a significantly different slope for bin 29-36 (Wilcoxon $p>0.05$) and higher, which holds for the PURR-PFS (Wilcoxon $p>0.05$). There is a significant difference between the mean actual slope for all PFS when compared to the PURR-PFS for bins 45-59 and >59. In addition, large standard deviations of the actual slope were found, increasing with p_{muo}, indicating a wide variation in the slope between $p_{detQmax}$-Q_{max} and p_{muo}. More characteristics of the distribution of the slope can be found in Tables B1 and B2.

Table 4: Overview of the distribution of the PFS over the PmuoAct bins, shown as cmH_2O ranges. Abbreviations: see Table 1.

	PmuoAct Bins					
cmH_2O	<21	21-29	29-36	36-45	45-59	>59
All PFS (n=1662)	247	296	281	303	270	265
PURR-PFS (n=376)	71	77	67	66	50	45

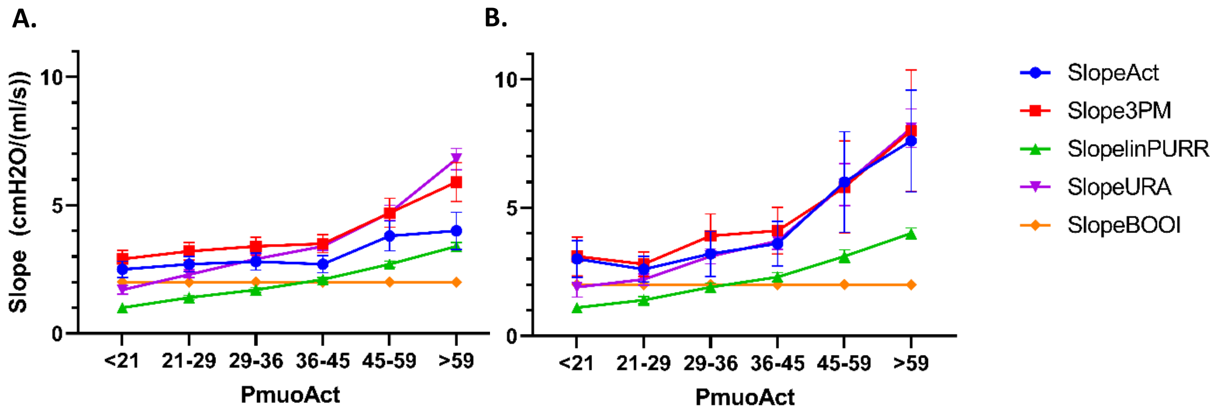

Figure 6: Slope with estimated error bars for the actual mean slope, and the mean slope as estimated by the four methods, grouped by PmuoAct bins, for all PFS (A) and the PURR-PFS (B). Abbreviations: see Table 1.

Discussion

We found that the use of a multiparameter method resulted in a significantly more accurate quantification of p_{muo} when compared to three one-parameter methods in quantifying urethral resistance in men.

In addition, a correlation was found between the mean slope of the PURR and PmuoAct, especially within the PURR-PFS sub-cohort. However, the large standard deviation suggests that this slope is not constant, indicating that one-parameter quantification methods are less accurate in predicting p_{muo}. The one-parameter methods imply a fixed slope for a particular $p_{detQmax}$-Q_{max} (linPURR and URA) or a constant slope (BOOI). Although the slopes of linPURR as well as URA are adapting to the $p_{detQmax}$ pressure, this seems insufficient because of the large variation of slope versus PmuoAct. BOOI was stated to be an easy-to-use tool and resulted in a meaningful possibility to diagnose the presence or absence of BOO.[16] We found that BOOI is significantly imprecise with an over-quantification for higher p_{muo} in the quantification of BOO. We also found that URA showed a significant under-quantification of p_{muo} for higher values of p_{muo}. While comparing these we found linPURR to be superior within the one-parameter quantification methods.

The use of more degrees of freedom, e.g. parameters, within a quantification method will likely result in a more accurate method, albeit at increased algorithmic complexity. In the past, any extension beyond a linear fit was found to be not reproducible and not of added value for describing the PURR.[14] However, we showed that a linear fit is rather inaccurate when only based on $p_{detQmax}$-Q_{max}, as all (linear) one-parameter methods were found significantly less accurate in predicting p_{muo} when compared to the three-parameter method. Within the linPURR, a two-point linear fit of the PURR was originally proposed, which was based on both the real p_{muo} and $p_{detQmax}$-Q_{max}. Later, p_{muo} was found not consistently determinable, and deviations of the real p_{muo} from the estimated p_{muo} by the nomogram were thought of to be not representative for men with BPH/LUTS.[14] In this study, however, the proportion of deviations of PmuolinPURR of more than 10 cmH_2O from PmuoAct was found almost 50% in men with LUTS. Therefore, the neglecting of this deviation by one-parameter methods could result in different quantification of UR in a significant part of men, as the real p_{muo} could significantly be higher or lower than estimated.

We found a positive correlation between p_{muo} and the slope of the PFS curve between p_{muo} and $p_{detQmax}$-Q_{max} for all PFS, even stronger in the PURR-PFS. This agrees with the linPURR nomogram and URA but is not included in the currently used ICS standard[16]. Using ICS standard BOOI only will result in an over-quantification of the UR in men with higher grades of BOO. Additional classification of men with BOO, e.g., severely obstructed, should take this into account. Additionally, the large standard deviations for the higher p_{muo} bins suggest a variable association between $p_{detQmax}$-Q_{max} and p_{muo}, indicating that a one-parameter method is probably not sufficient for the precise quantification of UR. This was earlier observed, as a distinction between constrictive and compressive PURR was made[7] and the value of the slope was included in the CHESS classification.[21] This study suggests that two-parameter linPURR analysis (including both p_{det} and the slope) as included in the CHESS classification could extend the currently used classification of UR. However, this is not included in the currently used ICS standard.

This study has a few limitations. First, the actual p_{muo} is taken as a gold standard for evaluating the other methods. It is known that this actual p_{muo} value is often not unambiguously automatically detectable. Therefore, we only included PFS of high quality, by using strict quality selection criteria, including the complementary analysis of the PURR-PFS, and used a derivative for p_{muo} within the analysis, which removed the influence of terminal dribbling. In addition, although the three-parameter PURR was found superior, it is not known whether this method, (but also the other methods), also performs well on lower-quality measurements. Theoretical performance in those lower-quality studies is not easily studied, as the actual p_{muo} is expected to be inaccurate.

In clinical practice, only the classification of BOO as obstructed, unobstructed or equivocal is currently used in the treatment decision. It is known that there is a correlation between the effect of (surgical) treatment and the quantification of BOO[14]. Hence, the quantification of BOO could be used for the quantification of the treatment effect. However, as a wider variety of treatment options became available, new studies on this correlation or of disease stage: subtyping of the UR-shape; more or fewer dynamics; more or less slope; constrictive or compressive, may bring additional value. As the 3PM method is expected to represent the most precise prediction of p_{muo}, and thereby the UR for men with LUTS, subtyping and more precise grading of UR in men with BPH is more accurate with 3PM than with BOOI only. Therefore, the 3PM method can be used to evaluate proof of principle of the treatment options and to individualize management.

Conclusion

In conclusion, in order to quantify bladder outlet obstruction in men, we found that the three-parameter PURR model performed significantly better in quantifying the actual p_{muo} than the one-parameter methods in all PFS in our database with high technical quality. This holds for the sub-selection containing studies with low variance during the voiding phase. The linPURR method performs better than BOOI and URA, and has little systemic deviations over the whole range of BOO. Two or more parameter (lin)PURR analysis will be relevant to improve diagnostic accuracy.

Appendix A: Automatic detection of catheter artifacts

Catheter artifacts may occur in urodynamic measurements and should be corrected before analysis. Catheter artifacts are non-physiological measurements and could be caused by a dislocation of the catheter or external factors. Although most artifacts are easily identified by an experienced urodynamicus or urologist, an algorithm for the automatic detection of those artifacts does not exist. This algorithm is considered an advantage when analyzing a large dataset, as manually analyzing large amounts of data is time-intensive.

The automatic detection of catheter artifacts is based on a few premises. First, if p_{ves} and p_{abd} include an artifact at the same time, it is expected that the amplitude of this artifact is significantly different. In addition, it is supposed that the high-frequency variations, caused by movement or talking, within both the abdominal and intravesical pressure measurements will have similar amplitude.

Within the algorithm used for the automatic detection of catheter artifacts, the following steps are performed, see Figure A1. First, both the abdominal and intravesical pressure signals were filtered with a 1-second moving average filter, which is expected to include all physiological changes caused by variations of the abdominal and intravesical pressure. The difference between the filtered pressure signal and the original signal was calculated, resulting in a signal containing only high-frequency noise. To detect a dislocation of the intravesical catheter during micturition, it was proposed that there should be a minimum high-frequency variation amplitude when the catheter is measuring correctly. Therefore, the intravesical pressure was divided into sections of 5 seconds. If for one of those sections, the standard deviation of the high-frequency variation of the intravesical pressure is less than 0.12 cmH_2O, indicating a more or less flat line, the measurement was excluded from further analysis.

In addition, the measuring quality of either catheter was checked by calculating the difference in the high-frequency noise of both signals. It is expected that both catheters will approximately detect the same noise amplitude. If the difference in the standard deviation of the resulting signals is more than 1 cmH2O, the likelihood of an artifact is considered high, so the signal is excluded. The proposed cut-off values are based on empirical observations and the performance of the algorithm was checked by an experienced urodynamicist, and was found adequate.

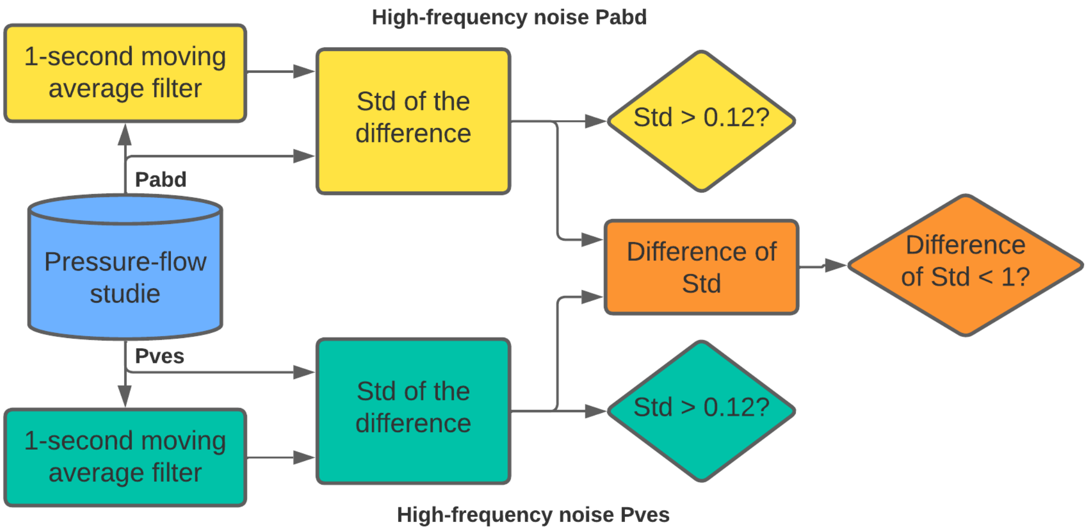

Figure A1: Overview of the steps performed within the automatic detection algorithm for catheter artifacts. If a study passed all checks, it was considered a 'high-quality' PFS, with a low likelihood of catheter artifacts during micturition, and was included in this study.

Appendix B: Additional tables

Table B1: Additional descriptives for the slope, grouped by a range of the actual p_{muo} for all PFS. Note that for larger p_{muo} the standard deviation increases for all methods with variable slope.

Pmuo	N	SlopeAct		Slope3PM		SlopelinPURR		SlopeURA		SlopeBOOI	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
<21	247	2.5	2.5	2.9	2.7	1.0	0.6	1.7	1.3	2	0
21-29	296	2.7	2.6	3.2	3.0	1.4	0.7	2.3	1.1	2	0
29-36	281	2.8	2.8	3.4	3.0	1.7	0.8	2.9	1.3	2	0
36-45	303	2.7	2.9	3.5	3.1	2.1	0.8	3.4	1.4	2	0
45-59	270	3.8	4.8	4.7	4.7	2.7	1.0	4.7	2.4	2	0
>59	265	4.0	6.0	5.9	6.3	3.4	1.2	6.8	3.4	2	0

Table B2: Additional descriptives for the slope, grouped by a range of the actual p_{muo} for the PURR-PFS. Note that for larger p_{muo} the standard deviation increases for all methods with variable slope, except for the linPURR method.

Pmuo	N	SlopeAct		Slope3PM		SlopelinPURR		SlopeURA		SlopeBOOI	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
<21		3.0	3.0	3.1	3.2	1.1	0.8	1.9	1.6	2	0
21-29		2.6	2.2	2.8	2.1	1.4	0.6	2.2	1.0	2	0
29-36		3.2	3.6	3.9	3.5	1.9	0.7	3.1	1.2	2	0
36-45		3.6	3.5	4.1	3.7	2.3	0.7	3.7	1.3	2	0
45-59		6.0	6.9	5.8	6.3	3.1	0.9	5.9	2.9	2	0
>59		7.6	6.6	8.0	7.9	4.0	0.7	8.1	3.5	2	0

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Clinical and urodynamic differences between compressive and constrictive bladder outflow obstruction

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Laetitia M.O. de Kort

In edit

Introduction

Bladder outflow obstruction (BOO) is a common diagnosis in the older male population with lower urinary tract symptoms (LUTS).[1] The presence and severity of the urethral resistance (UR) can be graded using a pressure-flow study (PFS), part of the ICS standard urodynamic test (UDS). BOO represents a UR above a limit that has proven to be of clinical relevance.[2]

For grading and qualification of this UR, several models of the urethral outflow tract were proposed[3], which all include a defined relation between the flow rate (Q) and the detrusor pressure (p_{det}) during voiding. Those models are based on the distensible and collapsible tube - flow-controlling zone hydrodynamic paradigm.[4,5] Most models include a quadratic relation between Q and p_{det} during the voiding following Q_{max}, which is seen as the most representative to grade UR and to diagnose BOO in men with an enlarged prostate.[6] This defined (but also conceptual or idealized) relation between p_{det} and Q was stated to be the passive urethral resistance relation (PURR) and can be observed in the pressure-flow graph as the lower pressure border.[3] From this graph several urodynamic relevant parameters can be observed, including Q_{max} and the corresponding p_{det} ($p_{detQmax}$, together $p_{detQmax}$-Q_{max}), and and the minimal urethral opening pressure (p_{muo}), found at the end of the voiding.

The PURR was later simplified into a linear variant, linPURR, as additional information beyond $p_{detQmax}$-Q_{max} and p_{muo}, was considered of minor importance for the determination of relevant bladder outflow conditions.[7] Based on the 2 remaining parameters, $p_{detQmax}$-Q_{max}, and p_{muo}, UR is quantified using the linPURR nomogram.[7] The ICS Bladder outflow obstruction index (BOOI) is a further simplification and uses only $p_{detQmax}$-Q_{max}, with a fixed linear extrapolation.[8]

It is possible to add an additional distinction of the outflow tract during voiding, above 'one-dimensional' grading of BOO. This distinction is based on the slope of the PURR, between p_{muo} and $p_{detQmax}$-Q_{max} towards the pressure axis. See Figure 1: A relatively low slope would be categorized as the constrictive subtype of BOO and the steeper slope would represent a compressive obstruction.[6] Compressive obstruction is stated to be the 'standard' subtype of obstruction, caused by an enlarged prostate; distension and collapse of the flow-controlling zone behave 'as predicted' by the paradigm mentioned here above.[3] Within the constrictive obstruction subtype, this distension is relatively more limited than predicted, with a lesser effect of pressure on flowrate, and therefore a steeper slope and relatively low p_{muo}.

Classification of UR in terms of the grade of obstruction (linPURR grade or BOOI) and here above-mentioned subtypes were included in the CHESS classification.[9] The CHESS classification uses a 16-field crosstab graph that combines 4 slope cutoffs and four p_{muo} cutoffs and therefore delineates 16 classes of UR. This combination of grading and subtyping of BOO was considered to be of value in predicting the result of an intervention in a small study.[10] In other studies, an association of detrusor wall thickness with grade and subtype of obstruction was found[11], and a change in the distribution of the patients in the CHESS classification after water vapor ablation of the prostate was also shown.[12] However, evaluation of the subtype of obstruction is not common urodynamic practice, and although mentioned in the recent guidelines on pressure-flow studies (PFS), it is stated that there is a lack of evidence about the relevance and specificity of this additional qualifier of UR or BOO.[13]

To uncover the potential relevance of distinguishing constrictive from compressive BOO, differences in patient and urodynamic characteristics, based on a large amount of high-quality urodynamic data could be helpful. Therefore, the aim of this study is to explore several clinical and urodynamic parameters of male patients without BOO versus those with constrictive BOO versus compressive BOO, based on the original definition of constrictive/compressive and on the CHESS classification system.

Methods

1370 urodynamic pressure–flow studies (PFS) were included in this study. Those were selected from 5657 PFS of men, performed between 2003 and 2020. Patients with relevant interventions in the past (e.g. TURP or other prostatic interventions) were not included. Studies with minimal or no artifacts, based on an computer algorithm, and with physiological urodynamic values ($2<Q_{max}<35$, Voided volume > 100ml) were included. Of the resulting 1656 studies, 286 (17.3%) of the PFS were removed, as they displayed a substantial p_{det} increase of >15 cmH2O after Q_{max}, indicating an additional contraction, which results in unrealistic values of p_{muo}. Data was acquired from routine clinical care urodynamic studies, which were performed in accordance with the ICS Good Urodynamic practices.[14,15] More about data acquisition and selection can be found in an earlier publication.[16]

PFS were classified into three categories: no BOO, compressive BOO, and constrictive BOO, based on two methods. The first method includes the original definition of constrictive vs compressive: There is no quantitative distinction known between compressive and constrictive BOO, apart from the four slope classes defined by the CHESS classification, which are not named as compressive or constrictive.[9] In the original linPURR paper, it is stated that for typical men with enlarged prostates – thereby an expected compressive URR – it is rare that the linPURR will cross a whole grade in the linPURR nomogram. The mean p_{det} difference between the grades in the linPURR nomogram for grade III and higher is approximately 20 cmH_2O. We, therefore, define compressive BOO to have an actual p_{muo} ($p_{muo.act}$) which is not more than 20 cmH_2O lower than expected in the linPURR nomogram ($p_{muo.exp}$), which is based on $p_{detQmax}$-Q_{max}. Constrictive BOO is defined to have a larger difference than

20 cmH_2O between $p_{muo.act}$ and $p_{muo.exp}$. PFS with a linPURR grade <III (identical to BOOI ≤40) were defined as no BOO. The classification rules are summarized in Figure 1 and Table 1.

Table 1: Overview of the 3 UR classes: no BOO, compressive BOO, and constrictive BOO with the corresponding classification rules according to classification method 1

	$p_{muo.exp}$ - $p_{muo.act}$ > 20 cmH_2O	$p_{muo.exp}$ - $p_{muo.act}$ ≤ 20 cmH_2O
BOOI < 40 or linPURR grade < III	No BOO	No BOO
BOOI ≥ 40 or linPURR grade ≥ III	Constrictive BOO	Compressive BOO

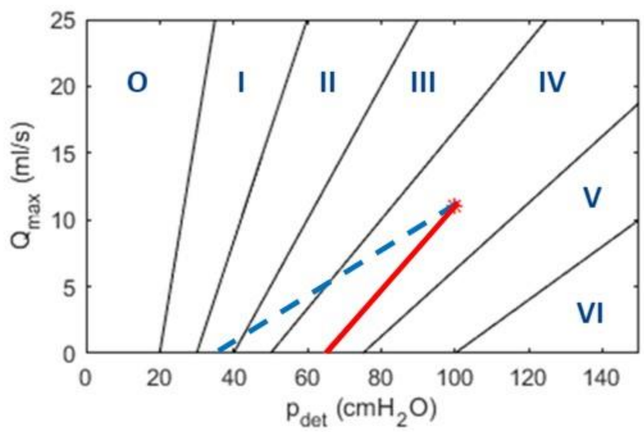

Figure 1: Discrimination between constrictive and compressive BOO. The red asterisk indicates $p_{detQmax}$-Q_{max}, with the blue line indicating the actual linPURR relation, with $p_{muo.act}$ = 35 cmH_2O. The red line indicates the expected relation for compressive BOO, with $p_{muo.exp}$ = 65 cmH_2O and linPURR > III. As $p_{muo.act}$ is more than 20 cmH_2O lower than $p_{muo.exp}$, and linPURR > III, the BOO is classified as constrictive.

The second method is based on the CHESS classification system. Although the interpretation of the corners in the CHESS is given[9], A1: normal (no BOO), A4 and D4: stricture, unelastic BPH (constrictive), and D1: perfect BPH (compressive).[9] For all other classes, no definition is given. The division into four quadrants made in a subsequent article[10] is arbitrary, and results in four classes instead of three. In Figure X, our definition of no BOO, constrictive BOO, and compressive BOO within the CHESS system is given, which is based on established cut-off values for BOOI and has a similar distribution of constrictive and compressive as displayed in the first method.

To reduce post-void dribbling artifacts in the analysis, the average p_{det} with the flow rate between 1 and 0.5 ml/s at the end of voiding was taken as a substitute for $p_{muo.act}$, for both methods. The two classification methods were visually compared and the Spearman's correlation coefficient was calculated.

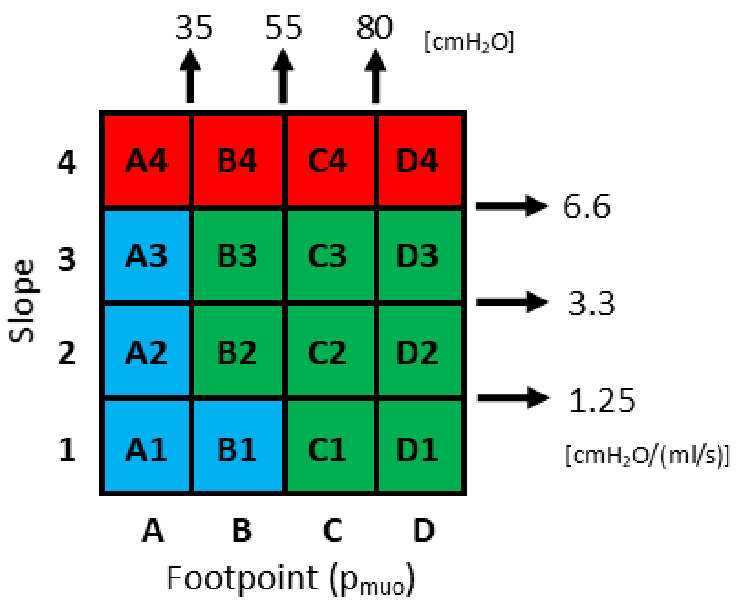

Figure 2: Classification in no BOO, constrictive BOO, and compressive BOO within the CHESS classification. Blue (A1,A2,A3,B1): no BOO; Red (A4,B4,C4,D4): constrictive BOO; Green (B2,B3,C1,C2,C3,D1,D2,D3): compressive BOO. For the slope, the linPURR slope is implemented in the CHESS.[10] *Note that this is the slope in the old pressure-flow graph orientation, so with regard to the flow-axis.*

To analyze differences in patient characteristics between the groups, median age and prostatic size were explored for both methods. In addition, median PFS-PVR, percentage voided (PFS-void%), BOOI, PFS-Q_{max}, $p_{detQmax}$, $p_{muo.act}$, BCI, WF_{max} and WF_{Qmax} taken from the PFS measurement were analyzed. If available, FF-Q_{max}, FF-PVR, and FF-void% the free flow (FF) measurement with a voided volume >100ml, performed in the same session before the PFS was compared between the groups and differences with the PFS parameters were explored. In addition, the correlation between prostate size and UR and between BCI and the UR was analyzed using Spearmans correlation coefficient and visualized for both types of BOO. Statistic differences between the 3 UR classes were analyzed using the Independent Samples Median Test using SPSS, version 27 (IBM, Armonk, USA).

Results

According to method 1, the UR of 771 (56.3%) measurements was classified as “no BOO”, 468 (34.2%) as “compressive BOO”, and 131 (9.6%) as “constrictive BOO”. Within the men with BOO, constrictive BOO was found in 21.9% of the cases. For method 2. 798 (58.2%) were classified as “no BOO”, 449 (32.8%) as “compressive BOO”, and 123 (9.0%) as “constrictive BOO”, with constrictive BOO found in 21.5% of the BOO cases. There was no significant difference between the distribution in method 1 when compared to method 2 (N-1 Chi-squared test p>0.05).

In Figure X, the two methods are displayed together. The main difference between those methods is found for CHESS A3 and B2. A3 is a mixed class, with an almost equal distribution of all the groups according to method 1 (no BOO: 39%; compressive BOO 39%; constrictive BOO 22%). B2 includes 30.2% of patients with no BOO according to BOOI.

Overall, 89.6% were classified the same by method 1 and method 2. This resulted in Spearman's correlation coefficient of 0.786, which is considered a strong correlation.

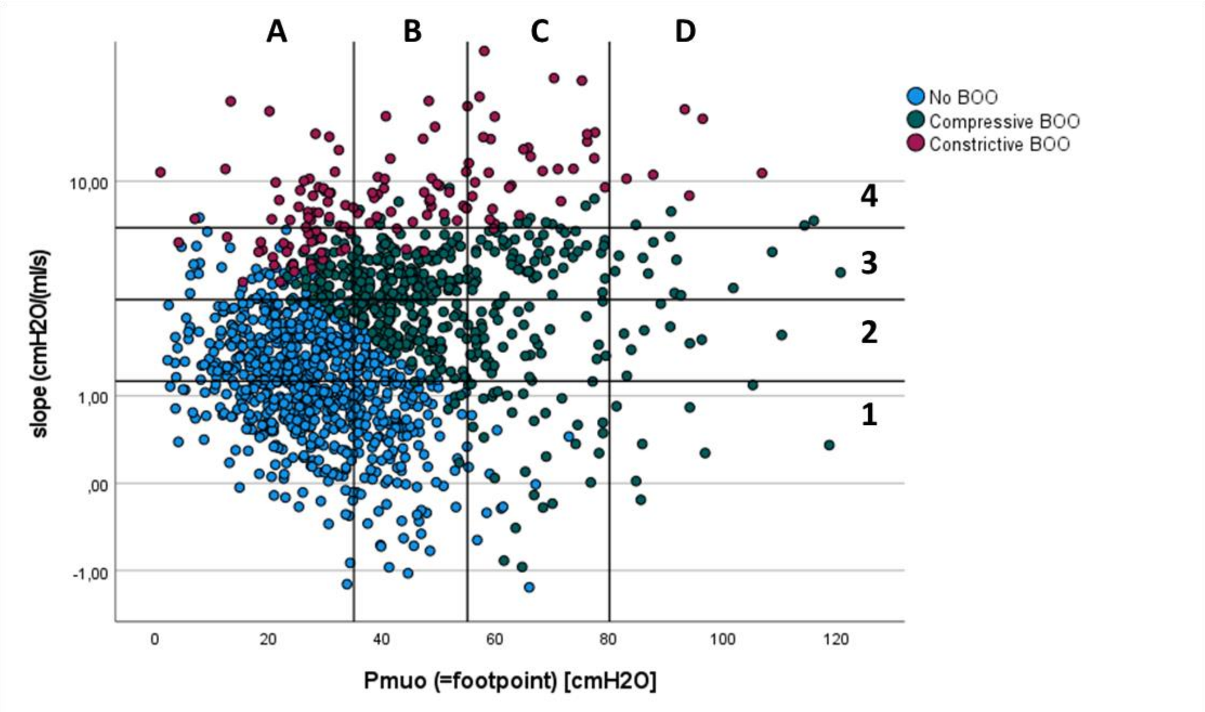

Figure X: Scatterplot of the slope between p_{muo} and $p_{detQmax}$-Q_{max} against p_{muo}, called the footpoint within the CHESS classification system. Cut-off values for the CHESS classes are displayed. Constrictive curves according to method 1 are mostly located in class 4 and A3.

There is a significant difference between the three groups for all features, see table A1 and A2. This is partly due to the observed difference between the obstructed and the unobstructed patients. When comparing compressive with constrictive BOO, no significant differences in patient characteristics as age and prostate size are observed, although BOOI is significantly higher in the constrictive population. p_{muo} is significantly smaller in the constrictive BOO group. The correlation between the prostate size and BOOI was weak (0.25) for compressive BOO and insignificant (0.09, p=0.44) for constrictive BOO. The correlation between the prostate size and p_{muo} was identical for both BOO subtypes (0.24).

Patients with constrictive BOO had significantly more PVR and a lower percentage voided for both the PFS measurement and the FF measurement. In addition, the BCI, WF_{max} and WF_{Qmax} were significantly higher when the BOO is constrictive.

Classification according to method 2 yielded similar results as method 1, except for nonsignificant differences for the FF-PVR and FF-Void%. In addition, the median $p_{muo.act}$ was similar for constrictive and compressive BOO, while in method 1 a substantial difference was observed. Despite the similar median, there was still a significant difference between the mean for both BOO groups.

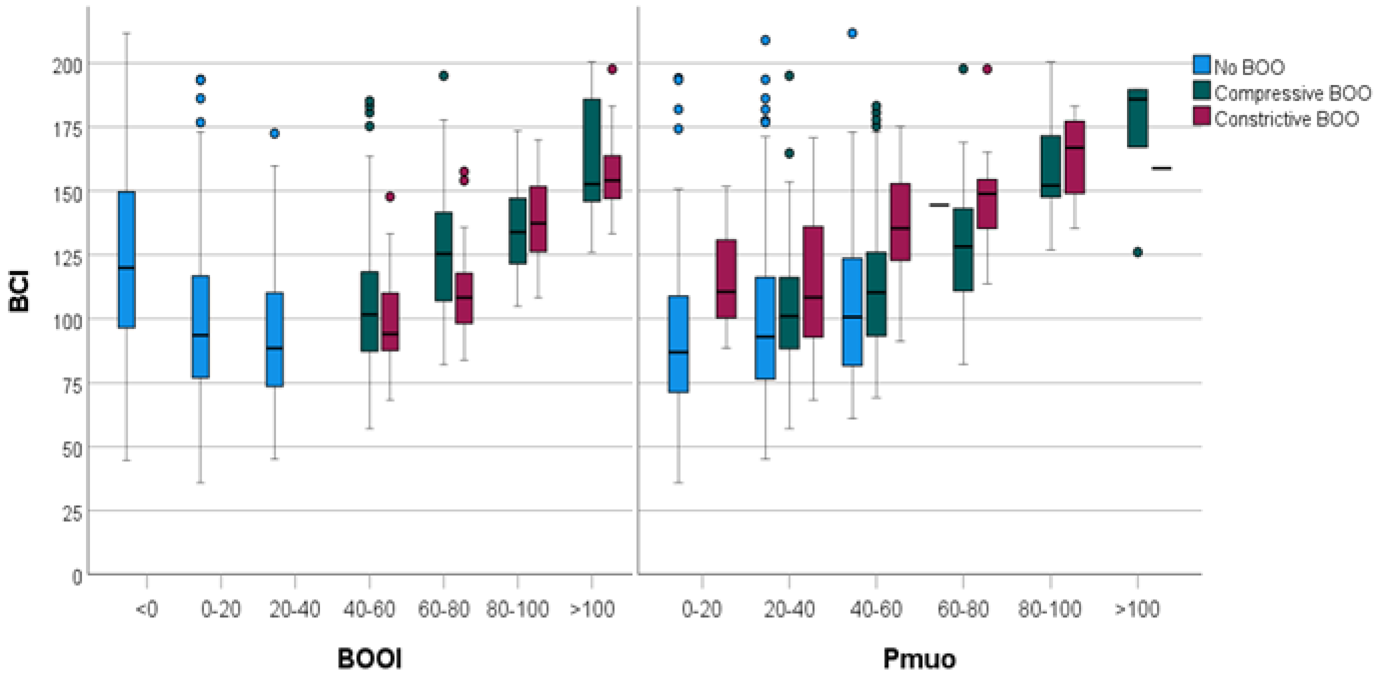

Figure X: BCI in relation to ranges of BOOI and p_{muo}. A significant difference between compressive and constrictive BOO was found for BOOI 60-80 and p_{muo} 40-60 and 60-80.

An overall dependency of the BCI on the UR was observed for both subtypes of BOO. A significant difference was found between compressive and constrictive BOO for BOOI 60-80 and p_{muo} 40-60 and 60-80 (Mann-Whitney U, $p < 0.05$). For BOOI, the compressive BOO showed a significantly larger BCI, while for p_{muo}, the BCI was larger for the constrictive BOO. The correlation between BCI and BOOI was found moderate to strong for compressive (0.56) and constrictive (0.80) BOO, and the correlation between BCI and p_{muo} was found moderate for compressive (0.52) and constrictive (0.54) BOO.

Discussion

Although discrimination between several subtypes of BOO was proposed decades ago, substantial evidence about the relevance of this distinction was not available. This study showed that there are significant differences the BOO subtypes for all included urodynamic parameters, as well as a substantial and significant difference for the PVR. No differences in age and prostatic size were demonstrated.

Although the mean prostatic size was not different for compressive and constrictive BOO, a difference in the correlation with BOOI was observed. Compressive BOO showed a weak correlation, consistent with earlier findings[17], and constrictive BOO showed an insignificant, very weak correlation. This is consistent with the suggested interpretation of compressive – constrictive in the CHESS classification where a constrictive BOO is stated to be probably caused by or unelastic BPH.[9] Stenose However, this difference in correlation was not found when expressing the UR in terms of p_{muo}. This results in an interesting difference between these two parameters describing UR. Conceptually, p_{muo} describes the collapsibility of the flow-controlling zone at low flow, which is assumed to be located in the prostate in the elder male population. BOOI however combines Q_{max} and $p_{detQmax}$, thereby giving an indication of the total UR. As there is no difference in correlation for constrictive and compressive BOO between p_{muo} and prostatic size, but there is between BOOI and prostatic size, BOOI seems to be less indicative of the resistance caused by the prostate.

A positive relation between BCI and the UR was observed, for both compressive and constrictive BOO. This positive relation was found earlier[18], and later confirmed[19] although in both studies no distinction between compressive and constrictive was made. For compressive BOO, the correlation between BCI and BOOI and between BCI and p_{muo} was similar, with similar median values of BCI for BOOI/p_{muo} <80, indicating that those (in compressive BOO conceptually similar) measures are likely to describe the same underlying physiologically parameter. For larger BOOI/p_{muo}, a deviation can be observed, which is consistent with the deviation found in an earlier publication.[16] This correlation was different for constrictive BOO, indicating that p_{muo} and BOOI do not describe the same physiological parameter in this group.

This study also includes some limitations. The retrospective nature of this study could have resulted in a non-generalizable population. However, as all high-quality data from almost 20 years of UDS are included, this is not very likely. In addition, clear cut-off values for constrictive and compressive are not defined in the literature and found differences could be influenced by the chosen definition. The classification of two distinct methods for discriminating between constrictive and compressive BOO was in almost 90% of the cases similar with a strong correlation between the methods, which reduces the possible influence of the chosen definition.

The correlation between BOOI and p_{muo} is greatly reduced for constrictive BOO, which could have clinical consequences. The classification method for BOO currently suggested by the ICS guidelines does not account for this difference, which could result in an overestimation of the treatment effect. However, this overestimation is currently only based on theoretical explorations. Further research is needed to analyze the treatment effect for the two subtypes of BOO in a substantial population, so the evidence of the (by this study suggested) added value of subclassification of BOO could be further established.

Conclusion

In conclusion, this study is a first step in establishing evidence about the added value of subclassification of BOO. Discriminating between compressive and constrictive BOO could be relevant, as we found significant urodynamic differences between constrictive and compressive BOO. In addition, the correlation of UR parameters with prostatic size was different for constrictive and compressive BOO, suggesting that there could be a difference in treatment effect for these groups.

Appendix A

Table A1: Overview of the median and interquartile range (IQR) for the three groups according to method 1. Significant differences between all classes and between constrictive – compressive BOO are shown.

	No BOO		Compressive BOO		Constrictive BOO		Significance (Independent-samples Kruskal-Wallis Test)	
Feature	N	Median + IQR	N	Median + IQR	N	Median + IQR	All groups	Constrictive vs Compressive BOO
Age (years)	771	58 [49-69]	468	65 [55-72]	131	64 [56-71]	<0.001	0.856
Prostate size (cm^3)	300	30 [20-42]	257	46 [32-65]	79	41 [31-54]	<0.001	0.169
PFS-PVR (ml)	302	0 [0-90]	248	30 [0-100]	68	100 [0-150]	<0.001	0.015
PFS-Void% (%)	302	100 [78-100]	248	90 [71-100]	68	77 [56-100]	<0.001	0.012
BOOI	771	21 [11-31]	468	56 [47-70]	131	84 [60-102]	<0.001	<0.001
PFS-Q_{max} (ml/s)	771	10.5 [7.6-13.8]	468	7.3 [5.3-9.8]	131	5.7 [4.4-7.6]	<0.001	<0.001
$p_{detQmax}$ (cmH_2O)	771	43 [34-50]	468	72 [63-88]	131	98 [73-115]	<0.001	<0.001
$p_{muo.act}$ (cmH_2O)	771	27 [20-35]	468	48 [40-61]	131	39 [27-57]	<0.001	<0.001
BCI	771	94 [77-116]	468	113 [96-131]	131	128 [107-152]	<0.001	<0.001
WF_{max}	771	7.6 [6.4-9.2]	468	11.7 [9.9-14.3]	131	14.7 [11.3-17.2]	<0.001	<0.001
WF_{Qmax}	771	6.5 [5.4-7.9]	468	10.2 [8.5-12.4]	131	12.5 [9.7-15.1]	<0.001	0.001
FF-PVR (ml)	113	0 [0-20]	89	10 [0-90]	32	5 [0-150]	<0.001	0.017
FF-Void% (%)	113	100 [93-100]	89	94 [72-100]	32	98 [58-100]	0.001	0.008
FF-Q_{max} (ml/s)	261	14.0 [10.5-20.1]	154	10.9 [8.0-14.3]	50	8.7 [6.1-11.8]	<0.001	0.008

Table A2: Overview of the median and interquartile range (IQR) for the three groups according to method 2. Significant differences between all classes and between constrictive – compressive BOO are shown.

	No BOO		Compressive BOO		Constrictive BOO		Significance (Independent-samples Kruskal-Wallis Test)	
Feature	N	Median + IQR	N	Median + IQR	N	Median + IQR	All groups	Constrictive vs Compressive BOO
Age (years)	798	58 [49-69]	449	65 [55-72]	123	63 [57-69]	<0.001	0.773
Prostate size (cm^3)	311	30 [20-43]	247	45 [32-65]	78	42 [32-60]	<0.001	0.561
PFS-PVR (ml)	303	0 [0-85]	248	30 [0-100]	67	80 [0-150]	<0.001	0.011
PFS-Void% (%)	303	100 [81-100]	248	89 [68-100]	67	75 [56-100]	<0.001	0.003
BOOI	798	22 [11-32]	449	56 [45-69]	123	89 [69-108]	<0.001	<0.001
PFS-Q_{max} (ml/s)	798	10.2 [7.3-13.7]	449	7.8 [5.7-10.4]	123	4.8 [3.9-6.1]	<0.001	<0.001
$p_{detQmax}$ (cmH_2O)	798	43 [34-52]	449	71 [61-88]	123	101 [79-121]	<0.001	<0.001
$p_{muo.act}$ (cmH_2O)	798	27 [21-33]	449	48 [41-61]	123	49 [31-64]	<0.001	0.001
BCI	798	95 [78-115]	449	114 [97-134]	123	128 [106-151]	<0.001	0.006
WF_{max}	798	7.8 [6.5-9.5]	449	11.7 [9.9-14.3]	123	15.3 [11.8-17.6]	<0.001	<0.001
WF_{Qmax}	798	6.7 [5.5-8.1]	449	10.3 [8.5-12.5]	123	12.8 [9.8-15.3]	<0.001	<0.001
FF-PVR (ml)	123	0 [0-20]	80	20 [0-100]	31	0 [0-120]	0.002	0.477
FF-Void% (%)	123	100 [93-100]	80	92 [71-100]	31	100 [61-100]	0.001	0.566
FF-Q_{max} (ml/s)	279	13.3 [10.1-19.2]	142	11.5 [8.2-15.0]	44	8.4 [5.9-10.3]	<0.001	<0.001

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4. Abstracts ICS

4.1 Large Sample Comparison of the Four Methods to Quantify Bladder Outflow Obstruction in Men

van Dort W, Rosier PFWM, van Steenbergen TRF, de Kort LMO. 155 - LARGE SAMPLE COMPARISON OF THE FOUR METHODS TO QUANTIFY BLADDER OUTFLOW OBSTRUCTION IN MEN, Continence, Volume 7, Supplement 1, 2023, ISSN 2772-9737, doi:10.1016/j.cont.2023.100873.

Hypothesis/aims of study

A pressure flow study (PFS), part of the ICS standard urodynamic test, is gold standard for the classification and quantification of bladder outflow obstruction (BOO). For men with benign prostatic hyperplasia (BPH), the minimal urethral opening pressure (p_{muo}) is considered the most objective parameter describing BOO. p_{muo}, is, consequential to the distensible collapsible tube uro(hydro)dynamic theory or paradigm, found at the termination of (male) voiding. Therefore, p_{muo} is, as seen from the (patho)physiology perspective, the most reliable parameter and the most independent of detrusor voiding contraction strength[1]. However, in clinical practice p_{muo} is easily influenced by artifacts, which are more common at the end of the voiding. For that reason, several methods were developed in the past to estimate p_{muo}, and thereby BOO. The maximal flow (Q_{max}) and the corresponding pressure ($p_{detQmax}$), both more unambiguously (automatically) detectable then pmuo, were used for extrapolation. These methods include linPURR with nomogram, URA, and BOOI. In addition, a method was developed including not only $p_{detQmax}$ but also all 'lowest pressure'-data points after Q_{max} to further increase the accuracy of the estimation of p_{muo}; the three -parameter model (3PM). The four different methods have never been mutually compared. The aim of this study was to compare the accuracy of these four methods in determining p_{muo}, using a large database of pressure flow measurements.

Study design, materials, and methods

2349 PFS of men referred with lower urinary tract symptoms (LUTS) without earlier lower urinary tract surgery between 2003 and 2020 were initially included. Measurements with a Q_{max} of > 35 ml/s or < 2 ml/s (4.3%) were excluded. Also, PFS with a voided volume < 100 ml (9.6%), and PFS with a p_{detmax} during voiding < 20 cmH_2O or > 200 cmH_2O (0.8%) were excluded from further analysis. Lastly, studies with catheter artefacts (e.g. kinking or slipping out) (12.9%) were also removed from the dataset.

From the 1717 resulting studies, p_{muo} was calculated according to Schäfer linPURR (PmuolinPURR), URA (PmuoURA), and BOOI (PmuoBOOI). In addition, a 3PM fit was performed through the lowest pressure flank of the pressure-flow plot, using the formula, $p_{det} = p_{muo} + A*Q^k$, with $2/3 \leq k \leq 2$ and A being a patient-specific factor, including all possible theoretical relations between $Q_{max}/p_{detQmax}$ and p_{muo}, as derived by Spangberg (Pmuo3PM) [2]. The resulting p_{muo}'s were compared with the actual p_{muo} for every PFS. For this study we defined the actual p_{muo} (PmuoAct) as the average p_{det} associated with the flowrate between 1 and 0.5 ml/s at the end of voiding. We considered that this was the best manner to reduce the pressure (with flow delay) -artifacts of the p_{muo}. For the comparison in this study, the four estimated p_{muo}'s were adjusted to represent the pressure at 0.75 ml/s as well. Differences between the predicted p_{muo}'s and the PmuoAct's per PFS were analyzed.

PFS with a flow variation smaller than 1 ml/s and a pressure variation < 5 cmH_2O after Q_{max} were expected to show the most realistic p_{muo} values, not confounded by abnormal dynamics or interruptions of voiding. A subselection of 376 (21.9% of all) PFS with this minimal variation throughout the secondary phase of voiding was selected and used in a secondary analysis.

Results

Of the 1717 studies, 55 studies (3.2%) were excluded because all pressures after Q_{max} were found higher than $p_{detQmax}$ and therefore 3PM analysis was impossible. Pmuo3PM was found most accurate in predicting p_{muo}, with 75.9% of the estimations found within a range of +10/-10 cmH_2O around PmuoAct. PmuoURA (52.0%) and PmuolinPURR (53.6%) showed similar performance, while PmuoBOOI was found significantly less accurate (40.0%) to predict PmuoAct (N-1 Chi-squared test $p<0.025$ when compared to all others). Within the minimal variation subset, the overall accuracy increased, with 93.0% of Pmuo3PM estimations within a bandwidth of 10 cmH_2O. PmuoURA (65.1%) and PmuolinPURR (57.0%) were found not significantly different, while PmuoBOOI (45.1%) again showed a smaller correctly estimated proportion.

Bland-Altman plots were created in which the average of one of the estimation methods with PmuoAct was compared with their differences, see figure 1. A significant, negative linear regression was seen for PmuoBOOI, (1B) indicating that PmuoBOOI tended to be higher when the average P_{muo} is larger. The opposite, although less prominent, was seen for PmuoURA (1C). No significant regression was found for Pmuo3PM and PmuolinPURR, but the 95% confidence interval was smaller for Pmuo3PM (1A). The subset analysis showed similar results, with a much smaller confidence interval (+- 15cmH_2O, compared to +-30 for the complete set) for Pmuo3PM and a non-significant linear regression for PmuoURA.

Interpretation of results

Although URA, BOOI, linPURR as well as 3PM are mentioned in the ICS standard for PFS a ‘quality ranking’ was not included and a comparison of their ability to predict p_{muo} has never been reported. We found that the 3PM was superior in predicting P_{muo} to three well-known one-parameter methods, although not applicable in 3.2% of the cases and requiring more complex calculation. From the one-parameter methods, Schäfers linPURR was found most accurate over the whole range of p_{muo}. BOOI, the current, but still provisional ICS standard, was found least accurate, with a tendency of overestimating p_{muo} in men with a higher grade of BOO. The clinical applicability should be studied further and cut-off values for BOO should be reformulated for the 3PM method.

Concluding message

Schäfer’s linPURR was found more accurate than BOOI or URA in estimating p_{muo}, and thus BOO. Although the (3PM) multiparameter model was the most accurate, it is currently not regularly available. Because p_{muo} is considered the best quantifier of BOO in men with BPH, we conclude that linPURR is preferrable over BOOI in the quantification of BOO.

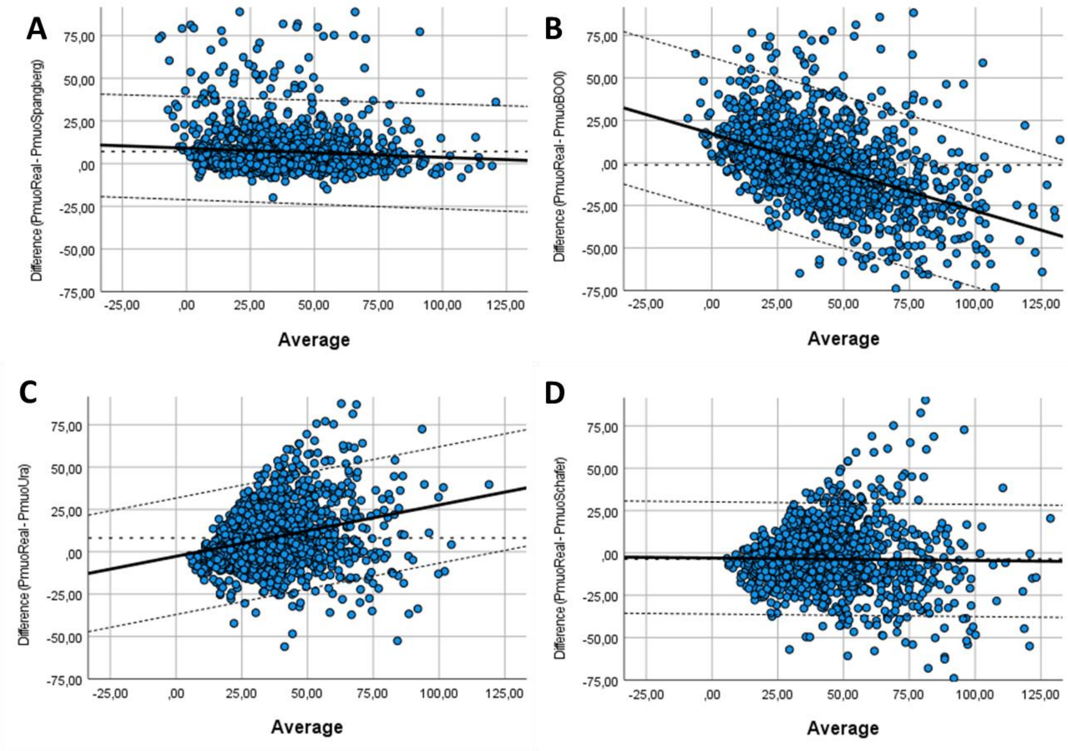

Figure 1: Bland-Altman plots for the difference between PmuoAct and PmuoSpangberg (A), PmuoBOOI (B), PmuoURA (C), PmuolinPURR (D) for all measurements. The linear regression is shown (thick line), including the 95% confidence limits (dashed lines).

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[2]: Spångberg, Teriö H, Engberg A, Ask P, Quantification of urethral function based on Griffiths' model of flow through elastic tubes, Neurourol Urodynam. 1989;8(1):29–52. doi: 10.1002/nau.1930080105.

4.2 CLINICAL INDICATORS OF CONSTRICTIVE VERSUS COMPRESSIVE BLADDER OUTFLOW OBSTRUCTION

van Dort W, Rosier PFWM. 153 - CLINICAL INDICATORS OF CONSTRICTIVE VERSUS COMPRESSIVE BLADDER OUTFLOW OBSTRUCTION, Continence, Volume 7, Supplement 1, 2023, ISSN 2772-9737, doi:10.1016/j.cont.2023.100871.

Hypothesis / aims of study

The Schäfer linPURR nomogram is one of the methods to diagnose and grade bladder outflow obstruction (BOO), based on a pressure flow study (PFS), part of the urodynamic test. linPURR was originally proposed as a two-parameter classification system. The maximum uroflow rate (Qmax) with the corresponding detrusor pressure (pdetQmax) and, the minimal urethral opening pressure (pmuo) were projected in the nomogram to grade BOO in men with -symptomatic- prostatic enlargement. A distinction was established between two types of BOO: Compressive BOO with both pdetQmax and pmuo above 'normal' was considered typical for BPH, while constrictive BOO was atypical, with a relatively low pmuo (see Fig 1). Based on Griffith's distensible collapsible tube paradigm, this constrictive type represents a limitation of distension of the bladder outflow tract. Although differentiation between compressive and constrictive BOO is used in a later developed CHESS classification and the benefit of this differentiation is shown in a small study, correlations between clinical data and the type of obstruction are never studied. The aim of this study is to explore differences in age, prostate size, and free uroflowmetry with PVR between patients with a constrictive versus a compressive BOO.

Study design, materials and methods

PFS of ICS standard uroflowmetry test, performed with a water filled pressure system and corrected for flow and pressure peak artifacts, of 698 symptomatic, referred men with BOO (linPURR grade ≥ III or BOOI >40) without earlier LUT surgery, that underwent UDS with PFS between 2003 and 2020, were included. PFS with 2<Qmax<35, Voided volume <100 ml were excluded. We determined compressive BOO when the actual pmuo, (PmuoAct) was within limits of +or- 20cm H2O from the pmuo predicted with linPURR (PmuolinPURR). PmuoAct is the average pdet associated with the flowrate between 1 and 0.5 ml/s at the end of voiding. We considered that this manner to determine PmuoAct was the best to reduce the pressure (with flow delay) -artifacts associated with assessment of pmuo. A PFS was considered constrictive if PmuoAct was more than 20 cmH2O lower than PmuolinPURR. This represents a difference, larger than the approximate width of one linPURR obstruction class. Differences of age, PVR, percentage voided, and prostate size, between the two types of BOO were investigated. In addition, differences between Qmax, PVR and void% between PFS and the free flow (FF) measurement were compared for the two obstruction types. Finally a sub-analysis was performed including only PFS with a bladder contractility index (BCI) >100, a normal detrusor voiding contraction strength.

Results

510 PFS (73%) were found of the compressive type, while 154 PFS (22%) were found constrictive. 34 PFS (6%) had a PmuoAct which was >20 cmH2O higher than PmuolinPURR, and were excluded from further analysis, see Fig 2. Significant differences between constrictive and compressive were found for PVR and void%, with on average a larger residue and a smaller percentage voided for the constrictive obstruction. No significant differences were found for age and the difference between the free flow and the PFS (Mann-Whitney U-test p>0.05), although a non-significant difference in prostate size between compressive BOO and constrictive BOO was observed. There was no

significant difference observed for the percentage prostate size <30 cm3. For the subanalysis, 480 PFS (69%) met the criteria of BCI > 100. 355 PFS (74%) were found compressive, while 125 PFS (26%) were found constrictive. A difference with a higher significance (see table 1) compared to the whole group was found for PVR and void%. In addition, a significant difference in prostate size was observed, with the prostate size of patients with a compressive BOO (57 cm3) being significantly larger than those with a constrictive BOO (46 cm3). No significant differences were observed for age and the difference between the free flow and PFS. There was a significantly larger proportion of patients with a small prostate <30 cm3 within the constrictive BOO-cohort (35%) than within the compressive BOO-cohort (18%).

Interpretation of results

The mean prostate size was smaller for constrictive BOO; this may lead to the speculation that other factors than prostate size only, e.g., prostate structure, have a role in the pathophysiology of BOO in these patients. This can also lead to the speculation that a proportion of the currently used invasive treatment options could be less effective (or necessary) for the constrictive type, as those are mainly focused on the reduction of the prostatic size. In addition, the voiding efficiency was significantly lower in patients with a constrictive BOO, as a significant difference in PVR and void% was found. This difference was even larger in the sub-group of patients with a normal detrusor voiding contraction strength. A difference in treatment efficiency of men with BPH with a constrictive or compressive BOO was earlier observed when patients were analyzed according to their CHESS class.

Concluding message

There are significant differences in voiding efficiency and prostate size between compressive and constrictive BOO that may have relevance for individualized selection of management.

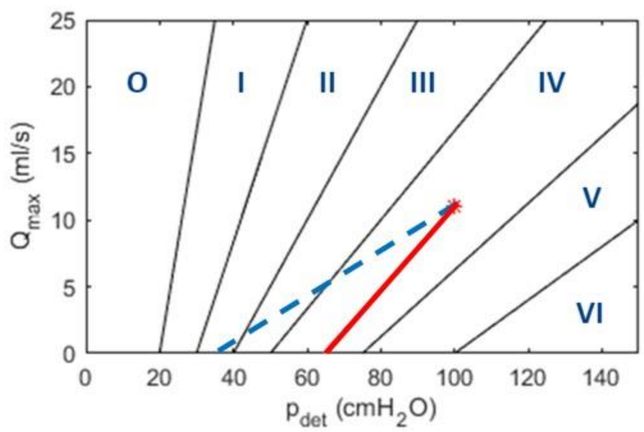

Fig 1: Overview of compressive (solid line) and constrictive (dashed line) BOO, as shown in a linPURR nomogram. Both types have the same Q_{max} /$p_{detQmax}$, but will result in different p_{muo} values (crossing of the x-axis).

A	Compressive BOO			Constrictive BOO			Significance
	N	Mean	SD	N	Mean	SD	MW-U
Age (Years)	510	62	13	154	62	12	0.636
PVR (ml)	267	76	113	76	102	119	0.031
Void% (%)	267	83	20	76	77	22	0.026
TRUS (cm^3)	279	53	31	89	45	23	0.063
TRUS < 30 (%)	279	22.6		89	27.0		0.396*
Qmax (PFS - FF) (ml/s)	220	-4.2	4.6	75	-3.4	4.8	0.131
PVR (PFS - FF) (ml)	77	24	80	30	34	63	0.395
Void% (PFS - FF) (%)	77	-4	18	30	-2	18	0.452

B	Compressive BOO			Constrictive BOO			Significance
	N	Mean	SD	N	Mean	SD	MW-U
Age (Years)	355	62	13	125	61	12	0.243
PVR (ml)	203	65	104	63	99	118	0.005
Void% (%)	203	86	18	63	77	21	0.003
TRUS (cm^3)	202	57	32	76	46	25	0.005
TRUS < 30 (%)	84	17.9		37	35.1		0.04*
Qmax (PFS - FF) (ml/s)	155	-3.7	4.7	61	-2.8	4.4	0.198
PVR (PFS - FF) (ml)	63	16	66	27	34	66	0.19
Void% (PFS - FF) (%)	63	-2	15	27	-3	18	0.89

Fig 2: Overview of the results of all patients (A) and patients with BCI > 100 (B). Mann-Whitney U-test = MW-U . (* N-1 Chi-Squared test for proportions used instead of Mann-Whitney U-test)

4.3 Classification of the Pressure-Flow Curve after Maximal Flow by using an Unsupervised Machine Learning Model

van Dort W, Rosier PFWM. 152 - CLASSIFICATION OF THE PRESSURE-FLOW CURVE AFTER MAXIMAL FLOWRATE BY USING AN UNSUPERVISED MACHINE LEARNING MODEL, Volume 7, Supplement 1, 2023, ISSN 2772-9737, doi:10.1016/j.cont.2023.100870.

Hypothesis / aims of study

The urodynamic pressure-flow study (PFS) is used to diagnose the properties of the bladder and the outflow tract during voiding. The part of the PFS curve after the maximum flow (Qmax) is most clinically relevant, based on the distensible and collapsible tube theory. Based on this model, the passive urethral resistance relation (PURR) was established, describing the expected ideal relation of pressure and flow after Qmax. In addition, the dynamic urethral resistance relation (DURR) was defined as the deviation of the measured curve from the PURR.[1] The (clinical) epidemiology of bladder outflow dynamics (PURR versus DURR) is not known. With this in mind, we have used Artificial intelligence (AI) based unsupervised machine learning (UML). AI-UML analysis can be used for the 'automated' and objective classification of signal pattern data in clusters with similar properties and is therefore a useful tool for screening a large dataset on pattern similarities. Some urodynamic studies used supervised machine learning (SML) to automatically classify patterns. However, these models are susceptible to human error, as the golden standard is set by expert opinion. AI-UML results in a consistency of analysis that is difficult or impossible to obtain with human-expert evaluation but requires additional steps for implementation of the result in the clinic. Therefore UML is an ideal tool for a first analysis of a large dataset of PFS on still-unknown or undescribed patterns. The aim of this study is to analyze outflow dynamics in a large set of male PFSs, by analyzing, classifying, and clustering the PURR - DURR using UML and to describe the properties of those clusters.

Study design, materials and methods

1662 PFS of men (age: mean 59 years (17-93)) with a 2<Qmax<35 mL/s, PFS voided >100mL without major artifacts (e.g., hitting flowmeter-peaks) were included. The detrusor pressure (pdet) and flowrate signals were filtered using a 2-second moving average filter, and a correction for flow measurement delay of 0.75 seconds was applied. To allow UML, the flowrate was normalized to a 30-point scale, based on the minimum and maximum flow within a PFS, and pdet to a 0-1 scale. Furthermore, the mean pdet around each normalized flow point was calculated. UML was applied, based on the K-means learning model, with the dynamic time-warping (DTW) metric. With DTW (or in this case 'dynamic flowrate warping' because not the time, but the flowrate was entered as the independent factor), the UML becomes less sensitive to small variations in the p and Q relation, resulting in a more applicable model. UML requires entering the 'requested' number of resulting clusters and the optimal amount of clusters was determined using the silhouette score. For each cluster, the amount included PFS, basic patient characteristics such as age and prostate size, and PFS parameters as Qmax, the corresponding pressure (pdetQmax), voided volume, and bladder outflow obstruction (BOO) according to linPURR, URA, and BOOI were compared using the Kruskal-Wallis Test.

Results

Based on the silhouette score, classification in four clusters of PFS -DURR types was found to be optimal. The UML-resulting four clusters can be found in figure 1. The largest cluster consists of 1084 PFS (65%), with high pressure at a high flowrate and low pressure at a low flowrate. The second cluster consist of 264 PFS (16%), with a temporary increase in pressure when flowrate decreased, but ending with low pressure at low flowrate. The third cluster consists of 210 PFS (13%), with an initial decrease of pressure, but an end-voiding increase of pressure. The last cluster consists of 104 PFS (6%), with an overall increase in pressure with a decrease in flowrate. The distribution of age, Qmax, pdetQmax, TRUS, linPURR, URA, and BOOI was significantly different across the four clusters ($p<0.006$). No significant difference was found for the voided volume ($p = 0.171$).

Interpretation of results

This study showed that the PFS pattern could be divided into four clusters by using AI-UML. As significant differences were found in the patient and urodynamic characteristics, the clustering likely resulted in clinically relevant patient categories. Additional classification of BOO has been performed in the past by the CHESS two-point PFS classification. However, the CHESS classification expects a positive relation between pressure and flow, as described by PURR, which is only fully true for (the largest) cluster 1. AI-UML 'discovered' 3 other clusters probably or potentially clinically relevant DURR -subtypes, not described earlier.

Concluding message

Based on unsupervised machine learning performed on an extensive database of PFS, we determined 4 types of pressure-flow PURR-DURR patterns, associated with different patient and PFS characteristics.

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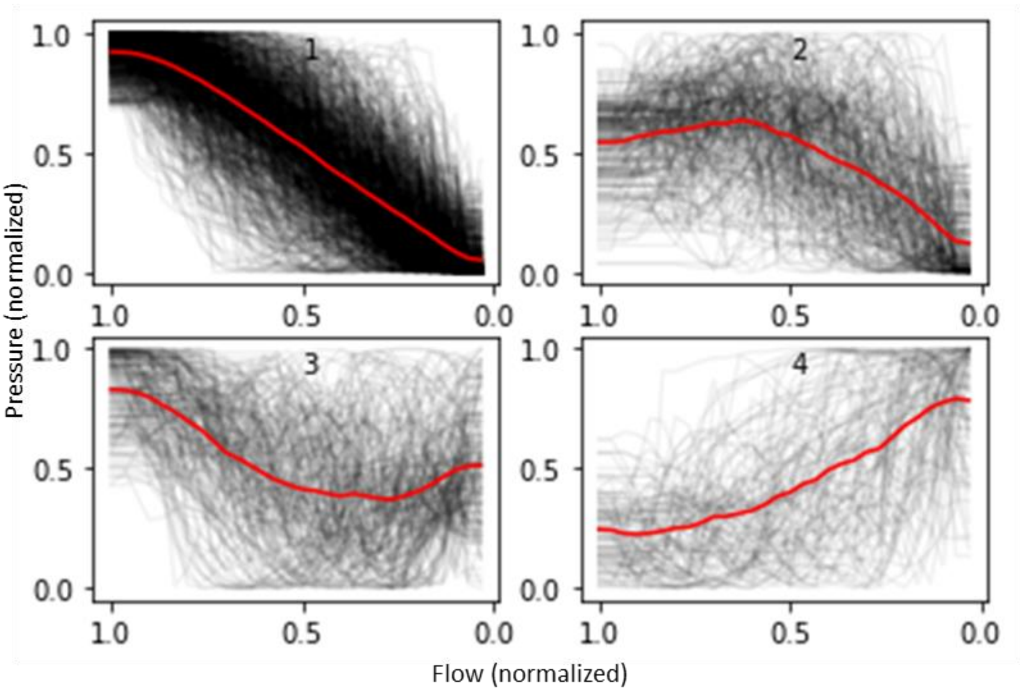

Fig 1: Clustering result of the AI-UML. For each cluster, all normalized PFS PURR-DURR curves are given (all black curve-lines), with the AI-UML clustering center (result) in red. Note that the pressure and flow are normalized, with 1 being the highest pressure

5. Final considerations and conclusion

Although measures for urethral resistance (UR) are known for decades, a direct comparison on their quantification of bladder outflow obstruction (BOO) was not published earlier. The currently included measure in the International Continence Society (ICS) standard, Bladder Outflow Obstruction Index (BOOI), was mainly selected for its simplicity, and evaluation on a large amount of high-quality data was not performed. The research included in this thesis resulted in the following findings:

- Of the investigated measures for UR, the use of more points of the pressure-flow relation resulted in a more accurate quantification of the UR.
- BOOI, currently included in the ICS standard, is the least accurate in the quantification of the UR when compared to the other measures.
- The discrimination of BOO in the type of obstruction resulted in significantly different patient and urodynamic characteristics, thereby giving some basic evidence about the usefulness of this discrimination.
- Unsupervised machine learning analysis resulted in the classification of four types of urethral resistance relations with significant differences between those groups.

This thesis included some small steps on the way to a more precise and more extensive quantification and classification of BOO. Additional research is needed to translate the statistically significant differences into clinically significant ones. In addition, the usefulness of subclassification of the type of obstruction for the choice of treatment needs additional investigation. An extension could also be made for women and children, who have different dynamics of voiding and for which, especially for children, the quantification of BOO is less established, and cut-off values for the UR are not quantitatively formulated. In the coming years, I hope I can further contribute to establishing a sufficient quantification method of BOO in children, especially in young boys, where the measuring equipment is likely to significantly influence the measurement.