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Benign Prostatic Hyperplasia

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

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Article info

Abstract

Background: Detrusor overactivity is one known cause of lower urinary tract symptoms and has been linked to bladder storage symptoms (urgency, frequency, or urge incontinence).

Objective: To determine clinical and urodynamic parameters associated with detrusor overactivity in patients with suspected benign prostatic hyperplasia.

Design, Setting, and Participants: During 1993–2003, urodynamic investigations were performed in patients aged 40 yr or older and with lower urinary tract symptoms, benign prostatic enlargement, and/or suspicion of bladder outlet obstruction (maximum flow rate < 15 ml/s or postvoid residual urine > 50 ml).

Measurements: Detrusor overactivity was defined according to the new International Continence Society classification (2002) as involuntary detrusor contractions during cystometry, which may be spontaneous or provoked, regardless of amplitude. The Schäfer algorithm was used to determine bladder outlet obstruction.

Results: In total, 1418 men were investigated (median age: 63 yr) of whom 864 men (60.9%) had detrusor overactivity. In univariate analysis, men with detrusor overactivity were significantly older, more obstructed, had larger prostates, higher irritative International Prostate Symptoms Score subscores, a lower voiding volume at free uroflowmetry, and a lower bladder capacity at cystometry. The prevalence of detrusor overactivity rose continuously with increasing bladder outlet obstruction grade. Multivariate analysis showed that only age and bladder outlet obstruction grade were independently associated with detrusor overactivity. After age adjustment, the odds ratios of detrusor overactivity compared to Schäfer class 0 were 1.2 for class I, 1.4 for class II, 1.9 for class III, 2.5 for class IV, 3.4 for class V, and 4.7 for class VI.

Conclusions: In patients with clinical benign prostatic hyperplasia, detrusor overactivity is independently associated with age and bladder outlet obstruction. The probability of detrusor overactivity rises with increasing age and bladder outlet obstruction grade.

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1. 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 sponta- neously 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 hetero- geneous 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.

2. Patients and methods

2.1. Patient selection

Between April 1993 and November 2003, all men with clinical BPH who came to the urological outpatient department of the Medical School of Hannover, Germany, were included in this study. Clinical BPH was defined by LUTS, BPE, and/or suspicion of BOO in men aged 40 yr 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 of the pelvis, 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 under current or previous medical treatment with 5α-reductase inhibitors and with BPH-related complications (urinary retention, bladder stones, or bladder diverticula) were also excluded. If α-blockers, antimuscarinic drugs, or plant extracts were used, the patient was asked to stop using the medication at least 1 wk before initial presentation.

2.2. Patient assessment

At initial presentation, patient history and a blood sample for prostate-specific antigen (PSA) measurement were taken and the International Prostate Symptoms Score (IPSS) question- naire was completed. 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 ultra- sound array was used to measure postvoid residual urine and a transrectal 7.5-MHz ultrasound array was used to measure prostate volume. Prostate biopsies to exclude prostate cancer were performed in men with palpable prostate tumours or elevated PSA concentrations ($> 4 \mu g/l$).

All men with LUTS, BPE, and/or reduced urinary flow (< 15 ml/s) or postvoid residual urine > 50 ml were investi- gated urodynamically 1 to 3 wk after initial presentation. Experienced investigators performed urodynamic investiga- tions that were in line with the suggested good urodynamics practice standards of the International Continence Society [17]. 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 trans- ducers, a 6-Fr double-lumen transurethral and a 10-Fr single- lumen rectal catheter. Sterile physiological saline solution at 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 two to four 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 regardless of amplitude [5]. In cases of involuntary detrusor contractions, patients were asked to suppress DO and urinary leakage by urethral sphincter contraction. BOO was assessed with the Schäfer algorithm [18]. The pressure-flow measurement with the lowest BOO grade was used for further analysis.

Directly after the urodynamic measurement and elimina- tion of measurement artefacts, the urodynamic traces were judged by the investigator together with a senior urologist (K.H.) and a diagnosis with regard to DO, DO-incontinence, and BOO grade was documented. In 2005 all urodynamic measure-

Table 1 – Clinical and urodynamic parameters of all patients investigated in this study (n = 1418)

Parameter	Range	Median (25th–75th percentiles)
Age (yr)	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)
Irritative IPSS subscore (questions 2, 4, 7)	0–15	7 (4–10)
Obstructive IPSS subscore (questions 1, 3, 5, 6)	0–20	9 (4–13)
Prostate volume (ml)	11–190	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 first involuntary detrusor contraction (ml)	1–1178	124 (45–260)
Maximum amplitude of involuntary detrusor contraction (cm H$_2$O)	5–330	35 (18–70)
Schäfer class (linPURR)	0–VI	II (I–III)

IPSS, International Prostate Symptom Score; Q_{max}, maximum flow rate of free uroflowmetry; linPURR, linear passive urethral resistance relation.

ments 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, body mass index), total IPSS (questions 1–7), irritative (questions 2, 4, and 7) and obstructive IPSS subscores (questions 1, 3, 5, and 6), prostate volume determined by transrectal ultrasound, parameters of free uroflowmetry (maximum 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, cystometric bladder capacity).

2.3. Statistical analyses

Nonparametric tests were necessary to compare groups with or without DO because the data was unevenly distributed; the Mann-Whitney or Kruskal-Wallis test was used to compare numerical data. The χ^2-test for trend was used to analyze the frequencies in the different age and BOO groups. Correlation analysis and the Spearman rank test was applied to examine 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. Variable selection was based on the backward-stepwise method. 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 ≤0.05 was considered significant. SPSS version 12.0.2 (SPSS, Inc, Chicago, IL, USA) was used for statistical analyses.

3. Results

Urodynamic investigations were performed in 1460 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 1418 patients are listed in Table 1. Eighty-six men (6.1%) had an IPSS of 7 or less, whereas 1332 men (93.9%) had an IPSS of more than 7.

During filling cystometry, 864 patients (60.9%) had involuntary detrusor contractions. Men with DO were significantly older, had a higher irritative IPSS subscore, greater prostate volume, lower voiding volume at free uroflowmetry, and a lower maximum cystometric bladder capacity (each parameter $p < 0.05$, Mann-Whitney test; Table 2). The relationship between DO and different age groups is shown in Fig. 1. Older men had a significantly higher chance to have DO ($p = 0.047$, χ^2-test for trend).

In pressure-flow analysis, BOO grades were unevenly distributed, with more men classified within the lower Schäfer classes. Patients with DO were significantly more obstructed than patients without DO (median Schäfer class II vs. I, $p < 0.01$, Mann-Whitney test; Table 2). The prevalence of DO rose continuously with increasing BOO grade, ranging from 51.4% in Schäfer class 0 to 83.3% in Schäfer class VI ($p < 0.001$, χ^2-test for trend; Fig. 2). There was a 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, $p = 0.017$; Fig. 3) and a weak positive correlation between BOO and maximum amplitude of involuntary detrusor contractions (Spearman rank test 0.097, $p = 0.006$; Fig. 4).

Logistic regression analysis with all clinical and urodynamic parameters 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

Table 2 – Median values and 25th–75th percentiles of clinical and urodynamic parameters in groups with or without detrusor overactivity

Parameter	Detrusor overactivity		p value[*]
	Absent ($n = 554$)	Present ($n = 864$)	
	Median (25th–75th percentile)	Median (25th–75th percentile)	
Age (yr)	61 (56–68)	64 (59–70)	<0.001
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 subscore (questions 2, 4, 7)	6 (3–9)	8 (5–11)	<0.001
IPSS obstructive subscore (questions 1, 3, 5, 6)	9 (4–13)	9 (5–12)	0.311
Prostate volume (ml)	33 (25–45)	38 (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)	<0.001
Postvoid residual urine (ml)	64 (20–150)	60 (20–124)	0.574
Cystometric bladder capacity (ml)	409 (299–574)	357 (268–493)	<0.001
Schäfer class (linPURR)	1 (0.75–3)	2 (1–3)	<0.001

IPSS, International Prostate Symptom Score; Q_{max}, maximum urinary flow rate of free uroflowmetry; linPURR, linear passive urethral resistance relation.

[*] Mann-Whitney test.

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, ranging from 1.2 in Schäfer class I to 4.7 in Schäfer class VI.
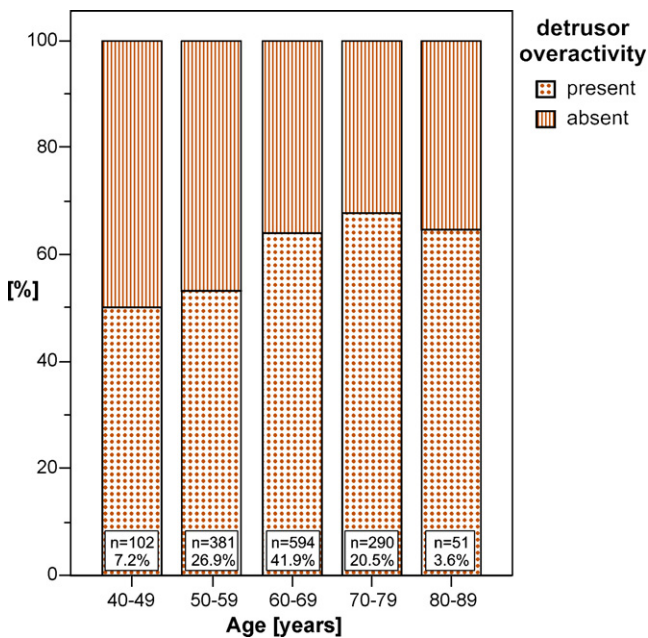

Fig. 1 – Prevalence of detrusor overactivity in relation to different age groups. The y-axis shows the percent of patients with (▦) or without (▥) detrusor overactivity within the age group. The number of men (%) in each age group is listed at the base of the column. Patients in the older age groups had a significantly higher chance of detrusor overactivity ($p = 0.047$, χ^2-test for trend).
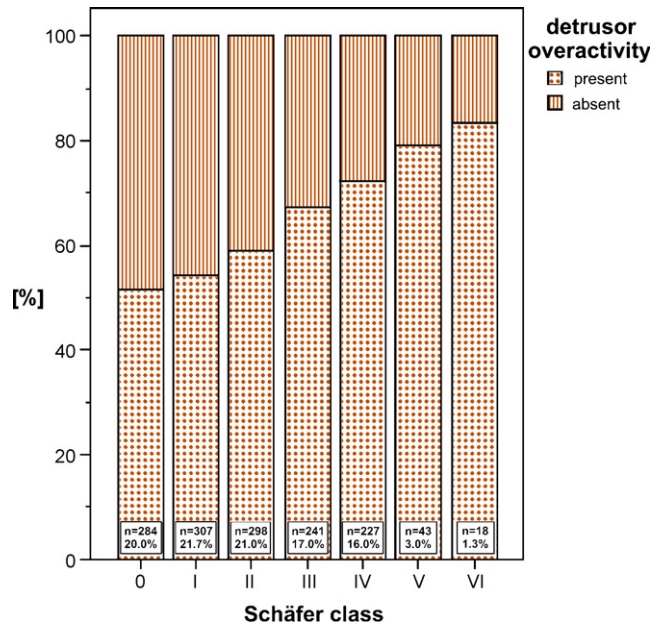

Fig. 2 – Prevalence of detrusor overactivity in relation to the bladder outlet obstruction grade (Schäfer class). The y-axis shows the percent of patients with (▦) or without (▥) detrusor overactivity within the Schäfer class. The number of men (%) in each Schäfer class is listed at the base of the column. The prevalence of detrusor overactivity increases continuously from 51.4% in Schäfer class 0 to 83.3% in Schäfer class VI ($p < 0.001$, χ^2-test for trend).
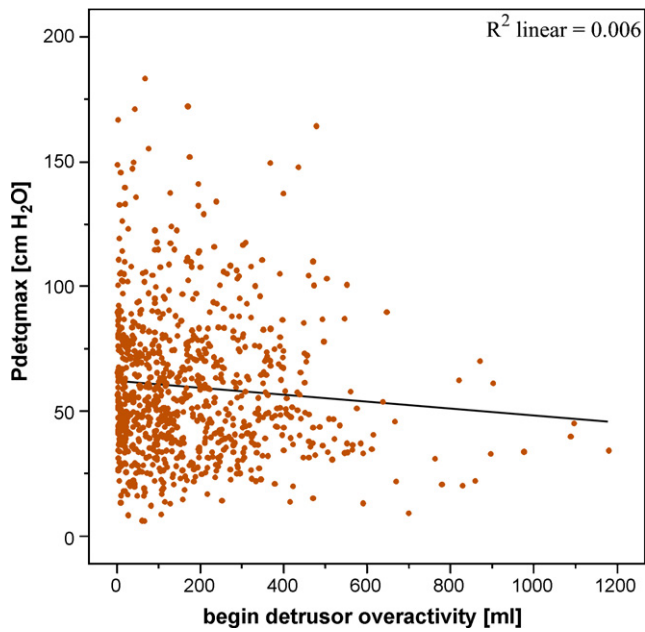
Fig. 3 – Relationship between detrusor pressure at maximum flow (Pdet$_{qmax}$) and bladder filling volume at begin of involuntary detrusor contractions. With increasing bladder outlet obstruction, involuntary detrusor contractions appeared at lower bladder volumes (Spearman rank test: −0.082, p = 0.017).

Table 3 – Logistic regression analysis of relationship of detrusor overactivity with age and various grades of bladder outlet obstruction compared to Schäfer class 0 (no bladder outlet obstruction)

Parameter	p value	Odds ratio (95% CI)
Age	<0.001	**1.03** (1.01, 1.04)
Bladder outlet obstruction grade		
Schäfer 0		
Schäfer I	0.282	**1.2** (0.86, 1.66)
Schäfer II	0.044	**1.4** (1.01, 1.95)
Schäfer III	<0.001	**1.9** (1.33, 2.71)
Schäfer IV	<0.001	**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)

4. Discussion

Our study demonstrated that the appearance of DO in filling cystometry in men with BPH is associated independently only with age and BOO. With increasing BOO grade, there was an increasing probability of DO and tendency towards an earlier appearance and higher amplitude of DO.

This study included men with clinical BPH who were evaluated in the Medical School of Hannover during a 10.5-yr 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 LUTS, BPE, and/or BOO most likely attributable to BPH.

Although diseases other than BPH were not evident at the time of assessment, other causes of LUTS, BPE, or BOO still might have been latently present. Prostate biopsies were only taken in men with a PSA concentration of more than 4 μg/l or palpable tumours and, therefore, latent prostate cancer might have been overseen. The majority of men investigated in our study sought help for moderate to severe LUTS (IPSS > 7, 93.9%). All baseline characteristics of patients in our study are nearly identical with those of the 4979 European men with clinical BPH who were investigated to determine health-seeking behaviour [19]. 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 men with LUTS who do not seek medical help because the characteristics of these men are mainly unknown.

Urodynamic studies with large numbers of BPH patients are sparse. Therefore, our study also provides information about the distribution of BOO grades within a group of BPH patients. Pressure-flow studies of our patients revealed that

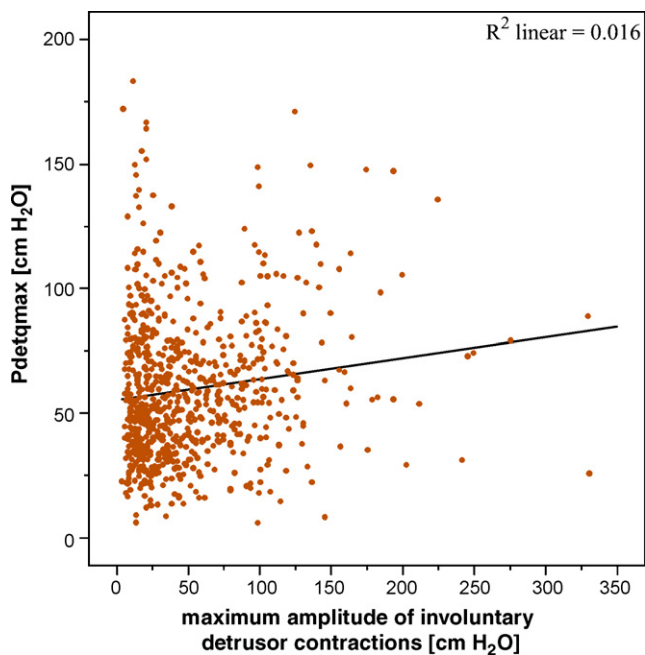Fig. 4 – Relationship between detrusor pressure at maximum flow (Pdet$_{qmax}$) and maximum amplitude of involuntary detrusor contractions. With increasing bladder outlet obstruction the maximum amplitude of involuntary detrusor contractions increased as well (Spearman rank test: 0.097, p = 0.006).

58.3% had BOO. Although patients were not selected after initial assessment to undergo urodynamic investigation, younger patients ($\geq$ 40 yr) were also investigated, pressure-flow measurements were repeatedly performed and the lowest BOO grade was used for analysis, the probability of BOO was nearly identical to that of the International Continence Society BPH study. That urodynamic study included 1271 patients with clinical BPH and demonstrated BOO in 60% [20]. In some patients, the BOO grade might have been determined during voiding initiated by involuntary detrusor contractions. However, the BOO grade measured in these patients seems to be representative of the BOO grade measured by voluntary detrusor contractions [21]. Our results indicate that BOO grades are not normally distributed within the group of 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 (eg, hesitancy, slow urinary stream, or extended micturition time) are reported more frequently, storage symptoms (urgency, pollakisuria, nocturia, or urge incontinence) are more bothersome and reduce the quality of life more substantially [22,23]. Storage symptoms can be caused by DO but might also be related to other myogenic, neurogenic, hormonal, or behavioural abnormalities (eg, post-void residual urine due to BOO or detrusor underactivity, increased fluid intake, or insufficiency of vasopressin production) [24,25]. The incidence of DO in our group of clinical BPH patients was 60.9% and, therefore, nearly identical with the prevalence of DO reported in the meta-analysis of urodynamic studies (60.2%) [6].

In univariate analysis, several parameters were significantly different in patients with DO compared to those without DO (age, IPSS irritative subscore, prostate volume, voided volume in free uroflowmetry, maximal cystometric bladder capacity, and BOO grade). Even though the individual relationships between DO and most of these clinical or urodynamic parameters have been reported before, no study has investigated all parameters in one patient group thus 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 Schäfer class I did not have an increased prevalence of DO;

this mild BOO grade, however, is clinically considered as nonobstruction as well.

We demonstrated 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 thus far. Some authors did not find a significant relationship between DO and BOO [7,14], whereas others demonstrated an increased prevalence in men with BOO [9–13]. Therefore, our study confirmed the findings of the latter studies, but these used the old DO definition of the International Continence Society (involuntary detrusor contractions with an amplitude > 15 cm H_2O); other BOO assessment algorithms (eg, 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 without further patient selection, used a well-accepted BOO assessment algorithm, and applied the new DO definition of the International Continence Society. 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.

Although BOO in BPH patients is caused by obstruction of the prostatic urethra due to BPE, the main focus for the understanding of storage symptoms and DO has shifted from the prostate to the bladder [25,26]. Theories explaining DO in men with BOO focus on myogenic, epithelial, neurogenic, or combined origins. BOO leads to morphological (eg, detrusor wall thickening, increased collagen content, hypertrophy of neurons, increase and alteration of adrenoceptors) and functional changes in the bladder wall (eg, ischemia, partial denervation, supersensitivity of muscarinic receptors to acetylcholine, neurotransmitter imbalance, changes in electrical properties of detrusor smooth muscle cells, reorganization of the spinal micturition reflex) [3,8,26,27]. Microscopic investigations of the detrusor in patients with DO revealed abnormal intercellular connections (protrusion junctions or ultraclose abutments) that seem to be responsible for the propagation of spontaneous depolarization of detrusor cells leading to synchronous involuntary contractions of detrusor regions [28]. Because the detrusor wall thickens continuously with increasing BOO grade, it is likely that 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].

The results of our study suggest that BOO is partly responsible for DO and treatment of BOO is potentially able to reverse bladder wall changes and DO. This concept is supported by a study that evaluated DO in BOO patients before treatment and 5 yr afterwards. The authors only found a significantly reduced prevalence of DO after transurethral resection of the prostate (68% vs 31%), whereas no difference appeared after therapies without BOO relief (medical treatment or watchful waiting) [30]. In patients with DO but without BOO, aging or other unknown factors seem to play an important role in the pathophysiology of DO and treatment of BOO is unlikely to resolve DO in the majority of these men [15]. Therefore, BOO assessment in BPH patients with suspected DO seems to be crucial to anticipate postoperative symptom relief. Because pressure-flow studies are invasive, unpleasant for the patient, time-consuming, and expensive, other minimally or noninvasive tests for BOO assessment should be considered (eg, ultrasound detrusor wall thickness measurement) [29].

5. Conclusions

Age and BOO are independently associated with DO in men with BPH. The odds ratio of DO rises with age and increasing BOO grade. In contrast, prostate volume or other patient characteristics are 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.

Author contributions: Matthias Oelke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Oelke, Jonas, Höfner.
Acquisition of data: Oelke, Baard.
Analysis and interpretation of data: Oelke, Baard, Wijkstra, de la Rosette.
Drafting of the manuscript: Oelke, Baard, Wijkstra.
Critical revision of the manuscript for important intellectual content: Oelke, Wijkstra, de la Rosette.
Statistical analysis: Oelke, Baard.
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Administrative, technical, or material support: Jonas, Höfner.
Supervision: de la Rosette, Jonas.
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