Critical Evaluation of Urodynamic Studies in the Assessment and Treatment of Men with Lower Urinary Tract Symptoms

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Contents

GENERAL INTRODUCTION

Lower urinary tract symptoms (LUTS)

THE PREVALENCE OF voiding symptoms in the elderly male population is high and an increasing number of those patients is seeking medical consultation for their complaints. In former days these complaints were considered to be caused by an enlarged prostate and were therefore summarized in the term 'prostatism'. These voiding symptoms, however, are not pathognomonic for benign prostatic hyperplasia (BPH). Other possible causes of LUTS are detrusor instability, detrusor underactivity, urinary tract infection, and urolithiasis. Consequently, the term 'prostatism' was replaced by 'lower urinary tract symptoms'.[1] The majority of complaints are caused by BPH. BPH is a histologic diagnosis and has a prevalence that increases with age. BPH occurs in 88% of men aged over 80.[2]

The pathophysiologic concept of clinical BPH is a cascade of events, starting with histologic BPH that may cause benign prostatic enlargement (BPE). BPE may result in bladder outlet obstruction (BOO) often leading to the development of LUTS. BPH does not always result in BOO and not all patients with BOO have accompanying symptoms. Hald clearly illustrated the relation between LUTS, BPH, and BOO.[3]

Assessment of men with LUTS

Since LUTS are not specific to BPH or BOO, complementary diagnostic tests are necessary to establish or reject the diagnosis of BOO in order to choose an appropriate treatment, to predict efficacy and durability of a treatment and to evaluate treatment effect.

It is important for the urologist to know to what extent he may rely on a certain diagnostic test. Ideally, a test that provides 100% certainty about the presence of a disease would be available; a so-called gold standard test. Unfortunately, in clinical practice such a test is hardly ever available and the doctor has to combine results of several diagnostic tests, being aware of their different values. The value of a diagnostic test is dependent on its validity and its reproducibility.[4]

The symptoms cause the patients' search for medical care. Therefore, diagnosing BOO starts with a reliable assessment of symptoms. Several symptom scores have been developed and validated, of which the International Prostate Symptom Score (IPSS) is the most popular. As LUTS do not correlate well to BOO, however, more objective diagnos-

tic tools are used. Uroflowmetry is a rough method to estimate BOO, by measuring the free flow rate and in particular the maximum flow rate (Qmax). Although this cheap and simple test can provide valuable information, the disadvantages of it are: the Qmax is influenced by the voided volume, there is a large variation between various flows of the same patient and it is doubtful whether patients are able to produce representative flows in the hospital flowmeter.[5] Ultrasound measurement of the prostate volume is of importance in deciding the surgical approach of the prostate, but the correlation between the size of the prostate and BOO is poor. In addition, urethrocystoscopy and measurement of post-void residual volume are used in the diagnosis of LUTS. All these parameters, however, are not well related to each other and to BOO.[6-11]

Assessment of men with LUTS: urodynamics

Urodynamic studies determine the response of the lower urinary tract to filling and emptying. The investigation consists of a filling and voiding cystometry and intravesical pressure recording to determine filling sensations, bladder capacity, compliance and to observe the presence of detrusor contractions. During micturition the intravesical pressure and the uroflow are measured simultaneously (pressure-flow study). The relation of pressure and flow can be visualized in a X-Y graph, in which detrusor pressure is plotted against flow rate during voiding. Usually, the detrusor pressure at maximum flow (pdetQmax) is used to prove or rule out BOO, since a high intravesical pressure with a synchronous low flow is the characteristic of BOO. To determine the grade of obstruction, pressure-flow plots can be drawn on the provisional ICS-nomogram (three classes: obstructed, equivocal, unobstructed) or on the Schäfer nomogram (seven classes ranging from unobstructed to severely obstructed).[12]

To study patients with LUTS it is generally accepted that urodynamic studies including pressure-flow analysis are the 'gold standard' in differentiating between BOO and impaired detrusor contractility or detrusor instability. The use of urodynamic studies in the assessment of patients with LUTS reduces the subjective failure of TURP significantly.[13,14] Owing to the invasiveness of the test and the costs, however, the standard use of urodynamic studies in the routine work-up of patients with LUTS remains controversial.[12,14]

Treatments for LUTS

Transurethral resection of the prostate (TURP) is still considered the 'gold standard' treatment for BPH. Nevertheless, the disadvantage of the considerable risk of post-operative morbidity of approximately 18% and even a mortality rate of approximately 0.7% is acknowledged.[15] In addition to TURP and open prostatectomy, the last two decades a large number of new therapeutic modalities have become available, some of which have achieved a definite place in the armamentarium of urologists. The gap between watchful waiting and surgery stimulated the development of these new medical, minimal invasive and surgical therapies that aim at diminished morbidity. The co-morbidity of the patient, which is frequently present in the population presenting with LUTS and fear of surgery or anaesthesia may be other arguments to decide to minimal or non-invasive therapies.

Surgical alternatives for TURP are vaporization or laser techniques, which destroy prostatic tissue without significant bleeding. Other minimal invasive techniques, such as microwave thermotherapy of the prostate, use heat to relieve prostatic obstruction. The advantages of these techniques are: no need of anaesthesia, a low percentage of serious complications, and an outpatient setting.

Pharmacotherapy can influence both mechanisms by which BPH produces BOO. First, prostatic size can be reduced via a hormonal mechanism. The enzyme 5-alpha-reductase enables the transformation of testosterone into dihydrotestosterone (DHT), which stimulates prostate growth. A pharmacologic inhibition of 5-alpha-reductase can achieve reduction of prostate size. Second, the factor of obstruction that is caused by prostatic smooth muscle tone can be diminished by blockade of sympathetic adrenergic nerves. Several pharmacologic agents are available that block alpha-1-adrenoceptors in the prostate and bladder neck.

Evaluation of treatment effect

Since symptoms result in the patient's consultation of a physician, the evaluation of a treatment in an individual patient should start with an assessment of a change in symptoms. Dependent on the mode of action of a particular treatment, other more objective evaluation tools can be used. For example, if a treatment aims at reducing prostatic size, the reduction can be measured using transrectal ultrasound.

The evaluation of a new therapeutic modality for LUTS should include investigations that delineate the different aspects of the pathophysiology of the lower urinary tract, attempting to define the mechanism of action of the particular treatment, but also to acquire insight in the pathophysiology of BPH. Therefore, it seems logical to include urodynamic studies in the evaluation of new treatment modalities for patients with LUTS, besides other evaluation tools. If urodynamic studies are the best tool to establish BOO, one can suppose that they are also the best means to evaluate the effect of a specific treatment that aims at a reduction of BOO.

LUTS and the bladder wall

As LUTS are neither disease-specific to BPH nor characteristic of BOO, other parts of the lower urinary tract may be involved in the pathogenesis of LUTS. In men with LUTS changes of the bladder, such as trabeculation, are frequently visible during urethrocystoscopy. The condition of the bladder may on itself cause LUTS or may be influenced by BOO and play a role in LUTS suggestive of BOO. Furthermore, if urodynamics appear to be not such a reliable 'gold standard' to prove BOO as we assumed, another diagnostic tool for men with LUTS may be useful.

Animal studies have shown an association between BOO and morphologic changes in the bladder wall. If such a relation can be found in humans too, bladder wall histology may be useful in the assessment of men with LUTS. Up till now, however, a clear association between BOO in men and bladder wall histology has not been established and it has been suggested that histologic changes in the bladder wall of elderly men should be more attributed to the effects of aging than to BOO.[16] The indistictness on this subject needs clarification and lead to one of the studies presented in this thesis.

Rationale

Extensive research has already been performed on urodynamic studies and many reports on urodynamics can be found in literature. Most of these reports describe theoretical and technical aspects of urodynamic studies. In theory, urodynamic studies precisely describe the filling and voiding pattern of a patient with LUTS and provide an exact degree of obstruction. Little attention has yet been paid, however, to the clinical

value of urodynamic studies in the assessment and treatment of men with LUTS. The assumptions regarding urodynamics in clinical practice, such as the reliability and the bother to the patient, are not based on solid research. Neither has the value of urodynamics in medical treatment been thoroughly studied. It is not known whether urodynamics are the appropriate means to measure treatment effect or to predict treatment effect in an individual patient by a pre-treatment assessment of BOO. Furthermore, until now there has not been developed a better or more reliable assessment tool in the diagnosis of LUTS than urodynamics. If the condition of the bladder would also be taken into consideration in the assessment of a patient with LUTS, it is likely that a more reliable diagnosis can be made. In this thesis, an attempt is made to provide more understanding on the issues mentioned above.

Outline of the thesis

Urodynamic studies play a role in the assessment and follow-up of men with LUTS. To what extent one may rely on the results of these studies, however, needs further evaluation. In part I several aspects of urodynamic studies are considered. First, a patient evaluation on the tolerability of urodynamic studies is presented, including objective and subjective evaluation parameters. Furthermore, the results of two studies on the reproducibility of urodynamic studies are presented. The reproducibility of two urodynamic studies performed at two different occasions was determined and the intra- & inter-investigator variation in the analysis of 200 pressure-flow studies were analyzed.

Part II describes the urodynamic effects of alpha-adrenoceptor antagonists, in short alpha-blockers, in men treated for LUTS. First, all available clinical trials on the urodynamic effects of alpha-blockers are reviewed. Second, a retrospective study is presented on the urodynamic effects in 163 patients treated for LUTS with alfuzosin, tamsulosin, or terazosin. Urodynamic studies were performed at baseline and six months treatment. Third, a study is presented that assessed the risk of retreatment and prognostic parameters regarding this risk in 316 patients treated with an alpha-blocker.

To gain insight in the pathogenesis of LUTS and BOO, a light-microscopic study on the bladder wall of patients with LUTS was performed. Part III deals with the association between BOO and histopathologic features in the bladder wall. In 63 patients with LUTS pre-treatment urodynamic parameters were correlated with histopathologic features of bladder biopsies, obtained during prostate surgery.

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PART I

CONSIDERATIONS REGARDING URODYNAMIC STUDIES

Chapter 1

Tolerability of urodynamic studies and flexible urethrocystoscopy

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Objective: To determine the overall tolerability of urodynamic studies, used in the assessment of men with lower urinary tract symptoms (LUTS), by assessing the objective and subjective morbidity experienced during and after urodynamic studies. In addition, the voiding complaints caused by the combination of urodynamic studies with a flexible urethrocystoscopy were assessed.

Methods: One hundred and three men with LUTS received urodynamic studies with flexible urethrocystoscopy. They completed a questionnaire to assess objective and subjective symptoms and degree of bother with emphasis on the urodynamic study. Urine was analyzed and cultured. Seventy-eight patients received another urodynamic study and completed the questionnaire twice.

Results: Data of the first questionnaire showed that more than half of the patients experienced some urge after the urodynamic study and the urethrocystoscopy (56%). Thirty five percent of the patients experienced little and 19% experienced severe voiding discomfort following the combined investigations compared to 24% and 5% respectively following an urodynamic study alone. Three patients (3%) had a symptomatic urinary tract infection. Hematuria, increased voiding frequency, and increased nycturia occurred occasionally. The majority of patients found the urodynamic study less bothersome than expected (64%) and only 9% found it worse than expected. The overall degree of discomfort experienced during and following the urodynamic study combined with a urethrocystoscopy was low. After a second urodynamic study, this degree was even lower.

Conclusion: In contrast with earlier results, we found that in our clinic urodynamic investigations are associated with a low percentage of urinary tract infection and low objective and subjective morbidity. The combination of an urodynamic study with a flexible urethrocystoscopy does not cause significant additional voiding complaints. Most patients experience urodynamic studies as tolerable and not very bothersome.

Introduction

LOWER URINARY TRACT SYMPTOMS (LUTS) are common among elderly men.[1] The majority of these patients have symptoms that are caused by benign prostatic obstruction, whereas up to one third of the symptoms have other causes of LUTS, such as detrusor instability or detrusor underactivity.[2]

It is generally accepted that urodynamic studies, including pressure-flow analysis, are the 'gold standard' in making the diagnosis of bladder outlet obstruction.[3,4] Combinations of symptom scores, uroflowmetry, ultrasound measurement of the prostate volume, urethrocystoscopy and post-void residual volume measurements have been unable to accurately identify the precise pathology behind LUTS.[5-8] Moreover we have learned that treatment outcomes are better when bladder outlet obstruction has been confirmed by urodynamic studies with pressure-flow analysis.[9] Consequently, the ICS-'BPH' study group advises to use such urodynamic studies in the evaluation and treatment decision of the patient presenting with LUTS.[8] Disregarding these considerations, the need for urodynamic studies in the standard work-up of patients with LUTS is still controversial.[2,10,11] Those who are not in favor of the routine use of urodynamic studies argue that they are invasive, costly, time-consuming and bothersome for the patient. Moreover, the success rate following surgery is also high, even though urodynamic documentation of bladder outlet obstruction is not obtained.[10]

These are strong arguments not to perform urodynamic studies on a routine base. But are these arguments valid? Are these studies indeed very bothersome to the patients and to what extent does the invasive character of urodynamic studies cause morbidity? Several studies have been performed addressing the incidence of urinary tract infections following urodynamic studies and the need of antibiotic prophylaxis. Urinary tract infection following urodynamic studies appeared to occur in approximately 2% of the patients, independent of the use of prophylactic antibiotics.[12-14] Apart from the infection rate associated with urodynamic studies, in only a few studies attention has been paid to the morbidity caused by urodynamic studies.[15,16] The objective morbidity (hematuria, fever, urinary tract infection, etc.), but especially the subjective experiences (discomfort, pain, urge, etc.) of the patients have not yet been described profoundly. Only Gonnermann et al. included the acceptance of urodynamics by patients.[17] Benness et al. evaluated the subjective symptoms and embarrassment associated with urodynamic studies in female patients.[18]

To be able to justify the standard use of urodynamic studies in the assessment of patients with LUTS, we should take all aspects of urodynamic studies into account and tolerability is one of those. The aim of the present prospective study was to determine the overall tolerability of urodynamic studies, used in the assessment of patients with LUTS, by evaluating the objective and subjective morbidity and discomfort experienced during and after an urodynamic study. In addition, we assessed the difference in tolerability of a first and a second urodynamic study. Since we usually combine an urodynamic study with a flexible urethrocystoscopy in our standard work-up of patients with LUTS, we also included the tolerability of a urethrocystoscopy in our assessment and analyses.

Methods

One hundred and three consecutive patients, recruited from our Outpatient Department, were included in this study. Patients are referred to the Outpatient Department by general practitioners or urologists from other hospitals. All patients presenting with LUTS received a standard diagnostic work-up including a free urinary flow, an urodynamic study, a transrectal ultrasound of the prostate and a urethrocystoscopy. The urethrocystoscopy was performed using a flexible cystoscope (15.5F, Storz, Germany). To exclude any influence of these investigations on the urodynamic study, work-up was performed in this order. All patients received written information on the urodynamic study.

Each urodynamic study was performed under the same conditions. Before placing the catheters, an instillation gel, containing lidocaine and antibacterial agents (Farco Pharma, Germany), was used. An 8F catheter mounted with a micro-tip sensor (MTC, Dräger, Germany), used for intra vesical filling and recording intra vesical pressures was placed under sterile conditions. An 8F micro-tip catheter was used for recording rectal pressures. During cystometry the bladder was filled with physiologic saline of 20°C at a filling rate of 50 ml/min. Antibiotic prophylaxis was not used routinely. Only few patients who were known with repeated urinary tract infections or a post-void residual volume of more than 100 ml received antibiotics. One week after the urodynamic study a urine specimen was obtained for chemical urinalysis and for urine culture to exclude urinary tract infection.

After the urodynamic study and the urethrocystoscopy were performed, patients living in the neighbourhood of our clinic, were asked to participate in a study, determining the reproducibility of urodynamic studies. This study is the subject of chapter 2.

Within the framework of this study, from November 1997 through June 1998, 103 male patients with LUTS, who underwent an urodynamic study, completed a questionnaire a week after the urodynamic study, independent from their agreement to participate in the reproducibility study. The questionnaire was designed to assess subjective symptoms, including urge, frequency, pain and dysuria (six questions) and objective symptoms, like hematuria, fever and incontinence (three questions) and degree of bother (three questions). In addition, the questionnaire contained a validated visual analog scale (VAS), to measure the degree of overall discomfort experienced during the urodynamic study and in the week after the urodynamic study (with a range of zero to ten, with zero indicating no discomfort and ten indicating extreme discomfort).[19] The questionnaire emphasized the tolerability of the urodynamic study and not the tolerability of the urethrocystoscopy. Patients who participated in the reproducibility study, underwent a second urodynamic study within a period of one to four weeks. Besides the urodynamic study, no other investigation was performed in the second session. One week after the second urodynamic study they completed the same questionnaire for a second time. Not all patients agreed to undergo a second urodynamic study and not all patients, who underwent a second urodynamic study, returned the questionnaire. Therefore, the numbers of patients that completed the second questionnaire was smaller than the number completing the first. There was no significant difference in tolerability of the urodynamic study between those two groups. Seventy-eight patients completed the questionnaire twice. The difference in tolerability of the urodynamic study, quantified by VAS, between both groups was tested with the Wilcoxon rank sum test, and was not statistically significant.

Results

Of 103 patients, nine (9%) had a positive urine culture after the urodynamic investigation combined with an urethrocystoscopy. As expected, in one urine specimen of the only patient with a supra pubic catheter several bacteria were cultured. Three patients (3% of all patients) having a positive urine culture had symptoms indicating a possible urinary tract infection. Two (2% of all patients) of those had fever of whom one also had a common cold. One of them visited his general practitioner because of his urinary

tract infection symptoms and received antibiotics. None of the patients with a positive urine culture had a history of repeated urinary tract infections or had post-void residual volumes. Consequently, these patients had not received antibiotic prophylaxis.

The frequencies of micturition complaints during and the week after the investigations are summarized in table 1. The symptoms urge and pain are mentioned most frequently in the first as well as in the second questionnaire. More than half of the patients experienced at least some urge after the urodynamic investigation (with or without urethrocystoscopy).

Table 1 Symptoms experienced during and after urodynamic study (UDS) number (%)

		First UDS (n = 103)	Second UDS (n = 78)
Voiding frequency	less than usual	15 (14.9)	14 (17.9)
	as usual	70 (69.3)	47 (60.3)
	more than usual	16 (15.8)	17 (21.8)
Nycturia	less than usual	21 (21.0)	16 (20.8)
	as usual	74 (74.0)	49 (63.6)
	more than usual	5 (5.0)	12 (15.6)
Change in voiding	no change	73 (72.3)	52 (66.7)
	easier	22 (21.8)	23 (29.5)
	more difficult	6 (5.9)	3 (3.8)
Urge	no	44 (44.0)	34 (44.2)
	little	49 (49.0)	38 (49.3)
	severe	7 (7.0)	5 (6.5)
Pain	no	47 (46.1)	55 (70.5)
	little	36 (35.3)	19 (24.4)
	severe	19 (18.6)	4 (5.1)
Hematuria	no	82 (80.4)	72 (92.3)
	little	18 (17.6)	5 (6.4)
	severe	2 (2.0)	1 (1.3)

Not all numbers count up to the total number of patients due to missing data.

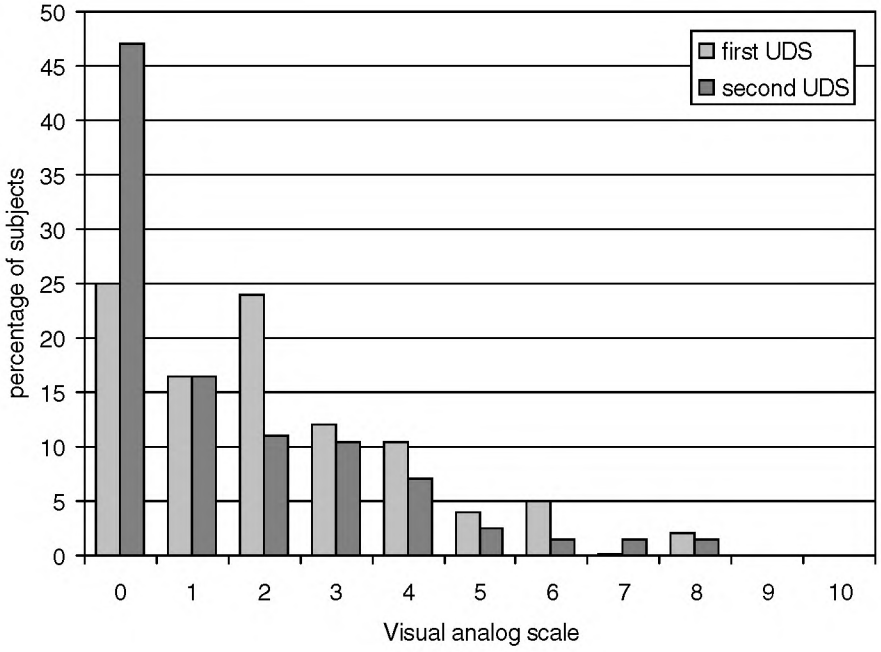

Figure 1 Distribution of visual analog scale (VAS) as a measure for discomfort experienced during and the week after urodynamic studies.

From all the questions regarding the degree of bother and discomfort patients experienced during and after the urodynamic study, it appeared that for most patients the investigation was 'less bothersome than they had expected' (64%). Of all patients, 27% rated the investigation 'as expected', while 9% thought the investigation was 'worse than expected'. Of 32 patients (31%), who considered the urodynamic study 'quite bothersome', 26 patients found the transurethral introduction of the catheter most unpleasant. Only one patient considered the urodynamic study 'very bothersome'. Both the results of the questions regarding the degree of bother experienced and the visual analog scale (VAS), in which patients describe the overall discomfort experienced during and after the urodynamic study, show that patients experience the second urodynamic study as less bothersome than the first one (figure 1). The mean score on the VAS (range 0.0 to 10.0) was 2.7 (SD = 1.9) after the first urodynamic study. After the second urodynamic study, the mean score was 2.0 (SD = 2.0).

Discussion

The percentages of positive urine culture and clinically significant urinary tract infection that we found are in accordance with the percentages of about 10% and 2%, respectively, reported in literature and are rather low considering the fact that urodynamic studies and urethrocystoscopies are minimal invasive investigations.[13,16]

During the first visit to the Outpatient Department, the urodynamic study was followed by a flexible urethrocystoscopy and a transrectal ultrasound of the prostate. From the questionnaires regarding the first urodynamic study it appeared that patients found it difficult to indicate the degree of bother they experienced due to the urodynamic study apart from the other investigations. To the question what was most bothersome many patients answered that the introduction of the cystoscope was most awkward. The voiding complaints and discomfort patients experienced following the urodynamic study combined with the urethrocystoscopy are probably caused by both investigations. To get a clear picture of the discomfort caused by an urodynamic study itself, we should focus on the second questionnaire, in which the degree of bother during and after the second urodynamic study is described (table 1). Comparison of the results of the first and the second questionnaire reveals that patients experience less pain and hematuria after the second urodynamic study. The frequency of other symptoms did not differ significantly between the first and second urodynamic study.

Of all lower urinary tract symptoms, only the occurrence of urge (56%) and pain (30%) following urodynamic studies was considerable. Given the low percentage of urinary tract infections following urodynamic studies, the symptoms 'urge' and 'pain' do not per se indicate urinary tract infection. This finding corresponds to the results of Carter et al.[16] Presumably dysuria following urodynamic studies has a mechanical and not a bacterial aetiology in most cases. The occurrence of other micturition symptoms is low, which is in contrast with the results of Klingler et al., who concluded that urodynamic studies are associated with considerable complications and morbidity.[15]

It is remarkable that the percentage of patients who report to void less frequently equals the percentage of patients who report to void more frequently than usual. The same is true for the percentages of change in nycturia. The reason that part of the patients void less frequent than usual after an urodynamic study combined with a urethrocystoscopy may be related to the dilating effect of the cystoscope, but it is remarkable that after the second urodynamic study, which was not combined with a urethrocystoscopy, even more patients reported to void easier. In the first and in the

second questionnaire 22% and 30% of the patients, respectively, report to void easier than before the investigation. This improvement may also be explained by a minimal dilating effect of the cystometry catheter, although a placebo effect of the investigation on subjective symptoms is a more probable explanation.

In contrast with the small change in symptoms, the subjective degree of discomfort experienced did decrease considerably. Besides the additional bother due to the urethrocystoscopy performed at the first visit, the decrease may be due to habituation to the investigation. The fact that most patients agreed to participate in the study on reproducibility of urodynamics and to undergo a second urodynamic study also indicates that the investigation was generally well tolerated. This result confirms the high acceptance of urodynamics reported by Gonnermann et al.[17]

Some of the initially investigated patients declined subsequent urodynamic studies and some patients failed to complete the second questionnaire. Some selection bias may therefore be present. Therefore, we also analyzed the decrease in discomfort while restricting the statistical analysis to the patients who underwent two urodynamic studies and completed two questionnaires. The degree of decrease in discomfort did not differ from the preceding analysis. Furthermore, there did not appear to be a difference in VAS-score between the patients who did and the patients who did not consent to subsequent testing after the first urodynamic study. Considering the decrease in discomfort after habituation to the investigation, it is important that patients receive clear information in order to make them acquainted with the investigation in advance.

The results of this study show that the invasive character of urodynamic studies, which is widely used as an argument against the routine use of urodynamics, does not cause unacceptable objective or subjective morbidity. We agree with Elbadawi, who stated that the invasive character on itself is not a realistic argument not to use urodynamics, considering the even more invasive diagnostic procedures, e.g. urethrocystoscopies and biopsies, which are commonplace in urologic practice and other disciplines.[20] Although we did not focus on the tolerability of urethrocystoscopy, we even found acceptable low morbidity for the combination of urodynamic studies and urethrocystoscopy.

In the present study, we did not consider aspects of costs and time. Nevertheless, we conclude that, considering the importance of urodynamic studies in the diagnosis of patients with LUTS and the low subjective and objective morbidity, there is no argument against the use of this investigation in the routine assessment of patients presenting with LUTS.

Conclusion

Urodynamic studies with pressure-flow analysis are associated with a relatively low percentage of urinary tract infection, despite the invasive character of the investigation, as was already known from literature. We found that in our clinic urodynamic studies are associated with little subjective and objective morbidity. A combination of urodynamic studies with flexible urethrocystoscopy does not cause significant additional voiding complaints. Urge and pain, however, frequently occurred during the first few days after the investigation. Therefore, patients should be notified that they are likely to experience these symptoms. Finally, most patients experience urodynamic studies as tolerable and little bothersome. The second urodynamic study was better tolerated than the first one. This improvement is probably mainly due to acquaintance with the investigation.

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Chapter 2

Variability of pressure-flow studies

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Objective: To assess the short-term test-retest variability of pressure-flow studies (PFS) in men with lower urinary tract symptoms (LUTS). By choosing a short interval between two consecutive PFS, but notably not performing two tests within a single session, both tests represent the same routine testing procedure.

Methods: Eighty-nine patients with LUTS suggestive of bladder outlet obstruction or detrusor underactivity, who received PFS, were asked to undergo a second urodynamic evaluation within four weeks following the initial test. At both visits, specialized physicians performed the PFS. Obstruction was quantified using the Abrams-Griffiths number (AG-number). Each patient was classified as obstructed, unobstructed or equivocally obstructed according to the International Continence Society nomogram.

Results: No systematic difference was observed in AG-number between the first and the second visit at the group level. There was, however, considerable variation at the individual level. The average within-patient standard deviation was 14 cmH_2O. This finding shows that if a patient's AG-number is 30 at the first visit, his true AG-number can be any value between 30 ± 1.96 * 14 = 3 to 57, due to random variability alone. The average within-patient standard deviation did not differ significantly between subgroups of obstruction and other variates such as patient age, symptom score, prostate volume or residual volume. The variability appeared to increase slightly with an increased interval between visits. Of all patients, 39% changed at least one category of obstruction at the second visit and 3% changed from definitely obstructed to definitely unobstructed or vice versa.

Conclusion: There is a considerable variability in PFS. Therefore, they cannot stand the test of serving as a gold standard to identify bladder outlet obstruction in patients with LUTS.

Introduction

THE MOST EFFECTIVE treatment in men with lower urinary tract symptoms (LUTS) secondary to bladder outlet obstruction (BOO), is removing the infravesical obstruction. Both symptoms and urodynamic effects improve after desobstructive therapy. Approximately one third of men with LUTS do not have BOO.[1] In these cases, detrusor instability or detrusor underactivity is often responsible for the complaints. The pretreatment diagnostic assessment of patients with LUTS therefore aims at establishing a correct probability of the patient being obstructed. Measuring detrusor pressure and urinary flow rate simultaneously enables pressure-flow studies (PFS) to quantify urethral resistance. Although there is yet no consensus on the clinical relevance of precisely grading the amount of urethral resistance, PFS are considered the best objective way to establish the presence or absence of BOO.[2] PFS are also used in the follow-up of treated patients and to compare treatment modalities in clinical trials.

In order to justify the standard use of PFS as a gold standard test, the test-retest variability must be small for practical purposes. Variability of PFS outcomes has been the subject of previous studies.[3-8] The interval between test and retest in these studies, however, has been either too short or too long to draw definite conclusions. A retest within the same session of testing is not representative of the initial test as it does not allow the detrusor muscle to regain strength and stretch receptors in the bladder wall may become less sensitive to filling.[9] Furthermore, factors that may be related to the outcome of PFS are more similar within a single session than between visits. Some examples include the physician carrying out the investigation, the time since the last meal and serum hormone levels. Alternatively, a retest 26 weeks or more after the initial test cannot preclude systematic changes in urethral resistance or detrusor contractility. Therefore, to assess the variability of PFS, we retested men with LUTS within a treatment-free period of four weeks after the initial test, thus preventing important changes in the anatomic condition of the lower urinary tract.

Methods

Patients enrolled in this study visited the Outpatient Department of Urology of the University Medical Centre Nijmegen with LUTS, suggestive of BOO between October 1997 and June 1998. All patients received extensive routine diagnostic assessment in-

cluding PFS. Patients living in the neighborhood of our clinic were informed about the aim of this study and were asked to be retested within four weeks of the initial urodynamic investigation. Patients who were on alpha-blocker therapy or other medication that alters the functions of the lower urinary tract were excluded from the study. Furthermore, patients who experienced severe problems during the initial PFS were not asked to participate.

Each PFS was performed under the same conditions by one of three specialized physicians. Before placing the catheters an instillation gel, containing lidocaine and antibacterial agents (Farco Pharma, Germany), was applied. An 8F catheter mounted with an microtip pressure transducer used for vesical filling and recording intra vesical pressures was placed under sterile conditions (MTC, Dräger, Germany). Abdominal pressure was recorded rectally with an 8F microtip sensor catheter. The pressure sensors were calibrated at atmospheric pressure before induction. During cystometry, the bladder was filled with saline of 20°C at a filling speed of 50 ml/min with the patient in supine position. Filling was stopped when the patient expressed a strong urge to void and micturition was allowed in standing position. During micturition flow parameters, intravesical and abdominal pressures are recorded simultaneously. Flow rates are recorded by a rotating disk flowmeter (Dantec Urodyn flowmeter, Dantec, Skovlunde, Denmark). All data are digitally stored and analyzed with an urodynamic analysis program, which was developed at our department (UIC/BME Research centre, Department of Urology, University Medical Centre Nijmegen, the Netherlands). A physician visually inspected all computer results, with correction for pressure or flow artefacts. PFS were repeated if the results were of poor technical quality. To quantify obstruction, the Abrams-Griffiths number (AG-number) was calculated according to AG-number = pdetQmax - 2 * Qmax. In this formula, Qmax is the maximum flow rate and pdetQmax is the detrusor pressure at maximum flow rate. The International Continence Society (ICS) nomogram was used to classify patients.[10] AG-numbers above 40 indicate obstruction, AG-numbers between 20 and 40 are equivocal, and AG-numbers below 20 suggest the absence of obstruction. The analyses were repeated using the urethral resistance factor URA instead of the AG-number. URA values above 29 cmH_2O represent obstruction.[11] The results of both PFS sessions were evaluated independently.

The skewness and kurtosis of AG-number and URA were calculated to indicate if a normal distribution could be assumed for these variates. If these parameters are between -1 to +1, it is reasonable to assume a normal distribution. The presence of systematic change in urethral resistance was evaluated by calculating the mean difference in AG-

number between the patients' first and second visit, and the null hypothesis of no difference was tested with a paired sample *t*-test.

In general, repeated measurements in the same patient will vary around the true mean value, because of measurement error and biologic variability.[12] To quantify the variability between consecutive measurements, the standard deviation (SD) of repeated measurements on the same subject is calculated. The individual SDs (or actually their variances) can be averaged, if we assume that the SD is the same for all subjects. To test this assumption, we assessed whether the variability was proportional to the size of the measurement by plotting the individual SDs against their associated mean values and calculated the coefficient of regression. In addition, the relation between the individual SDs and age, prostate volume, Qmax, voided volume, post-void residual urine, IPSS, quality of life and the period between visits was assessed using regression analysis. The average SD is also called the within-subject SD, and it can be used to calculate a confidence interval around the estimated true mean of each patient. For instance, if the average within-patient SD is 4 and the AG-number determined with PFS of a particular patient is 30, his true AG-number can be any value between $30 \pm 1.96 * 4 = 22$ to 38, due to random variability alone. The coefficient 1.96 originates from the characteristic property of the normal distribution that 95% of all of its observations fall within a range of ±1.96 SD from the mean. To describe the clinical relevance of the variability in PFS results, the percentage of patients that moved from one category of obstruction to another was determined.

Results

Eighty-nine patients were included in this study. Table 1 shows a summary of the patient characteristics. All patients were retested within four weeks of the first visit. Table 2 shows the characteristics of both pressure-flow sessions for all patients. AG-number and URA were approximately normally distributed and no statistically significant difference was observed in filling and voiding variates. At the first visit, 33% of the patients was unobstructed, 29% was obstructed, and the remainder of 38% had equivocal results. The corresponding percentages at the second visit were 40%, 26% and 34%. These differences were not statistically significant ($\chi^2 = 1.2$; $p = 0.55$). In conclusion, there is no evidence of a systematic change between both visits.

Table 1 Summary of clinical parameters

	Mean	Standard deviation	Centiles		
			2.5^{th}	50^{th}	97.5^{th}
Age (years)	65	8	48	65	79
IPSS (0-35)	15	8	1	14	31
Quality of life (0-6)	3	1	0	3	6
Prostate volume (ml)	36	17	15	32	83
Qmax (free flow) (ml/s)	13	7	4	12	30
Voided volume (free flow) (ml)	248	144	67	229	622
Post void residual urine (free flow) (ml)	51	86	0	10	280
Test-retest interval (days)	14	5	6	13	25

IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate

Table 2 Results of pressure flow studies

	First visit		Second visit		P-value	Average within patient SD
	Mean	SD	Mean	SD		
Cystometric capacity (ml)	451	140	438	140	0.25	66
Qmax (ml/s)	9	5	9	5	0.71	2
pdetQmax (cmH_2O)	45	19	45	20	0.70	12
Abram-Griffiths-number (cmH_2O)	28	26	28	25	0.81	14
URA (cmH_2O)	28	14	28	14	0.82	7

SD, standard deviation; Qmax, maximum urinary flow rate; pdetQmax, detrusor pressure at maximum flow rate
P-value testing the null hypothesis of no difference in mean values between visit one and visit two.

Table 3 Number (%) of patients per obstruction category according to the International Continence Society nomogram at the first and second visit

Result at first visit	Result at second visit		
	Unobstructed	Equivocal	Obstructed
Unobstructed	21 (72)	7 (24)	1 (4)
Equivocal	13 (38)	16 (47)	5 (15)
Obstructed	2 (8)	7 (27)	17 (65)

Percentages indicate the proportion of patients in each category at the second visit conditional on the result at the first visit

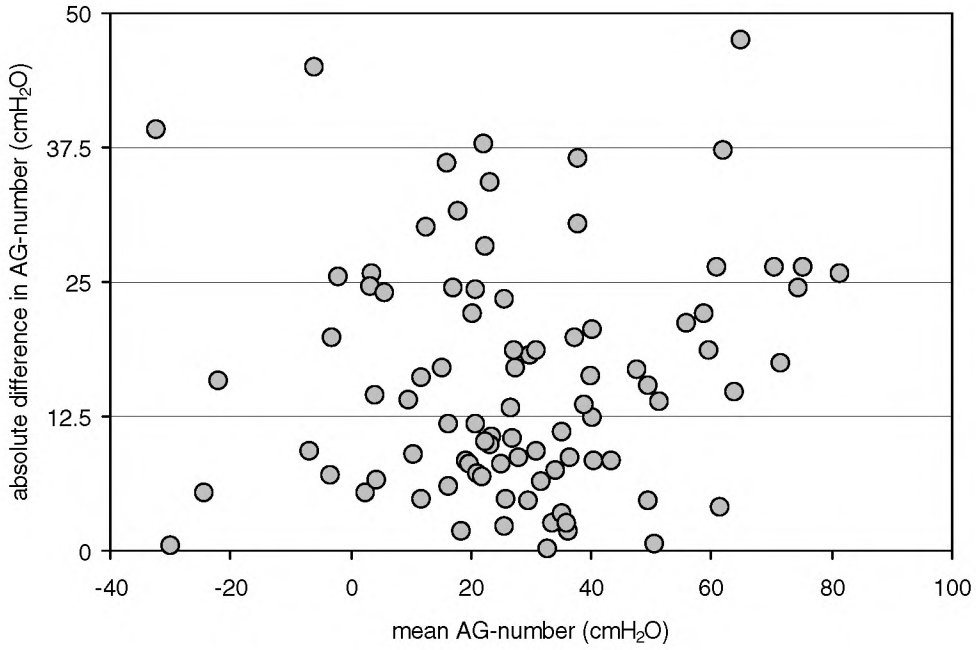

Figure 1 Individual absolute differences in AG-number plotted against the associated mean

Figure 1 plots the individual difference in AG-number between visit one and visit two against the associated average AG-numbers. This figure shows that the spread between both AG-numbers ranges between -50 and 50 cmH_2O and does not depend on the (average) size of the measurement. Thus, there is no evidence that the error depends on the grade of obstruction. Furthermore, no significant relation was detected between the individual spread in AG-number and any other clinical variate, other than a weak relation with the time between visits (results not shown). The average within-patient SD was 14 cmH_2O (95% confidence interval (CI): 12 - 16). This means that the difference between a patient's measured and true AG-number may be as large as 1.96 * 14 = 27 cmH_2O due to random variability alone. Thus, if a patient's AG-number is 30 at the first visit, his true value can be anywhere between 3 and 57. The average SD in pdetQmax was 12 cmH_2O, and in Qmax 2 ml/s. The average SD in URA was 7 cmH_2O, which shows that a patient's true URA may deviate 14 cmH_2O from the URA value determined at a single visit. Based on the ICS provisional nomogram, 39% of the patients changed at least one category of obstruction and 3% changed from definitely obstructed to definitely unobstructed or vice versa (figure 2 and table 3). The majority of changers had equivocal results at the first visit. Based on Schäfer's classification of obstruction, 63% of the patients changed at least one category, and 11% changed two or more categories.[27]

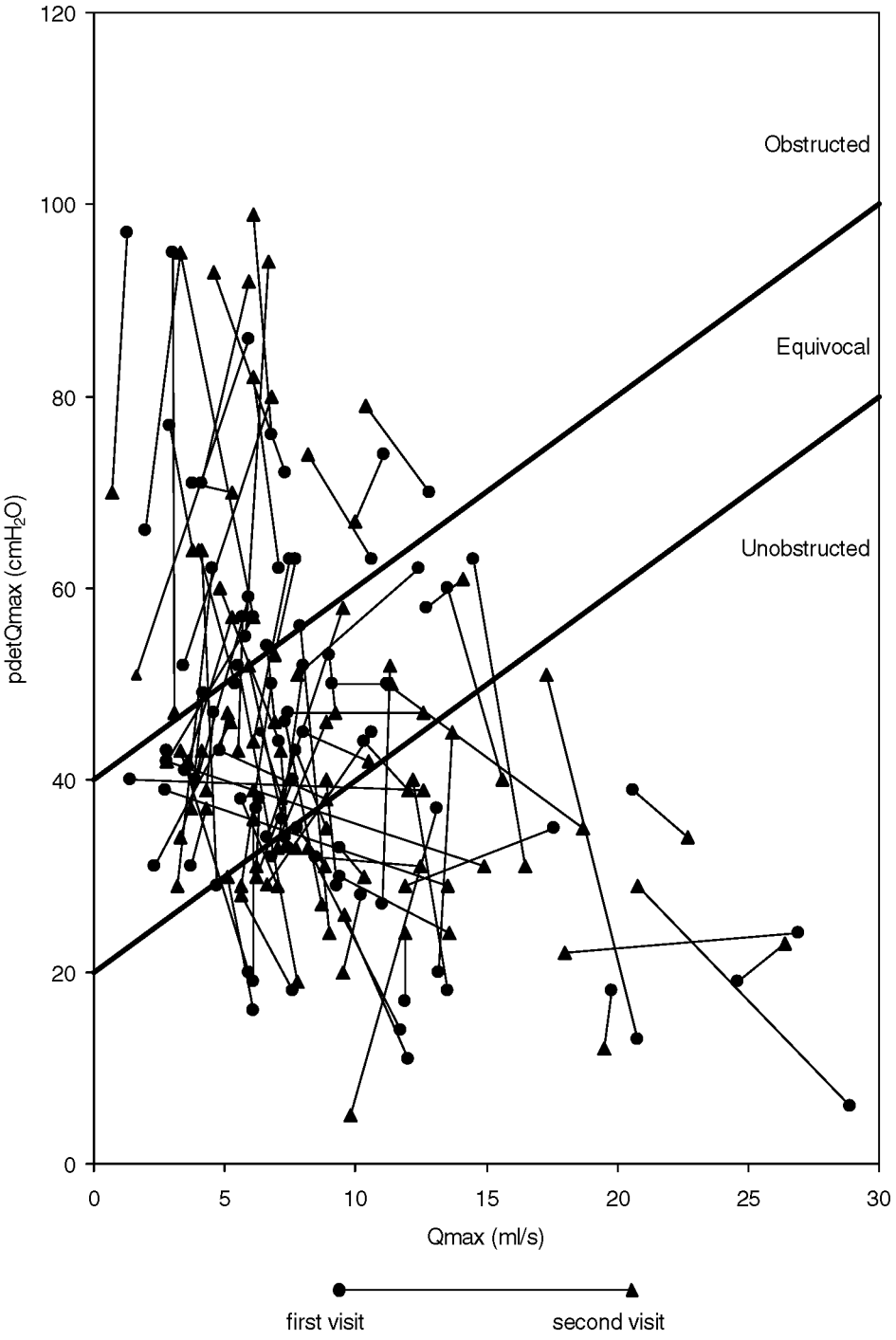

Figure 2 Change in pressure-flow study result plotted on the International Continence Society provisional nomogram

Discussion

Pressure flow studies are considered the gold standard test in the pre-treatment assessment of men with LUTS and are often used to evaluate the objective response to treatment. Standard use of PFS, however, is not commonly accepted. Those who oppose standard use claim that its additional value to identify obstruction does not compensate the associated complications, physician time and expenses.[2] In a previous report we showed that, contrary to common belief, the morbidity associated with PFS is relatively low.[13] In the present study, we evaluated the variability of PFS outcomes. The within-patient SD in AG-number of 14 cmH_2O shows that a considerable deviation of approximately 27 cmH_2O may exist between the observed and the true value. This variability is also reflected in the 39% of patients moving between categories of obstruction of the ICS nomogram between visits. As AG-number is determined by pdetQmax and Qmax, also its variance is determined by the variances of Qmax and pdetQmax*. The variability in AG-number was influenced more by variability in pressure than by variability in flow.

Variability in test results can be caused by biologic variability and by measurement error. It is difficult to distinguish both sources of variability. Measurement error is the extent to which a test yields identical results at multiple occasions in the absence of a true change. Biologic variability can only be assessed accurately if the measurement error is known.

Technical problems may cause measurement error. It is of great importance to exclude PFS with poor technical quality and have them repeated. For instance, pressing the micro-tip catheters against the bladder or rectum wall induces irregularities in pressure measurement. Thus being more prone to artifacts, this type of catheters may also increase the intra-individual variability compared to fluid filled catheters. In order to test the latter hypothesis, the study must be repeated with balloon catheters. Similarly, transurethral pressure measurement may be different from a suprapubic method.

Measurement error may be due to difficulties reading PFS recordings. There may be more than one potential Qmax value, with different corresponding detrusor pressures. Furthermore, the methods used by computer programs to exclude artifactual high ini-

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* The variance in AG-number is equal to $\sigma^2_{AG} = \sigma^2_{p_{det}Q_{max}} + 4*\sigma^2_{Q_{max}} - 4*\text{covariance}(p_{det\,Q_{max}}, Q_{max})$, with σ^2 indicating the variance.

tial flow rates or sharply peaking flow rates and detrusor pressures are not always adequate nor is there consensus on manual artifact correction. Nevertheless, Tammela and co-workers have recently reported excellent agreement between the pressure-flow readings of various investigators compared to a blinded central reader.[14]

The models used to estimate urethral resistance all simplify reality. Although likely to be useful for clinical purposes, modeling makes an obstructive index subject to variation. It has been suggested that various methods of analysis score differently on reproducibility.[15] When comparing their reproducibility, it is important to take the scale at which obstruction parameters are measured into account rather than the respective mean values.

In our study, the biologic variability in grade of the obstruction was only affected by random fluctuations, since we reassessed patients within four weeks of the initial test, but notably not within the same session. This time frame is in accordance with most questionnaires assessing urinary symptoms, which also inquire about symptoms experienced during the previous month. A four-week period is likely to exclude important changes in the anatomic condition of the lower urinary tract. In addition, systematic changes and similarities in the test environment resulting from performing two tests in a single session were prevented, although we had to repeat voidings in the same session due to poor technical quality in five patients. While assuring PFS of high quality, these retests may have influenced our results.

The variation in test results appeared to increase slightly if the interval between visits was longer. This finding suggests that some factors influencing PFS outcome change over relatively short periods of days or weeks. Fluctuations in PFS outcome may be caused by dynamic changes in prostatic smooth muscle tone and bladder response to rapidly changing neurologic stimuli. Ghoniem further suggested the presence or absence of residual urine and the individual variability in responding to the test environment to contribute to variable urodynamics.[9] Possibly, patients were more relaxed at the second visit as they were already familiar with the testing procedure, preventing inhibitory sphincter reflexes. Circadian changes, as have been described for free uroflowmetry, may also explain part of the variability in PFS outcomes. Our study was conducted to describe the total variability present in everyday urologic practice and not to assess possible causes of variation. Further investigations may help to identify variance components, and possibly to account for these components in decreasing PFS variability.

In a previous study from our department, Rosier and coworkers studied the variability of pressure flow variates in two sequential voidings in a single session.[6] In agreement to our results, individual differences between the two voidings larger than one Schäfer class of obstruction were found in less than 20% of the patients. By performing test and retest within a single session, however, the testing environment will be more similar, and some sources of variability will be eliminated. Moreover, systematic changes in the sensitivity of the stretch receptors in the bladder wall and the contraction strength of the detrusor muscle may occur.

Witjes et al. assessed the variability of PFS outcome after a treatment free interval of 26 weeks.[8] Because of prostatic growth, an increase in urethral resistance can be expected during this period. There was indeed some evidence of systematic changes in urethral resistance within subgroups of obstruction, although these can readily be explained by regression to the mean. Forty-four percent of the patients changed at least one ICS category of obstruction; seven percent changed from definitely obstructed to definitely unobstructed or vice versa. In an unpublished re-analysis of these data, the within-patient SD in AG-number was 15 cmH_2O.

Madsen et al. addressed the variability of transurethral PFS outcome in a small sample of seven patients, who were retested within the same session.[5] None was urodynamically unobstructed and all but one were obstructed. One patient changed category at the second measurement. Although insufficient quantitative results are reported for easy comparison, we agree with the conclusions of these authors that a single pressure-flow curve is of limited value due to considerable within-patient variation of the test.

Hansen and coworkers performed two sequential transurethral pressure-flow recordings in a single session in 49 men with LUTS.[4] A systematic variation in various pressure-flow variates was observed but no result was given for an obstructive index like AG-number or URA. Using the Abrams-Griffiths nomogram, 12% of the patients changed category of obstruction at the second voiding.

Van de Beek and colleagues studied variability of PFS outcome in 90 patients with LUTS, but did not state the test-retest interval.[3] A Pearson's correlation coefficient as high as 0.95 for two consecutive URA measurements was reported. The coefficient of correlation, however, has limited value in assessing the reproducibility of individual outcomes. Indeed, the authors found a low reproducibility of Schäfer's classification, as it was observed that in more than 30% of the cases the obstruction class differed between the first and the second voiding.

Many randomized controlled trials (RCTs) have been conducted in the field of BPH with urodynamic outcome variates.[7,16-24] The outcomes in the placebo arm of RCTs can be used to assess the variability of PFS, if an unchanged anatomic condition of the lower urinary tract can be assumed. Bosch provided a review of urodynamic responses to placebo therapy.[25] The interval between test and retest in most of these RCTs is six months or more. In addition, many studies are hampered by a small study size and usually the results are restricted to systematic changes between baseline and follow-up. Few reports mention individual variability in an obstructive index. Although systematic changes between consecutive testings may be absent, that is, at a group level the results of both tests are similar, considerable changes may be present at an individual level. Therefore, it is not sufficient to show a statistically insignificant difference in PFS results between consecutive tests in order to draw reassuring conclusions regarding the variability of test results. Instead, an evaluation of intra-individual changes is needed.

Studies on the variability in PFS outcomes conducted in the placebo arm of a RCT use patients who were scheduled for treatment, whereas PFS in fact are often used to indicate who will need treatment. These RCTs will thus comprise relatively few unobstructive patients. Hence, generalization of the results to a clinical population of men with LUTS is difficult. On the other hand, we evaluated patients with all grades of obstruction and did not observe different variability for obstructed patients compared to unobstructed patients.

Next to variability, correlation of the test results with those of a gold standard test must be assessed when determining the value of a diagnostic test. There is no superior reference to a gold standard test, and such a test is usually assumed to indicate true disease status based on theoretical grounds. When the gold standard test is likely not to be reliable, however, as we think is the case with PFS, more attention should be paid to the prognostic performance of the test.[26] In other words, treatment result should be considered as gold standard and PFS are evaluated for their ability to distinguish patients who will benefit from treatment from those who will not. Some of the nomograms to divide obstructed from unobstructed patients have in fact been determined by analyzing the success of prostatic surgery in samples of men who pre-operatively underwent PFS.[11,27]

It is well known that PFS provide valuable information on the function of the lower urinary tract. We found considerable variation, however, in the results of single PFS. Neither a numerical interpretation of PFS results nor a classification into obstruction categories provides the physician and his patient with an unambiguous test result. In

some urodynamic centres the large variation in PFS results is already recognized, and a second and sometimes third PFS are performed if the first was not conclusive. This practice, however, brings forth other problems: How many PFS are sufficient? Are the results of multiple PFS best summarized by their average obstruction grade, or is the lowest value more informative? What is the most valid, yet practical moment to repeat testing? These questions remain unanswered. Therefore, bearing the variability in mind, we conclude that PFS cannot stand the test of serving as a gold standard to identify BOO in patients with LUTS.

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Chapter 3

Intra- and inter-investigator variation in the analysis of pressure-flow studies

Kortmann BB, Sonke GS, Wijkstra H, Nordling J, Kallestrup E, Holm NR, de la Rosette JJ
Neurourol Urodynam 2000; **19:** 221

Objective: to assess the intra- and inter-investigator variation in the analysis of pressure-flow studies (PFS) that were performed in men with lower urinary tract symptoms.

Methods: Two hospitals were involved in this study. In each hospital, 100 PFS were selected. Six experienced investigators manually analyzed photocopies of printouts of all PFS, including determination of pdetQmax and Qmax. Afterwards all 200 PFS were analyzed again in a different order. For each Qmax and accompanying pdetQmax the AG-number was calculated. With these AG-numbers the intra-investigator standard deviation (SD) and the inter-investigator SD and the intra- and inter-investigator SD combined were calculated.

Results: The intra- and inter-investigator SD combined was 10.7. This result implies that if one investigator analyzes a PFS once and determines an AG-number of 40, another investigator may determine an AG-number between 40 ± 2.77 * 10.7 = 10 - 70, using a 95% confidence interval. The inter-investigator SD was 10.0 and the intra-investigator SD was 3.7.

Conclusion: The reproducibility of the manual analysis of urodynamic studies is moderate due to a considerable intra- and inter- investigator variation. This moderate reproducibility is mostly caused by the substantial intra-investigator variation.

Introduction

LOWER URINARY TRACT SYMPTOMS (LUTS) are common among elderly men. The majority of these patients have symptoms caused by benign prostatic obstruction (BPO), whereas up to one third of them have other causes of LUTS, such as detrusor instability or detrusor underactivity.[1]

Urodynamic studies, including pressure-flow analysis, are considered the 'gold standard' in diagnosing bladder outlet obstruction (BOO).[2,3] The combinations of symptom scores, uroflowmetry, ultrasonography of the prostate, measurements of post-void residual volume and urethrocystoscopy have been unable to predict the precise pathology underlying LUTS or to prove BOO.[4-8] Only pressure-flow studies (PFS) can distinguish between BOO and detrusor problems. Moreover, treatment outcome is better when BOO has previously been confirmed by urodynamic studies with pressure-flow analysis.[9,10]

In clinical practice a variety of diagnostic tools provide information on the patients lower urinary tract and it may be questionable whether a very precise grading of obstruction is always needed in the decision-making in that situation. It is obvious that in a research situation and in the evaluation and comparison of new therapies for patients with LUTS a more accurate establishment of grade of obstruction is of importance. In both situations we need to be aware to what extent we may rely on the test result. Therefore, the reproducibility of it should be known.

In order to justify the standard use of PFS as a 'gold standard' test in the diagnosis and follow-up of individual patients the reproducibility of the test must be high. In addition, with a high reproducibility, smaller numbers of patients need to be included in studies in which PFS are used to evaluate treatment outcome and to compare treatment outcomes with placebo. Studying the reliability of urodynamic studies, we should take into account all the factors that might influence this reliability.

The variation of pressure-flow parameters in repeated cystometry has been subject of several previous studies. In a recent study performed in our clinic we found a moderate intra-patient reproducibility of pressure-flow studies.[11] Better results concerning reproducibility, however, have been reported earlier.[12-16] A distinction should be made between reproducibility within one session of two PFS and reproducibility of PFS two performed at different occasions. In the latter case variation can be the result of real physiologic changes that may occur within weeks, days or even hours or of pathologic changes in the patient's lower urinary tract, which may occur after a longer period of

time. Other factors that may cause variation in PFS are the reliability of the instruments that are used. When these factors have been ruled out, the interpretation of PFS remains a possible cause of variation. Intra-investigator variation is the variation in two or more analyses that were performed by one investigator, of the same PFS. Inter-investigator variation is the variation in analyses that were performed by two or more investigators, who differ in their respective ways of analysis of the same PFS.

The variation of the analysis of measured parameters has been subject of two previous studies of which only abstracts have been published. Donovan et al. presented no quantitative result on variation in analyses. From their study they concluded that there was a minimal variation in readings for detrusor pressure at maximum flow (pdetQmax), and minor differences for minimum voiding detrusor pressure.[17] Kirschner et al. report on the variation of manual analysis and they found a coefficient of variation of 6.6 for Qmax and 5.0 for pdetQmax.[18] These data seem extremely high, but only limited information was presented on their methods. This lack of information makes comparison with our study impossible.

In summary, a previous study performed in our clinic revealed a moderate reproducibility of repeated PFS. Probably, this moderate reproducibility is partly caused by a true intra-patient variation. In the present study the contribution of the intra- and inter-individual variation in the analysis of PFS to the moderate reproducibility of PFS is assessed. This knowledge is of additional importance when comparing results of PFS performed in different urologic centres, as often happens in multi-centre studies.

Methods

PFS were performed at the University Medical Centre Nijmegen, the Netherlands (henceforth named centre one) and at the University Hospital of Copenhagen, Herlev, Denmark (henceforth named centre two). In both centres, each urodynamic study was performed under the same conditions. In Centre one the PFS were performed as follows: Before placing the catheters, an instillation gel, containing lidocaine and antibacterial agents (Farco Pharma, Germany), was used. An 8F catheter mounted with a micro-tip sensor (MTC, Dräger, Germany), used for intra vesical filling and recording of intra vesical pressures, was placed under sterile conditions. An 8F micro-tip catheter was used for recording rectal pressures. Before introduction of the catheters, the pressure sensors were zeroed at atmospheric pressure. During cystometry the bladder was

filled with physiologic saline of 20°C at a filling rate of 50 ml/min. Filling was stopped when the patient expressed a strong urge to void and micturition in standing position was allowed. During micturition, flow and intravesical and abdominal pressures were recorded simultaneously. Flow was measured by a rotating disk flowmeter (Dantec Urodyn flowmeter, Dantec, Skovlunde, Denmark). All data were digitally stored and analyzed with an urodynamic analysis program, which was developed at our department (UIC/BME Research centre, Department of Urology, University Medical Centre Nijmegen, the Netherlands).

In centre two, the procedure of performing urodynamic studies corresponds with the method used in centre one. The bladder was emptied using a 14F LoFric catheter. An 8F double lumen cystometry catheter was used for bladder filling and intravesical pressure recording (MMS), and an 8F balloon catheter used for rectal pressure measurement. External transducers (MMS) were fixed at the upper border of the symphysis pubis. Urodyn 2000 hard- and software were used (MMS).

In each centre, 100 consecutive pre-treatment pressure-flow studies were selected. Six experienced investigators (three from each centre) manually analyzed all 200 pressure-flow studies without knowledge of the computer analysis data. Photocopies of the 200 cystogram prints were distributed to the six investigators. The International Continence Society (ICS) standards on the analysis of urodynamics were appended.[19] The manual analysis of the pressure-flow studies consisted of determination of the following parameters on black-and-white print-outs of cystograms and PFS: baselines of the cystograms, maximum flow rate (Qmax) in ml/s, detrusor pressure at maximum flow (pdetQmax) in cmH_2O. After all investigators had returned their analyses, they received the same 200 copies of the cystogram prints, but in a different order and were asked to perform the analyses in the same way as they did in the first set of prints.

For each Qmax and accompanying pdetQmax the Abrams-Griffiths number (AG-number) was calculated to quantify obstruction on a continuous scale (AG-number = pdetQmax - 2 * Qmax). An AG-number classifies the degree of obstruction as follows: below 20 indicates no obstruction, between 20 and 40 is equivocal and above 40 indicates obstruction.[20] This classification corresponds to the boundaries between obstructed, equivocal and unobstructed on the ICS provisional nomogram.[21] Variations were calculated for AG-number, Qmax and pdetQmax. Following the ICS standard, the AG-number as a parameter of obstruction. As the AG-number is a single parameter for obstruction on a continuous scale, calculation of variation are possible.

Statistical analysis

In general, repeated ratings of a single test result vary around a true mean value. When consecutive patients are repeatedly analyzed by multiple investigators, three factors affect each analysis. First, natural variation exists in the condition of patients' lower urinary tract. Second, different investigators have different interpretations of the same cystogram. Third, variation occurs between multiple analyses of a single cystogram by the same investigator. Traditional analysis of variance is unable to partition the total amount of variation into these various components. Therefore, we used an analysis of variance including random effects to analyze the data. These methods are explained in the appendix. The interpretation of an intra-investigator standard deviation (SD) of x is that if an investigator determines an AG-number of y, the second time the same investigator may determine the AG-number of the same PFS between $y \pm 2.77 * x$. The coefficient 2.77 is equal to $1.96 * \sqrt{2}$, with 1.96 originating from the property of the normal distribution that 95% of all of observations fall within the range of ± 1.96 SD from the mean. The multiplication factor $\sqrt{2}$ accounts for the variances associated with the estimation of AG-number by the first and the second observer.

Results

The patients in centre one were classified as more obstructed by all investigators than those in centre two. The mean AG-number of all the PFS of centre one was 58 (range 52-66) versus a mean AG-number of 49 (range 46-54) in centre two. Table 1 shows the results of the analyses of the six individual investigators. The second time five out of six investigators judged the PFS more obstructed on average compared to the first time. This systematic change is taken into consideration in the statistical analysis.

Table 2 shows the results of the analyses of variance components with random effects. The mean AG-number was 54 cmH_2O with an inter-patient SD of 29. The overall intra-observer SD in AG-number was 10.0 cmH_2O. Thus, if an investigator determines an AG-number of 40, the second time the same investigator may determine an AG-number between $40 \pm 2.77 * 10.0 = 12 - 68$. The intra-investigator SD ranged between 7 and 14 across the investigators and set of analyses. There was no evidence for systematic change in intra-investigator variation. Some investigators analyzed the first set of PFS more consistently (1,3,4,5) while others performed better at the second set (2,6).

Table 1 Results of two times 200 PFS analyses, stratified by observer

	Observer					
	1	2	3	4	5	6
AG-number 1st reading (cmH_2O)	48.6	51.9	50.0	55.1	55.2	57.1
AG-number 2nd reading (cmH_2O)	50.4	51.5	50.2	59.2	55.3	58.9
Mean difference*	-1.8	0.3	-0.2	-4.1	-0.1	-1.8
P-value	0.03	0.64	0.83	0.00	0.88	0.02
Mean absolute individual difference	7.7	4.9	7.2	7.8	5.6	5.2
2.5th - 97th centile	0 - 41	0 - 30	0 - 41	0 - 36	0 - 21	0 - 41

The SD of the combined inter- & intra-investigator variation in AG-number was 10.7. Thus, if one investigator analyzes a PFS once and determines an AG-number of 40, another investigator may determine an AG-number between 40 ± 2.77 * 10.7 = 10 - 70.

The inter-investigator SD was estimated to be 3.7, but was not statistically different from zero (p = 0.12). Thus, given the considerable intra-investigator variation, the investigators are mutual relatively consistent. Nevertheless, the inter-investigator SD of 4 means that if one investigator determines a mean AG-number of a PFS of 40, a second investigator may determine a mean AG-number of the same PFS between 40 ± 2.77 * 3.7 = 30 - 50, using a 95% CI. The inter-investigator SD in AG-numbers was comparable at both sets of analyses.

As the calculation of the AG-number is based on Qmax and pdetQmax, the variance in AG-number depends on the variation in Qmax and the variation in pdetQmax*. The intra- and inter-investigator SDs in Qmax was 1 ml/s and 0 ml/s respectively (rounded to the nearest integer). The corresponding figures for pdetQmax were 10 cmH_2O and 3 cmH_2O. These figures show that the variation of pdetQmax has more influence on the variation of the AG-number than the variation of Qmax.

* Variance (AG-number) = Variance (pdetQmax) + 4*Variance (Qmax) - 4*Covariance (pdetQmax, Qmax)

Table 2 Results of analysis of variance with random effects

Description		Estimate	Model term (see appendix)
Overall mean AG-number (cmH2O)		53.6	α
Inter-patient SD (cmH_2O)		29.3	$\sqrt{(\sigma_s)^2}$
Inter- and intra-investigator SD combined		10.7	$\approx \sqrt{((\sigma_b)^2 + (\sigma_\varepsilon)^2)}$
Inter-investigator SD (cmH_2O)		3.7	$\sqrt{(\sigma_b)^2}$
Overall intra-investigator SD (cmH_2O)		10.0	$\sqrt{(\sigma_\varepsilon)^2}$
Intra-investigator SD stratified by investigator (1,2,...,6) and rating (1,2) (cmH_2O)	Investigator 1	(8.8; 11.1)	$\sqrt{\sigma^2_{\varepsilon_{1,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{1,2}}}$
	Investigator 2	(8.8; 8.3)	$\sqrt{\sigma^2_{\varepsilon_{2,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{3,2}}}$
	Investigator 3	(12.7; 14.0)	$\sqrt{\sigma^2_{\varepsilon_{6,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{3,2}}}$
	Investigator 4	(9.1; 10.1)	$\sqrt{\sigma^2_{\varepsilon_{4,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{4,2}}}$
	Investigator 5	(8.1; 10.7)	$\sqrt{\sigma^2_{\varepsilon_{6,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{3,2}}}$
	Investigator 6	(10.0; 7.1)	$\sqrt{\sigma^2_{\varepsilon_{6,1}}}$; $\sqrt{\sigma^2_{\varepsilon_{6,2}}}$

Discussion

From our data it appeared that there is a considerable variation in the manual analysis of PFS. The contribution to this variation of the intra-investigator variation is more than that of the inter-investigator variation. An intra-investigator SD of AG-number of 10 implies that PFS may be analyzed to be obstructed the first time and not obstructed the second time. In clinical practice the decision for desobstructive therapy is not solely dependent on PFS in most cases, but if it is, this intra-investigator variation may have quite some implications for the use of PFS.

The range of the respective intra-investigator SDs for both sets of analyses is large. Therefore, not all investigators are equally consistent at interpreting the PFS and maybe they do not always act at the best of their abilities. In daily practice, the intra-investigator variation may even be more, as it is likely that investigators, who need to perform analyses for research purposes perform better and more consistent than those who perform the analyses during their daily duties.

Theoretically, the inter-investigator SD of four refers to the variation in analysis of PFS without any effect of an intra-investigator variation. In daily practice, however, the intra-investigator variation and the inter-investigator variation always have effect on the variation in analyses simultaneously. Combining the intra- and inter-investigator variation resulted in a SD of 10.7, which is not very different from the intra-investigator SD. The variation in pdetQmax seems to be the greatest cause of the variation in AG-number between investigators. In case of an obstruction with a high pdetQmax and a low Qmax, the influence on the AG-number is more than that of the Qmax anyhow.

We have a complete arsenal of diagnostic tests for patients with LUTS at our disposal, but only urodynamic studies can establish or reject the diagnosis of BOO. Nevertheless, the need for urodynamic studies in the standard work-up of patients with LUTS is still controversial and in the past years we have been able to follow the lively discussion on the pro's and contra's of urodynamics.[1,22,23] Arguments against their routine use, which also have been countered, are invasiveness, costs, consumption of time and bother for the patient. The fact that for diagnosing BOO we have nothing more reliable than pressure-flow studies, however, cannot be disproved.

Presuming that pressure-flow studies are the 'gold standard' in diagnosing BOO, the question rises what we may expect from a 'gold standard'. As there is not a reference test available to provide us the 'truth' about the presence of obstruction, there is no way to establish the diagnostic value of an existing test. It is recommended by the ICS to use the provisional ICS method for definition of obstruction in which urethral resistance is specified by the maximum flow rate and the detrusor pressure at maximum flow rate.[19] These values are classified in three classes of obstruction: obstructed, equivocal and unobstructed. For clinical use, the ICS nomogram is a simple standard method and possibly sufficient for the diagnosis in individual patients with LUTS.

Hansen et al. investigated the short-time reproducibility of pressure-flow studies.[16] In 20 patients they performed four pressure-flow studies in two sessions. Of 20 patients, five patients changed to another obstruction class when comparing the first voiding of

the first session with the first voiding of the second session. The study does not provide information about the exact variation on a continuous scale or the variation of obstruction within an obstruction class. It is not mentioned whether the patients are recruited consecutively or not.

In a recent study performed in our clinic, reproducibility of pressure-flow studies was determined by calculating a within-patient standard deviation in AG-number, which is suggested as measure of reproducibility of continuous measures.[24] We found a moderate reproducibility at an individual level. Almost 40% of the patients changed at least one obstruction class at the second examination.[11] In consequence of different methods and analyses these two studies are not comparable.

Considering which factors may have had an influence on the variation, there appear to be several problems in the interpretation and the analysis of the pressure-flow studies. If, due to any technical disturbance, the baseline of the detrusor pressure does not correspond with the zero on the axis in the beginning, the investigator can lift or lower the graph to zero. In our study this problem occurred in several pressure-flow studies of the ones performed in centre one and in a few of centre two, and it appeared that some investigators felt uncertain about the way to deal with this baseline problem.

Reading of the exact numbers that correspond with the Qmax and pdetQmax in the graph can be difficult especially on indistinct printouts. In the present study we used photocopies of printouts, making exact measurement of especially the detrusor pressure even more difficult. Under normal conditions measures are probably performed more precisely aided by computer readings on screen. The scales on the Y-axis of detrusor pressure and flow are divided in sections of 10 cmH_2O and 10 ml/s respectively, which forces the investigator to estimate the numbers in between the lines.

It can be difficult to determine the Qmax in case of an artifact that causes a peak at the place of the Qmax (figure 1). Another problem rises when there are two points in the flowcurve of approximately similar height that may be the Qmax. The accompanying detrusor pressures can be very different values, causing a variation in degree of obstruction (figure 2).

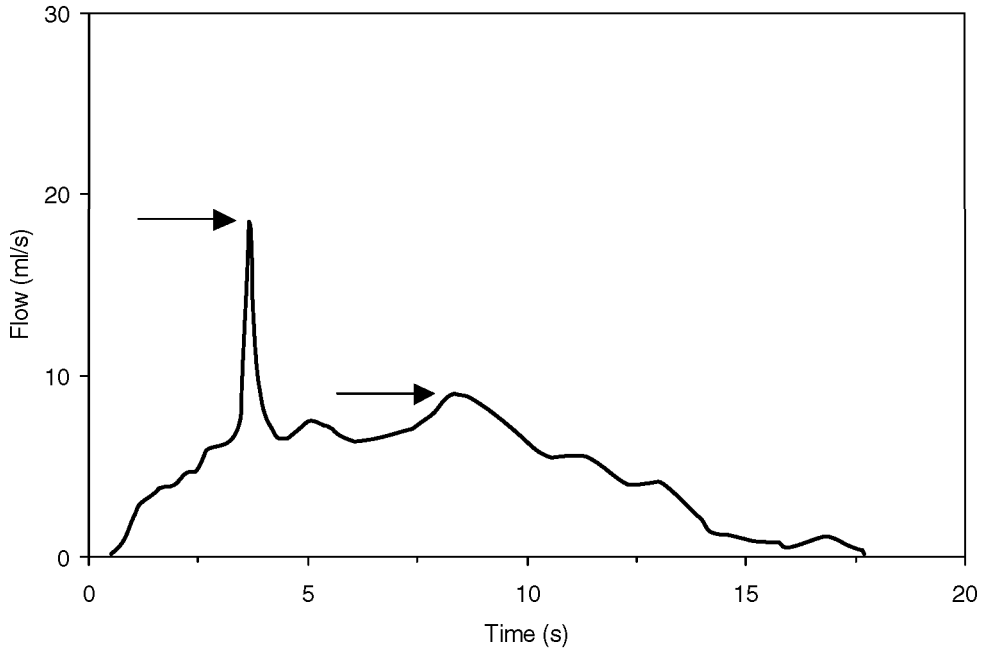

Figure 1 Drawing of uroflowmetry: what is Qmax?

It is a point of discussion whether it is relevant to analyze cystograms manually. In most clinics, the analysis of cystograms is nowadays computerized. Unfortunately, computer data of cystograms are deceptive as cystograms should always be inspected and if necessary corrected for disturbances and artifacts. Although we get the impression of precise computer data, due to the manual correction of these data their precision is determined by the precision of a manual analysis. The ICS-'BPH'-Study Group stated that automated computer analysis today is not acceptable as substitute for careful inspection and manual graphical control. Only 60% of their tracings were without artifacts.[17] Making a more precise agreement on artifact correction, baseline correction etceteras could reduce the variation in the analysis of pressure-flow studies. Some have tried to make international agreements on the method of analyzing and grading obstruction. Still different methods are used, which makes comparison of outcomes more difficult. In addition, urodynamicists should be educated in accordance with international agreements and they should be familiar with urodynamic backgrounds, technical aspects, and possible complications.

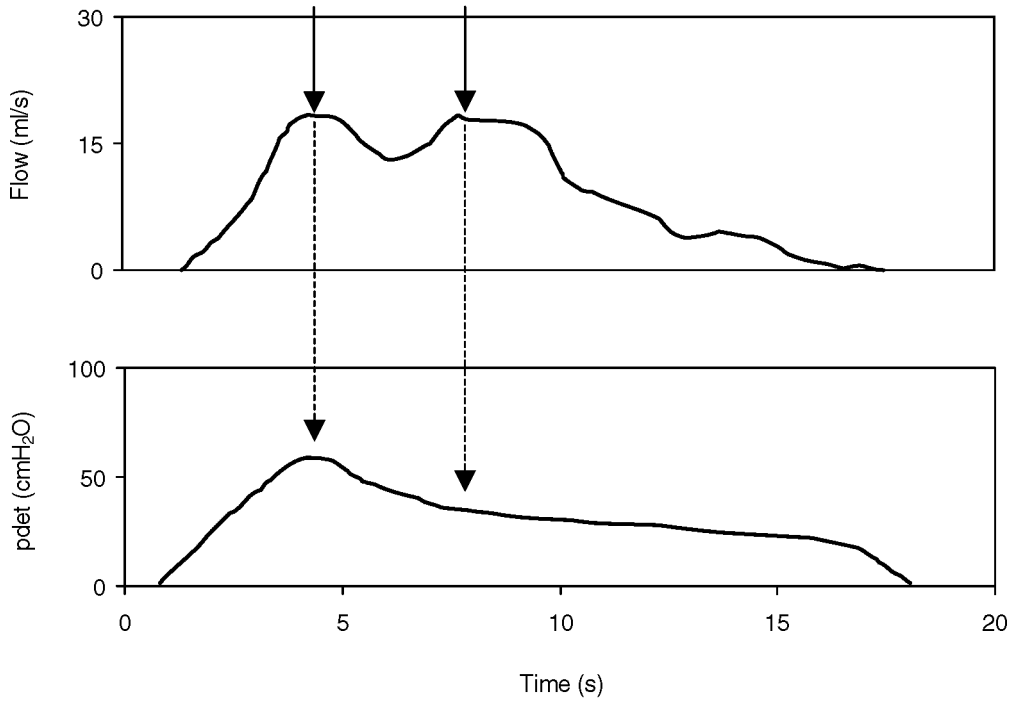

Figure 2 Drawing of pressure-flow study: what is Qmax and what is pdetQmax?

Pressure-flow studies may provide us a lot of information, but we should bear in mind that the reproducibility is moderate and interpretations of various investigators do not necessarily correspond. As pressure-flow studies are not unambiguous, they should be considered complementary to other diagnostic tools for LUTS.

Conclusion

The reproducibility of the manual analysis of urodynamic studies is moderate due to a considerable intra- and inter- investigator variation. The moderate reproducibility is mostly caused by the substantial intra-investigator variation. The variation on itself may be largely responsible for the moderate reproducibility of pressure-flow studies. Other factors that may influence the reproducibility of pressure-flow studies still need to be investigated.

Appendix

The term random effects in the context of analysis of variance is used to denote factors with levels that were not deliberately arranged by the experimenter, but which were sampled from a population of possible levels instead. For example, since we are interested in the effect that various observers have on the quantification of bladder outlet obstruction, we have selected a sample of all observers to estimate the amount of variance in AG-number that is attributable to differences between observers. If we were to repeat the study, it is unlikely that we would select the same observers again. In contrast, if we wanted to know the effect of gender on AG-number, we would always arrange two fixed groups: men and women. The basic distinction between fixed and random effects is that the variation in the levels of random factors is assumed representative of the variation of the whole population of possible levels. The variation in the levels of fixed factors is instead considered to be arbitrarily determined by the experimenter (i.e., the experimenter can make the levels of a fixed factor vary as little or as much as desired). Thus, the variation of a fixed factor cannot be used to estimate its population variance.

In our study, the 200 included patients are regarded as a sample from a large population of patients with LUTS and each patient has an additive or subtractive effect from the mean AG-number of all patients. The variance of these effects represents the natural variability between the patients. Likewise, the six observers are regarded as a sample from a large population of observers, each having an additive or subtractive effect from the mean effect of all observers. The variance of these random observer effects can be interpreted as the inter-observer variability. Finally, the residual variability in the ratings of AG-number after accounting for the variability between patients and variability between observers, can be interpreted as the intra-observer variability. The intra-observer variability may be similar for all observers, but since some observers are more experienced in rating cystograms than others, and moreover, since a second evaluation may be performed less accurately than an initial one we also estimated separate intra-observer variability for each observer and for both ratings of each observers. We assumed that the observations AG_{soh}, the h^{th} (h = 1,2) reading of AG-number of observer o (o = 1,2,3,..,6) on patient s (s = 1,2,3…,200) follow the following model:

$$AG_{soh} = \alpha + b_s + c_o + \varepsilon_{soh}$$

α = the overall mean of all AG_{soh}

b_s = the random effects for the subjects (one random effect for each subject). These can be seen as the biologic differences between the subjects. These random effects are inter-independent and normally distributed with zero mean and variance σ_s^2.

c_o = the random effects for the observers (one random effect for each observer). These can be seen as systematic differences between the observers and are inter-independent and normally distributed with zero mean and variance σ_o^2. This variance can be interpreted as the inter-observer variability.

ε_{soh} = the measurement errors. These can be seen as the random differences between two readings of an observer and are independent and normally distributed with zero mean and variance σ_ε^2. We let $[\sigma^2_{\varepsilon,\mathrm{oh}} \neq \sigma^2_{\mathrm{e,oi}}] \neq [\sigma^2_{\varepsilon,\mathrm{ph}} \neq \sigma^2_{\mathrm{e,pi}}]$ for all $o \neq p$ or $h \neq i$. In other words, σ_ε^2, which can be interpreted as the intra-observer variability, is different for all observers and for both interpretations of each observer.

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PART II

URODYNAMIC EFFECTS OF ALPHA-ADRENOCEPTOR ANTAGONISTS

Chapter 4

Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials

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Objective: Alpha-adrenoceptor blockers are clinically effective, producing a significant relief of symptoms and an increase in urinary flow. The effect of the various alpha-blockers on bladder outlet obstruction, however, is less clear. This article reviews the urodynamic effects of alpha-adrenoceptor blocking agents in patients with LUTS.

Methods: Fifteen studies on alpha-blockers were reviewed of which the pre- and post-treatment evaluation includes pressure-flow studies.

Results: In all but one study administration of an alpha-adrenoceptor blocking agent resulted in a decrease in detrusor pressure at maximum flow or in maximum voiding pressure. In the majority of the studies this decrease is small, although some studies show a decrease in urodynamic obstruction parameters of up to 50%. Patients suffering from LUTS may all benefit from an alpha-blocker, independent from the grade of bladder outlet obstruction. One study even indicated that unobstructed patients respond better to alpha-blockers with respect to improvement in symptoms and Qmax than obstructed patients.

Conclusion: The use of alpha-adrenoceptor blockers results in a decrease in urodynamic obstruction parameters. Obstructed as well as unobstructed patients, however, may benefit from alpha-blockers.

Introduction

THE PREVALENCE OF lower urinary tract symptoms (LUTS) is high in the male population and an increasing number of patients is seeking medical help for their complaints.[1] LUTS, however, are not pathognomonic for benign prostatic hyperplasia (BPH) or bladder outlet obstruction (BOO). Hald clearly illustrated the relation between LUTS, BPH and BOO.[2] Since LUTS are not specific to BPH or BOO, complementary diagnostic tools are necessary to establish or reject the diagnosis of BOO in order to choose an appropriate treatment.

Transurethral resection of the prostate (TURP) is still considered the 'gold standard' treatment for BOO, but the disadvantages of a considerable risk of postoperative morbidity of approximately 18% and even a mortality rate of approximately 0.7% are acknowledged.[3] The gap between watchful waiting and surgery encouraged the development of new therapies, such as medical, minimally invasive and new surgical therapeutic modalities, aiming at a lower morbidity.

With the introduction of alternative treatments, urologists were faced with a more complex patient selection and with the necessity to develop methods to evaluate these treatments and to predict efficacy and durability of treatments. The urologist has a large arsenal of tests at his disposal in the diagnosis of BOO, such as symptom scores, uroflowmetry including measurement of post-void residual volume, measurement of the prostate volume and urethrocystoscopy. The value of these parameters have been documented in numerous studies.[4-10]

To study patients with LUTS it, is generally accepted that urodynamic studies including pressure-flow analysis are the 'gold standard' in differentiating between BOO and impaired detrusor contractility or detrusor instability. Although the standard use of urodynamics in daily clinical practice is controversial, the evaluation of a new therapeutic modality for LUTS should include investigations that delineate the different aspects of the pathophysiology of the lower urinary tract, attempting to define the mechanism of action of the particular treatment, but also to acquire insight in the pathophysiology of BPH. Therefore, it seems logical to include urodynamic studies in the evaluation of new medical treatments, besides other evaluation tools.

In the medical field, two types of pharmaceutical agents have become available: alpha-adrenoceptor-blockers and 5-alpha-reductase inhibitors. Being interested in the indication for and effects of medical treatment, we can ask several questions: Does medical

treatment have any effect on the grade of BOO and if yes, how does the effect on BOO relate to the effect on other clinical parameters such as symptoms and flow? Is medical treatment only effective in patients with BOO, or do patients without BOO also benefit from medication?

Several authors have reviewed the role of alpha-blocking agents in the treatment of BPH. Most studies evaluating medical therapies for LUTS confine the analyses to symptom scores, free uroflowmetry, measurement of residual volume, and assessment of side effects.[11-16] The majority of the existing studies have demonstrated that alpha-blockers are clinically effective, producing an increase in urinary flow and a significant relief of symptoms. Few of the above-mentioned reviewers included urodynamic effects of alpha-blocking agents in their studies.

To answer the aforementioned questions on the role of urodynamic studies in treatment with alpha-adrenoceptor blocking agents, we surveyed the available literature and evaluated all clinical trials in which alpha-blockers were tested with urodynamics including pressure-flow analysis.

Pathophysiology and pharmacotherapy

Preceding research supports the hypothesis that two mechanisms exist by which BPH may cause BOO. The static factor is caused by mechanical compression of the urethra by the bulk of the prostatic adenoma. The alpha-adrenoceptor mediated sympathetic stimulation of the prostatic smooth muscle causes a fluctuating influence on BOO and is therefore called the dynamic factor of BOO and contributes up to 40% to the obstruction.[17]

It has been proven that both mechanisms can be influenced by pharmacotherapy. Considering the role of testosterone in the genesis of BPH, hormones can interfere with the development and maintenance of the adenoma. Treatment with the inhibitor of 5-alpha-reductase, finasteride, which prevents conversion of testosterone to dihydrotestosterone, results in an improvement in symptoms and Qmax with few side effects. The reduction of BOO measured by urodynamic studies is less pronounced.[18-21]

As pointed out above, the dynamic factor of BOO is mediated by alpha-adrenoceptors that are stimulated by noradrenaline. More than 20 years ago Caine et al. performed in vitro experiments that showed a predominance of alpha-1-adrenoceptors in human

prostatic stroma of which the greatest proportion is localized in the prostatic capsule.[22] They also showed a relatively slow response to alpha-adrenergic stimulation in the bladder neck. Later work showed that alpha-2-receptors are mainly localized in the epithelium and blood vessels and confirmed that there is a predominance of alpha-1-receptors in the prostatic stroma.[23]

The first alpha-blocker used for BPH was the combined alpha-1/alpha-2-adrenoceptor antagonist, phenoxybenzamine. Despite its efficacy, the use of it has been abandoned because of a significant incidence of side-effects and evidence of mutagenicity in bacterial and mouse-cell cultures.[24] The first alpha-blocking agents were originally developed for the treatment of hypertension as they also act on the alpha-adrenoceptors in the cardiovascular system, where they cause venodilatation. This mechanism accounts for the side effects of alpha-blockers when used for patients with LUTS. The first alpha-blocker that was originally developed for the treatment of hypertension and was later also used for LUTS, was prazosin, a selective alpha-1-adrenoceptor antagonist. With the recognition of the possibility to use these agents in blocking the sympathetic action in the prostate, attention has turned to the development and therapeutic use of selective alpha-1-andrenoceptor antagonists with reduction of the unintended, usually mild side-effects, such as headache, dizziness, postural symptoms and drowsiness.

While looking for effects of alpha-blockers that are more prostate specific, several alpha-1-adrenoceptor subtypes have been cloned and identified in the prostate. The concept of uroselectivity, however, is complex and pharmacologic uroselectivity does not necessarily correspond with functional/physiologic or clinical uroselectivity.[25-27] The contemporary alpha-blockers, such as alfuzosin, doxazosin, tamsulosin and terazosin, appear to have a very similar therapeutic efficacy, producing a 20-30% increase in Qmax and a significant improvement in patients' symptoms. They have a rapid onset of action and are likely to be effective in many patients within days to weeks. These effects are in contrast with those of 5-alpha-reductase-inhibitors, which take months to show therapeutic result. The subtype selectivity and pharmacokinetics of the various alpha-blockers discriminate between them.

In summary, the contemporary alpha-blockers have proved to be efficacious for both symptoms and urinary flow, with an acceptable rate of usually mild side effects. Nevertheless, the effect of alpha-blockers on BOO is not that clear yet.

Table 1 Summary of study designs

Medication	Nr	References	N	(Final) daily dose	Duration of treatment	Study method
Prazosin	1	Hedlund[28]	20	4 mg	4 weeks	double-blind, placebo-controlled, crossover
	2	Hedlund[29]	8	4 mg	4 weeks	double-blind, placebo-controlled, crossover
	3	Chapple[30]	22	4 mg	12 weeks	double-blind, placebo-controlled
	4	Chapple[31]	34	4 mg	12 weeks	double-blind, placebo-controlled, performed in two centres
	5	Kirby[32]	28	4 mg	4 weeks	double-blind, placebo-controlled
Doxazosin	6	Janknegt[33]	50	1-4 mg	5 weeks	double-blind, placebo-controlled, performed in two centres
	7	Abrams[34] & Chapple[35]	67	4 mg	14 weeks	double-blind, placebo-controlled, performed in two centres
	8	Gerber[36]	44	4 mg	12 weeks	open label
	9	Gerber[37]	17	2-8 mg	15 months	open label
Terazosin	10	Gleason[38]	19	10 mg	3-9 months	open label
	11	Risi[39]	15	5 mg	26 weeks	double-blind, placebo-controlled
	12	Witjes[40]	33	10 mg	26 weeks	open label
Alfuzosin	13	Martorana[42]	50	5 mg	4 weeks	double-blind, placebo-controlled, followed by single-blind
					+8 weeks	open label
Tamsulosin	14	Abrams[44]	35	0.2 mg	4 weeks	double-blind, placebo-controlled
			30	0.4 mg		
			32	0.6 mg		
	15	Miyatake[45]	18	0.2 mg	4 weeks	open label, (Japanese language)

N = number of patients treated with alpha-blocker and with a complete urodynamic follow-up

Table 2 Effects on urodynamic parameters and symptoms of various alpha-blockers

Medication	Nr	Change Qmax (ml/s)	P-value	Change pdetQmax (cmH_2O)	P-value	Change pmaxvoid (cmH_2O)	P-value	Change symptoms
Prazosin	1	2.0[1]	< 0.00	-7.4[3]	ns	-2.1	ns	improvement (obstructive symptoms)
	2	2.0[1]	ns	-13[3]	ns	-6	ns	not described
	3	3.2[2]	ns	-14.7	s	-17.7	s	no significant changes
	4	-0.9[2]	ns			-14.2	ns	no significant changes
		3.2[2]	s			-17.1	s	
	5	4.8[1]	< 0.005			-13	ns	60% of patients improved
Doxazosin	6	2.2[1]	s			-9.1	s	30-60% improvement
	7	2.6[2]	0.09			-4.7	s	30-60% improvement
	8	1.5[2]	0.20	-10.6	0.15			49% improvement (IPSS)
	9	2.1[2]	0.18	-23.5	0.04			36% improvement (IPSS)
Terazosin	10	5.0[2]	0.0007	0	ns			improved stream and emptying
	11	4.0[2]	s			-8.5	ns	45% improvement (Boyarski)
	12	2.3[2]	< 0.01	-13.2	< 0.01			52% improvement (IPSS)
Alfuzosin	13	15.6[2a]	< 0.01	-38.2	< 0.01	-40.1	< 0.01	25% improvement (Boyarski)[a]
		3.7[2b]	< 0.01	-28.9	< 0.01	-25.7	< 0.01	
Tamsulosin	14	1.1[2]	ns	-11.2	ns	-14.6	ns	20% improvement (modified Boyarski)
		2.3[2]	0.03	-26.6	ns	-21.1	ns	29% improvement (modified Boyarski)
		1.8[2]	< 0.05	-18.0	ns	-21.3	ns	28% improvement (modified Boyarski)
	15	mprovemen	ns	decrease	s			significant improvement (IPSS)

1: Qmax during UDS 2: Qmax of free urinary flow 3: Intravesical pressure at Qmax 4: Maximum intravesical voiding pressure
a: alfuzosin group b: placebo-alfuzosin group s: significant ns: not significant

In studies 6 & 7 the pressure-flow data were obtained from a table in the article by Janknegt et al. Considering the number of patients and the results of the study of Chapple et al, we assume that this report concerns the same study as that of Janknegt et al. and Abrams et al. With respect to study nr 13: Since the patients of the first study of Martorana are included in the second, multi-centre study, only the results of the multi-centre study are presented in the tables and figures. Unfortunately in study nr 15 no quantitative value was presented.

Urodynamic effects of alpha-blockers in clinical trials

Starting in 1980, we gathered literature by Medline search, from references in relevant literature, and from personal files. In the available literature we identified 15 studies that evaluated alpha-blockers using urodynamics including pressure-flow analysis.[28-45] There are more articles reporting preliminary results of the same studies, but in this review we only included the most complete reports. We approached pharmaceutical companies of alpha-blockers to find out whether studies had been performed of which the results have not been published, in order to exclude a publication bias. We included both placebo-controlled and open label studies. The designs of these studies are summarized in table 1. In the fourth column, the numbers of patients refer to patients who were treated with an alpha-blocker and with a complete follow-up including pressure-flow studies. Thus, patients who were in the placebo-arm of the study are not included in this number. Study number four was performed in two centres and since the results of the two centres were presented separately, we presented the urodynamic data separately in the tables and graphs.

The major urodynamic and clinical outcome parameters of these studies on alpha-adrenoceptor blockers are summarized in table 2. Some factors complicate comparison of the various studies: In some studies the detrusor pressure at maximum flow (pdetQmax) is used as the parameter of obstruction while in other studies the maximum voiding detrusor pressure (pmaxvoid) is used. Often little or no information is provided on confidence intervals of the effects on obstruction parameters. In table 2 we both presented absolute values and significance as stated in the articles. In all but one study, there is a decrease in urodynamic obstruction parameters ranging from 0 to 38.7 for pdetQmax and from 2.1 to 40.1 for pmaxvoid.

In 1996, Gerber et al. reported a significant subjective benefit of doxazosin and a decrease in pdetQmax.[36] The results of pre-treatment urodynamic evaluation could not predict subjective treatment response and the majority of patients had persistent BOO after treatment with doxazosin. In 1997, the same group reported the results of doxazosin treatment at 15 months.[37] Compared to the values at three months of follow-up, there was a deterioration of subjective symptoms despite continued improvements in Qmax and pdetQmax. Witjes et al. report on the urodynamic effects of terazosin and categorized their patients in responders and non-responders and in an obstruction and a non-obstruction group.[40,41] They found a significant improvement in Qmax and symptom score in both patients with and without BOO. Urodynamic improvement was

seen in patients with BOO, but in patients without obstruction, urodynamic changes were not detected. Patients without obstruction were more likely to improve in Qmax and symptoms, compared with those with obstruction. The three above described studies were not included in the tables due to the problems explained.

Discussion

Almost all studies on the effects of the various alpha-blockers demonstrate an improvement in LUTS and an increase in maximum and/or mean urinary flow. Several reviewers have already extensively discussed these effects. In the studies reviewed here, the improvement in symptoms ranged from 20 to 60%, without a clear difference between the different alpha-blockers studied. In these studies, the increase in Qmax was on average 2.9 ml/s with a range of -0.9 to 5.6 ml/s, with a tendency of a larger improvement in favour of terazosin and alfuzosin (3.8 and 4.6 ml/s respectively). Hitherto, the effect of the various alpha-blockers on outlet obstruction has been studied scarcely. After an extensive search, we could only identify 15 separate studies in which this effect was measured. We found some other publications, but these reports appeared to concern the same studies.

It is difficult to compare the urodynamic effects of the various alpha-blockers. Initially it was planned to perform a formal meta-analysis. Because of too many hindering factors, this analysis was impossible for these studies. There are differences in study designs, inclusion criteria, and the numbers of patients that are enrolled, the duration of treatment and sometimes in the dose of medication. In addition, the number of studies that have been performed differs for each type of alpha-blocker. In five out of 15 studies, a significant decrease in urodynamic parameters of obstruction was found. Statistical significance, however, depends on effect size and study size, both of which are different in all studies.[46] We were not able to demonstrate confidence intervals for the effects on urodynamics, as only a few studies provided standard errors.

One might question the power of the current study, not including a meta-analysis. Obviously there is a need to address the value of urodynamic studies in the assessment and follow-up of patients using medical treatment, but the possibilities to perform an objective, quantitative assessment are limited. Therefore, we are convinced that this analysis contributes to the our knowledge about this issue, as it provides an overview of the only available information on the clinical effect of alpha-blockers on BOO.

In order to present the urodynamic results in the various studies, we plotted the differences between the pdetQmax and/or pmaxvoid before and after treatment (figure 1). It is striking that in all but one study there is a decrease in urodynamic obstruction. The magnitude of this difference is not dependent of study size nor of the significance that was stated in the respective article. As expected, many studies of smaller size tend to show results that are not statistically significant.

In figure 1 the differences in obstruction parameters are stratified by type of alpha-blocker. The largest decreases in detrusor pressures are seen with alfuzosin and tamsulosin, although the number of studies on these alpha-blockers is limited. There is only one study with quantitative results on tamsulosin and one study on alfuzosin. Other investigators have not yet confirmed the results of these studies. Figure 1 shows that the average pre-treatment urodynamic parameters differ for each study group. In some studies more obstructed patients were included than in other studies. Very obstructed patients may improve more than slightly obstructed patients. To exclude this phenomenon we calculated the percentage improvement in urodynamic parameters for each study group, but that revealed no significant difference.

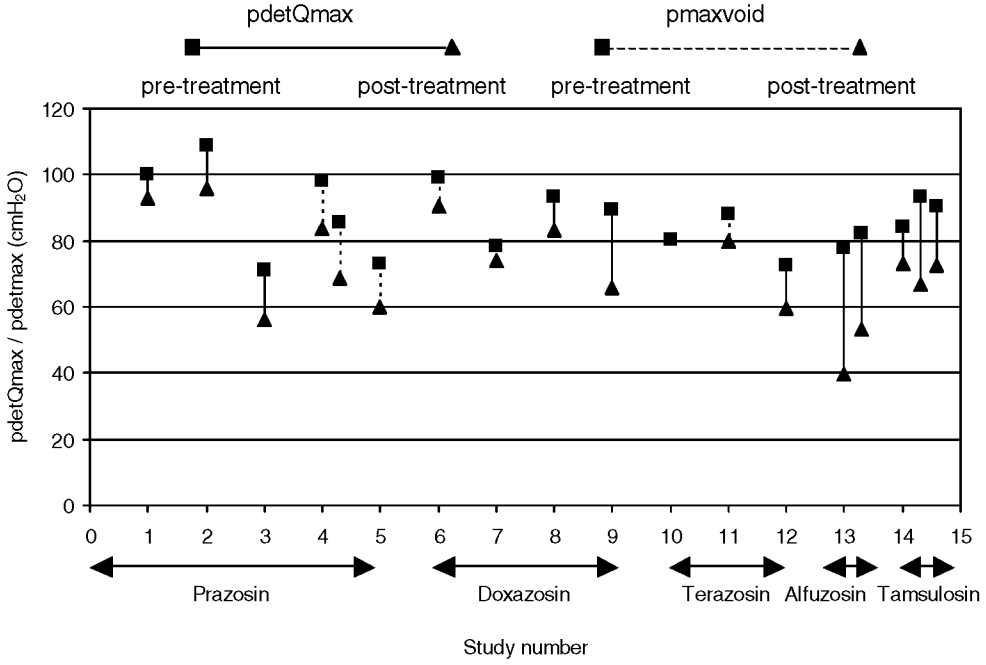

Figure 1 Difference between pre- and post treatment pdetQmax and pmaxvoid

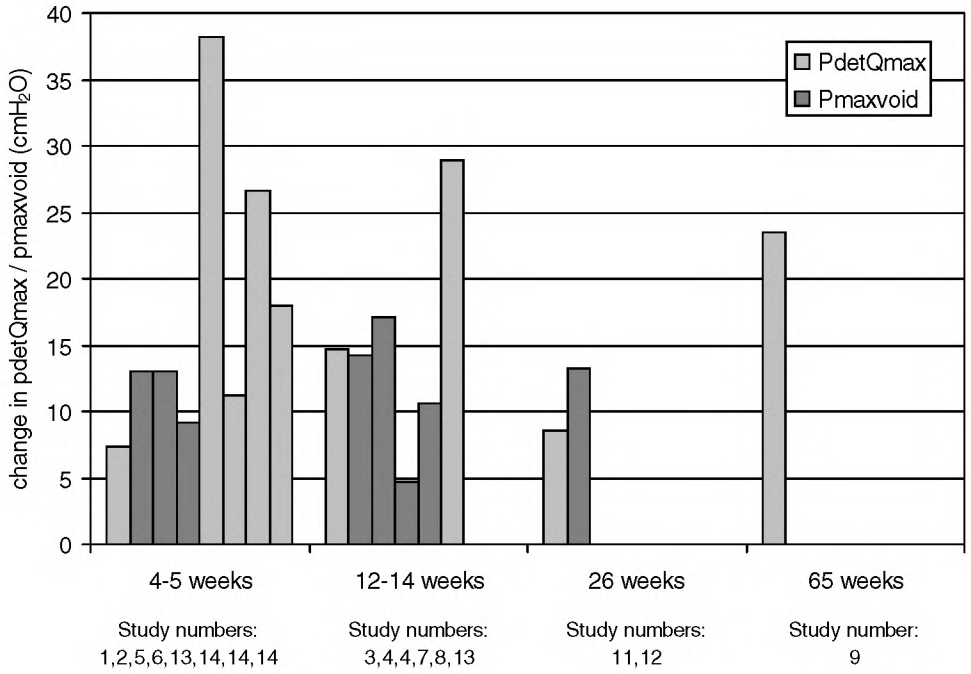

Figure 2 Absolute differences between pre- and post-treatment pdetQmax and pmaxvoid, stratified by duration of treatment

In figure 2 the absolute differences in obstruction parameters are stratified by duration of treatment. From this figure no correlation can be deduced between the duration of treatment and the urodynamic effect. From the study by Gerber et al. we can conclude that the urodynamic effect of alpha-blockers seems to be persistent over a longer period of time.[37] In this study, however, the initial improvement in subjective symptoms did not last during a longer period of follow-up. Therefore, it seems that urodynamic parameters are not predictive for subjective treatment outcome. Four studies are open-labeled, while the others have a double blind, placebo-controlled design. No tendency can be identified that open label studies have better urodynamic results.

In the introduction we posed the question who will benefit of alpha-adrenoceptor blocking treatment. An important conclusion can be drawn from the study by Witjes et al. Terazosin treatment resulted in a decrease of obstruction in obstructed patients, but no significant urodynamic effect was found in non-obstructed patients.[40] The unobstructed patients seemed to respond better to terazosin treatment with respect to improvement in symptoms and Qmax than obstructed patients. This differential effect suggests that alpha-blockers have a well-justified place in the management of patients who are not suitable for desobstructive treatment.

Using alpha-blockers for patients with LUTS, we should ask ourselves whether we intend to treat BOO or to treat LUTS. Ensuing from this question we should ask whether we should consider the urodynamic changes or the changes in LUTS using symptom scores when evaluating treatment effects. When prescribing alpha-blockers to relieve the patients' bothersome LUTS, there is no strong indication to perform urodynamic studies, as all patient with LUTS may benefit from the use of alpha-blockers. In addition, urodynamic changes after alpha-blocking therapy are not an important variable in the evaluation of the treatment effect, since a decrease of BOO can be achieved without an improvement of symptoms and vice versa.

There is no clue yet that indicates any predictive value of obstruction class in predicting durability of treatment effect. Most of the studies that have been reviewed had a relatively short period of follow-up. It would be interesting to know in advance who will need a more invasive prostatic therapy after a certain period and who will not. The degree of BOO might be indicative, but this field still needs to be unraveled.

Conclusion

Administration of an alpha-adrenoceptor blocking agent results in a small reduction of BOO, although a decrease in urodynamic obstruction parameters of up to 50% has been shown. Patients suffering from LUTS may all benefit from the use of alpha-blockers, whether or not they have severe BOO. There is an indication that unobstructed patients respond better to alpha-blockers with respect to symptoms and Qmax than obstructed patients. Generally, there is no strong indication to perform urodynamic studies, when prescribing alpha-blockers to relieve the patients' bothersome LUTS.

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Chapter 5

Alpha-blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it

Rossi C, Kortmann BB, Sonke GS, Floratos DL, Kiemeney LA, Wijkstra H, de la Rosette JJ
J Urol 2001; **165:** 38

Objective: We investigated the effect of the alpha-blockers alfuzosin, terazosin, and tamsulosin on urodynamic parameters after six months of therapy.

Methods: Between February 1992 and June 1998, 163 patients with lower urinary tract symptoms suggestive of bladder outlet obstruction were treated with alfuzosin (60), terazosin (66) and tamsulosin (37). Patients were evaluated with urodynamic studies including pressure-flow analysis, before treatment and after six months of therapy. Initially, all patients were also assessed by the International Prostate Symptom Score (IPSS) questionnaire and measurement of urinary flow rate.

Results: The majority of patients had no clear improvement in obstructive parameters, regardless of the alpha-blocker used, as urethral resistance factor and detrusor pressure at maximum flow rate decreased by only 4 cmH_2O. There was a clear subjective and statistically significant decrease in IPSS and in quality of life scores of six and two points, respectively. No relevant statistical difference was noted among the effects of the three alpha-blockers on relieving symptoms or improving urodynamic parameters of obstruction.

Conclusion: The alpha-blockers are effective for treating symptoms suggestive of bladder outlet obstruction in patients presenting with lower urinary tract symptoms but not for treating the obstruction.

Introduction

In the 1970s, the pioneering work of Caine et al. led to the discovery of alpha-1-adrenoceptor predominance in the prostatic stroma and capsule. This finding triggered the search for alpha-receptor blocking agents in patients with lower urinary tract symptoms (LUTS) suggestive of bladder outflow obstruction (BOO).[1] The initial agents were derived from antihypertensive drugs because of the alpha-receptor blocking capability.[2] More recently, several prostate specific drugs have been introduced.

During the last two decades the therapeutic efficacy of these drugs has been clearly demonstrated in several clinical trials and today alpha-adrenoceptor blockers are the first line medical treatment for patients with LUTS suggestive of BOO.[3] The alpha-blockers are valued for rapid onset of action, effectiveness independent of prostate size, minimal influence on sexual function and good therapeutic profile. The latter is supported by the development of selective alpha-1-adrenoceptor antagonists and by the excellent pharmacokinetics of these newly developed drugs.[4]

BOO can be attributed to a static component due to an enlarged prostate and a dynamic component related to the increased smooth muscle tone of the fibromuscular stroma inside the prostatic capsule and the bladder neck.[5] Blockage of the alpha-1-adrenoceptors reduces urethral resistance by relaxation of the prostate smooth muscle, thus, acting on the dynamic component of obstruction.[6] Surprisingly, there have only been a few reports on the urodynamic effect of alpha-1-blockers.[7-13] Moreover, the use of urodynamic studies at baseline and follow-up to evaluate changes in BOO in patients treated with alpha-blockers remains controversial.[14-15] Do alpha-blockers really relieve BOO? Is there a difference in urodynamic improvement among different alpha-blocking agents? Is it possible, based on urodynamic findings at baseline, to select patients who will respond favorably to treatment? We describe the effect of alpha-1-blockers on urodynamic parameters after six months of therapy and address these questions.

Methods

Between February 1992 and June 1998, 163 patients with LUTS suggestive of BOO were treated with alpha-blockers and underwent urodynamic studies before and after six months of therapy. All patients participated in different protocols on the effect of alpha-blockers that for purpose of study included urodynamic evaluation at six months

follow up. Patients with prostatic cancer, urethral stricture or neurologic disorders affecting lower urinary tract function, and those who previously had undergone prostate surgery or been treated with finasteride were excluded from study.

Treatment consisted of 2.5 mg alfuzosin three times daily in 60 cases, 0.4 mg tamsulosin daily in 37 and 5 mg terazosin daily in 66. Patients were selected to receive one of the three drugs based on availability at that time and not on baseline characteristics. All patients underwent routine investigation, consisting of medical history, assessment of symptoms and quality of life according to the International Prostate Symptom Score (IPSS), measurement of serum prostate specific antigen, digital rectal examination, transrectal ultrasonography of the prostate, and uroflowmetry, including determination of voided and post-void residual volume (PVR).

Each pressure-flow study was performed identically. An 8F catheter mounted with a microtip pressure transducer (MTC, Dräger, Germany) used for vesical filling and recording intravesical pressure was placed under sterile conditions. Abdominal pressure was recorded intrarectally with a 7F microtip sensor catheter. The pressure sensors were calibrated at atmospheric pressure before introduction. Intra-abdominal pressure was subtracted electronically from the intravesical pressure to obtain detrusor muscle pressure. Cystometry was performed with the patient sitting, and the bladder was filled with water at room temperature at a medium filling speed of 50 ml/min. Filling was stopped when the patient expressed a strong urge to void and voiding was allowed in standing position. During voiding, flow parameters and intravesical, abdominal and detrusor pressures were recorded simultaneously. All data were digitally stored and analyzed with an urodynamic analysis computer program developed at our department (UIC/BME Research centre, Department of Urology, University Medical Centre Nijmegen, the Netherlands). An experienced physician visually inspected all computer results using manual correction for artifacts.

To quantify obstruction the urethral resistance factor (URA) was determined by fitting the pressure-flow plot at the point of maximum flow (detrusor pressure at maximum flow). We chose URA as it is a continuous parameter suitable for studying small changes in the severity of BOO. URA values greater than 29 cmH_2O represent obstruction. Changes in urodynamic parameters between baseline and six months follow up were determined and p-values were calculated with the Wilcoxon signed rank test. The correlation between subjective (change in IPSS) and objective (change in URA) improvement was determined with Spearman's correlation coefficient. To evaluate whether changes in clinical parameters differed among the three drugs we used the

Kruskal-Wallis test, which is the equivalent of a Wilcoxon signed rank test for more than two treatment groups. Differences in baseline characteristics among the three drugs were also compared using the Kruskal-Wallis test.

Results

Patient characteristics at baseline and six month follow-up are presented in table 1. Alpha-blocker treatment resulted in subjective and objective improvement. The changes were relatively small, however, compared to patients who received transurethral resection of the prostate (TURP).[16] Subjective improvement was measured with the IPSS and was six points. Median improvement was 4 cmH_2O in URA and 1 ml/s in maximum flow rate (Qmax).

The figure shows the correlation between subjective improvement represented by IPSS on the Y-axis and objective improvement represented by URA on the X-axis. Each dot represents an individual patient. The Spearman coefficient of correlation was 0.09 (p-value = 0.39), indicating that there was no significant correlation between urodynamic and symptomatic improvement. We evaluated whether the effects of alpha-blockers differed between patients who were obstructed at baseline (URA > 29 cmH_2O) and those who were unobstructed. Urodynamic changes between baseline and six months were greater in the obstructed than in the unobstructed group. PdetQmax and URA decreased 6 and 7 cmH_2O, respectively, in the obstructed group and one and two in the unobstructed group; p-values comparing classes were 0.02 for pdetQmax and 0.00 for URA. Symptomatic improvement and increase in Qmax were identical in both groups.

Table 2 shows the baseline characteristics of patients treated with alfuzosin, tamsulosin, and terazosin. Despite the lack of randomization, no statistically significant difference in baseline characteristics was present among the three groups.

Changes in clinical parameters between baseline and six months follow-up for each drug are summarized in table 3. All parameters improved in each treatment group without significant differences among the effects of the different types of medication. A decrease in PVR was only noted for alfuzosin. Despite a statistically significant difference (p = 0.027), however, a reduction of 15 ml in the PVR has no clinical importance.

Table 1 Clinical and urodynamic outcomes of all the patients at baseline and after six months of treatment with alpha-blockers.

	Number of patients	Centiles: 50th (25th - 75th)			P-value*
		Baseline	Six Months	Difference	
Age (years)	163	64 (56-70)	-	-	-
Qmax (ml/s) [free flow]	156	10 (8 ; 13)	11 (8 ; 14)	1 (-1 ; 4)	0.002
PVR (ml)	154	36 (0 ; 94)	17 (0 ; 56)	19 (-41; 15)	0.018
IPSS (0 - 35)	151	18 (13 ; 23)	12 (7 ; 16)	-6 (-10 ; -1)	0.000
QoL (0 -6)	87	4 (3 ; 4)	2 (2 ; 3)	-2 (-2 ; 0)	0.000
Qmax (ml/s) [PFS]	163	6 (5 ; 8)	7 (6 ; 11)	1 (0 ; 3)	0.000
pdetQmax (cmH_2O)	163	50 (36 ; 65)	46 (33 ; 63)	-4 (-15 ; 8)	0.015
URA (cmH_2O)	163	31 (23 ; 41)	27 (18 ; 38)	-4 (-11 ; 3)	0.001

* p-value baseline versus six months
Qmax indicates maximum urinary flow rate; PVR indicates post void residual volume at free flow; IPSS indicates international prostate symptoms score; QoL indicates quality of life score; pdetQmax indicates detrusor pressure at maximum flow rate; URA indicates urethral resistance factor.

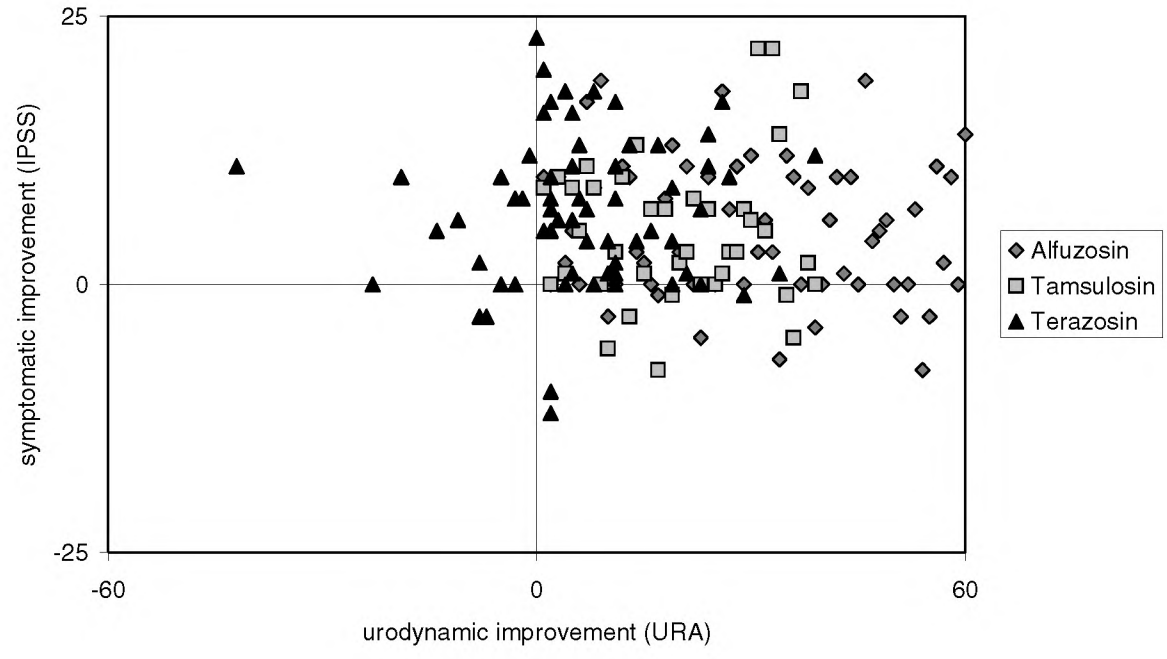

Figure 1 Improvement in URA in cmH_2O (X-axis) and IPSS (Y-axis) plotted for individual patients with and without obstruction, after six months of treatment with alpha-blockers.

Table 2 Baseline values stratified by treatment.

	Centiles: 50th (25th ; 75th)			P-value*
	Alfuzosin (N = 60)	Tamsulosin (N = 37)	Terazosin (N = 66)	
Age (years)	64 (58 ; 71)	61 (54 ; 68)	64 (55 ; 72)	0.445
Qmax (ml/s)	10 (8 ; 12)	10 (7 ; 13)	9 (7 ; 14)	0.961
PVR (ml)	40 (3 ; 95)	12 (0 ; 79)	40 (10 ; 95)	0.100
IPSS	19 (14 ; 24)	17 (12 ; 25)	18 (14 ; 23)	0.855
QoL	4 (3 ; 4)	4 (3 ; 5)	4 (3 ; 4)	0.853
UDQmax (ml/s)	7 (5 ; 8)	6 (5 ; 10)	7 (5 ; 8)	0.622
pdetQmax	50 (33 ; 59)	51 (39 ; 68)	50 (35 ; 67)	0.690
URA (cmH_2O)	30 (23 ; 38)	29 (23 ; 48)	32 (23 ; 42)	0.494
Prosvol (ml)	32 (27 ; 50)	31 (22 ; 41)	33 (25 ; 48)	0.123

* p-value comparing treatments. Abbreviations as in table 1.

Table 3 Difference at baseline versus six months: median and 25th; 75th centiles, with p-value testing the effect of treatment per drug.

	Treatment			P-value*
	Alfuzosin (n = 60)	Tamsulosin (n = 37)	Terazosin (n = 66)	
Qmax (ml/s)	1 (-1 ; 5)	1 (-1 ; 4)	1 (-1 ; 4)	0.91
	0.02	0.10	0.03	
PVR (ml)	-15 (-60 ; 4)	0 (-35 ; 24)	0 (-39 ; 26)	0.03
	0.00	0.72	0.69	
IPSS	-6 (-10 ; -1)	-5 (-9 ; -1)	-7 (-11 ; -1)	0.42
	0.00	0.00	0.00	
QoL	0 (-2 ; 1)	-1 (-2 ; 0)	-1 (-2 ; 0)	0.33
	0.45	0.00	0.00	
UDQmax (ml/s)	0 (-1 ; 2)	1 (0 ; 3)	1 (0 ; 3)	0.01
	0.17	0.00	0.00	
pdetQmax (cmH_2O)	-4 (-13 ; 11)	0 (-15 ; 8)	-5 (-17 ; 5)	0.48
	0.36	0.49	0.02	
URA (cmH_2O)	-2 (-8 ; 5)	-4 (-12 ; 5)	-5 (-13 ; -1)	0.06
	0.30	0.07	0.00	

* p-value comparing differences in effect between treatments
Abbreviations as in table 1

Discussion

Following Abrams' statement that "pressure-flow investigation is the only way of diagnosing BOO", some investigators consider the necessity of an assessment of pressure-flow changes in the evaluation of the effects of medical therapy mandatory.[14] Others focus on the role of symptomatic improvement of alpha-1-blockers and judge urodynamic studies too invasive, too expensive and not predictive of treatment outcome.[9-15]

We present the results of urodynamic studies following medical therapy in order to evaluate the effect of three different alpha-blocking agents on BOO, establish possible differences in urodynamic outcomes among the three drugs used, as to date there are only three head-to-head trials available in the literature and identify selection criteria for medical treatment, based on urodynamic findings.[17-19]

Our study is retrospective and non-randomized. Patients were selected on availability of the drug at that time, however, and notably not on baseline characteristics. This way of patient selection resulted in three homogeneous and comparable groups of patients who were moderately symptomatic and slightly obstructed, with relatively poor flow and small-to-moderate prostate enlargement (table 2). The outcomes are comparable to other studies on urodynamic findings after alpha-blockade that in general reveal a mild decrease in obstructive parameters.[10,11,18,19] Only one study showed a considerably greater decrease in BOO.[12] Although there was no clinically significant relief of BOO, patients were satisfied with medical therapy since they had symptomatic improvement. This result confirms once again the poor relation between the severity of symptoms and the grade of BOO.[20]

Our results reveal that 2.5 mg alfuzosin three times daily, 0.4 mg tamsulosin daily or 5 mg terazosin daily for LUTS suggestive of BOO provided comparable subjective and objective improvement after six months of therapy. Alfuzosin, terazosin, and tamsulosin induced only small increases in urinary flow (median 1 ml/s), and alfuzosin was the only alpha-blockers that was effective in decreasing PVR, although this improvement was of no clinical significance (15 ml). The decrease in IPSS reflects the subjective improvement. Once again, no statistically significant difference was detected among the effects of the three alpha-blockers.

There was improvement in URA and pdetQmax without statistically significant differences the effects of the three drugs. The decrease in obstructive parameters was too small to be considered a genuine clinical desobstruction. The majority of patients had

objective evidence of persistent BOO after six months of treatment regardless the alpha-blocker used.

We divided patients at baseline into obstructed and unobstructed. It appeared that those with obstruction had the most improvement from medical therapy, as URA decreased 7 versus 2 cmH_2O and pdetQmax 6 versus 1 cmH_2O in the unobstructed population. Once again, however, this statistically significant improvement was too small to be considered a clinically relevant predictive parameter for treatment outcome.

We confirm that terazosin, alfuzosin and tamsulosin are three effective drugs for patients with LUTS suggestive of BOO. Even if there was not a genuine clinical amelioration in urinary flow, PVR and obstruction parameters at six month follow up, patients were satisfied with the medical therapy, whichever alpha-blocker was used, as symptoms were referred to as less bothersome and quality of life improved.

In our study, no important clinical improvement in BOO was detected after six months of treatment with alpha-blockers, despite the statistically significant decrease in obstructive parameters, and urodynamic status at baseline was not predictive of treatment outcome. Recent basic and clinical research reveals many other possible mechanisms by which alpha-blockers may influence LUTS. Extraprostatic localization of alpha-adrenoceptors seems to be involved in the pathogenesis of LUTS. Except for the presence of alpha-adrenoceptors in the prostatic stroma, they occur in the detrusor, trigone, urethra, ganglia, spinal, and supraspinal structures. The relief of filling symptoms can be explained by a beneficial effect of alpha-blockers on bladder compliance and/or capacity. An additional mechanism suggested is induction of prostatic apoptosis by alpha-blockers in patients with BPH, but is in unclear whether this mechanism adds to the therapeutic effect of the drug.[21] Many studies, including ours, suggest involvement of mechanisms other than a decrease of the dynamic component of obstruction. The clinical significance of these various possible modes of action, however, remains to be established.

Because of the complex relation between LUTS, BOO and BPH, attention should be given to the most appropriate initial evaluation of patients affected by voiding symptoms, not only as a means to choose the appropriate therapy, but also to assess response to medical or surgical treatment. From our results, urodynamic studies do not appear to be helpful in evaluating patients with LUTS before and after medical treatment, as the outcome following medical treatment is unrelated to the grade of BOO and to the choice of alpha-blockers. Durability of treatment outcome, however, may be related to

the grade of BOO at baseline. The literature is still lacking on this theory, and studies on durability may provide outcomes on BOO different from those obtained after a short period of treatment. Nevertheless, this factor was not within the scope of our study and deserves attention in a separate analysis.

Conclusion

We could not find any significant clinical improvement in the parameters of BOO after six months of therapy with alfuzosin, tamsulosin, and terazosin. There was no important statistical difference in the subjective and objective effects of the three drugs. Although we achieved the best statistical results in patients who were obstructed at baseline there was no correlation between statistical and clinical improvement, or stated differently, urodynamic status at baseline does not seem to be a selection criterion to predict response to therapy. Because of these results, we can assert that alpha-blockers are effective for treating the symptoms suggestive of BOO in patients with LUTS but not for treating the obstruction.

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Chapter 6

Long-term risk of retreatment in patients using alpha-blockers for lower urinary tract symptoms

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Submitted

Objective: The efficacy of alpha-adrenoceptor blockers in the treatment of lower urinary tract symptoms (LUTS) has been proven in numerous studies. Little is known, however, about the efficacy on the longer term. We investigated the long-term risk of retreatment in patients using alpha-adrenoceptor blockers for LUTS and the parameters that influence this risk.

Methods: We reviewed 316 files of patients with LUTS, who were treated in our department with the alpha-blockers terazosin, alfuzosin, or tamsulosin. Baseline and follow-up data up to five years were assessed. Retreatment percentages were calculated in each treatment group and predictive values for retreatment of the baseline parameters were calculated.

Results: At five years of follow-up the retreatment percentages of patients with mild, moderate and severe symptoms were 27, 33 and 70%. Of patients with a maximum uroflow of less than 10 ml/s and more than 10 ml/s the percentages were 58 and 47%, of patients with a prostate volume of less than 40 ml and more than 40 ml these were 48 and 72%, and of unobstructed versus obstructed patients 44 and 59%. At three years of follow-up, the retreatment percentages of the different alpha-blockers were 27% for tamsulosin, 37% for alfuzosin, and 49% for terazosin.

Conclusion: Patients using alpha-blockers for LUTS have a considerable risk of retreatment. Severe symptoms, a poor uroflow, an enlarged prostate, and urodynamically proven bladder outlet obstruction increase the risk of treatment failure. Pre-selection of the best suitable candidates for alpha-blockade may reduce this risk.

Introduction

Lower urinary tract symptoms (LUTS) suggestive of bladder outlet obstruction (BOO), formerly called 'prostatism', is a prevalent micturition disorder in the male population.[1,2] An enlarged prostate in the presence of moderate to severe LUTS and/or a decreased urinary flow occurs in about 25% of men in the community, rising from 14% in men aged 40-49 years to 43% in men aged 60-69 years.[3] In the past, LUTS were usually treated by either watchful waiting or surgery, primarily transurethral resection of the prostate (TURP), but the disadvantages of the invasiveness and morbidity of such a surgical intervention were acknowledged. The last two decades medical therapy has filled the gap between the two treatment options.

Preceding research supports the hypothesis that two mechanisms exist by which benign prostatic hyperplasia (BPH) may cause BOO: The static factor is caused by mechanical compression of the urethra by the bulk of the prostatic adenoma. The alpha-adrenoceptor mediated sympathetic stimulation of the prostatic smooth muscle causes a fluctuating influence on BOO and is therefore called the dynamic factor of BOO. The last factor contributes up to 40% to the obstruction.[4] It has been proven that both mechanisms can be influenced by pharmacotherapy: 5-alpha-reductase inhibitors reduce the size of the prostatic adenoma, and alpha-1-adrenoceptor blockers relax the prostatic smooth muscles.

Drug therapy is recommended for patients with moderate to severe symptomatic disease, for patients who are awaiting surgery and for those who are not candidates for surgery at all. Nowadays, alpha-blockers are widely used as a first line medical treatment for patients affected by LUTS as their safety and effectiveness have been proven in numerous randomized studies.[5] It was rightly asserted that this class of drugs has the advantage of being fully adapted to the natural history of BPH as alpha-blockers produce a rapid relief of symptoms during an exacerbation of LUTS and may be temporarily stopped in case of remission of disease. Reasons of discontinuation of alpha-blocker therapy may be satisfaction or dissatisfaction with the actual micturition pattern. Thus, discontinuation is not similar to treatment failure.

Little is known about the effect of alpha-blockers on the course of LUTS in daily practice. The evaluation of this aspect necessitates an analysis of the long-term efficacy of these drugs, which can be based on the rate of secondary interventions. The rate of treatment failure and consequently the risk of retreatment for these patients are one aspect of alpha-adrenoceptor blockers that received little attention in previous studies.

In particular, long-term risk of retreatment (> three years) has not yet been evaluated, although most patients suffer from LUTS for many years. In addition, little is known about predictive factors for treatment outcome. Increased knowledge of predictive factors for long-term treatment success may help to select the best suitable candidates for alpha-blocker-treatment.

Currently, there are several alpha-blockers in clinical use. On the short term, they have comparable results concerning improvement in symptoms and flow rate, but they may differ in pharmacokinetics, side effects, and alpha-adrenoceptor subtype selectivity. Differences in long-term risk of retreatment are not known yet. The aim of the present study was to investigate the long-term risk of retreatment in patients using alpha-blocking agents for LUTS and the parameters that influence this risk.

Methods

We reviewed the files of 316 newly diagnosed patients with LUTS suggestive of BOO, who were treated with alpha-blockers in our department between February 1992 and June 1998. Our clinic is a referral university hospital, to which patients are referred by their general practitioner or by a urologist from another hospital. No patient had been treated for his complaints yet. Treatment consisted of 2.5 mg alfuzosin three times daily in 126 cases, 0.4 mg tamsulosin daily in 96 and 5 mg terazosin daily in 94. Patients received one of the three drugs based on the availability at that time and not on baseline parameters. Patients with prostate cancer, a urethral stricture, neurologic disorders affecting the lower urinary tract function and those previously surgically or medically treated were excluded from the study.

The assessment and follow-up schedule was standardized and similar for all groups. All patients were investigated at baseline with medical history, assessment of symptoms and quality of life according to the International Prostate Symptom Score (IPSS), digital rectal examination, transrectal ultrasonography of the prostate, measurement of serum prostate specific antigen, urinalysis, uroflowmetry including determination of post void residual volume (PVR) and an urodynamic study including pressure-flow analysis.[6] To quantify obstruction, the urethral resistance factor (URA) was calculated.[7]

A database was made including baseline data of the patients and follow-up data up to five years. Patients who received any form of retreatment during the follow-up period

were classified as non-responders. Patients who continued using alpha-blockers were classified as responders. Patients who were lost to follow-up and patients who stopped using alpha-blockers without retreatment were censored at the date of last reported treatment use. Baseline parameter values (age, IPSS, prostate volume, maximum flow rate, voided volume, PVR, BOO defined by URA) in the groups of patients treated with the three types of alpha-blockers were calculated and differences were tested using the Mann-Whitney-U-test. The overall discontinuation percentage was calculated after three and five years of follow-up. The risk of retreatment in the whole group was calculated while accounting for loss-to-follow-up using Kaplan-Meier survival analysis. Differences in risk of retreatment were tested with the Log-Rank test. The predictive value for treatment failure of other baseline parameters, including treatment was evaluated in the same way. Finally, we performed a Cox proportional hazard analysis to evaluate the retreatment rate of each baseline parameter while accounting for all other baseline parameters. The predictive values of all baseline parameters were calculated up to five years of follow-up, except for the type of alpha-blocker, for which we calculated the predictive value at three years of follow-up. The follow-up data from the tamsulosin group were restricted to three years, due to the recent date that this drug has become available. The analyses were performed using SAS 6.12 for windows (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of all patients and of patients divided by type of alpha-blocker are shown in table 1. Calculation of differences in baseline parameters between the alfuzosin, tamsulosin and terazosin group revealed statistically significant differences for PVR, pdetQmax, and prostate volume. All the other parameters were comparable for the three groups. Mean PVR after free uroflow was lower in the group of patients treated with tamsulosin (9 ml) than in the alfuzosin or terazosin group (31 and 40 ml respectively).

In the whole group the discontinuation percentage was 64% after three years and 79% after five years of follow-up (standard errors (SE) were 3% for both percentages). The overall retreatment percentage was 38% after three years and 54% after five years of follow-up (SEs were 4% and 5%, respectively).

Table 1 Baseline characteristics of all patients

	Median (centiles 25 ; 75)				P-value
	All patients (n = 316)	Alfuzosin (n = 126)	Tamsulosin (n = 96)	Terazosin (n = 94)	
Age(years)	62 (55 ; 68)	63 (55 ; 68)	61 (55 ; 67)	63 (55 ; 69)	0.67
Qmax(ml/s)	10 (8 ; 13)	10 (8 ; 12)	10 (8 ; 13)	10 (7 ; 14)	0.82
PVR(ml)	26 (0 ; 80)	31 (0 ; 87)	9 (0 ; 49)	40 (11 ; 94)	0.00
IPSS	18 (14 ; 23)	19 (14 ; 24)	18 (13 ; 23)	18 (14 ; 23)	0.69
Quality of Life	4 (3 ; 4)	4 (3 ; 4)	4 (3 ; 4)	4 (3 ; 5)	0.91
pdetQmax	47 (34 ; 66)	49 (35 ; 66)	44 (32 ; 59)	52 (35 ; 71)	0.05
URA (cmH2O)	28 (21 ; 37)	29 (22 ; 37)	27 (21 ; 36)	29 (21 ; 38)	0.76
Prostate volume (ml)	31 (25 ; 43)	32 (26 ; 45)	27 (22 ; 38)	34 (26 ; 50)	0.00

Figure 1 shows the retreatment percentage up to five years of follow-up for patients with mild, moderate, and severe symptoms (total IPSS of 0-7; 8-19 and 20-35 respectively). Patients with severe symptoms at baseline had the highest risk of retreatment at five years (70%), while patients with a baseline IPSS between 0 and 7 and 8 and 19 had a retreatment percentage of 27 to 33 at five years, respectively.

Figure 2 shows the retreatment percentage up to five years of follow-up for a baseline maximum flow (Qmax) of less than 10 ml/s and more than 10 ml/s. There is a small difference in retreatment percentage of 58% and 47%, respectively, between the two groups (p-value = 0.19). Using a cut-off value of 15 ml/s the difference in risk of retreatment becomes obvious: 58% and 21% for a Qmax of < 15 ml/s and > 15 ml/s, respectively. Thus, patients with a Qmax of less than 15 ml/s are much more likely to receive a retreatment within five years than patients with a higher Qmax. Retreatment percentages were also calculated for voided volume and PVR, but did not show any significant difference using a cut-off value of 150 ml for both voided volume and PVR.

Figure 3 shows the difference in retreatment percentage with prostate volume as predictive parameter. Patients with prostates larger than 40 ml are more likely to receive a retreatment within five years than patients with a smaller prostate (72% versus 48%).

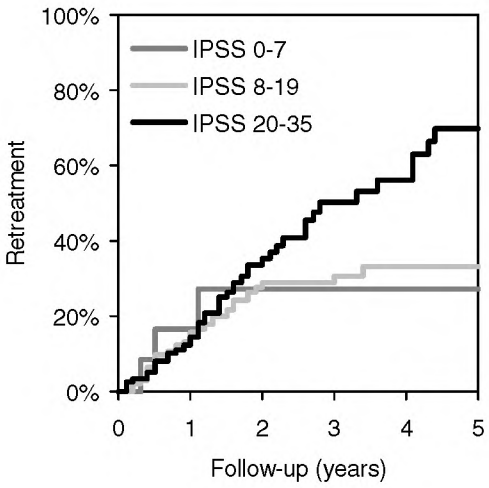

Figure 1 Retreatment stratified by IPSS

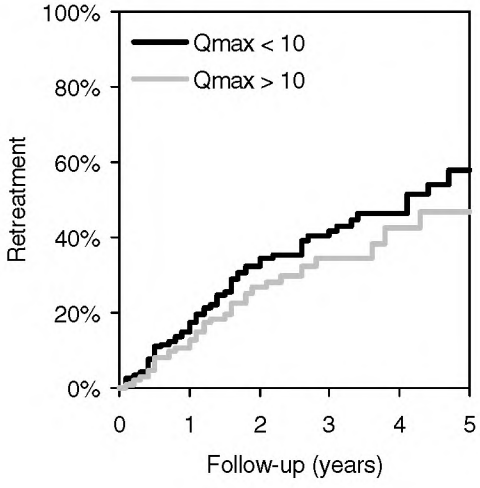

Figure 2 Retreatment stratified by Qmax

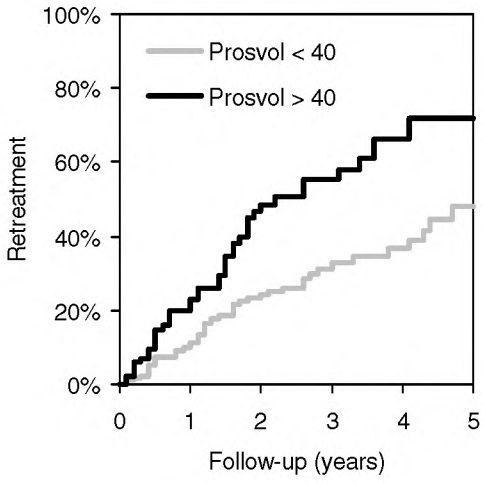

Figure 3 Retreatment stratified by prostate volume

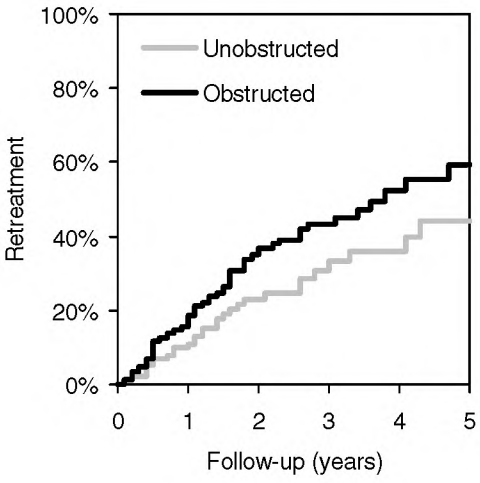

Figure 4 Retreatment stratified by obstruction

Figure 4 illustrates the rate of failure of medical treatment in obstructed (URA > 29) and in unobstructed (URA < 29) patients. Those who were obstructed at baseline had a retreatment in 59% of cases, while patients without obstruction received retreatment in the 44% of cases after five years of follow-up.

Figure 5 shows the retreatment rate, dividing patients by type of alpha-blocker, up to three years of follow-up. The differences in retreatment percentages between the three types of alpha-blocker were significant. Terazosin had the greatest proportion of treat-

ment failure (49%), followed by alfuzosin (37%), while tamsulosin had a retreatment rate of 27%. As the baseline values for mean prostate volume differed for the treatment groups, we corrected the retreatment percentages of the three alpha-blockers for prostate volume. This adjustment did not have an influence on the results. In the first two years of follow-up, the lines representing alfuzosin and terazosin run parallel and diverge after the second year of follow-up, while the line representing tamsulosin is the lowest throughout the whole period.

Table 2 shows the results of the multivariate analysis. Especially the risk of retreatment remains significantly different for the small and the larger prostates. For the other baseline parameters similar trends are visible as in the survival analyses.

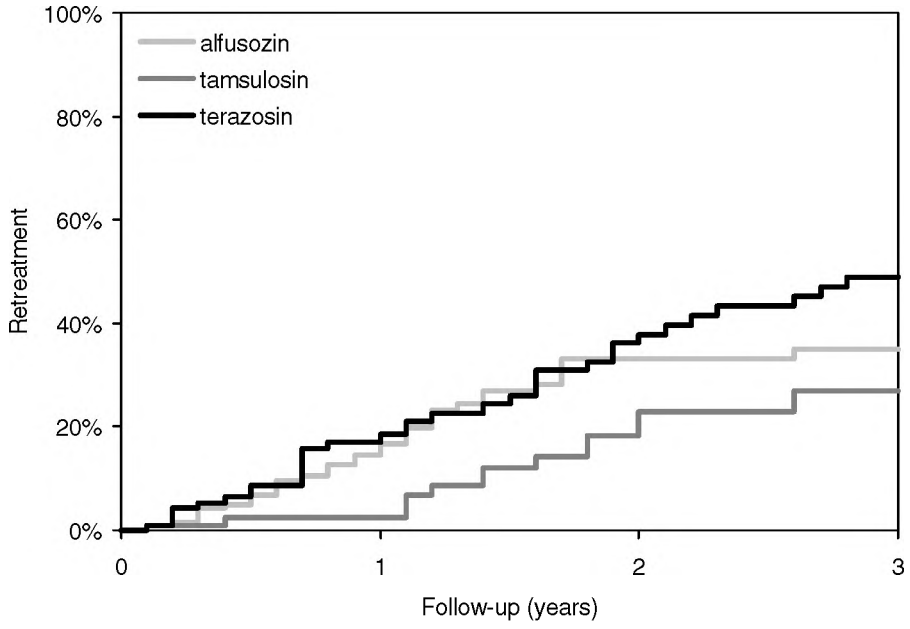

Figure 5 Retreatment percentages of three alpha-blockers during three years of follow-up

Table 2 Proportional hazard analysis evaluating the retreatment rate of each baseline parameter, while accounting for the other baseline parameters

	Label	N	Hazard Ratio(95% CI)	P-value
Treatment	alfuzosin	101	1	-
	tamsulosin	86	0.59 (0.30 - 1.18)	0.14
	terazosin	79	1.16 (0.67 - 2.01)	0.59
IPSS	0-7	11	1.00	
	7-19	143	0.85 (0.26 - 2.80)	0.79
	20-35	112	1.30 (0.40 - 4.27)	0.66
Obstruction	absent	132	1.00	-
	present	134	1.27 (0.75 - 2.14)	0.38
Qmax	> 10	117	1.00	-
	<= 10	149	1.12 (0.67 - 1.89)	0.66
Prostate volume	< 40	187	1.00	-
	>= 40	79	2.11 (1.28 - 3.47)	0.00

Discussion

Success of a treatment for BPH is usually defined by improvement in uroflowmetry parameters and symptoms, but it also depends on the necessity for retreatment and the interval between the initial treatment and the time of retreatment. In most studies on the effect of alpha-blockers, retreatment is not included in the evaluation, as it requires a longer period of follow-up of preferably several years. Few reports on open-label extensions of placebo-controlled trials exist that evaluate long-term efficacy of alpha-blockers. Jardin et al. report the long-term results of alfuzosin treatment after 30 months follow-up, but a withdrawal rate can not be deduced from their study.[8] Lepor et al. showed 43% withdrawal from terazosin treatment after 42 months follow-up.[9] In a study on the long-term effects of doxazosin by Lepor et al. 49% of patients discontinued the use of doxazosin within four years of follow-up. In a study on the long-term efficacy of tamsulosin by Schulman et al. a discontinuation rate of 60% after three years of follow-up is mentioned.[10,11] In these studies the withdrawal rate due to adverse events ranges from 15 to 20%. The withdrawal rate in the present study of 64% after three years corresponds with the results by Schulman et al.

The considerations underlying the decision to put emphasis on retreatment and not on discontinuation in this analysis are as follows. The discontinuation rate includes patients who do not need therapy anymore, as their LUTS are sufficiently relieved, patients

who prefer to bear their LUTS without therapy and patients who need a retreatment. Patients lost to follow-up may also be included in the discontinuation rate. Therefore, discontinuation rate is not a good measure to determine the efficacy of a treatment. Retreatment rate, on the other hand, includes only those patients who need additional therapy, as their LUTS are not relieved. The disadvantage of using retreatment rates is that they do not include patients who are not satisfied with a treatment, but do not want additional therapy.

Patients enrolled in a clinical trial under randomized and double-blind, placebo controlled conditions rather differ in terms of their perception of treatment effectiveness and their reaction to minimal or no symptom improvement from those patients, who are treated outside of trials, in private practices and community settings. The present study is not a prospective, randomized study. We retrospectively evaluated the group of patients that were treated with alfuzosin, tamsulosin, or terazosin in our clinic and underwent a standardized assessment and follow-up schedule. Therefore, this study gives a realistic picture of the course of these patients in the daily practice. A non-randomized treatment assignment does not make evaluation of predictive parameters impossible, if all the prognostic factors are incorporated into the analysis.[12]

From our results, several baseline parameters appeared to be predictive for the risk of retreatment within five years. In patients with severe symptoms alpha-blocker treatment will fail in 50% after three years and in 70% after five years. It is interesting that in the first two years of follow-up the risk of retreatment seems similar, regardless of the total symptom score. A low Qmax, which often goes together with a higher grade of BOO, increases the risk of retreatment. Many studies on alpha-blockers use a cut-off value for inclusion of 15 ml/s for Qmax, although urologists and general practitioners often prescribe alpha-blockers for LUTS in patients with a better flow. Apparently, these patients are satisfied with alpha-blocker treatment for a longer period.

Patients with larger prostates have higher retreatment percentages than those with smaller prostates. There has not been a guideline yet that tells us not to treat someone with a big prostate with an alpha-blocker. Therefore, these results may help the doctor to choose between an alpha-blocker and finasteride in a specific patient based on the patient's estimated prostate volume. A patient with a large prostate may be better off with a 5-alpha-reductase inhibitor, as this drug has proven to be more effective for bigger prostates, while a patient with a smaller prostate may need an alpha-blocker, because his symptoms are mainly caused by a dynamic obstruction.

Combining baseline parameters enables the identification of patients with the highest risk of retreatment. For patients with an IPSS < 20 and for patients with a Qmax > 15 ml/s the risk of retreatment stabilizes after two years, but for all the other predictive parameters this risk gradually increases during the years. If we extrapolate the lines, one may expect that after five years of treatment the risk of retreatment will continue to increase. Such an increase may be explained by the theory that alpha-blockers do not influence BPH progression, although they do relieve symptoms.

The different retreatment percentages after two years are small for most parameters. Only after three or more years, the lines diverge. This finding underlines the necessity for studies with a long-term follow-up if one is interested in differences in efficacy of treatments. We cannot conclude from our study whether the differences in retreatment rate are caused by a difference in efficacy or in side effects. Patients may well be less compliant or choose another treatment based on the experienced side effects.

Moreover, one may question whether the study groups were identical at baseline. As patients were not randomized to use one of the three alpha-blockers, one may expect differences in baseline characteristics between the three groups. After calculation of these differences, it appeared that only PVR, pdetQmax, and prostate volume were not statistically comparable. The mean PVR in the tamsulosin group was evidently less than in the other groups, but although the difference was statistically significant, it is not clinically relevant. The same holds for the statistically significant differences in pdetQmax and prostate volume between the three groups. The difference between a prostate of 27, 32 or 34 ml is clinically irrelevant as they are all in the range of 'small prostates'. One could even ask whether these differences in PVR and prostate volume are real, considering the reproducibility of the measurement of PVR and prostate volume using transabdominal and transrectal ultrasound respectively.

Since the prevalence of men with LUTS is high in the community, there is a big need for alpha-blockers. They are widely prescribed by family practitioners and urologists without pre-treatment patient selection. In other words, in all men with LUTS one can give an alpha-blocker on a trial base. In this way of prescribing alpha-blocker, treatment has a substantial macro-economical impact. Therefore, improvement in selection of patients who will benefit from alpha-blocker treatment on the long term will have considerable consequences for health service costs. The results of this study enable us to define patients with a high risk of retreatment, i.e., the patient with severe symptoms, a poor uroflow, a big prostate, and significant urodynamic obstruction. Moreover, this study indicates that durability of alpha-blockers may be different.

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Part III

Urodynamics and histopathology of the bladder wall

Chapter 7

Bladder outlet obstruction does not change bladder wall morphology

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Submitted

Objective: Histologic changes in the human bladder wall are believed to be related more to aging than to bladder outlet obstruction. These changes however, have never been correlated with urodynamic obstruction parameters. The aim of this study was to determine if there is a correlation between microscopic changes in the bladder wall and urodynamic obstruction parameters.

Methods: Deep bladder biopsies were taken in 63 consecutive patients who underwent a transurethral resection of the prostate. The biopsies were independently evaluated using light microscopy by two pathologists for the following histologic features: fibrosis, elastosis, inflammation and muscle cell degeneration, after which consensus was achieved. The pre-surgical clinical and urodynamic data were correlated with the histologic observations.

Results: Of the 63 biopsies, 54 could be evaluated. More than half of the biopsies were normal. No correlation was found between the histologic features and Schäfer class, URA, instability, post-void residual volume, symptom score, and prostate volume. Furthermore, no correlation was found with patient age, although in the group of patients with histologic abnormalities, severity increased with age.

Conclusion: Histologic changes in the bladder wall do not correlate with urodynamic obstruction parameters, clinical parameters, or patient age.

Introduction

In two thirds of the cases, lower urinary tract symptoms (LUTS) are caused by benign prostatic obstruction (BPO), a disease with a generally gradual onset and a long duration.[1] Considering the close relationship between prostate and bladder, it seems probable that bladder outlet obstruction (BOO) effects the anatomy and function of the bladder.

Animal studies show that BOO may result in morphologic and functional changes in the bladder wall. Artificial BOO in animal species, such as the rabbit, rat, cat and pig, show that BOO causes an eight- to tenfold increase in bladder weight attributable to hypertrophy and hyperplasia of smooth muscle cells and increased interstitial collagen.[2-9] In all these studies the most outstanding functional change caused by BOO is an impaired ability to empty the bladder without a decrease in maximum voiding pressure. Recovery after short-term artificial partial BOO occurs rapidly but incompletely. The bladder weight remains high compared to controls and the ability to empty the bladder remains partially impaired.[3,10] Based on the results of these animal studies it was hypothesized that changes in the human bladder wall may be correlated with BOO and LUTS. Gilpin et al. observed smooth muscle hypertrophy and increased interstitial collagen in the detrusor bundles in response to BOO.[11] Other studies, however, do not confirm the relationship between histologic features and obstruction. Some suggest that morphologic changes in the bladder wall related to aging may make it difficult to evaluate the effects attributable to BOO.[12] Holm et al. studied the presence of fibrosis of the detrusor in men with LUTS suggestive of BOO and in controls. They observed similar degrees of fibrosis in both obstruction and aging.[13]

Histologic changes in the bladder wall could be essential in explaining the variability in therapeutic results of desobstructive therapy, particularly in cases in which therapeutical intervention does not result in alleviation of LUTS. In this last group of patients, a bladder biopsy may have a role in pre-treatment work-up. To our knowledge, a study in which urodynamically proven BOO has been correlated with light microscopic histologic features has never been performed. Thus, to date, there is no clear concept regarding the effect of BOO on the human bladder wall. In this study, we assessed the correlation between histologic features in the human detrusor muscle and the grade of obstruction as assessed by urodynamic studies including pressure-flow analysis.

Methods

Sixty-three consecutive patients with LUTS, who were eligible for transurethral resection of the prostate (TURP) based on the diagnostic work-up results, were recruited from our outpatient clinic (Department of Urology, University Medical Centre, Nijmegen, the Netherlands) for this study. Work-up included assessment of symptoms using the International Prostate Symptoms Score (IPSS), digital rectal examination, blood and urine analysis, uroflowmetry, and measurement of post-void residual volume, transrectal ultrasound measurement of prostate volume, urethrocystoscopy and urodynamic studies including pressure-flow analysis.

All urodynamic studies with pressure-flow analysis were performed under standardized conditions. Before introducing the catheters an instillation gel, containing lidocaine and antibacterial agents (Farco Pharma, Cologne, Germany), was applied. An 8F catheter mounted with a micro-tip sensor (MTC, Dräger, Germany), to fill the bladder and to record intravesical pressures, was introduced under sterile conditions, while a second 8F micro-tip catheter was used to record rectal pressures. During cystometry, the bladder was filled with physiologic saline of 20°C at a filling rate of 50 ml/min. During micturition, uroflow, and intravesical and abdominal pressures were recorded simultaneously. Flow rate was measured with a rotating disk flowmeter (Dantec Urodyn flowmeter, Dantec, Skovlunde, Denmark). All data were digitally stored and analyzed with an urodynamic analysis program developed in our department (UIC/BME Research centre, Department of Urology, University Medical Centre Nijmegen, the Netherlands).

During the transurethral surgery, cold-cup full thickness biopsies were taken from the bladder wall. Care was taken not to include tissue from the trigone. Directly after removal the tissue, samples were snap frozen in liquid nitrogen and stored at -70°C. All biopsies were transferred to a 4% buffered formalin solution for approximately 24 hours after which they were processed through paraffin. The remaining biopsies were stored for future immunohistochemical and biochemical studies. From each paraffin block, ten consecutive 4 µm thick sections were cut and mounted on coated slides. Sections were stained for microscopic evaluation with H&E, Van Gieson, picric acid and orcein methods for routine evaluation, assessment of smooth muscle, fibrous tissue, and elastin fibers respectively.

Two experienced pathologists (TH, FS) separately evaluated the following features in each biopsy: Intra- and interfascicular (1) fibrosis and (2) elastosis of the detrusor mus-

cle, (3) degenerative changes of the detrusor muscle cells, (4) signs of inflammation and (5) any other remarkable change. An overall diagnosis of normal or abnormal was given for each biopsy, which in the case of an abnormality was graded. Aforementioned features were semiquantitatively scored according to the following scale: absent: (-), mildly present: (+), moderately present: (++), severely present: (+++). After independent evaluation, the pathologists re-evaluated each biopsy during a consensus meeting. The results of this joint evaluation were used in the analyses. Histologic features were correlated with the urodynamic obstruction parameters, several clinical parameters, and patient age.

Statistical analysis

In order to evaluate the effect of urodynamic obstruction and age (as well as other clinical parameters such as prostate volume, post-void residual volume after free uroflowmetry, bladder instability, compliance and bladder capacity) on histology of the bladder wall, we used logistic regression analyses. In these analyses, the consensus diagnosis of both pathologists (normal versus abnormal) was considered as independent variable. The obstruction parameters urethral resistance factor (URA), detrusor pressure at maximum flow (pdetQmax), and Schäfer class and age were considered possible predictors. In order to avoid arbitrary cut-off values all these parameters were entered in the models as continuous variables. For each histologic parameter three models were constructed: age + URA, age + Schäfer score, and age + pdetQmax. Furthermore, a stepwise model (inclusion and exclusion criteria $p = 0.10$ and $p = 0.15$, respectively) was constructed for consensus diagnosis and age, URA, prostate volume, post-void residual volume, bladder instability, bladder compliance, and bladder capacity as possible predictors.

In order to visualize the strength of the association between the predictors and the histologic features, we summarized the results in receiver operating characteristic (ROC) curves. The area under the curve (AUC) was calculated as a single measure for association. In case a (combination of) predictor(s) has no influence on histology, the AUC is close to 0.5. In case there is a strong association, the AUC will be close to 1.0. Absence of the value 0.5 in the 95% confidence interval for the AUC indicates a statistically significant predictive value. The analyses were performed using SPSS release 9.0.

Results

Of the 63 patients, 54 could be further evaluated. Nine patients were not included because their biopsies did not include detrusor muscle, and in three patients the urodynamic studies were incomplete. Table 1 shows the distribution of the various histologic features observed in the bladder biopsies. Intra-fascicular fibrosis, intra-fascicular elastosis, and fatty infiltration are most frequently observed (figures 1-3). Atrophy of detrusor muscle, degenerative changes in the artery wall, fibrosis of the mucosa, hypertrophy of the muscularis mucosae and variation in the nuclear density were sporadically observed in the biopsies.

Table 2 shows the correlation between the overall histologic diagnosis and the grade of BOO, expressed in Schäfer class. There was not any patient without obstruction (Schäfer class '0'). The histologic features are equally distributed over all Schäfer classes and in each Schäfer class at least half the patients have a bladder biopsy diagnosed as normal (figure 4). There was no correlation between the features; intra- and inter-fascicular fibrosis, intra- and inter-fascicular elastosis and fatty infiltration and the urodynamic obstruction parameters Schäfer class, URA and pdetQmax. There was no correlation between histologic features and patient age. There was a weak correlation between the severity of histologic features and age.

Table 1 Distribution of histologic features in 54 bladder biopsies from patients with bladder outlet obstruction

	Absent (-)	Mildly present (+)	Moderately present (++)	Severely present (+++)	Missing
Intra-fascicular fibrosis	35	11	4	4	0
Inter-fascicular fibrosis	45	2	3	2	2
Intra-fascicular elastosis	38	12	4	0	0
Inter-fascicular elastosis	48	4	1	0	1
Muscle cell degeneration	50	3	1	0	0
Inflammation*	49	5	-	-	0
Fatty infiltration*	38	16	-	-	0

* only present or absent

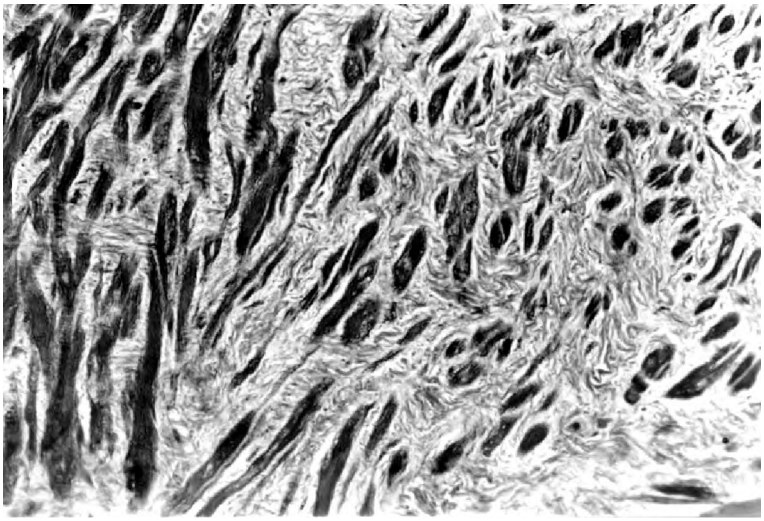

Figure 1 Severe intrafascicular fibrosis of the bladder wall. Individual and small groups of muscle fibers are separated by collagenous tissue. (Magnification 400x, AZAN staining)

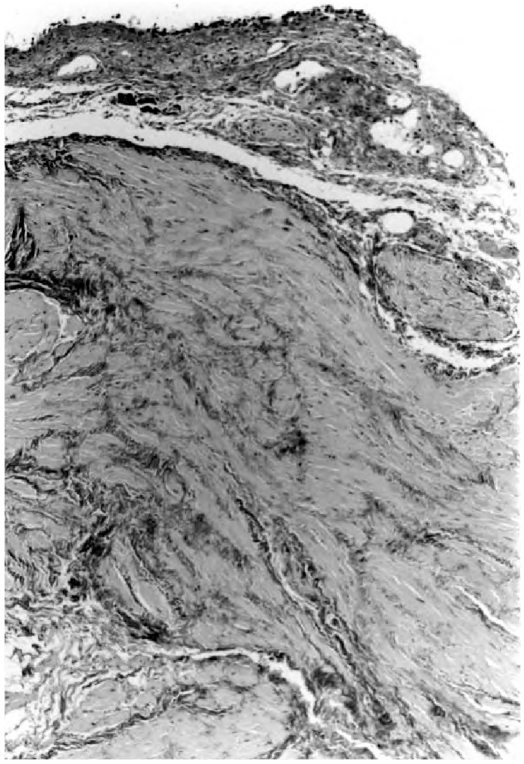

Figure 2 Intrafascicular elastosis of the bladder wall. The detrusor muscle is split up by darkly staining elastic fibers. (Magnification 250x, van Gieson`s elastin staining)

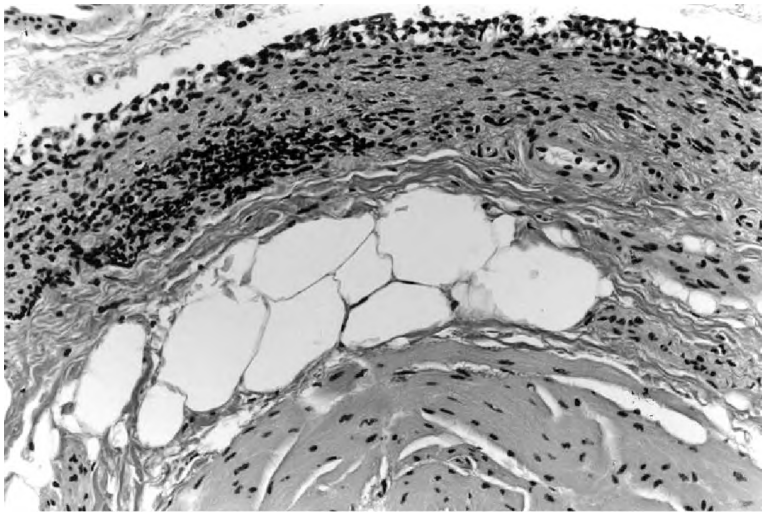

Figure 3 Fatty infiltration of the bladder wall. Note the fatcells as oval to round white spaces just above the detrusor muscle. Note also the lymphocytic infiltration between urothelium and fat. (Magnification 250x, HCE staining)

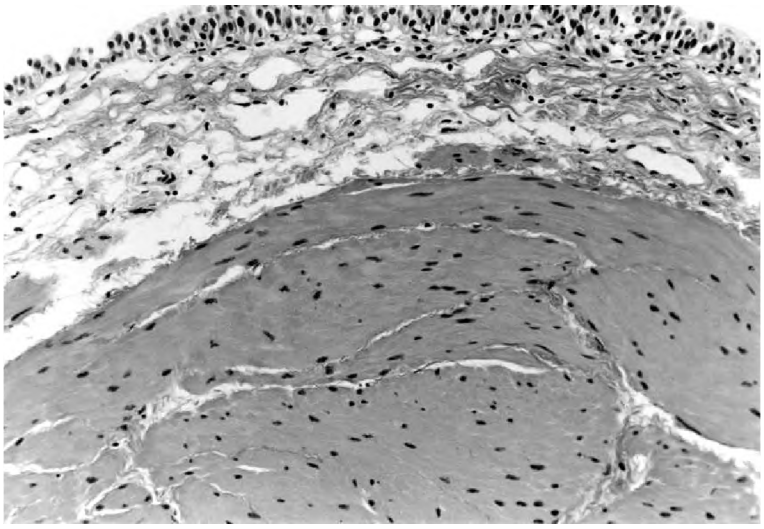

Figure 4 Normal bladder biopsy lined by four to five layers of urothelial cells lying on a narrow mucosa under which there is a normal detrusor muscle. (Magnification 250x, HCE staining)

One patient with severe BOO had severe fibrosis and elastosis of the detrusor and a hypertrophic muscularis mucosae. This 59-year old patient also had severe LUTS, a prostate of 32 grams, a trabeculated bladder on cystoscopic examination, but a stable bladder during cystometry. He had a mild urinary tract infection two months before surgery, but had no evidence of any other disease that might have inflicted the bladder condition.

Table 2 Correlation between Schäfer class and overall histologic diagnosis of biopsy

Schäfer class	Diagnosis			
	Normal	Abnormal	Very abnormal	Highly abnormal
One	2	2	0	0
Two	6	2	2	0
Three	10	0	3	1
Four	13	4	0	1
Five	3	1	0	0
Six	0	0	0	1

Figure 5 shows ROC curves illustrating how age and urodynamic parameters can discriminate between abnormal and normal bladder biopsies. Small areas under the curve indicate a weak predictive value of the urodynamic obstruction parameters and age, whatever obstruction parameter was used. Figure 5D shows that instability of the detrusor, residual volume after free uroflowmetry, and prostate volume are not able to predict histologic changes either, as they were not included in the final stepwise model. Compliance and capacity of the bladder, however, do have a small and statistically significant predictive value.

Discussion

In the present analyses, the histology of the bladder wall does not appear to correlate with BOO nor with any other clinical parameter, including age. The last is in contrast with a light microscopic study by Holm et al. and a study using quantitative morphometry by Lepor et al. showing an association between BOO and age.[12,13]

The only remarkable result was observed in the group of patients with one or more abnormalities in the detrusor muscle. In this group, there was a positive correlation between the severity of the histologic changes and age. This observation can be explained by accepting that in some people the detrusor muscle can withstand aging and retain its normal morphology while in others the detrusor is susceptible to aging, which is accompanied amongst others by severe fibrosis. One patient had severe BOO and severe histologic changes. Although this is only one case, it may indicate that severe BOO does cause damage to the detrusor.

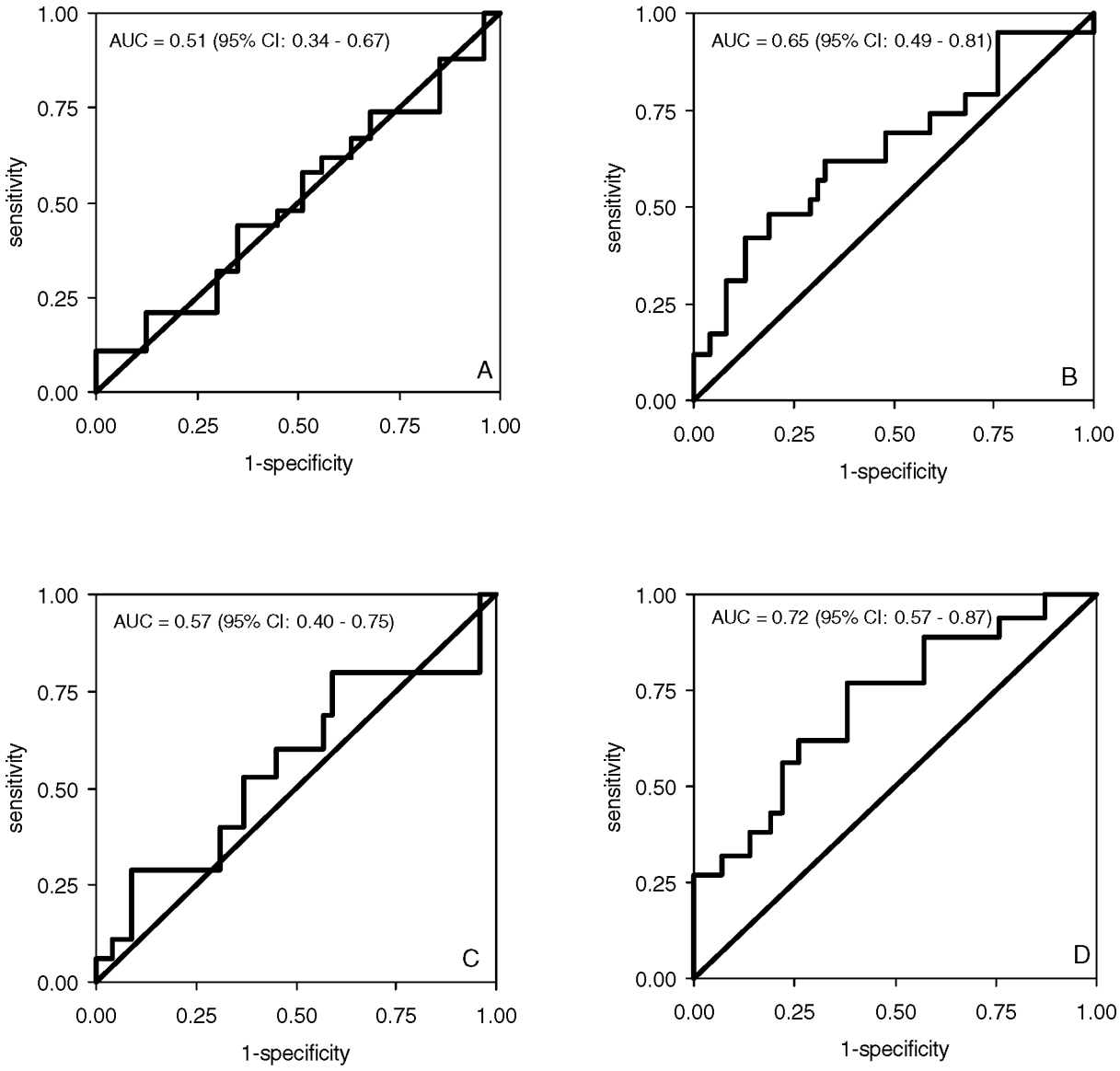

Figure 5 ROC curves depicting the ability of age and urodynamic parameters to discriminate between an abnormal versus a normal bladder wall.

A: age and URA
B: age and pdetQmax
C: age and Schäfer class
D: stepwise model with inclusion and exclusion criteria p = 0.10 and p = 0.15

Although an association could be expected between the urodynamic bladder function parameters and histology of the bladder wall, we only found a weak correlation between bladder compliance and capacity, measured by urodynamics, and histology. An important question is why we did not observe a correlation between BOO and histology

of the bladder wall, as opposed to animal studies, in which clear correlations have been reported. Closely related to this question, is there indeed no correlation or are we just not able to demonstrate it?

In this study the intra- & inter- investigator variation between two pathologists in the microscopic evaluation of histopathology of bladder biopsies were considerable. The variation was not only limited to individual features but also to the overall diagnosis of normal or abnormal (tables 3 & 4). This finding underlines the conclusion that evaluating biopsies with respect to various features and coming to a diagnosis of normal or abnormal is not unambiguous and perhaps very difficult. Several explanations are possible. First, one small biopsy with a diameter of approximately 2 mm may not be representative of the whole bladder. Second, during evaluation of the biopsy a pathologist may place more or less emphasis on a particular feature, especially if it is only marginally present. This problem is not unique for the evaluation of bladder biopsies, the whole problem of intra- and inter-observer variation has been extensively researched e.g. in the uterine cervix and particularly in low-grade pre-malignant cervical lesions moderate kappa correlations are the very best one can achieve.[14] Furthermore pathologists concede that what constitutes a normal biopsy in the context of patient age is difficult to define.

Urodynamic studies, including pressure-flow analysis, are considered the gold standard to assess BOO, but have their limitations as a diagnostic tool.[15,16] First, there are factors that influence the reproducibility of the urodynamic results. Second, the investigation is performed in an iatrogenic and non-physiologic environment. Third, operator and technical equipment influence test results. Furthermore, there may be physiologic variability in the grade of obstruction. The maximum flow appears to fluctuate due to a circadian rhythm.[17] This circadian rhythm in uroflow may very well be caused by a fluctuation in BOO or detrusor contractility. This matter has not been clarified.

Table 3 Intra-observer variation in biopsy evaluation

Conclusion one	Conclusion two			
	Normal	Abnormal	Very abnormal	Highly abnormal
Normal	14	6	0	0
Abnormal	5	13	2	0
Very abnormal	1	4	2	0
Highly abnormal	0	0	1	0

six biopsies were considered inconclusive in at least one of the two evaluations

Table 4 Inter-observer variation in biopsy evaluation between the pathologists TH and FS

Conclusion TH	Conclusion FS			
	normal	abnormal	very abnormal	highly abnormal
normal	17	3	0	0
abnormal	3	15	2	0
very abnormal	1	5	3	0
highly abnormal	0	0	1	0

four biopsies were considered inconclusive by at least one of the two pathologists

Recently, we performed two studies on the reproducibility of pressure-flow studies, in which we found a moderate intra-patient reproducibility of pressure-flow studies, performed during two different sessions and a considerable intra- and inter-investigator variation in the analysis of pressure-flow studies.[18,19] A fluctuation in the grade of obstruction makes correlation with bladder wall histology difficult, but, to date, we have no better tool to establish BOO than urodynamics.

Urodynamic studies provide a random picture of the lower urinary tract at a particular moment. Meanwhile bladder biopsies may show effects that are caused by poorly defined pathologic processes of unknown duration, such as BOO, aging, infection, and other factors that may influence bladder wall morphology.

In contrast to human studies, BOO in all animal studies was created artificially by a urethra stenosis. Consequently, a permanent, constant degree of obstruction is created and the time of implementation is precisely known. The degree of obstruction is related to functional and structural changes.[20]

The above-mentioned factors may explain why we did not find a correlation. Larger numbers of patients may be needed. Our overall patient group was not very large, but especially the fact that most histologic features were not frequent, may be important. On the other hand, there may be more sensitive histologic parameters, than fibrosis and elastosis of the detrusor to determine changes caused by BOO. Better correlations may be found using other techniques, such as quantitative morphometry or immunohistochemistry. If changes due to BOO are too subtle to be light microscopically identified, electron microscopy may give better results. Elbadawi performed extensive studies in this field concluding that BOO is associated with specific ultrastructural changes in the detrusor muscle that can explain resultant voiding dysfunction.[21,22]

All patients enrolled in this study had LUTS suggestive of BOO and were judged to be eligible for TURP, although some patients had only mild BOO, as established by urodynamics. Of course, a study with biopsies from a control group of age-matched men without LUTS and BOO, would have been preferable. Understandably, it is difficult to recruit men for this control group who are willing to undergo urodynamic studies and bladder biopsies.

Conclusion

This study shows that there is no correlation between urodynamic obstruction parameters and fibrosis or elastosis of the detrusor muscle. These features are observed in both severely obstructed patients and in patients with only mild obstruction and in the presence of BOO bladder wall morphology may be completely normal. Furthermore, it shows that the histology of the bladder wall does not significantly correlate with clinical parameters, including patient age. Thus, elderly males with BOO may have normal appearing bladder walls, while younger males with hardly any BOO may have bladder walls that show considerable abnormalities.

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General discussion

Summary

This thesis addresses aspects of urodynamic studies in men with lower urinary tract symptoms (LUTS). There are different underlying causes of LUTS, but LUTS are usually associated with benign prostatic hyperplasia (BPH). Up till now, the pathogenesis of LUTS has not been completely clarified and the assessment of LUTS is not unambiguous.

In the introduction, the concept of LUTS and the supposed relationship between LUTS, BPH and bladder outlet obstruction (BOO) are explained. Different tools in the assessment of LUTS are symptom scores, uroflowmetry, transrectal ultrasound of the prostate, and urodynamic studies including pressure-flow analysis. Urodynamic studies are considered the gold standard to diagnose BOO, but the standard use of urodynamic studies in the diagnosis of LUTS is controversial.

There are several treatments for LUTS suggestive of BOO, such as medical, minimal invasive and surgical therapies. As urodynamics are considered the best tool to establish BOO, they should also be part of the evaluation of the treatment effect.

One of the arguments not to use urodynamics in the standard work-up of men with LUTS, is the invasiveness of the investigation. In part I, a study on the tolerability of urodynamic studies is presented. Urodynamic studies in our clinic appeared to be associated with a low proportion of urinary tract infection, and low subjective and objective morbidity. Most patients found urodynamic studies tolerable and not very bothersome. Furthermore, we studied the reproducibility of pressure-flow studies (PFS) by assessing the variability of PFS, performed at two different occasions and the intra- and inter-investigator variation in the analysis of PFS. A considerable variability in the results of a single pressure-flow study was present. The reproducibility of the manual analysis of PFS was moderate owing to a considerable intra- and inter-investigator variation, mostly caused by a substantial intra-investigator variation. This variation in itself may be largely responsible for the moderate reproducibility of PFS.

Part II addresses the urodynamic effects of alpha-adrenoceptor antagonists in the treatment of LUTS. A literature review revealed that alpha-blocker treatment generally results in a small decrease of urodynamic obstruction parameters. All patients with LUTS, however, may benefit from an alpha-blocker with respect to symptoms and uroflow, whether they have BOO or not. In our clinic, a retrospective study was performed on the urodynamic effects of the alpha-blockers, alfuzosin, tamsulosin, or

terazosin, in 163 patients. The results of this study showed that the majority of patients had a significant improvement in symptom score, but no clear improvement in urodynamic obstructive parameters, irrespective of the alpha-blocker used. Furthermore, we retrospectively reviewed 316 patients treated with an alpha-blocker for LUTS to determine the efficacy on the long-term. Retreatment percentages and the parameters that influence the risk of retreatment were calculated. The overall retreatment percentage after five years of follow-up was 54%. Severe symptoms, a poor uroflow, an enlarged prostate, and urodynamically proven bladder outlet obstruction appeared to increase the risk of treatment failure.

In part III, a study on the correlation between urodynamic obstruction parameters and histologic features of the bladder wall in men with LUTS is described. Of 54 evaluable bladder wall biopsies, half did not show any abnormality. No correlation was found between the histologic features and urodynamic obstruction parameters or clinical parameters, such as symptom score, post void residual volume, prostate volume, and patient age. Thus, in our clinical study in men with LUTS we could not confirm the results of animal studies that show a clear relation between BOO and histologic changes in the bladder wall.

Future perspectives

Urodynamic studies in men with LUTS

Urodynamic studies may provide us with valuable information on the function of the lower urinary tract. It is informative about the presence of instable contractions of the bladder, the compliance, and bladder capacity, sensations of bladder filling and occurrence of incontinence. The pressure-flow analysis shows the pressures in the bladder generated during micturition. We should bear in mind, however, that the reproducibility of pressure-flow studies (PFS) is moderate and interpretations of various investigators do not necessarily correspond. Now the question rises in which cases urodynamic studies should be performed and how many PFS should be performed to be conclusive.

If on the basis of simple diagnostic tools bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) is strongly suspected in an individual patient, additional urodynamic studies are not indicated. If there is any uncertainty about the diagnosis urodynamic studies may be useful. One should be prepared, however, to repeat the investigation once or twice if the quality of the investigation was not optimal, an artifact occurred or any unreliability is suspected. Furthermore, if the result of the pressure-flow study does not correspond with other diagnostic test results of the same patient, the investigation should be repeated. In this case, the test result may vary owing to true variation in obstruction in the patient or to the moderate reproducibility of the test itself.

Urodynamic studies should continue to play a role in the evaluation of a new treatment modality for LUTS as urodynamic studies may provide insight in the mode of action of a particular treatment. In an individual patient, the moderate reproducibility of pressure-flow studies may have a great impact on a single test result. The disadvantage of the moderate reproducibility of urodynamic studies has less impact on the results of a group of patients when larger numbers of patients are tested, which is usually the case in efficacy studies of new treatment modalities.

Urodynamic studies in the way they are performed at present are costly, time-consuming and minimal invasive. New techniques are under development, which aim

at providing valuable information on bladder function and bladder outlet obstruction. They should be non-invasive and easy to perform and to repeat. A technique that can be performed on an ambulatory basis in the home situation is preferable, because it displays the normal micturition pattern during the day. An example of non-invasive urodynamics is measurement of isovolumetric bladder pressures during micturition using a pressure transducer attached to the penis with a condom catheter.[1,2] Another non-invasive method is bladder electromyography to measure bladder contraction.[3] Up till now, however, none of these techniques have proven to be preferable in clinical use to minimal invasive urodynamics.

Alpha-blockade for LUTS

Alpha-blockade will continue to play a role in the treatment of men with LUTS, as their efficacy and safety have been firmly established. In the last decade, drugs have been developed that block prostatic alpha-1-adrenoceptors selectively, aiming at an improvement in uroflow and elimination of LUTS without bothering side effects. New developments in this field will aim at more uroselectivity. Better results as for uroflow and decrease of symptoms are not to be expected, as the efficacy of the present alpha-blockers is practically comparable, irrespective of the degree of uroselectivity. Side effects may be further reduced using alpha-blockers that are more selective.

It has been assumed that the working mechanism of alpha-blockers is relieving the dynamic component of prostatic obstruction by blocking the sympathetic stimulation of alpha-adrenoceptors in the prostate. The work presented on the urodynamic effects of alpha-blockers, however, cannot confirm a decrease in obstruction. From these results, we may conclude that even in the presence of BOO, LUTS can be relieved significantly with an alpha-blocker without a decrease in obstruction. Recent research revealed other possible mechanisms by which alpha-blockers may influence LUTS. Extra-prostatic localizations of alpha-adrenoceptors, such as the urethra, detrusor, trigone, ganglia, and spinal and supra-spinal structures, seem to be involved in the pathogenesis of LUTS. Further research is necessary to clarify which mechanism is responsible for the therapeutic effect of alpha-blockers. Generally, when prescribing alpha-blockers to relieve the patients' LUTS, there is no strong indication to perform urodynamic studies, as patients with and without BOO both may benefit from an alpha-blocker.

In view of the high costs of medical care, patient selection will be more emphasized in future to reduce these costs. Looking for the best suitable candidate for long-term alpha-blocker treatment, urodynamics may help to identify these patients. Results presented in this thesis indicate that patients with significant BOO need more often a retreatment on the long term than patients without obstruction.

LUTS and the bladder wall

From the results of the studies performed we could not confirm any relation between histology of the bladder wall and BOO, symptoms or any other clinical parameter. This result does not imply, however, that no relation exists. Up till now, limited research has been done on the human bladder wall in men with LUTS. Animal studies have shown a clear association between histology and obstruction, but those studies are performed in a much more controllable situation. Bladder biopsies may show the effects that are caused by poorly defined processes of unknown duration, such as BOO, but also aging, infections or other factors may influence the bladder wall morphology. It would be interesting to investigate the changes in bladder wall morphology that have taken place after a de-obstructive therapy. It would show which histologic features are caused by BOO and are reversible.

Better correlations may be found using other techniques, such as morphometry, imunohistochemistry or electron microscopy. Elbadawi performed extensive studies on ultrastructural changes in the detrusor associated with BOO.[4] This association, however, could not be confirmed by the results of a study that was performed in a collaborating hospital in Denmark (unpublished data).

With our current knowledge, bladder wall histology will not be of any value in the diagnosis of men with LUTS. Nevertheless, knowledge on the condition of the bladder in patients with LUTS remains important and diagnostic tools should be developed to investigate the bladder condition. Earlier reports showed an association between bladder wall thickness and BOO.[5] BOO causes an increase in bladder weight attributable to hypertrophy and hyperplasia of smooth muscle cells and increased interstitial collagen.[6-8] Bladder wall thickness can be measured using transabdominal ultrasound. This technique may be used as a diagnostic tool in men with LUTS in the future. The feasibility and reliability of such a test should be investigated.

The concept of LUTS reconsidered

The pathogenesis of LUTS has not been completely clarified yet. As the term LUTS implies, it only is a collection of symptoms without comprehension of any underlying disease. In two third of cases LUTS are attributed to BOO, although a clear correlation between LUTS and BOO has never been established. The studies on the urodynamic effects of alpha-blockers give rise to the question whether LUTS should be attributed to BOO, even when an obstruction has been established urodynamically.

Treatment outcomes of transurethral resection of the prostate (TURP) are better when BOO has previously been confirmed by urodynamic studies, but most patients with LUTS without proven obstruction also benefit from a TURP.[9,10] By resecting the prostate one does not only remove obstructing tissue. Sensory nerves are eliminated, receptors are removed and the anatomy of the prostatic urethra is changed. The local anatomy changes from an enlarged prostate pressing on the surrounding tissues and often bulging into the bladder to a large cavity from trigone to verumontanum. This anatomical change probably has more influence on the function of the lower urinary tract than just the removal of a resistance.

The mechanism of micturition is complex and needs a many-sided approach, considering anatomical, neurologic, functional and psychologic aspects, and their interaction. A more complete view at the lower urinary tract may give us more understanding as for possible disturbances and modes of therapeutic intervention. For example in the field of neurourology a disturbance in the neurologic balance of the lower urinary tract, which is needed for the storage and voiding function, can be influenced. At present for urgency, frequency an urge-incontinence neuromodulation or percutaneus stimulation of the posterior tibial nerve is used.[11,12] The precise working mechanisms and indications of these therapies still have to be determined and maybe in the future they will play a role in the treatment of men with LUTS as well.

Considering the complex nature of LUTS and the difficulties in the diagnosis of LUTS, there are two different approaches of a patient with LUTS. The first is a straightforward trial-and-error approach, using only simple diagnostic tools and starting a therapy without a reliable diagnosis. The advantage of this approach is that no sophisticated diagnostic equipment and knowledge about the equipment is needed. Starting with alpha-blocker therapy is a good choice as it is generally harmless and treatment can be interrupted without lasting consequences. The disadvantage of this approach is that a considerable period may pass before an effective therapy is selected, while trying differ-

ent therapies is quite expensive. The second approach consists of a complete diagnostic work-up including determination of predictive factors for treatment outcome of the various treatment modalities and a treatment is chosen based on the highest probability of success. In future, neural networks may prove useful in improving prediction of treatment outcome. They have the ability to detect non-linear relations and complex interactions between variables. The role of neural networks in the diagnosis of men with LUTS has recently been investigated. Neural networks turned out to have no additional value over traditional regression analysis at present.[13] The disadvantage of the extensive approach is that all the necessities should be at one's disposal including knowledge about the various diagnostic tests and trained personnel. Based on the pros and cons of the different diagnostic approaches, an algorithm should be development to guide urologists and general practitioners in the assessment and choice of therapy in men with LUTS.

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Samenvatting

Dit proefschrift behandelt verscheidene aspecten van het urodynamisch onderzoek in mannen met lagere urinewegsymptomen (lower urinary tract symptoms of kortweg luts). Er zijn verschillende onderliggende oorzaken van luts, maar meestal worden luts veroorzaakt door benigne prostaat hyperplasie (bph). De pathogenese van luts is echter nog niet geheel opgehelderd en de diagnostiek van luts is niet eenduidig.

In de introductie worden het concept luts en de relatie tussen luts, bph en blaasuitgangsobstructie uitgelegd. De verschillende middelen in de diagnostiek van mannen met luts zijn symptoomscores, urinestraalmeting, transrectaal echo-onderzoek van de prostaat en het urodynamisch onderzoek inclusief pressure-flow analyse. Het urodynamisch onderzoek wordt beschouwd als de gouden standaard in de diagnostiek van blaasuitgangsobstructie, maar het standaard gebruik van het urodynamisch onderzoek is controversieel.

Er zijn verschillende behandelingen voor luts, zoals medicatie, minimaal invasieve behandelingen en operatieve ingrepen. Aangezien het urodynamisch onderzoek geacht wordt het beste middel te zijn om blaasuitgangsobstructie vast te stellen, moet het ook een onderdeel van de evaluatie van een (nieuwe) behandelmethode zijn.

Een van de argumenten om het urodynamisch onderzoek niet standaard te gebruiken in de diagnostiek van mannen met luts is de invasiviteit van het onderzoek. In deel I wordt een studie beschreven naar de tolerantie van het urodynamisch onderzoek. Het urodynamisch onderzoek bleek weinig urineweginfecties te veroorzaken en weinig subjectieve en objectieve morbiditeit. De meeste patiënten vonden het onderzoek tolerabel en niet erg vervelend. Verder hebben we de reproduceerbaarheid van pressure-flow studies (pfs) onderzocht, door middel van een studie naar de variabiliteit van pfs, verricht op twee verschillende tijdstippen en een studie naar de intra- en inter-onderzoeker variatie in de manuele analyse van pfs. Er werd een aanzienlijke variabiliteit gevonden in de resultaten van een pfs. De reproduceerbaarheid van de manuele analyse van pfs was matig als gevolg van een aanzienlijke intra- en inter-onderzoeker variatie. Dit werd grotendeels veroorzaakt door de grote intra-onderzoeker variatie. Deze variatie op zich kan al verantwoordelijk zijn voor de matige reproduceerbaarheid van pfs.

Deel II behandelt de urodynamische effecten van alpha-adrenoceptor antagonisten in de behandeling van LUTS. Een literatuuronderzoek liet zien dat behandeling met een alpha-blokker over het algemeen resulteert in een kleine vermindering van urodynamische obstructie parameters. Echter, alle patiënten kunnen baat hebben bij een alpha-blokker wat betreft verbetering in symptomen en plasstraal, onafhankelijk van de aanwezigheid van blaasuitgangsobstructie. In onze kliniek is een retrospectieve studie verricht naar de urodynamische effecten van de alpha-blokkers alfuzosin, tamsulosin en terazosin in 163 patiënten. De resultaten van deze studie lieten zien dat het merendeel van de patiënten een significante verbetering in symptomen hadden, maar geen duidelijke verbetering in urodynamische obstructie parameters, onafhankelijk van het type alpha-blokker dat werd gebruikt. Verder hebben we 316 patiënten, die behandeld werden met een alpha-blokker voor LUTS, retrospectief onderzocht om het lange termijn effect vast te stellen. Herbehandelingspercentages en de parameters die het risico van herbehandeling beïnvloeden werden berekend. Het herbehandelingspercentage van de hele groep na vijf jaar follow-up was 54%. Ernstige symptomen, een slechte plasstraal, een vergrote prostaat en urodynamisch bewezen blaasuitgangsobstructie bleken de kans op falen van de behandeling te vergroten.

In deel III wordt een studie beschreven waarin urodynamische obstructie parameters werden gecorreleerd met histologische kenmerken in de blaaswand van mannen met LUTS. Van 54 evalueerbare blaaswandbiopten liet de helft geen afwijkingen zien. Er werd geen correlatie gevonden tussen de histologische kenmerken en urodynamische obstructie parameters noch klinische parameters, zoals symptoomscore, blaasresidu, prostaat volume and leeftijd van de patiënt. Onze klinische studie in mannen met LUTS kon dus de resultaten van dierstudies, die een duidelijk verband laten zien tussen blaasuitgangsobstructie en histologische veranderingen in de blaaswand, niet bevestigen.

Toekomstverwachtingen

Het urodynamisch onderzoek kan ons waardevolle informatie verschaffen over de functie van de lagere urinewegen. Omdat de reproduceerbaarheid van het onderzoek slechts matig is en omdat de interpretatie van het onderzoek lang niet altijd eenduidig is, kan het urodynamisch onderzoek niet functioneren als de gouden-standaard-test in de diagnostiek van mannen met LUTS. Wanneer er op basis van simpele diagnostische tests geen betrouwbare diagnose kan worden gesteld, kan een urodynamisch onderzoek zin-

vol zijn. In dat geval moet men echter bereid zijn het onderzoek te herhalen wanneer de kwaliteit van het onderzoek niet optimaal is.

Het urodynamisch onderzoek moet een rol blijven spelen bij de evaluatie van nieuwe behandelmethoden, aangezien het onderzoek inzicht kan geven in het werkingsmechanisme van een specifieke behandeling.

Urodynamische onderzoeken, zoals deze momenteel worden uitgevoerd, zijn kostbaar, tijdrovend en minimaal invasief. Daarom worden nieuwe technieken ontwikkeld die informatie verschaffen over de functie van blaas en blaasuitgang, zoals het isovolumetrisch meten van de blaasdruk met een drukmeter, die aan de penis wordt vastgemaakt met een condoomcatheter of het meten van de blaasdruk middels electromyografie. In de praktijk blijken deze technieken nog niet beter te zijn dan het urodynamisch onderzoek.

In de behandeling van LUTS zullen alpha-blokkers een rol blijven spelen, omdat de effectiviteit en veiligheid van deze medicijnen duidelijk zijn vastgesteld. Er is verondersteld dat alpha-blokkers de dynamische component van blaasuitgangsobstructie opheffen. De resultaten van het onderzoek beschreven in dit proefschrift konden een vermindering van blaasuitgangsobstructie door alpha-blokkade niet bevestigen. Wanneer alpha-blokkers worden voorgeschreven is er geen sterke indicatie om tevoren een urodynamisch onderzoek te verrichten, aangezien zowel mannen met als zonder blaasuitgangsobstructie baat kunnen hebben bij een alpha-blokker.

Met onze huidige kennis zal blaashistologie geen rol spelen in de diagnostiek van mannen met LUTS, omdat er geen relatie kon worden aangetoond tussen blaashistologie en LUTS of blaasuitgangsobstructie. Bij gebruik van andere onderzoekstechnieken zoals morfometrie, immunohistochemie of electronen microscopie, zal wellicht wel een dergelijke relatie worden gevonden.

De pathogenese van LUTS is nog niet geheel opgehelderd. De studies in dit proefschrift doen de vraag rijzen of LUTS wel geheel toegeschreven moeten worden aan blaasuitgangsobstructie, zelfs wanneer obstructie bewezen is. Het mictiemechanisme is complex en behoeft een veelzijdige aanpak, waarbij anatomische, neurologische, functionele en psychologische aspecten en hun interactie beschouwd moeten worden. Een volledige kijk op de lage urinewegen zorgt wellicht voor meer begrip betreffende mogelijke verstoringen en aangrijppunten voor therapeutische interventie. Op het gebied van de neurourologie bijvoorbeeld kan een verstoring in het neurologisch evenwicht

van de lage urinewegen worden verholpen middels neuromodulatie of percutane stimulatie van de nervus tibialis posterior. Het precieze werkingsmechanisme van deze technieken en de indicaties moeten nog vastgesteld worden en misschien zullen zij in de toekomst ook een rol spelen in de behandeling van LUTS.

De complexe aard van LUTS en de moeilijkheden in de diagnostiek ervan in ogenschouw nemend, zijn er twee benaderingen mogelijk van een patiënt met LUTS. De eerste is een proefondervindelijke aanpak, waarbij gestart wordt met een therapie zonder betrouwbare diagnose. De tweede aanpak bestaat uit een compleet diagnostisch traject, inclusief het bepalen van prognostische factoren voor het behandelingsresultaat van de verscheidene behandelingsmogelijkheden. Bij deze aanpak wordt een behandeling gekozen met de meeste kans op succes. Beide benaderingen hebben vanzelfsprekend hun voor- en nadelen. Op basis van deze voor- en nadelen zou een algoritme ontwikkeld moeten worden om urologen en huisartsen te leiden in de diagnostiek en behandelingkeuze bij mannen met LUTS.

List of abbreviations

AG-number	Abrams-Griffiths number
AUC	Area Under the Curve
BOO	Bladder Outlet Obstruction
BPE	Benign Prostatic Enlargement
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CI	Confidence Interval
CV	Coefficient of Variation
DHT	Dihydrotestosterone
ICS	International Continence Society
IPSS	International Prostate Symtom Score
LUTS	Lower Urinary Tract Symptoms
pdetQmax	Detrusor pressure at maximum flow rate
PFS	Pressure-Flow Studies
PSA	Prostate Specific Antigen
PVR	Post-Void Residual Volume
Qmax	Maximum urinary flow rate
QOL	Quality of Life
RCT	Randomised Controlled trial
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SE	Standard Error
TRUS	Transrectal ultrasound of the Prostate
TUMT	Transurethral Microwave Thermotherapy
TURP	Transurethral Resection of the Prostate
UDS	Urodynamic Study
URA	Urethral resistence index
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale

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Curriculum vitae

Barbara Kortmann werd geboren op 28 april 1972 te Nijmegen. In 1990 behaalde zij het VWO-diploma aan het Stedelijk Gymnasium te Nijmegen. Daarna begon zij aan de studie Geneeskunde aan de Medische Faculteit van de Rijksuniversiteit Leiden. In 1995 behaalde zij haar doctoraaldiploma. Tijdens haar co-schappen lag haar interesse met name op het gebied van de obstetrie. In 1995 verbleef zij een aantal maanden in het St. Mary's hospital te Isingiro, Tanzania, alwaar zij onderzoek deed naar de effectiviteit van de training van traditionele vroedvrouwen *(Measurement of the effectiveness of traditional birth attendant training).* Tijdens haar keuze-co-schap schreef zij een studieprotocol voor een studie naar de preventie en de gevolgen op lange termijn van de totaalruptuur *(Prevention and long-term follow-up of obstetric anal sphincter ruptures)* (Begeleider: Dr. J. van Roosmalen). De interesse voor de urologie werd gewekt tijdens het co-schap urologie, dat slechts twee weken duurde. In augustus 1997 behaalde zij haar artsexamen cum laude.

Na haar artsexamen liep zij een wetenschappelijke stage op het steencentrum urologie van het Universitair Medisch Centrum St Radboud te Nijmegen (Hoofd: Dr. J.J.M.C.H. de la Rosette), alwaar de eerste bouwstenen van dit proefschrift werden gelegd. Van december 1997 tot november 1998 werkte zij als AGNIO op de afdeling urologie van het Canisius Wilhelmina Ziekenhuis te Nijmegen (Opleider: Dr H.F.M. Karthaus). In juni 1998 werd zij aangenomen voor de opleiding urologie in het cluster Nijmegen in een AGIKO-constructie, een constructie waarbij promotie-onderzoek met opleiding wordt gecombineerd. Van november 1998 tot en met december 2000 was zij verbonden aan de afdeling urologie van het Universitair Medisch centrum St Radboud te Nijmegen (Hoofd: Prof. Dr. F.M.J. Debruyne). In deze periode werd het onderzoek verricht dat tot dit proefschrift heeft geleid.

In het kader van de opleiding tot uroloog begon zij in januari 2001 aan haar chirurgische vooropleiding in het Canisius Wilhelmina Ziekenhuis te Nijmegen (Opleider: Dr. E.D.M. Bruggink).

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