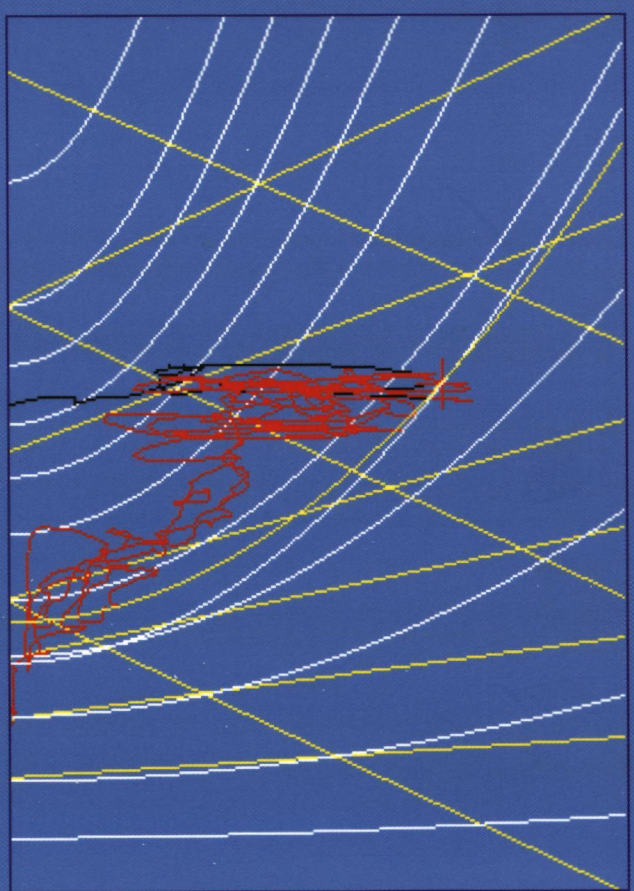
Micturition variables in the assessment and treatment of patients with lower urinary tract symptoms



Wim P.J. Witjes

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List of Abbreviations

A_{theo}	theoretical cross-sectional urethral lumen during urodynamic investigation
AUA	American urological association
AUA-7 index	the sum of the specific answers to the AUA symptom questions (identical to total I-PSS)
BOO	bladder outlet obstruction (urodynamical diagnosis)
BPH	benign prostatic hyperplasia (histological diagnosis)
BPE	benign prostatic enlargement (clinical diagnosis)
BPO	benign prostatic obstruction (urodynamical diagnosis of BOO due to BPE)
CIs	confidence intervals
CLIPS	clinical prostate score
DBP	diastolic blood pressure
Free Qmax	maximum flow during free urinary flow
Free res vol	residual volume after free flow
Free void perc	voided percentage after free flow
Free void vol	voided volume after free flow
ICS	international continence society
ICS-'BPH' study	study of the ICS in patients with LUTS
I-PSS	international prostate symptom score
I-PSS fill	the sum of the answers to I-PSS questions 2+4+7 (related with the filling phase of the urinary bladder)
I-PSS void	the sum of the answers to I-PSS questions 1+3+5+6 (related with the voiding phase of the urinary bladder)
ITT	international terazosin trial
LUTS	lower urinary tract symptoms
L-PURR	linear passive urethral resistance relation
Noc	nocturia score (answer to I-PSS question number 7)
OPD	out-patient department
$P_{det}Qmax$	detrusor pressure at maximum flow
$Pvoid_{min}$	minimum urethral opening pressure at the end of flow
PSA	prostate specific antigen
pabd	intra-abdominal pressure
pdetr	detrusor pressure (pves minus pabd)
pves	intravesical pressure

Qmax	maximum urinary flow
QoL	quality of life
SD or sd	standard deviation
total I-PSS	the sum of the specific answers to the I-PSS questions (identical to AUA-7 index)
TRUS	transrectal ultrasound of the prostate
TUMT	transurethral microwave thermotherapy
TURP	transurethral prostatectomy
TZ	transition zone of the prostate
TZ index	ratio between TZ volume and total prostate volume
UIC/BME	urological information centre / biomedical engineering research center of the department of urology, Nijmegen
URA	urethral resistance factor
Urod Qmax	maximum flow during urodynamic investigation
Urod res vol	residual volume after urodynamic investigation
Urod void perc	voided percentage at pressure-flow study
WW	depending on context: watchful waiting or Wim P.J. Witjes

Chapter 1

Introduction and scope of the thesis

Lower urinary tract symptoms (LUTS) are accepted by most cultures as an inevitable consequence of aging.[1,2] LUTS are suggested to be caused by benign prostatic hyperplasia (BPH) and are traditionally labelled as 'prostatism'. The term 'prostatism' implies both cause and remedy and has been in widespread usage for over two decades. This term regrettably does not describe what it implies.[3] Therefore, Abrams suggested that the terminology in this area should be redefined.[4] BPH is a histological diagnosis that affects approximately 45 % of men at 60 years of age[1] and has been shown by Berry et al to occur in 88 % of men aged over 80.[5] Although BPH is prevalent, it may not lead to the clinical diagnosis benign prostatic enlargement (BPE) or to the urodynamical diagnosis benign prostatic obstruction (BPO). Similarly, even though BPO exists, the patient may not be troubled by LUTS.[4] Consequently, prior to any treatment one should be informed about the origin of the complaints.

The incidence and clinical significance of LUTS have been increasingly difficult to evaluate, since the indications for therapeutic intervention have shifted from attempts to preserve life in elderly patients to those improving quality of life of younger patients. Also, as we move into an era where alternatives to surgery are increasingly used, the time has come to consider which diagnostic criteria should be established before any pharmacological, minimally invasive or invasive treatment can be recommended. To assess patient's complaints, subjective variables can be used such as symptom scores and/or objective variables such as prostate volume and voiding studies. Most urologists agree that only patients with BPO should undergo surgical intervention but nevertheless, the decision for surgery is usually based primarily on the nature and severity of symptoms.

Considerable controversy surrounds not only the initial evaluation of men with LUTS but also the most appropriate means of assessing response to treatment.[6,7] In this thesis, in chapter 2-5, the significance of the aforementioned micturition variables in the assessment of patients with LUTS is investigated. Furthermore, in chapter 6-8, the impact of noninvasive, minimally invasive and invasive treatments on subjective and objective micturition variables is quantified and compared within groups with various degrees of bladder outlet obstruction (BOO).

Evaluation of men with LUTS: Symptoms

A significant advance in recent years has been the introduction of validated symptom questionnaires used by the majority of urologists.[8] The most popular of these, the American Urological Association (AUA) symptom index, later adopted by the World Health Organization as the Interna-

tional Prostate Symptom Score (I-PSS), has been demonstrated to have high test-retest reliability and to correlate strongly with the patients' degree of bother from their urinary condition.[9-12] The total symptom score derived from this index can be divided into storage and voiding symptoms.[4] Storage symptoms are correlated with the filling phase of the urinary bladder and voiding symptoms with the voiding phase. Examples of storage symptoms derived from the I-PSS questionnaire are repeated micturition, urge, and nocturia. Examples of voiding symptoms are intermittency, weak stream and push or strain to begin micturition.

Although the I-PSS is now widely used, there are several potential difficulties with its use in men with LUTS. First, the ability of men to translate their voiding characteristics accurately into a scoring index is unclear. Matzkin et al prospectively correlated the AUA symptom score with voiding patterns determined subsequently by a home uroflowmetry system in 42 men referred for the evaluation and treatment of LUTS.[13] They found that men overestimated daytime frequency and that the perception of intermittent and weak stream was poorly correlated with the results of uroflowmetry. Second, LUTS are nonspecific and may be attributed to physiologic changes in the aging detrusor,[3] or even from habit and changes in lifestyle that commonly occur as men grow older. This is well demonstrated by the similar pattern and intensity of voiding symptoms seen in an age-matched female population.[14] Third, symptom questionnaires have been validated in groups of patients with the clinical diagnosis of 'BPH', but in only one, the I-PSS, has the relationship between symptoms and clinical objective measurements including the urodynamic diagnosis of BOO been investigated.[15-18] The relationship between symptoms and urodynamic findings of the I-PSS questionnaire appeared to be rather poor. Obviously, symptom scores measure the severity of symptoms but do not tell a physician the reasons for the symptoms. Fourth, the prevalence of symptoms in the community is greater than the number of men who seek medical or surgical help indicating that men do not always perceive that their LUTS cause them problems.[1,11] The perception of LUTS seems to be a personal matter that could be dissimilar among men in different age groups and various environmental and socio-demographic circumstances.

In 1991, the International Continence Society (ICS) started an international multicentre study in patients with LUTS suggestive of BOO, to validate a new questionnaire incorporating all urinary symptoms (22 questions measuring 20 symptoms), related problems (from 19 symptoms) and quality of life issues that could be indicative of BPO, detrusor instabil-

ity and detrusor underactivity and other urinary conditions.[19] The ICS-'BPH' questionnaire differs from the AUA questionnaire in the number of questions and in the sequence of the problem questions. In the AUA questionnaire, the symptoms questions are the first that have to be completed. Hereafter, for each specific symptom question, the degree of problem that they cause is assessed. In the ICS-'BPH' questionnaire the degree of problem is assessed directly after each specific symptom question (example in chapter 3). The aims of the ICS-'BPH' study were: 1) to investigate the relationship between the results of urodynamic studies and a wide range of urinary symptoms; 2) to develop and validate an ICS-'BPH' symptom score for use in research and clinical practice and 3) to compare pre- and post-treatment symptoms with the results of advanced urodynamic pressure-flow study evaluation, used as the 'gold standard' for the quantification of the degree of obstruction in elderly men[20], in order to be able to define the characteristics of patients who will benefit from the currently used therapies.

In chapter 2 and 3, the results of the ICS-'BPH' study are reported. In ***chapter 2***, international differences in the reporting of LUTS, and related bother in patients with LUTS suggestive of BOO are investigated. In ***chapter 3***, the relationship between a wide range of symptoms from the ICS-'BPH' questionnaire and the results of urodynamic pressure-flow studies is reported.

Evaluation of men with LUTS: prostate volume

Estimation of the prostate volume is an important variable in the assessment of patients with LUTS. Transrectal ultrasound (TRUS) of the prostate is now widely used to support the diagnosis and choice of treatment.[21] TRUS currently provides the most accurate means of measuring prostate volume and also demonstrates the true extent of transition zone (TZ) enlargement.[22] According to McNeal's assumption of zonal anatomy of the prostate, the TZ is the major site for development of benign prostatic hyperplasia.[23] The traditional theory is that with the enlargement of the adenoma, the adenoma compresses the outer part of the gland, the peripheral zone that is traditionally known as the surgical capsule. The relationships between symptoms and total prostate volume have been described by Ezz El Din et al who in 803 patients found no correlation.[18] The correlation between urodynamic variables of obstruction and total prostate volume have been shown to be statistically significant but weak.[24,25] The value of volumetric determination of the TZ was recently reported in several studies. Hammerer et al assessed the unique

relationship of TZ tissue to prostate specific antigen (PSA) elevation and underscored the importance of considering the TZ as a source of false-positive diagnosis of prostate cancer.[26] Hence, determination of the whole prostate volume and TZ volume by TRUS may increase the sensitivity of PSA in detecting prostate cancer. Tempany et al analyzed differential zonal volumes and their changes after treatment with finasteride and concluded that the TZ was more affected by medical treatment than the peripheral zone.[27] Using these ideas, some studies investigated whether separation of the peripheral zone volume from the adenoma would improve the correlation with other clinical and urodynamic variables. Furthermore, the relation between the TZ and total gland volume, expressed as TZ index was reported to correlate better than total volume alone with other clinical and urodynamic variables.[28]

Chapter 4 deals with the question if transrectal ultrasound measurement of the TZ of the prostate and the ratio between TZ volume and total prostate volume (TZ index) correlates better with the results of clinical and urodynamic investigations than total prostate volume alone.

Evaluation of men with LUTS: Uroflowmetry

For decades uroflowmetry has played a major role in the evaluation of LUTS. Urologists use measurements of uroflowmetry along with patient symptoms and other clinical findings to make decisions regarding the need for therapeutic intervention. Besides its diagnostic role, uroflowmetry has evolved as one of the most important investigations in the assessment of the efficacy of drug treatments and other therapies in patients with LUTS. It is a noninvasive measurement technique that is simple to perform, the results are readily available, and sophisticated flowmeters are easy to use.[29] The most modern flowmeters allow the measurement of voided volume, maximum flow, mean flow, time to maximum flow, voiding time and flow time. Moreover, the flow pattern can be described. Among the many variables, maximum flow is regarded as the most useful to assess the degree of obstruction and to monitor treatment effects. Despite its popularity, uroflowmetry is hampered by several draw-backs including its inability to differentiate between bladder outlet obstruction and impaired detrusor activity,[30] artifacts,[31] reproducibility,[32] circadian changes[32-35] and intra and interobserver variation.[36]

It is clear that in clinical trials, these draw-backs may have a negative impact on sample size requirements to achieve statistical power.[31] In ***chapter 5***, a computerized method of validation of

uroflowcurves is described. This computerized method of validation of uroflowcurves was developed for clinical research purposes with the aim to part with the interexperts variation and to minimize the intraobserver variation and the variability of maximum flow rate by automatic artifact detection and correction. The results of this computerized method were compared with the results obtained after visual correction by the experts.

Single uroflowmetry may not be sufficiently reliable for the determination of bladder outlet obstruction because many patients are unable to relax and void in the normal fashion while at the clinic. Therefore, Blaivas suggested that multiple samples are most efficient for enhancing an accurate assessment.[37] For this reason, many units have developed urine-flow clinics to obtain multiple uroflowmetry results. Although this approach increases the number of reliable measurements, it is still not an ideal situation, being time-consuming for both the patient and doctor, while the patient is still not voiding under 'normal conditions'. To overcome these problems, several home-based systems of uroflowmetry have been introduced.[32-34,38] In ***chapter 5***, a new portable home-based uroflowmetry system designed and developed to provide reliable results, is easy to use by the patient at home, has quality-control of flow-measurement, is hand-held for practical use, uses hygienic disposable beakers and from which the results are quickly and easily available, was used to investigate variability and circadian changes of uroflow.

Evaluation of men with LUTS: Urodynamic pressure-flow studies

During the WHO international consultation on BPH in 1993, it was advised that, if obstruction is the endpoint of the study, pressure-flow studies before and after treatment should be used in the evaluation of new therapies.[39] A pressure-flow study is recognized as the gold standard in diagnosing bladder outlet obstruction.[20] Urodynamic investigation is a physiologic study that determines the response of the bladder to filling and emptying. The investigation consists of artificial bladder filling; a cystometrogram and intravesical pressure recording. To evaluate bladder function during micturition the intravesical pressure is measured with simultaneous recording of uroflow. The analysis of BOO by means of urodynamic investigation with analysis of the ratio of pressure and flow during micturition will be discussed in detail in ***chapter 6*** of the thesis.

The current treatment modalities available for the patient with LUTS are diverse. Transurethral resection of the prostate is no longer the only treatment option available. Presently, watchful waiting and a variety of medical, minimally invasive and surgical approaches exist for the patient

with LUTS. With regard to medications, there are the α1-adrenergic antagonists (alfuzosin, doxazosin, tamsulosin and terazosin) and the 5-α-reductase inhibitors (finasteride). The minimally invasive procedures that are now available include balloon dilatation of the prostate, urethral stents, transurethral thermotherapy, transurethral needle ablation, laser ablation of the prostate, transurethral incision of the prostate and there are a number of new approaches now under development and being investigated. All these treatment modalities have shown that they are able to improve the symptoms of patients with LUTS. However, there is a large placebo factor: more than one third of the patients with LUTS who remain untreated or are treated with a sham procedure or a placebo experience spontaneous improvement based on subjective criteria.[40] The spontaneous improvement based on objective criteria is reported to be smaller than that based on subjective criteria.[40] Pressure-flow studies enable us to investigate the relationship between subjective efficacy of treatment and objective voiding variables.

Previously, when the therapeutic choice was limited to surgery or watchful waiting, pressure-flow evaluation was simply used to diagnose bladder outlet obstruction. Because new, less invasive treatment modalities are now available, precise grading of obstruction is increasingly important in the objective evaluation of treatment efficacy.[41] The clinical nomogram used in our study has 7 obstruction categories, and is more detailed than a diagnosis of obstruction or no obstruction.[42] Pressure-flow evaluation is able to provide a continuous numeric scale of obstruction and, therefore, is even more refined.

Although the use of pressure-flow studies does lead to a more accurate diagnosis of BOO, the most important issue remains whether this improved distinction leads to a sufficiently better treatment outcome to justify its use.[7]

In ***chapter 6-8***, the impact of noninvasive, minimally invasive and invasive treatments on subjective and objective micturition variables is quantified and compared within groups with various degrees of BOO.

References

1 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. The Lancet **338**: 469, 1991.

2 Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, Lieber MM: The prevalence of prostatism: A population-based survey of urinary symptoms. J Urol **150**: 85, 1993.

3 Schäfer W, Nopponey R, Rübben H, Lutzeyer W: The value of free flow rate

and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

4 Abrams P. New words for old: lower urinary tract symptoms for 'prostatism'. Brit Med J **308**: 929, 1994.

5 Berry SJ, Coffey DS, Walsh PC and Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol **132**: 474, 1984.

6 Abrams P: In support of pressure-flow studies for evaluating men with lower urinary tract symptoms. Urology **44**: 153, 1994.

7 McConnell JD: Why pressure-flow studies should be optional and not mandatory in studies for evaluating men with benign prostatic hyperplasia. Urology **44**: 156, 1994.

8 Gee WF, Holtgrewe HL, Albertsen PC, Litwin MS, Manyak MJ, O'Leary MP, Painter MR: Practice trends in the diagnosis and management of benign prostatic hyperplasia in the United States. J Urol **154**: 205, 1995.

9 Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK: Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarksy, and Maine Medical Assessment Program symptom indexes. Measurement Committee of the American Urological Association. J Urol **248**: 1558, 1993.

10 Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett ATK: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol **148**: 1549, 1992.

11 Sagnier PP, MacFarlane G, Teillac P, Botto H, Richard F, Boyle P: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. J Urol **153**: 669, 1995.

12 Guess HA, Chute CG, Garraway WM, Girman CJ, Panser LA, Lee RJ, Jacobsen SJ, McKelvie GB, Oesterling JE, Lieber MM: Similar levels of urological symptoms have similar impact on Scottish and American men, although Scots report less symptoms. J Urol **150**: 1701, 1993.

13 Matzkin H, Greenstein A, Prager-Geller T, Sofer M, Braf Z: Do reported micturition symptoms on the American Urological Association Questionnaire correlate with 24-hour home uroflowmetry recordings ? J Urol **155**: 197, 1996.

14 Lepor H, Machi G: Comparison of the AUA symptom index in unselected males and females between 55 and 79 years of age. Urology **42**: 36, 1993.

15 Barry MJ, Cockett ATK, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol **150**: 351, 1993.

16 Ko DSC, Fenster HN, Chambers K, Sullivan LD, Jens M, Goldenberg SL. The correlation of multichannel urodynamic pressure-flow studies and American Urological Association Symptom index in the evaluation of benign prostatic hyperplasia. J Urol **154**: 396, 1995.

17 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH. The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156**: 1020, 1996.

18 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Debruyne FMJ, de la Rosette

JJMCH. Correlation between uroflowmetry, prostate volume, postvoid residue, and lower urinary tract symptoms as measured by the international prostate symptom score. Urology **48**: 393, 1996.

19 Abrams P, Donovan J, van Kerrebroeck P, Nordling J, Schäfer W, Thuroff J, Neal D and the ICS-'BPH' study group: The ICS-'BPH' Study: background and design. Neurourol Urodyn **13**: 483, 1994.

20 Abrams P and Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Brit J Urol **51**: 129, 1979.

21 Ezz El Din K, de la Rosette JJMCH: Transrectal ultrasound of the prostate. Br J Urol **78**: 2, 1996.

22 Kirby RS: The clinical assessment of benign prostatic hyperplasia. Cancer **70**: 284, 1992.

23 McNeal JE: Normal histology of the prostate. Am J Surg Path **12**: 619, 1988.

24 Rosier PFWM, de la Rosette JJMCH: Is there a correlation between prostate size and bladder outlet obstruction? World J Urol **13**: 9, 1995.

25 Bosch JLHR, Kranse R, van Mastrigt R, Schröder FH: Reasons for the weak correlation between prostate volume and urethral resistance parameters in patients with prostatism. J Urol **153**: 686, 1995.

26 Hammerer PG, McNeal JE, Stamey TA: Correlation between serum prostate specific antigen levels and the volume of the individual glandular zones of the human prostate. J Urol **153**: 111, 1995.

27 Tempany CM, Partin AW, Zerhouni EA, Zinreich EA, Zinreich SJ, Walsh PC: The influence of finasteride on the volume of peripheral and periuretheral zones of the prostate in men with benign prostatic hyperplasia. Prostate **22**: 39, 1993.

28 Kaplan SA, Te AE, Pressler LB, Olsson CA: Transition zone index as a method of assessing benign prostatic hyperplasia: correlation with symptoms, urine flow and detrusor pressure. J Urol **154**: 1764, 1995.

29 Jensen KM-E: Uroflowmetry in elderly men. World J Urol **13**: 21, 1995.

30 McLoughlin J, Gill KP, Abel PD, Williams G: Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. Brit J Urol **66**: 303, 1990.

31 Grino PB, Bruskewitz R, Blaivas JG, Siroky MB, Andersen JT, Cook T, Stoner E: Maximum urinary flow rate by uroflowmetry: automatic or visual interpretation. J Urol **149**: 339, 1993.

32 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147**: 1044, 1992.

33 Nakamura S, Ishiyama S, Kobayashi Y, Tokue A: Automatic integrated circuit card system for recording 24-hour uroflowmetry. J Urol **150**: 926, 1993.

34 Nakamura S, Kobayashi Y, Tozuka K, Tokue A, Kimura A, Hamada C: Circadian changes in urine volume and frequency in elderly men. J Urol **156**: 1275, 1996.

35 Burgio KL, Engel BT, Locher JL: Normative patterns of diurnal urination across 6 age decades. J Urol **145**: 728, 1991.

36 Jørgensen JB, Jensen KM-E, Klarskov P, Bernstein I, Abel I, Mogensen P: Intra- and inter-observer variations in classification of urinary flow curve

patterns. Neurourol Urodyn **9**: 535, 1990.

37 Blaivas JG: Techniques of evaluation. In: Neurourology and Urodynamics. Principles and Practice. Edited by SV Yalla, EJ McGuire, A Elbadawi and JG Blaivas. New York: Macmillan Publishing Co., chapt. 10, pp. 155-198, 1988.

38 Meier AHP, van Waalwijk van Doorn ESC, van der Vleuten CPM, Delaere KPJ, Janknegt RA: Reliability of free uroflowmetry using repeated measurements of homeflowmetry in males. Neurourol Urodyn **13**: 453, 1994.

39 Aso Y, Boccon-Gibod L, Brendler CB, Calais da Silva F, Cockett ATK, Fowler JE, Homma Y, Moriyama N, Okajima E, Richard F: Clinical research criteria, in Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K and Murphy G: Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH). Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 343-359.

40 Isaacs JT: Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate **3**: 1, 1990.

41 McGuire EJ: The role of urodynamic investigation in the assessment of benign prostatic hypertrophy. J Urol **148**: 1133, 1992.

42 Schäfer W, Waterbär F, Langen PH, Deutz FJ: A simplified graphical procedure for detailed analysis of detrusor and outlet function during voiding. Neurourol Urodyn **8**: 405, 1989.

Chapter 2

International differences in symptoms and related bother

The ICS-'BPH' Study: International differences in lower urinary tract symptoms and related bother.

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Abstract

Purpose: We investigated international differences in the reporting of lower urinary tract symptoms (LUTS) and related bother in patients with LUTS suggestive of bladder outlet obstruction (BOO).

Material and methods: Multiple logistic regression analysis has been used to evaluate international differences in the reporting of LUTS and related bother in 1271 patients from 12 countries who participated in the ICS-'BPH' study.

Results: Country of origin was significantly associated with the prevalence of a large number (10 out of 20) of lower urinary tract symptoms, even after adjusting for potentially confounding variables including both physical and socio-demographic factors. Country of origin was also significantly associated with the reporting of bother, but for a much smaller number (2) of symptoms.

Conclusions: In different countries, LUTS may be reported to different extents. Therefore, the results of studies in particular countries may not be generally applicable to other countries. It is likely that symptom scores will conceal this variation, necessitating either the consideration of individual symptoms (as in the ICS-'BPH' study) or the development of country-specific scoring systems. An alternative would be to focus on bother, which appeared to be much less sensitive to international differences.

Introduction

Lower urinary tract symptoms (LUTS), traditionally labelled as 'prostatism', are accepted by most cultures as an inevitable consequence of aging.[1,2] The term 'prostatism' implies both cause and remedy, whereas in reality the condition results not only from infravesical bladder outlet obstruction (BOO) caused by the enlarged prostate gland, but also from motor or sensory abnormalities of detrusor and urethral function[3], or even from changes in habits and lifestyle that commonly occur as men grow older. Race, food, country of origin and other environmental factors are reported to be related to the prevalence of LUTS, but epidemiological studies are subject to many pitfalls, and the data have to be interpreted with great caution particularly because a widely accepted definition of 'clinical benign prostatic hyperplasia' ('BPH') has not been established.[2,4,5] The reported international differences in the prevalence of LUTS may reflect true differences in the prevalence of 'BPH', but they may also be related to cultural differences in the perception of or in the willingness to report symptoms. The prevalence of symptoms in the community is

greater than the number of men who seek medical or surgical help, indicating that men do not always perceive that their LUTS cause them problems.[1,6] The perception of LUTS seems to be a personal matter that could be dissimilar among men in different age groups, and various environmental and socio-demographic circumstances. Recently, Abrams has suggested that the terminology in this area should be redefined.[7] BPH is a histological diagnosis that has been shown by Berry et al to occur in 88 % of men older than 80 years.[8] Although prevalent, BPH may not lead to the clinical diagnosis of benign prostatic enlargement (BPE) or to the urodynamical diagnosis of benign prostatic obstruction (BPO). Similarly, even though BPO exists, the patient may not be troubled by LUTS.[7]

Many questionnaires have been developed for use by patients with LUTS.[9,10,11,12,13] Four questionnaires [9,10,13,14] have been validated in patients with the clinical diagnosis of 'BPH', but to our knowledge none has investigated the relationships with the urodynamic diagnosis of BOO.

In 1991, the International Continence Society (ICS) started an international multicentre study in patients with LUTS suggestive of BOO, to validate a new questionnaire incorporating all urinary symptoms, related problems and quality of life issues that indicate BPO, detrusor instability, detrusor underactivity and other urinary conditions. The aims of the study were: 1) to investigate the relationship between the results of urodynamic studies and a wide range of urinary symptoms; 2) to develop and validate an ICS-'BPH' symptom score for use in research and clinical practice and 3) to compare pre- and posttreatment symptoms with the results of advanced urodynamic pressure-flow study evaluation, used as the 'gold standard' for the quantification of the degree of obstruction in elderly men[15], in order to be able to define the characteristics of patients who will benefit from the currently used therapies.

We investigated international differences in the reporting of LUTS and related bother in patients with LUTS suggestive of BOO.

Patients and methods

In the ICS-'BPH' study, 1271 patients over 45 years of age with LUTS suggestive of BOO who were well enough to undergo prostatic surgery, if appropriate, were recruited from general urology practices in 12 countries (table 1). Patients were excluded from the study if they had an abnormal result of the mid-stream urinary specimen analysis or if they had significant other urological disease, such as prostate cancer, neurological disease or previous prostatic surgery, or if they were taking medication

Table 1. *Patient data by country. Presented are medians for each country separately, plus for the total sample, medians, 5th and 95th percentiles.*

Country	Number of patients (%)	Age (years)	Prostate Volume (cc)	Qmax (ml/s)	Voided Volume (cc)	Residual Volume (cc)
United Kingdom	214 (17)	67	30	11.3	260	100
Canada	35 (3)	61	25	10.5	158	45
Denmark	121 (9)	70	40	10.5	157	73
Germany	129 (10)	68	35	10.0	180	69
Italy	58 (4)	67	40	8.6	240	75
Netherlands	391 (31)	65	35	12.0	228	45
Portugal	49 (4)	65	50	13.4	270	67
Sweden	73 (6)	67	30	9.9	202	50
Australia	47 (4)	65	30	17.0	200	*
Israel	10 (1)	65	40	9.7	208	90
Japan	105 (8)	70	20	10.0	170	38
Taiwan	39 (3)	69	*	16.0	250	50
Total	1271 (100)	67	35	11.0	213	60
5-95th percentiles		52-80	20-60	5-24	68-489	9-274
p-value between countries		< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

* not given

active on the lower urinary tract.

All patients were evaluated at baseline by medical history, including questions concerning the location of the patient's home (city/town centre, suburbs, village/rural), marital status (married/living as married, single), work situation (in active work, retired, unemployed), and the pre-operative anaesthetic risk as indicated by the physician (minimal, moderate/severe). Symptoms were evaluated by the ICS-'BPH' study questionnaire, which allows men to report the frequency of symptoms associated with the filling, voiding and post-voiding phases, and also to assess the degree of bother that they cause.[14] The questionnaire also contains specific questions that focus on issues concerned with sexual function and the effects of symptoms on daily life. The ICS*male* questionnaire was developed in English and then professionally translated into 10 other languages. Each translation was then back translated and evaluated by a lay advisor or senior urologist from each country who was nominated as a national co-ordinator for the ICS-'BPH' study.[14] Donovan et al demonstrated that with the ICS*male* questionnaire it was possible to differentiate between men in clinical and community populations, and to detect the expected positive age gradient for most symptoms in the community group. There was reasonable agreement between relevant parts of the questionnaire, and the frequency and volume charts. Internal consistency was high, and overall the questionnaire demonstrated good test-retest reliability.[14] Furthermore, patients underwent a physical examination, including digital rectal examination with estimation of the prostatic volume and an optional ultrasonographic examination of the prostate, three free urinary flowmetries with subsequent measurement of residual urine volume, the flow with the highest maximum flow rate being used for the analysis, and urodynamic pressure-flow studies.

Statistics were used to describe the patient population, and to provide an overview of the reported prevalence of each symptom and related problem for each country. Differences across the countries in medians for quantitative variables, and differences in distributions for categorical variables, were tested with the Kruskal Wallis One Way analysis of variance and chi-square tests, respectively. The impact of country of origin was studied on the reported prevalence of symptoms and related bother by using multiple logistic regression analyses.

Initially, international differences for each symptom and related bother were tested by entering country alone (represented by 10 dummy variables) into a logistic regression model. The second step was to determine if adjusting for confounding variables changed these results. The possible confounding variables included location of the patient's home,

marital status, patient's work situation and pre-operative anaesthetic risk as indicated by the physician (all categorical); age, maximum flow rate and prostatic volume (quantitative).

The logistic regression analysis was carried out using data from 977 patients for whom complete data were available. Odds ratios and 95% confidence intervals (CIs) were calculated for each country using the UK as the reference country. Given the number of significance tests performed in each analysis, statistical significance should be interpreted with caution. Applying the Bonferroni correction for multiple testing would imply a cutoff point of about 0.0025 for each individual p value to retain an overall 5% significance level. Since the symptoms were strongly associated with each other, such a correction would be conservative. Therefore, for the present analyses a cutoff point of 1% was used, with significance between 1% and 5% being regarded as marginal.

Results

Patients with a wide range of objective variables, such as maximum flow rate, voided volume and residual volume, were included in the study (table 1). When comparing age, voided volume, maximum flow rate, residual volume, estimated prostatic volume, marital status, location of the patient's home, type of house, work situation and pre-operative anaesthetic risk, significant differences ($p < 0.02$) were apparent for all of the variables, indicating that overall patients recruited from the various countries were different.

This can be illustrated by the following factors. The largest group of patients from the UK were aged between 60 and 69 years (45%), lived in the suburbs (88%) and were retired (72%), while 24% were in active work. In Germany equal percentages of patients were between 60 and 69 years old (40%) and less than 60 years old (40%). German patients were more likely to live in a city (65%) and 77% were retired, while 21% were in active work. The largest group of patients in Italy were older than 70 years (43%), lived in a village (50%), and 77% of them were retired. Although the majority of Japanese patients (53%) were older than 70 years, the proportion in active work was considerable (40%), while only 60% were retired.

The prevalence of each of the symptoms and the proportion of men reporting problems among those who had the symptom for the various countries as well as in the entire study group are shown in tables 2 and 3. In the entire study group voiding symptoms tended to be the most frequently reported, whereas the most bothersome were storage symptoms.[16]

Table 2. *Prevalence of symptoms for each country and for the total sample. Indicated in bold are the most frequently reported symptoms for each country.*

Country No. patients	UK 214	Can 35	Den 121	Ger 129	Ital 58	Neth 391	Port 49	Swe 73	Aus 47	Isr 10	Jap 105	Taiw 39	Total 1271
terminal dribble	***95***	***97***	92	92	90	***98***	***92***	93	***98***	60	82	90	***94***
reduced stream	92	***97***	***97***	***93***	***91***	95	83	***96***	87	***90***	***93***	95	93
intermittency	88	***97***	90	88	74	91	73	92	89	80	79	***97***	88
hesitancy	87	91	81	83	71	84	67	88	81	***90***	81	***97***	83
incomplete emptying	83	91	82	86	72	77	87	81	83	70	72	***97***	81
urgency	84	79	***97***	76	61	73	55	71	72	80	51	82	75
nocturia[1]	78	70	79	80	83	64	71	74	79	40	85	87	74
repeated urination	78	79	76	78	57	72	48	70	66	70	48	92	71
strain to continue	57	72	77	77	62	73	56	70	62	60	64	85	69
postmicturition dribble	78	58	67	69	60	70	52	70	66	40	49	85	68
strain to start	50	69	67	72	47	68	61	60	60	***90***	55	87	61
urge incontinence	58	39	60	46	50	44	29	66	49	30	27	59	48
frequency[2]	50	64	50	37	40	48	35	49	30	50	46	43	46
burning	39	55	41	49	45	42	52	36	42	50	17	82	42
bladder pain	49	51	42	46	33	39	47	37	32	60	22	69	41
incontinence no cause	21	24	22	18	29	20	4	30	8	0	8	49	20
sitting to urinate	10	15	26	29	19	21	6	22	13	10	10	13	18
stress incontinence	21	15	17	17	9	15	4	15	19	10	3	31	15
urinary retention	2	0	12	24	10	7	10	11	15	10	15	26	10
nocturnal incontinence	6	12	7	12	14	14	0	14	4	0	2	10	10

[1] Nocturia is defined by urination at least 2 times per night
[2] Frequency is defined by urination at least 9 times per day.

Table 3. *Proportions reporting a symptom to be at least a bit of a problem amongst those reporting the symptom for each country and for the total sample. Indicated in bold are the most bothersome symptoms for each country.*

Country	UK	Can	Den	Ger	Ital	Neth	Port	Swe	Aus	Isr	Jap	Taiw	Total
terminal dribble	67	77	74	81	72	78	74	87	63	50	89	97	77
reduced stream	60	81	71	80	63	75	74	71	63	67	84	92	73
intermittency	51	74	66	67	74	68	66	65	55	62	81	92	66
hesitancy	58	82	70	80	73	65	87	69	63	55	88	95	70
incomplete emptying	70	86	63	82	80	70	74	80	89	71	93	95	76
urgency	79	72	85	84	70	72	81	90	82	***100***	94	94	80
nocturia[1]	81	91	86	86	79	83	76	***91***	78	75	94	94	73
repeated urination	67	87	70	71	73	68	68	75	73	86	94	92	72
strain to continue	60	73	67	72	80	64	88	78	79	50	86	97	71
postmicturition dribble	80	94	81	85	80	84	92	80	77	50	88	97	***84***
strain to start	69	75	67	77	85	47	79	64	71	57	86	97	73
urge incontinency	79	85	90	82	83	82	86	85	77	67	***100***	96	***84***
frequency[2]	***88***	89	***96***	74	78	***88***	87	***91***	71	80	94	94	76
burning	68	78	74	70	81	65	88	58	80	60	94	94	72
bladder pain	60	86	67	83	84	66	78	88	53	50	96	89	72
incontinence no cause	72	***100***	88	78	***88***	73	***100***	***91***	75	-	***100***	84	81
sitting to urinate	57	60	33	43	45	35	67	44	33	0	60	60	42
stress incontinence	52	80	58	76	80	58	50	64	67	***100***	***100***	***100***	64
nocturnal incontinence	83	***100***	88	***93***	62	73	-	80	***100***	-	***100***	***100***	81

[1] Nocturia recoded as 0-1 times per night; 2-3 times per night; 4 times or more per night.

[2] Frequency of urination recoded as 1-8 times per day; 9-12 times per day; 13 times or more per day.

The results of the logistic regression analysis are shown in tables 4-7. After controlling for possible confounding variables, country of origin was strongly significantly associated ($p<0.01$) with the prevalence of 10 of the 20 symptoms: terminal dribble, intermittency, hesitancy, urgency, repeated urination, postmicturition dribble, urge incontinence, burning, bladder pain and sitting to urinate (table 4). In addition, 5 symptoms were marginally significant ($0.01<p<0.05$): nocturia, strain to continue, strain to start, incontinence of no apparent cause, and urinary retention. Only one symptom, stress incontinence, was significant before but not after controlling for confounding factors. On the other hand, hesitancy became more significant after adjustment.

Table 5 presents odds ratios (95% CIs) for the symptoms listed as significant in table 4. All countries were compared to the UK. Results for Canada, Portugal, Australia and Israel should be interpreted with caution given the relatively small numbers. The patterns evident are different for each country but there were some similarities. For example in the Netherlands, Denmark and Germany, the symptoms of strain to continue, strain to start and sitting to urinate were considerably more prevalent than in the UK, whereas hesitancy was less prevalent. Urgency and repeated urination were both less prevalent in Italy, Sweden, Japan, the Netherlands and Germany than in the UK. In other respects a considerably different pattern of symptoms was evident in Japan. In Japan only urinary retention was more prevalent than in the UK, while terminal dribble, intermittency, hesitancy, urgency, repeated urination, post-micturition dribble, urge incontinence, burning, bladder pain, and incontinence of no known cause were all less prevalent. Interestingly, all countries had a greater prevalence of urinary retention than the UK. Overall there were marked variations in the symptomatology across countries.

After controlling for possible confounding variables, country of origin was strongly significantly associated ($p<0.01$) with bothersomeness for only 2 of the 19 symptoms for which bothersomeness was assessed: hesitancy and strain to start (table 6). In addition, 4 symptoms were marginally significant ($0.01<p<0.05$): terminal dribble, reduced stream, incomplete emptying and strain to continue. Three of these 4 symptoms had been highly significant before controlling for confounding factors, while strain to continue was unaffected by adjustment. Of the 13 symptoms not significant after adjustment only 3 were even marginally significant originally (intermittency, urgency and bladder pain).

Table 7 presents odds ratios (95% CIs) for the symptoms listed as significant in table 6. All countries were compared to the UK. Results for

Table 4. *Statistical significance from logistic regression models of the association between the prevalence of each symptom and country of origin before and after adjusting for confounding factors.*

Symptom	Unadjusted p value for country	Adjusted p value for country
terminal dribble	< 0.01	< 0.01
reduced stream	0.42	0.51
intermittency	< 0.01	< 0.01
hesitancy	0.02	< 0.01
incomplete emptying	0.07	0.14
urgency	< 0.01	< 0.01
nocturia ≥ 2 per night	< 0.01	0.01
repeated urination	< 0.01	< 0.01
strain to continue	0.02	0.01
postmicturition dribble	< 0.01	< 0.01
strain to start	0.02	0.03
urge incontinence	< 0.01	< 0.01
frequency ≥ 9 per day	0.12	0.10
burning	< 0.01	< 0.01
bladder pain	< 0.01	< 0.01
incontinence no cause	0.03	0.03
sitting to urinate	0.01	< 0.01
stress incontinence	0.04	0.15
urinary retention	0.03	0.02
nocturnal incontinence	0.18	0.56

Canada, Portugal, Australia and Israel should be interpreted with caution given the relatively small numbers. Again, the pattern for Japan was rather different from the other countries, with all 6 symptoms much more bothersome than in the UK. In Germany, terminal dribble, reduced stream, hesitancy and incomplete emptying were also highly bothersome, whereas for the other countries, only Italy and Sweden had a suggestion of markedly greater levels of bother than the UK for 2 symptoms each (terminal dribble and strain to continue). There was only 1 instance when bothersomeness was significantly less than in the UK - for strain to start in the Netherlands.

Table 5. *Odds ratios (95% confidence intervals) for presence of symptoms for the indicated country when compared with the UK, for those symptoms with a significant association with country of origin after adjusting for confounding factors. Underlined are the odds ratios for individual countries which are significantly different from the UK. *. All patients reported the symptom. **: No patient reported the symptom*

Symptoms	Canada	Denmark	Germany	Italy	Netherlands	Portugal	Sweden	Australia	Israël	Japan
terminal dribble	*	0.80	0 30	0.30	2.31	0.35	0.57	*	0.04	0.25
		0 25-2 57	0 09-0 98	0 08-1 08	0 70-7 65	0 08 1 55	0 17 1 81		0 01-0 22	0 09-0 70
intermittency	1.66	0.97	0.61	0 22	0.84	0.27	0.83	1.91	0.33	0.33
	0 20-14 11	0 37 2 52	0 23-1 61	0 08-0 57	0 39-1 79	0 10 0 74	0 29-2 35	0 22 17 0	0 06-1 82	0 14-0 77
hesitancy	0.68	0.44	0.43	0.14	0 49	0.18	0.48	1.30	0.59	0.45
	0 14-3 48	0 20-0 99	0 17 1 04	0 06-0 35	0 24-0 99	0 07 0 50	0 19 1 21	0 23-7 36	0 06-5 76	0 19-1 06
urgency	1.06	6 93	0.56	0.26	0.50	0.12	0.46	0.41	0.60	0.18
	0 32-3 57	1 53 31 42	0 26-1 21	0 11 0 59	0 28 0 89	0 05-0 29	0 22 0 93	0 13-1 34	0 11 3 35	0 09-0 36
nocturia ≥ 2 per night	0.48	1.30	1.07	1.07	0 55	0.61	0.85	0.76	0 24	1.51
	0 18-1 25	0 65 2 60	0 50 2 30	0 45 2 58	0 32-0 93	0 25 1 46	0 42 1 71	0 24-2 45	0 06-0 97	0 72 3 17
repeated urination	0.64	0.85	0.56	0 24	0 46	0.16	0.41	0.32	0.33	0.16
	0 21 1 94	0 43 1 65	0 27 1 17	0 11 0 53	0 27-0 78	0 07 0 38	0 21-0 81	0 11-0 95	0 07-1 47	0 08-0 30
strain to continue	1.43	2.88	2.82	1.30	2 07	0.93	1.68	1.49	1.04	1.62
	0 53-3 81	1 53 5 43	1 39-5 71	0 62 2 73	1 28 3 37	0 41 2 07	0 89-3 19	0 50-4 47	0 26-4 24	0 87 2 99
postmicturition dribble	0.65	0.77	0.73	0.63	0.81	0.22	0.73	0.43	0.18	0.36
	0 25 1 70	0 42 1 41	0 37 1 44	0 30-1 33	0 49-1 34	0 10 0 50	0 38-1 39	0 15 1 28	0 04 0 71	0 20-0 67
strain to start	1.68	2.13	2 27	0.71	2.14	1.17	1.36	0.91	1.84	1.14
	0 61 4 63	1 17 3 85	1 15 4 48	0 34-1 49	1 03 4 46	0 52 2 62	0 73 2 51	0 31 2 63	0 41-8 29	0 62 5 46
urge incontinence	0.93	1.28	0.60	0.92	0.77	0 23	1.88	0.54	0.37	0.31
	0 37 2 34	0 72-2 26	0 32 1 13	0 44-1 89	0 49 1 23	0 09 0 58	1 01 3 52	0 18-1 58	0 08 1 67	0 17-0 59
burning	1.32	1.38	1.68	1 36	1.02	1.92	0.83	1.03	1.43	0.29
	0 53 3 28	0 79 2 41	0 90 3 13	0 66 2 77	0 64 1 63	0 86 4 29	0 45 1 53	0 35 3 01	0 36 5 71	0 14-0 59
bladder pain	0.75	0.72	0.81	0 45	0 54	0.72	0 47	1.11	1.30	0.21
	0 30-1 87	0 41 1 26	0 43 1 52	0 21 0 93	0 34-0 86	0 32 1 60	0 26 0 88	0 39-3 20	0 32 5 28	0 11-0 41
inc no cause	1.93	1.11	0.98	1.65	0.97	0 17	1.85	**	**	0.46
	0 69-5 40	0 56 2 22	0 46 2 09	0 73 3 75	0 55 1 73	0 04-0 78	0 92 3 71			0 19 1 15
sitting to urinate	1.59	3.16	3 81	2.79	2.93	0.97	2.10	2.08	1.20	0.84
	0 46 5 44	1 53-6 53	1 74 8 35	1 11 7 02	1 55-5 54	0 25 3 74	0 95-4 64	0 51 8 51	0 13 11 1	0 34-2 11
urinary retention	**	2.62	3 49	1.74	1.44	2.41	3 62	10.7	2.46	5.17
		0 78 8 85	1 04-11 68	0 44-6 92	0 47 4 37	0 53 10 91	1 08 12 14	2 07 55 9	0 23 26 8	1 59 16 8

Table 6. *Statistical significance from logistic regression models of the association between the bothersomeness of each symptom and country of origin before and after adjusting for confounding factors.*

Bother	Unadjusted p value for country	Adjusted p value for country
terminal dribble	< 0.01	0.03
reduced stream	< 0.01	0.04
intermittency	0.02	0.31
hesitancy	< 0.01	< 0.01
incomplete emptying	< 0.01	0.01
urgency	0.04	0.14
nocturia ≥ 2 per night	0.07	0.17
repeated urination	0.23	0.17
strain to continue	0.03	0.03
postmicturition dribble	0.57	0.66
strain to start	< 0.01	< 0.01
urge incontinence	0.93	0.33
frequency ≥ 9 per day	0.84	0.82
burning	0.31	0.25
bladder pain	0.02	0.11
incontinence no cause	0.75	0.33
sitting to urinate	0.88	0.74
stress incontinence	0.93	0.96
nocturnal incontinence	0.93	0.88

Discussion

Although international variations in the prevalence of specific LUTS were clearly demonstrated in this study, the evidence that related bother differed among countries was much weaker. However, it must be considered that in this study the participating countries contributed dissimilar groups of patients with respect to the investigated variables of age, voided volume, maximum flow rate, residual volume, estimated prostatic volume, marital status, the location of the patient's home, the patient's work situation and the preoperative anaesthetic risk as indicated by the physician. Since these confounding factors may explain some of the international variations, we examined these variations after adjusting for potentially confounding factors. It must be recognized that there are several other potential confounding factors for which data were not available,

Table 7. *Odds ratios (95% confidence intervals) for bothersomeness of symptoms for the indicated country when compared with the UK, for those symptoms with a significant association between bothersomeness and country of origin after adjusting for confounding factors. Underlined are the odds ratios for individual countries which are significantly different from the UK.*

Bother	Canada	Denmark	Germany	Italy	Netherlands	Portugal	Sweden	Australia	Israël	Japan
terminal dribble	**1.26** 0.44-3.57	**1.13** 0.60-2.14	**2.61** 1.13-6.03	**1.29** 0.55-3.03	**1.73** 1.02-2.96	**1.29** 0.55-3.34	**2.73** 1.21-6.16	**1.22** 0.39-3.85	**0.39** 0.07-2.24	**3.82** 1.57-9.33
reduced stream	**4.17** 0.88-19.69	**1.34** 0.71-2.51	**2.90** 1.25-6.73	**0.73** 0.33-1.62	**1.63** 0.96-2.76	**1.04** 0.41-2.66	**1.15** 0.59-2.23	**2.03** 0.58-7.16	**0.78** 0.17-3.65	**2.42** 1.16-5.06
hesitancy	**5.38** 1.12-25.88	**1.18** 0.61-2.27	**3.94** 1.64-9.49	**1.70** 0.65-4.45	**1.17** 0.68-2.01	**5.41** 1.12-26.17	**1.38** 0.69-2.75	**1.61** 0.49-5.30	**0.77** 0.18-3.37	**4.78** 2.07-11.05
incomplete emptying	**1.43** 0.43-4.82	**0.78** 0.40-1.53	**2.89** 1.17-7.16	**1.57** 0.60-4.15	**0.96** 0.55-1.69	**1.01** 0.38-2.67	**1.33** 0.61-2.87	**3.10** 0.61-15.91	**0.61** 0.10-3.80	**5.18** 1.80-14.96
strain to continue	**2.03** 0.50-8.17	**1.07** 0.53-2.14	**1.40** 0.63-3.12	**2.14** 0.76-6.02	**0.98** 0.54-1.78	**2.93** 0.74-11.63	**2.16** 0.92-5.05	**1.86** 0.44-7.94	**0.48** 0.08-2.82	**3.53** 1.42-8.79
strain to start	**0.89** 0.25-3.17	**0.73** 0.34-1.61	**2.00** 0.77-5.18	**3.91** 0.91-16.74	**0.40** 0.16-0.99	**2.66** 0.64-11.11	**0.63** 0.27-1.44	**2.42** 0.26-22.62	**0.53** 0.09-3.08	**2.81** 0.95-8.27

such as financial status, religion, occupation, hobbies, linguistic problems and cultural differences in the perception of or willingness to report symptoms, as well as variations in decision making by general practitioners, variations in the availability of treatments for LUTS, underlying variations in the prevalence of benign prostatic enlargement and prostatic obstruction and differences in health care delivery systems.

After adjustment, country of origin was significantly associated with half of the symptoms measured, including both storage and voiding symptoms of both high and low prevalences. Controlling for a range of potential confounding variables had little effect on these relationships. There are two possible explanations for this finding. It may be that insufficient allowance has been made for potential confounders, or there may be real international differences in symptom reporting among these men. However, these international differences may arise from a number of sources, such as patient selection, health care organisation and perceptions of symptoms. In particular, the wide differences noted in the prevalences of urinary retention support the suggestion that patient selection may be different in these countries.

It is notable that there were not such marked differences for bothersomeness, although the symptoms for which there were international differences were all voiding symptoms. For symptoms in which differences were evident, reported levels of bothersomeness clearly were much lower in the UK than elsewhere, whereas Japan and Germany reported the greatest levels of bothersomeness. For bothersomeness, controlling for the confounding variables had some impact on the pattern of relationships, in most cases reducing the significance of the variation across countries.

These observations were different from the report of Burton et al, who assessed differences in attitudes to incontinence in different migrant groups in Australia. Some ethnic groups were very concerned about their incontinence but did not tell their family or seek help, while others were very active in seeking treatment. Some ethnic groups were ashamed to be incontinent, while others accepted it.[17]

It has been shown that the most frequently reported symptoms are not necessarily the most bothersome.[16] In the northern European countries UK, Denmark, the Netherlands and Sweden, the storage symptom of frequency appeared to be one of the most bothersome symptoms. In Canada, Germany, the southern European countries Italy and Portugal, Australia, Israel, and the Asian countries Japan and Taiwan, incontinence was the most bothersome symptom. This suggests that cultural differences in the perception of symptoms may be important. Generally, the most frequently reported symptoms were those associated with the

voiding phase and the most bothersome symptoms were those associated with the storage phase or incontinence.[16] This appears to be true for the majority of individual countries.

Conclusions

Nevertheless, our study indicates that international differences are relevant in the reporting of specific LUTS and related bother. Inevitably, individual countries have different cultural backgrounds and specific health care delivery systems. Therefore, the results of studies in specific countries may not be generally applicable in other countries. In particular, it may be important to consider different patterns of reporting of symptoms and bothersomeness when interpreting the results of studies using common questionnaires. Of course, symptoms are extremely important for monitoring disease progression and outcome of treatment in individual patients. Many studies use symptom scores that amalgamate individual symptom differences into 1 overall measure, thus potentially concealing this variation. The ICS*male* questionnaire avoids these difficulties by considering each symptom separately. For studies that use symptom scores it may be necessary to evaluate the effectiveness, cost-effectiveness, and influences on quality of life of treatments for LUTS in each country, or to develop country-specific scores. An alternative is to focus on bother, which appeared much less sensitive to international differences.

In addition, the ICS-'BPH' study will allow the investigation both of the role of BOO in the symptomatic evaluation of therapy, and demonstrate the ability of urodynamic and clinical parameters to predict response to new treatments. Thus, the association between urinary symptoms and BOO may be evaluated so that obstruction caused by the prostate gland can be differentiated from other conditions causing LUTS.

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References

1 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. The Lancet **338**: 469, 1991.
2 Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, Lieber MM: The prevalence of prostatism: A population-based survey of urinary symptoms. J Urol **150**: 85, 1993.
3 Schäfer W, Nopponey R, Rübben H, Lutzeyer W: The value of free flow rate and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.
4 Ekman P: BPH Epidemiology and risk factors. The Prostate (Suppl) **2**: 23, 1989.
5 Tsukamoto T, Kumamoto Y, Masumori N, Miyake H, Rhodes T, Girman CJ, Guess HA, Jacobsen SJ, Lieber MM: Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. J Urol **154**: 391, 1995.
6 Sagnier P, MacFarlane G, Teillac P, Botto H, Richard F, Boyle P: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. J Urol **153**: 669, 1995.
7 Abrams P: New words for old: lower urinary tract symptoms for 'prostatism'. Brit Med J **308**: 929, 1994.
8 Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hypertrophy with age. J Urol **132**: 474, 1984.
9 Epstein RS, Deverka PA, Chute CG, Panser L, Oesterling JE, Lieber MM, Schwartz S, Patrick D: Validation of a new quality of life questionnaire for benign prostatic hyperplasia. J Clin Epidemiol **45**: 1431, 1992.
10 Fowler FJ, Wennberg JE, Timothy RP, Barry MJ, Mulley AG, Hanley D: Symptom status and quality of life following prostatectomy. JAMA **259**: 3018, 1988.
11 Boyarsky S, Jones G, Paulson DF, Prout GR: A new look at bladder neck obstruction by the Food and Drug Administration regulators: Guidelines for investigation of benign prostatic hypertrophy. Trans Am Assoc Genital-Urin Surg **68**: 29, 1976.
12 Madsen PO, Iversen P: A point system for selecting operative candidates. In: Benign Prostatic Hypertrophy. Edited by F. Hinman Jr. New York: Springer Verlag, pp 763-765, 1983.

13 Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett ATK and the measurement committee of the American Urological Association: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol **148**: 1549, 1992.

14 Donovan JL, Abrams P, Peters TJ, Kay HE, Reynard J, Chapple C, de la Rosette J, Kondo A: The ICS-'BPH' study: The Psychometric validity and reliability of the ICS*male* questionnaire. Brit J Urol **77**: 554, 1996.

15 Abrams PH, Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Brit J Urol **51**: 129, 1979.

16 Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette JJMCH, Porru D, Thuroff JW and the ICS-'BPH' Study Group: The ICS-'BPH' study: The bothersomeness of urinary symptoms. J Urol, In Press.

17 Burton G, Mathie L: An assessment of attitudes to incontinence in different migrant groups. Neurourol Urodyn **14**: 544, 1995.

Chapter 3

Relationships between lower urinary tract symptoms and bladder outlet obstruction

The relationships between lower urinary tract symptoms and bladder outlet obstruction - results from the ICS-'BPH' study.

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Abstract

Background: Despite the lack of evidence in the literature for close relationships between lower urinary tract symptoms and bladder outlet obstruction, the majority of urologists rely on symptomatology when selecting patients for prostatic surgery. We investigated the relationships between a wide range of symptoms from the ICS*male* questionnaire and the results of urodynamic pressure and flow studies.

Methods: We evaluated 933 patients with lower urinary tract symptoms suggestive for bladder outlet obstruction from 12 countries who participated in the ICS-'BPH' study with the ICS*male* questionnaire and urodynamic pressure and flow studies. Spearman rank correlation coefficients were obtained between symptoms and measures of bladder outlet obstruction.

Results: There was little or no correlation between a wide range of symptoms and the results of pressure and flow studies.

Conclusions: From symptoms alone, it is not possible to diagnose bladder outlet obstruction. Pressure and flow studies and symptom profiles measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with lower urinary tract symptoms.

Introduction

Lower urinary tract symptoms (LUTS), traditionally labelled as 'prostatism', are accepted by most cultures as an inevitable consequence of aging.[1,2] The term 'prostatism' implies both cause and remedy, whereas in reality the condition results not only from infravesical bladder outlet obstruction (BOO) caused by the enlarged prostate gland, but also from motor or sensory abnormalities of detrusor and urethral function, or even from changes in habits and lifestyle that commonly occur as men grow older.[3]

Despite the lack of evidence in the literature for close relationships between LUTS and BOO, over half of the UK urologists rely on symptomatology when selecting patients for prostatic surgery.[4] The remaining urologists used urine flow studies, a commonly used objective method to measure the urinary stream and to quantify the effect of treatment. However, the reliability of this method is not optimal because there is a great variability in consecutive measurements.[5] Furthermore, in up to 25 % of patients with LUTS, the poor urinary stream is not due to BOO caused by the enlarged prostate gland but to a hypoactive detrusor

muscle.[3] Conversely, about 10-28 % of the patients with normal flow rate are obstructed.[6,7] Urodynamic investigation with pressure and flow analysis is used as the 'gold standard' for the quantification of the degree of obstruction in elderly men.[8] Precise grading of obstruction is becoming increasingly important in the evaluation and comparison of new treatment modalities in the treatment of patients with LUTS and BOO. Based on this precise grading of obstruction, stratification of therapeutic options has recently become available.[9,10]

Besides the assessment of objective voiding parameters, the development and use of a valid symptom questionnaire are prerequisites in both the evaluation of patients' symptoms and the measurement of outcome in clinical studies. In the past decades, at least 6 symptom questionnaires have been introduced and employed in patients with LUTS.[11-16] In 4 of these, the reliability and validity have been assessed in groups of patients with the diagnosis of 'clinical benign prostatic hyperplasia' (BPH),[11,12,15,16] but in only one has the relationships between symptoms and clinical objective measurements including the urodynamic diagnosis of BOO been investigated.[17-19]

Recently, Abrams has suggested the following redefinition of terminology.[20] BPH is a histological diagnosis that has been shown by Berry et al. to occur in 88 % of men aged over 80.[21] Although BPH is prevalent, in some patients the gland enlarges and this is then termed benign prostatic enlargement (BPE). In approximately half of the patients with BPE bladder outlet obstruction (BOO) results. BOO due to BPE is now termed benign prostatic obstruction (BPO).[20]

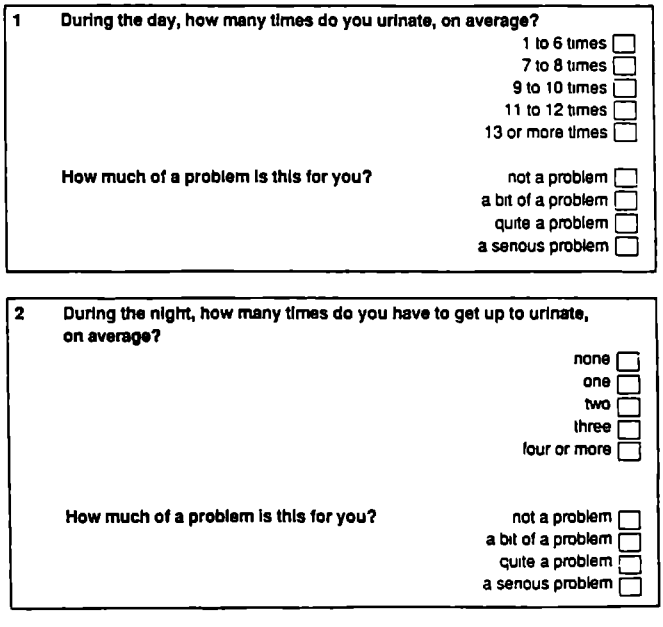
In 1991, the International Continence Society (ICS) started an international multicentre study of patients with LUTS suggestive of BOO - the ICS-'BPH' study, The aim was to validate a new questionnaire incorporating all urinary symptoms, related problems and quality of life issues that could be indicative of BOO, detrusor instability and detrusor underactivity. The aims of this study were: 1) to investigate the relationships between the results of urodynamic studies and a wide range of urinary symptoms; 2) to develop and validate an ICS-'BPH' symptom questionnaire for use in research and clinical practice and 3) to compare pre- and post-treatment symptoms with the urodynamic confirmation of BOO in order to be able to define the characteristics of patients who would be more likely to benefit from currently used therapies.

In this paper, the relationships between a wide range of urinary symptoms and BOO were investigated.

Patients and methods

In the ICS-'BPH' study, 1271 patients over 45 years of age attending urology departments in 12 countries with LUTS suggestive of BOO completed the ICS*male* questionnaire between January 1992 and December 1994. Patients were excluded from the study if they had an abnormal result of the mid-stream urinary specimen analysis or if they had significant other urological disease (such as prostate cancer), neurological disease, previous prostatic surgery, or were taking medication active on the lower urinary tract. Among these, 933 patients had evaluable pressure and flow studies.

All patients were evaluated at baseline by medical history. LUTS were evaluated by the ICS*male* questionnaire, designed to be patient-completed. The ICS*male* questionnaire contains 22 questions measuring 20 urinary symptoms, with 19 also assessing the degree of problem that they cause, as well as 7 condition-specific quality of life questions and 4 items concerning sexual functioning.[22] The majority of questions have five possible ranked responses from 1 to 5 (figure 1), 1 indicating the least severe and 5 the most severe. The problem questions have four response categories, ranging from 'not a problem' to a 'serious problem' (see figure 1). The questionnaire was developed in English and then professionally


1 During the day, how many times do you urinate, on average?

1 to 6 times ☐
7 to 8 times ☐
9 to 10 times ☐
11 to 12 times ☐
13 or more times ☐

How much of a problem is this for you?

not a problem ☐
a bit of a problem ☐
quite a problem ☐
a serious problem ☐

2 During the night, how many times do you have to get up to urinate, on average?

none ☐
one ☐
two ☐
three ☐
four or more ☐

How much of a problem is this for you?

not a problem ☐
a bit of a problem ☐
quite a problem ☐
a serious problem ☐

Figure 1. Example of the ICS*male* questionnaire.

translated into 10 other languages. Each translation was then back-translated and checked by a lay advisor or senior urologist from each country who was nominated as a national co-ordinator for the ICS-'BPH' study. Patients were also evaluated by physical examination including digital rectal examination with estimation of the prostatic volume and an optional ultrasonographic examination of the prostate. Each patient had up to three free urine flow measurements including ultrasonic estimation of residual urine (the highest maximum flow rate being used for the analysis), followed by a pressure and flow study according to the ICS standards.[23] Patients' bladders were filled at 50 ml/min; both intravesical (pves) and intra-abdominal pressure (pabd) were measured. Detrusor pressure (pdet) was derived by electronic subtraction (pdet = pves - pabd). From the voiding phase, the maximum urine flow rate and the detrusor pressure at maximum flow were recorded. These data were plotted on a Schäfer linear passive urethral resistance relation (L-PURR) nomogram to quantify the obstruction from grade 0 (no obstruction) to 6 (severe obstruction).[24]

Spearman's rank correlation coefficients were calculated between each separate symptom question and the following urodynamic measures: linear passive urethral resistance relation classification, detrusor pressure at maximum flow and maximum free flow rate. The statistical significance of these correlations was ascertained with a two-sided p value. In addition, to remove any confounding effect of age on these relationships, partial rank correlation coefficients were calculated. Specifically, each correlation between symptoms and urodynamic measures were recalculated partialed for age.

Furthermore, using chi-squared tests the prevalence of each symptom was compared between patients who were obstructed (linear passive urethral resistance relation 3 or more) and those who were not (linear passive urethral resistance relation less than 3). Similarly, symptom prevalence was compared between those with a residual urine volume after free flowmetry of below and above 100 ml, and between those with a calculated bladder capacity (voided volume + residual volume) of below and above 300 ml.

Results

Table 1 and figures 2 and 3 present descriptive statistics of the urodynamic variables for the study patients. For the maximum free flow rate (figure 2) and detrusor pressure at maximum flow, the means are higher than the medians (table 1), indicating that the distributions of these

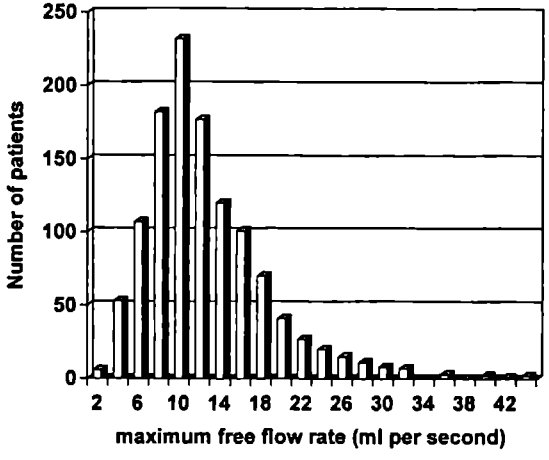


Figure 2. Histogram of maximum urinary flow rates for the study patients.

values are skewed to the right. The prevalence of each of the reported symptoms have been presented previously.[25]

Table 2 presents the Spearman rank correlation coefficients and p values for the relationships between each symptom question and the urodynamic measures. Although a substantially greater number of these correlations achieve statistical significance than would be expected by chance alone, the largest coefficient is about 0.20, and even those of magnitude 0.10 are highly statistically significant, due to the large sample size involved. Considering combinations of symptoms within the groups of storage and voiding symptoms did not lead to stronger associations with BOO than for the individual symptoms. The relationships between each symptom question and urodynamic measures were recalculated after

Table 1. *Descriptive statistics of the urodynamic parameters of the study patients.*

	Mean ± s.d.	Median (range)
Free maximum flow (ml/s)	12.3 ± 6.3	11.0 (1.0-55.0)
Detrusor pressure at maximum flow (cm water)	68 ± 30	63 (15-200)
L-PURR	3.0 ± 1.4	3.0 (0-6)

Table 2. *Spearman rank correlation coefficients and their significance levels for each symptom with pressure and flow measurements.*

	Free maximum flow		Detrusor pressure at maximum flow		L-PURR obstruction class	
	r	p-value	r	p-value	r	p-value
terminal dribble	< 0.01	0.97	0.02	0.46	0.02	0.53
reduced stream	-0.19	< 0.01	0.04	0.19	0.06	0.06
intermittency	-0.09	< 0.01	< 0.01	0.81	0.02	0.47
hesitancy	-0.16	< 0.01	0.02	0.60	0.05	0.10
incomplete emptying	-0.02	0.52	< 0.01	0.80	0.02	0.63
urgency	-0.03	0.33	0.17	< 0.01	0.14	< 0.01
nocturia	-0.09	< 0.01	0.07	0.03	0.07	0.02
repeated urination	-0.02	0.57	0.04	0.24	0.03	0.41
strain to continue	-0.06	0.04	<-0.01	0.78	< 0.01	0.81
postmicturition dribble	0.09	< 0.01	-0.01	0.71	-0.02	0.48
strain to start	-0.03	0.32	-0.02	0.55	< 0.01	0.83
urge incontinence	0.02	0.53	0.15	< 0.01	0.11	< 0.01
frequency (times)	-0.07	0.03	0.03	0.33	0.05	0.15
burning	-0.04	0.20	0.09	< 0.01	0.10	< 0.01
bladder pain	-0.02	0.52	0.05	0.15	0.07	0.04
incontinence no cause	-0.02	0.50	0.04	0.19	0.03	0.36
sit to urinate	-0.11	< 0.01	0.02	0.53	0.02	0.45
stress incontinence	0.07	0.02	0.01	0.66	<-0.01	0.92
urinary retention	-0.10	< 0.01	0.08	0.01	0.10	< 0.01
nocturnal incontinence	-0.01	0.71	0.02	0.59	0.01	0.66
strength of stream	-0.21	< 0.01	0.05	0.10	0.09	< 0.01
frequency (intervals)	0.07	0.02	-0.09	< 0.01	-0.10	< 0.01

adjustment for age. The results were not noticeably different when compared to the correlation coefficients in table 2, indicating that age has little or no confounding effect on these relationships.

Table 3 shows the results of the comparison of the prevalence of each symptom between the groups with (n = 563) and without bladder outlet obstruction (n = 370). The prevalence of urge and urge incontinence were significantly higher in the groups with bladder outlet obstruction. This is in accordance with low (albeit statistically significant) correlations presented in table 2. In addition, the prevalence of urinary retention was marginally significantly ($0.01 < p < 0.05$) higher in the group with bladder outlet obstruction.

Table 3 also presents the results of the comparison of the prevalence of each symptom between the groups with (n = 300) and without

Table 3. *Prevalence (%) of each symptom in the groups with (n = 563) and without (n = 370) bladder outlet obstruction, with (n = 300) and without (n = 622) a residual volume ≥ 100 ml. after free uroflowmetry and in the groups with (n = 450) and without (n = 471) a calculated bladder capacity ≥ 300 ml. (p-value indicates the comparison of prevalences between both groups using the chi square test).*

	Obstruction category (L-PURR)			Residual volume (ml)			Bladder capacity (ml)		
	≥ 3	< 3	p-value	≥ 100 ml	< 100 ml	p-value	≥ 300 ml	< 300 ml	p-value
terminal dribble	94	93	0.69	92	93	0.33	93	92	0.59
reduced stream	94	92	0.39	93	94	0.67	92	94	0.20
intermittency	89	87	0.40	92	86	0.02	89	87	0.35
hesitancy	84	81	0.23	89	82	< 0.01	86	82	0.14
incomplete emptying	80	82	0.40	83	79	0.13	82	79	0.37
urgency	78	67	< 0.01	80	72	< 0.01	73	76	0.19
nocturia	74	73	0.94	76	75	0.75	72	78	0.06
repeated urination	73	69	0.11	78	70	< 0.01	73	72	0.66
strain to continue	68	69	0.86	71	67	0.31	70	67	0.25
postmicturition dribble	67	69	0.49	70	66	0.19	69	66	0.39
strain to start	60	64	0.32	67	56	< 0.01	62	58	0.26
urge incontinence	52	42	< 0.01	51	46	0.25	44	52	0.02
frequency	47	44	0.33	51	46	0.25	45	50	0.13
burning	44	38	0.08	45	37	0.01	44	35	< 0.01
bladder pain	42	37	0.08	44	39	0.17	43	38	0.16
incontinence no cause	20	19	0.93	30	18	0.09	19	21	0.45
sitting to urinate	17	18	0.92	25	18	0.49	19	19	0.91
stress incontinence	15	16	0.69	14	14	0.82	13	14	0.65
urinary retention	10	6	0.04	10	9	0.55	8	10	0.33
nocturnal incontinence	8	10	0.73	10	9	0.88	10	9	0.90

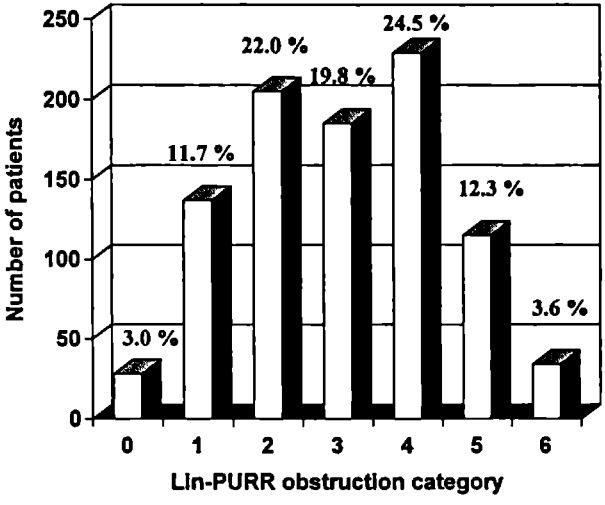


Figure 3. Histogram of linear passive urethral resistance relation (L-PURR) for the study patients.

(n = 622) a residual volume of at least 100 ml after free uroflowmetry, and between the groups with (n = 450) and without (n = 471) a calculated bladder capacity of at least 300 ml. The prevalences of hesitancy, urgency, repeated urination and strain to start were significantly higher in the group with a larger residual volume. The prevalences of intermittency and burning were marginally significantly ($0.01 < p < 0.05$) higher in the group with a higher residual volume. The prevalence of burning was significantly higher in patients with a larger calculated bladder capacity. The prevalence of urge incontinence was marginally significantly ($0.01 < p < 0.05$) higher in the group with a smaller calculated bladder capacity.

Discussion

The present study has investigated the associations between the various questions from the ICS*male* questionnaire and the results of pressure and flow studies. For only one of the published questionnaires has the relationships with urodynamic measurements been investigated[17-19], specifically, the relationship of the AUA-7 index (the sum of the specific answers) with the grade of obstruction. No correlations were found for the AUA-7 index in relation to maximum free urinary flow rate, linear passive urethral resistance relation obstruction category and detrusor strength.[18,20] Using the AUA-7 symptom index, the severity of LUTS correlated well

with overall health status but not with free urinary flow rate, prostate size, degree of bladder trabeculation and the amount of post-void residual urine.[17] This is not surprising because the AUA-7 questions are a heterogeneous group of storage and voiding symptoms (frequency, intermittency, urgency, nocturia, weak stream and hesitancy and the feeling of incomplete bladder emptying). Combining symptoms within the storage and voiding groups made no difference to the results of the study reported here.

The main finding of the present study was that there is little or no correlation between the various symptoms and either the data from the pressure flow study or from the maximum free flow rate. This is in agreement with a previous study which investigated the correlation between the diagnosis of BOO and individual symptoms of the International-Prostate Symptom Score (I-PSS) - a symptom score that is the same as the AUA-7 questionnaire but with the addition of an extra question on the overall quality of life.[18] Although this previous study concluded that there was a statistically significant correlation between the specific questions of the I-PSS and objective grade of obstruction, the clinical significance of this finding is doubtful because none of the Spearman rank correlation coefficients was above 0.23, indicating very weak correlations. Furthermore, there was considerable overlap of symptom scores between patients with different grades of BOO.[18]

The impact of age on the prevalence of symptoms has been described before. For instance, although an increasing trend was observed with increasing age in a population based study,[27] the present group of patients exhibited a broadly negative correlation between the prevalence of symptoms from the ICS*male* questionnaire and increasing age.[25] Possible explanations put forward for these observations were that the selection process of the patients is of considerable importance and that the tolerance of LUTS may increase with age. To correct for the possible confounding effect of age on the relationship between the prevalence of symptoms and urodynamic measurements, the correlation coefficients were adjusted for age. In the event, the confounding effect of age on the relationship between each symptom and the urodynamic measures was negligible indicating that the relationships are independent of the age pattern.

In conclusion, there are objective methods which quantify both urine flow rate and BOO. In addition, there are valid and reliable methods to quantify the presence of LUTS. These methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with LUTS. Since earlier studies have indicated that inclusion of pressure flow data in

the preoperative evaluation and patient selection for interventional therapies such as transurethral resection of the prostate and transurethral microwave thermotherapy may improve the overall clinical results,[9,10,28] the conclusion from the present study is that symptoms alone should not be used as the main indication for surgical management.

Future analyses of the ICS-'BPH' study will provide vital information on the relative potential of symptoms, urodynamic and other clinical parameters to predict a favourable response to current and innovative treatments. Only then can the treatment of LUTS be individualized according to the pathophysiology, symptomatic complaints and expectations of the patient.

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References

1 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. The Lancet **338**: 469, 1991.

2 Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, Lieber MM: The prevalence of prostatism: A population-based survey of urinary symptoms. J Urol **150**: 85, 1993.

3 Schäfer W, Nopponey R, Rübben H, Lutzeyer W: The value of free flow rate and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

4 Emberton M, Neal DE, Black N, Harrison M, Fordham M, McBrien MP, Williams RE, McPherson K, Devlin HB: The National Prostatectomy Audit: the clinical management of patients during hospital admission. Brit J Urol **75:** 301, 1995.

5 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147:** 1044, 1992.

6 Gerstenberg TC, Andersen JT, Klarskov P, Ramirez D, Hald T: High flow infravesical obstruction in men: symptomatology, urodynamics and the results of surgery. J Urol **127:** 943, 1982.

7 Poulsen A, Schou J, Puggaard L, Torp-Pedersen S, Nordling J: Prostatic enlargement, symptomatology and pressure/flow evaluation: interrelations in patients with symptomatic BPH. Scand J Urol Nephrol **157:** (suppl.) 67, 1994.

8 Abrams PH, Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Brit J Urol **51:** 129, 1979.

9 Rollema HJ, van Mastrigt R: Objective analysis of prostatism: A clinical application of the computer program CLIM. Neurourol Urodyn **10:** 71, 1991.

10 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153:** 1526, 1995.

11 Epstein RS, Deverka PA, Chute CG, Panser L, Oesterling JE, Lieber MM, Schwartz S, Patrick D: Validation of a new quality of life questionnaire for benign prostatic hyperplasia. J Clin Epidemiol **45:** 1431, 1992.

12 Fowler FJ, Wennberg JE, Timothy RP, Barry MJ, Mulley AG, Hanley D: Symptom status and quality of life following prostatectomy. JAMA **259:** 3018, 1988.

13 Boyarsky S, Jones G, Paulson DF, Prout GR: A new look at bladder neck obstruction by the Food and Drug Administration regulators: Guidelines for investigation of benign prostatic hypertrophy. Trans Am Assoc Genital-Urin Surg **68:** 29, 1976.

14 Madsen PO, Iversen P: A point system for selecting operative candidates. In: Hinman F Jr (ed) Benign Prostatic Hypertrophy. New York, Springer Verlag, 1983, pp 763-765.

15 Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett ATK and the measurement committee of the American Urological Association: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol **148:** 1549, 1992.

16 Hansen BJ, Flyger H, Brasso K, Schou J, Nordling J, Thorup Andersen J, Mortensen S, Meyhoff H-H, Walter S, Hald T: Validation of the self-administered Danish Prostatic Symptom Scrore (DAN-PSS-1) system for use in benign prostatic hyperplasia. Br J Urol **76:** 451, 1995.

17 Barry MJ, Cockett ATK, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN: Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol **150:** 351, 1993.

18 Ko DSC, Fenster HN, Chambers K, Sullivan LD, Jens M, Goldenberg SL: The correlation of multichannel urodynamic pressure-flow studies and American Urological Association Symptom index in the evaluation of benign prostatic

hyperplasia. J Urol **154**: 396, 1995.

19 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156**: 1020, 1996.

20 Abrams P: New words for old: lower urinary tract symptoms for 'prostatism'. Brit Med J **308**: 929, 1994.

21 Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hypertrophy with age. J Urol **132**: 474, 1984.

22 Donovan JL, Abrams P, Peters TJ, Kay HE, Reynard J, Chapple C, de la Rosette J, Kondo A: The ICS-'BPH' study: The Psychometric validity and reliability of the ICS*male* questionnaire. Brit J Urol **77**: 554, 1996.

23 Abrams P, Blaivas JG, Stanton SL, Andersen JT: Standardization of terminology of lower urinary tract function. Neurourol Urodyn **7**: 403, 1988.

24 Schäfer W, Waterbär F, Langen PH, Deutz FJ: A simplified graphical procedure for detailed analysis of detrusor and outlet function during voiding. Neurourol Urodyn **8**: 405, 1989.

25 Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette JJMCH, Porru D, Thuroff MJ and the ICS-'BPH' Study Group: The ICS-'BPH' study: The bothersomeness of urinary symptoms. J Urol 1996; In Press.

26 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Debruyne FMJ, de la Rosette JJMCH: Correlation between uroflowmetry, prostate volume, postvoid residue, and lower urinary tract symptoms as measured by the international prostate symptom score. Urology **48**: 393, 1996.

27 Jolleys JV, Donovan JL, Nanchahal K, Peters TJ, Abrams P: Urinary symptoms in the community: how bothersome are they ? Br J Urol **74**: 551, 1994.

28 de la Rosette JJMCH, de Wildt MJAM, Höfner K, Carter SStC, Debruyne FMJ, Tubaro A: High energy thermotherapy in the treatment of benign prostatic hyperplasia: results of the European Benign Prostatic Hyperplasia Study Group. J Urol **156**: 97, 1996.

Chapter 4

Relationships between symptoms, urodynamics and prostate (transition zone) volume

The correlation between prostate volume, transition zone volume, transition zone index and clinical and urodynamic investigations in patients with lower urinary tract symptoms.

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Abstract

Objectives: To determine if, in patients with lower urinary tract symptoms, transrectal ultrasound measurement of the transition zone (TZ) of the prostate and the ratio between TZ volume and total prostate volume (TZ index) correlates better with clinical and urodynamic investigations than total prostate volume alone.

Methods: A total of 150 consecutive patients with lower urinary tract symptoms were subjected to a standardized screening program including I-PSS, physical examination, transrectal ultrasound of the prostate, and urodynamic investigations with pressure-flow studies. Total prostate volume as well as TZ volume was assessed ultrasonographically using the ellipsoid formula. Spearman's rank correlation coefficients were calculated between different prostate volume measurements and specific symptomatic and urodynamic parameters.

Results: The relationships between specific I-PSS symptoms, symptom scores and the investigated prostate volume measurements were not statistically significant except for one question, nocturia that appeared to be statistically significantly correlated with TZ index ($r = 0.25$). The correlations for free flow, pressure-flow parameters and prostate volume measurements were stronger but only moderate at best. The highest correlations were between TZ volume and L-PURR obstruction category, urethral resistance factor and detrusor pressure at maximum flow ($r = 0.43$, 0.44 and 0.40, respectively). The differences between the correlations of prostate volume and TZ index and these parameters were small ($r = 0.39$, 0.38 and 0.37, respectively for prostate volume and $r = 0.38$, 0.40 and 0.33, respectively for TZ index).

Conclusions: There were very small differences between the correlations of total prostate volume, TZ volume and TZ index and clinical as well as pressure-flow parameters. In the assessment of clinical and pressure-flow parameters, estimation of the total prostate volume by TRUS was a reasonable way to obtain the required information concerning the prostate size and measuring TZ volume and calculating TZ index was of limited additional value. Symptoms and bladder outlet obstruction were mainly determined by other factors than prostate and, specifically, TZ volume. Since earlier studies have indicated that inclusion of pressure-flow data in the preoperative evaluation and patient selection for interventional therapies may improve the overall clinical results, it is our opinion that prostate volume, TZ volume or symptoms alone should not be used as the main indication for deciding on the appropriate invasive treatment options.

Introduction

Estimation of the prostate volume is an important evaluative parameter in the assessment of patients with lower urinary tract symptoms (LUTS). Transrectal ultrasound (TRUS) of the prostate is now widely used to support the diagnosis and choice of treatment.[1] TRUS currently provides the most accurate means of measuring prostate volume and also demonstrates the true extent of transition zone (TZ) enlargement.[2] According to McNeal's assumption of zonal anatomy of the prostate, the TZ is the major site for development of benign prostatic hyperplasia.[3] With the enlargement of the adenoma it compresses the outer part of the gland, the peripheral zone which is traditionally known as the surgical capsule.

The value of volumetric determination of the TZ was recently reported in several studies. Hammerer et al assessed the unique relationship of TZ tissue to prostate specific antigen (PSA) elevation and underscored the importance of considering the TZ as a source of false-positive diagnosis of prostate cancer.[4] Hence, determination of the whole prostate volume and TZ volume by TRUS may increase the sensitivity of PSA in detecting prostate cancer. Tempany et al analyzed differential zonal volumes and their changes after treatment with finasteride and concluded that the TZ was more affected by medical treatment than the peripheral zone.[5] Tewari et al analyzed the differences in TZ and total volume reduction among patients who improve peak urinary flow rates following finasteride therapy.[6] Patients who had an improvement of peak urinary flow rate of more than 3 ml/s had a significantly greater reduction of TZ volume and TZ index, that is the ratio between the TZ volume and total gland volume, when compared with those who had not. They concluded that pretreatment TZ index may help in predicting peak flow improvement following finasteride therapy.[6]

Using these ideas, some studies investigated whether separation of the peripheral zone volume from the adenoma would improve the correlation with other clinical and urodynamic parameters. Furthermore, the relation between the TZ and total gland volume, expressed as TZ index was reported to correlate better than total volume alone with other clinical and urodynamic parameters.[7]

We conducted a study to delineate the relation between the three methods of adenoma assessment (total prostate volume, TZ volume and TZ index) and their correlations with age, symptoms and the results of urodynamic investigations.

Patients and methods

A total of 150 consecutive patients with LUTS was analyzed. All patients included in the present study were subjected to a standardized screening program including history (including international prostate symptom scores [I-PSS]), physical examination (including digital rectal examination), biochemistry (including PSA), urinalysis and culture, urine cytology, TRUS of the prostate, and urodynamic investigations with pressure-flow studies.

The prostate size was determined using the Kretz combison 330 ultrasound scanner with a 7.5 MHz transrectal probe (multi 3-D VRW 177 AK). The prostate was imaged from base to apex, documenting the presence of prostate abnormalities and measuring the prostate volume using the ellipsoid formula height x width x length x $\pi/6$.[8] The TZ volume was calculated by using the same formula. Maximum diameters were used for each measurement. TZ index was defined as the ratio between TZ volume and total gland volume.

Urodynamic investigations were performed using an 8F transurethral lumen catheter and an 8F transrectal catheter both equipped with a microtip pressure sensor (MTC, Dräger, The Netherlands). Before cystometry, the bladder was emptied through the lumen of a transurethral catheter to quantify residual urine after free uroflowmetry. The pressure sensors were zeroed to atmospheric pressure before introduction. The bladder was filled with water of 20°C with a filling speed of 50 ml/min with the patient supine. Filling was stopped when the patient expressed a strong urge to void and micturition in standing position was allowed in private. Digitally stored data were analyzed with equipment developed at our department (UIC/BME Research center, Department of Urology, Nijmegen, The Netherlands). In order to get useful information from pressure-flow curves, it was necessary to relate detrusor pressure to corresponding flow. To quantify the grade of outlet obstruction, we used the concept of the Linear-Passive Urethral Resistance Relation (L-PURR), relating minimal urethral opening pressure observed at the end of voiding ($Pvoid_{min}$) with detrusor pressure at maximum flow ($p_{det}Qmax$).[9] Patients in L-PURR classes 0 and 1 had no bladder outlet obstruction, patients in classes 2 and 3 had mild and moderate bladder outlet obstruction and patients in higher classes had increasingly severe obstruction. We also used the urethral resistance factor (URA) for grading bladder outlet obstruction. Calculation of URA was based on the point of maximum flow and corresponding detrusor pressure.[10] A URA value > 29 cm water indicated obstruction.

Descriptive statistics were used to illustrate the studied population.

Spearman's rank correlation coefficients were calculated between different measurements of prostate volume and age, each separate symptom question, symptom scores and the following urodynamic measures: maximum free flow rate (Qmax), free voided volume, residual urinary volume after free flowmetry, minimal urethral opening pressure ($Pvoid_{min}$), detrusor pressure at maximum flow ($p_{det}Qmax$), urethral resistance factor (URA) and linear passive urethral resistance relation classification (L-PURR). The total score of I-PSS questions 2; repeated urination, 4; urge and 7; nocturia represented the filling component of the I-PSS symptom score, while the total score of question 1; incomplete emptying, 3; intermittency, 5; reduced stream and 6; strain to start represented the voiding component. The statistical significance of these correlations was ascertained with a two-sided p value. Applying the Bonferroni correction for multiple testing would imply a cutoff point of about 0.0025 for each individual p value to retain an overall 0.05 significance level. Since the symptoms and urodynamic variables are associated with each other, such a correction would be conservative, hence for the present analyses, a cutoff point of 0.01 was used, with significance between 0.01 and 0.05 being regarded as marginal. On the basis of a cutoff point equal to the median value of total prostate volume, TZ volume and TZ index, the group of patients was divided in 2 and mean symptom scores, free Qmax, $p_{det}Qmax$ and L-PURR between groups were compared using the Wilcoxon rank sum W test.

Results

Descriptive statistics with respect to the patients, ages, prostate volumes measurements, and urodynamic parameters are summarized in table 1. The correlation between the prostate volume, TZ volume and TZ index and age and symptomatic parameters are presented in table 2. When evaluating the relationship between age, total prostate volume and TZ volume we noted a statistically significant positive correlation ($r = 0.48$ and $r = 0.47$, respectively). The TZ index was also statistically significantly correlated with age ($r = 0.35$).

The relationships between specific I-PSS symptoms, symptom scores and the investigated volume measurements were not statistically significant except for one question, nocturia that appeared to marginally significantly correlate with TZ volume and statistically significantly correlate with TZ index. However, the magnitude of the correlation was only weak as demonstrated by a Spearman correlation coefficient of 0.19 and

Table 1. *Descriptive statistics of the parameters of the study patients (n = 150).*

	Mean ± SD	Median	Range
Age (years)	63 ± 10	63	34 - 85
I-PSS	17.3 ± 6.9	16.0	1 - 33
Prostate Volume (ml)	41.6 ± 20.8	36.8	15.7 - 123.0
TZ Volume (ml)	22.5 ± 15.9	19.2	1.8 - 81.1
TZ Index	0.50 ± 0.17	0.50	0.10 - 0.88
Qmax (ml/s)	12.5 ± 6.9	11.3	2.6 - 50.1
$p_{det}Qmax$ (cm water)	49.4 ± 25.6	44.0	4.0 - 145.0
L-PURR	2.1 ± 1.5	2.0	0 - 6

0.25, respectively. As a result of this significant correlation with nocturia, the cumulative filling component of the I-PSS score was also marginally significantly correlated with TZ volume and TZ index. When the nocturia question was removed from the filling component of the I-PSS score the correlation was not significant anymore.

Table 3 indicates the correlation between prostate volume measurements and specific urodynamic values. Statistical significant but moderate correlations were found between prostate volume, TZ volume and TZ index and free flowmetry parameters Qmax and voided volume. The correlations between TZ volume and TZ index and Qmax were both 0.26 and the correlations with voided volume were 0.34 and 0.31, respectively, indicating slightly higher correlations than with prostate volume (r = 0.22 for Qmax and 0.28 for voided volume, respectively). The correlations of prostate volume measurements and residual volume were not statistically significant for prostate volume and marginally significant but weak for TZ volume (r = 0.18) and TZ index (r = 0.20), respectively. The correlations for the pressure-flow parameters and prostate volume measurements were stronger than those of free flowmetry parameters. The highest correlations were between TZ volume and L-PURR (figure 1), URA and $p_{det}Qmax$ (r = 0.43, 0.44 and 0.40, respectively). The differences between the correlations of prostate volume and TZ index and these parameters were not great (r = 0.39, 0.38 and 0.37, respectively for prostate volume and r = 0.38, 0.40 and 0.33, respectively for TZ index)(figure 1). The correlations

between specific measurements of the TZ zone (height, width and length) and the specific urodynamic and symptomatic parameters were within the same range as those of TZ volume and TZ index. Table 4 lists the mean I-PSS, free Qmax, p_{det}Qmax and L-PURR category for those below and above the median value of the prostate volume (36.8 ml), TZ volume (19.2 ml) and TZ index (0.50), respectively. There were no significant differences in I-PSS scores while the differences in Qmax, p_{det}Qmax and L-PURR were significant for the cutoff points of all volume measurements.

Table 2. *Spearman's rank correlation coefficients and their significance levels in italics for each prostate value with age, symptoms and symptom scores.*

	Prostate Volume	TZ Volume	TZ index
Age	.48 *<.001*	.47 *<.001*	.35 *<.001*
I-PSS 1; incomplete emptying	.02 *.79*	.02 *.80*	.02 *.86*
I-PSS 2; repeated urination	.06 *.62*	.11 *.20*	.15 *.08*
I-PSS 3; intermittency	.04 *.66*	.07 *.44*	.04 *.68*
I-PSS 4; urge	.10 *.27*	.11 *.20*	.08 *.37*
I-PSS 5; reduced stream	.04 *.66*	.02 *.81*	.03 *.74*
I-PSS 6; strain to start	.17 *.06*	.16 *.06*	.08 *.34*
I-PSS 7; nocturia	.11 *.22*	.19 *.03*	.25 *.004*
I-PSS fill (I-PSS 2+4+7)	.12 *.17*	.19 *.03*	.21 *.02*
I-PSS void (I-PSS 1+3+5+6)	.09 *.31*	.10 *.26*	.04 *.64*
total I-PSS	.03 *.76*	.04 *.62*	.08 *.35*

Discussion

Estimation of prostate volume may be useful in a variety of ways. A precise estimate of the amount of BPH would help to decide upon the appropriate therapy and assist in the interpretation of serum PSA level for the presence of cancer.[11] Also, the decrease in prostate mass after hormonal manipulation or radiation can be used as an indication of therapeutic efficacy.[12] As the goal of many researchers has been an accurate

Table 3. *Spearman's rank correlation coefficients and their significance levels in italics for each prostate value with specific urodynamic values.*

	Prostate Volume	TZ Volume	TZ index
Qmax	.22 *.009*	.26 *.002*	.26 *.002*
Voided Volume	.28 *.001*	.34 *<.001*	.31 *<.001*
Residual Volume	.14 *.11*	.18 *.03*	.20 *.02*
$Pvoid_{min}$	.26 *.002*	.32 *<.001*	.31 *<.001*
$p_{det}Qmax$	.37 *<.001*	.40 *<.001*	.33 *<.001*
URA	.38 *<.001*	.44 *<.001*	.40 *<.001*
L-PURR	.39 *<.001*	.43 *<.001*	.38 *<.001*

Table 4. *Mean micturition variables for those below and above the median value of prostate volume (36.8 ml), TZ volume (19.2 ml) and TZ index (0.50) respectively. P value (bold) indicates the comparison between the groups below and above the median value using the Wilcoxon rank sum W test.*

	I-PSS	Qmax (ml/s)	$p_{det}Qmax$ (cm water)	L-PURR
Prostate Volume	**p = 0.95**	**p = 0.04**	**p < 0.001**	**p < 0.001**
≥ 36.8 ml	17.1	11.3	57.9	2.6
< 36.8 ml	17.6	13.7	41.1	1.5
TZ Volume	**p = 0.53**	**p = 0.02**	**p = 0.002**	**p < 0.001**
≥ 19.2 ml	17.7	11.2	55.4	2.5
< 19.2 ml	17.0	13.8	43.6	1.6
TZ Index	**p = 0.28**	**p = 0.01**	**p = 0.006**	**p = 0.001**
≥ 0.50	18.0	10.7	54.5	2.4
< 0.50	16.7	14.4	44.0	1.7

estimation of prostate volume, there have been several studies performed to this end.[13,14] Earlier studies applied suprapubic ultrasound to measure prostate size. Although some studies reported accurate results with this technique, others felt this method had an inherent problem.[14] An accurate estimation of the prostate volume only seems possible when the investigation is performed transrectally. The most commonly used methods for

estimation of the size of the prostate are the planimetric method and the ellipsoid method using the three dimensions of the prostate. It is generally accepted that the step section planimetric method of volume determination is most accurate but it is tedious and time consuming.[14,15] In addition, this method requires sophisticated software to execute the program. In the present study we used the ellipsoid formula to obtain an accurate assessment of prostate volume and TZ volume.

In the present study, total prostate volume and TZ volume correlated statistically significantly with age of the patients which is in agreement with the assumption that the prostate gland increases in size as men age. The increase in prostate size seems to be mainly attributed to the TZ since the correlation between the TZ index and age was also highly significant ($r = 0.35$).

The relationships between symptoms and total prostate volume have also been described by Ezz El Din et al who in 803 patients found no correlation.[17] We confirmed the results of this study finding no correlations between total prostate volume, TZ volume or TZ index and each separate symptom and cumulative symptom score. There was only one exception, nocturia, that had a marginally significant but weak correlation with TZ volume ($r = 0.19$) and a statistically significant correlation with TZ index ($r = 0.25$). The clinical relevance of this finding is questionable.

The correlation between urodynamic parameters of obstruction and total prostate volume have been shown to be statistically significant but

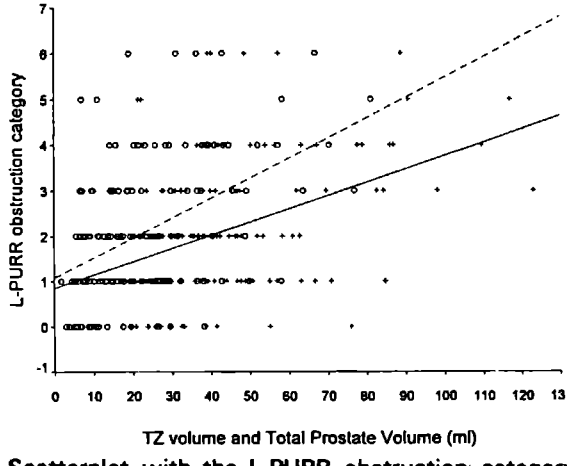

Figure 1. Scatterplot with the L-PURR obstruction category on the Y-axis and the total prostate volume (+) and transition zone volume (O) in ml on the X-axis with the regression lines (correlation coefficients $r_{\text{Total Prostate Volume}} = 0.39$; $p < 0.001$ [solid line] and $r_{\text{TZ volume}} = 0.43$; $p < 0.001$ [striped line], respectively).

weak. This has been reported by Rosier et al and by Bosch et al.[18,19] Rosier et al, retrospectively evaluated 521 men with micturition complaints and determined the relationship between total prostate volume and bladder outlet obstruction. Their study showed a statistically significant weak correlation between bladder outlet obstruction and prostate size. Urodynamic outlet obstruction was confirmed in 90% of the patients with a prostate size of more than 80 ml.[18] Bosch et al distinguished between urodynamic parameters that selectively quantify compression, those correlated weakly to moderately with total prostate volume, and urodynamic parameters that quantify constriction that do not correlate with prostate volume et al.[19] The compressive type is characterized by a high urethral opening pressure and a prolonged isovolumetric contraction phase before flow starts, and the constrictive type by a normal opening pressure and an increased slope of the passive urethral resistance relation reflecting a narrow urethral lumen during voiding. This stratification can only be done when the results of pressure-flow studies are available and this stratification may be of prognostic importance. Tubaro et al showed that patients with a constrictive obstruction had a higher likelihood to benefit from transurethral microwave thermotherapy using the low energy (2.0) software when compared to patients with a compressive obstruction.[20] On the other hand, in patients who were treated with high energy (2.5 software) transurethral microwave thermotherapy, patients with large prostates benefitted most from therapy.[21] In the current study we confirmed the statistically significant but moderate correlation between prostate volume and the results of pressure-flow studies. Also TZ volume and TZ index were significantly correlated with urodynamic parameters but the correlation was only moderate at best (table 3). There were very small differences among total prostate volume, TZ volume and TZ index concerning their correlations with the clinical parameters as well as the results of urodynamic investigations with pressure-flow analysis (tables 2, 3 and 4). Moreover, precise determination of the TZ volume is not an easy task and requires an expert TRUS investigator. Therefore, we conclude that in the assessment of clinical and pressure-flow parameters, estimation of the total prostate volume by TRUS is a reasonable way to obtain the required information concerning the prostate size and measuring TZ volume and calculating TZ index is of limited additional value. These results are at variance with the results of a similar study reported by Kaplan et al.[7] The correlation between AUA symptom score, Qmax and TZ index in their study appeared to be strong and highly significant ($r = 0.75$; $p = 0.001$ and $r = 0.71$; $p = 0.001$, respectively). The correlation between TZ index and $p_{det}Qmax$ was moderate ($r = 0.43$; $p = 0.001$) and higher than in the present study. They concluded that TZ index may serve as a useful proxy

for the evaluation of worsening obstruction. We agree with their conclusion but have to add that TZ volume and total prostate volume alone are in this context equally useful (table 4).

From our study we conclude that symptoms and bladder outlet obstruction are mainly determined by other factors than prostate and, specifically, TZ volume alone. Since the correlation between clinical and urodynamic investigations and prostate volume and TZ volume is weak or moderate at best, the size of the prostate should not be an important consideration when determining the necessity of therapy. However, the choice of therapy could depend on the distinction between the compressive and constrictive types of obstruction. If there is an obstructive condition and a large prostate gland, it is likely that the prostate is the major cause of obstruction and the therapy should be designed to reduce the prostate volume medically or surgically.

A correlation between symptoms and urodynamically proven obstruction has been shown in 1 study only, and only for the symptoms of weak stream and hesitancy.[16] Other studies were, to our knowledge, not able to confirm these findings.[23] The correlation of isolated objective non-urodynamic parameters is generally believed to be too inaccurate for clinical decision making. However, a combination of the objective noninvasive measurements prostate size, post-void residual volume, voided volume and maximum flow, named the clinical prostate score (CLIPS), correlated well with the results of urodynamics in a retrospective investigation in a large group of patients.[24] Using this scoring system, we may be able to distinguish groups of patients with and without bladder outlet obstruction without the need for an invasive and costly urodynamic pressure-flow analysis. However, for the individual patient, CLIPS has predictive value but without a urodynamic investigation with pressure-flow analysis a quantitative assessment of bladder outlet obstruction is not possible. From the four investigations used in CLIPS, maximum flow is considered to be the most relevant and consequently has the highest weight. Prostate volume is the investigation which after maximum flow has the highest weight and is therefore less important.[24]

Since earlier studies have indicated that inclusion of pressure-flow data in the preoperative evaluation and patient selection for interventional therapies such as transurethral resection of the prostate[22] and transurethral microwave thermotherapy[20] may improve the overall clinical results, it is our opinion that prostate volume, TZ volume or symptoms alone should not be used as the main indication for deciding on the appropriate (minimal) invasive treatment options.

References

1 Ezz El Din K, de la Rosette JJMCH: Transrectal ultrasound of the prostate. Br J Urol **78:** 2, 1996.

2 Kirby RS: The clinical assessment of benign prostatic hyperplasia. Cancer **70:** 284, 1992.

3 McNeal JE: Normal histology of the prostate. Am J Surg Path **12:** 619, 1988.

4 Hammerer PG, McNeal JE, Stamey TA: Correlation between serum prostate specific antigen levels and the volume of the individual glandular zones of the human prostate. J Urol **153:** 111, 1995.

5 Tempany CM, Partin AW, Zerhouni EA, Zinreich EA, Zinreich SJ, Walsh PC: The influence of finasteride on the volume of peripheral and periuretheral zones of the prostate in men with benign prostatic hyperplasia. Prostate **22:** 39, 1993.

6 Tewari A, Shinohara K, Narayan P: Transition zone volume and transition zone ratio: Predictor of uroflow response to finasteride therapy in benign prostatic hyperplasia patients. Urology **45:** 258, 1995.

7 Kaplan SA, Te AE, Pressler LB, Olsson CA: Transition zone index as a method of assessing benign prostatic hyperplasia: correlation with symptoms, urine flow and detrusor pressure. J Urol **154:** 1764, 1995.

8 Terris MK, Stamey TA: Determination of prostate volume by transrectal ultrasound. J Urol **145:** 984, 1991.

9 Schäfer W: Analysis of bladder outlet function with linearized passive urethral resistance relation, linPURR, and a disease specific approach for grading obstruction: from complex to simple. World J Urol **13:** 47, 1995.

10 Griffiths DJ, van Mastrigt R, Bosch R: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size in urethral obstruction due to benign prostatic hyperplasia. Neurourol Urodyn **8:** 17, 1989.

11 Lee F, Littrup PJ, Loft-Christensen L, Kelly BS Jr, McHugh TA, Siders DB, Mitchel AE, Newby JE: Predicted prostate specific antigen results using transrectal ultrasound gland volume: Differentiation of benign prostatic hyperplasia and prostate cancer. Cancer **70:** 211, 1992.

12 Saitoh M, Ramirez E, Babaian RJ: Ultrasonic volume monitoring in patients with prostate cancer treated by external beam radiation therapy. Urology **43:** 342, 1994.

13 Clements R, Griffiths GJ, Peeling WB, Edwards AM: Transrectal ultrasound in monitoring response to treatment of prostate disease. Urol Clin N Am **16:** 735, 1989.

14 Stone NN, Ray PS, Smith JA, Scardino PT, Smith RB, Khanna OM, Paulson DF: Ultrasound determination of prostate volume: Comparison of transrectal (ellipsoid v planimetry) and suprapubic methods. J Endourol **5:** 251, 1991.

15 Aarnink RG, Giesen RJB, de la Rosette JJMCH, Huynen AL, Debruyne FMJ, Wijkstra H: Planimetric volumetry of the prostate: how accurate is it ? Physiol Meas **16:** 141, 1995.

16 Abrams PH, Feneley RCL: The significance of the symptoms associated with bladder outflow obstruction. Urol Int **33:** 171, 1978.

17 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Debruyne FMJ, de la Rosette

JJMCH: Correlation between uroflowmetry, prostate volume, postvoid residue and lower urinary tract symptoms as measured by the international prostate symptoms score. Urology **48:** 393, 1996.

18 Rosier PFWM, de la Rosette JJMCH: Is there a correlation between prostate size and bladder outlet obstruction? World J Urol **13:** 9, 1995.

19 Bosch JLHR, Kranse R, van Mastrigt R, Schröder FH: Reasons for the weak correlation between prostate volume and urethral resistance parameters in patients with prostatism. J Urol **153:** 686, 1995.

20 Tubaro A, St. Clair Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153:** 1526, 1995.

21 de la Rosette JJMCH, de Wildt MJAM, Höfner K, Carter SStC, Debruyne FMJ, Tubaro A: Pressure-flow study analyses in patients treated with high energy thermotherapy. J Urol **156:** 1428, 1996.

22 Rollema HJ, van Mastrigt R: Objective analysis of prostatism: A clinical application of the computer program CLIM. Neurourol Urodyn **10:** 71, 1991.

23 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156:** 1020, 1996.

24 Rosier PFWM, de Wildt MJAM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Clinical diagnosis of bladder outlet obstruction in patients with benign prostatic enlargement and lower urinary tract symptoms: Development and urodynamic validation of a clinical prostate score for the objective diagnosis of bladder outlet obstruction. J Urol **155:** 1649, 1995.

Chapter 5

Variability in uroflow measurements

Chapter 5.1

Computerized artifact detection and correction of uroflowcurves: Towards a more consistent quantitative assessment of maximum flow.

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Abstract

Objectives: To evaluate a computerized method of artifact detection and correction of uroflow and compare the quantitative assessment of maximum flow obtained by the computer with visual correction by experts.

Methods: A total of 90 randomly chosen flows was scanned into the computer whereafter automated artifact detection and correction was performed according to pre-established rules implemented in the software. Three experts visually corrected the flows using the same artifact detection and correction specifications as the computer. Measuring agreement between different methods of assessment of maximum flow was evaluated by calculating the difference and the standard deviation (SD) of the differences. The repeatability of assessing the maximum flow value by the computer and by expert 1 was assessed by calculating the difference between 2 readings and the coefficient of repeatability.

Results: The coefficient of repeatability of maximum flow after detection and correction of artifacts by the computer (0.38 ml/s) was slightly better when compared with the coefficient of repeatability between 2 observations by one expert (1.12 ml/s). The interobserver variation for the quantitative assessment of maximum flow appeared to be great. A total of 51 % of the maximum flow values assessed by expert 2 was 1 ml/s or more greater than those assessed by expert 1. When comparing the results of the computer with those of the experts the mean value of maximum flow from expert 1 was 0.71 ml/s smaller than the computer value ($p < 0.01$), the mean value from expert 2 was 0.53 ml/s greater ($p < 0.01$) and the mean value from expert 3 was not significantly different (0.25 ml/s greater). The SD of maximum flow after correction by the computer was 0.3 ml/s smaller than the SD of the raw data from the flowmeter and the corrected values by 2 experts.

Conclusions: Computerized artifact detection and correction eliminates an important fraction of the variability of manually corrected maximum flow values. This may lead to smaller sample size requirements, especially in studies where the primary objective is to assess a small (± 1 ml/s) difference in mean maximum flow between groups.

Introduction

For decades uroflowmetry has played a major role in the evaluation of lower urinary tract symptoms (LUTS). Urologists use measurements of uroflowmetry along with patient symptoms and other clinical findings to make decisions regarding the need for therapeutic intervention. Besides its

diagnostic role, uroflowmetry has evolved as one of the most important investigations in the assessment of the efficacy of drug treatments and other therapies in patients with LUTS. It is a noninvasive measurement technique that is simple to perform, the results are readily available, and sophisticated flowmeters are easy to use.[1] The most modern flowmeters allow the measurement of voided volume, maximum flow, mean flow, time to maximum flow, voiding time and flow time. Moreover, the flow pattern can be described. Among the many parameters maximum flow is regarded as the most useful to assess the degree of obstruction and to monitor treatment effects. Despite its popularity, uroflowmetry is hampered by several draw-backs including its inability to differentiate between bladder outlet obstruction and impaired detrusor activity,[2] artifacts,[3] reproducibility,[4] and intra and interobserver variation.[5]

In clinical trials, these draw-backs may have a negative impact on sample size requirements to achieve statistical power.[3] Therefore, artifacts such as wag-artifacts (caused by moving the stream)[6] or artifacts due to defective damping of the device[7] are usually corrected visually by experts who apply pre-established rules. However, visual validation is time-consuming and subjected to intra an interexpert variations.

We present a computerized method of validation of uroflowcurves that was developed with the aim to part with the interexpert variation and to minimize the intraobserver variation and the variability of maximum flow rate by automatic artifact detection and correction and compared the results with those obtained after visual correction by the experts.

Patients and methods

We evaluated a set of 90 randomly chosen flows with different types of artifacts from 35 patients out of 9 centres participating in the ALFSTOP trial, a multicentric trial in which patients with LUTS and benign prostatic enlargement were treated with alfuzosin. The flows were generated at different times during the study period by using a Dantec Urodyn 1000 flowmeter that recorded the uroflow parameters automatically.

The automatically recorded uroflowparameters were blinded and maximum flow and flow time, that is the total duration of micturition minus interruptions, were assessed by one of the experts (JdlR). At this first stage no specifications were given to the expert how artifacts should be corrected. When comparing the results with the automatically recorded parameters by the flowmeter, there appeared to be a large number of differences that were likely to be a result of inconsistencies of the interpre-

tation of the definition of an artifact and how it should be corrected.

Therefore, we developed the following artifact definition and correction specifications: 1) Incomplete curves and curves with faulty position of the baseline (e.g. maximum flow is not zero at time zero or at the end of the curve) should be detected and not validated. 2) Defective damping of the flowmeter with oscillations of the peak flow during less than 1 second should be detected and corrected whatever the amplitude. 3) Wag-artifacts defined as an increase of the flow up to 2 ml per second up and down (or down and up) within 4 seconds should be detected and corrected. 4) The last drops less than 2 ml of voided volume should not be used in the calculation of flow time. 5) Very acute initial peaks (related to ejection of the rinsing fluid in the rotating disk when it begins to turn) should be disregarded. 6) The maximum flow is the highest flow value after artifact correction.

Hereafter, the curves were scanned (HP Deskjet scanner) into an MS-DOS computer (Pentium 90 Mhz). After scanning, a specific software program analyzed the scans and reconstructed the flowcurves. Then, the parameters were calculated before and after correcting for artifacts automatically using the above mentioned specifications implemented in the software. The raw data as well as the corrected data generated by the computer were compared with the automatically reported results of the flowmeter.

Test-retest repeatability of the computer was evaluated by re-scanning 44 curves into the computer and recalculating the parameters. Furthermore, using the above mentioned artifact definition and correction specifications implemented in the software the maximum flow and flow time was assessed by three experts (JdlR, GV, MZ) who were blinded for the automatically recorded results. The experts quantified maximum flow values manually by using the following scale: ... 4.0 - 4.5 - 5.0 - 5.5 ... ml/s. Flow time values were assessed manually without using decimals. One expert also re-assessed the maximum flow and flow time values after a period of 2 weeks.

We analyzed the differences between the results of the computer and the results of the three experts and calculated the impact on sample size requirements of the applied method for a hypothetical trial. To assess the measuring agreement of two methods of measurement, we used the statistical approach recommended by Bland and Altman:[8] the paired differences between two measurements were plotted against the mean of the two readings and the mean difference and the standard deviation (SD) of the differences were calculated. Values obtained by two methods of measurement were compared by using the paired Student's t test or signed rank test. To assess the repeatability of the method of measure-

ment, the absolute differences between the measurements were plotted against the average of the two readings. Furthermore, test-retest repeatability for expert 1 and the computer was determined by calculating the SD of the differences between two readings and the repeatability coefficient (2SD) as defined by the British Standards Institution.[9]

Results

In table 1 the mean values of maximum flow, flow time and voided volume and their standard deviations obtained from the Dantec machine, the computer and the experts are presented. The SD of maximum flow after correction by the computer was 0.3 ml/s smaller than the SD of maximum flow from the Dantec machine. Flow time and voided volume values were not different between the Dantec machine and the computer either before or after correction.

The mean difference ± SD between maximum flow calculated after scanning by the computer (raw data) and the maximum flow value from

Table 1. *Mean maximum flow, flow time and voided volume values as measured by the applied methods ± SD. na: not available; The experts assessed the values without using specified correction rules (1a) and using specified correction rules (1b, 1c, 2 and 3, respectively).*

	Mean max. flow (ml/s)	Maximum flow range (ml/s)	Mean flowtime (s)	Mean voided volume (ml)
Dantec value	11.4 ± 3.3	5.8 - 26.0	47 ± 19	236 ± 75
Raw computer value	11.3 ± 3.3	5.7 - 25.6	47 ± 19	236 ± 75
Calculated computer value	10.7 ± 3.0	5.2 - 25.2	47 ± 19	236 ± 74
Expert 1a	9.9 ± 2.7	4.0 - 21.0	48 ± 20	na
Expert 1b	10.1 ± 2.8	5.0 - 22.0	50 ± 20	na
Expert 1c	10.0 ± 2.6	5.0 - 21.0	50 ± 20	na
Expert 2	11.3 ± 3.4	6.0 - 26.0	49 ± 19	na
Expert 3	11.0 ± 3.3	7.0 - 25.0	46 ± 18	na

the Dantec machine was 0.10 ± 0.22 ml/s (paired Student's t test; $p < 0.01$). In figure 1, a plot of the differences between the maximum flow value from the Dantec machine and the raw data from the computer against their mean is indicated. This figure suggests that more than 95 % of the differences between the maximum flow values as calculated by the computer (raw data) and those from the Dantec machine were less than 0.44 ml/s and that the differences were normally distributed. After artifact detection and correction by the computer the mean difference ± SD of maximum flow with the Dantec machine was 0.66 ± 0.95 ml/s (paired Student's t test; $p < 0.01$) and the median value was 0.40 ml/s (signed rank test; $p < 0.01$). As indicated in figure 2, the differences between the maximum flow values calculated by the computer and those from the Dantec machine were not normally distributed and the maximum flow values calculated by the computer were, except for 1 flow, smaller than the Dantec value.

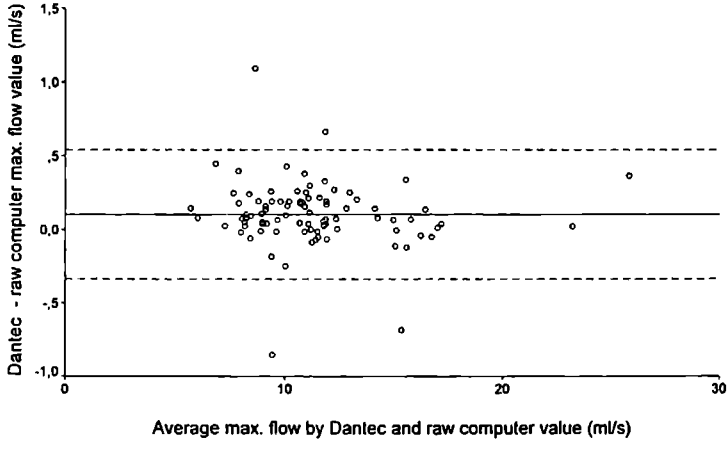

Figure 1. Scatterplot of the differences between the Dantec maximum flow values and the raw maximum flow values as assessed by the computer against their mean. Reference lines that are indicated are the mean difference Y = 0.10 ml/s [solid line] and the mean ± 2 SD (SD = 0.22 ml/s) [dotted line].

The mean difference ± SD between the 2 observations by one expert was 0.10 ± 0.56 ml/s (not significantly different; $p = 0.09$). Figure 3 suggests that the within flow SD for expert 1 was not associated with the magnitude of the flow value. The calculated coefficient of repeatability was 1.12 ml/s, agreeing with figure 3 where 95 % of the differences between the 2 observations by expert 1 were ≤ 1 ml/s. In 69 % of the flows the interpretation of the value of maximum flow by expert 1 was similar after reassessing the maximum flow values and in 18 % the

difference was 0.5 ml/s.

The test-retest repeatability of the computer was tested by scanning and calculating and rescanning and recalculating the maximum flow values of 44 randomly chosen flows. The mean difference between scan-rescan values of the raw maximum flow was 0.00 ± 0.14 ml/s with a coefficient of repeatability of 0.28 ml/s, indicating that 95 % of the differences between raw maximum flow values was less than 0.28 ml/s.

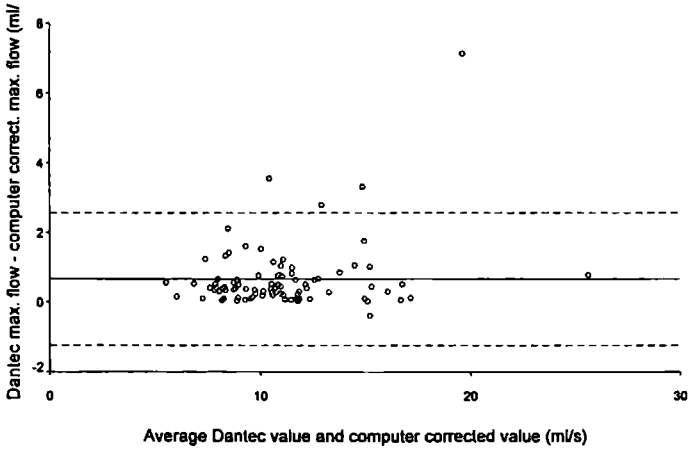

Figure 2. Scatterplot of the differences between the Dantec maximum flow values and the corrected values as assessed by the computer against their mean. Reference lines that are indicated are the mean difference Y = 0.66 ml/s [solid line] and the mean ± 2 SD (SD = 0.95 ml/s) [dotted line].

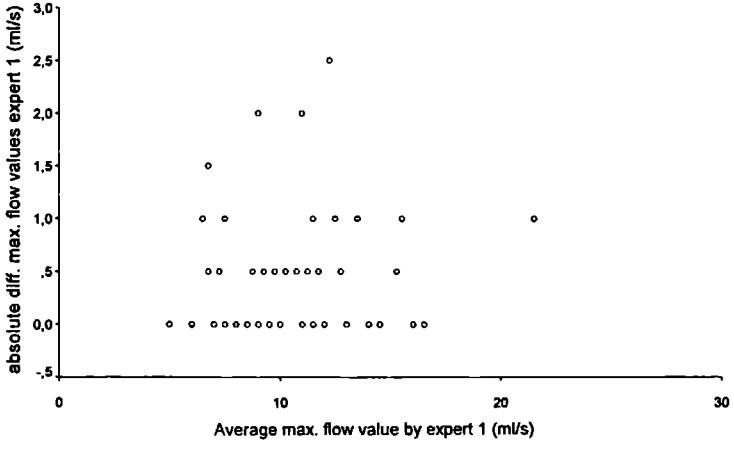

Figure 3. Scatterplot of the absolute differences of maximum flow values between 2 observations of expert 1 against their mean.

The difference between scan-rescan values of the raw data was 0.40 ml/s or less in all flows. The mean difference between scan-rescan values of maximum flow values after detection and correction for artifacts was 0.00 ± 0.19 ml/s with a coefficient of repeatability of 0.38 ml/s. The difference between scan-rescan values of the corrected data was 0.50 ml/s or less in all flows.

When comparing the mean corrected maximum flow values from the computer, with those of the experts, expert 1 had a significantly smaller mean maximum flow value, expert 2 had a significantly greater mean maximum flow value and expert 3 had a greater mean maximum flow value but the difference was not statistically significant (table 1,2). The interobserver difference between expert 1 and 2 is depicted in figure 4. It is remarkable that, using the same correction specifications, 70 % of the maximum flow values assessed by expert 2 were greater (mean difference ± SD = 1.24 ± 1.66, range 0 - 10 ml/s) when compared to those assessed by expert 1. Moreover, 51 % of the maximum flow values assessed by expert 1 were 1 ml/s or more smaller than those assessed by expert 2. Some of the discrepancies could easily be explained by simply 'overlooking' the scale of the flowcurve (Dantec machine gives 25 and 50 ml/s full scale). Two flows with large discrepancies between expert 1 and 2 are shown in figure 5.

In figure 6, the sample size requirements of a hypothetical study to detect a difference in maximum flow change between treatment groups with a type 1 error of 0.05 and a type 2 error of 0.10 are plotted when the computer is used (SD = 3.0 ml/s) and when the uncorrected results of the Dantec flowmeter or the corrected results of expert 2 or 3 are used (SD = 3.3 ml/s). As shown by figure 6, the smaller the detectable difference, the larger the gain when using the calculated values by the computer. When the aim is to detect a difference of 1.5, 1.0 or 0.75 ml/s -

Table 2. *Mean differences ± SD and range of maximum flow between experts and computer using the same artifact detection and correction specifications. Also indicated is the p-value when comparing the computer calculated value with the expert.*

	Mean ± SD (ml/s)	range (ml/s)	p-value
Expert 1 - computer corrected value	-0.71 ± 1.13	-6.05/2.76	< 0.01
Expert 2 - computer corrected value	+0.53 ± 1.62	-6.05/8.92	< 0.01
Expert 3 - computer corrected value	+0.25 ± 1.22	-1.55/6.92	0.05

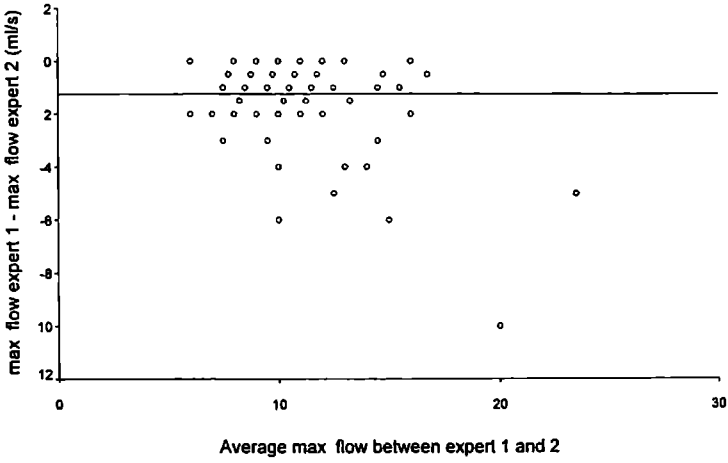

Figure 4. Scatterplot of the differences of maximum flow values between experts 1 and 2 against their mean. Reference line that is indicated is the mean difference Y = -1.24 ml/s [solid line]. Note that 70 % of the maximum flow values assessed by expert 1 are smaller than those assessed by expert 2

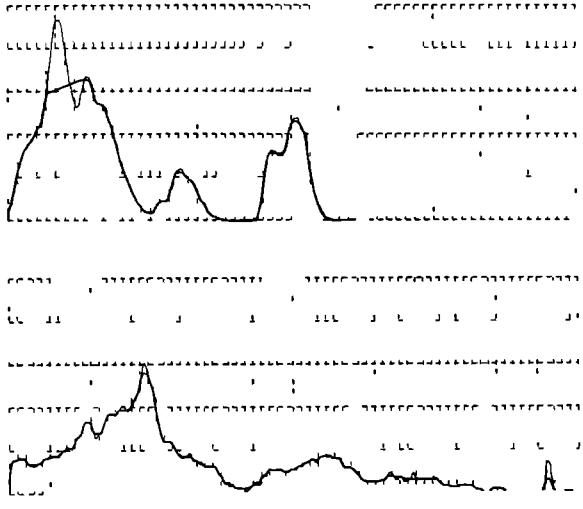

Figure 5. Two flowcurves with the raw flowdata (thin line) and the calculated flowdata (bold line) (X-axis: timescale = 70 sec, Y-axis: flowscale = 25 ml/s). The values of maximum flow of the dantec machine, ***expert 1***, expert 2, ***expert 3***, raw maximum flow and ***calculated maximum flow by the computer*** were for flow 1: 23 2, ***15.0***, 25.0, ***23.0***, 23.3 and ***16.4*** ml/s and for flow 2: 15 0, ***10.0***, 15 0, ***15.0***, 15.1 and ***14.0*** ml/s, respectively.

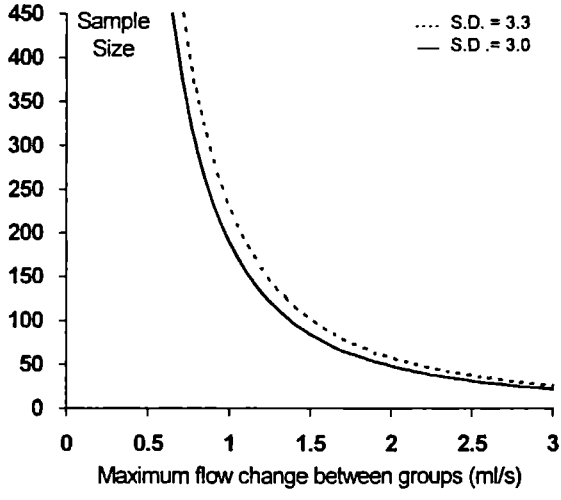

Figure 6. Sample size requirements (Y-axis) in hypothetical studies with a type 1 error of 0.05 and a type 2 error of 0.10 to detect a difference in maximum flow change between treatment groups (X-axis). The solid and dotted line indicate the sample size requirements when the SD of maximum flow is 3.0 (computer) and 3.3 ml/s (Dantec machine and expert 2 and 3), respectively.

between two treatments, 18, 40 and 71 patients less, respectively, are needed in each treatment arm.

Discussion

Since considerable variability between consecutive flow measurements may be found in various voiding parameters, and specifically maximum flow, any decision based on a single flow measurement seems to be questionable. The problem of reproducibility has been illustrated recently. Reynard et al. showed that there is a significant increase in maximum flow with each successive voiding when men with LUTS performed multiple free-flow measurements.[10] The specificity and positive predictive value of maximum flow for bladder outlet obstruction was significantly improved by multiple free-flow measurements. If the highest maximum flow after 3 voidings was less than 10 ml/s, the specificity and positive predictive values for bladder outlet obstruction were 90 and 94 %, respectively. As specificity and positive predictive value for bladder outlet obstruction improve when multiple free-flow measurements are used, the

specificity and positive predictive value of a genuine improvement of free flow as a result of treatment may also be improved when the results of multiple free-flow measurements are evaluated. We agree with Reynard that multiple free-flow measurements are most efficient for an accurate assessment.[10] For this reason, many units have developed urine flow clinics to obtain multiple uroflowmetry results. Although this approach increases the number of reliable measurements, this still is not an ideal situation. It is time consuming both for the patient and doctor while the patient is still not voiding under 'normal conditions'. Therefore, another method was recently suggested to get multiple reliable measurements: home-based uroflowmetry.[11] Home-based uroflowmetry is now used as an accurate tool to quantify and document changes in flow as a result of therapy. Besides obtaining reliable measurements, the interpretation of the flow should show minimal intra and inter observer variability.

Jørgensen et al reported the interobserver variation between experienced and inexperienced physicians in a study where 176 flow curves were classified according to their flow-curve pattern into 1 of 5 categories.[5] The experienced physicians disagreed on 20 % of the flowcurves whereas the inexperienced physicians disagreed on 45 % of the flowcurves. When experienced urodynamicists were asked to reevaluate the flows, the percentage of disagreement was as high as 16 %.

In the present study, the interobserver variation in the quantitative assessment of maximum flow also appeared to be great. Using the same artifact definition and correction specifications, in 70 % of the flows expert 2 assessed the values of maximum flow greater than expert 1. A total of 51 % of the maximum flow values assessed by expert 2 was 1 ml/s or more greater than those assessed by expert 1. The coefficient of repeatability for expert 1 was 1.12 ml/s and this indicates that 95 % of the differences between the 2 observations by one expert was equal to or less than 1 ml/s. Hence, in the present study, the intraobserver variation for expert 1 was smaller than the interobserver variation.

Can the quantitative assessment of maximum flow be improved by using sophisticated flowmeters or computers with special developed software ? A variant of observer variation has arisen due to the automatic quantitative assessment of flow-rate of some new uroflowmeters. Due to the high sensitivity of the flowmeter that registers any change in flow rate lasting 0.25 seconds or more, small oscillations that have no physiological meaning frequently occur. Another artifact that is frequently seen is caused by changing the direction of the urinary stream abruptly. Rollema described these artifacts as wag-artifacts.[6] It is clear that the commonly used flowmeters do not exclude these artifacts. The error as a result of

these artifacts has been shown to be more than 3 ml/s in 9 % of the flows, more than 2 ml/s in 20 % of the flows and more than 1 ml/s in 62 % of the flows.[3] Grino et al manually corrected the maximum flow rate values as given by the flowmeter in a study with 23.857 flows.[3] They concluded that manual reading of the maximum urinary flow rate eliminates an important fraction of the high variability of machine read maximum flow rate values.

The coefficient of repeatability of maximum flow after detection and correction of artifacts by the computer (0.38 ml/s) was slightly better when compared with the coefficient of repeatability between 2 observations by one expert (1.12 ml/s). This implies that the computer assesses maximum flow more consistent than expert 1. When comparing the coefficients of repeatability between the by the computer corrected maximum flow values (0.38 ml/s) and the raw maximum flow data generated by the computer (0.28 ml/s), the coefficient of the corrected flow values was slightly but not relevantly greater. This could be explained by the fact that the raw values depend on the scanning process only, but the corrected values also depend on the variation in the correction algorhythm as a result of the variation in the scanning.

However, when the test-retest results of the computer or the intraobserver results of expert 1 are reproducible, this does not persé mean that the measurement is correct. The absence of a reference value in the individual patient and the absence of a commonly agreed upon 'golden standard' for the correction algorhythm complicates the quantitative assessment of maximum flow. Furthermore, there is a great variation of maximum flow values within one patient and from the majority of the flows performed in the hospital we do not know whether a particular flow is entirely representative for the patient. In common clinical practice representability of the flow can easily be assessed by asking the patient and artifacts can easily be identified and manually corrected by the urologist. This is not easily done in large multicenter clinical trials where thousands of flows have to be assessed manually. A great interobserver variation can decrease the power of the study considerably.[3] Using a computerized artifact detection and correction program the interobserver variation problem is not of any relevance anymore and the intraobserver variation may be decreased further because the artifact detection and correction is always performed on the same way by the computer whereas the interpretation of the artifact detection and correction rules may differ among experts and may not be consistent when one expert evaluates the same flows at different time points of the day. When comparing the results of the computer with those of the experts the mean value of maximum flow of expert 1 was statistically significantly smaller than the

computer value whereas the mean value of maximum flow of expert 2 was statistically significantly greater than the computer value (table 2). The mean value of maximum flow assessed by expert 3 was not significantly different when compared to the by the computer corrected value. This again shows that the computer may correct artifacts on a more consistent way when compared to experts.

Furthermore, computerized handling of flowdata offers the possibility to create and evaluate new uroflowparameters that may be of relevance in the evaluation of patients with LUTS such as voiding time for the central 90% of the voided volume, time of the descending leg of the flow rate pattern, maximum flow during 2 seconds, maximum flow 2 seconds after start of the micturition etc. The creation of new or recalculated parameters is very difficult or, for some of the above mentioned new parameters, impossible when using manual artifact correction. Also maximum flow can easily be corrected for age as has been suggested by Drach[12] and for voided volume as has been suggested by Siroky[13] and Haylen.[14] Is this of clinical value ? One of the key-issues in deciding on the most appropriate treatment is whether the physician should focus on relieving symptoms and related bother or relieving urodynamically proved obstruction. Earlier studies have indicated that inclusion of pressure flow data in the preoperative evaluation and patient selection for interventional therapies such as transurethral resection of the prostate and transurethral microwave thermotherapy may improve the overall clinical results.[15,16] The correlation between symptoms and the results of urodynamic pressure-flow studies and maximum free flow have been reported to be poor, indicating that these methods measure different aspects of the clinical condition.[17,18] The correlation of isolated objective parameters is generally believed to be too inaccurate for clinical decision making. However, a combination of prostate size, post-void residual volume, voided volume and maximum flow correlated well with the results of urodynamics.[19] This combination of objective noninvasive measurement is named the clinical prostate score (CLIPS). Using this scoring system, we may be able to distinguish patients with and without bladder outlet obstruction without the need for an invasive and costly urodynamic pressure-flow analysis. From the four investigations used in this clinical prostate score, maximum flow is considered to be the most relevant and consequently has the highest weight. This confirms that maximum flow is regarded as the most useful investigation to assess the degree of obstruction and to monitor treatment effects.

Due to a more consistent detection and correction of artifacts, the coefficient of repeatability of maximum flow after computerized artifact

detection and correction is smaller when compared to the expert. Maximum flow is a quantitative variable on which the sample size of the study is frequently based. Clearly, a small coefficient of repeatability is of benefit because, with less variability due to the consistent detection and correction of artifacts, less patients are needed to assess a difference between treatment arms. Obviously, the large variability of maximum flow due to circadian changes, psychogenic inhibition, different urinary volumes or abdominal pressing is not influenced by this correction algorhythm.

In the present study, we have illustrated the potential advantages of a computerized method for artifact detection and correction of uroflows including its possible repercussions on sample size requirements. It is now time to assess the value of the presented method in a multicenter (drug treatment) trial.

Conclusions

Computerized artifact detection and correction eliminates an important fraction of the variability of manually corrected maximum flow values. This may lead to smaller sample size requirements especially in studies where the primary objective is to assess a small (± 1 ml/s) difference in mean maximum flow between groups.

References

1 Jensen KME: Uroflowmetry in elderly men. World J Urol **13**: 21, 1995.

2 McLoughlin J, Gill KP, Abel PD, Williams G: Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. Brit J Urol **66**: 303, 1990.

3 Grino PB, Bruskewitz R, Blaivas JG, Siroky MB, Andersen JT, Cook T, Stoner E: Maximum urinary flow rate by uroflowmetry: automatic or visual interpretation. J Urol **149**: 339, 1993.

4 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147**: 1044, 1992.

5 Jørgensen JB, Jensen KM-E, Klarskov P, Bernstein I, Abel I, Mogensen P: Intra- and inter-observer variations in classification of urinary flow curve patterns. Neurourol Urodyn **9**: 535, 1990.

6 Rollema HJ: Uroflowmetry in males. Reference values and clinical application in benign prostatic hypertrophy. Groningen, Drukkerij van Denderen B.V., 1981.

7 Christmas TJ, Chapple CR, Rickards D, Milroy EJG, Turner-Warwick RT: Contemporary flow meters: an assessment of their accuracy and reliability. Brit J Urol **63**: 460, 1989.

8 Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet i, 307, 1986.

9 British Standards Institution: Precision of test methods I: Guide for the determination and reproducibility for a standard test method (BS 5497, part 1). London: BSI, 1979.

10 Reynard JM, Peters TJ, Lim C, Abrams P: The value of multiple free-flow studies in men with lower urinary tract symptoms. Brit J Urol **77**: 813, 1996.

11 de la Rosette JJMCH, Witjes WPJ, Debruyne FMJ, Kersten PL, Wijkstra H: Improved reliability of uroflowinvestigations: Results of a portable home-based flowmeter study. Brit J Urol **78**: 385, 1996.

12 Drach GW, Layton T, Bottaccini MR: A method of adjustment of male peak urinary flow rate for varying age and volume voided. J Urol **128**: 960, 1982.

13 Siroky MB, Olsson CA, Krane RJ: The flow rate nomogram: I. Development. J Urol **122**: 665, 1979.

14 Haylen BT, Ashby D, Sutherst JR, Frazer MI, West CR: Maximum and average urine flow rates in normal male and female populations - the Liverpool nomograms. Brit J Urol **64**: 330, 1989.

15 Rollema HJ, van Mastrigt R: Objective analysis of prostatism : A clinical application of the computer program CLIM. Neurourol Urodyn **10**: 71, 1991.

16 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153**: 1526, 1995.

17 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156**: 1020, 1996.

18 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Debruyne FMJ, de la Rosette JJMCH: Correlation between uroflowmetry, prostate volume, postvoid residue, and lower urinary tract symptoms as measured by the international prostate symptom score. Urology **48**: 393, 1996.

19 Rosier PFWM, de Wildt MJAM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Clinical diagnosis of bladder outlet obstruction in patients with benign prostatic enlargement and lower urinary tract symptoms: Development and urodynamic validation of a clinical prostate score for the objective diagnosis of bladder outlet obstruction. J Urol **155**: 1649, 1995.

Chapter 5.2

Improved reliability of uroflowmetry investigations: results of a portable home-based uroflowmetry study.

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British Journal of Urology **78**: 385-390, 1996.

Abstract

Purpose: To compare the results obtained using a portable home-based uroflowmeter with the results of traditional flowmetry in the out-patient department.

Patients and methods: Sixty-seven patients (mean age 61 years, range 38-79) with lower urinary tract symptoms and/or benign prostatic enlargement used a home-based uroflowmeter comprising a datalogger and specially designed fluid sensors incorporated into disposable beakers. The results of these measurements were compared with those from uroflowmetry in the out-patient department and with other clinical variables.

Results: There was a good correlation between the uroflow results obtained when voiding at home and at the out-patient department. The highest measured maximum flow and voided volume were obtained with the home-based uroflowmeter system. However, the mean of all consecutive home-based maximum flow and voided volume measurements were lower than those obtained by single-void uroflowmetry in the out-patient department.

Conclusions: Home-based uroflowmetry provides reliable voiding results which are comparable with those obtained in the out-patient department.

Introduction

About one-third of men older than 50 years present with lower urinary tract symptoms;[1] such symptoms eventually develop in most men and the predominant mechanism for this disorder is bladder outlet obstruction, caused by the prostatic adenoma.[2] However, clinical experience suggests that the degree of obstruction is not always related to the volume of the prostate. Small prostates in younger men can cause severe obstruction and voiding disorders, but large adenomas can be present without causing obstruction.[3] In the treatment of patients with lower urinary tract symptoms and benign prostatic enlargement, the success of (surgical) treatment seems to be closely related to the presence of bladder outlet obstruction.[4,5] Therefore, if patients with lower urinary tract symptoms and benign prostatic enlargement are to be treated appropriately, information about the grade of obstruction should be obtained.

A urodynamic investigation with pressure-flow study analysis is considered to be the 'gold standard' to determine bladder outlet obstruction.[6] However, rather than performing this invasive investigation, uroflowmetry is most often used to document voiding disorders because it

is simple, readily available, and easy to use.[7] The most recent uroflowmeters measure voided volume, the maximum flow rate (Qmax), the mean flow rate, time to maximum flow, and the duration of flow. Moreover, the pattern of flow can be described and characterized. In general, urologists use measurements of Qmax, with patient's symptoms and other clinical findings, to make decisions about the need for therapeutic intervention to relieve lower urinary tract symptoms and/or bladder outlet obstruction. These clinical investigations can also be used in the followup of patients and to document the outcome of therapy.

The uroflow can be measured using several methods, e.g. a rotating disc, an electronic dipstick or gravimetric measurement. These systems are used mainly in the clinical environment and consequently the results are seldom obtained under conditions equivalent to 'voiding at home'; indeed, the patient has to void in an environment that can be very embarrassing. He must also void with a bladder full enough to obtain a representative voided volume. Moreover, the results of uroflowmetry may vary during the day.[8] To overcome these problems, a home-based system of uroflowmetry has been introduced. A system was designed and developed that would provide reliable results, was easy to use by the patient, had quality-control of flow-measurement, was hand-held for practical use, used hygienic disposable beakers and from which the results were quickly and easily available. In the present pilot study, the results from a portable home-based uroflowmeter were compared with other clinical variables and the results from uroflowmetry performed in the out-patient department.

Patients and methods

Sixty-seven consecutive patients (mean age 61 years, range 38-79) with voiding complaints were seen in the out-patient department; all were evaluated initially by a medical history, an International Prostate Symptom Score (I-PSS), a physical examination including digital rectal examination and transurethral ultrasonographic examination of the prostate, free urinary flowmetry in the hospital, a urodynamic evaluation (including pressure-flow studies), and a series of measurements from the home-based uroflowmeter. Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner with a multiplane 3-D rectal transducer (VRW 177AK). For free urinary flowmetry in the hospital, the Dantec Urodyn 1000 flowmeter was used. Home-based uroflowmetry was performed with a portable flowmeter using disposable beakers. The patients were asked to produce consecutive flows starting in

the morning and asked to void 'as they would normally do'. The results of these uroflowmetry readings were stored in the portable flowmeter and transferred to a computer for analysis during the second visit to the out-patient department.

The portable flowmeter

To meet with the requirements of a home-based uroflowmeter, a new method of measuring urine volume and flow was developed consisting of four self-calibrating cup-shaped volume sensors, printed on paper-like material that was disposable and not re-useable (figure 1), with each sensor comprising a measuring and calibration section. The flowmeter measures the changes in the electrical properties of the sensors caused by the fluid and the results are independent of the chemical properties of the fluid. The sensors can be shaped into a collecting beaker and disposed of after use. The goal was to develop a measuring system which could be held in the hand during the flow measurement. The system was designed so that the height of the fluid column could be determined accurately even when the system was tilted. The upper surface of the fluid column is measured by four sensors, although three sensors would be sufficient for determining a surface in three dimensions. However, a fourth sensor was added to allow quality control; using four sensors allows possible artifacts (e.g. caused by strong shaking) to be detected. Each sensor has a section which calibrates the measuring section during the measurement. After each voiding session, a new disposable beaker is mounted on the registra-

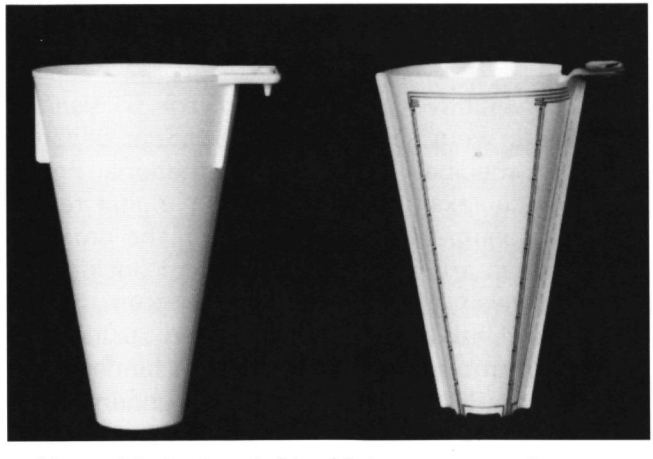

Figure 1. Disposable beaker (left) with its contents: the sensors are printed on paper-like material (right).

tion device (figure 2). Voiding is performed into this beaker after activatingthe system by pressing a red button (figure 2). The voiding record is terminated by pressing the same button again and each flow measurement is stored in the device. The system is easy to use; it is activated and deactivated with a single button, and two coloured lights and a 'beeper' present the status of the system. After activation, all sensors are tested, the measuring electronics calibrated and, when the test is successful, a green indicator is lit, the 'beeper' sounds and voiding can start. When the test is unsuccessful, a red indicator is lit and several beeps are generated, indicating a fault in the sensor. The tests are completed successfully 99.9% of the time because all sensors are tested during production. The power supply to the system consists of three small batteries which can be used for several flow sessions. When the battery voltage becomes too low, a flashing green and red light indicate that the user should replace the batteries.

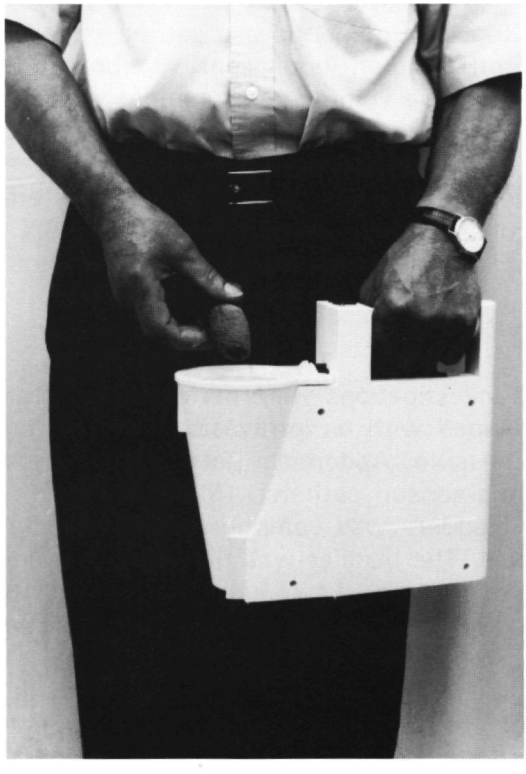

Figure 2. Demonstration of the use of the home-based uroflowmeter.

The device includes a micro-processor board, memory, a real-time clock and the measurement electronics. Each measurement is stored in the memory, together with the exact time and date. After completion of the required flow measurements, the system is returned to the physician. At the out-patient department, the device is connected to a desktop computer and the contents of the memory (the flow records and times) read from the flowmeter. Flow curves can be presented on the computer screen and printed as hardcopy. Flow variables, e.g. peak flow and mean flow rates, are calculated, stored in a database and can be presented on the screen or printer. These variables are also presented as a flow diary with all variables, including date and time, displayed; the mean, minimum and maximum values are also calculated. A program to automatically detect artifacts was also implemented and was able to identify those flows that were probably measured incorrectly.

The variables are stored in a database on the computer (in a standard Dbase format), together with data identifying the patient; the data can thus be exported to other programs like spreadsheets or statistical packages.

Almost 7 hours of continuous use can be stored and processed by the home-based uroflowmeter, equivalent to about 400 flow measurements. The accuracy of the volume measurement was determined by filling the beakers with known quantities of fluid and was also tested with the beakers in two angles (0° and 15°); the error of the measured volume was < 1 % of full scale (800 ml.) at any angle. The flow error was measured similarly using a constant flow source and was < 5% of full scale (50 ml./s.).

Urodynamic evaluation

Urodynamic investigations were performed with an 8F transurethral lumen catheter equipped with an intravesical microtip pressure sensor for recording bladder pressure. Abdominal pressure was recorded intrarectally with an 8F microtip-sensor catheter (MTC, Dräger, Germany). Before cystometry, the bladder was emptied through the lumen of the transurethral catheter. The bladder was filled with water of 20°C and at a filling speed of 50 ml./min. Equipment developed at our department (UIC/BME Research Centre, Department of Urology, Nijmegen, The Netherlands) was used to record the pressure and flow data. The linear passive urethral resistance (L-PURR) concept was used to provide an objective and accurate grading of obstruction;[9] in this system, patients graded 0-2 are minimally obstructed and those graded 3-6 definitely obstructed.

Descriptive statistics were used to assess the results of the home-

based uroflowmeter and the other clinical findings. Student's t-test was used to compare the mean Qmax and mean voided volume obtained at home and at the out-patient department.

Results

All the patients confirmed that the system was easy to use. All 67 patients received 12 beakers each and completed several micturitions free of artifacts. During a 3 day period, 6-12 (mean 10) measurements were obtained from each patient. A total of 673 flow-measurements were recorded and the quality-control system indicated that there were possible artifacts in 142 flows (21%). After visual evaluation of these records, there were 572 (85 %) correctly measured flows in total.

The mean prostate volume was 43 ml. (range 16-115) and the mean I-PSS score was 15.4 (range 1-33). The mean values of voided volume and Qmax for the consecutive measurements made at home are shown in table 1, which shows that the means were stable but with a large dispersion, indicated by the 95% CI. Evaluation of the uroflowmetry studies showed that the Qmax at the out-patient department ranged from 3.0 to 35.0 ml./s. and the comparison between the mean Qmax using the home-based uroflowmeter and at the out-patient department is shown in figure 3. The mean Qmax at the out-patient department (13.7 ml./s.) was slightly higher, but not significantly, than the mean Qmax from the home-based uroflowmeter (12.9 ml./s.; $p = 0.11$), possibly because the mean voided volume was significantly higher at the out-patient department (277 ml.) compared to that from the home-based uroflowmeter (215 ml.; $p < 0.01$). There was a difference in the highest Qmax achieved with the home-based uroflowmeter and at the out-patient department (figure 4); in most cases, the highest Qmax of the individual home-based uroflowmeter sessions was considerably higher than that obtained in the out-patient department. There was a similar pattern for the measurements of voided volume.

The Qmax at home was larger than that obtained in the out-patient department on 234 occasions (41 %), was similar on 7 occasions and smaller on 331 (58 %). The differences between the Qmax obtained at home and in the out-patient department were very variable; figure 5 shows that these differences appeared to have a Gaussian distribution, either negative or positive. On 373 occasions (65%), the absolute difference between the Qmax obtained at the out-patient department and at home was < 4 ml./s. and on the other 199 occasions, the absolute difference

Table 1. *Mean values and their 95 % confidence intervals [CI] of voided volume and maximum flow for consecutive measurements at home.*

Number of home-based uroflowmeter estimates	Number of patients	Mean voided volume (ml. [95% CI])	Mean maximum flow (ml./s. [95% CI])
1	67	194 [57-381]	13.1 [3.0-28.4]
2	67	211 [71-427]	13.0 [3.5-22.6]
3	67	211 [74-556]	12.9 [3.3-25.4]
4	65	226 [73-545]	12.6 [2.9-25.6]
5	64	224 [95-551]	13.4 [2.8-25.5]
6	62	209 [67-493]	12.5 [2.1-22.1]
7	57	212 [89-434]	12.6 [2.2-21.6]
8	50	202 [45-488]	11.6 [1.9-22.1]
9	34	211 [47-440]	12.3 [2.1-25.0]
10	24	196 [94-430]	10.7 [1.6-20.5]
11	15	240 [96-420]	12.6 [1.8-26.0]

was > 4 ml./s. (figure 5). There was a similar distribution of differences between the measurements of voided volume at the out-patient department and at home; on 396 occasions (69%) the voided volume at home was smaller than the flow at the out-patient department. On urodynamic study using pressure-flow analysis, the L-PURR ranged from 0-6 (mean 1.8). There were no significant differences in the variability of values from the home-based uroflowmeter between the groups with minimal (n = 49) and definite bladder outlet obstruction (n = 18) (figure 5).

Discussion

For decades, uroflowmetry has played a major role in the evaluation of voiding complaints. Urologists use the results of uroflowmetry with the patient's symptoms and other clinical findings to make decisions about the need for therapeutic intervention to relieve bladder outlet obstruction.

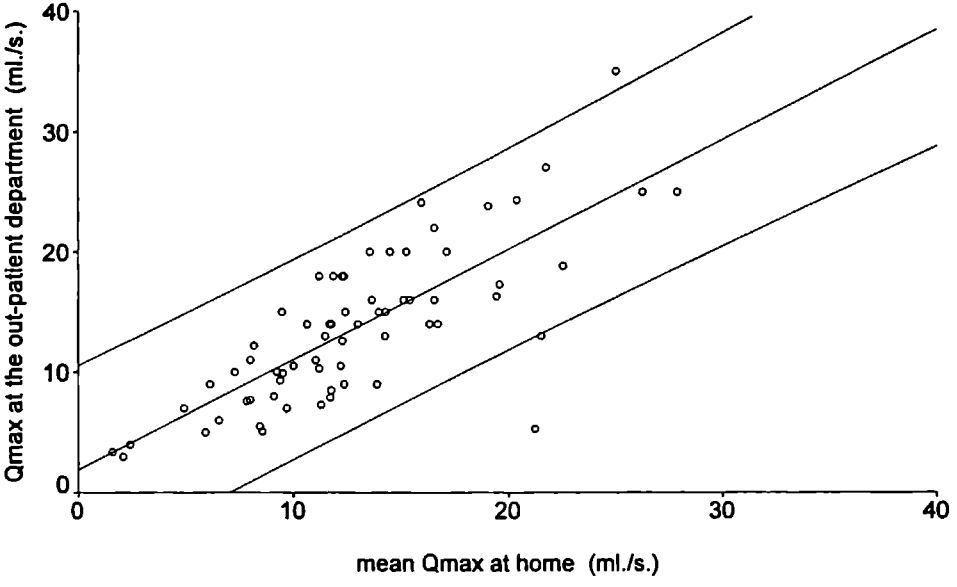

Figure 3. Comparison between the mean maximum flow using the home-based uroflowmeter and at the outpatient department. The regression line with individual 95 % confidence intervals is indicated.

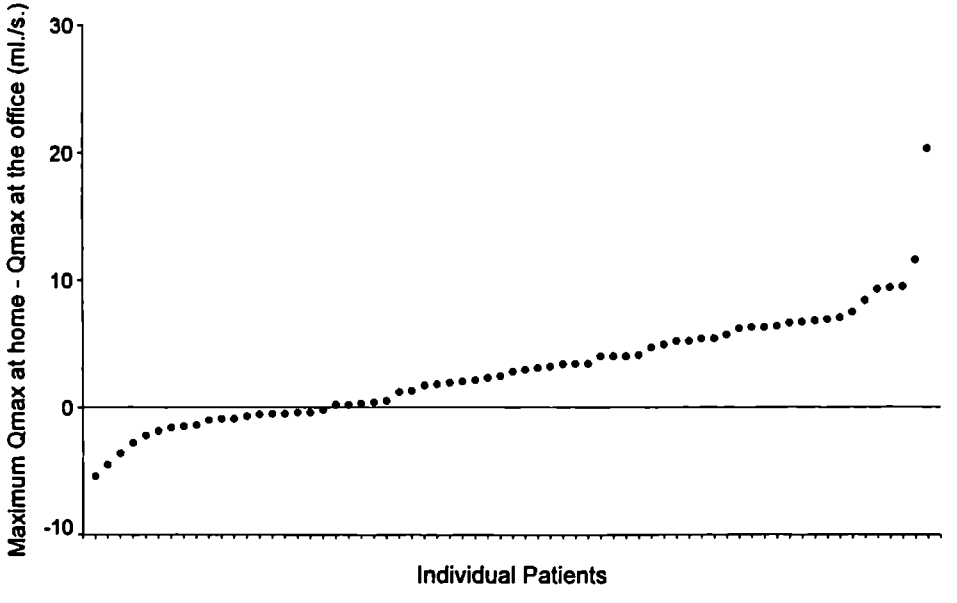

Figure 4. The difference between the highest maximum flow measured with the home-based uroflowmeter and the maximum flow obtained at the outpatient department for each patient.

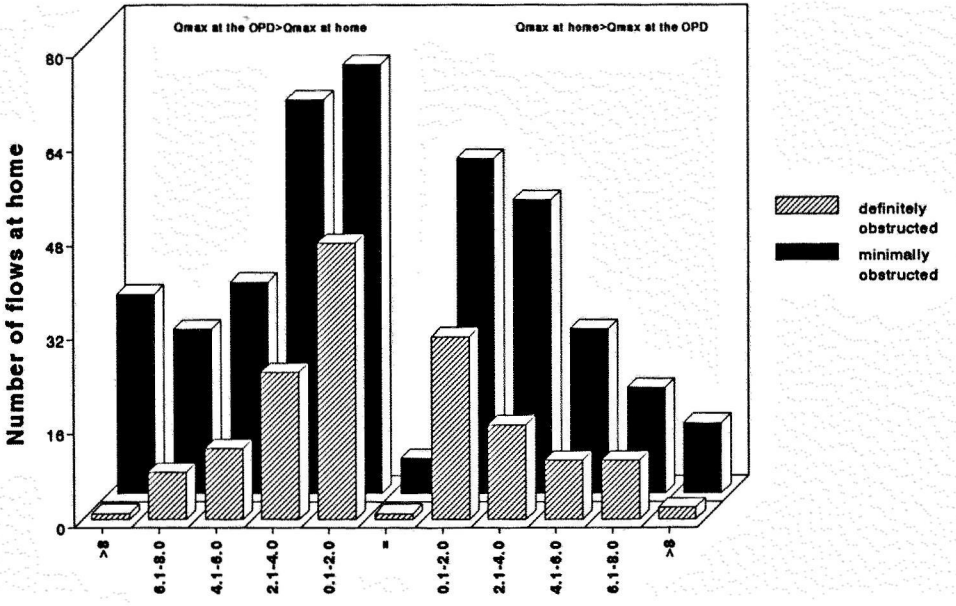

Figure 5. The number of flows from the home-based uroflowmeter with a Qmax greater (right) or smaller (left) than that obtained at the out-patient department (OPD). The absolute differences (ml./s.) between the flow at home and at the out-patient department for each group (striped definitely obstructed, L-PURR $\geq$ 3; and, black, minimally obstructed, L-PURR $<$ 3) are indicated below the figure.

Although uroflowmetry can provide useful information suggesting whether a patient has bladder outlet obstruction, and a particular flow pattern may suggest the possible underlying pathology, the interpretation of results may sometimes be difficult and misleading. For the appropriate use of the results of uroflowmetry, certain aspects should be considered, i.e. reproducibility, artifacts, circadian changes, variation within and between observers, association with volume and outlet obstruction, reference values and the clinical relevance to benign prostatic enlargement.[10-13]

Reliability is a prerequisite for any measuring technique; because consecutive flow measurements can produce variable results, particularly for Qmax, any decision based on a single-flow measurement is questionable. We agree with Blaivas that multiple samples are the most reliable for an accurate assessment.[14] For this reason, many units have developed urine-flow clinics to obtain multiple uroflowmetry results. Although this approach increases the number of reliable measurements, it is still not an ideal situation, being time-consuming for both the patient and doctor, while the patient is still not voiding under 'normal conditions'. Therefore,

another method was suggested to obtain multiple and reliable measurements, i.e. ambulatory home uroflowmetry. Golomb et al. were among the first to report about the results of a home uroflowmetry study,[8] in which the Home UroData System (Biodan Medical Systems Ltd, Rehovot, Israel) was used, and they concluded that there was large variability between consecutive maximum flows. This was confirmed by Meier et al.[15] who presented results from 140 men with micturition disorders using another home flowmeter.

In view of the importance of obtaining reliable uroflowmetry results, a portable home-based uroflowmeter was developed in our department. The present pilot study assessed the practical use of this flowmeter for both the patient and the urologist and whether it is possible to overcome some of the disadvantages of the 'traditional' uroflowmetry.

There was a close relationship between the mean Qmax and voided volume from the home-based uroflowmeter and those obtained in a single void at the out-patient department. However, during the voids at the out-patient department, there was a slightly higher mean Qmax and a significantly higher mean voided volume when compared with the results from the home-based uroflowmeter. The slightly higher maximum flow at the out-patient department could be explained by the higher voided volume, probably because the results in the out-patient department were obtained under 'forced' conditions. When the highest maximum flow achieved during voids at home was compared with the maximum flow at the out-patient department, a considerable number of patients showed a significant difference in voiding performance, as expected, because more voids were performed using the home-based uroflowmeter. However, almost one-third of the patients produced their highest maximum flow at the out-patient department, which is not surprising because the sole aim at the out-patient department is to have the bladder as full as possible, while at home the timing of micturition is related to other normal daily activities. The value of the 'supranormal' values obtained in the conditions of the out-patient department may be questioned when they are used as inclusion criteria in treatment protocols.

How many voiding sessions are needed to obtain reliable uroflowmetry results and should these be obtained by using the home-based uroflowmeter ? By establishing a 'flow clinic', several recordings of voids can be obtained and the results of such repeated uroflowmetry can then be assessed.[16] It is generally accepted that at least two or three voiding sessions, with an adequate voided volume, are required; indeed the maximum flow and voided volumes of the first 3 consecutive home-based uroflowmeter measurements show 'stable' results (table 1). Whether this

is enough to judge the voiding performance accurately needs to be assessed further. However, few would question that the 'voiding under normal conditions' is better achieved when using the home-based uroflowmeter than in the out-patient department.

One of the key questions in the treatment of patients with lower urinary tract symptoms and benign prostatic enlargement is whether or not they have bladder outlet obstruction. However, when using the home-based uroflowmeter, the relationship between the grade of obstruction and the results of uroflowmetry were no better than those from the out-patient department. There was a large variation in maximum flow in minimally obstructed patients and in those with definite obstruction (figure 5). Although a low maximum flow (< 10 ml./s. at an appropriate volume) has a higher probability of originating from a patient with bladder outlet obstruction, only a full urodynamic study with pressure-flow analysis can determine the exact grade of obstruction.

Another important factor in improving the reliability of uroflowmetry is quality control; all voiding studies are subject to numerous artifacts and many stem from the lack of privacy. Because environmental factors can significantly influence the results of voiding, a considerable effort should be made to make patients comfortable with their surroundings during any flow studies. The home-based uroflowmeter used in the present study complies with these requirements. Artifacts may also occur during flow recording; all modern flowmeters are sufficiently accurate, but need to be used with care; modern technology creates other problems, often explicable as incorrect instructions to the patient and/or incorrect use by the patient. For example, a patient may vary his urine stream across the collecting beaker or squeeze his penis or prepuce, leading to changes in the flow recording. He may also simply shake the home-based uroflowmeter or handle the device incorrectly. In the present study, the program to automatically detect artifacts indicated problems in 21 % of the voiding registrations. However, after visual inspection, the number of artifacts detected correctly was decreased to 15%. In conjunction with the technical specifications, this guarantees reliable uroflowmetry results if the home-based uroflowmeter reports no abnormalities. Many artifacts were detected in the present study; because the threshold values were determined by the software; based on the present results, the software has been adapted and the thresholds modified so that fewer flows are inspected unnecessarily.

Irrespective of age and education, patients confirmed that the home-based uroflowmeter was easy to use; it is relatively small and the functions are easily available. Thus, the home-based uroflowmeter can be installed easily for practical use at home and during outdoor activities. The

device is readily available and hygienic because of the disposable beakers used with the device. Thus, specific voiding difficulties that cannot be assessed by uroflowmetry in a daily clinical practice can be documented. We are aware that there is a significant circadian change in voiding values; a multicentre study has been initiated to examine these changes and to investigate the precise role of the home-based uroflowmeter.

In conclusion, home-based uroflowmetry studies are an interesting diagnostic investigation which provide more detailed information than does single-void traditional uroflowmetry. However, the exact utility of home-based uroflowmetry still needs to be determined.

References

1 Mebust WK, Holtgrewe HL, Cockett ATK: Transurethral prostatectomy, immediate and postoperative complications: a cooperative study of 13 participating institutions evaluating 3885 patients. J Urol **141**: 243, 1989.

2 Chapple CR: Introduction: The clinical Problem. In: Prostatic obstruction - pathogenesis and treatment. Edited by CR Chapple. London: Springer Verlag, pp. 3-11, 1994.

3 Rosier PFWM and de la Rosette JJMCH: Is there a correlation between prostate size and bladder outlet obstruction? World J Urol **13**: 9, 1995.

4 Rollema HJ, van Mastrigt R: Improved indication and follow up in transurethral resection of the prostate using the computer program CLIM: a prospective study. J Urol **148**: 111, 1992.

5 Schäfer W, Rübben H, Noppeney R, Deutz FJ: Obstructed and unobstructed prostatic obstruction. A plea for urodynamic objectivation of bladder outflow obstruction in benign prostatic hyperplasia. World J Urol **6**: 198, 1989.

6 Nordling J: A clinical view of pressure-flow studies. World J Urol **13**: 70, 1995.

7 Jensen KME: Uroflowmetry in elderly men. World J Urol **13**: 21, 1995.

8 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147**: 1044, 1992.

9 Schäfer W: Analysis of bladder-outlet function with the linearized passive urethral resistance, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. World J Urol **13**: 47, 1995.

10 Meyhoff HH, Glahn BE: Uroflowmetry. Methods Clin Urodyn **1**: 2, 1991.

11 Jensen KME, Jørgensen JB, Mogensen P: Reproducibility of uroflowmetry variables in elderly males. Urol Res **13**: 237, 1985.

12 Matzkin H, van der Zwaag R, Chen Y, Patterson LA, Braf Z, Soloway MS: How reliable is a single measurement of urinary flow in the diagnosis of obstruction in benign prostatic hyperplasia? Br J Urol **72**: 181, 1993.

13 Jørgensen JB, Jensen KME, Klarskov P, Bernstein I, Abel K, Mogensen P: Intra- and inter-observer variations in classification of urinary flow curve pat-

terns. Neurourol Urodyn **9**: 535, 1990.

14 Blaivas JG: Techniques of evaluation. In: Neurourology and Urodynamics. Principles and Practice. Edited by SV Yalla, EJ McGuire, A Elbadawi and JG Blaivas. New York: Macmillan Publishing C, pp. 155-198, 1988.

15 Meier AHP, van Waalwijk van Doorn ESC, van der Vleuten CPM, Delaere KPJ, Janknegt RA: Reliability of free uroflowmetry using repeated measurements of homeflowmetry in males. Neurourol Urodyn **13**: 453, 1994.

16 Abrams P: The urine flow clinic. In: Non-surgical treatment of BPH. Edited by JM Fitzpatrick. Edinburgh: Churchill Livingstone, pp. 33-43, 1992.

Chapter 5.3

Quantitative assessment of uroflow: Is there a circadian rhythm ?

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Urology, In Press.

Abstract

Objectives: To investigate if the circadian rhythm of urinary flow values varies within groups of patients with various degrees of bladder outlet obstruction.

Methods: A total of 170 patients with lower urinary tract symptoms suggestive of bladder outlet obstruction used a home-based uroflowmeter and produced a total of 1670 correctly measured flows at home. These patients also underwent a screening program with free urinary flowmetry in the hospital and a urodynamic pressure and flow study.

Results: There is a circadian variability in that men with higher grades of obstruction having a higher peak urinary flow with a smaller voided volume and a shorter flow time as a result of the above two in the early afternoon when compared to late evening, early morning, and the mid-night to morning periods.

Conclusions: This significantly greater maximum flow in the afternoon in men with higher grades of obstruction, can be an important bias in studies where the primary endpoint is to assess a small improvement of maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment. Patients participating in clinical research studies should produce their urinary flow in the clinic always in the same time period, either in the morning or in the afternoon, and should not switch their appointment time.

Introduction

Single uroflowmetry may not be sufficiently reliable for the determination of bladder outlet obstruction because many patients are unable to relax and void in the normal fashion while at the clinic. Therefore, Blaivas suggested that multiple samples are most efficient for enhancing an accurate assessment.[1] For this reason, many units have developed urineflow clinics to obtain multiple uroflowmetry results. Although this approach increases the number of reliable measurements, it is still not an ideal situation, being time-consuming for both the patient and doctor, while the patient is still not voiding under 'normal conditions'. To overcome these problems, several home-based systems of uroflowmetry have been introduced.[2-5] We recently reported on a system designed and developed to provide reliable results, is easy to use by the patient at home, has quality-control of flow-measurement, is hand-held for practical use, uses hygienic disposable beakers and from which the results are quickly and easily available.[4] However, it was concluded that when multiple samples

are available the problem arises which sample(s) should be used for the evaluation particularly if the reported circadian changes are of clinical relevance.[2,6-7]

In the present study, the results from the aforesaid portable home-based uroflowmeter were used to evaluate circadian changes in uroflowmetry parameters in patients with lower urinary tract symptoms. Furthermore, we investigated if circadian changes vary within various obstruction groups according to the Schäfer linear passive urethral resistance relation (L-PURR) nomogram.[8]

Patients and methods

A total of 170 consecutive patients (mean age 62 years, range 38-80) with voiding complaints was seen in the out-patient department; all were evaluated initially by a medical history, an International Prostate Symptom Score (I-PSS), a physical examination including digital rectal examination and transurethral ultrasonographic examination of the prostate, one free urinary flowmetry in the hospital, a urodynamic evaluation (including pressure-flow studies), and a series of measurements from the home-based uroflowmeter. Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner with a multiplane 3-D rectal transducer (VRW 177AK). For free urinary flowmetry in the hospital, the Dantec Urodyn 1000 flowmeter was used. Home-based uroflowmetry was performed with the home-based uroflowmeter, P-flow®. Patients were supplied with the home-based uroflowmeter and 12 disposable beakers and were instructed to use the home-based flowmeter at 12 consecutive flows during 2 or 3 days. The patients were asked to start producing flows in the morning and to void 'as they would normally do'. The results of the uroflowmetry readings were stored in the home-based uroflowmeter and transferred to a computer for analysis during the second visit to the out-patient department (figure 1). When the patient used the home-based uroflow system incorrectly, an automatic artifact detection program indicated whether an artifact could be expected. The home-based uroflowmeter has been described in detail previously.[4] Excluded were patients previously treated with transurethral (laser) resection of the prostate, transurethral microwave thermotherapy or 5α-reductase inhibitors. Patients using α1 receptor antagonists were also excluded.

Urodynamic investigations were performed using an 8F transurethral lumen catheter and an 8F transrectal catheter both equipped with a microtip pressure sensor (MTC, Dräger, The Netherlands). Before

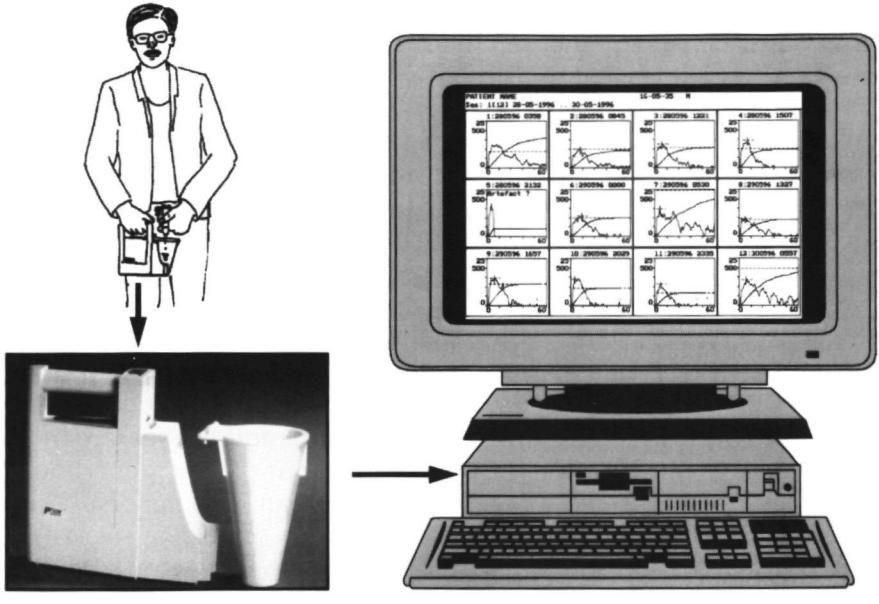

Figure 1. Demonstration of the P-flow®.

cystometry, the bladder was emptied through the lumen of a transurethral catheter to quantify residual urine after free uroflowmetry. The pressure sensors were zeroed to atmospheric pressure before introduction. The bladder was filled with water of 20°C with 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 in standing position was allowed in private. Digitally stored data were analyzed with equipment developed at our department (UIC/BME Research center, Department of Urology, Nijmegen, The Netherlands). In order to get useful information from pressure-flow study curves, it was necessary to relate detrusor pressure to corresponding flow. To quantify the grade of outlet obstruction, we used the concept of the linear-passive urethral resistance relation (L-PURR), relating minimal urethral opening pressure observed at the end of voiding with detrusor pressure at maximum flow.[8] Patients in L-PURR classes 0 and 1 had no bladder outlet obstruction, patients in classes 2 and 3 had moderate bladder outlet obstruction and patients in higher classes had severe obstruction. We also used the urethral resistance factor (URA) for grading bladder outlet obstruction. Calculation of URA was based on the point of maximum flow and corresponding detrusor pres-

sure.[9] A URA value > 29 cm water indicated obstruction.

Circadian changes were examined by dividing the 24 hour recording period into 4 periods with daytime periods 1 to 4 corresponding to midnight to 6 a.m. (night), 6 a.m. to noon (morning), noon to 6 p.m. (afternoon) and 6 p.m. to midnight (evening). The following parameters were evaluated for each of the obstruction categories: voided volume, maximum flow, mean flow and flow time. Mean values of these parameters were calculated for each daytime period per patient. These mean values were used to calculate the mean of the studied population. Descriptive statistics were used to illustrate the studied population. The Kruskal-Wallis one Way ANOVA test, the Wilcoxon matched pairs signed rank test and the Wilcoxon rank sum W test were used for the statistical analysis.

Results

A total of 170 patients with a median prostate volume of 34 ml. (range 16-120) and a median I-PSS score of 15 (range 1-33) received 12 beakers each and completed several micturitions free of artifacts. During a 2 or 3 days period, 3-12 (median 10) measurements were obtained from each patient. A total of 1850 flowmeasurements were recorded at home and the quality control system indicated that there were possible artifacts in 223 flows (12%). After visual evaluation of all flows by one of the authors (WW), there appeared to be 1670 (90 %) correctly measured flows in total. The median number of registered flows per patient for each daytime period as well as the total number of flows within each obstruction category is indicated in table 1. This table shows that the number of flows produced at specific daytime periods was not significantly different between obstruction groups.

Table 2 and figures 2a-c indicate the mean flow values for the flow produced in the hospital and the flows produced at home for each daytime period within obstruction categories. Except for voided volumes produced between midnight and 6 h a.m., the differences in voided volume and maximum flow between obstruction groups were all statistically significant (table 2). Severely obstructed patients (L-PURR $\geq$ 4) had a significantly smaller mean voided volume and mean maximum flow.

Table 2 and figure 2a show that in all obstruction categories the mean voided volume produced between midnight and 6 h a.m. was significantly greater compared with the flows produced in the afternoon and evening while the smallest mean voided volume at home is produced in the afternoon (figure 2a). For the groups without obstruction (L-PURR =

Table 1. *The median number (range) of flows per patient for each daytime period as well as, in italics, the total number of flows within each obstruction category.*

	midnight-6 h a.m.	6-12 h a.m.	12-6 h p.m.	6 p.m.-midnight	Total
L-PURR = 0,1 (n = 64)	1.0 (0-4) *89*	2.0 (0-5) *154*	3.0 (0-6) *181*	3.0 (0-6) *181*	10.0 (3-12) *605*
L-PURR = 2,3 (n = 70)	1.0 (0-5) *98*	3.0 (0-5) *206*	3.0 (0-6) *208*	3.0 (0-5) *194*	11.0 (3-12) *706*
L-PURR = 4,5,6 (n = 36)	1.0 (0-4) *49*	3.0 (1-6) *108*	3.0 (0-6) *105*	3.0 (0-6) *97*	10.5 (4-12) *359*

0,1) and with moderate obstruction (L-PURR = 2,3), mean voided volume produced at the hospital was significantly greater compared to that produced at home in the afternoon (figure 2a).

The mean maximum flow in patients without obstruction was not significantly different between specific daytime periods (table 2, figure 2b). In the patients with moderate and severe obstruction, the maximum flow produced at home in the afternoon was significantly greater than that produced in the morning. Moreover, in severely obstructed patients the maximum flow in the evening was again significantly smaller (figure 2b).

In the moderate and severely obstructed patients, the significant greater mean voided volumes and smaller mean maximum flow values between midnight and 6 a.m. resulted in statistically significant differences in mean flow time in that period but not in other periods of the day. Severely obstructed patients had approximately a doubling of their flow time between midnight and 6 a.m. when compared to the afternoon and evening. This difference was less pronounced in not obstructed patients. Mean flow time at the hospital was comparable with that produced at home between midnight and 6 h a.m. (figure 2c).

We further investigated the group with extreme differences in voided volume and maximum flow between the flows produced in the morning and those produced in the afternoon. The median absolute difference for voided volume was 50 ml and for maximum flow 2 ml/s. As indicated by statistically significant differences in the urodynamic values detrusor pressure at maximum flow, URA and L-PURR obstruction category, the group with absolute differences in voided volume exceeding 50

Table 2. *Mean flow values for the flow produced in the hospital and for those produced at home for each daytime period indicated for each obstruction category. Bold p values indicate the comparison between obstruction groups (Kruskal Wallis One Way ANOVA test). Wilcoxon p values indicate the comparison between specific periods of time (Wilcoxon matched pairs signed rank test).*

	Hospital Flow	midnight-6 h a.m.	*Wilcoxon p value*	6-12 h a.m.	*Wilcoxon p value*	12-6 h p.m.	*Wilcoxon p value*	6 p.m.-midnight
Volded volume (ml)	***p < 0.01***	***p = 0.14***		***p < 0.01***		***p < 0.01***		***p < 0.01***
L-PURR = 0,1	293	300	→ *0.25* ←	249	→ *< 0.01* ←	204	→ *0.12* ←	222
L-PURR = 2,3	240	277	→ *< 0.01* ←	209	→ *< 0.01* ←	189	→ *0.20* ←	198
L-PURR = 4,5,6	191	232	→ *< 0.01* ←	167	→ *0.05* ←	143	→ *0.42* ←	149
Maximum flow (ml/s)	***p < 0.01***	***p < 0.01***		***p < 0.01***		***p < 0.01***		***p < 0.01***
L-PURR = 0,1	13.9	14.8	→ *0.57* ←	14.3	→ *0.13* ←	14.3	→ *0.96* ←	14.4
L-PURR = 2,3	11.1	11.9	→ *0.49* ←	11.9	→ *< 0.01* ←	13.0	→ *0.54* ←	12.7
L-PURR = 4,5,6	7.9	7.6	→ *0.06* ←	8.3	→ *0.03* ←	9.6	→ *0.03* ←	8.7
Mean flow (ml/s)	***p < 0.01***	***p < 0.01***		***p < 0.01***		***p < 0.01***		***p < 0.01***
L-PURR = 0,1	7.2	8.4	→ *0.93* ←	7.8	→ *0.13* ←	8.0	→ *0.38* ←	8.2
L-PURR = 2,3	5.7	6.2	→ *0.23* ←	6.5	→ *0.03* ←	7.0	→ *0.72* ←	7.0
L-PURR = 4,5,6	4.0	4.3	→ *0.03* ←	4.8	→ *0.02* ←	5.7	→ *0.05* ←	5.0
Flow time (sec)	***p = 0.09***	***p < 0.01***		***p = 0.14***		***p = 0.84***		***p = 0.29***
L-PURR = 0,1	45	43	→ *0.15* ←	33	→ *< 0.01* ←	28	→ *< 0.01* ←	31
L-PURR = 2,3	46	49	→ *< 0.01* ←	37	→ *< 0.01* ←	30	→ *0.04* ←	32
L-PURR = 4,5,6	55	63	→ *< 0.01* ←	40	→ *< 0.01* ←	29	→ *0.08* ←	33

Table 3. *Patient characteristics of the groups of patients with and without extreme absolute differences (Δ) in voided volume and maximum flow.*

	Δ morning/afternoon voided volume ≤ 50 ml (n = 73)	Δ morning/afternoon voided volume > 50 ml (n = 86)	Δ morning/afternoon maximum flow ≤ 2 ml/s (n = 81)	Δ morning/afternoon maximum flow > 2 ml/s (n = 76)
Age (years)	62 ± 8	61 ± 9	63 ± 9	60 ± 8
Total I-PSS score	15.9 ± 6.7	15.7 ± 6.5	15.5 ± 6.4	16.1 ± 6.8
Prostate Volume (ml)	41 ± 17	40 ± 22	43 ± 22	39 ± 18
Bladder capacity (ml)	365 ± 117	419 ± 132 *	383 ± 110	407 ± 145
Detrusor pressure at maximum flow (cm water)	58.2 ± 30.5	45.8 ± 20.0 *	55.0 ± 25.3	47.0 ± 25.8 *
URA (cm water)	37.4 ± 20.9	29.9 ± 16.1 *	36.3 ± 19.5	29.4 ± 16.0 *
L-PURR category	2.5 ± 1.6	1.9 ± 1.3 *	2.4 ± 1.5	1.9 ± 1.4 *

* indicates significant difference ($p < 0.05$) between groups (Wilcoxon rank sum W test)

ml and in maximum flow exceeding 2 ml/s, was significantly less obstructed compared to those without extreme differences whereas the other clinical parameters age, total I-PSS and prostate volume were not significantly different (table 3).

We also investigated differences between patients who had a voided volume of over 150 ml in less than 50 % of de flows produced at home versus those with voided volumes over 150 ml in 50 % or more of the flows produced at home. A total of 125 patients (74%) had voided volumes over 150 ml in ≥ 50 % of the flows produced at home. Patients who had voided volumes over 150 ml in < 50 % of the flows had significant differences in the urodynamic values bladder capacity, detrusor

Table 4. *Patient characteristics of the groups of patients with < 50 % of the voided volumes produced at home > 150 ml (n = 45) and those with ≥ 50 % of the voided volumes produced at home > 150 ml (n = 125).*

	< 50 % of the voided volumes produced at home > 150 ml	≥ 50 % of the voided volumes produced at home > 150 ml
Age (years)	61 ± 9	62 ± 8
Total I-PSS score	19.0 ± 7.7	14.6 ± 5.9 *
I-PSS 1; incomplete emptying	2.4 ± 1.8	1.8 ± 1.6
I-PSS 2; repeated urination	3.4 ± 1.5	2.5 ± 1.5 *
I-PSS 3; intermittency	2.7 ± 2.0	2.2 ± 1.6
I-PSS 4; urge	3.1 ± 2.0	1.9 ± 1.7 *
I-PSS 5; reduced stream	3.7 ± 1.6	3.2 ± 1.5
I-PSS 6; strain to start	1.5 ± 1.6	1.2 ± 1.3
I-PSS 7; nocturia	2.4 ± 1.3	1.9 ± 1.1 *
Prostate Volume (ml)	44 ± 25	39 ± 17
Bladder capacity (ml)	307 ± 91	428 ± 123 *
Detrusor pressure at maximum flow (cm water)	63.9 ± 34.9	46.3 ± 19.5 *
URA (cm water)	43.1 ± 26.3	29.1 ± 13.2 *
L-PURR category	2.8 ± 1.9	1.9 ± 1.3 *

* indicates significant difference ($p < 0.05$) between groups (Wilcoxon rank sum W test)

pressure at maximum flow, URA and L-PURR obstruction category, indicating that they were more obstructed compared to those who had voided volumes over 150 ml in ≥ 50 % of the flows. The other clinical parameters age and prostate volume were not significantly different among both groups (table 4). Total I-PSS symptom score was significantly greater in those who had voided volumes over 150 ml in < 50 % of the flows. When evaluating the specific symptoms, it appeared that this significant greater total symptom score originated mainly from symptoms related to frequency: repeated urination, urge and nocturia. All these symptoms were significantly more frequently reported than in those who had voided volumes over 150 ml in < 50 % of the flows.

The effect of excluding flows with voided volumes of less than 100 ml and 150 ml on the mean voided volume and maximum flow produced in the morning and afternoon is indicated in table 5.

Discussion

For decades uroflowmetry has played a major role in the evaluation of patients with lower urinary tract symptoms. Urologists use uroflowmetry measurements together with patient symptoms and other clinical findings to decide upon the need for therapeutic intervention. Most urologists nowadays agree that only patients with bladder outlet obstruction should undergo surgical intervention[10] but nevertheless the decision for surgery is usually based primarily on the nature and severity of symptoms and the results of uroflowmetry. A urodynamic investigation with pressure-flow studyanalysis is considered to be the 'gold standard' to determine bladder outlet obstruction.[11] However, rather than performing this invasive investigation, uroflowmetry is most often used to document voiding disorders because it is simple to perform, the results are quickly available and refined flowmeters are easy to use.[12] Besides its diagnostic role, uroflowmetry has evolved as one of the most important evaluation methods in the assessment of the efficacy of drug treatments and other therapies in patients with lower urinary tract symptoms. The most modern flowmeters allow the measurement of voided volume, maximum flow, mean flow and flow time. Moreover, the flow pattern can be described. Among the many parameters maximum flow is regarded as the most useful to assess the degree of obstruction and to monitor treatment effects. Despite its popularity, uroflowmetry is hampered by several difficulties including its inability to differentiate between bladder outlet obstruction and impaired detrusor activity, artifacts, reproducibility, and circadian changes.[2,5-7,13-16]

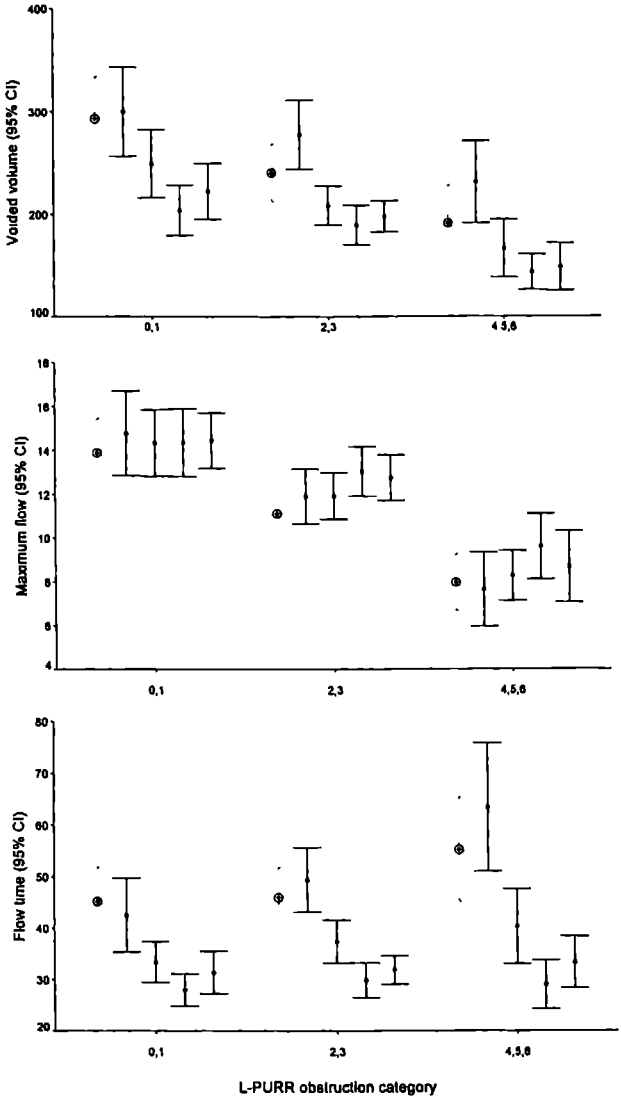

Figure 2. Mean voided volume (2a), maximum flow (2b) and flow time (2c) values and their 95 % Confidence Intervals (CI) for each L-PURR obstruction category.
The circle and dotted CI indicate the mean values for the flow produced at the hospital. The squares and the striped CI's indicate from the left to the right side respectively the mean values of the flows produced at night (between midnight to 6 a.m.), in the morning (6 a.m. to noon), in the afternoon (noon to 6 p.m.) and in the evening (6 p.m. to midnight).

Table 5. *The effect of excluding flows with voided volumes of less than 100 ml and 150 ml on mean flow values ± standard deviation for the flows produced in the morning and the afternoon in the obstruction categories. P values indicate the comparison between the flows produced in the morning and afternoon (Wilcoxon matched pairs signed rank test).*

	All flows (1670 flows)			Flows < 100 ml excluded (1477 flows)			Flows < 150 ml excluded (1087 flows)		
	morning	*p value*	afternoon	morning	*p value*	afternoon	morning	*p value*	afternoon
Voided volume (ml)									
L-PURR = 0,1	249 ± 128	→ < *0.01* ←	204 ± 96	275 ±120	→ < *0.01* ←	225 ± 91	316 ± 114	→ < *0.01* ←	258 ± 84
L-PURR = 2,3	209 ± 79	→ < *0.01* ←	189 ± 80	228 ± 83	→ < *0.01* ←	203 ± 78	261 ± 73	→ < *0.01* ←	229 ± 71
L-PURR = 4,5,6	167 ± 84	→ *0.05* ←	143 ± 50	198 ± 72	→ < *0.01* ←	158 ± 43	229 ± 66	→ < *0.01* ←	191 ± 28
All patients	214 ± 105	→ < *0.01* ←	185 ± 84	239 ± 100	→ < *0.01* ←	202 ± 81	275 ± 95	→ < *0.01* ←	234 ± 75
Maximum flow (ml/s)									
L-PURR = 0,1	14.3 ± 5.9	→ *0.13* ←	14.3 ± 6.0	15.4 ± 5.3	→ *0.33* ←	15.2 ± 5.7	16.2 ± 5.4	→ *0.12* ←	16.5 ± 5.5
L-PURR = 2,3	11.9 ± 4.4	→ < *0.01* ←	13.0 ± 4.6	12.2 ± 4.5	→ < *0.01* ←	13.6 ± 4.4	12.4 ± 4.5	→ < *0.01* ←	14.5 ± 4.9
L-PURR = 4,5,6	8.3 ± 3.4	→ *0.03* ←	9.6 ± 4.3	8.4 ± 3.0	→ *0.12* ←	10.0 ± 4.2	8.4 ± 3.1	→ *0.01* ←	11.3 ± 4.1
All patients	12.0 ± 5.3	→ < *0.01* ←	12.8 ± 5.4	12.6 ±5.2	→ < *0.01* ←	13.4 ± 5.2	13.0 ± 5.4	→ < *0.01* ←	14.7 ± 5.3

Golomb et al studied circadian changes in a group of patients with benign prostatic hyperplasia (BPH) and a group of healthy men and reported in patients with BPH an increase in voided volume, interval to maximum flow and flow time, from midnight to 6 a.m. and a decrease in volume adjusted peak flow from midnight to noon and in peak flow from 6 a.m. to noon.[2] Nakamura et al reported typical circadian rhythms for the majority of patients investigated.[5] Most patients showed a decreased frequency at night and an increased voided volume in the early morning, which was considered the typical rhythm of urination.[5] Nakamura et al also showed that, from midnight to 6 a.m., the frequency in elderly men was significantly greater than that in a middle-aged group. This increased frequency was primarily due to an increase in diuresis in the elderly men investigated.[5] Burgio et al reported a frequency of diurnal urination of 5.5 for this age category.[6] Unfortunately, we were not able to report circadian changes in frequency or diuresis. In the present study, the total number of flows measurements obtained from each patient during a 2-3 days period was between 3-12 (median 10). This is less than what could be expected when the home-based uroflowmeter was used continuously for this period of time. Although the flowmeter was not used continuously by all patients and we cannot, therefore, report on circadian changes in frequency, some important findings can be gleaned from the present study.

We reported an increase in voided volume and flow time, both interrelated parameters, from midnight to 6 a.m. which is in agreement with the results of Golomb et al and Nakamura et al. Despite a clearly greater voided volume at night, maximum flow was not significantly greater.

There was a close relationship between voided volume produced between midnight and 6 a.m. and voided volume produced at the hospital. The greater voided volume produced at the hospital could be explained probably because the results were obtained under 'forced' conditions. This is not surprising because the sole aim at the out-patient department in the hospital is to have the bladder as full as possible, whereas at home the timing of micturition is related to other normal daily activities. The value of the 'supranormal' values obtained in the conditions of the out-patient department may be questioned when they are used as inclusion criteria in treatment protocols.

In the present study, it was shown that there is a circadian variability in that men with higher grades of obstruction having a higher peak urinary flow with a smaller voided volume and a shorter flow time as a result of the above two in the early afternoon when compared to late evening, early morning, and the mid-night to morning periods. This signifi-

cantly greater maximum flow in the afternoon in men with higher grades of obstruction, can be an important bias in studies where the primary endpoint is to assess a small improvement of maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment.

Circadian changes in voided volume and maximum flow result in marked differences in flow time. While the differences between obstruction categories in flow time for the voidings produced at the hospital were not statistically significant, the difference in flow time for the voidings produced at home between midnight and 6 a.m. was statistically significant. Between midnight and 6 a.m., severely obstructed patients have approximately a doubling of flow time compared with the flows produced in the afternoon and evening.

How can we explain this circadian variability ? Kaplan et al., based on the similarity of patterns of occurrence between hypertension and BPH, suggested a shared underlying mechanism.[17] He stated that "There is substantial evidence that the sympathetic nervous system plays an important etiologic role in both hypertension and BPH. The level of sympathetic drive may have a circadian rhythm reaching a peak in the early morning, the time of the day at which most cardiovascular events occur." If this level of sympathetic drive really influences the lower urinary tract, the maximum flow of flows produced during the morning would be lower and this appeared to be true in our paper. This circadian rhythm also exists in asthmatic patients who experience a circadian variation with increased airway responsiveness and decreased lung function at night and the early morning compared with the rest of the day.[18] Future studies are needed to elucidate the pathophysiology of the circadian variation in patients with hypertension, asthma and BPH.

Patients with extreme differences between the morning and afternoon flow were more likely to be without bladder outlet obstruction. Obviously, patients without obstruction have greater voided volumes and greater maximum flows and consequently a greater variability may be expected.

In the group of patients with severe obstruction, the flow produced in the afternoon had a mean voided volume of 143 ml with a standard deviation of 50 ml. This indicates that a considerable percentage of patients has an initial voided volume of less than 150 ml, a cut-off point that is frequently used as selection criterion in clinical trials. Evidently, some patients with obvious bladder outlet obstruction do not enter these trials whereas the largest urodynamic treatment responses are reported in patients with low maximal flow rates.[19] When the flows with voided volumes less than 150 ml are excluded from the analysis and the morning

and afternoon results of flow at home are compared, it is clear that the improvement in maximum flow seems to increase. This may be explained by the fact that the afternoon flow has a significant lower voided volume and relatively more flows are excluded in the afternoon because the volume is less than 150 ml which may overemphasize the increase in maximum flow in the afternoon.

In the present study, patients who had voided volumes less than 150 ml in the majority of their flows were more obstructed than those who had voided volumes over 150 ml in the majority of their flows. Moreover, the total I-PSS score was significantly smaller in the latter group. This smaller total I-PSS score in patients who had voided volumes over 150 ml in the majority of their flows was primarily due to symptoms that are related to frequency: repeated urination, urge and nocturia. All these symptoms were significantly less frequently reported in patients who had voided volumes over 150 ml in the majority of their flows. Obviously, there is a direct relationship between obstruction, these patients have lower voided volumes, and frequency. These results are in agreement with the results of Ezz el Din et al who investigated the correlation between the diagnosis of bladder outlet obstruction and individual symptoms of the International-Prostate Symptom Score (I-PSS). They concluded that there was a statistically significant correlation between the specific questions of the I-PSS and objective grade of obstruction. Also in the study of Ezz el Din et al, the questions related to frequency: repeated urination, urge and nocturia showed better correlations with obstruction than other questions. However, the clinical significance of this finding was considered to be doubtful because none of the Spearman rank correlation coefficients was above 0.23, indicating very weak correlations. Furthermore, there was considerable overlap of symptom scores between patients with different grades of bladder outlet obstruction.[20] We agree with their conclusion that subjective and objective methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the symptomatic patient.

Conclusions

There is an important circadian variability in that men with higher grades of obstruction having a higher peak urinary flow with a smaller voided volume and a shorter flow time as a result of the above two in the early afternoon when compared to late evening, early morning, and the mid-night to morning periods. This significantly greater maximum flow in

the afternoon in men with higher grades of obstruction, can be an important bias in studies where the primary endpoint is to assess a small improvement of maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment. Patients participating in clinical research studies should produce their urinary flow in the clinic always in the same time period, either in the morning or in the afternoon, and should not switch their appointment time.

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References

1 Blaivas JG: Techniques of evaluation. In: neurourology and Urodynamics. Principles and Practice. Edited by SV Yalla, EJ McGuire, A Elbadawi and JG Blaivas. New York: Macmillan Publishing Co., chapt. 10, pp. 155-198, 1988.

2 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147:** 1044, 1992.

3 Meier AHP, van Waalwijk van Doorn ESC, van der Vleuten CPM, Delaere KPJ, Janknegt RA: Reliability of free uroflowmetry using repeated measurements of homeflowmetry in males. Neurourol Urodyn **13:** 453, 1994.

4 de la Rosette JJMCH, Witjes WPJ, Debruyne FMJ, Kersten PL, Wijkstra H: Improved reliability of uroflowmetry investigations: results of a portable home-based uroflowmetry study. Brit J Urol **78:** 385, 1996.

5 Nakamura S, Ishiyama S, Kobayashi Y, Tokue A: Automatic integrated circuit card system for recording 24-hour uroflowmetry. J Urol **150:** 926, 1993.

6 Nakamura S, Kobayashi Y, Tozuka K, Tokue A, Kimura A, Hamada C: Circadian changes in urine volume and frequency in elderly men. J Urol **156:** 1275, 1996.

7 Burgio KL, Engel BT, Locher JL: Normative patterns of diurnal urination across 6 age decades. J Urol **145:** 728, 1991.

8 Schäfer W: Analysis of bladder outlet function with linearized passive urethral resistance relation, linPURR, and a disease specific approach for grading obstruction: from complex to simple. World J Urol **13:** 47, 1995.

9 Griffiths DJ, van Mastrigt R, Bosch R: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size in urethral obstruction due to benign prostatic hyperplasia. Neurourol Urodyn **8:** 17, 1989.

10 Rollema HJ, van Mastrigt R: Improved indication and follow up in transurethral resection of the prostate using the computer program clim: a prospective study. J Urol **148:** 111, 1992.

11 Abrams PH, Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Brit J Urol **51:** 129, 1979.

12 Jensen KM-E: Uroflowmetry in elderly men. World J Urol **13:** 21, 1995.

13 McLoughlin J, Gill KP, Abel PD, Williams G: Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. Brit J Urol **66:** 303, 1990.

14 Grino PB, Bruskewitz R, Blaivas JG, Siroky MB, Andersen JT, Cook T, Stoner E: Maximum urinary flow rate by uroflowmetry: automatic or visual interpretation. J Urol **149:** 339, 1993.

15 Reynard JM, Peters TJ, Lim C, Abrams P: The value of multiple free-flow studies in men with lower urinary tract symptoms. Brit J Urol **77:** 813, 1996.

16 Jørgensen JB, Jensen KM-E, Klarskov P, Bernstein I, Abel I, Mogensen P: Intra- and inter-observer variations in classification of urinary flow curve patterns. Neurourol Urodyn **9:** 535, 1990.

17 Kaplan SA and Kaplan NM: Alpha-blockade: Monotherapy for hypertension and benign prostatic hyperplasia. Urology **48:** 541-550, 1996.

18 Martin RJ: Nocturnal asthma: circadian rhythms and therapeutic interventions. Am Rev Respir Dis **147:** 25-28, 1993.

19 Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P and the BPH-ALF Group: Alfuzosin for treatment of benign prostatic hypertrophy. Lancet **337:** 1457, 1991.

20 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156:** 1020, 1996.

Chapter 6

Watchful waiting in patients with lower urinary tract symptoms

Variability of clinical and pressure-flow study variables after 6 months of watchful waiting in patients with lower urinary tract symptoms and benign prostatic enlargement.

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Abstract

Purpose: We quantified the physiological variability of clinical and pressure-flow study variables in patients with symptomatic benign prostatic enlargement.

Material and Methods: Symptom scores were measured, and advanced urodynamic studies with pressure-flow analysis were performed in 121 patients before and 6 months after a period of watchful waiting.

Results: Patients without bladder outlet obstruction experienced statistically significant symptomatic improvement. Symptoms in patients with obvious bladder outlet obstruction did not improve significantly. The reproducibility of mean pressure-flow variables was evident. However, there was an important intra-individual variability. Patients with obvious bladder outlet obstruction showed a significant decrease in detrusor pressure at maximal flow of 14 cm. water, a significant decrease in the urethral resistance factor URA of 7 cm. water and a significant decrease of 1 obstruction class on the linear passive urethral resistance relation nomogram, indicating less severe bladder outlet obstruction.

Conclusions: Mean differences among therapy groups must be regarded critically, especially when the differences are slight and possibly within physiological variability.

Introduction

Lower urinary tract symptoms (LUTS) in elderly men are traditionally labeled prostatism. The term implies cause and remedy, whereas in reality the condition results not only from infravesical bladder outlet obstruction caused by the enlarged prostate gland, but also from motor or sensory abnormalities of detrusor and urethral function,[1] or even from changes in habits and lifestyle that commonly occur as men age. Patients and physicians are anxious to know whether the symptoms are likely to be progressive and whether there is a risk of complications, such as obstructive nephropathy, acute or recurrent urinary retention, infection, bleeding, bladder stones or other complications that directly affect patient well-being.

The gold standard for treatment of patients with intractable urinary retention or obstructive uropathy in the upper urinary tract is still transurethral prostatectomy. In the past, physicians performed prostatectomy for all patients who presented with symptoms. Patients and physicians now have a variety of treatment modalities from which to choose. Presently, in most situations other factors must be considered

when deciding on the appropriate treatment, particularly bothersomeness of the voiding disturbances and patient preferences for treatment. A key issue is whether the physician should focus on relieving symptoms or obstruction. Unfortunately, lower urinary tract symptoms, prostate size, free uroflowmetry parameters and post-void residual urine are associated with obstructive voiding but the correlation with the grade of obstruction is poor.[2-6] Furthermore, subjective efficacy of treatment cannot always be extrapolated to objective efficacy.[7]

A non-invasive treatment approach is watchful waiting. More than a third of men with lower urinary tract symptoms who remain untreated or are treated with a placebo experience spontaneous improvement based on subjective criteria, and more than 20 % improve based on objective criteria.[7] This spontaneous improvement usually occurs within the first 6 months if at all.[7] Due to the variable natural history of patients with lower urinary tract symptoms, and because new treatment modalities do not always result in such dramatic subjective and objective effects compared to prostatectomy, inclusion of a control-arm that allows quantification of these spontaneous effects is becoming increasingly important in any trial to evaluate accurately the efficacy of a new treatment modality.

Urodynamic investigation is considered to be the gold standard to quantify the grade of bladder outlet obstruction in elderly men with lower urinary tract symptoms.[8] Precise grading of obstruction is becoming increasingly important in the evaluation and comparison of new treatment modalities in patients with lower urinary tract symptoms and bladder outlet obstruction. However, precise grading is relatively sensitive to the effect of normal intra-individual variability. Rosier et al. showed that there is a considerable intra-individual variability in urodynamic pressure-flow variables when the filling and voiding session during a single urodynamic investigation is repeated.[9] The second voiding session resulted in better voiding in a significant number of patients (65 %), with a lower detrusor pressure at maximum flow rate and a larger theoretical urethral area.[9]

To compare the efficacy of new instrumental and non-invasive treatment modalities, and to investigate the reported spontaneous subjective and objective improvement after 6 months without active treatment, we determined the physiological variability of clinical and urodynamic pressure-flow study variables in patients with lower urinary tract symptoms and benign prostatic enlargement who were followed with the watchful waiting approach for 6 months.

Patients and methods

In 1992, we initiated a prospective study to evaluate clinical and urodynamic changes in patients with lower urinary tract symptoms and benign prostatic enlargement in whom a watchful waiting approach was chosen. All patients were evaluated at baseline by medical history, international prostate symptom score (I-PSS), prostate specific antigen (PSA) - analysis, physical examination, including digital rectal examination and ultrasonography of the prostate, and free uroflowmetry with subsequent ultrasonographic measurement of residual urinary volume. The I-PSS consists of seven questions (total range 0 to 35), one of which constitutes nocturia score (range 0 to 5). The nocturia score indicates the number of times the patient must awaken to urinate during the night. A separate question constitutes quality of life (range 0 to 6; a greater score indicates worse perception of urinary performance). PSA was determined with the Hybritech Tandem-E PSA assay.

Prostatic volume was calculated via the planimetric method with a Kretz Combison 330 ultrasound scanner with a multiplane 3-dimensional rectal transducer. For free uroflowmetry the Dantec Urodyn 1000 flowmeter was used. For evaluation of the voiding efficiency the voided percentage, which is the relative amount of bladder contents expelled during micturition, was calculated. All patients were considered neurologically normal based on history, symptoms and physical examination (no motor, sensory or reflex deficits). Patients in whom prostatic carcinoma or other diseases beyond the prostate, influencing the lower urinary tract symptoms (for example urethral stricture or bladder neck contracture) could be expected, ass well as those who had received previous treatment for lower urinary tract symptoms were excluded from the study. After clinical diagnosis of lower urinary tract symptoms and benign prostatic enlargement, patients were informed about the treatment options. When a urodynamic investigation showed no existence of bladder outlet obstruction and the patient experienced relatively few symptoms, or he was not bothered by symptoms, watchful waiting was recommended besides pharmacological treatment or other minimal invasive therapies. On the other hand, patients sometimes preferred watchful waiting even when bladder outlet obstruction was confirmed. I-PSS and urodynamic pressure-flow studies before and after 6 months of watchful waiting were performed to evaluate symptomatic and urodynamic changes. Urinalysis and culture were negative at the pressure-flow studies.

Urodynamic pressure-flow studies were performed with an 8F transurethral lumen catheter equipped with an intravesical microtip pressure sensor for bladder pressure recording. Abdominal pressure was

recorded intrarectally with an 8F microtip sensor catheter. Before cystometry, the bladder was emptied through the lumen of the transurethral catheter. The bladder was filled with water of 20°C with a filling speed of 50 ml. per minute with the patient supine. Commercially available equipment was used to record pressure and flow data.

The pressure-flow relation during voiding was analyzed by a graph of flow and pressure with pressure projected on the Y-axis and flow on the X-axis. A pressure-flow graph near the Y-axis indicating a high pressure that generates a low flow, is the result of more obstructed voiding than a graph near the X-axis. Visual evaluation of a pressure-flow graph allows for a rough estimation of grade of obstruction. However, for an objective and quantitative definition of the pressure-flow relationship we used the passive urethral resistance relation analysis and urethral resistance factor URA. With passive urethral resistance relation analysis, a quadratic curve, the passive urethral resistance relation curve, is fitted to the lowest pressure part of the pressure-flow graph which is normally the phase of voiding subsequent to maximum flow (figure 1).[10,11] The detrusor pressure at maximum flow during the urodynamic investigation was recorded. The passive urethral resistance relation parameter minimal urethral opening pressure during micturition was observed at the end of voiding. The theoretical cross-sectional urethral lumen was computed from the slope of the passive urethral resistance relation curve.[11] A steep curve with a slight angle to the pressure axis reflected a narrow urethral cross-sectional area. Griffiths et al. found a statistical correlation between theoretical cross-sectional urethral lumen and minimal urethral opening pressure during voiding.[12] This correlation was used to decrease both parameters to 1 urethral resistance factor URA. URA quantifies obstruction by computing a preset curve with a fixed theoretical cross-sectional urethral lumen to minimal urethral opening pressure during voiding ratio, through the point of detrusor pressure at maximum flow.

The digitally stored pressure and flow data were translated to a urodynamic analysis computer program developed by the research centre at our department. This program provides a semiautomatic pressure-flow study analysis with passive urethral resistance relation and urethral resistance factor analysis. The minimal urethral opening pressure during micturition and theoretical cross-sectional urethral lumen were calculated automatically based on the manually adjusted passive urethral resistance relation curves. Correction for flow artifacts was performed when necessary. We also added a nonparametric analysis of obstruction with clinical classes according to the linear passive urethral resistance relation pressure-flow nomogram (figure 1).[11] The linear passive urethral resistance relation

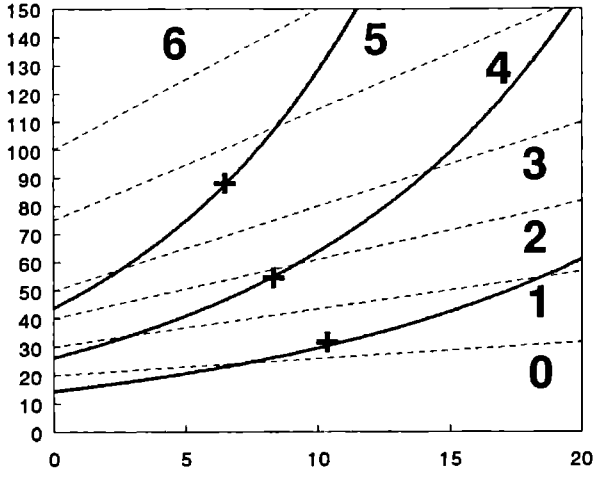

Figure 1. Passive urethral resistance relation curves of studied population. Detrusor pressure (cm. water) is projected on Y-axis and flow (ml. per second) is shown on X-axis. Indicated are passive urethral resistance relation curves based on mean urodynamic values of patients without (lower quadratic curve), with moderate (middle quadratic curve) and with obvious (upper quadratic curve) bladder outlet obstruction. Also indicated are 7 linear passive urethral resistance relation obstruction classes according to Schäfer et al.[11] +, points of mean detrusor pressure at maximum flow.

(L-PURR) was determined by drawing a straight line between the detrusor pressure at maximum flow and the minimal urethral opening pressure during micturition points on the pressure-flow curve. The position of this line defined the outlet condition in a simple manner and afforded classification of the severity of bladder outlet obstruction. Urodynamic variables analyzed included free maximum flow rate, free voided volume, residual volume after free flowmetry and free voided percentage according to free flowmetry, bladder capacity at cystometry, maximum flow at urodynamic investigation, detrusor pressure at maximum flow, minimal urethral opening pressure during micturition, theoretical cross-sectional urethral lumen, urethral resistance factor URA, residual volume after urodynamic pressure-flow study and voided percentage at pressure-flow study according to pressure-flow study. Variables were investigated for the entire group of patients and for subgroups categorized without (L-PURR class 0 or 1), with moderate (L-PURR class 2 or 3) or with obvious (L-PURR class 4 or more) bladder outlet obstruction. Statistical analysis was performed using the Wilcoxon matched pairs signed rank test for analysis of numerical data and

the Kruskal-Wallis 1-way analysis of variance to compare baseline characteristics among groups. The Spearman correlation coefficient was calculated to correlate bladder capacity and detrusor pressure at maximum flow.

Results

From January 1992 to November 1994, 750 new patients with lower urinary tract symptoms and benign prostatic enlargement were referred to our clinic for evaluation: 17 % were treated with transurethral thermotherapy, 20 % were treated surgically (laser, transurethral or open prostatectomy, bladder neck-incision), 37 % received medication (α1 blockers or 5α-reductase inhibitors), 2 percent were treated with intermittent or suprapubic catheterisation, and 178 (24%) chose watchful waiting. Four of the latter 178 patients were excluded from analysis because the initial L-PURR category could not be assessed. No pressure-flow study was done in 1 patient because he was unable to produce any flow at the initial intended voiding. Three other patients lost the transurethral (pressure recording) catheter during the initial voiding. The baseline characteristics of all 174 patients studied, and subgroups, without (44 %), with moderate (36 %) and with obvious (20 %) bladder outlet obstruction are indicated in table 1. In patients with obvious bladder outlet obstruction, the baseline mean prostatic volume was significantly larger ($p = 0.02$), while mean free voided volume ($p = 0.01$), free maximum flow rate ($p < 0.01$), bladder capacity ($p < 0.01$) and maximum flow at urodynamic investigation ($p < 0.01$) were significantly smaller. A total of 53 patients were not urodynamically evaluable at month 6 because they were lost to followup (31), refused the second urodynamic evaluation (19), began pharmacological treatment (2) or underwent surgery (1). In figure 2 the initial I-PSS total symptom score and initial detrusor pressure at maximum flow, labeled according to the reason for dropping out before month 6, are plotted for each individual. This scatterplot indicates that for these variables patients who were lost to followup or who refused the second clinical and pressure-flow study evaluation were heterogeneously distributed amongst those who completed watchful waiting for 6 months.

We evaluated 121 patients clinically and urodynamically after 6 months (median 26 weeks, mean 31, range 19-116) of watchful waiting (figure 3). Analysis of the pressure-flow relationship on the clinical nomogram[11] showed that 47 % of these patients were without, 35 % had moderate and 18 % had obvious bladder outlet obstruction. Mean urodynamic variables, and median symptom scores at baseline and after 6

Table 1. *Mean ± SD and median (range) (for symptom scores and linear passive urethral resistance relation category) baseline characteristics in 174 patients, and for subgroups without, with moderate and with obvious bladder outlet obstruction.*

	Linear Passive Urethral Resistance Relation Class			
	0 and 1 (n = 77)	2 and 3 (n = 63)	4 and 6 (n = 34)	0 to 6 (n=174)
Age (years)	65 ± 8	63 ± 8	65 ± 8	64 ± 8
PSA (ng/ml)	2.5 ± 2.2	2.7 ± 2.3	4.7 ± 5.5	3.0 ± 3.3
Prostate volume (cc)	37 ± 13	37 ± 14	49 ± 22*	39 ± 16
Total I-PSS score	13 (1-31)	13 (2-28)	13 (2-33)	13 (1-33)
I-PSS nocturia score	2 (0-5)	2 (0-5)	2 (0-5)	2 (0-5)
I-PSS QoL score	4 (0-6)	3.5 (0-6)	3 (1-5)	3 (0-6)
Free void. vol. (ml)	324 ± 169	336 ± 204	230 ± 108*	310 ± 176
Free Qmax (ml/sec)	14.0 ± 5.8	13.2 ± 4.9	10.0 ± 3.8*	12.9 ± 5.3
Free res. vol. (ml)	39 ± 59	53 ± 73	63 ± 82	49 ± 70
Free void. perc. (%)	89 ± 15	86 ± 17	82 ± 18*	87 ± 16
Bladder capacity (ml)	467 ± 132	470 ± 125	383 ± 96*	451 ± 127
Urod. Qmax (ml/sec)	10.6 ± 4.2	8.3 ± 2.8	6.5 ± 3.2*	8.9 ± 3.9
Urod. res. vol. (ml)	39 ± 74	62 ± 87	80 ± 102	54 ± 85
Urod. void. perc.(%)	92 ± 15	87 ± 18	80 ± 24	88 ± 18
$P_{det}Qmax$ (cm. water)	31.0 ± 12.2	54.9 ± 12.7	87.9 ± 20.8*	50.9 ± 25.6
$Pvoid_{min}$ (cm. water)	14.4 ± 7.2	26.3 ± 9.7	43.8 ± 21.7*	24.6 ± 16.3
A_{theo} (mm^2)	6.21 ± 3.08	3.63 ± 1.27	2.23 ± 0.96*	4.50 ± 2.74
URA (cm. water)	18.5 ± 10.4	30.6 ± 6.0	50.2 ± 10.6*	29.1 ± 14.9
L-PURR	1 (0-1)	2 (2-3)	4 (4-6)*	2 (0-6)

* Statistically significant difference ($p < 0.05$) in baseline characteristics among 3 groups without, with moderate and with obvious bladder outlet obstruction.

I-PSS: International Prostate Symptom Score.
I-PSS QoL score: I-PSS Quality of Life Score.
Urod. Qmax: maximum flow at urodynamic study.
Urod. res. vol.: residual volume after urodynamic study.
Urod. void. perc.: voided percentage at pressure-flow study.
$P_{det}Qmax$: detrusor pressure at maximum flow.
$Pvoid_{min}$: minimum urethral opening pressure.
A_{theo}: theoretical cross-sectional urethral lumen.
URA: urethral resistance factor.
L-PURR: linear passive urethral resistance relation class.

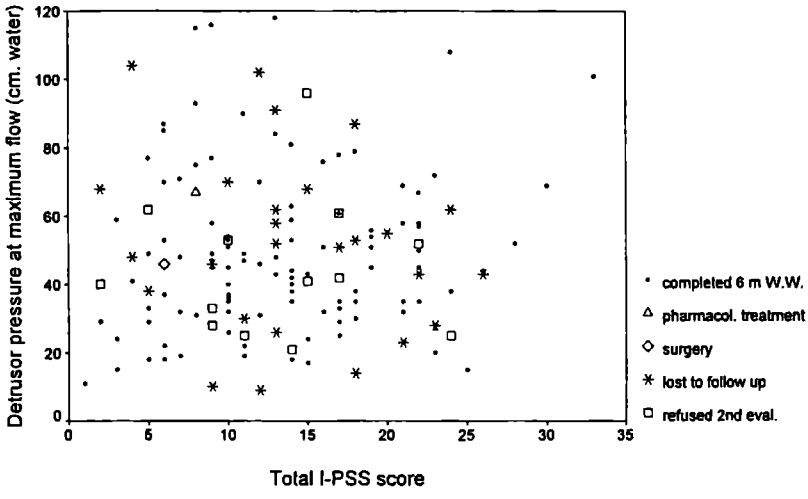

Figure 2. Scatterplot of reasons for dropping-out of study during first 6 months for each individual. Initial detrusor pressure at maximum flow (cm. water) is shown on Y-axis and total I-PSS is shown on X-axis. Indicated are patients who completed watchful waiting (W.W.) for 6 months, were lost to followup, refused their second urodynamic and clinical evaluation (2nd eval.), began pharmacological treatment or underwent surgery.

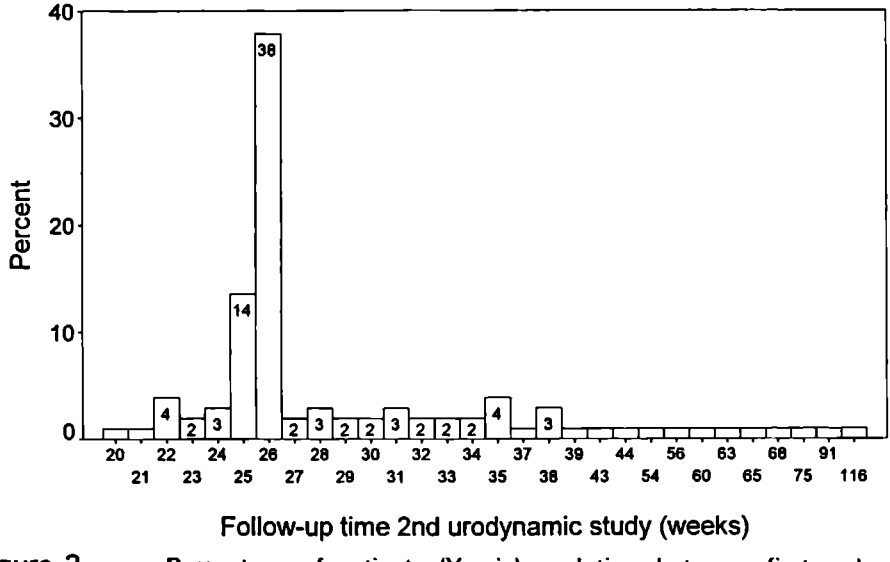

Figure 3. Percentage of patients (Y-axis), and time between first and second urodynamic study in weeks (X-axis).

Table 2. *Mean ± SD and median (range) (symptom scores and linear passive urethral resistance relation category) variables at baseline and after 6 months of watchful waiting in 121 patients who completed the second urodynamic investigation. Legend see table 1.*

	Baseline	Month 6	Wilcoxon p Value	% Second voiding	
				Larger	Smaller
Total I-PSS score	13 (1-33)	11 (1-30)	< 0.01	33	64
I-PSS nocturia score	2 (0-5)	1 (0-5)	< 0.01	13	34
I-PSS QoL score	3 (0-6)	2 (0-6)	< 0.01	6	51
Free voided vol. (ml)	314 ± 167	257 ± 145	0.01	40	59
Free Qmax (ml/sec)	13.2 ± 5.0	12.1 ± 4.6	0.03	38	58
Free residual vol. (ml)	48 ± 64	34 ± 56	0.21	37	44
Free voided perc. (%)	87 ± 16	89 ± 15	0.93	42	43
Bladder capacity (ml)	460 ± 123	435 ± 144	0.02	41	59
Urod. Qmax (ml/sec)	8.9 ± 3.6	8.8 ± 3.7	0.29	57	38
Urod. residual vol. (ml)	58 ± 89	46 ± 96	0.16	25	38
Urod. voided perc. (%)	87 ± 20	90 ± 20	0.10	38	23
$P_{det}Qmax$ (cm. water)	50.6 ± 24.5	46.9 ± 21.0	0.02	41	59
$Pvoid_{min}$ (cm. water)	24.1 ± 14.8	21.3 ± 14.0	0.10	40	58
A_{theo} (mm^2)	4.34 ± 2.23	4.38 ± 2.20	0.97	48	52
URA (cm. water)	28.2 ± 13.6	26.9 ± 12.6	0.35	44	51
L-PURR	2 (0-5)	2 (0-4)	0.30	27	35

Also indicated are the percentages of patients with a larger or smaller value at the 2nd voiding. P values indicate the comparison of results at baseline versus month 6.

months of watchful waiting for the 121 patients who completed watchful waiting for 6 months, are indicated in table 2, as are the percentages of patients with a larger or smaller result at the second voiding. At the second free flowmetry, 59 % of the patients voided with a smaller volume and, consequently, 58 % voided with a decreased free maximum flow rate compared to the first free flowmetry. There was almost no difference in mean maximum flow at urodynamic investigation (0.1 ml. per second) but a significant number of patients (59%) voided with a lower detrusor pressure at maximum flow rate the second time. Bladder capacity and detrusor pressure at maximum flow decreased statistically significant at the second voiding. Calculation with the Spearman correlation coefficient showed that there was no significant correlation ($r = -0.15$, $p = 0.10$) between bladder capacity and detrusor pressure at maximum flow. Fur-

thermore, patients with a smaller voided volume at the second urodynamic investigation (59 %) had a mean decrease in detrusor pressure at maximum flow of 3.9 cm. water, while those with a larger voided volume (42 %) had a mean decrease of detrusor pressure at maximum flow of 2.1 cm. water. When the theoretical urethral area and urethral resistance factor URA were considered, no significant mean differences were shown at the second voiding. A statistical significant number of patients had an improved total I-PSS, an improved I-PSS nocturia score and an improved I-PSS quality of life score after 6 months of watchful waiting. However, mean improvement was clinically not relevant.

Table 3 shows the mean individual absolute differences, that is the positive difference resulting from the subtraction of both voidings. Themean absolute difference plus or minus standard deviation in maximum flow at urodynamic investigation between both voidings was 2.3 ± 2.1 ml. per second. Values of extreme, large and small differences are shown in this table, as well as the number of patients exceeding these differences. In 50 patients (42 %) the difference in maximum flow at urodynamic investigation between both voidings was more than 2.0 ml. per second and in 36 (30 %) there were only slight differences (less than 1 ml. per second). Mean maximum flow at urodynamic investigation in patients with extreme differences did not change significantly. In the entire group mean maximum flow at urodynamic investigation was 8.9 ± 3.8 ml. per second initially and 8.8 ± 3.7 ml. per second at the second study. In the group with extreme differences mean maximum flow at urodynamic investigation was 8.9 ± 3.9 ml. per second initially, and 9.4 ± 3.8 ml. per second at the second study. When evaluating patients with extreme differences of detrusor pressure at maximum flow, it appeared that they had either an extreme small or an extreme large detrusor pressure at maximum flow at the initial voiding. Patients with extreme differences in theoretical cross-sectional urethral lumen were mainly those with an extreme large theoretical cross-sectional urethral lumen at the initial voiding. When we performed the statistical analysis without the patients with extreme values as indicated in table 3, the mean results remained unchanged, indicating that extreme differences in the entire group of patients occurred at the same magnitude in the negative and positive directions.

In table 4, the clinical and urodynamic parameters at baseline and after 6 months of watchful waiting are shown for 121 patients, grouped by L-PURR classification. In patients without bladder outlet obstruction total I-PSS, I-PSS nocturia score and the I-PSS quality of lifescore improved significantly. These improvements were slight and

Table 3. *Mean individual absolute differences in symptoms and urodynamic results, and number of patients with clinically extreme, clinically large and slight differences among 121 who completed the second clinical and urodynamic pressure-flow study. Legend see table 1.*

	Mean Absolute Difference ± SD	Extreme Differences		Large Differences		Slight Differences	
		Value	No. Pts. (%)	Value	No. Pts. (%)	Value	No. Pts. (%)
Total I-PSS score	5.3 ± 3.9	> 18	1 (1)	> 10	10 (11)	< 5	47 (53)
Free voided volume (ml)	142 ± 131	> 200	22 (20)	> 100	60 (56)	< 50	25 (23)
Free Qmax (ml/sec)	3.5 ± 3.1	> 2.8	54 (50)	> 2	62 (57)	< 1	23 (21)
Free residual volume (ml)	40 ± 54	> 200	2 (2)	> 100	12 (11)	< 50	78 (74)
Bladder capacity (ml)	75 ± 65	> 200	5 (4)	> 100	36 (30)	< 50	53 (45)
Urod. Qmax (ml/sec)	2.3 ± 2.1	> 2.8	34 (29)	> 2	50 (42)	< 1	36 (30)
Urod. residual volume (ml)	63 ± 87	> 200	9 (8)	> 100	26 (24)	< 50	66 (61)
$P_{det}Qmax$ (cm. water)	15.6 ± 14.8	> 27	15 (13)	> 15	47 (40)	< 5	29 (25)
$Pvoid_{min}$ (cm. water)	10.9 ± 9.8	> 34	4 (4)	> 15	21 (19)	< 5	24 (22)
A_{theo} (mm^2)	1.46 ± 1.39	> 2.3	26 (22)	> 15	41 (35)	< 5	30 (26)
URA (cm. water)	7.6 ± 6.1	> 18	8 (7)	> 15	14 (12)	< 5	41 (35)

Table 4. *Mean ± SD and median (range) (symptom scores and linear passive urethral resistance relation classification) variables at baseline and after 6 months of watchful waiting in 121 patients who completed the second urodynamic investigation. Legend see table 1.*

	Linear Passive Urethral Resistance Relation					
	0 and 1 (57 pts.)		2 and 3 (42 pts.)		4 to 6 (22 pts.)	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Age (years)	66 ± 8		62 ± 8		64 ± 8	
Prostate volume (cc)	37 ± 14		37 ± 12		45 ± 20	
Total I-PSS score	12 (1-31)	10 (1-26)*	14 (3-28)	10.5 (3-24)*	13 (6-33)	12,5 (3-30)
I-PSS nocturia score	2 (0-5)	1 (0-4)*	2 (0-5)	1 (0-4)	2 (1-5)	2 (1-5)
I-PSS QoL score	3 (0-6)	2 (0-6)*	3 (0-6)	2 (0-5)*	4 (2-5)	2 (0-5)
Free voided volume (ml)	331 ± 149	272 ± 139	334 ± 202	271 ± 160	237 ± 118	182 ± 99
Free Qmax (ml/sec)	14.2 ± 5.4	12.8 ± 5.0	13.4 ± 4.3	12.3 ± 4.4	10.0 ± 3.7	9.6 ± 3.2
Free residual volume (ml)	40 ± 59	25 ± 38	46 ± 54	42 ± 72	62 ± 89	31 ± 34
Free voided percentage (%)	90 ± 15	92 ± 12	86 ± 16	87 ± 19	83 ± 19	86 ± 12
Bladder capacity (ml)	481 ± 121	470 ± 135	468 ± 126	438 ± 162	390 ± 96	347 ± 86*
Urod. Qmax (ml/sec)	10.1 ± 3.9	9.8 ± 3.8	8.8 ± 2.7	8.8 ± 3.7	6.0 ± 2.3	6.2 ± 2.1
Urod. residual volume (ml)	43 ± 77	40 ± 90	57 ± 85	60 ± 115	93 ± 109	36 ± 68*
Urod. voided percentage (%)	91 ± 16	92 ± 18	88 ± 18	87 ± 24	77 ± 25	90 ± 17*
$P_{det}Qmax$ (cm. water)	32.7 ± 12.5	37.9 ± 17.0	55.8 ± 14.4	46.1 ± 18.7*	86.4 ± 18.9	72.3 ± 14.6*
$Pvoid_{min}$ (cm. water)	15.1 ± 6.8	15.6 ± 8.8	26.6 ± 10.4	21.7 ± 13.3*	40.8 ± 19.3	35.7 ± 16.8
A_{theo} (mm^2)	5.57 ± 2.36	5.22 ± 2.13	3.85 ± 1.24	4.32 ± 2.11	2.06 ± 0.67	2.30 ± 0.81
URA (cm. water)	18.1 ± 4.6	20.9 ± 7.7*	29.6 ± 5.7	26.5 ± 11.9	51.4 ± 9.8	44.4 ± 9.1*
L-PURR	1 (0-1)	1 (0-3)*	2 (2-3)	2 (0-4)	4 (4-5)	3 (2-4)*

* Statistically significant difference ($p < 0.05$) comparing results at baseline versus month 6.

clinically not relevant. In the group with moderate bladder outlet obstruction the improvements in total I-PSS and I-PSS quality of life score were also statistically significant but clinically irrelevant. In the group with obvious bladder outlet obstruction a significant improvement in total I-PSS, I-PSS nocturia score and I-PSS quality of life score could not be shown. Mean free voided volume and free maximum flow rate were decreased at the second voiding but the differences were not statistically significant in the 3 groups. Compared to the first result, the second mean detrusor pressure at maximum flow was 5.2 cm. water larger ($p = 0.18$) in the group without bladder outlet obstruction, 9.7 cm. water smaller ($p < 0.01$) in the group with moderate obstruction and 14.1 cm. water smaller ($p = 0.01$) in the group with obvious bladder outlet obstruction. When patients with extreme differences in detrusor pressure at maximum flow (table 3) were excluded, the differences in mean detrusor pressure at maximum flow were not significant. The second mean detrusor pressure at maximum flow in the group without bladder outlet obstruction was then 1.7 cm. water larger ($p = 0.46$) and in the group with moderate obstruction it was 9.0 cm water smaller ($p < 0.01$), while in the group with obvious bladder outlet obstruction the second mean detrusor pressure at maximum flow was 5.6 cm. water smaller ($p = 0.11$).

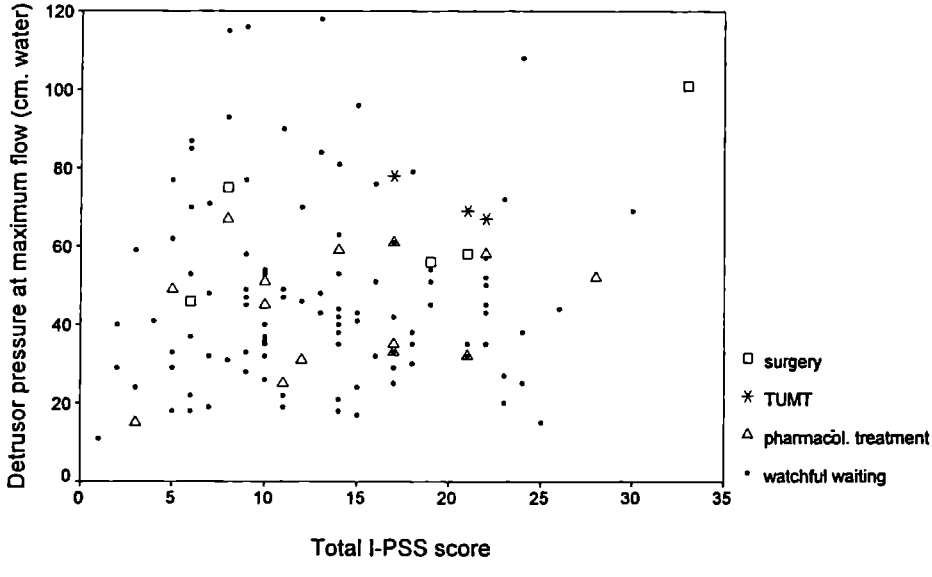

Figure 4. Scatterplot indicates initial detrusor pressure at maximum flow (cm. water) on Y-axis and initial total I-PSS on X-axis for all patients with followup longer than 6 months, according to last treatment: watchful waiting, pharmacological treatment, transurethral microwave thermotherapy (TUMT) or surgery.

Compared to the first result, the second mean minimal urethral opening pressure during voiding and urethral resistance factor were 0.5 and 2.8 cm. water larger in the group without bladder outlet obstruction ($p = 0.99$ and $p = 0.02$, respectively), and 4.9 and 3.1 cm. water lower in the group with moderate bladder outlet obstruction ($p = 0.03$ and $p = 0.08$, respectively). In the group with obvious bladder outlet obstruction the second mean minimal urethral opening pressure during voiding and urethral resistance factor were 5.1 and 7.0 cm. water smaller ($p = 0.52$ and $p = 0.02$, respectively). Mean theoretical cross-sectional urethral lumen did not change significantly. The second mean theoretical cross-sectional urethral lumen was 0.35 $mm.^2$ smaller in the group without bladder outlet obstruction ($p = 0.23$), 0.47 $mm.^2$ larger in the group with moderate obstruction ($p = 0.29$) and 0.24 $mm.^2$ larger in the group with obvious bladder outlet obstruction ($p = 0.14$). Although the median linear passive urethral resistance relation in the group without bladder outlet obstruction remained unchanged (class 1), the second linear passive urethral resistance relation category was larger in 22 patients, smaller in 10 and remained unchanged in 22. This difference was statistically significant ($p = 0.01$). In the group with moderate bladder outlet obstruction the median linear passive urethral resistance relation classification remained unchanged (class 2). The second linear passive urethral resistance relation category in these patients was greater in 10, smaller in 18 and remained the same in 13 ($p = 0.05$). In the group with obvious bladder outlet obstruction the median linear passive urethral resistance relation changed from 4 (range 4 to 5) to 3 (range 2 to 4), which was significant. Of these patients 14 had a smaller linear passive urethral resistance relation at the second voiding, 7 remained unchanged and none had a larger value ($p < 0.01$).

After evaluation at month 6, 102 patients (84%) continued watchful waiting, 9 began pharmacological treatment, 4 underwent transurethral microwave thermotherapy and 6 underwent surgery. Thereafter, 66 patients were followed for a median of 31.4 weeks (range 1 to 97), during which time 2 underwent surgery and 2 began pharmacological treatment. In figure 4 the initial detrusor pressure at maximum flow and total I-PSS are indicated for each individual, with a followup of longer than 6 months, labeled according to the last treatment policy: surgery in 9, transurethral thermotherapy in 4, pharmacological treatment in 16 and watchful waiting in 114. This figure indicates that all patients who underwent surgery or who received transurethral thermotherapy had a large initial detrusor pressure at maximum flow (all but 1 had an initial detrusor pressure at maximum flow of more than 55 cm. water), and that patients who

received pharmacological treatment had a small initial detrusor pressure at maximum flow (all but 1 had an initial detrusor pressure at maximum flow of less than 55 cm. water). Initial total I-PSS values were heterogeneously distributed among the different treatment options.

Discussion

Urodynamic investigation with pressure-flow study evaluation and symptom scores enabled us to investigate the relationship between objective and subjective efficacy of treatment. Previously, when the therapeutic choice was limited to surgery or watchful waiting, pressure-flow evaluation was simply used to diagnose bladder outlet obstruction. Because new, less invasive treatment modalities are now available, precise grading of obstruction is increasingly important in the evaluation of treatment efficacy.[13] The clinical nomogram used in our study has 7 obstruction categories, and is more detailed than a diagnosis of obstruction or no obstruction.[11] Pressure-flow evaluation is able to provide a continuous numeric scale of obstruction and, therefore, is even more refined. Furthermore, stratification of therapeutic options based on the individual, accurately assessed, grade of obstruction has recently become available.[14,15] For a reliable assessment of grade of obstruction on a numeric scale, it is essential that the test result is accurate and reproducible. The accuracy and reproducibility of a test can be determined by repeating it directly after the test has been done, and by repeating it at different times or with different equipment depending on the circumstances. Rosier et al showed that the test result of pressure-flow studies is reproducible, with only slight variability when the filling and voiding session during a single urodynamic pressure-flow study is repeated.[9] We studied the intra-individual variability of the test results of symptom scores and pressure-flow studies when the test was repeated after 6 months without treatment.

When evaluating the total investigated group of patients and comparing our results with those of Rosier et al,[9] the mean changes in detrusor pressure at maximum flow, maximum flow at urodynamic investigation and urethral resistance factor were comparable. In the study of Rosier et al 63 % of the patients voided the second time with a smaller detrusor pressure at maximum flow, and the mean difference of 3.0 cm. water was statistically significant.[9] In our study 59 % of the patients voided the second time with a smaller detrusor pressure at maximum flow, and the mean difference of 3.7 cm. water was statistically significant. However, the mean difference in theoretical cross-sectional urethral lumen in the study of Rosier et al was 0.36 $mm.^2$, which was statistically signifi-

cantly larger the second time,[9] while in our study there was only an insignificant difference of 0.04 mm.[2]. Regarding the variations of pressure-flow study variables in our study, the percentage of patients with extreme or large differences of urodynamic pressure-flow study variables was greater but the mean pressure-flow study variables were not relevantly different (table 3). However, there was a statistically significantly smaller detrusor pressure at maximum flow and bladder capacity at the second evaluation (table 2). However, the magnitude of the changes in detrusor pressure at maximum flow and bladder capacity was slight and the clinical relevance must be questioned. A smaller bladder capacity may theoretically result in decreased pressure at micturition with a smaller detrusor pressure at maximum flow. Therefore, we calculated the Spearman correlation coefficient in our patients. There appeared to be no significant correlation ($r = -0.15$, $p = 0.10$) between bladder capacity and detrusor pressure at maximum flow. Furthermore, 62 patients with a smaller voided volume at the second urodynamic investigation had a mean decrease in detrusor pressure at maximum flow of 3.9 cm. water, while those with a larger voided volume at the second urodynamic investigation had a mean decrease of 2.1 cm. water. This finding indicates that in our study it is not likely that a smaller bladder capacity is the important factor resulting in a decreased detrusor pressure at maximum flow. Rosier et al studied relatively more patients with an increased grade of bladder outlet obstruction and, therefore, we must be cautious when drawing conclusions from a comparison of, in essence, 2 different populations.[9] The greater variability found in our study could be due to the variations in the dynamic component as described by Caine.[16] Caine suggested that a combination of mechanical and dynamic components has a significant impact on lower urinary tract symptoms. The mechanical component, that is the enlarged prostate gland, does not spontaneously decrease with time.[17] In contrast, the dynamic component is subject to rapid changes depending on a variety of factors that influence sympathetic activity. Among these factors, stress, cold, and use of sympathomimetic agents can increase clinical symptoms, indicating that these dynamic components probably involve the smooth muscle tone in the prostate, prostate capsule and bladderneck.[16,18] With a longer interval between investigations the dynamic component may have a greater impact on the differences between the test results.

The values at baseline confirm that patients with obvious bladder outlet obstruction have decreased maximal flow rates. In our study patients with obvious bladder outlet obstruction also had significantly decreased free voided volumes and a significantly smaller bladder capacity. In the obvious bladder outlet obstruction group a free voided volume of

230 ± 108 ml. indicates that, although they are instructed to present to the outpatient clinic with a full bladder, a considerable percentage of patients have an initial voided volume of less than 150 ml., which is a cut-off point frequently used as a selection criterion in clinical trials. Evidently, some patients with obvious bladder outlet obstruction do not enter these trials, while the largest urodynamic treatment responses are reported in those with low maximal flow rates.[19] Consequently, the study results may not be linearly extrapolated to the population. In fact, clinical trials in patients with a free voided volume of 150 ml. or more may underestimate the urodynamic treatment responses that could be detected in the population.

At the second free flowmetry study 59 % of the patients voided with a smaller volume and, consequently, 58 % voided with a decreased free maximum flow rate compared to the first study. When comparing the free voided volumes with free maximum flow rate using the Liverpool nomograms, it appeared that the mean values of the first voiding, that is voided volume of 314 ml. and free maximum flow rate 13.2 ml. per second, correspond with the 7th percentile, while the mean values of the second voiding, that is voided volume 257 ml. and free maximum flow rate of 12.1 ml. per second, correspond with the 8th percentile of the healthy men investigated.[20] This finding indicates that the changes in flow rates were merely a result of changes in voided volumes.

The prostatic volume in patients with obvious bladder outlet obstruction was significantly higher, confirming the statistically significant although moderate correlation between prostate size and bladder outlet obstruction.[5,8]

After 6 months of watchful waiting, total I-PSS was significantly less in 64 % of the patients, I-PSS nocturia score was significantly less in 34 % and I-PSS quality of life score was significantly less in 51 %, confirming that subjective differences do not always correlate with objective differences in urodynamic variables.[7] In patients without bladder outlet obstruction all subjective tests were statistically significantly improved after 6 months of watchful waiting. In patients with moderate bladder outlet obstruction, only total I-PSS and I-PSS quality of life score were statistically significantly improved. One may argue that the subjective difference after 6 months of watchful waiting in patients without and with moderate bladder outlet obstruction was statistically significant but clinically irrelevant, although it is remarkable that in those with obvious obstruction no subjective improvement was shown. There was not even a tendency for improvement in total I-PSS and I-PSS nocturia score. This finding confirms the results of the Veterans Affairs Cooperative Study on transurethral resection of the prostate versus watchful waiting.[21] In this

study the symptomatic patients were randomized for either watchful waiting or surgery. In the watchful waiting group 30 to 40 % of the patients showed symptomatic improvement. This group may, in fact, be patients without bladder outlet obstruction (44 % of our patients). The authors concluded that watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay surgery. We agree with their conclusion because we have shown that in patients with obvious bladder outlet obstruction symptoms may not improve but certainly they do not worsen. Moreover, the urodynamical status after 6 months of watchful waiting in patients with obvious bladder outlet obstruction does not seem to worsen. However, the long-lasting urodynamical effect in patients with obvious bladder outlet obstruction is still uncertain. Hopefully we will be able to extend our study and to repeat the investigations in some patients who remained on watchful waiting to evaluate the natural history of lower urinary tract symptoms and benign prostatic enlargement with or without bladder outlet obstruction. However, with time more patients will be lost to followup or treated as shown in figure 4.

At our centre, patients with a large initial detrusor pressure at maximum flow were treated with transurethral thermotherapy or surgery, while those with a low initial detrusor pressure at maximum flow were treated pharmacologically. The initial symptom scores were heterogeneously distributed among the different treatment options. Apparently, for the physicians at our centre the results of pressure-flow studies rather than symptom scores have an important role in determining the choice of therapy (figure 4).

The changes in mean pressure-flow study variables between the 3 linear passive urethral resistance relation groups were remarkably different. Patients without bladder outlet obstruction had changes indicating more obstruction, while those with bladder outlet obstruction initially had less obstruction. The increases of mean urethral resistance factor and mean linear passive urethral resistance relation in patients without bladder outlet obstruction were slight but statistically significant. The decreases in mean detrusor pressure at maximum flow and mean minimal urethral opening pressure during voiding in patients with moderate bladder outlet obstruction were significant, and the decreases in mean detrusor pressure at maximum flow, urethral resistance factor and linear passive urethral resistance relation in patients with obvious bladder outlet obstruction were significant. Even mean residual volume and mean voided percentages at pressure-flow study improved significantly in patients with obvious bladder outlet obstruction. The difference in mean detrusor pressure at maximum

flow in patients with obvious obstruction was 14.1 cm. water, which comes close to the suggested clinically relevant cutoff point for differences in pressure classes of 15 cm. water.[9] These findings could be explained by regression towards the mean, a statistical phenomenon in which, if a followup sample is chosen based on extreme scores, the retest scores will tend to be closer to the population mean than the initial scores. As suggested by Caine,[16] numerous varying factors may influence the dynamic part of the obstruction, and these factors may occasionally combine to produce a result that is either extremely large or extremely small. When measurements are repeated, it is unlikely that components that involve a random element should combine again in this extreme fashion. Large values accordingly tend to decrease, while small values tend to increase. Just as these extreme values tend to regress to the population mean on reexamination, patients with chronic but fluctuating conditions tend to seek medical attention in the 'bad' periods during exacerbations. Consequently, patients are more prone to improve than to deteriorate further regardless of the treatment the physician institutes.

We compared the previously reported urodynamic treatment efficacy of new instrumental and noninvasive therapies to the physiological variability reported in our study. After laser prostatectomy, an individual mean improvement of detrusor pressure at maximum flow of 37 cm. water was reported.[22] This result is unequivocal and larger than the expected physiological variability. After transrectal high intensity focused ultrasound and transurethral thermotherapy of the prostate, statistically significant improvements in mean detrusor pressure at maximum flow of 11 and 10 cm. water have been reported.[23,24] Based on our results, these findings could be obtained simply by repeating the urodynamic pressure-flow evaluation after 6 months without therapy. Tammela and Kontturi reported a mean decrease in detrusor pressure at maximum flow of 39 cm. water after finasteride treatment for 6 months and a mean increase of detrusor pressure at maximum flow of 3 cm. water in the placebo treated group, indicating a significant response to treatment.[25] The results of this study conflict with our results. Considering the large mean detrusor pressure at maximum flow in the study by Tammela and Kontturi (120 cm. water), the majority of the patients studied had severe bladder outlet obstruction, and we would also expect a decrease in detrusor pressure at maximum flow in the placebo treated group.[25] The urodynamic response in a study evaluating the efficacy of doxazosin, an $\alpha 1$ selective blocker, although significantly better compared to placebo treatment, was slight (improvement in detrusor pressure at maximum flow 5 cm. water) and within physiological variability.[26] These findings indicate that mean differences among therapy groups must be regarded critically, particularly when the reported differ-

ences are slight and possibly within physiological variability. The variability of pressure-flow parameters in our study was greater than in a previous study when the filling and voiding session during a single urodynamic pressure-flow study was repeated. However, mean pressure-flow parameters were only slightly different. This finding indicates that the dynamic component of obstruction actually exists and should be considered in the evaluation of new treatment modalities for patients with lower urinary tract symptoms and benign prostatic enlargement.

Conclusions

We demonstrated that patients without bladder outlet obstruction experienced statistically significant but slight symptomatic improvement after 6 months of watchful waiting. Symptoms of patients with obvious bladder outlet obstruction did not improve significantly. From a clinical and diagnostic viewpoint, the reproducibility of mean pressure-flow study results after 6 months of watchful waiting was evident. However, there was an important intra-individual variability. Patients with extreme values at the initial pressure-flow study tended to experience regression towards the mean of the population at the second evaluation. Patients with obvious bladder outlet obstruction showed a significant decrease in detrusor pressure at maximum flow of 14 cm. water, a significant decrease of urethral resistance factor of 7 cm. water and a significant decrease of 1 obstruction class on the linear passive urethral resistance relation nomogram, indicating less severe bladder outlet obstruction. Mean differences among therapy groups must be regarded critically, particularly when the reported differences are slight and possibly within their physiological variability. Due to the physiological variability caused by the dynamic component of obstruction any clinical trial evaluating a new treatment modality should include a control arm that allows quantification of this physiological variability.

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References

1 Schäfer W, Nopponey R, Rübben H and Lutzeyer W: The value of free flow rate and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

2 Blaivas JG: Multichannel urodynamic studies in men with benign prostatic hyperplasia Indications and interpretation. Urol Clin N Amer **17**: 543, 1990.

3 Rosier PFWM, Rollema HJ, van de Beek C and Janknegt RA: Diagnosis of "prostatism"; relation between symptoms and urodynamic evaluation of obstruction and bladder function. Neurourol Urodynam **11**: 399, A64, 1992.

4 Tan HK, Höfner K, Kramer AEJL, Thonn WF, Grünewald V and Jonas U: Benign prostatic hypertrophy (BPH): prostatic size, obstruction parameters, detrusor contractility and their interdependence. Neurourol Urodynam **12**: 412, A63, 1993.

5 Bosch JLHR, Kranse R, van Mastrigt R, Schröder FH: Reasons for the weak correlation between prostate volume and urethral resistance parameters in patients with prostatism. J Urol **153**: 689, 1995.

6 Rosier PFWM, de la Rosette JJMCH: Is there a correlation between prostate size and bladder-outlet obstruction ? World J Urol **13**: 9, 1995.

7 Isaacs JT: Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate **3**: 1, 1990.

8 Abrams PH and Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Brit J Urol **51**: 129, 1979.

9 Rosier PFWM, de la Rosette JJMCH, Koldewijn EL, Debruyne FMJ, Wijkstra H: Variability of pressure-flow analysis parameters in repeated cystometry in patients with benign prostatic hyperplasia. J Urol **153**: 1520, 1995.

10 Schäfer W: The contribution of the bladder outlet to the relation between pressure and flowrate during voiding. In: Benign Prostatic Hypertrophy Edited by F Hinman Jr. Berlin: Springer Verlag, pp 470-496, 1983.

11 Schäfer W, Waterbär F, Langen PH, Deutz FJ: A simplified graphical procedure for detailed analysis of detrusor and outlet function during voiding. Neurourol Urodyn **8**: 405, 1989.

12 Griffiths DJ, van Mastrigt R, Bosch R: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size in urethral obstruction due to benign prostatic hyperplasia. Neurourol Urodyn **8**: 17, 1989.

13 McGuire EJ: The role of urodynamic investigation in the assessment of benign prostatic hypertrophy. J Urol **148**: 1133, 1992.

14 Jensen KME: Clinical evaluation of routine urodynamic investigation in prostatism. Neurourol Urodyn **8**: 545, 1989.

15 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153**: 1526, 1995.

16 Caine M: The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. J Urol **136**: 1, 1986.

17 Watanabe H: Natural history of benign prostatic hypertrophy. Ultrasound Med Biol **12**: 567, 1986.

18 Furuya S, Kumamoto Y, Yokoyama E, Tsukamoto T, Izumi T, Abiko Y: Alpha-adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. J Urol **128**: 836, 1982.

19 Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P and the BPH-ALF Group: Alfuzosin for treatment of benign prostatic hypertrophy. Lancet **337**: 1457, 1991.

20 Haylen BT, Ashby D, Sutherst JR, Frazer MI, West CR: Maximum and average urine flow rates in normal male and female populations - the Liverpool nomograms. Brit J Urol **64**: 330, 1989.

21 Wasson JH, Reda DJ, Bruskewitz RG, Ellisson J, Keller AM, Henderson WG: A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. N Engl J Med **332**: 75, 1995.

22 De Wildt MJAM, te Slaa E, Rosier PFWM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Urodynamic results of laser treatment in patients with benign prostatic hyperplasia Can outlet obstruction be relieved ? J Urol **154**: 174, 1995.

23 Madersbacher S, Klingler HC, Schmidbauer CP, Marberger M: The impact of transrectal high intensity focused ultrasound on prostatic obstruction in BPH assessed by pressure-flow studies. J Urol **153**: Abstract 827, 1995.

24 Porru D, Scarpa RM, Delisa A, Usai E: Urodynamic changes in benign prostatic hyperplasia patients treated by transurethral microwave thermotherapy. Eur Urol **26**: 303, 1994.

25 Tammela TL, Kontturi MJ: Urodynamic effects of finasteride in the treatment of bladder outlet obstruction due to benign prostatic hyperplasia. J Urol **149**: 342, 1993.

26 Chapple CR, Carter P, Christmas TJ, Kirby RS, Bryan J, Milroy EJG, Abrams P: A three month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. Brit J Urol **74**: 50, 1994.

Chapter 7

Treatment of patients with lower urinary tract symptoms with terazosin

Chapter 7.1

The International Terazosin Trial: A multicentre study of the long-term efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia.

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Abstract

Objectives: To evaluate the long-term efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia (BPH).

Patients and methods: Thirty-three sites in 13 countries enrolled men with BPH who had an International Prostate Symptom Score (I-PSS) ≥ 12. After a 2-week, no-treatment lead-in period and a 24-week, single-blind treatment period, patients responding to terazosin were randomly assigned to receive either terazosin or placebo for a 24-week, double-blind withdrawal period.

Results: Of the initial 427 patients enrolled, 378 were evaluable, 273 of whom completed the single-blind period, of which 186 patients were randomized. During the single-blind treatment period, I-PSS, quality of life score (QoL), peak flow rate (Qmax), and nocturia score (Noc) improved significantly ($p \leq 0.05$). During the double-blind withdrawal period, I-PSS, QoL, Qmax, and Noc deteriorated significantly in the placebo group compared with the terazosin group. The most common adverse event resulting in premature termination from the study was dizziness. There were no clinically important mean reductions in diastolic blood pressure (DBP) for patients normotensive at baseline. Terazosin significantly reduced mean DBP in hypertensive patients during the single-blind period and maintained the reduction during the double-blind period.

Conclusions: Treatment with terazosin has a beneficial effect on BPH, continuing for at least 12 months, and can be safely considered for medium- to long-term use in those who benefit.

Introduction

Benign prostatic hyperplasia (BPH) is a condition that affects many men after middle age. A meta-analysis of 10 autopsy studies shows that approximately 50% of men aged 60 years or older have histological evidence of BPH; the percentage rises to nearly 80% for men aged 80 years or older.[1]

Patients suffering from BPH have conventionally been treated by surgical resection of the enlarged prostate gland. Since it is known that α_1-adrenoceptors are present in the bladder neck and prostate smooth muscle,[2] α_1-blocking agents have been successfully used to relieve symptoms and improve urinary flow rates in patients with BPH. Terazosin is a long-acting α_1-selective blocking agent that was originally used for the treatment of arterial hypertension. The effects of terazosin on symptom scores and urinary flow rates have been previously documented.[3-10]

This randomized, placebo-controlled, double-blind, multicentre study was performed to evaluate the long-term efficacy and safety of terazosin in the treatment of patients with BPH. While many terazosin studies have focused primarily on changes in symptom scores and flow rates, this study examines four additional aspects of terazosin therapy: 1) changes in patient quality of life (QoL); 2) the effect of randomized withdrawal following an initial treatment period; 3) the effect of terazosin on prostate-specific antigen (PSA) in a prospective study; and 4) the effect of terazosin on blood pressure in normotensive and hypertensive patients, whether or not the patients were controlled with other antihypertensive therapy.

Patients and methods

Patients

Men ≥ 45 years old with BPH were to be enrolled in the study if they had an International Prostate Symptom Score (I-PSS) ≥ 12,[11] a peak urinary flow rate (Qmax) between 5 and 15 ml/s, a voided volume ≥ 100 ml, no urinary tract infection (determined by urine analysis), and a residual volume < 300 ml (determined by ultrasound). Diagnosis of BPH was based on medical history, physical examination (including digital palpation of the prostate), and assessment of symptoms listed on the I-PSS form. PSA was measured to aid the diagnosis of prostate cancer (an exclusion criterion). The study included normotensive patients (diastolic blood pressure (DBP) < 90 mm Hg), untreated hypertensive patients whose DBP was ≤ 115 mmHg, and hypertensive patients treated with antihypertensive agents other than verapamil. Investigators could adjust at their discretion the dosage of antihypertensive agents.

The study excluded hypotensive patients, as well as patients taking or recently having received experimental drugs or other medications that might interfere with the study (eg, α-blockers, anti-androgens, gonadotrophin-releasing hormone analogues, and herbal extracts). Also excluded were patients who had suffered a myocardial infarction or transient ischaemic attack within the past 6 months, and patients having histories of cerebrovascular accidents, fainting spells, blackouts, known or suspected prostate cancer, urethral stricture, gross haematuria, insulin-dependent diabetes mellitus, renal or hepatic impairment, and certain genito-urinary disorders (eg, urinary tract infection). Patients having received pelvic radiation or prior surgery for BPH or bladder-neck obstruc-

tion were also excluded. In addition, patients known to be hypersensitive to or non-responsive to α_1-blockers were not included in the study.

Criteria for the evaluability of patients for efficacy analysis were determined prior to initiation of the study. After the study was completed, patient evaluability was assessed prior to breaking the study blind.

Treatment schedule

This study was divided into three successive parts (figure 1): 1) a 2-week, no-treatment lead-in period; 2) a 24-week, single-blind treatment period; and 3) a 24-week, randomized, double-blind withdrawal period for patients responding to treatment. Responders were those patients whose I-PSS decreased ≥ 30% from baseline and whose Qmax increased ≥ 10% from baseline to the end of the single-blind treatment period.

Investigators screened patients for selection criteria at the initial visit. After the 2-week lead-in period, baseline values were established for the following study variables: I-PSS, QoL, Qmax, voided volume, nocturia score (Noc), PSA level, blood pressure, and pulse rate. After baseline values were established, qualifying patients received at the evening of this visit an initial dose of 1 mg terazosin and then 2 mg daily for the next 13 days. Patients then received daily doses of 5 mg for 4 weeks followed by 10 mg for another 4 weeks. Patients not tolerating the 10 mg dose then had their dosage decreased to 5 mg. At week 26, responders were randomly assigned to continue receiving the same maintenance dose (5 or 10 mg) of terazosin that they had been given during the single-blind treatment period or to begin receiving placebo. The randomization schedule was prepared by computer and was performed by the statisticians inde-

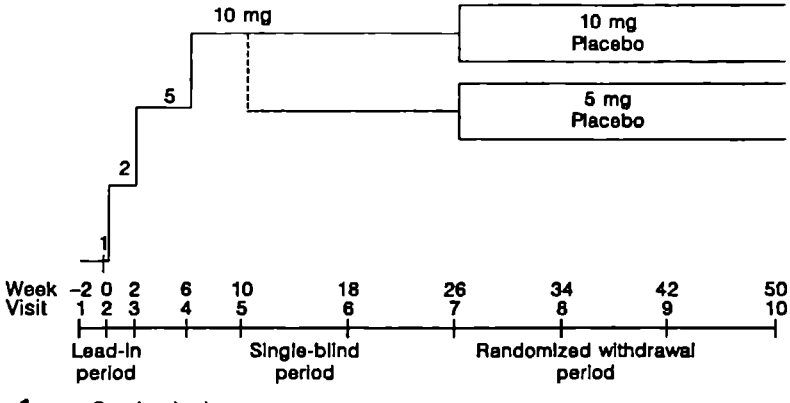

Figure 1. Study design.

pendently of the clinical group. All study medications were taken at bedtime; placebo tablets were identical to terazosin tablets in colour, shape, size and appearance. Clinical supplies were provided by Abbott Laboratories, International Division.

For the first 4 weeks of the study, patients were seen every other week. For the next 8 weeks, patients were seen every fourth week. For the last 40 weeks, patients were seen every eighth week.

Study procedures

Prior to all study procedures, each patient gave informed consent. Patients were evaluated at baseline and at each visit using an I-PSS form. Seven questions on the evaluation form constituted I-PSS (range 0–35). One of these seven questions constituted Noc (range 0–5). (A Noc of 0-4 directly represents the average number of times per night that a patient got out of bed to urinate; a Noc of 5 represents five or more times per night.) A separate question constituted QoL (range 0–6). Higher scores indicate worse symptoms and quality of life. Vital signs, including blood pressure and pulse rate, were also evaluated at baseline and at each visit thereafter. Uroflowmetry variables, including peak and mean urinary flow rates and total voided volume, were electronically measured at baseline, at 26 weeks, and at each visit thereafter. The total volume voided during each uroflowmetric measurement was required to be $\geq$ 100 ml.

Additional study procedures included a PSA assay, evaluation of treatment failure, and urine analysis. Blood samples were obtained for PSA assays at baseline, at week 26, and at the last visit; these samples were drawn prior to digital palpation of the prostate. PSA levels were measured using IMx testing kits (Abbott Laboratories, North Chicago, Illinois, USA).

During the single-blind period, to determine the statistical significance of observed differences for I-PSS, QoL, Qmax, and Noc, a t-test on mean change from baseline to final visit was used. During the double-blind period, statistical significance of differences between treatment groups for I-PSS, QoL, Qmax, Noc, vital signs, and PSA was determined using a one-way analysis of variance. The carry-forward convention was used for I-PSS, QoL, Qmax, and Noc. Fisher's exact test comparison was used for adverse events.

Demographics

Four hundred and twenty-seven patients were enrolled in the single-blind treatment period from 33 sites in 13 countries. Of those

patients, 49 were not evaluable because they either failed to meet inclusion criteria, were disqualified because of exclusion criteria, had no valid baseline, or had no evaluable visits. Of the 378 evaluable patients, 273 completed the single-blind treatment period; the other 105 patients were lost to follow up or withdrew due to adverse events. Of those who completed the single-blind study period, 186 patients from 29 sites in 11 countries qualified for randomization into the double-blind withdrawal period. Nonqualification was largely due to insufficient improvement in symptom score and/or Qmax. Eleven patients were erroneously randomized and thus were not evaluable. Of the 175 evaluable, randomized patients, 149 completed the double-blind period. Among the 26 patients who withdrew from the study during the double-blind period, the I-PSS measures of 19 patients were carried forward from the termination visit and included in efficacy analysis. The I-PSS for one of the patients who completed the double-blind period was invalid and was therefore excluded; this resulted in 167 evaluable patients for I-PSS analysis.

After having their terazosin dosage escalated to a 10 mg dose during the single-blind treatment period, 86.9% (152/175) of patients who were later randomized continued at that dosage while 13.1% (23/175) had their dosage reduced to 5 mg. At entry to the single-blind period the mean age for all patients was 63.6 years.

Results

Single-blind efficacy

The four primary efficacy variables in this study were I-PSS, QoL, Qmax, and Noc. During the single-blind treatment period, terazosin produced statistically significant improvements from baseline to the final visit in all four variables. These improvements were shown not only in patients who qualified for the double-blind period, but also for all patients who completed the single-blind period (table 1). There were no differences in responses between patients who were later randomized to terazosin compared with those randomized to placebo.

Regarding the onset of action of terazosin, 51.3% (138/269) of all patients completing the single-blind period experienced $\geq$ 30% improvement in I-PSS by week 2; by week 10 this percentage increased to 82.2% (208/253) and by week 26 to 85.2% (219/257).

While 67.0% (175/261) of all patients completing the single-blind period experienced improvement in nocturia (12 patients whose baseline Noc was 0 were excluded from this result), 98.1% (51/52) of patients

Table 1. *Mean changes in efficacy variables from baseline to the final visit of the single-blind period.*

	Patients who were later randomized into the double-blind period			
	n	Mean baseline	Mean change	% change
Symptom score	175	19.1	-12.4*	64.9
Quality of life score	175	3.7	-2.0*	53.6
Qmax (ml/s)	159	9.7	4.7*	47.8
Nocturia score	175	2.6	-1.3*	50.6
	All patients completing the single-blind period			
	n	Mean baseline	Mean change	% change
Symptom score	273	18.5	-10.7*	57.7
Quality of life score	273	3.6	-1.7*	47.2
Qmax (ml/s)	239	9.8	3.1*	31.8
Nocturia score	273	2.4	-1.0*	42.9

*Statistically significant ($p \leq 0.05$) difference from baseline.

whose baseline Noc was 4 or 5 experienced improvement. (Improvement in nocturia was defined as a reduction of Noc by at least 1.)

Double-blind efficacy

During the double-blind withdrawal period, the mean changes in I-PSS, Noc, QoL, and Qmax were significantly less for the terazosin group compared with the placebo group (table 2). Except for Noc at the final visit, the differences between groups for all four efficacy variables were statistically significant ($p \leq 0.05$) at all three visits of the double-blind period (figures 2-4). Also, from the start of the double-blind period to the final visit, the changes in QoL and Qmax were not statistically significant in the terazosin group. In the placebo group, changes were statistically significant ($p \leq 0.05$) for all four efficacy variables.

As estimated by the Kaplan-Meier method, the cumulative rate of

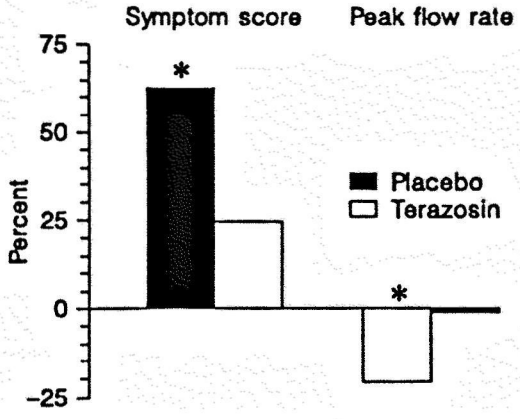

Figure 2. Percent deterioration. Randomized withdrawal period, baseline to final. * $p \leq 0.05$ between groups.

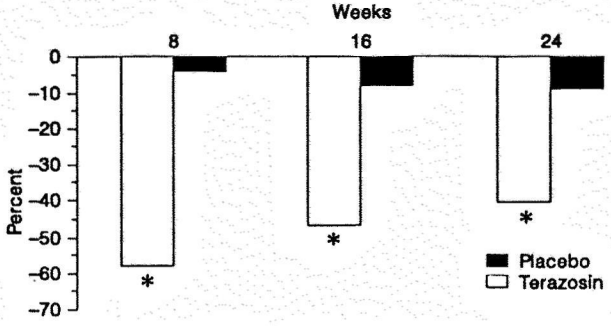

Figure 3. Percent deterioration in quality of life score during randomized withdrawal period. * $p \leq 0.05$ between groups.

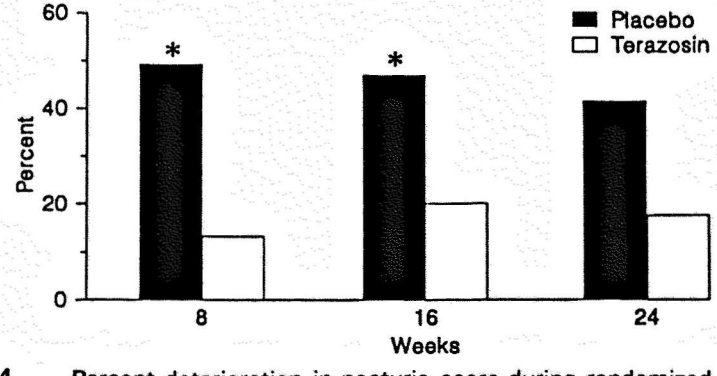

Figure 4. Percent deterioration in nocturia score during randomized withdrawal period. * $p \leq 0.05$ between groups.

relapse at 180 days in the placebo group (61.6%) was statistically greater ($p \leq 0.05$) compared with the terazosin group (25.2%) (figure 5). Relapse was defined as a patient's withdrawal from the study because of lack of response to treatment or as a patient's I-PSS increasing by $\geq$ 50% of the improvement experienced during the single-blind period. A clinically important difference in relapse rates appeared as early as 70 days, when the rates were 36.9% and 10.8% for the placebo and terazosin groups, respectively. Also, the number of patients withdrawing from the study due to failure to respond was 11 in the placebo group and one in the terazosin group.

The efficacy data reported above reflect the results for evaluable patients, not for intent-to-treat patients. However, there were no differences between the two sets of results.

Table 2. *Mean changes in efficacy variables from baseline at each visit of the double-blind period.*

Efficacy variable	Patient group	n	Mean Week 26	week 34 mean change	week 42 mean change	week 50 mean change
Symptom score	Placebo	83	6.5	4.4*	4.5*	4.1*
	Terazosin	84	6.9	1.3	1.8	1.7
Quality of life score	Placebo	83	1.6	1.0*	0.8*	0.7*
	Terazosin	84	1.9	0.1	0.1	0.2
Qmax (ml/s)	Placebo	74	14.8	-3.7*	-2.7*	-2.7*
	Terazosin	76	13.7	-0.7	-0.4	-0.6
Nocturia score	Placebo	83	1.2	0.6*	0.6*	0.5
	Terazosin	84	1.3	0.2	0.3	0.2

* Statistically significant ($p \leq 0.05$) difference between treatment groups.

Single-blind safety results

The three primary safety variables in this study were blood pressure, PSA levels, and adverse event reporting.

Of patients evaluated for blood pressure during the single-blind period, 57.4% (233/406) had a normal baseline DBP (< 90 mmHg) and 42.6% (173/406) had a higher than normal baseline DBP ($\geq$ 90 mmHg). The group with normal DBP included normotensive patients and well-

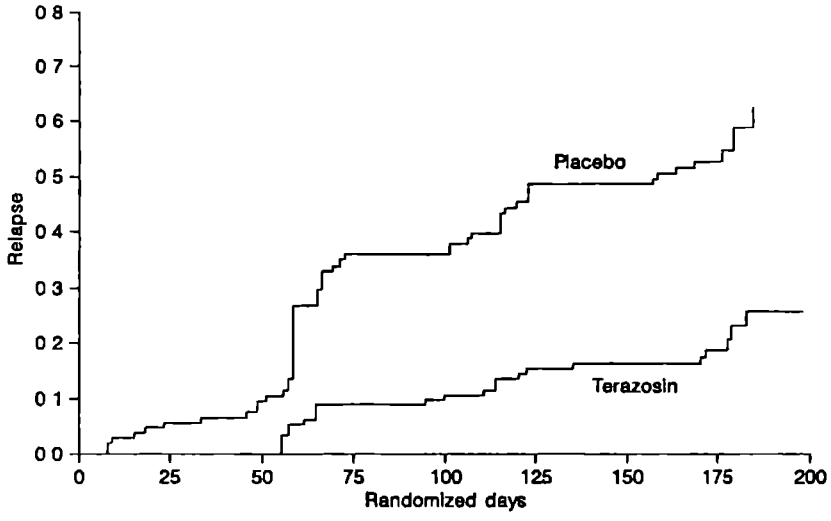

Figure 5. Time to relapse.

controlled hypertensive patients. The group with higher than normal DBP included untreated and treated hypertensive patients.

Terazosin produced no clinically significant mean blood-pressure changes in patients with a normal baseline DBP (normotensives and well-controlled hypertensives). However, for patients with a higher than normal baseline DBP, mean blood-pressure changes were clinically and statistically significant ($p \leq 0.05$). Such changes were seen by week 2, when DBP decreased from a mean of 93.9 mmHg to 85.5 mmHg amongst patients receiving no additional antihypertensives (n = 133); among patients receiving additional antihypertensives (n = 40), DBP decreased from 95.0 mmHg to 87.3 mmHg.

For patients who completed the single-blind period, the mean change in PSA level from baseline to final visit was not statistically significant for the total group, nor for any one age group (table 3).

The most common adverse events reported for all patients (n = 427) during the single-blind period were dizziness (21.1%), headache (12.6%), asthenia (6.6%), pharyngitis (5.2%), somnolence (4.9%), back pain (4.2%), flu syndrome (3.7%), and abdominal pain (3.0%). Adverse events caused 20.4% of patients to withdraw from the study. The most common adverse events causing termination from the single-blind period were dizziness (6.8%), headache (2.1%), asthenia (1.9%), somnolence (1.2%), dyspnoea (1.2%), and arrhythmia (0.9%).

Table 3. *Mean changes in PSA levels single-blind period.*

Patient age group	n	Mean baseline (ng/ml)	Mean change (ng/ml)
40-49 years	8	1.2	-0.1
50-59 years	74	2.5	0.0
60-69 years	127	3.4	0.2
70-79 years	57	3.7	-0.3
80- years	4	3.4	1.6
All patients	271*	3.2	0.03

* One patient was not categorized by age group.

Double-blind safety results

Of the patients evaluated for blood pressure, 62.2% (125/201) had a normal DBP (< 90 mmHg) at baseline (visit 2) and 37.8% (76/201) had a higher than normal DBP (≥ 90 mmHg) at the same visit. Hypertensive patients randomized to placebo continued to receive the antihypertensive treatment they had been receiving during the single-blind treatment period or they received no antihypertensive treatment.

From the start of the double-blind period to the final visit, there were no clinically significant mean DBP changes in either the terazosin or the placebo group. These findings were shown in normotensive, well-controlled hypertensive, and non-controlled hypertensive patients, regardless of concurrent antihypertensive treatment. Further, with one exception, none of the changes were statistically significant ($p \leq 0.05$). DBP results of the double-blind period are summarized in Table 4.

An additional safety variable was pulse rate. Mean changes in pulse rate from baseline to the final visit were not statistically significant between randomized groups.

The mean change in PSA level from the start of the double-blind period to the final visit was not statistically significant for either randomized group. In the placebo group (n = 72), the mean PSA level increased from 3.0 ng/ml at the start of the double-blind period to 3.3 ng/ml at the final visit; in the terazosin group (n = 73), mean PSA level increased from 3.5 ng/ml to 3.7 ng/ml. Further, there were no clinically significant changes in mean PSA level in any age group during the double-blind period.

Seventy-nine patients reported adverse events during the double-blind period – 40 in the placebo group and 39 in the terazosin group. In the

Table 4. *Double-blind mean changes in diastolic blood pressure (DBP).*

		n	Mean Week 26	Mean Week 50	Mean Change
Patients with DBP < 90 mmHg at baseline					
No antihypertensives	Placebo	51	77.8	80.8	3.0*
	Terazosin	51	76.7	76.1	-0.6
Using antihypertensives	Placebo	9	77.8	79.4	1.7
	Terazosin	14	76.4	77.1	0.7
Patients with DBP ≥ 90 mmHg at baseline					
No antihypertensives	Placebo	26	81.2	84.8	3.7
	Terazosin	30	82.8	82.8	0.0
Using antihypertensives	Placebo	13	79.8	82.6	2.8
	Terazosin	7	87.1	81.7	-5.4

* Statistically significant ($p \leq 0.05$) difference from week 26, but not clinically significant.

placebo group (n = 102), the most common adverse events were pharyngitis (3.9%), hypertension (2.9%), urinary retention (2.9%), and flu syndrome (2.0%). In the terazosin group (n = 105), the most common adverse events were pharyngitis (3.8%), dizziness (2.9%), dyspepsia (2.9%), flu syndrome (2.9%), and urinary retention (2.9%). Seven patients in the terazosin group and 9 in the placebo group were discontinued because of adverse events (angina pectoris, dizziness (n = 2), hepatitis, pneumonia, somnolence, and urinary retention in the terazosin group; and kidney calculus, kidney pain, myocardial infarct, second-degree atrioventricular block, syncope, urinary retention (n = 3), and urinary tract infection in the placebo group).

Discussion

The design of the present study reflects clinical practice by identifying a group of patients who responded beneficially to terazosin during a 6-month period when all patients with lower urinary tract symptoms, an enlarged prostate gland, and a poor urinary stream took the drug. The advantage of initiating medical treatment in patients with BPH is its

reversibility: it can be stopped when patients do not respond or when side-effects occur. In clinical practice, a trial of treatment is often appropriate, and only those patients who benefit should continue taking the drug. A decision should then be made whether treatment should continue indefinitely or whether stopping would be possible without relapse; a beneficial effect might attenuate with prolonged treatment. This study's protocol was designed to investigate these issues.

We treated a heterogenous group of patients with lower urinary tract symptoms, enlargement of the prostate, and poor urinary flow rate. The fact that 175 of 378 evaluable patients were eligible to enter the second part of the study suggests that approximately half of the men treated with terazosin might find it suitable for long-term use. This proportion is almost certainly lower than what would be expected in clinical practice, however, because of the stringent trial protocol, which required improvements in Qmax as well as in I-PSS. A substantial number of patients not meeting the Qmax requirement had a sufficient I-PSS improvement: 58% (219/378) experienced ≥ 30% I-PSS improvement by the end of single-blind period.

The percentage of patients who experienced dizziness was rather high in comparison with previous experience with terazosin.[12-16] The ways in which adverse events were collected may have contributed to this discrepancy: centres reporting high numbers were required by their ethical committees to enquire specifically about this symptom, whereas in centres reporting lower numbers patients were asked if they had experienced any ill effects. It should be noted that less than one third of the patients reporting dizziness had discontinued treatment, which suggests that the majority of dizziness events were tolerable and transient.

Patients who responded during the single-blind period were randomized for the double-blind period into two groups, one continuing on terazosin and one being withdrawn from active treatment and placed on placebo. Patients withdrawn from terazosin experienced a significant deterioration in I-PSS and Qmax, while those continuing on terazosin maintained their improved Qmax, with only a small, clinically insignificant deterioration in I-PSS. The deterioration in the placebo group did not, however, return to baseline, suggesting that 1) there is variability in the evolution of BPH (symptoms fluctuate over time and patients have a high chance to enter the trial when they experience a period with severe lower urinary tract symptoms); 2) there is a continuing placebo effect, and 3) the full effect of withdrawal of terazosin takes longer than 24 weeks. Another more speculative suggestion could be that 6 months of α-blockade might reduce the sensitivity of the α-adrenergic receptor. All these suggestions

are applicable for the effects on DBP, which paralleled the findings in BPH symptoms and flowmetry.

While this study's minimum required voided volume of 100 ml is lower than the standard 150 ml level, at entry to this study's single-blind period there were no statistically significant differences between the mean Qmax of patients whose voided volume was 100–149 ml (9.2 ml/s, n = 99) and of patients whose voided volume was ≥ 150 ml (10.3 ml/s, n = 279).

In this study terazosin was taken at night rather than the conventional daytime dosing regimen. Nocturia improved in 67% (175/261) of patients compared with only 43% (51/119) in a previous study using daytime dosing. However, historical comparisons of this type are unreliable; furthermore, a different symptom score was used in the daytime dosing study. Despite this, these results may warrant a further comparison of the effects of daytime and bedtime dosing on nocturia.

Studies have shown that therapy with 5α-reductase inhibitors such as finasteride lowers PSA levels by around 50%, thereby possibly masking a diagnosis of prostate cancer.[17] In the present study, terazosin did not affect PSA levels. (It should be noted that 1 patient unexpectedly was diagnosed with carcinoma of the prostate during the single-blind period of this study.)

Previous studies have demonstrated the efficacy of terazosin as a treatment for the symptoms of BPH.[3-10] In the first part of this study, nearly half of the patients benefitted sufficiently to justify long-term treatment. During the second phase, this effect continued; withdrawal led to a recurrence of symptoms. The authors of this study conclude that terazosin has a beneficial effect on BPH continuing for at least 12 months and can safely be considered for medium- to long-term use in those who benefit.

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References

1 Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol **132:** 474, 1994.

2 Caine M: Alpha-adrenergic mechanisms in dynamics of benign prostatic hypertrophy. Urology **32:** (suppl) 16, 1988.

3 Cohen A, Winton L, Luther R, Laddu A, Shorter H, Maurath C, DeBartolo M: Effect of terazosin on the symptoms of benign prostatic hypertrophy (BPH). Clin Pharmacol Ther **45:** 183, 1989.

4 Di Silverio F: Use of terazosin in the medical treatment of benign prostatic hyperplasia: Experience in Italy. Br J Urol **70:** (suppl 1) 22, 1992.

5 Fabricius PG, Weizert P, Dunzendorfer U, MacHannaford J, Maurath C: Efficacy of once-a-day terazosin in benign prostatic hyperplasia: A randomized, double-blind placebo-controlled clinical trial. The Prostate **3:** (suppl 3) 85, 1990.

6 Lepor H: Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. Terazosin Research Group. Urology **45:** 406, 1995.

7 Lepor H, Auerbach S, Puras-Baez A, Narayan P, Soloway M, Lowe F, Moon T, Leifer G, Madsen P: A randomized placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. J Urol **148:** 1467, 1992.

8 Lepor H, Knapp-Maloney G, Sunshine H: A dose titration study evaluating terazosin, a selective, once-a-day alpha-1-blocker for the treatment of symptomatic benign prostatic hyperplasia. J Urol **144:** 1393, 1990.

9 Lepor H, Knapp-Maloney G, Wozniak-Petrofsky J: The safety and efficacy of terazosin for the treatment of benign prostatic hyperplasia. Int J Clin Pharmacol Ther Toxicol **27:** 392, 1989.

10 Lloyd SN, Buckley JF, Chilton CP, Ibrahim I, Kaisary AV, Kirk D: Terazosin in the treatment of benign prostatic hyperplasia: A multicentre, placebo-controlled trial. Br J Urol **70:** (suppl 1) 17, 1992.

11 Mebust WK, Bosch R, Donovan J, Okada K, O'Leary MA, Villers A, Ackermann R, Batista JE, Boyle P, Denis L, Leplege A, Sagnier P: Symptom evaluation, quality of life and sexuality. In Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K, Murphy G (eds): Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH). Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 153–209.

12 Di Silverio F: Use of terazosin in medical treatment of benign prostatic hyperplasia: Experience in Italy. Br J Urol **70:** (suppl 1) 22, 1992.

13 Fabricius PG, MacHannaford J: Placebo-controlled study of terazosin in the

treatment of benign prostatic hyperplasia with 2-year follow-up. Br J Urol **70:** (suppl 1) 10, 1992.

14 Lepor H, Laddu A: Terazosin in the treatment of benign prostatic hyperplasia: The Unetid States experience. Brit J Urol **70:** (suppl 1) 2, 1992.

15 Lloyd SN, Buckley JF, Chilton CP, Ibrahim I, Kaisary AV, Kirk D: Terazosin in the treatment of benign prostatic hyperplasia: A multi-centre, placebo-controlled trial. Brit J Urol **70:** (suppl 1) 17, 1992.

16 Roehrborn CG, Oesterling JE, Auerbach S, Kaplan SA, Lloyd LK, Milam DF, Padley RJ, for the HYCAT Investigator Group: The Hytrin Community Assessment Trial Study: A one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. Urology **47:** 159, 1996.

17 Gormley GJ, Stoner E, Bruskewitz C, Imperato-McGinley J, Walsh PC, McConnel JD, Andriole GL, Geller J, Bracken BR, Tenover JS, Darracott Vaughan E, Pappas F, Taylor A, Binkowitz B, Ng J, for the Finasteride Study Group: The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med **327:** 1185, 1992.

Chapter 7.2

Urodynamic and clinical effects of terazosin therapy in patients with symptomatic benign prostatic hyperplasia.

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Journal of Urology **155:** 1317-1323, 1996.

Abstract

Purpose: We evaluated the urodynamic and clinical effects of terazosin in patients with symptomatic benign prostatic hyperplasia (BPH).

Material and Methods: A total of 45 patients who participated in a multicentric trial was evaluated with urodynamic pressure-flow studies before and after 26 weeks of treatment.

Results: Maximum flow rate and symptom score improved significantly in 22 patients with and 11 without bladder outlet obstruction who completed 26 weeks of treatment. In patients with bladder outlet obstruction, the condition was significantly reduced and in patients without obstruction, significant urodynamic changes could not be detected.

Conclusion: Terazosin treatment results in symptomatic relief and improved urinary flow in patients with and without bladder outlet obstruction and in significant improvement in patients with urodynamically proved obstruction.

Introduction

Benign prostatic hyperplasia (BPH) develops in almost half of all men older than 50 years.[1] Traditionally, the first choice of treatment in patients with symptomatic BPH was prostatectomy. The incidence of postoperative complications (5% to 10%),[2] treatment failures (25%)[3] and reoperations (10%)[4] after prostatectomy, and the knowledge that this condition is not inevitably of a rapidly progressive, deteriorating nature have led to the development of new safe and effective nonoperative treatments.

In 1976 Caine et al demonstrated that phenoxybenzamine, a nonselective α1-2 blocker, could be effective for the treatment of patients with BPH.[5] However, the widespread use of this compound was limited by the appearance of a significantly high incidence of side effects. With the introduction of prazosin, an α1 selective blocking agent, similar efficacy but fewer side effects were shown.[6] Since then, several reports have documented the beneficial effects of new selective α1 blockers in patients with symptomatic BPH.[7,8]

Terazosin is a long-acting α1 selective blocking agent that was originally used in the treatment of patients with hypertension. The effects of terazosin on symptom scores and urinary flow rates in patients with symptomatic BPH have been documented in several studies.[7,9] The reported incidence of side effects is low. Side effects are related to the α adrenergic blocking effect and include headache, dizziness and asthenia.

An advantage of terazosin over prazosin is that the longer half-life allows for a once daily dosage regimen. Terazosin administered at bedtime minimizes the percentage of patients who experience tiredness and dizziness during the day, and increases the percentage of responders who have severe nocturia.[10]

Besides evaluation of symptom score and free urine flow, we examined at 1 center the outcome of pressure-flow studies on the treatment of patients with symptomatic BPH who participated in a multicenter international randomized withdrawal trial (International Terazosin Trial: ITT) designed to evaluate the long-term safety and efficacy of terazosin.

Patients and methods

We report the urodynamic and clinical results of terazosin therapy in patients with symptomatic BPH who were included in a multicenter international randomized withdrawal trial at our centre in Nijmegen. The results of the multicenter trial have been reported previously.[9] Symptomatic BPH was diagnosed in all patients by medical history, physical examination (including digital palpation and ultrasonographic examination of the prostate), blood analysis, baseline International Prostate Symptom Score (I-PSS) of 12 or more and a maximum free urinary flow rate of 5 to 15 ml. per second inclusive, with a total voided volume of 100 ml. or more and a post-void residual volume of less than 300 ml. Prostatic volume was calculated using the planimetric method on an ultrasound scanner with a multiplane 3-dimensional rectal transducer. All patients were considered neurologically normal based on history, symptoms and physical examination (no motor, sensory or reflex deficits).

After symptomatic BPH was diagnosed clinically patients began treatment with terazosin administered at bedtime and increasing to a maximum dose of 10 mg. per day at 6 weeks. During part 1 of the study urodynamic pressure-flow tests before and after 26 weeks of treatment with terazosin were used to evaluate urodynamic changes. Urinary sediment and culture were negative at the time of pressure-flow studies. To control patient compliance, plasma terazosin levels were measured at 26 weeks of treatment. According to the study protocol, at 26 weeks of therapy patients were categorized based on the symptomatic response and free flow result into those who did and did not respond to treatment. Responders, that is patients with an I-PSS improvement of 30% or more from baseline and an increase in maximum free urinary flow rate of 10% or more from baseline, were then randomly allocated to maintain the dosage

of terazosin or to receive placebo. The patients then entered part 2 of the study (24 weeks), during which they were seen at 8-week intervals to receive the double-blind medication and to record symptoms and free urinary flow rates.

The pressure-flow studies were performed with an 8F transurethral lumen catheter with an intravesical microtip pressure sensor for bladder pressure recordings. Abdominal pressure was recorded intrarectally with an 8F microtip sensor catheter. Before cystometry the bladder was emptied through the lumen of a transurethral catheter to quantify residual volume after free uroflowmetry. Thereafter, the bladder was filled with water of 20°C with a filling speed of 50 ml. per minute with the patient supine. In consideration of the micturition diary, free uroflowmetry and residual urine volume, care was taken to fill the bladder until the maximum bladder capacity was reached and filling was stopped when the patient expressed a strong urge to void. To provide an objective and precise grading of obstruction, pressure-flow graphs were fitted with a passive urethral resistance relation curve at the lowest pressure part of the graph.[11] Minimal detrusor pressure during micturition and computed theoretical cross-sectional urethral area were calculated automatically based on the manually adjusted passive urethral resistance relation curves.[11] The detrusor pressure at maximum flow during the urodynamic investigation was recorded. Correction for flow artifacts was performed when necessary. The parameter urethral resistance relation URA was determined by fitting the pressure-flow plot at the point of maximum flow (at detrusor pressure at maximum flow). Urethral resistance relation was computed to classify patients on a continuous, 1-parameter scale of obstruction.[12] The linear passive urethral resistance relation was determined by drawing a straight line between the 2 points on the pressure-flow curve that corresponded to the detrusor pressure at maximum flow and the minimal detrusor pressure during voiding.[13] The position of this straight line defined the outlet condition in a simple way and afforded classification of the severity of outlet obstruction. Urodynamic parameters analyzed were maximum free urinary flow rate, free voided volume, maximum flow during urodynamic investigation, detrusor pressure at maximum flow, minimal detrusor pressure during voiding, theoretical cross-sectional urethral area and urethral resistance relation for all patients, for those without obstruction (linear passive urethral resistance relation less than 3) and for those with obstruction (linear passive urethral resistance relation 3 or more).[14] We investigated the possible differences in treatment effects between the obstruction and no obstruction groups using previously defined response criteria for each urodynamic parameter and symptom score (table 1). We also examined possible differences in initial

urodynamic parameters between the patients who did and did not respond to treatment according to the definition of the study protocol. Statistical analysis was performed using the Wilcoxon matched pairs signed rank test and the Wilcoxon rank sum W test for analysis of numerical data, and the chi-square test for the comparison of categorical data.

Table 1. *Percentages of urodynamic and symptomatic responders in the obstruction and no obstruction groups after 26 weeks of terazosin treatment.*

	% Obstruction (22 pts.)	% No obstruction (11 pts.)	p Value*
Maximum free flow rate:			
increase ≥ 10 %	59	91	0.06
increase ≥ 50 %	32	18	0.41
Free voided volume: increase ≥ 50 ml.	23	45	0.18
Minimal detrusor pressure during voiding: decrease ≥ 10 cm. water	55	22	0.09
Maximum urodynamic flow rate: increase ≥ 2 ml./sec.	36	45	0.61
Detrusor pressure at maximum flow: decrease ≥ 10 cm. water	64	36	0.14
Theoretical cross-sectional urethral area: increase ≥ 1 $mm.^2$	36	14	0.27
Urethral resistance relation decrease ≥ 10 cm. water	55	0	< 0.01
Total I-PSS symptom score:			
decrease ≥ 30 %	67	100	0.03
decrease ≥ 50 %	57	64	0.72
Responders@	41	91	< 0.01

* Chi-square test

@ Responders are those who, after 26 weeks of treatment, have an increase in maximum free flow rate ≥ 10% and a decrease in total I-PSS ≥ 30%.

Results

A total of 45 patients (mean age 64 years, range 50-76) began treatment with terazosin increasing to a maximum dose of 10 mg. per day at 6 weeks. The ultrasonographically detected prostatic volume ranged from 20 to 94 cc (mean 44). A total of 30 patients (64%), including 3 unable to void during the pressure-flow investigation, was categorized as having obstruction and 12, including the 3 unable to void during the initial investigation, stopped treatment during part 1 of the study due to dizziness in 2, asthenia in 4, cardiac arrhythmia in 1, dyspnea in 2, poor compliance in 2 and progressive complaints with a urinary tract infection in 1. Of the patients 33, including 22 (67%) with obstruction, underwent pressure-flow studies before and after 26 weeks of terazosin treatment. The initial I-PSS total symptom score and initial detrusor pressure at maximum flow labeled according to the reason for dropping out before week 26 and response status according to the definition of the study protocol at 26 weeks of treatment, are plotted for each individual in figure 1. Patients who dropped out of the study because of toxicity had symptomatic and urodynamic values that were heterogeneously distributed amongst those who completed the first 26 weeks of therapy. Mean urodynamic parameters and symptom scores at baseline for the initial 45 patients, and at baseline and after 26 weeks of treatment for 33 patients, divided in 2 subgroups with and without obstruction are shown in table 2. Maximum free urinary flow rate and I-PSS symptom score improved significantly in the entire group of patients (mean 2.3 ml. per second and 10 points respectively; $p < 0.01$ and $p < 0.01$ respectively). In the obstruction group the mean maximum free urinary flow rate improved by 1.6 ml. per second, which was not statistically significant ($p = 0.06$). However, mean improvement in maximum flow during urodynamic investigation (1.9 ml. per second) was significant ($p = 0.01$). In the no obstruction group mean improvement in maximum free urinary flow rate (3.6 ml. per second) was statistically significant ($p = 0.01$) but mean improvement in maximum flow during urodynamic investigation (1.6 ml. per second) was not ($p = 0.32$). Symptom scores improved significantly in both groups ($p < 0.01$ with and $p < 0.01$ without obstruction).

Mean pressure-flow parameters of maximum flow during urodynamic investigation, minimal detrusor pressure during voiding, detrusor pressure at maximum flow, theoretical cross-sectional urethral area and urethral resistance relation in the obstruction group significantly improved after 26 weeks of terazosin treatment. In the patients without obstruction significant changes could not be detected. Figure 2 shows the improvements in urethral resistance relation and I-PSS symptom score

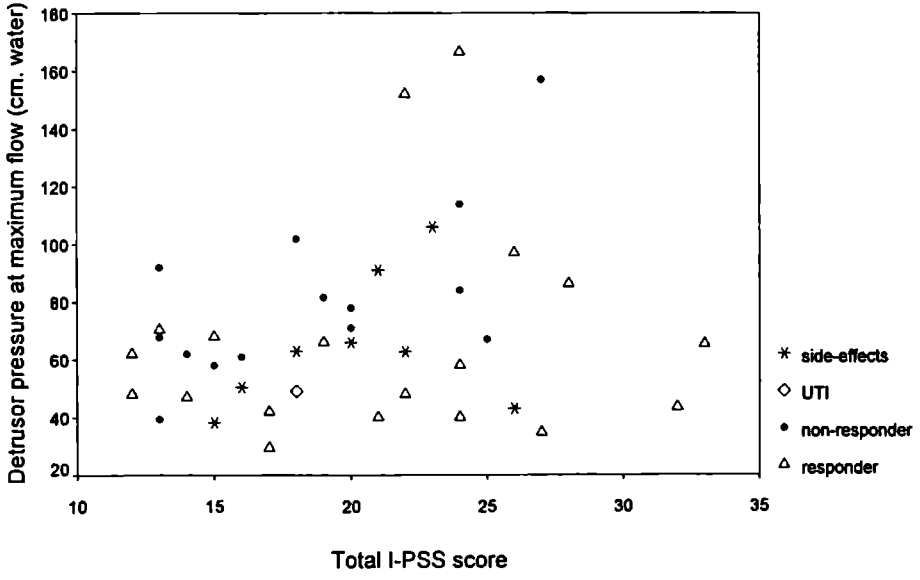

Figure 1. Scatterplot of detrusor pressure at maximum flow in cm. water (Y-axis) and total I-PSS (X-axis) for each individual, labeled according to reasons for dropping out of study during first 26 weeks of treatment and response status according to definition of study protocol at 26 weeks of treatment. UTI, urinary tract infection.

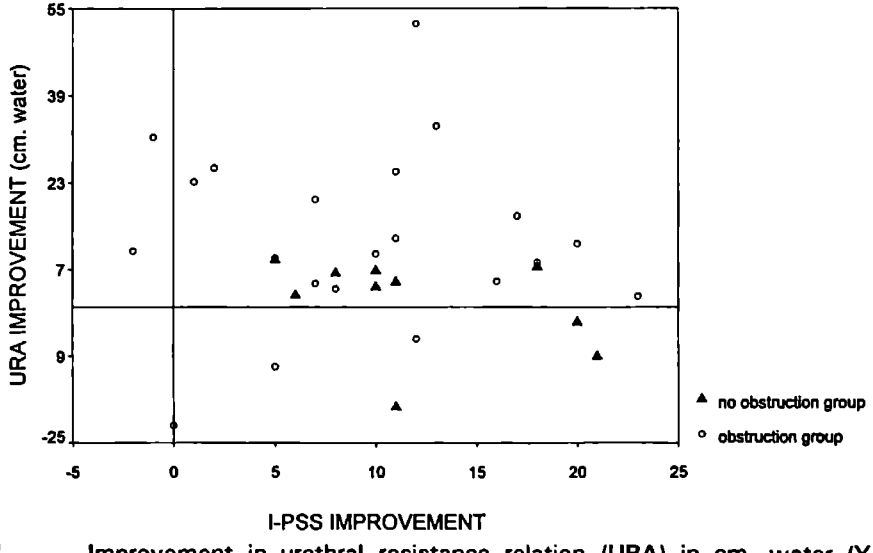

Figure 2. Improvement in urethral resistance relation (URA) in cm. water (Y-axis) and I-PSS symptom score (X-axis) plotted for each individual patient with and without obstruction who completed 26 weeks of terazosin therapy.

Table 2. *Urodynamic and symptomatic results at baseline for the initial 45 patients, and at baseline and 26 weeks after starting terazosin treatment for 33 patients divided into subgroups of 11 without and 22 with obstruction. Legend see chapter 6, table 1.*

		33 patients completing 26 weeks terazosin		
	Initial group (45 pts.)	Total group	No Obstr. (11 pts.)	Obstruction (22 pts.)
Free Qmax (ml/s)				
Baseline	9.1 ± 2.7	9.0 ± 2.8	9.7 ± 2.6	8.6 ± 2.9
Week 26	-	11.3 ± 4.4	13.3 ± 3.8	10.2 ± 4.3
p Value		< 0.01	0.01	0.06
Free void. vol. (ml)				
Baseline	224 ± 98	203 ± 91	224 ± 129	192 ± 66
Week 26	-	215 ± 111	244 ± 98	200 ± 117
p Value		0.97	0.66	0.76
Free res. vol. (ml)				
Baseline	62 ± 87	67 ± 99	22 ± 24	76 ± 111
Week 26	-	60 ± 81	55 ± 56	66 ± 90
p Value		0.82	0.12	0.36
$Pvoid_{min}$ (cm. water)				
Baseline	37.2 ± 22.0	38.7 ± 24.2	20.3 ± 9.5	46.3 ± 24.5
Week 26	-	29.5 ± 16.8	23.0 ± 16.0	33.3 ± 16.9
p Value		0.13	0.44	0.04
Urod. Qmax (ml/s)				
Baseline	7.3 ± 3.5	7.1 ± 3.6	9.0 ± 4.2	6.2 ± 2.9
Week 26	-	8.9 ± 5.2	10.6 ± 6.1	8.1 ± 4.6
p Value		0.01	0.32	0.01
$P_{det}Qmax$ (cm. water)				
Baseline	70.7 ± 32.0	72.7 ± 34.2	43.4 ± 9.2	87.3 ± 32.6
Week 26	-	59.4 ± 28.2	44.6 ± 18.8	66.7 ± 29.5
p Value		0.01	0.79	0.01
A_{theo} (mm^2)				
Baseline	3.2 ± 3.2	3.2 ± 3.6	3.4 ± 1.7	2.3 ± 0.9
Week 26	-	3.9 ± 2.4	3.7 ± 1.4	3.7 ± 2.5
p Value		< 0.01	0.50	< 0.01
URA (cm. water)				
Baseline	42.1 ± 18.4	43.6 ± 19.6	25.2 ± 6.9	51.9 ± 17.7
Week 26	-	34.2 ± 17.7	24.2 ± 12.4	38.8 ± 18.5
p Value		< 0.01	0.51	< 0.01
Total I-PSS score				
Baseline	19.7 ± 6.5	20.1 ± 6.9	21.1 ± 7.3	19.6 ± 6.3
Week 26	-	9.7 ± 5.4	8.6 ± 5.4	10.3 ± 5.4
p Value		< 0.01	< 0.01	< 0.01

Comparison of baseline versus week 26 values (mean ± standard deviation) using Wilcoxon matched pairs signed rank test.

plotted for each patient who completed 26 weeks of therapy. The majority of obstruction patients had symptomatic and urodynamic improvement after 26 weeks of terazosin treatment. Symptomatic improvement in the group without obstruction was comparable with that of the group with obstruction. The changes in urethral resistance relation in the no obstruction group were not great and the majority were within physiological variability.

Table 1 shows the number of responders according to the study protocol, and the number of responders for each urodynamic parameter and symptom score in both groups. Of 22 patients with and 11 without obstruction 13 (59%) and 10 (91%), respectively, had a 10% or greater increase in maximum free urinary flow rate ($p = 0.06$). In comparison, 7 of 22 patients (32%) with and 2 of 11 (18%) without obstruction had greater differences in maximum free urinary flow rate (50% or more)($p = 0.41$). A total of 12 of 22 patients (55%) with and none without obstruction had a decrease in urethral resistance relation of 10 cm. water or more, and this difference was statistically significant ($p < 0.01$). The number of patients classified as responders according to the study protocol definition was significantly greater in the group without obstruction ($p < 0.01$). Passive urethral resistance relation curves based on mean urodynamic values for both groups at baseline and after 26 weeks of treatment are shown in figure 3.

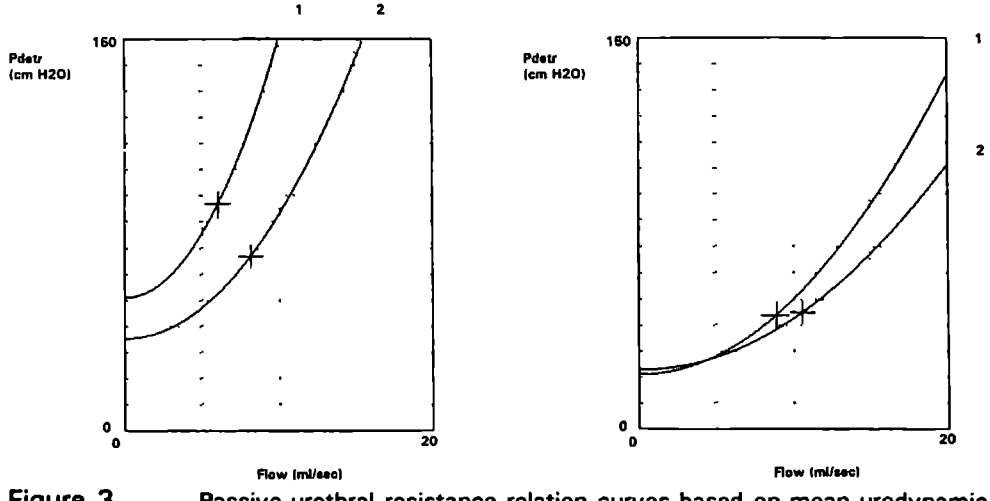

Figure 3. Passive urethral resistance relation curves based on mean urodynamic values for obstruction (a) and no obstruction (b) groups at baseline (1) and after 26 weeks of treatment (2). +, mean detrusor pressure at maximum flow. Pdetr, detrusor pressure.

Table 3 provides an overview of the mean initial urodynamic parameters between the groups who did and did not respond to treatment. The mean urodynamic parameters of theoretical cross-sectional urethral area, urethral resistance relation and linear passive urethral resistance relation were significantly different, indicating that patients without obstruction were more likely to respond to treatment according to the study protocol definition compared to those with obstruction (figure 1).

After the first 26 weeks of treatment 19 of 33 patients were categorised as responders according to the protocol definition and were randomized to receive further treatment. For the next 24 weeks, 5 obstruction and 4 no obstruction responders were randomized to maintain the dosage of terazosin, and 4 obstruction and 6 no obstruction responders received placebo. During part 2 of the protocol 3 patients (1 randomized to continue terazosin and 2 receiving placebo) interrupted treatment because of progressive complaints. Table 4 shows the mean values of maximum free urinary flow rate and symptom scores for all patients, as well as for those with versus without obstruction and randomized to receive placebo versus terazosin. During part 2 of the study symptom scores deteriorated significantly in the placebo group ($p = 0.02$), whereas the improved symptom scores in the terazosin group were maintained. A mean terazosin level of 114 ng./ml. (range 66-187) 26 weeks after beginning therapy showed good drug compliance in the study population.

The most frequent treatment related side effects were mild headache, dizziness and asthenia. Usually, these side effects were mild and transient. Six patients stopped treatment because of such events. In one patient treatment was stopped because of progressive complaints after 8 weeks of therapy that later were found to be related to a culture proved urinary tract infection. Dyspnea and cardiac arrhythmia were other reasons for cessation of treatment but these events were not considered to be treatment related.

Discussion

Traditionally, an important objective method to assess the effect of a new treatment modality in BPH is urinary flow measurement. However, there is a great variability in consecutive measurements of uroflowmetry. Golomb et al evaluated the variability of urinary flow in 32 patients with BPH and 16 healthy volunteers.[15] The variability between consecutive maximum flow rates was observed in the BPH group from at least 1 standard deviation (5.7 ml. per second) in 28 of 32 patients to at least 2 standard deviations in 15 of 32. Furthermore, on voiding nomograms the

highest recorded maximum flow rate was greater than the 2 standard deviation plot, while the lowest maximum flow rate was less than the 2 standard deviation plot. It is obvious that this great variability in measurements of uroflowmetry has a marked negative impact on the power of statistical tests to assess a difference in the intra-individual and interindividual urinary flow rate. Furthermore, it largely increases sample size requirements to achieve statistical power. These difficulties were

Table 3. *Initial clinical and urodynamic values for patients with and without response according to the study protocol definition.*

	Mean ± standard deviation		
	Response (19 pts.)*	No Response (14 pts.)	p Value●
Maximum free flow rate (ml./sec.)	10.2 ± 3.6	8.0 ± 2.4	0.11
Free voided volume (ml.)	216 ± 105	197 ± 67	0.86
Residual volume (ml.)	46 ± 68	95 ± 124	0.20
Minimal detrusor pressure during voiding (cm. water)	34.0 ± 25.0	44.5 ± 22.9	0.05
Maximum urodynamic flow rate (ml./sec.)	8.6 ± 4.0	5.2 ± 1.6	< 0.01
Detrusor pressure at maximum flow (cm. water)	66.5 ± 37.1	81.0 ± 29.0	0.05
Theoretical cross-sectional urethral area ($mm.^2$)	4.2 ± 4.8	2.0 ± 0.7	0.03
Urethral resistance relation (cm. water)	36.3 ± 19.4	52.9 ± 16.2	< 0.01
Linear passive urethral resistance relation	2.6 ± 1.5	3.9 ± 1.0	< 0.01
Total I-PSS symptom score	21.2 ± 6.5	18.6 ± 4.9	0.31

* Increase in maximum free flow rate of ≥ 10% and decrease in total I-PSS of ≥ 30% after 26 weeks of treatment.

● Wilcoxon rank sum W test.

Table 4. *Maximum free flow rate (Free Qmax in ml./sec.) and I-PSS symptom scores (Total I-PSS score) * for patients with and without obstruction and for all patients*

	Baseline	Week 2	Week 6	Week 10	Week 18	Week 26	Week 34		Week 42		Week 50	
							Plac.	Ter.	Plac.	Ter.	Plac.	Ter.
Obstruction												
Number of patients	30	30	30	27	25	22	4	5	4	5	4	4
Free Qmax	8.7					10.2	8.3	16.4	10.1	15.0	10.1	16.4
± SD	± 2.8					± 4.3	± 0.9	± 8.7	± 2.6	± 5.3	± 1.3	± 10.0
Total I-PSS score	19.3	14.4	10.5	8.1	9.8	10.3	10.3	10.2	12.0	6.8	16.8	6.5
± SD	± 4.8	± 6.2	± 4.9	± 4.5	± 5.4	± 5.4	± 9.6	± 4.7	± 10.2	± 1.3	± 9.0	± 1.7
No Obstruction												
Number of patients	15	15	14	13	12	11	6	4	5	4	4	4
Free Qmax	9.9					13.3	10.1	8.9	10.1	11.3	14.5	11.4
± SD	± 2.6					± 3.8	± 2.8	± 1.8	± 1.5	± 2.1	± 9.0	± 2.9
Total I-PSS score	20.5	12.8	13.4	9.1	8.8	8.6	15.0	13.8	13.2	13.8	11.3	12.3
± SD	± 6.7	± 5.9	± 6.3	± 5.2	± 4.7	± 5.4	± 5.8	± 9.8	± 3.6	± 7.9	± 4.3	± 8.7
All patients												
Number of patients	45	45	44	40	37	33	10	9	9	9	8	8
Free Qmax	9.1					11.3	9.3	13.1	10.1	13.4	12.3	13.9
± SD	± 2.7					± 4.4	± 2.3	± 7.3	± 1.8	± 4.4	± 6.4	± 7.3
Total I-PSS score	19.7	13.9	11.4	8.4	9.5	9.7	13.1	11.8	12.7	9.9	14.0	9.4
± SD	± 5.5	± 6.1	± 5.5	± 4.7	± 5.1	± 5.4	± 7.5	± 7.1	± 6.8	± 6.2	± 7.0	± 6.6

* Mean ± standard deviation (SD).

already recognised in 1982 by Drach et al, who suggested to adjust the maximum urinary flow rate for varying age and volume voided.[16] Presently, it is accepted that the poor urinary stream in 20 to 25% of patients with symptomatic BPH is due to a hypoactive detrusor muscle.[3] This fact emphasizes the relative importance of urinary flow measurement in assessing the effect of a treatment modality in patients with symptomatic BPH, especially in small groups.

During the international consultation on BPH in 1993 it was advised that, if obstruction is the end point of the study, pressure-flow studies before and after treatment should be used in the evaluation of new therapies.[17] Pressure-flow studies enable us to investigate the relationship between subjective efficacy of treatment and objective voiding parameters. Moreover, the use of pressure-flow studies may help to select patients for a given treatment and, therefore, dropout and over treatment percentages may decrease considerably.

Patients may be selected for a given treatment using the linear passive urethral resistance relation diagram, a classification of the degree of bladder outlet obstruction.[14] This diagram is divided into 7 bands, labeled 0 to 6, representing increasing severity of obstruction. Bands 0 and 1 represent an unobstructed, bands 2 and 3 a minimally obstructed, and bands 4 to 6 an increasingly severe obstructed outlet condition.[13,14] In patients with a linear passive urethral resistance relation of 0 or 1, categorized as without obstruction, the poor urinary stream is caused by a hypoactive detrusor muscle. These patients have little chance to benefit from transurethral resection of the prostate.[14] Pharmacotherapy in this group must have been used frequently but to our knowledge efficacy results in this specific group of patients have not been reported, probably because they were not identified by pressure-flow analyses.

Between unobstructed and obviously obstructed groups, with poor urinary streams and high intravesical pressures noted by a linear passive urethral resistance relation of 4 or more, there is a gray zone of patients with a linear passive urethral resistance relation of 2 and 3 who have minimal bladder outlet obstruction. We divided the gray zone of patients with minimal obstruction into 2 groups: 1) those with a linear passive urethral resistance relation of 2 or less were classified as without obstruction and 2) those with a linear passive urethral resistance relation of 3 or more were classified as with obstruction. With this classification we were able to show differences in clinical and urodynamic treatment responses between the 2 groups.

In the obstruction group all mean values for maximum flow during urodynamic investigation, minimal detrusor pressure during voiding,

detrusor pressure at maximum flow, theoretical cross-sectional urethral area and urethral resistance relation after 26 weeks of terazosin improved significantly. From a theoretical viewpoint, the mechanism of voiding using an $\alpha 1$ adrenergic blockader is changed towards a better outlet distensibility during voiding and, thus, becomes more efficient. The first effect of a decrease in outlet obstruction is presumably a change in the balance of bladder outlet and detrusor contraction towards a lower pressure micturition with improved efficacy. Theoretically, the increase in maximum urinary flow rate might not be as high as may be expected, which may be partly attributed to a decrease in voiding detrusor pressure. More efficient voiding can also be shown by lower post-void residual volumes but this could not be demonstrated by our patients who had a low mean residual volume of 62 ml. with a high standard deviation of 87 ml. In our study more efficient micturition after terazosin is clearly evident in the obstruction group in which urodynamic parameters improved significantly, particularly the improvement in maximum urinary flow rate. A significant change in theoretical cross-sectional urethral area together with a significant change in minimal detrusor pressure during voiding indicates that terazosin has relaxed the bladder outlet so that more efficient voiding can occur.

The patients without obstruction showed no significant urodynamic changes. Ironically, the group with the highest percentage of patients showing slight improvements in free flow and symptoms had no urodynamic obstruction. When we evaluated greater improvements in free flow and symptoms, there was no significant difference between the percentage of patients in either group (table 1), which demonstrates that in our patients without obstruction statistically significant improvements in symptoms or free flow were not confirmed by significant improvements of urodynamic variables. This finding suggests that the way we analyze efficacy in the majority of pharmacotherapy studies for BPH (that is improvements in symptoms and maximum free urinary flow rate) is not entirely representative of the urodynamic mechanism of action. Moreover, the results of urodynamic studies in men who received treatment for BPH depend on the percentage of included patients who actually have obstruction. In other words, a high percentage of patients without obstruction will mask the urodynamic effect that is clearly shown in those with obstruction. Tammela and Kontturi reported a mean decrease of detrusor pressure at maximum flow of 39 cm. water after finasteride treatment for 6 months and a mean increase of detrusor pressure at maximum flow of 3 cm. water in the placebo treated group, indicating a significant urodynamic response to treatment.[18] Such a large urodynamic response can only be expected in patients with severe outlet obstruction. Considering the high mean detrusor pressure at maximum flow values in the study of Tammela and

Kontturi (mean detrusor pressure at maximum flow 120 cm. water), the majority of the included patients had severe bladder outlet obstruction. The urodynamic response in a study evaluating the efficacy of doxazosin, an $\alpha 1$ selective blocker, although significantly better compared to placebo, was slight (improvement of detrusor pressure at maximum flow 5 cm. water).[8] Mean detrusor pressure at maximum flow in the doxazosin study was 78 cm. water indicating that a higher percentage had less severe obstruction compared to the study of Tammela and Kontturi. These findings imply that mean urodynamic differences between therapy groups must be regarded critically.

The maximum flow during urodynamic investigation is lower than the maximum free urinary flow rate and this difference is systematic, probably due to the transurethral catheter and the different type of investigation. The large variability in consecutive measurements in urinary flow measurement is also illustrated in this study. In all patients significant improvements in maximum flow during urodynamic investigation (1.8 ml. per second) and maximum free urinary flow rate (2.3 ml. per second) could be detected, which is in accordance with the results of the multicenter trial in which 239 patients completing the first 26 weeks of therapy had a significant improvement in maximum free urinary flow rate of 3.2 ml. per second.[9] The differences in our study were statistically significant only for maximum free urinary flow rate in the no obstruction group and maximum flow during urodynamic investigation in the obstruction group. In the no obstruction group the power to detect a true difference of 2.0 ml. in maximum flow during urodynamic investigation at a significance level α of 0.05 was only 21%. In the obstruction group the power to detect a true difference of 2.0 ml. in maximum free urinary flow rate at a significance level α of 0.05 was only 64%. Evidently, more patients are needed in these subgroups to detect a significant difference in these parameters.

Symptoms obviously responded well to terazosin in both groups. This symptomatic response can be differentiated from a placebo response, since symptoms during part 2 of this study deteriorated significantly in the placebo group, whereas the improved symptom score at week 26 in the terazosin group was maintained until the end of the study. In our study terazosin resulted in significant symptomatic relief and significant improved urinary flow in the majority of patients. Terazosin also resulted in improved efficiency of micturition and a significant decrease in bladder outlet obstruction in the majority of patients with urodynamically proved obstruction. As indicated in the multicenter trial[9] and our study (figures 1 and 2), few patients do not benefit symptomatically or urodynamically from terazosin treatment. To date laboratory studies have indicated that in the

human prostate the relative expression of α1c adrenergic receptor subtypes is predominant.[19] A large interindividual variation of α1c expression in BPH specimens could explain why not all men react favorably to treatment with α1 selective blocking agents.[20] Future laboratory studies should be directed towards the search for more prostate specific α1 receptor subtypes, which would allow development of new α1-subtype selective blocking agents resulting in increased therapeutic efficacy and fewer side effects.

We have shown that a stratified analysis, based on urodynamic classification of bladder outlet obstruction, provides meaningful insight into the working mechanism of terazosin in patients with symptomatic BPH. We also have shown that significantly more patients without obstruction, in whom no significant urodynamic changes could be detected, had slight improvements in maximum free urinary flow rate and symptom score compared to those with obstruction, which demonstrates that in pharmacotherapy studies that include many patients without obstruction clinical response to treatment is not necessarily identical to urodynamic response.

Further prospective clinical investigations in patients classified according to the grade of obstruction are necessary to provide the still needed information on the role of bladder outlet obstruction in the evaluation of pharmacological therapy, and the capability of urodynamic and clinical parameters to predict a favorable response to new treatments. Only then can the treatment of symptomatic BPH be individualized according to the pathophysiology, complaints, and expectations of the patient.

Conclusions

Terazosin results in significant symptomatic relief and improved urinary flow in patients with and without bladder outlet obstruction. Terazosin also results in improved efficiency of micturition and significantly decreased bladder outlet obstruction in patients with urodynamically proved obstruction.

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References

1 Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. Lancet **338**: 469, 1991.

2 Bruskewitz RC, Larsen EH, Madsen PO, Dørflinger T: 3 year follow-up of urinary symptoms after transurethral resection of the prostate. J Urol **136**: 613, 1986.

3 Schäfer W, Nopponey R, Rubben G, Lutzeyer W: The value of free flow rate and pressure-flow studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

4 Roos NP, Wennberg IC, Malenka DJ, Fischer ES, McPherson K, Andersen TF, Cohen MM, Ramsey E: Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med **320**: 1120, 1989.

5 Caine M, Pfau A and Perlberg S: The use of α adrenoceptor blockers in benign prostatic obstruction. Brit J Urol **48**: 255, 1976.

6 Kirby RS, Copinger SW, Corcoran MO, Chapple CR, Flanigan M, Milroy EJG: Prazosin in the treatment of prostatic obstruction: a placebo-controlled study. Brit J Urol **60**: 136, 1987.

7 Lepor H, Knapp-Maloney G, Sunshine H: A dose titration study evaluating terazosin, a selective, once-a-day $\alpha 1$ blocker for the treatment of symptomatic benign prostatic hyperplasia. J Urol **144**: 908, 1990.

8 Chapple CR, Carter P, Christmas TJ, Kirby RS, Bryan J, Milroy EJG, Abrams P: A three month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. Brit J Urol **74**: 50, 1994.

9 Debruyne FMJ, Denis L, Arocena F, Kirk D, Kirby R, and the ITT group: Efficacy of terazosin in benign prostatic hyperplasia from a randomized withdrawal international terazosin trial (ITT). J Urol **153**: 273A, 1995.

10 Ekman P, Witjes WPJ, and the ITT Group: Nocturia results from the International Terazosin Trial (ITT) A double blind, placebo-controlled randomized withdrawal study of the symptomatic treatment of BPH. Proc 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A98, 1994.

11 Schäfer W: The contribution of the bladder outlet to the relation between pressure and flowrate during voiding. In: Benign Prostatic Hypertrophy Edited by F Hinman Jr Berlin: Springer verlag, pp 470-496, 1983.

12 Griffiths DJ, Mastrigt van R, Bosch R: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size in urethral obstruction due to benign prostatic hyperplasia. Neurourol Urodyn **8**: 17, 1989.

13 Schäfer W: Basic principles and clinical application of advanced analysis of bladder voiding function. Urol Clin N Am **17**: 553, 1990.

14 Abrams P, Blaivas J, Nordling J, Griffiths DJ, Kondo A, Koyanagi T, Neal D, Schäfer W, Yalla S: The objective evaluation of bladder outflow obstruction. In: Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH) Edited by: ATK Cockett, S Khoury, Y Aso, C Chatelain, L Denis, K Griffiths and G Murphy. Jersey, United Kingdom: Scientific Communication International Ltd, pp 153-209, 1993.

15 Golomb J, Lindner A, Siegel Y, Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. J Urol **147:** 1044, 1992.

16 Drach GW, Layton T, Bottaccini MR: A method of adjustment of male peak urinary flow rate for varying age and volume voided. J Urol **128:** 960, 1982.

17 Aso Y, Boccon-Gibbod L, Brendler B, Calais da Silva F, Cockett TK, Fowler JE, Homma Y, Moriyama N, Okajima E, Richard F: Clinical research criteria. In: Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH) Edited by ATK Cockett, S Khoury, Y Aso, C Chatelain, L Denis, K Griffiths and G Murphy Jersey, United Kingdom: Scientific Communication International Ltd, pp 343-358, 1993.

18 Tammela TL, Kontturi MJ: Urodynamic effects of finasteride in the treatment of bladder outlet obstruction due to benign prostatic hyperplasia. J Urol, **149:** 342, 1993.

19 Price DT, Schwinn DA, Lomasney JW, Allen LF, Caron MG, Lefkowitz RJ: Identification, quantification, and localization of mRNA for three distinct alpha$_1$ adrenergic receptor subtypes in human prostate. J Urol **150:** 546, 1993.

20 Schalken JA, Stratum van P, Smit F, Bokhoven van A, Rosette de la J, Korstanje C, Debruyne FMJ: Differential expression of alpha1-adrenergic receptor subtypes in BPH determined by reverse transcriptase PCR (Polymerase Chain Reaction). Proc 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A648, 1994.

Chapter 7.3

Urodynamic and clinical effects of terazosin therapy in symptomatic patients with and without bladder outlet obstruction. A stratified analysis.

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Abstract

Objectives: To evaluate clinical and urodynamic changes in patients with and without bladder outlet obstruction (BOO) and to compare the clinical and urodynamic results of terazosin treatment between patients with and without BOO.

Methods: In a prospective study, 97 patients who completed a full screening program including urodynamic investigation with pressure-flow study analysis, started treatment with terazosin. A total of 60 patients completed 6 months of treatment and were re-evaluated with international prostate symptom scores (I-PSS), uroflowmetry and urodynamic investigation with pressure-flow study analysis. Patients were stratified using the linear passive urethral resistance relation (L-PURR) classification according to Schäfer. Patients with a L-PURR of 3 or more were classified as patients with and patients with a L-PURR of 2 or less were classified as patients without BOO. The clinical and urodynamic changes within and between the groups with and without BOO were evaluated.

Results: Terazosin resulted in significant symptomatic relief (9 points on the I-PSS scale, $p < 0.01$) and a significant improvement of free urinary flow (3.0 ml/s; $p < 0.01$). In patients with BOO, a statistically significant improvement of all urodynamic obstruction variables ($p < 0.01$) was shown. In patients without BOO, a significant improvement of free urinary flow (4.4 ml/s; $p < 0.01$), a statistically significant improved bladder capacity (increase of 70 ml; $p = 0.01$) and no statistically significant changes in urodynamic obstruction variables ($p > 0.05$) were shown. Patients with a hypo-active detrusor were more prone to early dropout. When comparing the changes of symptoms ($p = 0.89$), quality of life ($p = 0.85$) and the number of patients with improvements of free uroflow of at least 30 % ($p = 0.15$), there appeared to be no significant difference between the groups with and without BOO.

Conclusions: Although there is a statistically significant difference in urodynamic response to terazosin treatment between patients with and without BOO, we cannot recommend the use of pressure-flow studies in the selection of patients for terazosin treatment because the clinical results of treatment appear not to be significantly different between patients with and without BOO. It seems more useful, and certainly less expensive and less invasive, to start $\alpha 1$ blocker therapy if, on clinical grounds, the urologist considers the patient to be a candidate for $\alpha 1$ blocker therapy and to continue therapy in those who respond.

Introduction

Lower urinary tract symptoms (LUTS) in elderly men are traditionally labelled as prostatism. The term suggests that the enlarged prostate gland, causing infravesical bladder outlet obstruction (BOO), is exclusively responsible for the LUTS. However, benign prostatic hyperplasia (BPH) is a histological diagnosis, and LUTS are not necessarily related to urodynamically proven bladder outlet obstruction or histologically proven BPH.[1,2] LUTS have shown to be prevalent in an age-matched female population indicating that the prostate is not required for the occurrence of these symptoms.[3] It has also been recognized that LUTS are related to detrusor instability or detrusor underactivity in an important percentage of elderly men.[4,5] Obviously, the pathophysiology of LUTS is not always clear without an advanced urodynamic pressure-flow study investigation. Urodynamic pressure-flow study investigation is the reference standard to quantify the grade of BOO in elderly men with LUTS.[6] Precise grading of obstruction is becoming increasingly important in the evaluation and comparison of new therapeutic options in the treatment of patients with LUTS.

Because it is known that α1-adrenoreceptors are predominantly present in the bladder neck and prostate smooth muscle, α1-blocking agents have successfully been used to relieve symptoms in patients with LUTS.[7-9]

Terazosin is a long-acting α1-selective blocking agent originally used in the treatment of patients with hypertension. The effects of terazosin on symptom scores and urinary flow rates in large groups of patients with LUTS have been well documented.[8,9] These studies indicate that approximately 60 % of patients respond well on treatment with terazosin. So far, it is unknown if it is possible to predict a good response on α1-blocker treatment in the individual patient. Consequently, selection of patients who should be preferably treated with an α1-blocker or one of the other treatment modalities is still not based on scientific grounds. Earlier studies indicated that inclusion of urodynamic pressure-flow data in the preoperative evaluation may improve the overall clinical results, as does an indication for transurethral resection of the prostate.[5,10,11] Jensen showed that symptomatic patients without BOO have a higher likelihood of subjective postoperative treatment failure when compared to symptomatic patients with BOO.[11] It is unknown if a stratification based on the grade of BOO has any predictive value for patients who are treated with an α1-selective blocking agent. In our study, we investigated possible differences in treatment outcome in patients with and patients without BOO who were

treated with terazosin.

Patients and methods

In 1992, we started a prospective study to evaluate the outcome of therapy in patients with LUTS treated with terazosin. Between September 1992 and October 1994, all patients were evaluated at baseline by medical history, International Prostate Symptom Score (I-PSS), prostate-specific antigen analysis, physical examination including digital rectal examination, ultrasonographic examination of the prostate, and free urinary flowmetry with subsequent ultrasonographic measurement of residual urinary volume. Prostate specific antigen was determined using the Tandem-E PSA assay (Hybritech, San Diego, Calif). Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner and a multiplane 3-D rectal transducer (VRW 177AK). For free urinary flowmetry the Dantec Urodyn 1000 flowmeter was used. For evaluation of the voiding efficiency, the voided percentage, (the relative amount of bladder contents that was expelled during micturition) was calculated. All patients were considered neurologically normal, based on history, symptoms and physical examination (no motor, sensory or reflex deficits). Patients in whom a prostatic carcinoma or other disease beyond the prostate could be expected which could possibly influence their LUTS (for example, urethral stricture or bladder neck contracture), were evaluated more extensively first (by prostate biopsy or urethra-cystoscopy) and excluded if these diseases were confirmed. Excluded were patients previously treated with transurethral (laser) resection of the prostate, transurethral microwave thermotherapy, or 5α-reductase inhibitors. Patients treated with α blockers within 4 weeks before the baseline pressure-flow study was performed were also excluded. There were no explicit urodynamic pressure-flow study selection criteria. After the clinical diagnosis was established, patients were informed about the treatment options. When the patient experienced moderate symptoms or the patient was bothered by his symptoms, terazosin treatment was recommended in addition to other minimal invasive therapies. Patients started treatment with an increasing dose, to a maximum of 10 mg per day terazosin at 6 weeks of treatment, administered at bed time. Every patient's dose was titrated up to 10 mg, but patients not tolerating the 10 mg-dose had their dosage decreased to 5 mg. Urodynamic pressure-flow studies before and after 6 months of treatment with terazosin were used to evaluate urodynamic changes. Urinalysis and culture were negative at the time of pressure-flow studies. After 6 months of treatment, patients were re-

evaluated both clinically and urodynamically.

Urodynamic pressure-flow studies were performed with an 8F transurethral lumen catheter equipped with an intravesical microtip pressure sensor for bladder pressure recording. Abdominal pressure was recorded intrarectally with an 8F microtip sensor catheter (MTC®. Dräger, Germany). Before cystometry, the bladder was emptied through the lumen of the transurethral catheter. The bladder was filled with water of 20°C at a rate of 50 ml per minute; with the patient in supine position. In consideration of the micturition diary, free uroflowmetry and residual urine, care was taken to fill the bladder until the maximum bladder capacity was reached. Filling was stopped when the patient expressed a very strong urge to void. Commercially available equipment (UD 2000®; MMS, Enschede, the Netherlands) was used to record the pressure and flow data. Digitally stored data were translated to a urodynamic analysis computer program developed at our own department. This program provides a half automatic pressure-flow study analysis with passive urethral resistance relation (PURR) and urethral resistance factor (URA).

To provide an objective and precise grading of obstruction, pressure-flow graphs were fitted with a PURR curve at the lowest pressure part of the graph.[12] The minimal urethral opening pressure during micturition ($Pvoid_{min}$) and theoretical cross-sectional urethral lumen (A_{theo}) were calculated automatically, on basis of these manually adjusted PURR curves.[12] The pressure at maximum flow during the urodynamic investigation ($P_{det}Qmax$) was recorded. Correction for flow artifacts was performed when necessary. URA was determined by fitting the pressure-flow plot at the point of maximum flow (at $P_{det}Qmax$). URA was used to classify patients on a continuous, one-parameter scale of obstruction.[13] We also added a nonparametric analysis of obstruction with clinical classes according to the linear PURR (L-PURR) pressure-flow nomogram.[14] The linear PURR was determined by drawing a straight line between the $P_{det}Qmax$ and the $Pvoid_{min}$ points on the pressure-flow curve. The position of this line defined the outlet condition in a simple way and allowed classification of the severity of BOO. The following urodynamic variables were analyzed from free flowmetry: free Qmax; free voided volume; residual volume after free flowmetry and free voided percentage. Bladder capacity was analyzed from cystometry. Finally, the following were analyzed from pressure-flow study: maximum flow during urodynamic investigation (urod Qmax); $P_{det}Qmax$; $Pvoid_{min}$; A_{theo}; URA; residual volume after urodynamic pressure-flow study (urod residual volume) and voided percentage during pressure-flow study (urod voided percentage) for the whole group of patients and for subgroups of patients who were categorised as patients with BOO (L-

PURR of 3 or more) and patients categorised as patients without BOO (L-PURR less than 3).[15]

All statistical tests were two-sided and carried out at the 5% significance level. For numerical variables (such as symptom scores, quality of life scores, free flow parameters and urodynamic parameters) within-treatment changes were assessed using the paired t-test or the Wilcoxon matched-pairs signed-ranks test; between-treatment group changes using the t-test for independent samples or the Mann-Whitney U-test. The number of patients with an increase of voided volume of 50 ml or greater and with an improvement of Qmax of 10% or more from baseline in the groups with and without BOO were compared using the chi-square test.

Results

From september 1992 to october 1994, 97 patients started treatment with terazosin. The baseline characteristics of 97 patients, and for subgroups with and without BOO, who were included in the study are indicated in table 1. This table indicates that patients without BOO had, in addition to the significantly different urodynamic variables, a significant higher free Qmax and a significant higher free voided percentage.

Twenty-eight (29%) patients stopped terazosin treatment before the evaluation at month 6 because of side-effects (n = 13), no response to therapy (n = 12), or symptoms improving "spontaneously" (n = 3). The most frequent treatment-related side effects were mild headache, dizziness and asthenia. Usually, these side effects were mild and transient. Of the 13 patients who experienced side effects, 9 stopped treatment because of treatment-related side effects: dizziness (n = 2), asthenia (n = 4), palpitations (n = 1), peripheral edema (n = 1) and paraesthesia (n = 1). Dyspnea (n = 2), cardiac arrhythmia (n = 1), and visual disturbances (n = 1) were the reasons why the 4 other patients who experienced side effects stopped treatment; these events were not considered to be treatment related. Nine other patients were not available at 6 months because they were lost to follow-up (n = 4) or they refused their second clinical and urodynamic pressure-flow study evaluation (n = 5). Sixty patients, of whom 30 (50%) were classified as patients with BOO, were evaluated clinically and urodynamically before and after 6 months (median 28, range 17-45 weeks) of treatment.

The mean variables listed in table 1 were compared between the group that continued taking terazosin for 6 months and the group that stopped taking terazosin before 6 months. Patients who stopped terazosin

Table 1. *Mean baseline characteristics of 97 patients included in the study (standard deviation in parentheses). P-value indicates the significance of the comparison between the baseline characteristics between the groups with (L-PURR ≥ 3) and without (L-PURR < 3) BOO. Legend see chapter 6, table 1.*

	Whole group (n=97)	Patients with L-PURR < 3 (n=53)	Patients with L-PURR ≥ 3 (n=44)	p-value
Age (years)	62 (9)	61 (9)	63 (8)	0.31
PSA (ng/ml)	3.8 (3.8)	3.4 (3.5)	4.5 (4.1)	0.29
Prostate volume (cc)	38 (18)	34 (16)	42 (20)	0.06
total I-PSS	19.1 (5.9)	18.9 (5.8)	19.8 (5.8)	0.47
I-PSS QoL score	4.1 (1.2)	4.0 (1.2)	4.2 (1.2)	0.70
Free voided vol. (ml)	265 (136)	296 (154)	231 (100)	0.06
Free Qmax (ml/s)	10.5 (5.5)	11.6 (6.5)	9.0 (3.7)	<0.01
Free residual vol. (ml)	73 (120)	58 (86)	94 (154)	0.06
Free voided perc. (%)	81 (18)	85 (15)	77 (20)	0.02
Bladder capacity (ml)	424 (134)	437 (144)	400 (118)	0.28
Urod. Qmax (ml/s)	7.7 (4.1)	9.4 (4.5)	5.5 (2.0)	< 0.01
Urod. resid. vol. (ml)	113 (157)	79 (146)	142 (147)	< 0.01
Urod.void.perc. (%)	77 (28)	85 (25)	69 (26)	< 0.01
P_{det}Qmax(cm water)	57.5 (29.8)	39.8 (16.2)	80.5 (27.6)	< 0.01
$Pvoid_{min}$ (cm water)	29.1 (18.1)	18.4 (9.2)	42.8 (17.7)	< 0.01
A_{theo} (mm^2)	3.7 (2.7)	4.9 (3.1)	2.1 (0.8)	< 0.01
URA (cm water)	35.2 (19.3)	22.5 (7.7)	51.7 (17.3)	< 0.01
L-PURR	2.4 (1.5)	1.3 (0.7)	3.9 (0.9)	< 0.01

before 6 months were statistically significantly younger (mean age ± sd: 58 ± 9 years) when compared with patients who continued taking terazosin up to 6 months (64 ± 8 years, $p < 0.01$). The mean bladder capacity in those who discontinued terazosin was higher (458 ± 125 ml) when compared with those who continued treatment up to 6 months (403 ± 136 ml) ($p = 0.03$). When comparing the mean $Pvoid_{min}$ (23.3 ± 15 versus 32.3 ± 18.8 cm water; $p = 0.01$), the mean URA (29.3 ± 14.1 versus 38.6 ± 21.1 cm water; $p = 0.04$) and the mean L-PURR category (1.9 ± 1.4 versus 2.7 ± 1.5; $p = 0.02$) between those who stopped terazosin treatment and those who continued it for 6 months, respectively, the mean values of those who stopped were significantly smaller, indicating that patients without BOO had a higher likelihood of stopping terazosin for various reasons before month 6.

Table 2 outlines the mean symptom scores and mean urodynamic variables at baseline and after 6 months of treatment of the 60 patients who completed terazosin treatment for 6 months, the patients are divided into two subgroups, those with and without BOO. Also indicated in this table is the comparison of the changes in these variables between the groups with and without BOO. Mean total I-PSS improved significantly in both groups: from 19.7 to 10.6 in the group without BOO and from 20.1 to 11.1 in the group with BOO (for both groups, $p < 0.01$). The mean I-PSS quality of life score improved significantly in both groups: from 4.1 to 2.0 in the group without BOO and from 4.1 to 2.3 in the group with BOO (for both groups, $p < 0.01$). The mean symptom and quality of life related changes between the groups without and with BOO were not significantly different ($p = 0.89$ and $p = 0.85$, respectively). In patients without BOO, mean free Qmax improved significantly by 4.4 ml/s ($p < 0.01$), mean free voided volume increased by 24 ml ($p = 0.52$), and mean free residual volume did not change significantly ($p = 0.24$). In the patients with BOO, mean free Qmax improved significantly by 1.6 ml/s ($p = 0.04$), mean free voided volume decreased by 32 ml ($p = 0.15$) and mean free residual volume decreased significantly from 110 ml to 59 ml ($p = 0.03$). The mean change of free Qmax was significantly higher in the group without BOO when compared with the group with BOO ($p = 0.01$). This could have been related to an increase of voided volume of 24 ml in the group without BOO and a decrease of voided volume of 32 ml in the group with BOO. The statistical significant difference in the change of free Qmax between the groups with and without BOO was evaluated further. Small improvements in free Qmax (10 % or more from baseline) were found significantly more frequently in patients without BOO (77%) than in patients with BOO (48%) ($p = 0.02$). This higher number of patients with a small improvement of free Qmax could be related with an increase in free

Table 2. *Mean characteristics, at baseline and after 6 months of terazosin treatment, for the 60 patients who completed the second urodynamic evaluation, divided into subgroups of patients, with and without BOO. P-values in the columns regarding patients with and without BOO indicate the significance of the comparison of baseline versus month 6 within groups. P-value* between groups indicates the significance level of the comparison of the changes in the variables from baseline to month 6 between the groups with and without BOO. Legend see chapter 6, table 1.*

	Patients without BOO (L-PURR < 3) n = 30	Patients with BOO (L-PURR ≥ 3) n = 30	p-value*
total I-PSS	Baseline: 19.7 (6.4) Month 6: 10.6 (6.7) Change: 9.5 (7.1) p-value: < 0.01	Baseline: 20.1 (5.8) Month 6: 11.1 (5.7) Change: 9.7 (7.0) p-value: < 0.01	0.89
I-PSS QoL score	Baseline: 4.1 (1.2) Month 6: 2.0 (1.3) Change: 2.0 (1.2) p-value: < 0.01	Baseline: 4.1 (1.1) Month 6: 2.3 (1.4) Change: 1.9 (1.8) p-value: < 0.01	0.85
Free voided vol. (ml)	Baseline: 286 (163) Month 6: 311 (173) Change: 24 (191) p-value: 0.52	Baseline: 219 (99) Month 6: 189 (70) Change: 32 (111) p-value: 0.15	0.17
Free Qmax (ml/s)	Baseline: 11.4 (8.2) Month 6: 15.9 (8.2) Change: 4.4 (4.7) p-value: < 0.01	Baseline: 8.3 (2.7) Month 6: 9.9 (3.5) Change: 1.6 (3.4) p-value: 0.04	0.01
Free resid. vol. (ml)	Baseline: 59 (99) Month 6: 45 (129) Change: 11 (63) p-value: 0.24	Baseline: 110 (177) Month 6: 59 (85) Change: 53 (176) p-value: 0.03	0.23
Free void. perc. (%)	Baseline: 85 (14) Month 6: 91 (14) Change: 6 (15) p-value: 0.07	Baseline: 74 (22) Month 6: 82 (22) Change: 8 (22) p-value: 0.10	0.94

Table 2. (cont.)	Patients without BOO (L-PURR < 3) (n = 30)	Patients with BOO (L-PURR ≥ 3) (n = 30)	p-value*
Bladder capac. (ml)	Baseline: 420 (145) Month 6: 485 (192) Change: 70 (135) p-value: 0.01	Baseline: 388 (128) Month 6: 402 (127) Change: 14 (123) p-value: 0.93	0.06
Urod Qmax (ml/s)	Baseline: 9.7 (5.1) Month 6: 11.3 (5.6) Change: 1.6 (4.6) p-value: 0.02	Baseline: 5.3 (2.2) Month 6: 7.2 (3.5) Change: 1.9 (2.7) p-value: < 0.01	0.73
Urod resid. vol. (ml)	Baseline: 84 (151) Month 6: 72 (134) Change: 12 (161) p-value: 0.62	Baseline: 158 (158) Month 6: 95 (114) Change: 64 (85) p-value: < 0.01	0.12
Urod void. perc. (%)	Baseline: 84 (24) Month 6: 88 (22) Change: 4 (26) p-value: 0.35	Baseline: 65 (28) Month 6: 79 (22) Change: 14 (19) p-value: < 0.01	0.01
$P_{det}Qmax$(cm water)	Baseline: 42.5 (16.0) Month 6: 44.4 (19.4) Change: 1.9 (24.5) p-value: 0.70	Baseline: 81.6 (30.3) Month 6: 62 6 (29.4) Change: 19.0 (37.1) p-value: < 0.01	0.01
$P_{void_{max}}$ (cm water)	Baseline: 21.1 (9.8) Month 6: 19.1 (13.6) Change: 2.0 (15.6) p-value: 0.51	Baseline: 43.6 (19.1) Month 6: 29.8 (17.5) Change: 13.8 (22.3) p-value: < 0.01	0.02
A_{theo} (mm^2)	Baseline: 5.3 (3.7) Month 6: 5.8 (3.0) Change: 0.5 (3.3) p-value: 0.11	Baseline: 2.1 (0.8) Month 6: 3.3 (2.0) Change: 1.2 (1.6) p-value: < 0.01	0.57
URA (cm water)	Baseline: 23.7 (8.0) Month 6: 21.8 (10.6) Change: 1.9 (9.7) p-value: 0.07	Baseline: 53.5 (19.6) Month 6: 37.7 (17.3) Change: 15.8 (15.8) p-value: < 0.01	< 0.01
L-PURR	Baseline: 1.4 (0.7) Month 6: 1.2 (1.0) Change: 0.3 (1.0) p-value: 0.30	Baseline: 3.9 (1.0) Month 6: 2.8 (1.6) Change: 1.3 (1.2) p-value: < 0.01	< 0.01

voided volume in patients without BOO. Forty-seven percent of the patients without BOO had an increase of free voided volume of at least 50 ml, whereas of those in the group with BOO, only 14 % had an increase of free voided volume of 50 ml or greater ($p < 0.01$). When comparing the number of patients with larger improvements of free Qmax (30 or 50 % or more from baseline), there were no significant differences between the two groups. Sixty percent of the patients without BOO and 41 % of the patients with BOO had an increase of free Qmax of 30 % or more from baseline ($p = 0.15$) and 43 and 34 %, respectively, had an increase of free Qmax of 50 % or more from baseline ($p = 0.49$). The mean free voided percentage improved from 85 to 91% in the group without BOO and from 74 to 82 % in the group with BOO; changes within and between these groups were not significant.

The evaluation of the pressure-flow study variables urod Qmax, $P_{det}Qmax$, $Pvoid_{min}$, A_{theo}, URA and L-PURR in the patients with BOO revealed statistically significant improvements of all mean variables after 6 months of terazosin treatment (table 2). Significant changes of pressure-flow study variables in patients without BOO could not be detected, except for mean urod Qmax which improved significantly with 1.6 ml/s ($p = 0.02$). The mean bladder capacity in patients without BOO improved from 420 to 485 ml, which was statistically significant ($p = 0.01$). When evaluating the mean urodynamic changes between the groups with and without BOO, the changes for the variables urod voided percentage, $P_{det}Qmax$, $Pvoid_{min}$, URA and L-PURR were significantly higher in the group with BOO. In figure 1 the improvements of $P_{det}Qmax$ and total I-PSS are plotted for each patient who completed 6 months of treatment. The patients with BOO tended to have a larger urodynamical improvement when compared with patients without BOO. However, the symptomatic improvement is in the same range in both groups.

In table 3 the mean changes in symptoms, quality of life, free uroflow variables and urodynamic variables are compared between the group of patients who improved urodynamically (that is the group that had a L-PURR decrease of 1 point or more on the Schäfer nomogram) and the group who did not. Only the changes in the inter-related urodynamic variables $P_{det}Qmax$, $Pvoid_{min}$, URA and L-PURR were significantly higher in the group that improved urodynamically. The mean changes in symptoms, quality of life and free uroflow variables were not significantly different between those who improved urodynamically and those who did not.

After 6 months, 54 out of 93 patients (58%) continued terazosin treatment. The others were treated with trans urethral microwave thermotherapy ($n=4$), trans urethral laser ablation of the prostate ($n=9$),

other medication (n = 7) or unknown procedures of medications (n = 4) or they were followed with the watchful waiting policy (n = 15).

Discussion

During the World Health Organization international consultation on BPH in 1993, it was advised that, if obstruction is the endpoint of the study, pressure-flow studies before and after treatment should be used in the evaluation of new therapies.[16] Pressure-flow studies enable us to investigate the relationship between subjective efficacy of treatment and objective voiding parameters. Moreover, the use of pressure-flow studies may help to select patients for a given treatment; therefore, dropout and overtreatment percentages may decrease considerably.[11,17]

With respect to the efficacy of terazosin in the group with BOO, we showed that all mean values $P_{det}Qmax$; $Pvoid_{min}$; A_{theo}; and URA improved significantly after 6 months of treatment with terazosin. From a theoretical viewpoint, the mechanism of voiding using an $\alpha 1$-adrenergic blockader is changed toward better outlet distensibility during voiding; thus, it becomes more efficient. The first effect of a decrease in outlet obstruction is presumably a change in the balance of bladder outlet and contraction towards a lower pressure micturition with improved efficacy. Theoretically,

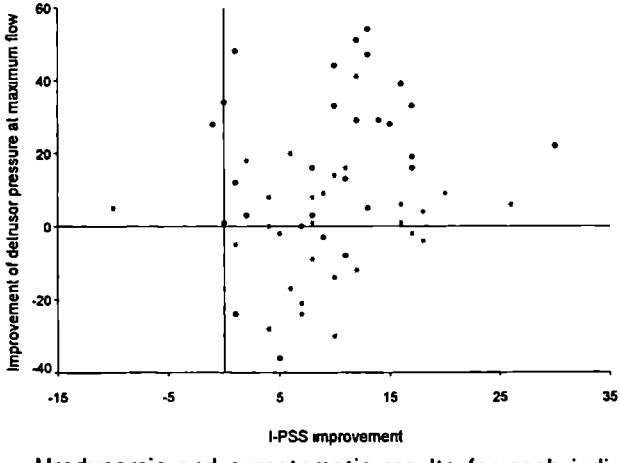

Figure 1. Urodynamic and symptomatic results for each individual patient who completed 6 months of terazosin therapy, labelled according to the BOO class, with [solid circle] (L-PURR ≥ 3) and without [asterisk] BOO (L-PURR < 3). Improvement of $P_{det}Qmax$ in cm. water on the Y-axis, defined as $P_{det}Qmax$ at baseline minus $P_{det}Qmax$ at month 6, and improvement of total I-PSS symptom score on the X-axis, defined as total I-PSS at baseline minus total I-PSS at month 6.

Table 3. *Comparison of the changes after terazosin treatment for 6 months between the group who improved urodynamically (L-PURR decrease of at least 1 point) and the group that did not (standard deviation in parentheses). Legend see chapter 6, table 1.*

	L-PURR decrease ≥ 1 (n = 35)	L-PURR decrease < 1 (n = 25)	p-value
total I-PSS	8.7 (5.2)	10.7 (8.7)	0.30
I-PSS QoL score	1.9 (1.5)	2.1 (1.5)	0.70
Free voided volume (ml)	3 (141)	-14 (181)	0.68
Free Qmax (ml/s)	3.1 (5.0)	3.1 (3.3)	0.98
Free residual volume (ml)	48 (164)	12 (71)	0.31
Free voided percentage (%)	9 (21)	4 (15)	0.94
Bladder capacity (ml)	29 (119)	60 (147)	0.33
Urod Qmax (ml/s)	2.4 (3.1)	0.9 (4.3)	0.13
Urod residual volume (ml)	55 (134)	13 (123)	0.21
Urod voided percentage (%)	12 (22)	5 (23)	0.43
$P_{det}Qmax$ (cm water)	24.5 (26.7)	-13.8 (27.5)	< 0.01
$Pvoid_{min}$ (cm water)	17.1 (18.9)	-5.0 (13.3)	< 0.01
A_{theo} (mm^2)	1.1 (2.6)	0.5 (2.7)	0.48
URA (cm water)	17.2 (11.8)	-2.9 (9.7)	< 0.01
L-PURR	1.6 (0.8)	-0.3 (0.6)	< 0.01

the increase in Qmax might not be as high as may be expected, which may be partly attributed to a decrease in $P_{det}Qmax$. More efficient voiding can also be shown by lower post-void residual volumes, but this could not be demonstrated by our patients; they had a low mean residual volume of 59 ml with a high standard deviation of 99 ml. A significant larger A_{theo} together with a significant decrease of $Pvoid_{min}$ indicates that terazosin has relaxed the bladder outlet so that more efficient voiding can occur.

In the patients without BOO, statistically significant changes of urodynamic variables could not be shown, except for free Qmax, urod Qmax and bladder capacity. When evaluating the present study, we have to realize that this study is a non controlled one, so we have to be careful in drawing far-reaching conclusions with respect to efficacy. Exact quantification of the urodynamic effect of treatment is only possible with a double-blind placebo-controlled study. This is mainly due to a large placebo effect that exists in patients treated with an α1-blocker such as terazosin. In a large randomized, double blind study Roehrborn et al showed an 7.6

point improvement in symptom score in the terazosin-treated group, whereas in patients treated with a placebo, symptom score improved by only 3.7 points. The improvements in free Qmax were an increase of 2.2 ml/s in the terazosin-treated group and an increase of 0.8 ml/s in the placebo-treated group.[18]

At baseline, patients with BOO had a significant different voiding mechanism with lower voided percentages and lower maximum flow rates when compared with the group without BOO (table 1). Because terazosin treatment improves the obstruction classification, some patients will shift from the group with BOO to the group without BOO and this could result in a favourable improvement of free Qmax.

In the present study, dropout percentages were relatively higher than those reported in literature. Lepor reported that, of 494 patients enrolled in a 42-month, open-label, multicenter study of terazosin, 213 (43%) withdrew prematurely, 55 (11%) because of lack of effectiveness, 96 (19%) because of adverse events, and 62 (13%) because of administrative reasons.[6] It could be that the 38% dropout rate in the present study (37 from 97 patients dropped out the study before 6 months) is relatively higher because we offered patients with moderate symptoms or patients who are bothered by their symptoms the choice between an α1-blocker treatment or other minimally invasive therapies. With a wide variety of minimal invasive treatment options, patients and urologists may more easily change their original treatment decision, compared with a situation where, after α1-blocker treatment, the only options are watchful waiting or prostatectomy.

Patients without BOO were more prone to early dropout for various reasons when compared with patients with BOO. In patients with a L-PURR of 0 or 1, the poor urinary stream is caused by a hypo-active detrusor muscle. These patients benefit little from transurethral resection of the prostate.[11] It could be that the unobstructed patients are also less likely to benefit from α1-blockers. This may be consistent with the assumption that it is unlikely that the detrusor function is improved by these drugs.

Our study design may be criticized for lack of a placebo control group and for potential selection bias. However, the mean changes of peak flow rates and symptom scores observed in this open label study were comparable to the data from a randomized study.[19] Earlier studies have indicated that the expected improvement of mean free Qmax after 6 months of treatment with terazosin is between 2.4 and 3.1 ml/s.[8,9,18,19] In our study, the mean improvement of free Qmax in the total group of patients was 3.0 ml/s. One may question the clinical relevance of 3.0 ml/s improvement of free Qmax. This study indicates that, besides the

improved free Qmax, more variables may change after terazosin therapy. In the present study, unobstructed patients had a statistically significantly increased bladder capacity. Patients with BOO had a statistically significantly decreased residual volume. As a result of these changes, another micturition pattern may develop that could result in a significant improvement of the I-PSS, especially when taking into account that the questions of the I-PSS questionnaire are concerned with bladder emptying, frequency, intermittency, urgency, nocturia, weak stream and hesitancy. All of these symptoms may improve as a result of improved free Qmax, bladder capacity, or residual volume.

When comparing the changes after 6 months of therapy between the patients with and without BOO, the changes in symptoms and quality of life were not significantly different (table 2). An improvement of free voided volume of 50 ml or more occurred significantly more frequently in the group without BOO. A larger voided volume in the group without BOO could result in a higher number of patients with slight improvements in free Qmax. When comparing the free voided volumes with the free Qmax, using the Liverpool nomograms, it appeared that the values of the first voiding in the group without BOO - a voided volume of 286 ml and a free Qmax of 11.4 ml/s - correspond with the 5th percentile whereas the values of the second voiding - a voided volume of 311 ml and a free Qmax of 15.9 ml/s - correspond with the 17th percentile of the healthy males investigated.[20] For the group with BOO, the values of the flows correspond with the 5th and 10th percentile for the first and the second voiding, respectively. This indicates that, despite the different voided volumes, the free Qmax increases, probably as a result of therapy. When we evaluated the number of patients with greater improvements in free Qmax, there was no significant difference between groups with and without BOO, which demonstrates that, in our patients without BOO, statistically significant improvements in free Qmax were not confirmed by significant improvements of urodynamic variables. Significant changes in urodynamic variables were only shown in the group with BOO. This finding suggests that the way we analyze efficacy in most pharmacotherapy studies for BPH (that is, improvements in symptoms and small improvements of Qmax) does not depend on the urodynamic mechanism of action. Therefore, we cannot recommend the use of pressure-flow studies in the selection of patients for terazosin treatment in daily urological practice because the changes of symptoms and quality of life between the groups with and without BOO were not significantly different. Moreover, the number of patients with improvements of free uroflow of at least 30% appeared not to be significantly different between groups with and without BOO. Hence,

it seems more useful and certainly less expensive and less invasive to start α1-blocker therapy if, on clinical grounds, the urologist considers the patient to be a candidate for α1-blocker therapy and to continue therapy in those who are satisfied.

However, it is unknown what the long-lasting effect of BOO on the bladder is for patients who are satisfied with their treatment but who remain urodynamically obstructed. Do they have a higher likelihood of developing complications on the long term, such as obstructive nephropathy, urinary retention, infection, bleeding, bladder stones or other complications that adversely affect their well-being ? Is there a difference in the probability of developing complications when compared with patients without BOO ? Further follow up and more prospective, well-controlled investigations are necessary to provide the still lacking information on the long-lasting effects and complications of pharmacological treatment.

Conclusions

We have shown that a stratified analysis, based on the urodynamic classification of BOO, provides insight into the working mechanism of terazosin in patients with and without BOO. Patients with a hypo-active detrusor muscle may be more prone to dropout early when compared with patients who have a normal detrusor function. We also showed that after 6 months of terazosin treatment, the changes of symptoms and quality of life and the number of patients with improvements of free uroflow of 30 % or greater appeared not to be significantly different between the groups with and without BOO. Therefore, we cannot recommend the use of pressure-flow studies in daily urological practice if, on clinical grounds, the urologist considers the patient to be a candidate for α1-blocker therapy. It seems more useful and certainly less expensive and less invasive, to start terazosin therapy for patients and to stop therapy in those who are not satisfied. In the dissatisfied patients, pressure-flow studies could be of help in selecting patients for more invasive treatments. In patients who are satisfied with their treatment, terazosin could be continued. However, as the long-term complications of pharmacological treatment in patients with bladder outlet obstruction are not well known, we recommend to follow up these patients on a regular basis.

References

1 Yalla SV, Sullivan MP, Lecamwasam HS, DuBeau CE, Vickers MA and Cravalho EG: Correlation of American Urological Association symptom index with obstructive and nonobstructive prostatism. J Urol **153:** 674, 1995.

2 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. Lancet **338:** 469, 1991.

3 Lepor H and Machi G: Comparison of the AUA symptom index in unselected males and females between 55 and 79 years of age. Urology **42:** 36, 1993.

4 McLoughlin J, Gill KP, Abel PD, Williams G: Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy Brit J Urol **66:** 303, 1990.

5 Jensen KME, Jorgensen JB, Mogensen P: Urodynamics in prostatism. II. Prognostic value of pressure-flow study combined with stop-flow test. Scand J Urol Nephrol **114:** 72, 1988.

6 Abrams PH, Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine Brit J Urol **51:** 129, 1979.

7 Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P and the BPH-ALF Group: Alfuzosin for treatment of benign prostatic hypertrophy. Lancet **337:** 1457, 1991.

8 Lepor H: Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. Urology **45:** 406, 1995.

9 Debruyne FMJ, Denis L, Arocena F, Kirk D, Kirby R, and the ITT group: Efficacy of terazosin in benign prostatic hyperplasia from a randomized withdrawal international terazosin trial (ITT). J Urol **153:** 273A, 1995.

10 Rollema HJ, van Mastrigt R: Objective analysis of prostatism : A clinical application of the computer program clim. Neurourol Urodyn **10:** 71, 1991.

11 Jensen KME: Clinical evaluation of routine urodynamic investigation in prostatism. Neurourol Urodynam **8:** 545, 1989.

12 Schäfer W: The contribution of the bladder outlet to the relation between pressure and flowrate during voiding, in Hinman F Jr. *Benign Prostatic Hypertrophy.* Berlin, Springer Verlag, 1983, pp 470-496.

13 Griffiths DJ, Mastrigt van R, Bosch R: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size in urethral obstruction due to benign prostatic hyperplasia. Neurourol Urodyn **8:** 17, 1989.

14 Schäfer W, Waterbär F, Langen PH, Deutz FJ: A simplified graphical procedure for detailed analysis of detrusor and outlet function during voiding Neurourol Urodyn **8:** 405, 1989.

15 Abrams P, Blaivas J, Nordling J, Griffiths DJ, Kondo A, Koyanagi T, Neal D, Schäfer W, Yalla S: The objective evaluation of bladder outflow obstruction, in Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K and Murphy G: *Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH).* Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 153-209.

16 Aso Y, Boccon-Gibod L, Brendler CB, Calais da Silva F, Cockett ATK, Fowler JE, Homma Y, Moriyama N, Okajima E, Richard F. Clinical research criteria, in

Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K and Murphy G: *Proceedings of the 2nd international consultation on benign prostatic hyperplasia (BPH).* Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 343-359.

17 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153:** 1526, 1995.

18 Roehrborn CG, Oesterling JE, Auerbach S, Kaplan SA, Lloyd LK, Milam DF, Padley RJ for the HYCAT investigator group: The Hytrin community assessment trial study: A one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. Urology **47:** 159, 1996.

19 Lepor H, Auerbach S, Puras-Baez A, Narayan P, Soloway M, Lowe F, Moon T, Leifer G, Madsen P: A randomized, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. J Urol **148:** 1467, 1992.

20 Haylen BT, Ashby D, Sutherst JR, Frazer MI, West CR: Maximum and average urine flow rates in normal male and female populations - the Liverpool nomograms. Brit J Urol **64:** 330, 1989.

Chapter 8

Urodynamic and symptomatic effects of various treatments in patients with lower urinary tract symptoms

Urodynamic and clinical effects of non-invasive and minimally invasive treatments in elderly males with lower urinary tract symptoms stratified according to the grade of obstruction.

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Abstract

Objectives: We investigated the symptomatic and urodynamic effects of several non-invasive and minimally invasive treatment modalities to quantify these effects and to compare subjective and objective results within groups with various degrees of obstruction.

Methods: In a prospective study at one centre, 487 patients who completed a full screening program including urodynamic investigation started treatment with: watchful waiting, terazosin, transurethral microwave thermotherapy or laser treatment of the prostate and were reevaluated symptomatically and urodynamically after 6 months of therapy. The symptomatic and urodynamic results of 87 patients from another centre who underwent a transurethral resection of the prostate and who had their second urodynamic evaluation 6 months postsurgery were also included.

Results: In patients without bladder outlet obstruction (BOO), improvement in maximum flow and symptom scores with little change in the degree of obstruction was most apparent whilst a decrease of detrusor pressure at maximum flow was observed mainly in patients with BOO. The urodynamic effect but not the symptomatic effect of treatments depended on the initial grade of BOO. Urodynamic changes were more marked in the minimally invasive treatment groups compared to the non-invasive treatment groups.

Conclusions: In symptomatic patients with BPH, symptomatic improvement in the short-term does not seem to depend on changes in urodynamic parameters. Future well controlled studies focussing on the durability of symptomatic and urodynamic effects will be needed to illustrate the relative potential of urodynamic and other clinical parameters to predict a favourable response to current and innovative treatments.

Introduction

Bladder outlet obstruction (BOO) in men due to benign prostatic hyperplasia (BPH), has presented a great clinical problem for many years. It has been estimated that BPH affects approximately 45 % of men at 60 years of age[1] and some estimate the prevalence to be approximately 80% by the age of 80.[2] The incidence and clinical significance of BPH have been increasingly difficult to evaluate, since the indications for therapeutic intervention have shifted from attempts to preserve life to those improving quality of life. Also, as we move into an era where alternatives to surgery are increasingly used to treat BPH, the time has come to consider which diagnostic criteria should be established before any pharmacological,

minimally invasive or invasive treatment can be recommended. To assess patient's complaints subjective parameters can be used such as symptom scores and/or objective parameters such as voiding studies. Most urologists agree that only patients with bladder outlet obstruction should undergo surgical intervention but nevertheless the decision for surgery is usually based primarily on the nature and severity of symptoms.

Despite an increasing number of reports on the relationships between symptoms and bladder outlet obstruction, the correlation between these entities remains unproved.[3] Also the correlation between subjective efficacy of treatment and objective (voiding parameters) efficacy is not clear.

We investigated symptomatic and urodynamic effects of several non-invasive and minimally invasive treatment modalities to quantify these effects and to compare the subjective and objective results of treatment within the various obstruction groups according to the linear passive urethral resistance relation (L-PURR) nomogram.[4]

Patients and methods

In 1992, a prospective study was initiated in our prostate centre to evaluate the outcome of therapy in patients with lower urinary tract symptoms (LUTS) treated with non-invasive or minimally invasive treatment modalities. All patients were evaluated at baseline by medical history, International Prostate Symptom Score (I-PSS), physical examination including digital rectal and ultrasonographic examination of the prostate, and free urinary flowmetry with subsequent ultrasonographic measurement of residual urinary volume. Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner and a multiplane 3-D rectal transducer (VRW 177AK). For free urinary flowmetry the Dantec Urodyn 1000 flowmeter was used. All patients were considered neurologically normal, based on history, symptoms and physical examination (no motor, sensory or reflex deficits). Patients in whom a prostatic carcinoma or other diseases beyond the prostate, possibly influencing their LUTS (e.g. urethral stricture or bladder neck contracture) could be expected were evaluated more extensively first e.g. by prostate biopsy or urethro-cystoscopy and excluded if these diseases were confirmed. Excluded were patients previously treated with transurethral (laser) resection of the prostate, transurethral microwave thermotherapy, or 5α-reductase inhibitors. Patients treated with α blockers within 4 weeks of the baseline pressure-flow study being performed were

also excluded.

Following this assessment patients were informed about the treatment options available at our prostate centre: watchful waiting (WW), pharmacological therapy, transurethral microwave thermotherapy (TUMT), laser therapy of the prostate and transurethral prostatectomy (TURP). Therapy was recommended depending on the severity of symptoms and the grade of bladder outlet obstruction (BOO). For example, when a urodynamic investigation showed no BOO and the patient experienced minimal symptoms, or he was not bothered by his symptoms, WW was recommended besides pharmacological treatment.[5] On the other hand, patients sometimes preferred WW even when BOO was confirmed. For those who were treated with terazosin treatment was started with an increasing dose, to a maximum of 10 mg per day at 6 weeks of treatment, administered at bed time.[6] When BOO was confirmed urodynamically, minimal invasive treatment modalities were recommended and the possibility of pharmacological treatment and WW was discussed with the patient whereafter the patient and the physician decided on the appropriate treatment. For those who were treated with TUMT the high energy 2.5 software was used.[7] In patients who were treated with laser prostatectomy a side fire laser technique was used.[8] The results of the few patients who underwent a TURP are not reported here.

Urodynamic pressure-flow studies were performed according to the procedure described before.[6] The following urodynamic variables were analyzed. From free flowmetry: free maximum flow (free Qmax); free voided volume; residual volume after free flowmetry. From pressure-flow study: detrusor pressure at maximum flow ($p_{det}Qmax$); urethral resistance factor (URA) and L-PURR obstruction category.[4]

I-PSS and cystometry with pressure-flow studies before and at 6 months after treatment were performed to evaluate symptomatic and urodynamic changes. Urinalysis and culture were negative at the time of pressure-flow studies.

Also the symptomatic and urodynamic results of 99 patients who underwent a TURP of whom 87 had their second conventional urodynamic evaluation 6 months postsurgery in the Freeman Hospital, Newcastle upon Tyne, United Kingdom were included. The results of patients from this centre have been described before.[9] The patients in this centre were selected differently. The indications for operation were symptoms of poor flow, hesitancy, dribbling micturition, or incomplete bladder emptying with or without additional symptoms of frequency, nocturia, urgency, or urge incontinence. All patients had a maximum urinary flow rate < 15 ml. per second when measured in the outpatient department. There were no

explicit urodynamic pressure-flow study selection criteria. The patients were evaluated at baseline by medical history, a standard symptom questionnaire based on that described by Frimodt-Møller et al,[10] physical examination including digital rectal examination of the prostate with estimation of the prostatic volume, and free urinary flowmetry with subsequent ultrasonographic measurement of residual urinary volume. All patients were considered neurologically normal, based on history, symptoms and physical examination. Patients were excluded if they were already on a waiting list (because those waiting for some time might not have been representative), if they had an acute urinary retention or if they had clinically apparent prostatic cancer.

Descriptive statistics were used to give an overview of the reported symptomatic and urodynamic changes after (starting) treatment for subgroups of patients who were categorised as patients without BOO (L-PURR $\leq$ 1) patients categorised as moderate BOO (L-PURR = 2,3) and patients categorised as patients with severe BOO (L-PURR $\geq$ 4). Within-treatment changes (before and 6 months after treatment comparison) were assessed using the Wilcoxon matched-pairs signed-ranks test. Differences in medians for the changes across the obstruction categories within treatment groups were tested with the Kruskal Wallis One Way ANOVA test.

Approval for the studies was obtained locally from the Newcastle District Ethical Committee as well as from the Medical Ethical Committee of the University Hospital of Nijmegen.

Results

From January 1992 to November 1995, 1015 new patients with lower urinary tract symptoms and benign prostatic hyperplasia were referred to the Nijmegen clinic for evaluation: 25 % were treated with transurethral thermotherapy, 20 % were treated surgically (laser, transurethral or open prostatectomy, bladder neck-incision), 30 % received medication (α1 blockers or 5α-reductase inhibitors), 2 % were treated with intermittent or suprapubic catheterisation, and 23 % chose WW. For this analysis the results of the first consecutive 178 men who were followed with WW, 97 men who were treated with terazosin, 180 men who were treated with TUMT, 114 men who were treated with laser therapy and 99 men from the Freeman Hospital who were treated with TURP were taken into account. In the total population, 27 % dropped out the study before the second investigation at 6 months. The main reason was that they were not available for evaluation because they refused the second urodynamic

and clinical investigation. A total of 487 men was investigated clinically and urodynamically before and 6 months after (the start of) treatment; 121 men were followed with WW,[5] 60 men received terazosin,[6] 136 men underwent TUMT, 83 men were treated with laser prostatectomy and 87 had a TURP.

In table 1 the baseline characteristics of the studied population are indicated across the various obstruction groups investigated. Table 2 presents the changes of the variables 6 months after (starting) therapy.

As indicated in table 2 and figure 1, in *patients without BOO (L-PURR = 0,1)*, the changes in $p_{det}Qmax$ after therapy were minimal and below the suggested clinical relevant cut-off point of 15 cm. water.[11] The improvements in free maximum flow were minimal (between 3 and 4 ml./s.) in the terazosin, the TUMT and TURP treated group. In the WW group, symptom scores improved significantly at 6 months (intragroup $p < 0.01$) but the magnitude of improvement was not clinically relevant. In the terazosin, TUMT and TURP treated group, symptom scores at 6 months improved statistically significantly (intragroup $p < 0.01$) with a median of 47 to 57 %.

In *patients with moderate BOO (L-PURR = 2,3)*, $p_{det}Qmax$ decreased slightly (< 10 cm. water) after WW and terazosin, and decreased significantly (> 15 cm. water) in the TUMT, the laser and the TURP treated group. Free maximum flow improved in all but the WW group, particularly after laser and TURP (> 8 ml./s.). In all groups particularly in the terazosin, TUMT, laser and TURP treated group, symptom scores at 6 months improved significantly (intragroup $p < 0.01$).

In *patients with severe BOO (L-PURR ≥ 4)*, $p_{det}Qmax$ decreased statistically significantly (intragroup $p < 0.01$) in all groups. In the WW group, the improvement was close to the suggested clinically relevant cut-off point of 15 cm. water. Qmax improved significantly except in the WW and terazosin treated group. At 6 months, symptom scores remained stable in the WW group and improved significantly (intragroup $p < 0.01$) in the other treatment groups.

The urodynamic effects of the specific therapies are indicated in figure 1. Evidently, patients with severe obstruction after TURP moved into the unobstructed area on the Abrams-Griffiths nomogram. The changes following the non-invasive and minimally invasive treatments were less clear.

Table 2 indicates that stratification based on the L-PURR nomogram according to Schäfer was able to predict the interrelated urodynamic outcome of therapy (figure 1a-c) but not the symptomatic outcome of therapy. Also this stratification did not seem to predict the outcome of free flow. An exception was the severe obstruction group treated with

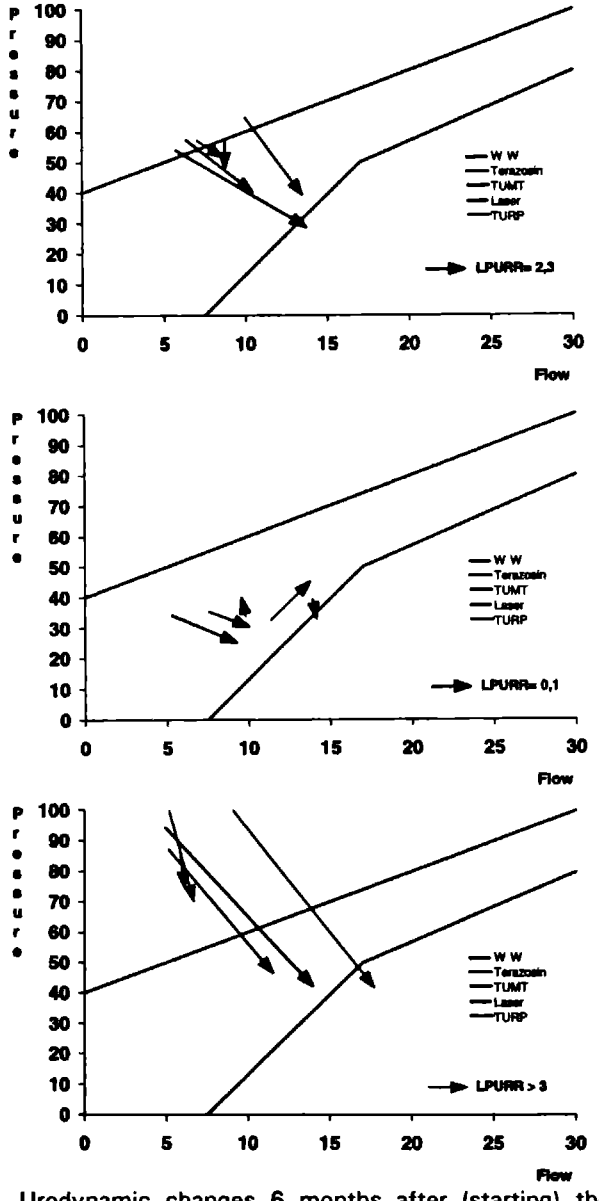

Figure 1. Urodynamic changes 6 months after (starting) therapy for patients who were initially unobstructed (L-PURR ≤ 1; figure 1a), who had moderate obstruction (L-PURR = 2,3; figure 1b) and for those who had severe bladder outlet obstruction (L-PURR ≥ 4; figure 1c). The basis of the arrow represents the baseline $p_{det}Qmax$ (Y-axis) at maximum flow during urodynamic investigation (X-axis). The top of the arrow represents this situation 6 months after (starting) treatment.

Table 1. *Mean ± standard deviation and median (ranges) [for symptomscores and L-PURR category] baseline characteristics of the studied population across the various obstruction groups investigated.*

BASELINE	n	Age (years)	Prostate Volume (ml)	Total Symptom Score	Free Voided Vol. (ml)	Free Qmax (ml/s)	Free Res.Vol. (ml)	p_{det}Qmax (cm water)	URA (cm water)	L-PURR
Watchful Waiting										
L-PURR= 0,1	57	66±8	37±14	12 (1-31)	331±149	14.2±5.4	40±59	32.7±12.5	18.1±4.6	1 (0-1)
L-PURR= 2,3	42	62±8	37±12	14 (3-28)	334±202	13.4±4.3	46±54	55.8±14.4	29.6±5.7	2 (2-3)
L-PURR ≥ 4	22	64±8	45±20	13 (6-33)	237±118	10.0±3.7	62±89	86.4±18.9	51.4±9.8	4 (4-5)
Terazosin										
L-PURR= 0,1	13	63±7	34±9	20 (15-17)	354±172	14.2±11.2	70±141	30.7±11.2	17.0±5.5	1 (0-1)
L-PURR= 2,3	30	64±8	41±20	17 (6 -33)	232±123	8.9±3.6	90±180	54.4±11.4	33.6±8.0	2 (2-3)
L-PURR ≥ 4	17	65±9	46±25	23 (12-33)	213±100	8.3±2.9	85±57	99.5±29.0	63.8±20.2	4 (4-6)
TUMT										
L-PURR= 0,1	21	65±7	47±20	15 (7-32)	246±140	9.5±2.8	53±82	33.0±8.8	22.5±4.4	1 (0-1)
L-PURR= 2,3	57	66±9	52±17	19 (8-33)	244±128	10.4±2.8	65±72	56.0±12.3	35.5±6.2	2 (2-3)
L-PURR ≥ 4	58	68±8	70±29	17 (6-33)	188±104	8.7±3.3	86±94	86.4±14.8	56.7±12.8	4 (4-6)
laser										
L-PURR= 0,1	2	60±6	38±18	19 (16-22)	282±124	9.8±1.1	45±38	32.5±9.2	24.5±0.7	1 (1)
L-PURR= 2,3	34	66±7	42±15	21 (12-35)	220±102	8.1±1.1	68±84	54.0±9.6	36.2±6.1	2 (2-3)
L-PURR ≥ 4	47	64±7	50±16	21 (11-33)	182±95	7.8±3.2	107±88	94.2±23.6	61.6±16.8	4 (4-6)
TURP			*	**						
L-PURR= 0,1	7	70±9	*28±19*	*5 (6-12)*	180±48	10.5±5.3	71±76	38.3±8.6	17.9±2.6	1 (1)
L-PURR= 2,3	36	69±8	*28±10*	*9 (0-14)*	207±141	9.9±5.7	93±152	64.3±11.6	30.8±4.7	3 (2-3)
L-PURR ≥ 4	44	68±8	*34±13*	*9 (2-16)*	172±128	8.8±6.4	138±157	107.9±31.2	47.8±14.1	4 (4-6)

* Prostatic volume in the TURP group was estimated at digital examination of the prostate. In the other groups it was measured ultrasonographically.

** Symptom questionnaire in TURP group was based on that described by Frimodt-Møller et al.[10] In the other groups the I-PSS was used.

Table 2. *Mean ± standard deviation and median (ranges) [symptomscores and L-PURR category] changes of the variables 6 months after (starting) therapy of the studied population across the various obstruction groups. P-values indicate the comparison of the changes within treatment groups across the various obstruction groups (Kruskal Wallis One Way ANOVA test). Underlined are the significant changes ($p < 0.05$) within treatment groups stratified according to the grade of obstruction using the Wilcoxon matched-pairs signed-ranks test.*

CHANGE	n	Symptom Score	Symptom Score (%)	Free Void.Vol. (ml)	Free Qmax (ml/s)	Free Res.Vol. (ml)	p_{det}Qmax (cm water)	URA (cm water)	L-PURR
Watchful Waiting		**p = 0.23**	**p = 0.25**	**p = 0.96**	**p = 0.67**	**p = 0.79**	**p < 0.0001**	**p < 0.0001**	**p < 0.0001**
L-PURR = 0,1	57	-3 (-19/16)	-25 (-88/533)	-50 ± 170	-1.2 ± 4.8	-10 ± 57	5.0 ± 19.9	2.7 ± 7.8	0 (-1/3)
L-PURR = 2,3	42	-3 (-14/6)	-25 (-77/86)	-81 ± 223	-1.0 ± 4.5	-2 ± 61	-9.9 ± 17.5	-3.2 ± 9.9	0 (-3/2)
L-PURR ≥ 4	22	0 (-10/7)	0 (-77/100)	-61 ± 139	-0.4 ± 4.1	-30 ± 92	-14.9 ± 22.9	-6.7 ± 10.5	-1 (-2/0)
Terazosin		**p = 0.72**	**p = 0.70**	**p = 0.73**	**p < 0.01**	**p = 0.88**	**p < 0.001**	**p < 0.0001**	**p < 0.001**
L-PURR = 0,1	13	-8 (-18/10)	-47 (-85/59)	30 ± 214	4.1 ± 3.7	0 ± 75	12.9 ± 24.0	2.2 ± 10.1	0 (-1/2)
L-PURR = 2,3	30	-9 (-26/02)	-56 (-90/0)	-5 ± 152	4.1 ± 4.8	-58 ± 173	-5.5 ± 23.5	-6.6 ± 10.6	-1 (-3/2)
L-PURR ≥ 4	17	-12 (-30/1)	-53 (-91/6)	-30 ± 116	0.3 ± 2.3	-12 ± 65	-30.4 ± 40.1	-21.1 ± 16.1	-1 (-4/1)
TUMT		**p = 0.40**	**p = 0.13**	**p = 0.40**	**p < 0.001**	**p = 0.86**	**p < 0.0001**	**p < 0.0001**	**p < 0.0001**
L-PURR = 0,1	21	-8 (-25/10)	-57 (-100/100)	105 ± 176	3.9 ± 5.4	-47 ± 74	-5.2 ± 17.3	-4.8 ± 7.9	0 (-1/2)
L-PURR = 2,3	57	-9 (-24/12)	-49 (-100/63)	52 ± 184	2.3 ± 4.9	-32 ± 108	-17.9 ± 16.7	-12.6 ± 11.4	-1 (-3/1)
L-PURR ≥ 4	58	-10 (-29/4)	-60 (-100/50)	78 ± 125	6.6 ± 7.0	-43 ± 125	-42.0 ± 22.8	-31.1 ± 17.2	-3 (-5/0)
laser		**p = 0.89**	**p = 0.17**	**p = 0.47**	**p = 0.90**	**p < 0.01**	**p < 0.0001**	**p < 0.0001**	**p < 0.001**
L-PURR = 0,1	2	-16 (-16) @	-100 (-100) @	0 ± 337	12.6 ± 2.0	-45 ± 38	-9.5 ± 20.5	-9.0 ± 8.5	-1 (-1/0)
L-PURR = 2,3	34	-15 (-29/-6)	-73 (-100/-35)	148 ± 165	12.1 ± 5.4	-42 ± 71	-25.9 ± 13.4	-21.4 ± 8.2	-2 (-3/0)
L-PURR ≥ 4	47	-17 (-30/9)	-81 (-100/53)	173 ± 156	12.9 ± 6.3	-100 ± 88	-55.0 ± 19.3	-42.8 ± 17.4	-3 (-6/-1)
TURP **		**p = 0.11**	**p = 0.22**	**p = 0.89**	**p = 0.38**	**p = 0.07**	**p < 0.0001**	**p < 0.0001**	**p < 0.0001**
L-PURR = 0,1	7	-3 (-8/1)	-50 (-100/11)	94 ± 87	3.0 ± 2.9	-42 ± 47	-4.7 ± 11.8	-1.1 ± 3.2	0 (-1/1)
L-PURR = 2,3	36	-6 (-13/4)	-75 (-100/150)	82 ± 175	8.8 ± 9.9	-61 ± 101	-21.7 ± 17.6	-12.3 ± 8.3	-1 (-3/1)
L-PURR ≥ 4	44	-7 (-14/3)	-80 (-100/60)	68 ± 146	9.4 ± 10.8	-121 ± 150	-69.8 ± 25.1	-31.5 ± 15.1	-4 (-6/-2)

** Symptom questionnaire in TURP group was based on that described by Frimodt-Møller et al.[10] In the other groups the I-PSS was used.
@ There was 1 patient who completed the I-PSS at 6 months post-treatment.

terazosin which, despite statistically significant improvements of symptoms and $p_{det}Qmax$ did not seem to benefit with regard to free maximum flow. Also in the TUMT treated groups with no or moderate obstruction the change in free maximum flow was significantly lower although the improvement in symptoms was considerable.

Discussion

The decision to treat and the selection of therapy are the result of the clinicians' diagnosis and the patients preference. In the past, physicians performed prostatectomy mainly for LUTS. Nowadays, prostatectomy is indicated most clearly in patients with recurrent urinary retention or evidence of obstructive uropathy in the upper urinary tract as a result of chronic urinary retention. Besides prostatectomy, physicians and symptomatic patients now have a variety of less invasive treatment modalities to choose from. One key issue is whether the physician should focus on relieving symptoms or relieving urodynamically proven obstruction. Unfortunately, LUTS, prostate size, free uroflowmetry parameters and the amount of post-void residual urine are associated with obstructive voiding but the correlation with the grade of obstruction is poor.[12-16] An imprecise relationship between symptoms and urodynamic findings was recently reported by Ezz el Din et al who, in one centre, evaluated the relationship between urodynamic findings and the International Prostate Symptom Score and specific questions in 803 patients. It was concluded that these methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the elderly male patient presenting with LUTS.[3]

The stratified analysis in the present study has demonstrated that the urodynamic effect of various treatments depends on the initial grade of BOO. In patients without BOO the increase in Qmax was most predominant, whilst a decrease of $p_{det}Qmax$ was principally observed in patients with BOO. Symptomatic changes of various therapies were not significantly different among the different obstruction classes. These observations are in line with previous reports. We have recently shown that urodynamics and symptom scores are unable to delineate which patients are at risk when left untreated.[5] Patients with severe obstruction on urodynamics did not worsen in the short-term; on the contrary, they were more likely to improve than to deteriorate urodynamically. Symptoms in this specific group of patients did not change significantly. On the other hand, patients without BOO became more obstructed urodynamically despite the fact that their symptoms improved significantly.[5] The present

study confirms the discrepancy between subjective and objective efficacy of treatment.

Our study design may be criticized for lack of control and potential selection bias. For an exact comparison and quantification of the urodynamic and symptomatic effects of specific treatments, a randomized controlled study design would be preferable. However, this was not possible in our situation. Many of the differences between non controlled studies can be explained by the selection of patients or by varying techniques of measurement. Our group of patients may be a specifically selected group of patients. With a wide variety of treatment options the group of patients who choose for a specific treatment in Nijmegen may be different when compared to the situation that the only treatment options are WW and prostatectomy as in the group of patients who underwent a TURP in Newcastle. Nevertheless, some information can be gleaned from this study.

The present study suggests that symptomatic efficacy in the short-term in the majority of studies for patients with LUTS suggestive for BOO does not seem to depend on decreasing obstruction. Hence other factors, such as morbidity of treatment, long-term outcome, patient preference and socio-economic aspects will determine the suitability of the alternatives to TURP, which remains the 'gold standard'. In patients within various obstruction classes, urodynamic improvement was greatest in the minimally invasive treatment groups compared to the non-invasive treatment groups. Specifically, the urodynamic effects in the laser treated group appeared to be larger than in the TUMT treated group and in the severely obstructed patients the highest urodynamic improvement was obtained with TURP (figure 1). The urodynamic effects may be related to the ablative power of the treatment which is obviously larger in TURP than in laser and TUMT respectively. Speculatively, in symptomatic patients with BOO, the durability of symptomatic improvement may be related to the urodynamic effects of treatment and thus with the ablative effect of treatment.

Since earlier studies have indicated that inclusion of pressure-flow data in the preoperative evaluation and patient selection for interventional therapies such as TURP and TUMT may improve the overall clinical results,[9,17,18] it is our opinion that symptoms alone should not be used as the main indication for deciding on the appropriate (minimal) invasive treatment options. Future well controlled studies focussing on the durability of symptomatic and urodynamic effects will be needed to illustrate the relative potential of symptoms, urodynamic and other clinical parameters to predict a favourable response to current and innovative treatments.

Conclusions

The present study indicated that the urodynamic effect of several treatments depended on the initial grade of BOO. Symptomatic improvement did not differ significantly among the different obstruction classes. Urodynamic changes were more marked in the minimally invasive treatment groups compared to the non-invasive treatment groups. The present study suggests that in symptomatic patients with BPH, symptomatic improvement in the short-term does not seem to depend on changes in urodynamic parameters.

References

1 Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. Lancet **338**: 469, 1991.

2 Berry SJ, Coffey DS, Walsh PC and Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol **132**: 474, 1984.

3 Ezz El Din K, Kiemeney LALM, de Wildt MJAM, Rosier PFWM, Debruyne FMJ, de la Rosette JJMCH: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol **156**: 1020, 1996.

4 Schäfer W, Waterbär F, Langen PH, Deutz FJ: A simplified graphical procedure for detailed analysis of detrusor and outlet function during voiding. Neurourol Urodyn **8**: 405, 1989.

5 Witjes WPJ, de Wildt MJAM, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Variability of clinical and pressure-flow study variables after 6 months of watchful waiting in patients with lower urinary tract symptoms and benign prostatic enlargement. J Urol **156**: 1026, 1996.

6 Witjes WPJ, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Urodynamic and clinical effects of terazosin therapy in symptomatic patients with and without bladder outlet obstruction. A stratified analysis. Urology, In Press, 1997.

7 de la Rosette JJMCH, de Wildt MJAM, Höfner K, Carter SStC, Debruyne FMJ, Tubaro A: Pressure-flow study analyses in patients treated with high energy thermotherapy. J Urol **156**: 1428, 1996.

8 de la Rosette JJMCH, te Slaa E, de Wildt MJAM, Debruyne FMJ: Experience with the Ultraline and Urolase laser fibers: is there any difference ? World J Urol **13**: 98, 1995.

9 Robertson AS, Griffiths CJ, Neal DE: Conventional urodynamics and ambulatory monitoring in the definition and management of bladder outflow obstruction. J Urol **155**: 506, 1996.

10 Frimodt-Møller PC, Jensen KM-E, Iversen P, Madsen PO, Bruskewitz RC: Analysis of presenting symptoms in prostatism. J Urol **132**: 272, 1984.

11 Rosier PFWM, de la Rosette JJMCH, Koldewijn EL, Debruyne FMJ, Wijkstra H: Variability of pressure-flow analysis parameters in repeated cystometry in

patients with benign prostatic hyperplasia. J Urol **153:** 1520, 1995.

12 Blaivas JG: Multichannel urodynamic studies in men with benign prostatic hyperplasia. Indications and interpretation. Urol Clin N Amer **17:** 543, 1990.

13 Rosier PFWM, Rollema HJ, van de Beek C, Janknegt RA: Diagnosis of "prostatism"; relation between symptoms and urodynamic evaluation of obstruction and bladder function. Neurourol Urodynam **11:** 399, 1992.

14 Tan HK, Höfner K, Kramer AEJL, Thonn WF, Grünewald V, Jonas U: Benign prostatic hypertrophy (BPH): prostatic size, obstruction parameters, detrusor contractility and their interdependence. Neurourol Urodynam **12:** 412, 1993.

15 Bosch JLHR, Kranse R, van Mastrigt R, Schröder FH: Reasons for the weak correlation between prostate volume and urethral resistance parameters in patients with prostatism. J Urol **153:** 689, 1995.

16 Rosier PFWM, de la Rosette JJMCH: Is there a correlation between prostate size and bladder-outlet obstruction ? World J Urol **13:** 9, 1995.

17 Rollema HJ, van Mastrigt R: Objective analysis of prostatism : A clinical application of the computer program clim. Neurourol Urodyn **10:** 71, 1991.

18 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F: The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153:** 1526, 1995.

Chapter 9

Summary and conclusions

The significance of micturition variables in the assessment of patients with lower urinary tract symptoms (LUTS) was investigated in chapter 2-5 of this thesis.

In ***chapter 2***, international differences in the reporting of LUTS and related bother was investigated in 1271 patients from 12 countries who participated in the International Continence Society - 'Benign Prostatic Hyperplasia' (ICS-'BPH') study. The International Prostate Symptom Score (I-PSS) questionnaire has been demonstrated to correlate strongly with the patients' degree of bother from their urinary condition. From the ICS-'BPH' questionnaire, it appeared that the most frequently reported symptoms are not necessarily the most bothersome. The most frequently reported symptoms were those associated with the voiding phase, the most bothersome symptoms were those associated with the storage phase or those associated with incontinence. Country of origin was significantly associated with half of the symptoms measured, including both storage and voiding symptoms of both high and low prevalences. Controlling for a range of potential confounding variables had very little effect on these relationships. There were not such marked differences for bothersomeness, although the symptoms where there were international differences were all voiding symptoms. The results of studies in particular countries, therefore, may not be generally applicable in other countries. In particular, it may be important to take into account different patterns of selection of patients and reporting of symptoms and bothersomeness in interpreting the results of studies using common questionnaires. It is likely that the use of symptom scores will conceal this variation, necessitating either the consideration of individual symptoms (as in the ICS-'BPH' questionnaire) or the development of country-specific scoring systems. An alternative would be to focus on bother, which appeared much less sensitive to international differences.

In ***chapter 3***, the relationship between a wide range of symptoms from the ICS-'BPH' questionnaire and the results of urodynamic pressure-flow studies was reported in 933 patients participating in the ICS-'BPH' study who had evaluable pressure-flow studies. It was confirmed that there was little or no correlation between a wide range of storage and voiding symptoms and the results of pressure-flow studies. Subjective and objective micturition variables measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with LUTS.

In ***chapter 4***, a study is reported in 150 patients who were subjected to a standardized screening program including I-PSS, transrectal ultrasound of the prostate with ultrasonographic measurement of the transition zone volume of the prostate and urodynamic investigation with

pressure-flow study. There were very small differences between the correlations of total prostate volume, transition zone volume and transition zone index and symptoms as well as free flow and pressure-flow variables. Obviously, symptoms and bladder outlet obstruction are mainly determined by other factors than prostate and, specifically, transition zone volume.

In ***chapter 5***, a computerized method of validation of uroflowcurves, developed for clinical research purposes, was described. For the validation process of this computerized method of uroflow validation, we used 90 randomly chosen flows with different types of artifacts from 35 patients out of 9 centres participating in a clinical trial with alfuzosin. These flows were scanned into a computer whereafter automated artifact detection and correction was performed according to preestablished rules implemented in the software. The results were compared with the manual artifact correction by three experts who used the same artifact detection and correction rules as implemented in the software. When comparing the results of the experts, a considerable interobserver variation was shown. The variability of the maximum flow values after computerized artifact correction was less than the variability of the maximum flow values reproduced by the flowmeter and also less than the variability of the manually corrected flows. This may lead to lower sample size requirements especially in studies where the primary objective is to assess a small (± 1 ml/s) difference in mean maximum flow between groups.

In ***chapter 5***, a new portable home-based uroflowmetry system was used to investigate variability and circadian changes of uroflow. The first manuscript introduces the portable home-based uroflowmetry system: P-flow®. A total of 67 patients used the home-based uroflowmeter and the results were compared with uroflowmetry in the out-patient department. There was a good correlation between the uroflow results obtained when voiding at home and at the out-patient department. The highest measured maximum flow and voided volume were obtained with the home-based uroflowmeter system. However, the mean of all consecutive home-based maximum flow and voided volume measurements were lower than those obtained by single-void uroflowmetry in the out-patient department. This was not surprising because the sole aim at the out-patient department was to have the bladder as full as possible, while at home the timing of micturition was related to other daily activities. It was concluded that home-based uroflowmetry provides reliable voiding results which are comparable with those obtained in the out-patient department. However, when multiple samples are available the problem arises which sample(s) should be used for the evaluation particularly if the reported circadian

changes are of clinical relevance.

These circadian changes of uroflow have been evaluated in the second manuscript dealing with the portable home-based uroflowmetry system. A total of 170 patients with lower urinary tract symptoms suggestive of bladder outlet obstruction used a home-based uroflowmeter and produced a total of 1670 correctly measured flows at home. These patients also underwent a screening program with free urinary flowmetry in the hospital and a urodynamic pressure-flow study. It appeared that, in all obstruction categories, the mean voided volume of the flow produced between midnight and 6 h a.m. was significantly greater compared with the flows produced in the afternoon and evening. The smallest mean voided volume at home is produced in the afternoon. Despite this significantly smaller voided volume in the afternoon, the maximum flow produced at home in the afternoon in moderately and severely obstructed patients was significantly greater than that produced in the morning. It was concluded that the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment, especially in obstructed patients.

In chapter 6-8, the impact of noninvasive, minimally invasive and invasive treatments on subjective and objective micturition variables was quantified and compared within groups with various degrees of bladder outlet obstruction (BOO).

In ***chapter 6***, the physiological variability of symptoms and pressure-flow study variables was assessed in 121 patients who underwent clinical and urodynamic pressure-flow study evaluation before and after a period of 6 months of watchful waiting. It was demonstrated that, after 6 months of watchful waiting, patients without BOO experienced statistically significant but slight symptomatic improvement. Symptoms of patients with obvious BOO did not improve significantly. From a clinical and diagnostic viewpoint, the reproducibility of mean pressure-flow study results after 6 months of watchful waiting was evident. However, there was an important intra-individual variability. Patients with extreme values at the initial pressure-flow study tended to experience regression towards the mean of the population at the second evaluation. Patients with obvious BOO showed a significant decrease in detrusor pressure at maximum flow of 14 cm. water, a significant decrease of urethral resistance factor of 7 cm. water and a significant decrease of 1 obstruction class on the linear passive urethral resistance relation nomogram, indicating less severe BOO. It was concluded that mean differences among therapy groups must be regarded critically, particularly when the reported differences are slight and possibly within their physiological variability. It was also concluded that due to the physiological variability caused by the dynamic component of

obstruction, any clinical trial evaluating a new treatment modality should include a control arm that allows quantification of this physiological variability.

Chapter 7 dealed with the results of terazosin treatment in patients with LUTS. The first manuscript describes the long-term efficacy and safety of terazosin in 427 symptomatic patients who started terazosin in the International Terazosin Trial (ITT), a clinical trial in which 33 centres in 13 countries enrolled patients with an initial total I-PSS of 12 or more. After a 2-week, no-treatment lead-in period and a 26-week, single-blind treatment period, patients responding to terazosin were randomly assigned to receive either terazosin or placebo for a 24-week, double-blind withdrawal period. During follow up, patients were evaluated with symptom scores and uroflowmetry at the out-patient department. During the single-blind period, symptoms, quality of life score and maximum flow improved significantly. During the double-blind withdrawal period, symptoms, quality of life score and maximum flow deteriorated significantly in the placebo group compared with the group that continued terazosin. The deterioration in the placebo group did not, however, return to baseline, suggesting that 1) there is variability in the evolution of LUTS (symptoms fluctuate over time and patients have a high chance to enter the trial when they experience a period with severe LUTS), 2) there is a continuing placebo effect, and 3) the full effect of withdrawal of terazosin takes longer than 24 weeks. Another more speculative suggestion could be that 6 months of α1-blockade might reduce the sensitivity of the α-adrenergic receptor.

The second manuscript described the group of patients participating in the ITT in the university hospital Nijmegen. Besides the follow up investigations as described before, these patients also underwent a urodynamic pressure-flow study at baseline and at week 26 of treatment. Terazosin treatment resulted in symptomatic relief and improved urinary flow in patients with and without BOO and in significant improvement in patients with urodynamically proven obstruction. Patients without urodynamically proven obstruction showed no significant urodynamic changes. Ironically, the group with the highest percentage of patients showing slight improvements in free flow and symptoms had no urodynamic obstruction. This finding suggested that the way we are used to analyze efficacy in the majority of pharmacotherapy studies for patients with LUTS (that is improvements in symptoms and maximum free urinary flow) is not entirely representative of the urodynamic mechanism of action.

The third manuscript described the results of treatment in 97 symptomatic patients treated with terazosin in the university hospital Nijmegen. Of the 97 patients who started with terazosin, 60 completed 6

months of treatment and were reevaluated with I-PSS, uroflowmetry and urodynamic investigation with pressure-flow study analysis. The clinical and urodynamic changes within and between the groups with and without BOO were evaluated. Patients with a hypo-active detrusor were more prone to early drop out. Overall, terazosin resulted in significant symptomatic relief (9 points on the I-PSS scale, $p < 0.01$) and a significant improvement of free urinary flow (3.0 ml/s; $p < 0.01$). In patients with BOO, a statistically significant improvement of all urodynamic obstruction variables ($p < 0.01$) was shown. In patients without BOO, a significant improvement of free urinary flow (4.4 ml/s; $p < 0.01$), a statistically significant improved bladder capacity (increase of 70 ml; $p = 0.01$) and no statistically significant changes in urodynamic obstruction variables ($p > 0.05$) were shown. When comparing the changes of symptoms ($p = 0.89$), quality of life ($p = 0.85$) and the number of patients with improvements of free uroflow $\geq$ 30 % ($p = 0.15$), there appeared to be no significant difference between the groups with and without BOO. It was concluded that although there is a statistically significant difference in urodynamic response to terazosin treatment between patients with and without BOO, we cannot recommend the use of pressure-flow studies in the selection of patients for terazosin treatment because the clinical results of treatment appeared not to be significantly different between patients with and without BOO. It seemed more useful and it would certainly be less expensive and less invasive to start $\alpha 1$ blocker therapy if, on clinical grounds, the urologist considers the patient to be a candidate for $\alpha 1$ blocker therapy and to continue therapy in those who respond.

In ***chapter 8***, the symptomatic and urodynamic effects of the noninvasive treatment modalities described in chapter 6 and 7 as well as the transurethral microwave thermotherapy (TUMT), transurethral laser ablation of the prostate and transurethral resection of the prostate (TURP) were quantified in a total of 574 patients who completed 6 months of treatment and were reevaluated with I-PSS, uroflowmetry and a urodynamic pressure-flow study at 6 months after (starting) treatment. The analysis was stratified according to the degree of obstruction and the subjective and objective changes after (starting) treatment were compared between obstruction groups. For each treatment modality, symptomatic improvement did not differ significantly among the different obstruction classes. Urodynamic changes were more marked in the minimally invasive treatment groups compared to the non-invasive treatment groups. Specifically, the urodynamic effects in the laser treated group appeared to be greater than in the TUMT treated group and in the severely obstructed patients the greatest urodynamic improvement was obtained with TURP. It was concluded that in patients with LUTS, independent from the treatment chosen, symptomatic improvement in the short-term does not seem to depend on changes in urodynamic parameters.

Chapter 10

Future perspectives

Lower urinary tract symptoms (LUTS) are common in men older than 50 years of age.[1] By the year 2000, more than 600 million of the elderly population will be over 60 years of age and two thirds of them will be living in the developed countries. This demographic shift has significant implications for the planning and delivery of services for men with LUTS in the coming decades. The observation that the prevalence of LUTS in the community is greater than the number of men who seek medical or surgical help[1,2] confirms that the perception of LUTS is a personal matter that could be dissimilar among men in different age groups and various environmental and socio-demographic circumstances. The high prevalence of undiagnosed and untreated LUTS in combination with the fact that the prevalence of LUTS in the aging community in the developed countries is likely to increase, suggests that costs related to the treatment of LUTS could escalate considerably as public awareness of the problem increases.

LUTS in the individual man can have diverse etiologies. They may originate from infravesical bladder outlet obstruction caused by the enlarged prostate gland, but also from motor or sensory abnormalities of detrusor and urethral function,[3] or even from changes in habits and lifestyle that commonly occur as men age.

Also the current treatment modalities for the individual man with LUTS are diverse. Transurethral resection of the prostate is no longer the sole treatment option available. Presently, watchful waiting and a variety of medical, minimally invasive and surgical approaches exist for the man with LUTS. With regard to medications, there are the α1-adrenergic antagonists (alfuzosin, doxazosin, tamsulosin and terazosin) and the 5-α-reductase inhibitors (finasteride). The minimally invasive procedures that are now available include transurethral incision of the prostate, laser ablation of the prostate, transurethral thermotherapy and there are a number of new approaches now under development and being investigated. The most commonly used surgical approaches today are transurethral resection of the prostate and transabdominal prostatectomy. Although the most invasive, these latter operations have the greatest efficacy.

The question now is how we will be able to further optimize the diagnostic evaluation so that the most optimal treatment for the individual man with LUTS can be selected. Before focusing on optimalisation of the diagnostic evaluation, we have to decide what are the most important aspects associated with the clinical condition of the man with LUTS we want to treat. Are we mainly interested in improving symptoms or should the aim of treatment be relieving urodynamically proven obstruction ?

In chapter 8 it was shown that the symptomatic change on the short term was not significantly different among groups with different

degrees of obstruction. From this observation one may conclude that if we are only interested in relieving symptoms on the short term, we do not have to perform a comprehensive evaluation including urodynamic investigation with pressure-flow analysis. It may be sufficient to exclude cancer and to inform the patient of the potential symptomatic benefits and side effects associated with the treatment options available. When the main aim of treatment is to relieve symptoms, a large placebo factor has to be taken into account.[4,5] When consulting the man with LUTS about the probability of symptomatic improvement, the practising urologist may use the guidelines published by the Agency for Health Care Policy and Research which indicate the median probabilities for symptomatic improvement following various treatments.[5] These guidelines suggest that transurethral resection of the prostate results in considerable higher symptomatic improvement (88 %, 95 confidence interval 75-96 %) than α1-andrenergic antagonists (74 %) and watchful waiting (42 %).[5] Other studies suggest that one quarter of men fail to improve symptomatically following a transurethral resection of the prostate[6,7] and this percentage may be greater when less invasive therapies are used.

Several studies have attempted to identify the individuals who are more likely to have poorer symptomatic outcomes than others. With symptoms alone it is not possible to identify these patients but other variables such as a small prostate volume, low detrusor pressures, bladder instability and urge incontinence are obviously associated with a poor outcome as a result of surgery.[6,7]

If the aim is to optimize the diagnostic evaluation so that the most optimal treatment for the individual can be selected, it is clear that taking into account symptoms only is not sufficient. We have to focus on relieving urodynamic proven bladder outlet obstruction. With the results of pressure-flow studies we are now able to identify patients who are at risk for a poor outcome after surgery and transurethral microwave thermotherapy of the prostate.[6-8] Furthermore, with urodynamic pressure-flow studies we may be able to predict the durability of symptomatic improvement (chapter 8) and failure rates may be reduced if only patients with bladder outlet obstruction are subjected to therapy.[9] The question arises whether we have to perform an invasive urodynamic pressure-flow study in every man with LUTS who needs therapy. The answer is probably no. With less invasive investigations, we may also be able to predict whether a man with LUTS has bladder outlet obstruction or not. Reynard et al indicated that the specificity and positive predictive value of maximum flow for predicting bladder outlet obstruction was significantly improved by multiple free-flow measurements in the out patient clinic.[10] If

the highest maximum flow after 3 voidings was less than 10 ml/s, the specificity and positive predictive values for bladder outlet obstruction were 90 and 94 % respectively. We agree with Reynard that multiple free-flow measurements are most efficient for an accurate assessment.[10] Home-based uroflowmetry in this respect is a more convenient tool than collecting flows at the out-patient clinic (chapter 5). Rosier et al in a retrospective study showed that with the help of a combination of objective noninvasive measurements (total prostate volume, maximum flow, post-void residual volume and voided volume), it was possible to distinguish between groups of patients with and without bladder outlet obstruction.[11] Whether a combination of objective noninvasive measurements is sensitive and specific enough to accurately predict the presence of bladder outlet obstruction in the individual patient needs to be confirmed.

Future analyses of studies such as the International Continence Society - 'Benign Prostatic Hyperplasia' study[12] may be able to provide vital information on the relative potential of urodynamic and other clinical parameters to predict a favourable response to current and innovative treatments.

References

1 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. The Lancet **338**: 469, 1991.

2 Sagnier PP, MacFarlane G, Teillac P, Botto H, Richard F, Boyle P: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. J Urol **153**: 669, 1995.

3 Schäfer W, Nopponey R, Rübben H and Lutzeyer W: The value of free flow rate and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

4 Isaacs JT: Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate **3**: 1, 1990.

5 McConnel JD, Barry MJ, Bruskewitz RC et al (Eds.): Benign Prostatic Hyperplasia: Diagnosis and Treatment. Clinical Practice Guideline. Rockville, Maryland: US Department of health and human services, Agency for Health Care Policy and Research, 1994.

6 Neal DE, Ramsden PD, Sharples L et al: Outcome of elective prostatectomy. BMJ **299**: 762, 1989.

7 George NJ, Feneley RC, Roberts JB: Identification of the poor risk patient with "prostatism" and detrusor failure. Brit J Urol **58**: 290, 1986.

8 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F. The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153**: 1526, 1995.

9 Abrams P, Blaivas J, Nordling J, Griffiths DJ, Jensen KM: The objective ealuation of bladder outlflow obstruction. In: Cockett ATK, Khoury S, Aso Y, Chatelain C, (Eds): Proceedings of the second international consultation on benign prostatic hyperplasia (BPH). Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 151-226.

10 Reynard JM, Peters TJ, Lim C, Abrams P: The value of multiple free-flow studies in men with lower urinary tract symptoms. Brit J Urol **77**: 813, 1996.

11 Rosier PFWM, de Wildt MJAM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Clinical diagnosis of bladder outlet obstruction in patients with benign prostatic enlargement and lower urinary tract symptoms: Development and urodynamic validation of a clinical prostate score for the objective diagnosis of bladder outlet obstruction. J Urol **155**: 1649, 1995.

12 Abrams P, Donovan J, van Kerrebroeck P, Nordling J, Schäfer W, Thuroff J, Neal D and the ICS-'BPH' study group: The ICS-'BPH' Study: background and design. Neurourol Urodyn **13**: 483, 1994.

Samenvatting en toekomstverwachtingen

Samenvatting

Het klinische belang en de plaats van subjectieve en objectieve mictie variabelen bij de diagnostiek van patiënten met lagere urinewegsymptomen wordt in hoofdstuk 2-5 beschreven.

In ***hoofdstuk 2*** worden internationale verschillen in de prevalentie van lagere urinewegsymptomen en gerelateerde hinder onderzocht door de gegevens van 1271 patiënten uit 12 landen die deelnamen aan de International Continence Society - 'Benign Prostatic Hyperplasia' (ICS-'BPH') studie te analyseren. Eerder onderzoek met de Internationale Prostaat Symptoom Score (I-PSS) vragenlijst had al aangetoond dat de ernst van de symptomen sterk correleert met de ernst van de symptoom gerelateerde hinder. Uit dit onderzoek met de ICS-'BPH' vragenlijst blijkt echter dat de meest frequent gerapporteerde symptomen niet persé als de meest hinderlijke worden ervaren. De meest frequent gerapporteerde symptomen bleken de symptomen te zijn geassocieerd met de ontledigingsfase van de blaas, de meest hinderlijke symptomen bleken de symptomen geassocieerd met de vullingsfase van de blaas en met incontinentie. Land van herkomst bleek significant geassocieerd met de prevalentie van de helft van de gemeten symptomen, geassocieerd met de vullingsfase en de ontledigingsfase van de blaas. Door middel van logistische regressie werd er nagegaan wat de invloed was van een reeks potentiële verstorende variabelen op de associatie van land van herkomst en de prevalentie van ieder symptoom en symptoom gerelateerde hinder. De invloed van deze potentiële verstorende variabelen bleek klein te zijn. In tegenstelling tot de associatie van land van herkomst en de prevalentie van symptomen bleek de associatie van land van herkomst met de symptoom gerelateerde hinder echter veel minder duidelijk te zijn. De weinige symptomen waarbij er een significante associatie was tussen land van herkomst en symptoom gerelateerde hinder waren symptomen gerelateerd aan de ontledigingsfase van de blaas. Geconcludeerd werd dat de resultaten van studies in bepaalde landen niet zondermeer geëxtrapoleerd kunnen worden naar andere landen. Bij de interpretatie van de resultaten van internationale studies waarbij algemene vragenlijsten worden gebruikt, is het van belang rekening te houden met de internationale verschillen in de selectie van patiënten en het melden van symptomen en gerelateerde hinder. Tevens is het waarschijnlijk dat het gebruik van symptoom scores (de som van de antwoorden op vragen die betrekking hebben op de ontledigingsfase en de vullingsfase en evt. ook incontinentie) deze variatie maskeert. Dit benadrukt het belang om individuele symptomen te beschouwen (zoals in de ICS-'BPH' vragenlijst) ofwel land-specifieke scoringssystemen te ontwikkelen. Een alternatief hiervoor zou kunnen zijn de analyse te concentreren op symptoom gerelateerde

hinder welke veel minder gevoelig bleek voor internationale verschillen.

In ***hoofdstuk 3*** wordt de relatie onderzocht tussen een groot aantal symptomen van de ICS-'BPH' vragenlijst en de resultaten van urodynamische druk-flow metingen door de gegevens van 933 patiënten met evalueerbare urodynamische studies die deelnamen aan de ICS-'BPH' studie te analyseren. Bevestigd werd dat er géén of een slechte correlatie bestaat tussen symptomen die geassocieerd zijn met de ontledigingsfase of de vullingsfase van de blaas en de resultaten van urodynamische studies. Subjectieve en objectieve mictie variabelen kwantificeren verschillende aspecten van de klinische conditie en moeten afzonderlijk beschouwd worden bij de diagnostiek en behandelingsindicatie van patiënten met lagere urineweg symptomen.

In ***hoofdstuk 4*** wordt een studie beschreven waarbij 150 patiënten een gestandaardiseerd onderzoekprogramma met de I-PSS vragenlijst, transrectaal echografisch onderzoek van de prostaat met meting van het volume van de transition zone van de prostaat en urodynamische druk-flow metingen, ondergingen. Er waren zeer kleine verschillen tussen de correlaties van totaal prostaat volume, het transition zone volume en de transition zone index enerzijds en symptomen, de resultaten van de vrije urinestraalmeting en de urodynamische druk-flow studies anderzijds. Deze correlaties waren indien zij statistisch significant waren nog maar matig. Kennelijk worden symptomen en blaasuitgangsobstructie voornamelijk bepaald door andere factoren dan het totale prostaat volume danwel het transition zone volume.

In ***hoofdstuk 5*** wordt ingegaan op de grote variabiliteit van vrije urinestraalmetingen en gezocht naar verklarende factoren hiervoor. In ***hoofdstuk 5.1*** wordt een gecomputeriseerde methode voor het automatisch detecteren en corrigeren van artefacten van vrije urinestraalmetingen gepresenteerd die ontwikkeld is voor klinische research doeleinden. Voor het proces van validatie werden 90 at random gekozen urinestraalmetingen met verschillende artefacten van 35 patiënten uit 9 verschillende centra die deelnamen aan een klinisch onderzoek met alfuzosine gebruikt. Deze urinestraalmetingen werden gescanned in de computer waarna automatische artefact detectie and correctie werd uitgevoerd volgens tevoren vastgestelde regels die geïmplementeerd waren in de software. De resultaten werden vergeleken met de handmatige artefact correctie door 3 experts die dezelfde artefact detectie en correctie regels gebruikten als die geïmplementeerd waren in de software. Bij de vergelijking van de resultaten tussen de 3 experts bleek er een belangrijke inter-expert variatie te bestaan. De variabiliteit van de maximale urinestraal waarden na automatische artefact correctie was minder dan de variabiliteit van de maximale

urinestraal waarden die direct afkomstig waren van de urinestraalmeter en tevens minder dan de variabiliteit van de - door de experts - handmatig gecorrigeerde urinestraalmetingen. Deze geringere variabiliteit kan resulteren in kleinere aantallen benodigde patiënten, vooral in studies waarbij het voornaamste doel is een klein (± 1 ml/s) verschil in de gemiddelde maximale urinestraal waarden tussen groepen aan te tonen.

In ***hoofdstuk 5.2 en 5.3*** wordt een nieuw systeem voor thuis-flowmetrie gebruikt om de variabiliteit en circadiane veranderingen van de kracht van de urinestraal in kaart te brengen. Het eerste manuscript (H 5.2) introduceert de draagbare thuis-flowmeter: P-flow®. 67 Patiënten gebruikten de thuis-flowmeter en de resultaten werden vergeleken met de resultaten zoals die op conventionele wijze verkregen waren: d.m.v. een urinestraalmeting m.b.v. een urinestraalmeter op de polikliniek. Er bleek een goede correlatie te bestaan tussen de resultaten die verkregen waren door gebruik van de thuis-flowmeter en de resultaten zoals die op conventionele wijze ter beschikking waren gekomen. De grootst gemeten kracht van de urinestraal en het grootste geplaste volume werden gemeten met de thuis-flowmeter. Echter, het gemiddelde van alle achtereenvolgende urinestraalmetingen was lager dan dat van de urinestraalmetingen in het ziekenhuis. Dit was niet verbazingwekkend want de patiënten worden, indien zij een urinestraalmeting in het ziekenhuis moeten ondergaan, geadviseerd te komen met een zo vol mogelijke blaas, terwijl thuis het tijdstip van de mictie gerelateerd is aan andere, dagelijkse, activiteiten. Eén van de voornaamste conclusies was dat d.m.v. thuis-flowmetrie betrouwbare urinestraalmetingen gegenereerd kunnen worden die vergelijkbaar zijn met de urinestraalmetingen in het ziekenhuis. Echter, wanneer vele urinestraalmetingen beschikbaar zijn ontstaat het probleem welke urinestraalmetingen nu gebruikt moeten worden voor de evaluatie van het effect van een mogelijke behandeling, vooral als er een klinisch relevant circadiaan ritme van de kracht van de urinestraal bestaat.

Deze circadiane veranderingen in de kracht van de urinestraal worden beschreven in het tweede manuscript (H 5.3) dat betrekking heeft op de thuis-flowmeter. 170 Patiënten met lagere urineweg symptomen gebruikten de thuis-flowmeter en produceerden in totaal 1670 correct gemeten urinestraalmetingen thuis. Deze patiënten ondergingen tevens een gestandaardiseerd screeningsprogramma dat bestond uit de I-PSS vragenlijst, een conventionele urinestraalmeting in het ziekenhuis en een urodynamische druk-flow meting. Het bleek dat bij alle obstructie categorieën het gemiddelde volume van de urinestraalmeting tussen middernacht en 6 h 's morgens significant groter was vergeleken met de urinestraalmetingen geproduceerd gedurende de middag of avond. Het kleinste gemiddelde volume thuis werd geproduceerd gedurende de middag. Ondanks dit

significant kleinere volume gedurende de middag was de kracht van de urinestraal bij patiënten met een matige en ernstige blaasuitgangsobstructie 's middags significant groter dan die geproduceerd gedurende de ochtend. De voornaamste conclusie was dat circadiane veranderingen van de kracht van de urinestraal van belang zijn en dat met deze veranderingen rekening gehouden dient te worden bij de evaluatie van de effectiviteit van een behandeling, vooral bij patiënten met een matige of ernstige blaasuitgangsobstructie.

In hoofdstuk 6-8, worden de subjectieve en objectieve resultaten van niet-invasieve en minimaal invasieve behandelingen gekwantificeerd en vergeleken tussen groepen patiënten met verschillende mate van blaasuitgangsobstructie.

In ***hoofdstuk 6*** wordt de fysiologische variabiliteit van symptomen en de resultaten van urodynamische druk-flow metingen gekwantificeerd door de gegevens van 121 patiënten die zowel klinisch als urodynamisch geëvalueerd werden vóór en 6 maanden ná een periode van waakzaam afwachten te analyseren. Deze studie toonde ons dat na 6 maanden waakzaam afwachten patiënten zonder blaasuitgangsobstructie symptomatisch statistisch significant verbeterden. De verbetering was echter gering en klinisch irrelevant. Symptomen van patiënten met ernstige blaasuitgangsobstructie veranderden niet significant. De reproduceerbaarheid van de gemiddelden van de urodynamische druk-flow variabelen was goed. Echter, er was een belangrijke variabiliteit tussen groepen patiënten met verschillende mate van blaasuitgangsobstructie. Bij de urodynamische evaluatie na 6 maanden neigden patiënten met extreme waarden bij de initiële druk-flow meting naar een regressie naar het gemiddelde van de onderzoekspopulatie: bij patiënten met een initiële evidente blaasuitgangsobstructie bleek na 6 maanden een significante verbetering van de detrusor druk bij maximale urinestraal van gemiddeld 14 cm. water, een significante verbetering van de urethrale resistance factor van gemiddeld 7 cm. water en een significante vermindering van gemiddeld 1 obstructie klasse (L-PURR), te bestaan hetgeen impliceert dat er, bij deze categorie patiënten, na 6 maanden waakzaam afwachten minder blaasuitgangsobstructie gemeten wordt. De belangrijkste conclusie was dat gemiddelde subjectief en objectief gemeten resultaten van behandelingen tussen behandelgroepen kritisch beschouwd dienen te worden vooral als de waargenomen verschillen klein zijn en mogelijk vallen binnen de fysiologische variabiliteit. Door deze aanzienlijke fysiologische variabiliteit die waarschijnlijk veroorzaakt wordt door de dynamische component van obstructie werd aanbevolen om bij ieder klinisch onderzoek waarbij het effect van een specifieke

behandeling in kaart wordt gebracht, een controle arm op te nemen zodat het mogelijk is deze fysiologische variabiliteit te kwantificeren.

In ***hoofdstuk 7*** worden de resultaten van behandeling van patiënten met lagere urineweg symptomen met terazosine in kaart gebracht. Het eerste manuscript (H 7.1) beschrijft de lange termijn resultaten van behandeling met terazosine bij 427 patiënten die deelnamen aan de Internationale Terazosine Trial (ITT), een klinische trial waarin 33 centra in 13 landen patiënten recruteerden met een initiële I-PSS score van 12 of meer. Na een 2 weken durende inloop periode waarin geen behandeling gegeven werd, volgde een 26 weken durende periode waarbij de patiënt, single-blind (de arts maar niet de patiënt weet dat de patiënt met terazosine behandeld wordt), met terazosine behandeld werd. Patiënten die goed op de behandeling reageerden werden na 26 weken gerandomiseerd voor een 24 weken durende periode waarbij de patiënt dubbel-blind (noch de arts, noch de patiënt weet of er met placebo of met terazosine behandeld wordt) ofwel de behandeling met terazosine continueerde danwel in plaats van terazosine met placebo werd behandeld. Tijdens de single-blind periode, verbeterden symptomen, de kwaliteit van leven score en de kracht van de urinestraal significant. Tijdens de dubbel-blinde periode verslechterden symptomen, de kwaliteit van leven score en de kracht van de urinestraal significant in de groep patiënten die met placebo behandeld werd maar niet in de groep patiënten die met terazosine behandeld werd. De verslechtering van variabelen in de placebo behandelde groep echter, was niet zodanig dat de initiële waarden weer bereikt werden. Deze bevindingen suggereren dat 1) er een variabiliteit bestaat in de evolutie van lagere urineweg symptomen (symptomen fluctueren in de tijd en patiënten hebben een grotere kans om in een slechte periode in een klinische trial te belanden), 2) er bestaat een voortdurend placebo effect, en 3) het duurt langer dan 24 weken voordat het effect van 26 weken behandeling met terazosine is verdwenen. Een andere meer speculatieve verklaring is dat 6 maanden van α1-blokkade mogelijk de gevoeligheid van de α-adrenerge receptor vermindert.

Het tweede manuscript (H 7.2) beschrijft de resultaten van de groep patiënten die deelnamen aan de ITT in het St. Radboud Ziekenhuis te Nijmegen. Behalve de follow up zoals hiervoor beschreven werden deze patiënten zowel vóór als 26 weken ná de start met terazosine, middels urodynamische druk-flow metingen, geëvalueerd. Behandeling met terazosine resulteerde in symptomatische verbetering en een verbetering van de kracht van de urinestraal zowel bij patiënten met als bij patiënten zonder blaasuitgangsobstructie. Bij patiënten zonder urodynamisch aangetoonde blaasuitgangsobstructie konden geen significante veranderingen van de urodynamische obstructie variabelen aangetoond worden. Ironisch genoeg

was het juist de groep zonder blaasuitgangsobstructie die het hoogste percentage patiënten met kleine verbeteringen van de kracht van de urinestraal en symptomen had. Deze bevinding suggereert dat de wijze waarop we de effectiviteit van een behandeling met geneesmiddelen evalueren (verbeteringen van symptomen en de kracht van de urinestraal) niet afhankelijk is van het urodynamisch meetbare effect van de behandeling.

Het derde manuscript (H 7.3) beschrijft de resultaten van behandeling met terazosine bij 97 patiënten met lagere urineweg symptomen in het St. Radboud Ziekenhuis te Nijmegen. Van de 97 patiënten die startten met terazosine, completeerden 60 de 6 maanden behandeling waarna zij opnieuw werden geëvalueerd met de I-PSS vragenlijst, urinestraalmeting en een urodynamisch druk-flow onderzoek. De klinische en urodynamische veranderingen binnen en tussen de groepen met en zonder blaasuitgangsobstructie werden geanalyseerd. Patiënten zonder blaasuitgangsobstructie hadden een groter risico vóór 6 maanden met de behandeling te stoppen. In zowel de groep met als de groep zonder blaasuitgangsobstructie resulteerde behandeling met terazosine in significante symptomatische verbetering (9 punten op de I-PSS schaal, $p < 0.01$) en een significante verbetering van de kracht van de urinestraal (gemiddeld 3.0 ml/s; $p < 0.01$). Bij patiënten met een blaasuitgangsobstructie werd een statistisch significante verbetering van alle urodynamische obstructie variabelen ($p < 0.01$) aangetoond. Bij patiënten zonder blaasuitgangsobstructie werd een significante verbetering van de kracht van de urinestraal (4.4 ml/s; $p < 0.01$), een statistisch significant verbeterde blaas capaciteit (toename van 70 ml; $p = 0.01$) en geen statistisch significante veranderingen van urodynamische obstructie variabelen ($p > 0.05$) aangetoond. Toen de veranderingen van mictie variabelen tussen de groepen met en zonder blaasuitgangsobstructie met elkaar vergeleken werden bleek dat er voor wat betreft symptomen ($p = 0.89$), kwaliteit van leven ($p = 0.85$) en het aantal patiënten met een verbetering van de maximale urinestraal $\geq$ 30 % ($p = 0.15$), geen significante verschillen tussen deze groepen bestaan. Een van de conclusies van dit manuscript was dan ook dat er ondanks een significant urodynamisch verschil tussen patiënten met en zonder blaasuitgangsobstructie, het gebruik van druk-flow metingen voor de selectie van patiënten die met terazosine behandeld moeten gaan worden niet aanbevolen kan worden omdat de klinische resultaten van behandeling niet significant verschilden tussen patiënten met en zonder blaasuitgangsobstructie. Het lijkt zinvoller en is zeker minder invasief en minder kostbaar om $\alpha 1$ blokker therapie te starten als de uroloog, op klinische gronden, de patiënt een geschikte kandidaat vindt voor $\alpha 1$ blokker therapie en deze behandeling te continueren bij diegenen die goed reageren op de behandeling (een

proefbehandeling).

In ***hoofdstuk 8*** worden de symptomatische en urodynamische effecten van niet-invasieve vormen van behandeling zoals beschreven in hoofdstuk 6 en 7 samen met de minimaal invasieve vormen van behandeling transurethrale microgolf thermotherapie (TUMT), transurethrale laser ablatie van de prostaat en de transurethrale resectie van de prostaat (TURP) gekwantificeerd bij een totaal van 574 patiënten die 6 maanden na de (start van) de behandeling geëvalueerd werden met de I-PSS vragenlijst, urinestraalmeting en een urodynamische druk-flow studie. De analyse werd gestratificeerd naar de mate van initiële blaasuitgangsobstructie en de subjectieve en objectieve veranderingen na de (start van) de behandelingen werden vergeleken tussen de diverse obstructie groepen. Voor iedere vorm van behandeling gold dat in tegenstelling tot de urodynamisch gemeten verbetering, de symptomatische verbetering na 6 maanden niet significant verschilde tussen de diverse obstructie klassen. Urodynamische veranderingen waren meer uitgesproken in de minimaal invasieve behandelgroepen vergeleken met de groepen die met niet-invasieve vormen van behandeling behandeld werden. De urodynamische effecten in de met laser behandelde groep bleken groter te zijn dan die in de TUMT behandelde groep en bij de patiënten met een ernstige blaasuitgangsobstructie werd de grootste urodynamisch gemeten verbetering gezien bij de patiënten die met een TURP behandeld waren. De conclusie van dit hoofdstuk was dat, onafhankelijk van de gekozen behandeling, symptomatische verbetering op de korte termijn niet afhankelijk lijkt te zijn van veranderingen in urodynamische obstructie variabelen.

Toekomstverwachtingen

Lagere urineweg symptomen komen frequent voor bij mannen ouder dan 50 jaar.[1] In het jaar 2000 zijn meer dan 600 miljoen mensen ouder dan 60 jaar en twee derde van hen leeft in de ontwikkelde landen. Deze vergrijzing heeft belangrijke gevolgen voor de planning en levering van de gezondheidszorg voor mannen met lagere urineweg symptomen in de komende jaren. Het feit dat de prevalentie van lagere urineweg symptomen in de populatie groter is dan het aantal mensen dat medisch advies vraagt vanwege deze lagere urineweg symptomen[1,2] bevestigt dat de perceptie van lagere urinewegsymptomen een individuele zaak is die kan verschillen tussen verschillende leeftijdscategorieën en groepen met een verschillende socio-demografische achtergrond. De hoge prevalentie van niet gediagnostiseerde en onbehandelde lagere urineweg symptomen in de vergrijzende bevolking van de ontwikkelde landen suggereren dat kosten

gerelateerd aan de behandeling van lagere urineweg symptomen snel kunnen escaleren indien het probleem gemakkelijker algemeen toegankelijk wordt.

Lagere urineweg symptomen bij het individu kunnen verschillende oorzaken hebben. De meerderheid van de lagere urineweg symptomen bij de oudere man worden veroorzaakt door een blaasuitgangsobstructie ten gevolge van een vergrote prostaat. Lagere urineweg symptomen kunnen echter ook een gevolg zijn van motore of sensore stoornissen van de musculus detrusor of van de urethra,[3] of zelfs van veranderingen in gewoonten en leefstijl die nogal eens voorkomen bij de ouder wordende mens.

Ook de huidige vormen van behandeling voor de patiënt met lagere urineweg symptomen zijn nogal divers. Transurethrale resectie van de prostaat en waakzaam afwachten zijn niet langer de enig beschikbare opties. Vandaag de dag zijn er diverse farmacologische, minimaal invasieve en chirurgische vormen van behandelingen voor de patiënt met lagere urineweg symptomen. Met betrekking tot de farmacologische vormen van behandeling, zijn er de α1-adrenerge antagonisten (alfuzosine, doxazosine, tamsulosine and terazosine) en de 5-α-reductase inhibitoren (finasteride). De minimaal invasieve vormen van behandeling die op dit moment beschikbaar zijn omvatten transurethrale incisie van de prostaat, laser ablatie van de prostaat, transurethrale thermotherapie en er zijn een aantal nieuwe minimaal invasieve vormen van behandeling die nu ontwikkeld en getest worden. De meest gebruikte chirurgische vormen van behandeling zijn transurethrale resectie van de prostaat en transabdominale prostatectomie. Deze chirurgische vormen van behandeling zijn het meest invasief en hebben de grootste effectiviteit.

De vraag is nu hoe we in de toekomst in staat zullen zijn de diagnostische evaluatie te optimaliseren zodat direct de meest optimale behandeling voor het individu geselecteerd kan worden. Echter, voordat de diagnostische evaluatie geoptimaliseerd kan worden moet eerst besloten worden welke de belangrijkste aspecten zijn die we willen en kunnen behandelen bij de patiënt met lagere urineweg symptomen. Zijn we hoofdzakelijk geïnteresseerd in het verbeteren van symptomen of zijn we met name geïnteresseerd in het verminderen van urodynamisch aangetoonde obstructie van de blaasuitgang ?

In hoofdstuk 8 werd aangetoond dat, bij een aantal niet-invasieve en minimaal invasieve vormen van behandeling, in tegenstelling tot de urodynamisch gemeten verbetering, de symptomatische verbetering na 6 maanden niet significant verschilde tussen de diverse obstructie klassen. Op grond van deze waarneming zouden we kunnen concluderen dat, indien

we hoofdzakelijk geïnteresseerd zijn in het verbeteren van symptomen op de korte termijn, we geen invasief urodynamisch druk-flow onderzoek hoeven te verrichten. Het is voldoende om een prostaatcarcinoom uit te sluiten en de patiënt te informeren over de potentiële symptomatische voordelen en bijwerkingen van de beschikbare vormen van behandeling. Als het verbeteren van symptomen het belangrijkste doel is van de behandeling, moeten we ons ervan bewust zijn dat symptomen ook significant verbeteren door behandeling met een placebo.[4,5] Richtlijnen die gebruikt kunnen worden wanneer de patiënt met lagere urineweg symptomen geadviseerd wordt over de te verwachten symptomatische verbetering na de beschikbare behandelingen zijn de richtlijnen gepubliceerd door de Agency for Health Care Policy and Research.[5] Deze richtlijnen suggereren dat transurethrale resectie van de prostaat resulteert in een aanzienlijk betere symptomatische verbetering (88 %, 95 betrouwbaarheids interval 75-96 %) dan α1-adrenerge antagonisten (74 %) en waakzaam afwachten (42 %).[5] Andere studies suggereren dat een kwart van de patiënten na een transurethrale resectie van de prostaat niet symptomatisch verbeteren.[6,7] en dit percentage zou groter kunnen zijn na minder invasieve vormen van behandeling.

Velen hebben getracht patiënten te selecteren die een grote kans hebben niet voldoende op de behandeling te reageren. Met symptomen alleen zijn deze patiënten niet te selecteren, maar andere variabelen zoals een klein prostaat volume, lage detrusor drukken, blaas instabiliteit en urge incontinentie zijn duidelijk geassocieerd met een slecht resultaat na chirurgische behandeling.[6,7]

Als het doel is de diagnostiek te optimaliseren zodat de optimale behandeling voor het individu geselecteerd kan worden, is het duidelijk dat afgaan op een verbetering van symptomen alléén niet voldoende is. We zullen ons moeten richten op het verminderen van blaasuitgangsobstructie. Met de resultaten van urodynamische druk-flow metingen zijn we nu al in staat groepen patiënten te selecteren die een marginale kans hebben op een goed resultaat van de behandeling na chirurgie en transurethrale microgolf thermotherapie van de prostaat.[6-8] Bovendien zouden we met de resultaten van urodynamische druk-flow metingen in staat kunnen zijn de duurzaamheid van de symptomatische verbetering te voorspellen (hoofdstuk 8) en de kans op mislukking van de behandeling zou verder gereduceerd kunnen worden indien alleen patiënten met blaasuitgangsobstructie behandeld zouden worden.[9] De vraag rijst vervolgens of we dan een invasief en kostbaar urodynamische druk-flow meting bij iedere patiënt moeten verrichten alvorens er een behandeladvies gegeven kan worden. Dit zal waarschijnlijk niet nodig zijn. Met minder invasief onderzoek zijn we ook in staat te voorspellen of een patiënt een blaasuitgangsobstructie heeft

of niet. Reynard et al toonde dat de specificiteit en de positieve predictieve waarde van maximale flow voor het voorspellen van de aanwezigheid van een blaasuitgangsobstructie significant verbeterde na meerdere vrije - poliklinische - urinestraalmetingen.[10] Indien de hoogste maximale flow na 3 urinestraalmetingen lager is dan 10 ml/s, is de specificiteit en positieve predictieve waarde voor blaasuitgangsobstructie respectievelijk 90 en 94 %. We zijn het met Reynard eens dat meerdere vrije urinestraalmetingen zeer efficiënt zijn om een nauwkeurige diagnose te stellen.[10] Thuis-flowmetrie is wat dit betreft meer geschikt om urinestraalmetingen te verzamelen dan de polikliniek (hoofdstuk 5). Rosier et al toonde in een retrospectieve studie dat met behulp van een combinatie van objectieve niet-invasieve metingen (totaal prostaat volume, maximale flow, volume van het urineresidu en geplast volume), het mogelijk was om onderscheid te maken tussen groepen patiënten met en zonder blaasuitgangsobstructie.[11] Of een combinatie van objectieve niet-invasieve metingen voldoende sensitiviteit en specificiteit heeft om nauwkeurig te voorspellen of de individuele patiënt een blaasuitgangsobstructie heeft of niet zal in de toekomst nog bevestigd moeten worden.

Toekomstige analyses van studies zoals de International Continence Society - 'Benign Prostatic Hyperplasia' studie[12] zouden ons de noodzakelijke informatie kunnen verschaffen of het in de toekomst mogelijk zal zijn om op grond van urodynamische of andere mictie variabelen bij de individuele patiënt een gunstig resultaat van huidige en nieuwe vormen van behandeling te voorspellen.

Referenties

1 Garraway WM, Collins GN, Lee RJ: High prevalence of benign prostatic hypertrophy in the community. The Lancet **338**: 469, 1991.

2 Sagnier PP, MacFarlane G, Teillac P, Botto H, Richard F, Boyle P: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. J Urol **153**: 669, 1995.

3 Schäfer W, Nopponey R, Rübben H and Lutzeyer W: The value of free flow rate and pressure flow-studies in the routine investigation of BPH patients. Neurourol Urodyn **7**: 219, 1988.

4 Isaacs JT: Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate **3**: 1, 1990.

5 McConnel JD, Barry MJ, Bruskewitz RC et al (Eds.): Benign Prostatic Hyperplasia: Diagnosis and Treatment. Clinical Practice Guideline. Rockville, Maryland: US Department of health and human services, Agency for Health Care Policy and Research, 1994.

6 Neal DE, Ramsden PD, Sharples L et al: Outcome of elective prostatectomy.

BMJ **299**: 762, 1989.

7 George NJ, Feneley RC, Roberts JB: Identification of the poor risk patient with "prostatism" and detrusor failure. Brit J Urol **58**: 290, 1986.

8 Tubaro A, Carter S, de la Rosette J, Höfner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F. The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: A European multicenter study. J Urol **153**: 1526, 1995.

9 Abrams P, Blaivas J, Nordling J, Griffiths DJ, Jensen KM: The objective ealuation of bladder outlflow obstruction. In: Cockett ATK, Khoury S, Aso Y, Chatelain C, (Eds): Proceedings of the second international consultation on benign prostatic hyperplasia (BPH). Jersey, United Kingdom, Scientific Communication International Ltd, 1993, pp 151-226.

10 Reynard JM, Peters TJ, Lim C, Abrams P: The value of multiple free-flow studies in men with lower urinary tract symptoms. Brit J Urol **77**: 813, 1996.

11 Rosier PFWM, de Wildt MJAM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Clinical diagnosis of bladder outlet obstruction in patients with benign prostatic enlargement and lower urinary tract symptoms: Development and urodynamic validation of a clinical prostate score for the objective diagnosis of bladder outlet obstruction. J Urol **155**: 1649, 1995.

12 Abrams P, Donovan J, van Kerrebroeck P, Nordling J, Schäfer W, Thuroff J, Neal D and the ICS-'BPH' study group: The ICS-'BPH' Study: background and design. Neurourol Urodyn **13**: 483, 1994.

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 22 augustus 1958 te Arnhem. Na het voorbereidend wetenschappelijk onderwijs (V.W.O.) aan het Katholiek Gelders Lyceum te Arnhem werd in 1976 de studie Geneeskunde aangevangen aan de Katholieke Universiteit te Nijmegen waar hij in 1984 zijn artsenbul in ontvangst mocht nemen. Gedurende de volgende 6 jaar was hij als arts-assistent in de orthopedie, chirurgie en urologie werkzaam in diverse ziekenhuizen waaronder het Militair Hospitaal te Utrecht, het St. Elisabeth Ziekenhuis te Amersfoort en het Canisius-Wilhelmina Ziekenhuis te Nijmegen. In deze periode maakte hij kennis met het patiëntgebonden onderzoek. Het verrichtte onderzoek werd succesvol afgerond, op congressen gepresenteerd en gepubliceerd. Deze kennismaking bleek later de opstap naar zijn huidige functie.

Sinds 1990 is hij als hoofd van de clinical research unit en als staflid verbonden aan de afdeling urologie van het St. Radboud Ziekenhuis te Nijmegen (Hoofd: Prof. Dr. F.M.J. Debruyne). De clinical research unit bestaat uit een multidisciplinair team van deskundigen dat verantwoordelijk is voor de opzet, uitvoer, analyse en rapportage van klinisch patiëntgebonden onderzoek ('clinical research'). Dit onderzoek wordt verricht conform de huidige standaarden van Good Clinical Practice. Patiënten die deelnemen aan dit onderzoek worden, volgens een tevoren vastgesteld protocol, behandeld door specialisten binnen het St. Radboudziekenhuis, door een actieve groep van specialisten in de regio of door internationale groepen specialisten (bijv. European Organisation for Research and Treatment of Cancer [EORTC]).

Hij is getrouwd met Christel Kusters en vader van drie kinderen: Marloes, Bart en Janne.

Scientific abstracts and publications

Scientific abstracts

- **Witjes WPJ**, Vollaard EJ, Crul BJP, Limpens C: Sublingual buprenorphine obviates the need for parenteral morphine in cholecystectomy patients. Pharmaceutisch weekblad 11: 21, 1989.
- **Witjes WPJ**, Barentsz JO, Corten RLFM, Karthaus HFM, Mravunac M, Ruijs SH, Debruyne FMJ: De waarde van magnetic resonance imaging ten opzichte van computertomografie bij de stadiëring van blaascarcinomen. Ned Tijdschr v Geneesk 134: 1525, 1989.
- **Witjes WPJ**, Witjes JA, Doesburg WH, van der Meijden APM, Debruyne FMJ: A prospective comparative study to evaluate the effect of intravesical instillation of Mitomycin-C, of BCG RIVM and of BCG Tice in pTa-pT1 papillary carcinoma and primary CIS of the urinary bladder. Proc. 1st International Congress of the Dutch Urological Association. "Progress and controversies in Oncological Urology III". Rotterdam, October 9-13: A54, 1991.
- **Witjes WPJ**, van der Meijden APM, Debruyne FMJ: Vergleichende Studie zur Intravesikalen Instillation von Mitomycin-C, BCG-RIVM und BCG-Tice beim oberflächlichen Urothelkarzinom der Harnblase (pTa-pT1 und primäres carcinoma in situ) Urologe A, 30· A71, 1991.
- **Witjes WPJ**, de Mulder PHM, Oosterhof GON, Punt CJA, Loriaux E, Debruyne FMJ: Phase II study of the combination of s.c. administered r-IFN-α-2a and r-IL-2 in patients with progressive metastatic renal cell carcinoma. Proc. 10th congress of the European Association of Urology, Genoa, 22-25 July: P245, 1992.
- **Witjes WPJ**, van der Meijden APM. Bacillus Calmette-Guérin versus Mitomycin-C intravesical therapy in patients with superficial bladder cancer. Eur Urol Today 2; 4: 6, 1992.
- **Witjes WPJ**, van der Meijden APM, Debruyne FMJ: Vergleichende Studie zur Intravesikalen Instillation von Mitomycin-C, BCG-RIVM und BCG-Tice beim oberflächlichen Urothelkarzinom der Harnblase (pTa-pT1 und primäres carcinoma in situ). Urologie Poster 4; 3. 118-120, 1992.
- **Witjes WPJ**, Debruyne FMJ, van der Meijden APM, de Pauw M, Sylvester R, Oosterhof GON and members of the EORTC GU Group and the Dutch Southeastern Cooperative Urological Group: Prospective randomised study of BCG-RIVM versus Mitomycin-C intravesical therapy in superficial bladder cancer. (EORTC study 30845) J Urol 151: 232A, 1994.
- **Witjes WPJ**, Horenblas S, Oosterhof GON et al.: Neo-adjuvant therapy in prostate cancer· Is it of any use ? Urology/Nephrology Digest 2: 11-14, 1994.
- **Witjes WPJ**, Debruyne FMJ, van der Meijden APM, de Pauw M, Sylvester R, Oosterhof GON and members of the EORTC GU Group and the Dutch South East Cooperative Urological Group: BCG-RIVM versus Mitomycin-C intravesical therapy in superficial bladder cancer. A prospective randomised EORTC study (30845). Proc. XIth congress of the European Association of Urology, Berlin, 13-16 July: A35, 1994.
- **Witjes WPJ**, Schulman CC, Oosterhof GON, van Cangh PJ, Debruyne FMJ and members of the European Study Group on Neoadjuvant treatment: Prospective randomised study of neoadjuvant combined androgen deprivation therapy in T2-3, N0, M0 prostatic carcinoma. Proc XIth congress of the European Association of Urology, Berlin, 13-16 July: A259, 1994.

- **Witjes WPJ**, van Cangh PJ and Schulman CC for the European Study Group on Neoadjuvant Treatment of Prostatic Carcinoma: Neoadjuvant combined androgen deprivation therapy in locally confined prostatic carcinoma. Proc. 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A410, 1994.
- **Witjes WPJ**: Introduction and rationale to the ALFIN study: alfuzosin, finasteride and their combination: therapeutic management of patients with complaints of benign prostatic hypertrophy. Eur Urol Today, Dec 1994.
- **Witjes WPJ**, Horenblas S, Oosterhof GON, Schaafsma HE, Debruyne FMJ: La thérapie néoadjuvante dans le cancer de la prostate: est-elle utile ? Dialogue en Urologie: Urologie annales 1993, 4-7, 1994.
- **Witjes WPJ**, de Wildt MJAM, Rosier PFWM, Caris CTM, van Iersel MP, Debruyne FMJ, de la Rosette JJMCH: Terazosin treatment in patients with symptomatic benign prostatic hyperplasia: Clinical and urodynamical results. J Urol 153: 273A, 1995.
- **Witjes WPJ**, de Wildt MJAM, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Watchful waiting in patients with symptomatic benign prostatic hyperplasia: clinical and urodynamical results. J Urol 153: 454A, 1995.
- **Witjes WPJ**, van Cangh PJ and Schulman CC for the European Study Group on Neoadjuvant Treatment of Prostatic Carcinoma: Neoadjuvant combined androgen deprivation therapy in locally confined prostatic carcinoma. Ned Tijdschr v Urologie 3: 2, 50, 1995.
- **Witjes WPJ**, Rosier PFWM, de Wildt MJAM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Terazosin treatment in patients with symptomatic benign prostatic hyperplasia: clinical and urodynamical results. Proceedings of the 3rd WHO consensus meeting on benign prostatic hyperplasia, Monaco, 1995.
- **Witjes WPJ**, de Wildt MJAM, Rosier PFWM, Caris CTM, van Iersel MP, Debruyne FMJ, de la Rosette JJMCH: Terazosin treatment in patients with symptomatic benign prostatic hyperplasia: Clinical and urodynamical results. In: "The integrated solution for prostate disease management: IMX PSA, terazosin BPH and Leuprolide acetate". Edited and published by Abbott Laboratories on behalf of the 3rd WHO consensus meeting on benign prostatic hyperplasia, Monaco, 1995.
- **Witjes WPJ**, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Prognostic value of pressure-flow study variables in the treatment of patients with symptomatic BPH with terazosin (Hytrin®). Proc. 3rd International Congress of the Dutch Urological Association. "Uro-technology: developments and progress in urology". Nijmegen, November 1-3: A10, 1995.
- **Witjes WPJ**: Prosperous recruitment in the ALFIN study. Eur Urol Today, Dec 1995.
- **Witjes WPJ**, Rosier PFWM, de Wildt MJAM, Debruyne FMJ, de la Rosette JJMCH: Short and long term 'natural' variability of bladder outlet resistance in the elderly male. J Urol 155: A283, 1996.
- **Witjes WPJ**, Debruyne FMJ: Neoadjuvant Therapy in Localized Prostate Cancer: Preliminary Results of the European Study on Neoadjuvant Maximal Hormonal Blockade in Patients with Localized Prostate Cancer. Proceedings First International Conference on Neoadjuvant Hormonal Therapy for Prostate Cancer. Boston, March 29-30, 1996.
- **Witjes WPJ**, Rosier PFWM, Wijkstra H, Debruyne FMJ, Abrams P, de la Rosette

JJMCH: Urodynamic effects of non-invasive and invasive therapies on the bladder outlet. A stratified analysis. Proc. XIIth congress of the European Association of Urology, Paris, 1-4 September: p 59, A 170, 1996.

- **Witjes WPJ**, Aarnink RG, Debruyne FMJ, Wijkstra H, de la Rosette JJMCH: Correlation between prostatic volume, transition zone volume, and clinical and pressure-flow study variables in patients with symptomatic benign prostatic hyperplasia. Proc. XIIth congress of the European Association of Urology, Paris, 1-4 September: p 100, A 333, 1996.
- **Witjes WPJ**, Schulman CC, Forster G, Debruyne FMJ, van Cangh PJ, Fava C for the European Study Group on Neoadjuvant treatment: Neoadjuvant combined androgen deprivation therapy in T2-3, N0, M0 prostatic carcinoma. Early results of a European study. Proc. XIIth congress of the European Association of Urology, Paris, 1-4 September: p 210, A 775, 1996.
- **Witjes WPJ**: Mitomycin followed by BCG versus Mitomycin instillation therapy in patients with superficial bladder carcinoma. In: Gianni Beretta (ed): Mitomycin C: Current status. Minerva Medica, Turin, p 105, 1996.
- **Witjes WPJ**, Schulman CC, Forster G, Debruyne FMJ, van Cangh PJ, Fava C for the European Study Group on Neoadjuvant treatment: Neoadjuvant combined androgen deprivation therapy in T2-3, N0, M0 prostatic carcinoma. Early results of a European study. Ned Tijdschr v Urologie 3: 3, 73, 1996.
- **Witjes WPJ**, Debruyne FMJ, Caris CTM: How to design a clinical trial. Programme and Course Book of the 1st Annual European Course in Urology (AECU), 4-5 Nov 1996, Roma, Italy.
- **Witjes WPJ**, Rosier PFWM, de Wildt MJAM et al: Urodynamic and clinical effects of terazosin therapy in symptomatic patients with benign prostatic hyperplasia. Urology Digest 6: 8-10, 1996.
- **Witjes WPJ**, de la Rosette JJMCH, Abrams P, Bosch JLHR, Dabhoiwala NF, Donovan J, Peters TJ, Kay HE, en de ICS-'BPH' Groep: Internationale verschillen in lagere urinewegsymptomen en gerelateerde hinder. Proc. NVU vergadering, 1-2 November, 1996, Hengelo.
- **Witjes WPJ**, Rosier PFWM, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Urodynamische en symptomatische effecten van niet,- minimaal invasieve en invasieve behandelingen bij BPH. Proc. NVU vergadering, 1-2 November, 1996, Hengelo.
- van der Staak FHJM, **Witjes WPJ**, Severijnen RSVM, Festen C: Dunne darmletsels bij kinderen a.g.v. stomp buiktrauma. Ned Tijdschr v Geneeskunde 128: 1599, 1984.
- van der Staak FHJM, **Witjes WPJ**, Severijnen RSVM, Festen C: Epidemiologische benadering van het stomp buiktrauma bij kinderen. Proc. 4e jaarcongres van de Nederlandse Vereniging voor Traumatologie, Amsterdam, Okt 1986.
- Debruyne FMJ, **Witjes WPJ**, Bemelmans BLH (eds): Proceedings teaching course "Update in diagnosis and treatment of prostate cancer"; EAU IXth Congress, Amsterdam (June 1990). Uitg: Afd. Urologie, Academisch Ziekenhuis Nijmegen, 1990.
- Fernandez del Moral P, **Witjes WPJ**, Debruyne FMJ, Stuckart RAH, Khoe GS: Mitoxantrone in hormone escaped prostatic carcinoma patients. Proc. 1st International Congress of the Dutch Urological Association "Progress and controversies in Oncological Urology III". Rotterdam, October 9-13: A30, 1991.

- Meuleman EJH, **Witjes WPJ**, Lycklama à Nijeholt AAB, van Driel MF, Oerlemans SH, Leliefeld HHJ: Intracavernous autoinjectiontherapy in erectile dysfunction. Proc. 1st International Congress of the Dutch Urological Association. "Progress and controversies in Oncological Urology III". Rotterdam, October 9-13: A50, 1991.
- Meuleman EJH, **Witjes WPJ**, Lycklama à Nijeholt AAB, van Driel MF, Oerlemans SH, Leliefeld HHJ: Therapie der erektilen dysfunktion mittels Schwellkörper Autoinjektionstechnik (SKAT). Urologe A, 30: A83, 1991.
- d'Hollosy W, **Witjes WPJ**, Buwalda P, Hendriks BTh, Debruyne FMJ, Wijkstra H: URIS: Een Urologisch database management systeem. Ned Tijdschr v Geneeskunde 137: 163, 1993.
- Rosier PFWM, **Witjes WPJ**, van Kerrebroeck PhEV, de la Rosette JJMCH, Debruyne FMJ, Wijkstra H: The effect of alfuzosine on the pressure/flow relation in male outflow obstruction. Proc. 2nd International Congress of the Dutch Urological Association. "New insights into the aetiology, diagnosis and management of BPH". Amsterdam, November 4-6: A67, 1993.
- Horenblas S, **Witjes WPJ**, Oosterhof GON, Debruyne FMJ: Preoperatieve hormonale behandeling bij T2-3 N0 M0 prostaatcarcinoom. De eerste resultaten van een prospectief gerandomiseerde studie. Ned Tijdschr v Geneesk 138: 2167, 1994.
- van Gils-Gielen CJM, **Witjes WPJ**, Caris CTM, Debruyne FMJ, van der Meijden APM: Mitomycine-C plus BCG-Tice versus mitomycine-C alleen in oppervlakkig blaascarcinoom en carcinoma in situ. Een toxiciteitsanalyse. Ned Tijdschr v Geneesk 138: 2174, 1994.
- de la Rosette JJMCH, **Witjes WPJ**, Donovan JL, Abrams P, Kay HE, Peters TJ and the ICS-'BPH' group: The ICS-'BPH' study: The assesment of lower urinary tract symptoms. Neurourol Urodyn 13 (4): 488-489, 1994.
- Rosier PFWM, **Witjes WPJ**, de Wildt MJAM, de la Rosette JJMCH and Debruyne FMJ: Urodynamic results of terazosin treatment for symptomatic BPH. In: "The integrated solution for prostate disease management: IMX PSA, terazosin BPH and Leuprolide acetate". Edited and published by Abbott Laboratories on behalf of the EAU XIth Congress, Berlin, pp 202-204, 1994.
- Rosier PFWM, **Witjes WPJ**, de Wildt MJAM, de la Rosette JJMCH, Debruyne FMJ: Urodynamic results of terazosin treatment for symptomatic BPH. Proc. XIth congress of the European Association of Urology, Berlin, 13-16 July: A240, 1994.
- van Iersel MP, **Witjes WPJ**, de la Rosette JJMCH, Oosterhof GON: Prostate specific antigen density: Correlation with histological diagnosis of prostatic cancer, BPH and prostatitis. Proc. XIth congress of the European Association of Urology, Berlin, 13-16 July: A290, 1994.
- van Gils-Gielen RJM, **Witjes WPJ**, Caris CTM, Debruyne FMJ, van der Meijden APM and members of the Dutch South-East Cooperative Urological Group: Mitomycin-C plus BCG-Tice versus Mitomycin-C alone in superficial bladder cancer and carcinoma in situ. A toxicity analysis. Proc. XIth congress of the European Association of Urology, Berlin, 13-16 July: A681, 1994.
- Ekman P, **Witjes WPJ** and the ITT Group: Nocturia results from the International Terazosin Trial (ITT). A double blind, placebo-controlled randomized withdrawal study of the symptomatic treatment of BPH. Proc. 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A98, 1994.

- Rosier PFWM, **Witjes WPJ**, de Wildt MJAM, de la Rosette JJMCH, Debruyne FMJ: Urodynamic results of terazosin treatment for symptomatic BPH. Proc. 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A486, 1994.
- Horenblas S, **Witjes WPJ**, Oosterhof GON, Debruyne FMJ: Neo-adjuvant combined androgen deprivation therapy in locally confined prostatic carcinoma. A prospective randomized study. Proc. 48e Oncologiedag, Amsterdam, 9 December 1994.
- d'Hollosy W, **Witjes WPJ**, Mars NJI, de Vries Robbé PF, Debruyne FMJ, Wijkstra H: Knowledge-based support in study design of scientific urological research. Proc. IEEE-EMBS: 17th Ann Int Conf of Engineering in Medicine and Biology Society, Montréal, 1995.
- Rosier PFWM, **Witjes WPJ**, de Wildt MJAM, de la Rosette JJMCH, Debruyne FMJ: Urodynamic results of terazosin treatment for symptomatic BPH. Ned Tijdschr v Urologie 3: 2, 52, 1995.
- de Wildt MJAM, **Witjes WPJ**, Rosier PFWM, Debuyne FMJ, Wijkstra H, de la Rosette JJMCH: A urodynamic view on watchful waiting in patients with benign prostatic hyperplasia. Neurourol Urodyn 14: 566-567, 1995.
- Schulman CC, **Witjes WPJ**, van Cangh PJ, Debruyne FMJ and the European Cooperative Group on Neoadjuvant Treatment: Neoadjuvant therapy in localized prostate cancer. Proceedings of the 5th International Symposium on Recent Advances in Diagnosis and Treatment of Prostate Cancer, Quebec City, 21-23 September, 1995.
- van der Meijden APM, Doesburg WH, **Witjes WPJ**, Debruyne FMJ: A comparative study of intravesical instillation of Mitomycin C, of BCG-RIVM and of BCG-Tice in pTa-pT1 papillary carcinoma and primary cis of the urinary bladder. Libro de Abstracts. 22nd Congress Societé Internationale d'Urologie, Sevilla, 3-7 november: A185, 1991.
- Lycklama à Nijeholt GAB, Meuleman EJH, **Witjes WPJ**, Oerlemans SH, van Driel MF, Leliefeld HHJ, Kropman RF: A prospective study on the use of papaverine-phentolamine-injection in erectile dysfunction. Int J Impotence Res (suppl) 2; 4: P120, 1992.
- Buwalda P, Laduc R, **Witjes WPJ**, Oosterhof GON, Debruyne FMJ: Heeft een incidenteel aangetroffen prostaatcarcinoom invloed op de levensverwachting? Ned Tijdschr v Geneeskunde 137: 160, 1993.
- van Iersel MP, Geboers ADH, **Witjes WPJ**, de la Rosette JJMCH, Oosterhof GON: "Prostate Specific Antigen Density" (PSAD): correlatie met histologische diagnose van prostaatkanker, BPH en prostatitis. Ned Tijdschr v Geneesk 138: 2169, 1994.
- van der Meijden APM, Debruyne FMJ, **Witjes WPJ**, de Pauw M, Sylvester R, Oosterhof GON and members of the Dutch South-East Cooperative Urological Group and the EORTC GU Group: BCG-RIVM versus Mitomycin-C intravesical therapy in superficial bladder cancer. A prospective randomised EORTC study (30845). Proc. 23rd Congress Societé Internationale d'Urologie, Sidney, 18-22 September: A248, 1994.
- van der Meijden APM, Debruyne FMJ, **Witjes WPJ**, de Pauw M, Sylvester R, Oosterhof GON and members of the Dutch South-East Cooperative Urological Group and the EORTC GU Group: BCG-RIVM versus Mitomycin-C intravesical therapy in superficial bladder cancer. A prospective randomised EORTC study (30845). Ned Tijdschr v Urologie 2: 4, 72, 1994.

- de Wildt MJAM, Rosier PFWM, **Witjes WPJ**, te Slaa E, Caris C, Debruyne FMJ, de la Rosette JJMCH: Watchful waiting in the treatment of prostatism complaints: Do urodynamic parameters change ? Neurourol Urodyn 13: 4; 394-395, 1994.
- Thomas CMG, Segers MFG, **Witjes WPJ**, Oosterhof GON: Analytical and clinical evaluation of the Berilux PSA assay and comparison with Hybritech Tandem-E PSA. Proceedings of the International Society for Oncological and Biological Methods. Groningen, September 1994.
- d'Hollosy W, Hendriks BTh, **Witjes WPJ**, Debruyne FMJ, Wijkstra H: Improvement of data management in scientific urological research. Proc. IEEE 16th Ann Int Conf in Med and Biol 2: 1394-1395, Baltimore, November 3-6, 1994.
- van Iersel MP, te Slaa E, **Witjes WPJ**, de Graaf R, de la Rosette JJMCH: Clinical implications of the rise and fall of PSA after laserablation of the prostate. J Urol 153: 299A, 1995.
- van Iersel MP, te Slaa E, **Witjes WPJ**, de Graaf R, de la Rosette JJMCH: Klinische aspecten van de stijging en daling van serum PSA na laserablatie van de prostaat. Proc. NVU vergadering, 12 mei 1995, Veldhoven.
- te Slaa E, van Iersel MP, **Witjes WPJ**, Debruyne FMJ, de la Rosette JJMCH: Preliminary results of laserprostatectomy with the SLT contact laser fiber in patients with symptomatic benign prostatic enlargement (BPE). Proc. 3rd International Congress of the Dutch Urological Association. "Uro-technology: developments and progress in urology". Nijmegen, November 1-3: A43, 1995.
- d'Ancona FCH, Fransisca EAE, **Witjes WPJ**, Welling L, Debruyne FMJ, de la Rosette JJMCH: Hoge energie transurethrale microwave thermotherapie (HETUMT) versus transurethrale resectie van de prostaat (TURP) bij de behandeling van benigne prostaathyperplasie (BPH): resultaten van een prospectieve gerandomiseerde studie met 1 jaar follow-up. Proc. NVU vergadering, 1-2 November, 1996, Hengelo.
- d'Hollosy W, Walrave MHF, Hendriks BTh, **Witjes WPJ**, Debruyne FMJ, Wijkstra H: Towards a urological information system to facilitate clinical and scientific datamanagement. Proc. XIth congress of the European Association of Urology, Berlin, 13-16 July: A386, 1994.
- de Vries JDM, Feitz WFJ, Damen LM, **Witjes WPJ**: Bladder capacity in the treatment of nocturnal enuresis with desmopressin (Minrin®). Proc. 3rd International Congress of the Dutch Urological Association. "Uro-technology: developments and progress in urology". Nijmegen, November 1-3: A13, 1995.
- Kil PJM, Montagne GJ, Schroeder JJM, **Witjes WPJ**: Gerandomiseerde studie tussen contact en non-contact Laser Prostatectomie (LP). Proc. NVU vergadering, 19 april 1996, Dronten.
- d'Hollosy W, Mars K, de Vries Robbé P, **Witjes WPJ**, Debruyne FMJ, Wijkstra H: Standardized protocol design of urological trials. Ned Tijdschr v Urologie 3: 3, 73, 1996.
- d'Hollosy W, de Vries Robbé PF, Mars NJL, **Witjes WPJ**, Debruyne FMJ, Wijkstra H: Representation of domain knowledge needed to define relevant study variables for clinical trials in urology. Proc. 18th Annual International Conference IEEE Engineering in Medicine and Biology Society.
- d'Hollosy W, Mars K, de Vries Robbé P, **Witjes WPJ**, Debruyne FMJ, Wijkstra H: Standardized protocol design of urological trials. Proc. XIIth congress of the

European Association of Urology, Paris, 1-4 September: p 104, A 349, 1996.
- Fernandez del Moral P, Dijkman GA, Debruyne FMJ, **Witjes WPJ**: Nieuwe strategie na falende eerstelijns hormonale therapie voor prostaatcarcinoom: resultaten van een klinische trial. Proc. NVU vergadering, 1-2 November 1996, Hengelo.
- Schulman CC, Oosterhof GON, van Cangh PJ, Debruyne FMJ, **Witjes WPJ** and the European Study Group on Neoadjuvant treatment: Multicentre study of neoadjuvant combined androgen deprivation therapy in T2-3, N0, M0 prostatic carcinoma. J Urol 151: 435A, 1994.
- Dijkman GA, Fernandez del Moral P, Debruyne FMJ, Denis L, **Witjes WPJ**: Liarozole in hormone resistant prostate cancer patients. Proc. 3rd International Congress of the Dutch Urological Association. "Uro-technology: developments and progress in urology". Nijmegen, November 1-3: A49, 1995.
- Debruyne FMJ, Forster G, Schulman CC, van Cangh PJ, **Witjes WPJ** and the European Study Group on Neoadjuvant treatment: European study of neoadjuvant combined androgen deprivation therapy in T2-3, N0, M0 prostatic carcinoma. J Urol 155: A1337, 1996.
- de Mulder PH, Debruyne FMJ, van Oosterom A, Bouffioux C, Vermeylen K, Sylvester R, **Witjes WPJ** on behalf of the EORTC-GU group: EORTC randomized phase II study of recombinant interferon alpha and gamma in advanced renal cell carcinom. Proc. 1st International Congress of the Dutch Urological Association. "Progress and controversies in Oncological Urology III". Rotterdam, October 9-13: A105, 1991.

Scientific publications

- **Witjes WPJ**, Vollaard EJ, Crul BJP, Helsper PE: Postoperative treatment of pain by sublingual "on demand" administration of buprenorphine in combination with naproxen or paracetamol. In: Topics in Clinical Pharmacy, Delporte JP, Moes A & Shafford A (eds) Uitg: European Society on Clinical Pharmacy, Uithoorn: 319-323, 1989.
- **Witjes WPJ**, Vollaard EJ, Crul BJP, Limpens C: Sublingual buprenorphine obviates the need for parenteral morphine in cholecystectomy patients. In: Progress in Clinical Pharmacy: Rational Use of Drugs, Muller NF & Hekster YA, (eds) Uitg: European Society on Clinical Pharmacy, Den Haag: 292, 1989.
- **Witjes WPJ**, Crul BJP, Vollaard EJ, Joosten HJM, van Egmond J: Application of sublingual buprenorphine in combination with naproxen or paracetamol for postoperative pain relief in cholecystectomy patients in a double blind study. Acta Anesthesiol Scand 36: 323-327, 1992.
- **Witjes WPJ**, van der Meijden APM, Roos EPM, Witjes JA, Steerenberg PA, Doesburg W, Debruyne FMJ: BCG-RIVM versus BCG-Tice versus Mitomycin-C in superficial bladder cancer. Rationale, design and interim analysis of the trial of the South-East Cooperative Urological Group, The Netherlands. In: Progr Clin Biol Res; Volume 378, EORTC GU Group Monograph 11: Recent Progress in Bladder and Kidney Cancer. Fritz H Schröder (Ed.) Wiley-Liss, New York: 59-67, 1992.
- **Witjes WPJ**, Meuleman EJH, Lycklama à Nijeholt GAB, van Driel MF, Leliefeld HHJ, Kropman RF, Doesburg WH: The efficacy and acceptance of autoinjectiontherapy with the combination of papaverine/phentolamine in patients with chronic erectile dysfunction. A prospective multicentre trial in 60 patients. Int J Impotence Res 4; 2: 65-72, 1992.
- **Witjes WPJ**, Horenblas S, Oosterhof GON, Schaafsma HE, Debruyne FMJ: Neo-adjuvant therapy in prostate cancer - Is it of any use ? Eur Urol 24: 433-437, 1993.
- **Witjes WPJ**, Oosterhof GON, Schaafsma HE, Debruyne FMJ: The value of neoadjuvant therapy in localized prostate cancer. Int J of Urology 2: 1; 1-5, 1995.
- **Witjes WPJ**, Oosterhof GON, Schaafsma HE, Debruyne FMJ: Current status of neoadjuvant therapy in localized prostate cancer. The Prostate 27: 297-303, 1995.

- **Witjes WPJ**, Horenblas S, Oosterhof GON, Schaafsma HE, Debruyne FMJ: Qual e il ruolo della terapia neo-adiuvante nel carcinoma prostatico ? Minerva Urol Nefrol 47: 209-214, 1995.
- **Witjes WPJ**, Witjes JA, Oosterhof GON, Debruyne FMJ on behalf of the Dutch South-East Cooperative Urological Group: Update on the Dutch cooperative trial: Mitomycin-C versus BCG-Tice versus BCG-RIVM in the treatment of patients with pTa-pT1 papillary carcinoma and carcinoma in situ of the urinary bladder. Seminars in Urology 14 (suppl. 1): 10-17, 1996.
- **Witjes WPJ**, Rosier PFWM, de Wildt MJAM, van Iersel MP, Debruyne FMJ, de la Rosette JJMCH: Urodynamic and clinical effects of terazosin therapy in symptomatic patients with benign prostatic hyperplasia. J Urol 155: 1317-1323, 1996.
- **Witjes WPJ**, de Wildt MJAM, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Variability of clinical and pressure-flow study variables after 6 months of watchful waiting in patients with lower urinary tract symptoms and benign prostatic enlargement. J Urol 156: 1026-1034, 1996.
- **Witjes WPJ**: Clinical trial management in het ziekenhuis. In: J.M.A. Penders (ed): Clinical trial management in het ziekenhuis. Boerhave commissie voor Postacademisch Onderwijs in Geneeskunde, Rijksuniversiteit Leiden. ISBN 90-6767-319-6. pp 31-41, 1996.
- **Witjes WPJ**, Schulman CC, Debruyne FMJ for the European study group on neoadjuvant treatment of prostate cancer: Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T_{2-3} N_0 M_0 prostatic carcinoma. Urology, In Press, 1997.
- **Witjes WPJ**, Rosier PFWM, Caris CTM, Debruyne FMJ, de la Rosette JJMCH: Urodynamic and clinical effects of terazosin therapy in symptomatic patients with and without bladder outlet obstruction. A stratified analysis. Urology 49: 197-206, 1997.
- **Witjes WPJ**, de la Rosette JJMCH, Donovan JL, Peters TJ, Abrams P, Kay HE, Höfner K, Kinn A-C, Walter S and the ICS-'BPH' study group: The ICS-'BPH' Study: International differences in lower urinary tract symptoms and related bother. J Urol, In Press, 1997.
- **Witjes WPJ**, Robertson A, Rosier PFWM, Neal DE, Debruyne FMJ, de la Rosette JJMCH: Urodynamic and clinical effects of non-invasive and

minimally invasive treatments in elderly males with lower urinary tract symptoms stratified according to the grade of obstruction. Urology, In Press. 1997.

- **Witjes WPJ**, Aarnink RG, Ezz-El-Din K, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: The correlation between prostate volume, transition zone volume, transition zone index and clinical and urodynamic investigations in patients with symptomatic benign prostatic hyperplasia. Brit J Urol, In Press. 1997.
- **Witjes WPJ**, de la Rosette JJMCH, Zerbib M, Vignoli GC, Geffriaud C, Debruyne FMJ, Wijkstra H: Computerized artifact correction of uroflow-curves: Towards a more consistent quantitative assessment of maximum flow. European Urology, In Press.
- **Witjes WPJ**, Wijkstra H, Debruyne FMJ, de la Rosette JJMCH: Quantitative assessment of uroflow: Is there a circadian rhythm ? Urology, In Press, 1997.
- Crul BJP, **Witjes WPJ**, Vollaard EJ, Joosten HJM, van Egmond J: Sublinguale toediening van buprenorfine in combinatie met naproxen of paracetamol als pijnstilling bij patiënten na galblaasoperatie - een dubbelblind onderzoek. Ned Tijdschr v Anesthesiol 5: 173-178, 1992.
- Fernandez del Moral P, **Witjes WPJ**: Prostaatcarcinoom; Algemeen medische informatie. Ned Tijdschr Tandheelkd 99: 131-133, 1992.
- Debruyne FMJ, **Witjes WPJ**: Overview of current status of Total Androgen Deprivation in Metastasized Prostate Cancer. Eur Urol 24: (suppl. 2) 67-71, 1993.
- Debruyne FMJ and **Witjes WPJ**: Overview of the current status of total androgen deprivation in metastasized prostate cancer. World J Urol 11: 233-236, 1993.
- Debruyne FMJ und **Witjes WPJ**: Uebersicht über den derzeitigen Stand der totalen Androgenblockade bei metastasierendem Prostatakarzinom. Niere Blase Prostata aktuell 4: 73-80, 1993.
- Debruyne FMJ, **Witjes WPJ**, Schulman CC, van Cangh PJ, Oosterhof GON and The European Study Group on Neoadjuvant Treatment: A multicentre trial of combined neoadjuvant androgen blockade with Zoladex and Flutamide prior to radical prostatectomy in prostate cancer. Eur Urol 26 (suppl.1): 4, 1994.
- van Gils-Gielen RJM, **Witjes WPJ**, Caris CTM, Debruyne FMJ, Witjes

JA, Oosterhof GON and members of the Dutch South East Cooperative Urological Group: Risk factors in carcinoma in situ of the urinary bladder. Urology 45: 581-586, 1995.

- van Iersel MP, **Witjes WPJ**, de la Rosette JJMCH, Oosterhof GON: Prostate specific antigen density: correlation with histological diagnosis of prostate cancer, benign prostatic hyperplasia and prostatitis. Brit J Urol 76: 47-53, 1995.
- de la Rosette JJMCH, **Witjes WPJ**, Debruyne FMJ, Kersten P, Wijkstra H: Improved reliability of uroflowmetry investigations: results of a portable home-based uroflowmetry study. Brit J Urol 78: 385-390, 1996.
- Debruyne FMJ, **Witjes WPJ**, Fitzpatrick J, Kirby R, Kirk D, Prezioso D for the ITT Group: The International Terazosin Trial (ITT): A multicentre study of the long-term efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. Eur Urol 30: 369-376, 1996.
- van Iersel MP, **Witjes WPJ**, Thomas CMG, Segers MFG, Oosterhof GON, Debruyne FMJ: Review on the simultaneous determination of total prostate specific antigen and free prostate specific antigen. The Prostate (suppl.) 7: 48-57, 1996.
- de la Rosette JJMCH, **Witjes WPJ**, Schäfer W. Abrams P, Donovan JL, Peters TJ, Millard RJ, Frimodt-Møller C, Kalomiris P and the ICS-'BPH'study group: The relationships between lower urinary tract symptoms and bladder outlet obstruction - results from the ICS-'BPH' study. Submitted for publication.
- Debruyne FMJ, Oosterhof GON, **Witjes WPJ**: Neo adjuvante (inductieve) chemotherapie bij blaascarcinoom: een kritische analyse. In: Recente ontwikkelingen in de behandeling van prostaathyperplasie, prostaatkanker en blaaskanker. FH Schröder (Ed) Uitg: Medicom: 87-96, 1991.
- Witjes JA, van de Meijden APM, **Witjes WPJ**, Doesburg W, Schaafsma HE, Debruyne FMJ and the members of the Dutch South-East Cooperative Urological Group: A randomised prospective study comparing intravesical instillations of Mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 rumors and primary carcinoma in situ of the urinary bladder. Eur J Cancer 29A; 12: 1672-1676, 1993.
- de Mulder PHM, Punt CJA, **Witjes WPJ**, Debruyne FMJ: Therapie mit Zytokinen beim fortgeschrittenen Nierenzellkarzinom. In: Rübben H, Goepel M, Schmitz-Dräger BJ (eds): Immuntherapie in der Uroonkologie. Springer-Verlag, Berlin, Heidelberg, New York, pp 273-282, 1993.

- Vegt PDJ, Witjes JA, **Witjes WPJ**, Doesburg WH, Debruyne FMJ, van der Meijden APM: A randomized study of intravesical Mitomycin-C, BCG-Tice and BCG-RIVM treatment in pTa-pT1 papillary carcinoma and carcinoma in situ of the bladder. J Urol 153: 929-933, 1995.
- van Iersel MP, Thomas CMG, **Witjes WPJ**, de Graaf R, de la Rosette JJMCH, Debruyne FMJ: Clinical implications of the rise and fall of PSA after laser prostatectomy. Brit J Urol 78: 742-746, 1996.
- Selli C, Travaglini F, **Witjes WPJ** for the European Study Group on Neo-Adjuvant Treatment of Prostatic Cancer: Neoadjuvant therapy in patients with prostatic carcinoma. J Chemother 8, 4 (suppl) : 320-322, 1996.
- Crul BJP, Vollaard EJ, Helsper PE, **Witjes WPJ**, Limpens C: Sublinguale "on demand" toediening van buprenorfine in combinatie met naproxen of paracetamol geeft goede pijnstilling bij laparotomieën. Ned Tijdschr v Anesthesiol 2; 1: 16-19, 1989.
- van Iersel MP, Thomas CMG, Segers MFG, **Witjes WPJ**, Debruyne FMJ, Oosterhof GON: The use of 'ultrasensitive' prostate-specific antigen assays in the detection of biochemical recurrence after radical prostatectomy. Brit J Urol 77: 418-422, 1996.
- Debruyne FMJ, Dijkman GA, Lee DCH and **Witjes WPJ** on behalf of the Dutch South East Cooperative Urological Group: A new long-acting formulation of the LHRH analogue, goserelin: results of studies in prostate cancer. J Urol 155: 1352-1354, 1996.
- Fernandez del Moral P, Dijkman GA, Debruyne FMJ, **Witjes WPJ**, Kolvenbag GJCM for the Dutch South East Cooperative Urological Group: Three-month depot of goserelin acetate: clinical efficacy and endocrine profile. Urology 48: 894-900, 1996.
- Buzelin JM, Fonteyne E, Kontturi M, **Witjes WPJ**, Khan A for the European Tamsulosin Group: Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction. Brit J Urol, In Press, 1997.

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Castles made of sand
slip into the see
eventually...

Jimi Hendrix

Stellingen behorende bij het proefschrift

Micturition variables in the assessment and treatment of patients with lower urinary tract symptoms

door

Wim P.J. Witjes

Nijmegen, 21 mei 1997

1 Good science is to find a problem difficult enough to attract the best minds, but central enough to attrack funds, and then to find the best people to work on it. *James Watson*

2 The sympathetic nervous system plays an important etiologic role in hypertension, asthma and benign prostatic obstruction; the level of sympathetic drive reaches a peak in the morning, the time of the day at which most cardiovascular events occur, at which asthmatic patients have a decreased lung function and at which patients with benign prostatic obstruction have the smallest maximum urinary flow. *this thesis*

3 The most frequently reported lower urinary tract symptoms are associated with the voiding phase and the most bothersome symptoms are associated with the storage phase or with incontinence. *this thesis*

4 On the short term, in patients with severe bladder outlet obstruction, the urodynamic condition is more prone to improve than to deteriorate further regardless of the treatment the physician institutes. *this thesis*

5 The results of pressure-flow studies rather than symptom scores have an important role in predicting the efficacy of therapy and should therefore be used in the determination of the first choice of therapy. *this thesis*

6 Aan de software van een pasgeboren kind moet langdurig geprogrammeerd worden voor een niveau van acceptabel functioneren bereikt wordt.

7 Sublinguale toediening van bupenorfine op geleide van de behoefte van de patiënt is een goede methode voor postoperatieve pijnstilling.

8 Patiënten die deelnemen aan klinisch onderzoek, of zij nu de meest effectieve behandeling krijgen of niet, doen het in vele opzichten beter dan patiënten die dit niet doen.

9 Met het traditionele gezegde:

"*'t Is van eiges gekomme en 't zal dus van eiges ok wer overgaon*" (Oma Marie Derksen-Claassen, 1899-1992)

geeft men aan te beschikken over inzicht in het natuurlijke beloop van de ziekte en de placebo werking van de hiervoor beschikbare geneesmiddelen.

10 De effectiviteit van een experimentele behandeling in een fase 2 onderzoek wordt met name bepaald door de studie opzet en de selectie van patiënten.

11 Als Laurent Fignon in 1989 de weg van de minste weerstand had gevolgd had hij zonder twijfel de Tour de France voor de derde keer op zijn naam gebracht.

12 Hoe groter een nest des te agressiever de mier die daarvan deel uitmaakt.

13 Omdat de steller van een ontkennende vraag een ontkenning van het tegendeel dat gevraagd wordt verwacht dient een dergelijke vraag niet correct beantwoord te worden.

14 Het moet verboden worden om op de verpakking van allerlei cosmetica aan te geven dat het "dermatologisch getest" is, zonder dat ook de uitslag van die test genoemd wordt. *Maarten van Alfen*

15 Aan het begin van invoegstroken van file gevoelige snelwegen zou een verplicht ***ritspunt*** aangegeven moeten worden om voordringen via deze strook te voorkomen. *Maarten van Alfen*

16 De samenwerking tussen clinici en wetenschappelijke onderzoekers dient krachtig gestimuleerd te worden.

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