LARGE-SCALE APPLICATION OF (THE CONDOM CATHETER METHOD FOR) NON-INVASIVE URODYNAMICS IN A LONGITUDINAL STUDY OF CHANGES IN BLADDER CONTRACTILITY SECONDARY TO BENIGN PROSTATIC ENLARGEMENT

John Huang Foen Chung

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Large-scale Application of (the condom catheter method for) Non-invasive Urodynamics in a Longitudinal Study of Changes in Bladder Contractility Secondary to Benign Prostatic Enlargement

Grootschalige toepassing van de condoom catheter methode in een longitudinaal onderzoek naar veranderingen in de blaascontractiliteit ten gevolge van goedaardige prostaatvergroting

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CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

BOO:	Bladder Outlet Obstruction
BOOI:	Bladder Outlet Obstruction Index
BPE:	Benign Prostatic Enlargement
FVC:	Frequency Volume Chart
GP:	General Practitioner
I-PSS:	International Prostate Symptom Score
LUTS:	Lower Urinary Tract Symptoms
ml:	milliliter
ml/s:	milliliter per second
$p_{cond.max}$:	maximum condom pressure measured
$p_{det.qmax}$:	maximum detrusor pressure
$p_{ves.max}$:	maximum intravesical pressure
PV:	prostate volume
PVR:	Post void residual urine
Q_{max}:	maximum flow rate
SD:	standard deviation
URR:	Urethral resistance
Vol:	volume
w_{qmax} :	detrusor contractility

Chapter 1

INTRODUCTION

AIM OF THE STUDY

In a longitudinal study the changes in bladder muscle contractility in response to increasing obstruction of the lower urinary tract caused by prostatic enlargement were studied using non-invasive urodynamics.

BACKGROUND OF THE STUDY

With increasing age, the prostate of most men enlarges. An enlarged prostate is very rare in men younger than 30 years of age, it is common in men over 50, and histological criteria for it are met by 88% of men over the age of 80 [1,2,3]. The overgrowth of prostatic tissue occurs usually in the transitional zone resulting in compression of the urethra and Bladder Outlet Obstruction (BOO). This may cause Lower Urinary Tract Symptoms (LUTS): both irritative and obstructive urinary symptoms, to a degree that makes emptying the urinary bladder literally impossible: urinary retention. Also, resulting from the increased bladder pressure, upper urinary tract damage, stone formation and /or renal failure may occur.

In response to the increasing resistance to urinary flow caused by the enlarging prostate, the urinary bladder anatomically and functionally changes. The bladder wall irregularly thickens, which is called trabeculation [4]. The pressure measured in the bladder during voiding also increases. This is called “compensation” of the bladder muscle. The occurrence of compensation has been disputed, as the increased voiding pressure in “compensated” bladders may also result from voiding at a different setpoint on an unaltered pressure-flow-rate characteristic, but it has been demonstrated in our animal model [5]. The existence of a decompensation phase is undisputed. In the decompensation phase the urinary bladder is damaged to such a degree, that effective bladder emptying is not possible anymore, even when the obstruction is relieved. However, the onset of this phase is poorly defined and no data is available on the reversibility of changes leading up to it. Compensation and decompensation of the urinary bladder muscle are thus important issues in the decisions on treatment of prostatic enlargement. In some stage of prostatic enlargement, preferentially before retention occurs, surgery becomes necessary. It is recommended that the decision to operate is (among others things) based on a measure of the degree of obstruction of the urinary stream by the prostate.

INVASIVE URODYNAMICS

When a man suffers from LUTS, an appropriate diagnosis is needed to distinguish between two main causes: an enlarged prostate obstructing the bladder outlet or a weakly contracting bladder muscle. Adequate information on the function of the bladder muscle can be acquired

by calculating its contractility from urodynamic measurements of pressure and flow-rate during voiding. Urodynamics is the discipline performing such measurements.

The International Continence Society (ICS) developed a provisional method to diagnose BOO in patients with LUTS: an invasive pressure-flow study [6], which is currently most used in the clinic. In a pressure-flow study the urinary flow rate is measured in combination with invasive measurement of bladder pressure during voiding. The pressure in the bladder and the abdomen are measured by a catheter inserted into the bladder via the urethra and another one inserted in the rectum. The bladder pressure minus the abdominal pressure is the detrusor pressure. The flow rate is recorded using (e.g.) a rotating-disk flow meter.

From the maximum flow rate and the detrusor pressure (at maximum flow rate) the Bladder Outlet Obstruction Index (BOOI) is calculated as: the detrusor pressure minus twice the flow rate. BOOI less than 20 is diagnosed as non-obstructed, higher than 40 as obstructed. If BOOI is between 20 and 40 the diagnosis is equivocal and further testing is needed. Thus, when a high bladder pressure is needed to produce a low flow rate an obstruction of the bladder outlet, possibly by an enlarged prostate, is the most probable cause of the symptoms. A low flow rate generated by a low bladder pressure is caused by a weakly contracting bladder. This invasive catheter method is effective, but also expensive, patient unfriendly and may induce urethral trauma [7,8]. For this reason these measurements are not performed as often as desirable, and have, with one exception [9], not been applied in epidemiological studies. In the one and only study that did involve pressure/flow studies in elderly males without voiding problems, attention was focussed on analysis of the urethral resistance, and detrusor function was not quantified. Therefore no reference data on the development of the contractility of the bladder muscle in response to prostatic enlargement is available, and it is not possible to predict if and when a certain degree of obstruction of the outflow tract will cause irreversible damage to the bladder wall muscle.

NON-INVASIVE URODYNAMICS

Recently, more patient friendly and non-invasive measurement techniques for diagnosing BOO have been developed and tested: Doppler Flowmetry [10], the condom catheter method [11], the cuff method [12], Penile Compression Release [13], ultrasonography of bladder wall thickness [14], and Perineal Noise Recording [15]. In this thesis a large-scale application of the condom catheter method in a longitudinal survey is presented.

Previous study showed that on the basis of a combination of isovolumetric bladder pressure and maximum flowrate, classification of Bladder Outlet Obstruction is possible [16]. Pel and van Mastrigt developed an external condom catheter to measure this bladder pressure

non-invasively [17,18]. Instead of measuring the pressure proximally of the urethra by using a transurethral catheter positioned in the bladder, the pressure is measured distally, in a condom attached to the urethra during an interruption of flow. The pressure measured in the condom during such an interruption represents the isovolumetric bladder pressure. The change of the location of measurement avoids the insertion of a catheter and reduces the risk of damaging and infecting the urethra and bladder.

Pel et al explored the possibilities of the condom catheter as a new classification tool to identify BOO in patients with LUTS [19]. The results of measurements done in healthy volunteers with dormant LUTS and patients with LUTS show that if the free flow rate of the subject exceeds 5.4 ml/s, straining during voiding is avoided and the flow of urine is continuous, then a reliable bladder pressure measurement can be done with the condom method. It was shown that this isovolumetric bladder pressure measured with the condom method can be used to classify BOO by combining it with the maximum free flow rate. In a non-invasive nomogram in which the maximum condom pressure is plotted versus the maximum flow rate, non-obstructed, equivocal and obstructed patients could be separated. This non-invasive method may widen the clinical application of urodynamics. It provides a patient friendly alternative to investigate a large group of patients or volunteers in epidemiological studies.

Diagnosis of BOO with the condom method is based on a combination of the isovolumetric bladder pressure and a separately measured free flow rate. In itself, the isovolumetric bladder pressure is a measure for urinary bladder contractility. Using the newly developed and validated method therefore, urethral resistance and urinary bladder contractility can be assessed non-invasively. The condom method creates a unique possibility to study changes in bladder contractility in the male population.

THREE STUDY ROUNDS IN FIVE YEARS

Prostatic enlargement develops over a very long period of time. To study its development, and the response of the urinary bladder to the increasing obstruction, it is necessary to regularly evaluate a group of (otherwise) healthy males during 40 years (ages 40-80). The practical implementation of this in this study is to follow a number of age stratified cohorts during a shorter period. Eight cohorts, with initial ages of 38-42, 43-47, 48-52, 53-57, 58-62, 63-67, 68-72, and 73-77 were formed. Each cohort will be followed for five years, so that the endpoint of each cohort matches the starting point of the next, and will be investigated at the start of the study, at approximately the midpoint, and after five years.

LARGE-SCALE APPLICATION

Statistically, the study aims at determining reliable reference values for bladder contractility. For the determination of these reference values it is necessary to estimate a statistically accurate standard deviation from the data. In the literature [20] the necessary number of subjects in each cohort has been stated to be 100. By assuming that de standard deviation changes gradually with age, regression analysis can be used to reduce the number of subjects in each age category to 75. The youngest cohort of subjects was made significantly larger (300) to enable longitudinal follow up of these subjects over a longer period of time. The necessary number of subjects was thus estimated at 300 + 7*75 =825.

OUTLINE

In chapter one (introduction) I briefly described the development of a feasible non-invasive method for measuring bladder presure, and its application in a longitudinal study on changes in bladder contractility in response to benign prostatic enlargement. In chapter two I report on applicability, suitability and reproducibility of this method for measuring the isovolumetric bladder pressure. The method was tested and evaluated in 1200 male vounteers. In each volunteer a bladder pressure measurement was done (at least) twice for comparative analysis. In chapter three the data from all the double bladder pressure measurements was used to compare the repeatability of the non-invasive method to that of pressure-flow studies in a comparable population of patients.

Epidemiological aspects of recruitment of the1200 male volunteers recruited by general practioners were studied in chapter four. The prostate volume in the longitudinal study was estimated non-invasively too. In chapter five the difference between a transabdominal and a transrectal ultrasound approach for measuring prostate volume was studied. Two series of measurements in 100 subjects were done. In the first series, transabdominal and transrectal sonography were pairwise compared in each subject. In the second series, transabdominal measurements were done with two devices (a hospital Aloka® SSD-1700 and a portable Aloka® SSD-900).

In chapter six the correlation between non-invasive urodynamic data, International Prostate Symptoms Score (I-PSS) and prostate volume was studied. In chapter seven a comparative analysis of the reproducibility and applicability of the condom catheter method for non-invasive urodynamics in two Dutch centres was done. Non-invasive data from the longitudinal study in Rotterdam were compared with those from a randomized controlled trial completed at the University of Maastricht in Maastricht.

As the volunteers also completed frequency volume charts, age and volume dependent normal values of frequency volume parameters of 935 healthy males are reported in chapter eight. From the diaries voiding parameters and age and voided volume stratified normal values were derived.

In chapter nine this thesis is concluded with a general discussion, which summarizes the findings and results from the first round of the non-invasive study on 1200 male volunteers conducted between 01 November 2001 and 31 december 2003.

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Chapter 2

APPLICABILITY AND REPRODUCIBILITY OF CONDOM CATHETER METHOD FOR MEASURING ISOVOLUMETRIC BLADDER PRESSURE

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ABSTRACT

Objectives. To report on the applicability, reproducibility, and adverse events of the noninvasive condom catheter method in the first 730 subjects of a longitudinal survey of changes in urinary bladder contractility secondary to benign prostatic hyperplasia, in which 1300 men will be evaluated three times in 5 years using this method.

Methods. Subjects were recruited by general practitioners, general publicity, and e-mail. Only those meeting the study criteria were entered in the study. If the free flow rate exceeded 5.4 mL/s, at least two consecutive condom pressure measurements were attempted using the condom catheter method. The condom pressure measured reflected the isovolumetric bladder pressure, a measure of urinary bladder contractility. The reproducibility of the method was quantified by a difference plot of the two maximal condom pressures measured in each subject.

Results. In 618 (94%) of 659 eligible participants, one condom pressure measurement was completed; two measurements were done in 555 (84%). The maximal condom pressure ranged from 28 to 228 cm H_2O (overall mean 101, SD 34). A difference between the two pressures of less than -21 cm H_2O was found in 80%. The mean difference was -1 cmH_2O (SD 18), significantly different from 0. Some adverse events such as terminal self-limiting hematuria were encountered.

Conclusions. The condom catheter method is very suitable for large-scale use. It has a success rate of 94% and a reproducibility comparable to that of invasive pressure flow studies.

INTRODUCTION

Because conventional urodynamic methods are invasive and patient unfriendly, they are not extensively applied. Recently, methods for noninvasive urodynamic studies were introduced. A complete overview of the noninvasive methods has been provided by van Mastrigt and Pel [1,2].

The condom catheter method [3] enables noninvasive measurement of the isovolumetric bladder pressure in a patient-friendly way. Therefore, it might offer an opportunity for large-scale applications, both clinically and epidemiologically. We started a longitudinal study of changes in urinary bladder contractility secondary to benign prostatic hyperplasia [4]. At the endpoint, 1300 men will have been studied three times in 5 years. Because the condom catheter method is quite new, the applicability, reproducibility, and adverse events of this method in the first 730 investigated subjects are reported here.

MATERIAL AND METHODS

RECRUITMENT

We plan to study 825 volunteers three times in 5 years. Because a number of volunteers will be lost to follow-up, the initial group will comprise approximately 1300 men. The present study reports the results for the first 730 subjects.

General practitioners in the municipality of Schiedam, with approximately 75,000 inhabitants, were approached to invite their male patients to participate in the study. The inclusion criteria were age 38 to 77 years, informed consent, and the ability to continuously void in the standing position with a maximal flow rate of at least 5.4 mL/s. Men with a history of any heart condition, congenital or acquired conditions, or surgery of the lower urinary tract, current lower urinary tract or anticoagulation therapy, and diseases altering urinary tract function, were excluded. To prevent contamination of the equipment, men with certain viral conditions such as human immunodeficiency virus were also excluded. The general practitioners primarily reviewed their patient records according to the inclusion and exclusion criteria and invited the selected men by mail.

Volunteers responding to publicity by the main sponsor of the study, the Dutch Kidney Foundation, also took part in the study. Employees of the Erasmus Medical Center were also invited by e-mail. In a different procedure, the male patients of some general practitioners were invited to the general practitioner's practice. There they were informed about the study,

their prostate volume was assessed by transabdominal ultrasonography, and they were invited to participate further in the study. In all cases, the men were asked to make an appointment for investigation at the Erasmus Medical Center.

DATA COLLECTION

Each session at the Erasmus Medical Center started with history taking and a short physical examination. Next, at least one free flow rate measurement was done to verify continuous voiding with a maximal flow rate of at least 5.4 mL/s. If so, the subject underwent at least two attempts to measure the bladder pressure noninvasively using the condom catheter method. A minimal flow rate of 5.4 mL/s is necessary for the condom pressure to reflect the bladder pressure accurately [5]. For the pressure measurement, a modified incontinence condom with a thickened shaft to withstand high pressures was fitted to the penis. Leakage of the condom was prevented by taping an elastic tape (Parafilm) over the condom and part of the skin of the penis. In between the pressure measurements, the condom remained attached to the penis, while the subjects "filled" their urinary bladder by drinking mineral water. Figure 1 illustrates how the condom was connected to a dome with three different metal outflow resistances fitted with tubes that could be independently closed by pneumatic valves. The dome was screwed on a pressure transducer. During voiding, eight different levels of outflow resistance could be selected by manipulating the switches on an Andromeda Medical Systems measuring unit. After setting the correct zero pressure, the measurement started. After the start of micturition, the outflow resistance was increased stepwise by closing different tubes. Consequently, the pressure in the condom began to rise to a preload pressure. At a value of approximately 40 to 50 cm H_2O [6], the remaining valves (ie, tubes) were closed, completely interrupting the urine outflow. The pressure in the condom quickly rose and reached a plateau value. At that equilibrium, the condom pressure reflected the isovolumetric bladder pressure. Shortly thereafter, the preload pressure was restored by reopening the corresponding valves to allow continuation of voiding, which was shortly thereafter interrupted again. This action was repeated several times. The outflow tubes drained into a Dantec rotating disk uroflow transducer. The flow rate, condom pressure, and valve settings were simultaneously recorded.

Once a week, the flow and pressure transducers were calibrated. The condoms and tubes were disposable and the domes and pressure transducer reusable. The domes were disinfected with 70% alcohol in accordance with the regulations of the Prevention of Infection Unit of the Hospital.

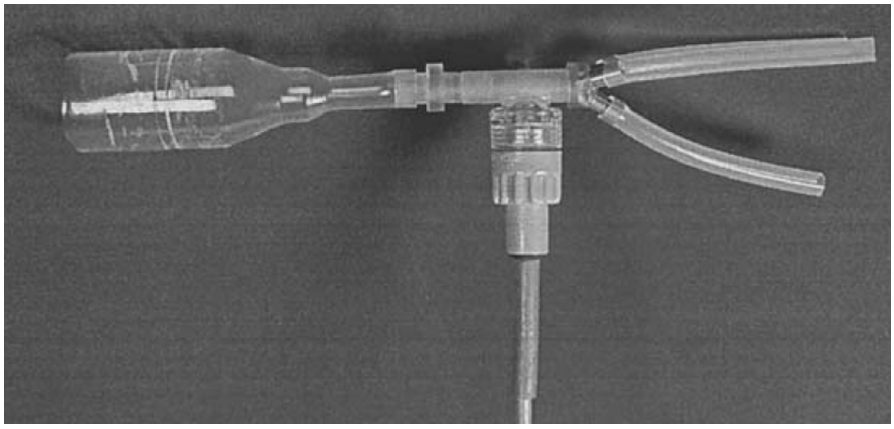

Figure 1. Main parts of condom catheter. Modified incontinence condom attached to dome screwed onto reusable pressure transducer. Dome has three different metal outflow resistances fitted with tubes that can be remotely and independently closed by pneumatic valves

DATA PROCESSING

The maximal values of the condom pressure attained during flow interruption were displayed by a Matlab program, and corrected if necessary.

For the evaluation of reproducibility, only subjects with at least two successful pressure measurements were selected. If more than two successful measurements had been obtained, the last two were chosen for this analysis. Generally, the last measurements are the most reliable, because the subjects have become accustomed to the procedure. Using the best (highest), rather than the last, measurements would introduce bias. The reproducibility was quantified using a difference plot according to Bland and Altman [7]. All history taking, physical examinations, measurements, and analyses were done by the primary author (J.W.N.C.H.F.C.).

RESULTS

Figure 2 is a flowchart illustrating the recruitment of subjects from November 19, 2001 to March 31, 2003. Of the 730 recruited men, 659 underwent the condom pressure measurement. One successful measurement was completed in 618 (94%) and twomeasurements were completed in 555 subjects (84%). All double bladder pressure measurements were done in the same session on the same day.

Figure 3 displays an example of a successfully completed measurement. On the upper trace, the pressure changes in the condom are shown, and on the lower trace, the interrupted flow rate is shown. The maximal condom pressure was attained during the first interruption of voiding. In all the measurements, the maximal condom pressure values ranged from 28 to 228 cm H_2O (median 99, overall mean 101, SD 34). The interquartile range was 43 cm H_2O, 80 to 123 cm H_2O.

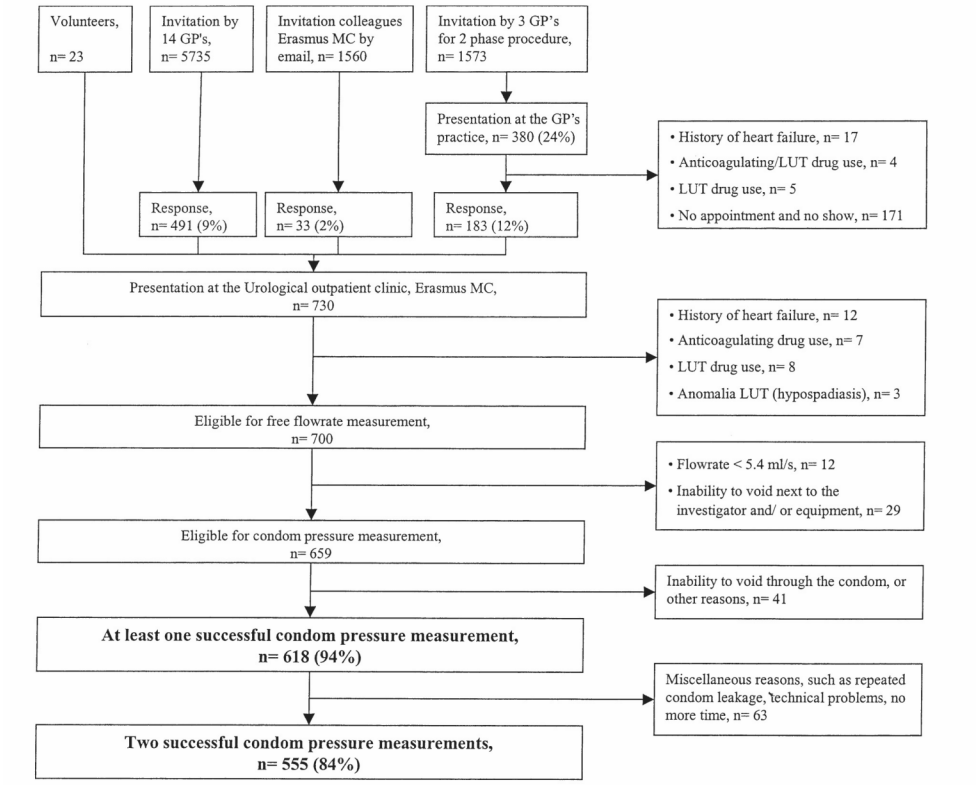

Figure 2. Flowchart illustrating recruitment of subjects, progress, and number of successful measurements

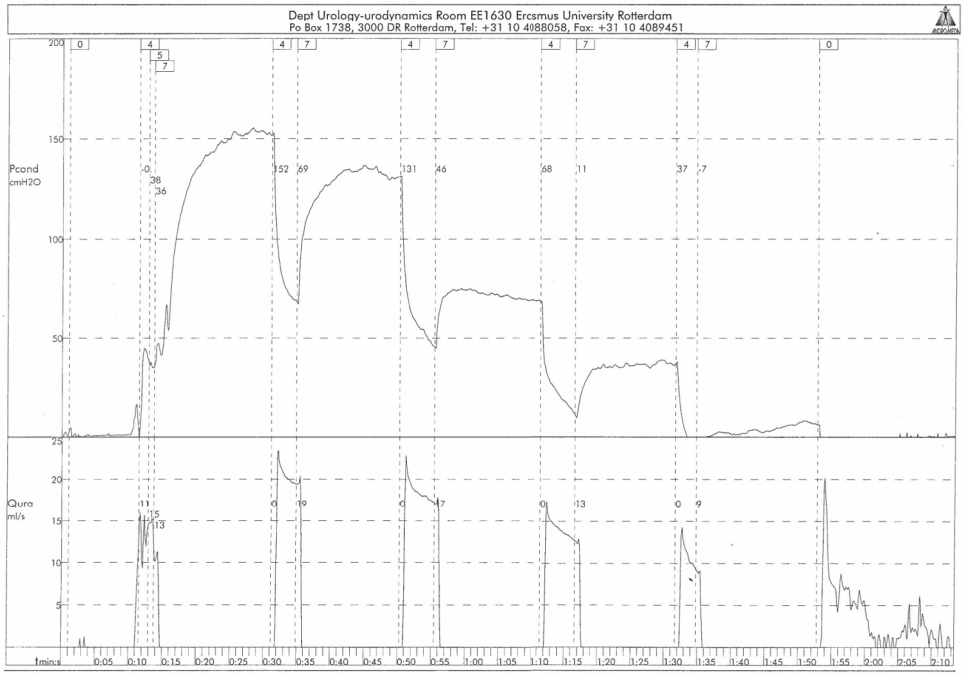

Figure 3. Upper trace shows pressure in condom. Lower trace shows interrupted flow rate. Numbered markers represent grades of outflow resistance applied; higher numbers indicate greater outflow resistance. Marker 7 represents complete closure of all valves, and thus complete interruption of flow rate. At time = 0 seconds, the subject was encouraged to start voiding, which happened at time = 11 seconds. Subsequently, outflow resistance was increased stepwise. As a consequence, the condom pressure began to rise quickly. At a preload pressure in the condom of approximately 40 cm H_2O, all valves were closed. Because the urine outflow was completely interrupted (lower panel), the pressure in the condom quickly reached a plateau value. At that equilibrium, the pressure in the condom reflected the isovolumetric bladder pressure. Shortly afterward, some valves were reopened to allow continuation of voiding at the preload pressure. Shortly thereafter, voiding was again interrupted. This action was repeated several times. In this example, the highest or maximal condom pressure measured, which occurred during the first interruption of voiding, was approximately 155 cm H_2O.

STATISTICAL ANALYSIS

Subjects with two completed condom pressure measurements were selected for the evaluation of the reproducibility. Figure 4 shows a difference plot of the results. On the vertical axis, the difference between the two maximal condom pressures measured in each subject is shown. The horizontal axis gives the mean of those two values. In 80% of the subjects, a difference in

pressure less than ±21 cm H_2O was found. The mean difference between the two measured pressures was -1 cm H_2O (SD 18), significantly different from 0 (Wilcoxon signed ranks test, $P<0.001$).

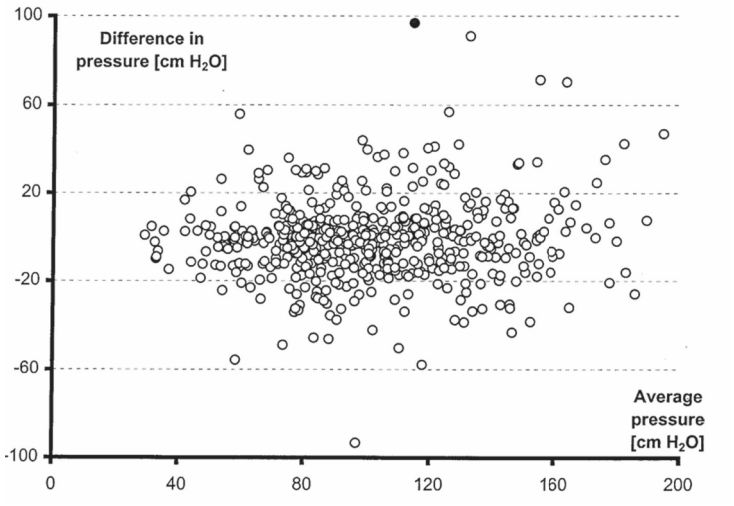

Figure 4. Difference between two maximal condom pressures measured in each subject plotted on vertical axis. Horizontal axis gives average of those two readings. The pressure difference was less than ±21 cm H_2O in 80% of subjects.

ADVERSE EVENTS

Quite unexpectedly, some adverse events occurred. These included a short-lasting tolerable stressing pain or an unpleasant feeling on the glans penis during the pressure measurement (65 [10%] of 659 men) and self-limiting, terminal (macroscopic) hematuria (45 men, 7%) during or immediately after the procedure. Other side effects were syncope after the pressure measurement (3 men, 0.5%), small hematomas on the skin of the penis (6 men, 0.9%), and a light oppressive pain, starting somewhat at the level of the bladder and radiating to the lumbar back region (7 men, 1%). Serious adverse events after the pressure measurement were acute urine retention in 1 man (0.2%) and, apparently, a bacterial infection of the lower urinary tract in 1 man (0.2%).

COMMENT

For this study, the recruitment of subjects was very difficult. The original method of directly inviting general practitioners' patients at the Erasmus Medical Center by letter gave a response rate of only 9% (number of patients presenting divided by number of letters). A small group of approximately 100 patients who were interviewed by telephone for their reasons for refusal, mostly indicated that the study was too time consuming. The "two-phase" procedure, inviting patients first to visit the general practitioners for ultrasound determination of the prostate volume had a greater response rate of 12%.

We have assumed that the different recruitment methods and the low response rate had no consequences for the conclusions drawn from the study, because the results do not reflect the properties of the general population but rather changes of properties of otherwise healthy volunteers.

The inclusion and exclusion criteria determined whether a subject might enter the study. Dormant lower urinary tract symptoms were not an exclusion criterion.

In the current study of 659 healthy volunteers, the success rate of the condom catheter method was 94% (number of subjects with at least one successful measurement divided by number of subjects eligible for pressure measurement).

In an earlier study [8], leakage around the condom was reported in 40% of the first 20 and 9% of the next 55 patients, showing a definite learning curve for preventing leakage. In the present study, the condoms remained attached to the penis in between the pressure measurements, probably increasing the risk of leakage as a result of the physiologic variation in the size of the penis. Nevertheless, only 73 (12%) of 618 had at least one leakage.

Figure 4 shows some remarkable outliers, representing a great difference between the twomaximal pressures measured. For example, the case marked by a filled circle was one of the very first volunteers, and an artefact in the pressure value was accidentally accepted as a correct maximal reading. To prevent bias in the analysis, no correction or repeated measurement was made when this outlier was observed in the plot. On average, the difference between the two measurements was very small (1 cm H_2O). Although this difference was statistically highly significant, it did not seem clinically relevant.

In a separate report [9], the within-session reproducibility of the condom catheter method was compared with that of invasive pressure flow studies in a comparable population examined at the Erasmus Medical Center. The standard deviation of the difference between the twomaximal condom pressure values measured divided by the difference between the

97.5 and 2.5 percentile of the mean was 0.15 for the noninvasive measurements. The same statistic was 0.12 for the detrusor pressure at maximal urinary flow rate, 0.21 for the maximal detrusor pressure, and 0.27 for maximal vesical pressure. This interim result confirmed that the reproducibility of the condom catheter method is comparable to, or slightly better than, that of invasive urodynamic studies.

Earlier, Rikken et al.10 demonstrated that the isovolumetric bladder pressure depended significantly on the voided volume and that the flow rate was unaffected after interruption for pressure measurement. We assumed that this was also true in the present study. Consequently, the variation in the maximal condom pressures measured in each volunteer may have been in part caused by variation in the bladder volume at the moment of the flow interruption. Controlling for this variation may further improve the reproducibility of this method.

Most adverse events were mild, short lasting, infrequent (overall less than 3%), and inherent to the subjects' sensibility and/or vulnerability. In the first 93 subjects, anticoagulation therapy was not an exclusion criterion. After introducing that criterion, the percentage of hematuria decreased from 16% to 7%. Two adverse events in two different men were more serious. The acute urinary retention in 1man was a rather unfortunate coincidence of circumstances. On his way home, he retained his urine too long, and at home, he did not seek medical attention until the next morning. A causal correlation between the second, bacterial infection of the lower urinary tract and the procedure was not certain.

CONCLUSIONS

For large-scale application, the condom catheter method is very suitable and useful, with reproducibility comparable to that of invasive pressure flow studies. The side effects were minimal, and some were avoidable. In this study, the method had a success rate of 94% in 659 men with a flow rate of at least 5.4 mL/s

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Chapter 3

COMPARISON OF REPEATABILITY OF NON-INVASIVE AND INVASIVE URODYNAMICS

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ABSTRACT

Aims: We have developed a method for the non-invasive measurement of urinary bladder pressure, and we apply this method in a longitudinal study of changes in bladder contractility in response to prostatic enlargement. In each volunteer in this study, we measure the bladder pressure twice. In the present study we have used this data to compare the repeatability of the non-invasive method to that of pressure-flow studies in a comparable population of patients.
Methods: Difference plots were made of non-invasive bladder pressure measurements in 457 volunteers and of pressure-flow studies in a comparable population of 397 male patients. To compare the repeatability of two different methods for clinical measurement, the standard deviation of differences between repeated measurements in one individual needs to be normalised. Often a normalisation by dividing by the mean is done. We show that that normalisation may lead to erroneous results.We have normalised the standard deviations by dividing by the difference between the 97.5th and 2.5th percentile of the mean of the two observations in each subject.
Results: Normalised repeatability of the non-invasive method was 0.15, that of the various parameters derived from the pressure-flow studies varied from 0.11 to 0.22.
Conclusions: We conclude that the repeatability of the tested non-invasive urodynamic method is comparable to, or slightly better than, that of pressure-flow studies. We further conclude that normalising standard deviations of differences by dividing by the difference between the 97.5th and 2.5th percentile of the mean is a suitable method to compare the repeatability of different methods for clinical measurement.

INTRODUCTION

We have developed a method for the non-invasive measurement of urinary bladder pressure [Pel and Mastrigt, 1999, 2001]. Basically, this method proceeds by an external and mechanical interruption of voiding through a modified incontinence condom, so that the isovolumetric bladder pressure is reflected in the condom, and can be measured there. Presently we apply this method in a longitudinal study of changes in bladder contractility in response to prostatic enlargement, with the aim of uncovering the time course of bladder compensation and decompensation [Huang Foen Chung et al., 2002]. A total of 1021 healthy men with ages 38-77 years and with a minimum urinary flow rate of 5.4 ml/sec were recruited by GP's and will be investigated three times in 5 years. The minimum flow rate requirement follows from our observation that at very small flow rates the accuracy of the non-invasive method rapidly declines [Pel and Mastrigt, 2003]. The reason for this degradation is that at very low flow rates it takes a long time for the pressure in bladder and condom to equalize, increasing the probability of bladder contraction inhibition or sphincter closure. This limitation probably also applies to other non-invasive methods of measuring isovolumetric pressure by interruption of voiding. To prevent regression to the mean, the flow rate cut-off will only be applied in the first evaluation of each subject. In a large number of men, two successive measurements of the bladder pressure in the first measurement session have been completed. We have used this data to assess the reproducibility or repeatability of the non-invasive measurement method [Huang Foen Chung et al., 2002, 2004].

The repeatability of a measurement method may be assessed by plotting the differences between repeated measurements on the same subject against their mean [Bland and Altman, 1986]. Provided there is no relation between differences and mean, repeatability may be quantified by the mean difference and the standard deviation of the differences. There is, however, no golden standard or norm to decide if the calculated repeatability is good or bad. For this reason, we wanted to compare the repeatability of the new, non-invasive, method for urodynamics with the existing invasive method. Such a comparison is not straightforward.

When two methods measure properties in different units, or at different scales, a normalisation is necessary to compare standard deviations. It is sometimes recommended to divide standard deviations by the mean for such a normalisation. However, this may introduce bias. As an example consider a series of 11 temperature readings [15, 16 ,17, 18, 19, 20, 21, 22, 23, 24, 25°C] and the same series of temperatures in degree Fahrenheit. Mean ± standard deviation of the readings in degree Celsius are 20 ± 3.32, whereas those of the readings in degree Fahrenheit are 68 ± 5.97. Although physically the variation in temperature in both series

is identical, the standard deviations in degree Celsius and degree Fahrenheit are different. Normalising by dividing by the mean yields 0.17 and 0.088, respectively, and therefore, does not help. In fact such normalising may be disastrous if the mean is close to zero. Earlier we suggested [Mastrigt, 2000] to normalise standard deviations by dividing by the difference between two extreme measurements, at both ends of the scale. In the case of the temperature measurements for instance by dividing by the difference between the temperature of boiling and freezing water. In the example this would yield two times 0.033, truly showing that the variation in both series is identical. For comparing noninvasive and invasive urodynamic repeatability, it is not easy to and examples of comparable extreme values. Therefore, we suggest to normalise the standard deviations of differences in repeatability tests by dividing by the range of the observations. More specifically, to exclude outliers, we suggest to divide by the difference between the 97.5th and the 2.5th percentiles. In the temperature example this gives two identical results of 0.33. On this basis we have compared the repeatability of non-invasive and invasive urodynamic measurements.

MATERIALS AND METHODS

We have analysed non-invasive measurements in the firrst 457 healthy male volunteers participating in our longitudinal study of changes in bladder contractility secondary to BPE. These volunteers first voided freely in a Dantec® rotating disc uroflow transducer. If the maximum free flowrate exeeded 5.4 ml/sec, a modified incontinence condom was attached to their penis. The outlet of the condom was connected to a plastic dome with a membrane, attached to a re-usable pressure transducer (Statham® P23XL).The dome had three metal outflow tubes with di!erent resistances to flow. Three tubes led from the resistances through pneumatic valves into aDantec® rotating disc uroflow transducer. The subjects voided through the condom, dome and tubes into the flowmeter. During voiding the resistance of the system was gradually increased by closing some of the pneumatic valves until a preload pressure in the order of 50 cm H_2O was attained. Subsequently all valves were closed, which interrupted the flow rate, while the subject was instructed to try to keep voiding without straining. The isovolumetric pressure in the bladder then equaled the pressure in the condom, which was recorded by the pressure transducer. After the pressure had reached a maximum, the earlier valve setting at the preload pressure was restored and the urinary stream resumed. The interruption was repeated several times in one voiding [Rikken et al., 1999]. The highest stable pressure reading $p_{cond.iso}$ represented the isovolumetric pressure of the bladder. In

conjunction with the maximum flow rate of a subject (obtained from the preceding free flow rate measurement) it may be used to non-invasively diagnose urethral obstruction [Pel et al., 2002].

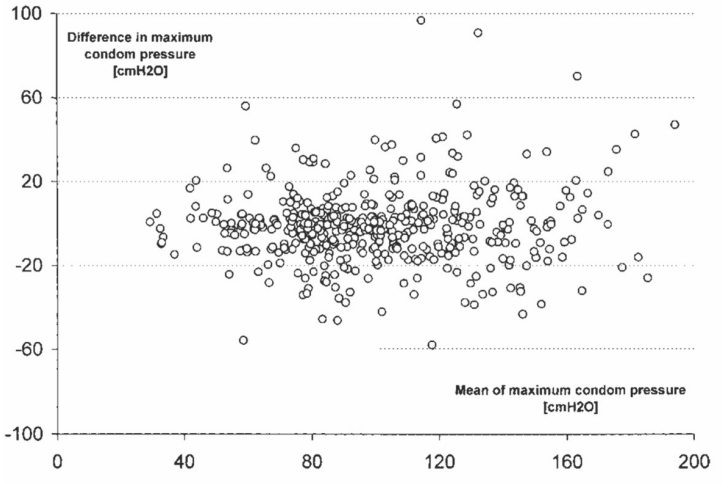
To compare the repeatability of the non-invasive method with the repeatability of the standard invasive method, we selected pressure-flow studies of 397 males in the same age range (38-77 years), with a maximum flowrate >5.4 ml/sec from the database of invasive urodynamic studies maintained in our centre since 1999. The studies were done with water filled lines (5F), transducers referenced to atmosphere and set at the level of the symphisis pubic, and a Dantec® rotating disc flowmeter. The maximum flowrate (Q_{max}), the associated detrusor pressure ($p_{det.qmax}$), the maximum detrusor ($p_{det.max}$) and intravesical ($p_{ves.max}$) pressures, the urethral resistance parameters URA [Griffiths et al., 1989] and BOOI [Abrams, 1999], and the detrusor contractility (w_{qmax}) [Griffiths et al., 1986] were automatically calculated. The maximum of Q_{max} was indicated in the tracings and could be corrected by the investigator if necessary. This was occasionally done if the indicated maximum was considered an artefact.

For both non-invasive and invasive parameters, the difference in parameter values of two measurements in the same subject was plotted as a function of the mean of the two values. When difference and mean were found independent, the standard deviation of the differences was calculated. The standard deviation was normalised by dividing by the difference between the 97.5th percentile and the 2.5th percentile of the mean of the two values.The term ‘‘percentiles of the mean’’ will be used for these percentiles. In both populations the measurements in each subject were taken on the same day so that disease progression or treatment did not contribute to the variability. It should be noted that the normalised standard deviations calculated in this way are population dependent, so that these repeatability indices can only be compared in the same population. Possible differences between the populations compared in this study were analysed and the consequences are discussed.

RESULTS

Figure 1 shows a di!erence plot of the non-invasive measurement results. The mean of the mean of each two values of $p_{cond.iso}$ and the standard deviation of the di!erence between those two values, see Table I, first row,were hardly di!erent fromthe results earlier reported in 73 volunteers [Huang Foen Chung et al., 2002], confirming the stability of these measures. The standard deviation of the differences divided by the di!erence between the 97.5th and 2.5th

percentile of the mean was 0.15.The second row of Table I gives statistics of the preceding free flow rate measurements in the same session.



Figur 1. Bladder pressure was non-invasively measured twice in one session in 457 male volunteers. The difference between each pair of two observations was plotted as a function of their mean.

Table 1. Statistics of Pairs of Non-Invasive (Rows 1–2) and Invasive (Rows 3–10) Urodynamic Parameters

Parameter	Unit	N	Mean	Percentile 2.5	Percentile 97.5	Standard deviation of difference	SD/(%97.5-2.5)
$p_{cond.iso}$	cm H_2O	457	101	44	166	18	0.15
Q_{max}	ml/sec	453	16	6	34	-	-
Q_{max}	ml/sec	397	12	6	30	3.6	0.15
$Q_{max>12}$	ml/sec	142	18	12	35	5.1	0.22
$p_{det.qmax}$	cm H_2O	397	48	16	108	110.12	
$p_{det.max}$	cm H_2O	397	66	29	141	24	0.21
$p_{ves.max}$	cm H_2O	397	136	77	233	42	0.27
URA	cm H_2O	397	24	7	55	6	0.12
BOOI		397	23	-32	94	14	0.11
w_{qmax}	W/m^2	126	8.8	4.7	19.1	3.1	0.22

N is the number of patients or volunteers, in each of which two measurements were done in one session. Mean is the mean of those two measurements, percentiles are percentiles of that mean, standard deviation is the standard deviation of the differences between the two observations in each individual. The second row shows statistics of separate, singlemeasurements of free flow rates in the volunteers that underwent the non-invasivemeasurements.The third row gives statistics for maximum flow rates in the patients that underwent the invasivemeasurements, the fourth row only for those patients with a maximum flow rate >12 (see text).

The other rows of the table give values for invasive urodynamic parameters in all 397 male patients in our database with age and flowrates comparable to the volunteers. Figure 2 gives an example of the di!erence plot of $p_{det.qmax}$, the plots of the other parameters were comparable, showing no relation between differences and mean, with one exception: the shape of the di!erence plot of Q_{max}, see Figure 3, suggested that the di!erences depended on the mean for low flow rates. For Q_{max},we therefore re-calculated the standard deviation of the differences for those patients in whom the mean Q_{max} was >12 ml/sec. These results are in the fourth row of the table. The third row gives statistics of Q_{max} in the entire population, for comparison with the non-invasive measurements. w_{qmax} results were only available for measurements made with the newest software version.

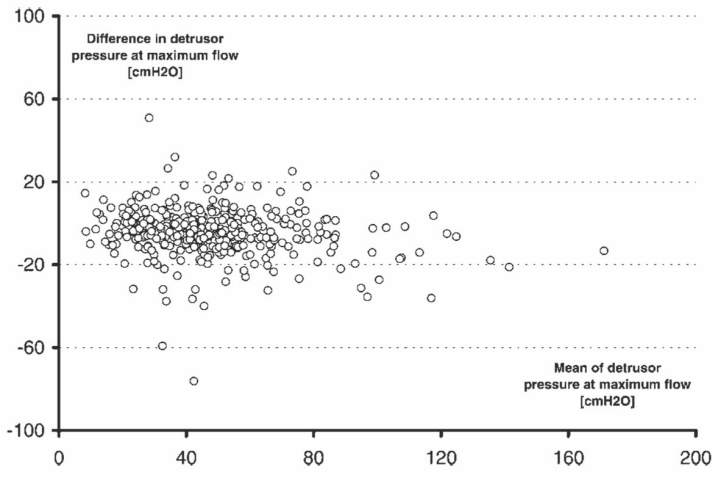


Figure 2. Detrusor pressure at maximum flow was measured twice in one session in 397 male patients. The difference between each pair of two observations was plotted as a function of their mean.

DISCUSSION

We have compared the repeatability of non-invasive and invasive urodynamics.We have done that because no gold standard exists for the repeatability of a test, so that it is not possible to conclude if a test has good or bad reproducibility. The comparison of both tests enables us to conclude that the repeatability of the condom catheter method for non-invasive urodynamics is in our hands comparable to, or slightly better than, that of an (invasive) pressure-flow study. Although there is considerable discussion on the repeatability or reproducibility of the latter,

see for instance [Sonke et al., 2000] and subsequent editorial comments, it is frequently used, and has been used for a considerable time, so it must at least have some value.

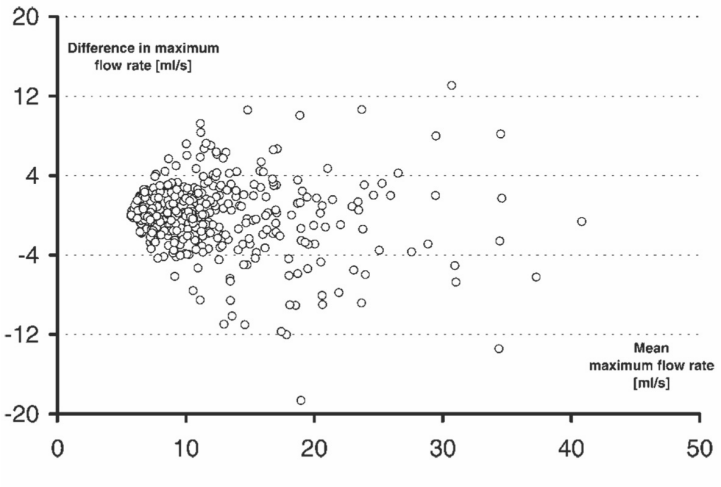


Figure 3. Maximum urine flow was measured in two pressure flow studies in one session in 397 male patients. The difference between each pair of two observations was plotted as a function of their mean

To compare the repeatability of two tests with different outcome variables, some kind of normalisation is required. The non-invasive method results in an estimate of the isovolumetric bladder pressure. The invasive method yields several pressures. Most often the detrusor pressure at maximum flow rate is used. This pressure is inherently di!erent from the isovolumetric bladder pressure. Not only is the detrusor pressure corrected for changes in abdominal pressure by subtraction of the rectal pressure, but it also is a pressure measured during voiding, which is smaller than an isovolumetric pressure as a result of the ongoing shortening of the detrusor muscle. We normalised the repeatability of the tests by dividing by the difference between the 97.5th and 2.5th percentile of the means of each pair of observations. The table shows that the normalised repeatability of $p_{det.qmax}$ was slightly better than that of $p_{cond.iso}$ (0.12 vs. 0.15). A factor contributing to this difference might be that $p_{cond.iso}$ is the maximum of a pressure signal, whereas $p_{det.qmax}$ is the reading of a pressure signal at a certain timepoint. As maxima are vulnerable to noise, this may favour the latter. $p_{det.max}$ and $p_{ves.max}$, both maxima, the first of the bladder pressure corrected for abdominal pressure, the second of the uncorrected bladder pressure have a normalised repeatability that is worse than that of $p_{cond.iso}$. Both straining effects and possible bladder instability may have

contributed to that. The urethral resistance parameters URA and BOOI are both calculated from the same primary variables, i.e., from Q_{max} and $p_{det.qmax}$ but using di!erent formulae. When properly normalised, they therefore should have the same repeatability although they measure resistance at very different scales, in different units. The BOOI range includes zero resulting in values of standard deviation/mean very different from those for URA, while the proposed normalised repeatability coefficient in Table I is approximately the same, illustrating the validity of the proposed normalisation. The parameter w_{qmax} conceptually approaches the non-invasively measured $p_{cond.iso}$ best, as it is roughly proportional to the isovolumetric detrusor pressure. It is estimated from measurements during voiding, and its repeatability seems inferior.

The difference plot of Q_{max}, measured in patients, has a shape suggesting that the di!erences in this parameter between two measurements in one subject depend on the mean. This is caused by the exclusion of subjects voiding with a Q_{max} <5.4 in the tested population. At for instance a mean Q_{max} of 8 ml/sec this means that the difference between two observations can never be larger than 2 x (8-5.4) = 5.2, causing an artificial cut off of differences at small flow rates. When differences depend on the mean, they cannot be characterised by an overall standard deviation. It has been suggested [Bland and Altman, 1986] that if differences are proportional to the mean, a log transformation should be applied. In our data however, the differences are only proportional to the mean over a limited range, as a result of the selection applied.We therefore calculated the standard devation of the di!erences only for flow rates >12 ml/sec when the differences were independent of the mean (see Figure 3). It may be expected that many variables will show a similar artificial limitation of differences. In fact, any variable with a ‘‘one sided’’ scale, such as a (bladder) pressure that cannot be negative, might suffer from this artefact. The difference plot of Figure 1 does not show this bias because voidings at very low pressures are unlikely. In the entire population the normalised repeatability of Q_{max} was smaller than in the subpopulation with Q_{max} >12 as expected.The better repeatability in the complete population must be considered an artefact: it is caused by the artificial limitation of di!erences.

As earlier remarked, the populations in which the two tests were done are different, which might bias the results obtained. Comparison of the maximum flow rates in both populations (rows 2 and 3 in Table I) shows, that the patients in which the invasive studies were done, tended towards lower flow rates so that they on average voided worse than the volunteers, possibly favouring the repeatability of the non-invasive method. The invasive measurements were done in a population of male patients, aged 38-77 years, with Q_{max} >5.4. In a population of 89 patients in another center, with lower urinary tract symptoms suggestive of bladder

outlet obstruction, considerable higher age (25th-75th percentile 60-72) and comparable Q_{max} (13 ± 7 (SD) ml/sec) the within patient standard deviations reported were similar to ours [Sonke et al., 2000]. Values for URA (7 cm H_2O), BOOI (14 dimensionless), and $p_{det.qmax}$ (12 cm H_2O) were in fact almost identical, but the within patient sd for Q_{max} was much smaller (2 ml/sec) than ours. This latter value may have been strongly biased by the above described selection effect. In yet another population of 105 patients with lower urinary tract symptoms [Hansen et al., 1997], with age range 43-88 years, more comparable to our population,with Q_{max} =11± 6 (SD) ml/sec) the standard deviation of the difference in $p_{det.qmax}$ was 13 cmH_2O, slightly worse than ours, and that of Q_{max} was 3 ml/sec, again better, probably as a result of the selection bias. The patient population we studied, therefore seems comparable to populations studied in other centres.

CONCLUSIONS

We conclude that the repeatability of the condom catheter method for non-invasive urodynamics in our population of volunteers is comparable to, or slightly better than, that of invasive urodynamics in a number of outpatient populations, both in our and in other centres. The latter repeatability is generally found acceptable [Sonke et al., 2000, editorial comments]. We further conclude that the repeatability of different medical tests, resulting in different physical variables, measured at different scales, may be compared by normalising the standard deviation of the differences between paired observations in one subject by dividing by the difference between the 2.5th and 97.5th percentiles of the mean of those observations. It should be noted that the data that we analysed was not measured for the purpose of this comparison. When reviewing difference plots of the data, some huge outliers were identified, some of which were caused by human error. These errors were not corrected for in this analysis, that therefore represents a worst case.

ACKNOWLEDGMENTS

This study was approved by theMedical Ethics Committee of Erasmus Medical Centre, number 202.680/2001/148. All volunteers signed an informed consent form.

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Chapter 4

EPIDEMIOLOGICAL ASPECTS OF RECRUITMENT OF MALE VOLUNTEERS FOR NON-INVASIVE URODYNAMICS

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ABSTRACT

Introduction: We studied epidemiological aspects of recruitment of volunteers for a non-invasive urodynamic study.

Materials and Methods: 9,236 volunteers were invited by 20 general practitioners (GPs), using two different recruitment methods, i.e. by mail only, or during a subsequent visit to the GP's office. Factors influencing the response rates were analyzed. We also tested how much the recruited population of volunteers differed from the general population, by comparing it to another, proven representative study carried out earlier in 1,662 subjects.

Results: In the recruited population the prostate volumes were not significantly different from the proven representative study, but the symptom score was statistically significantly higher, although the difference was so small it may be called clinically irrelevant. Recruitment of volunteers in two steps, i.e. asking them first to visit the GP's office, and inviting them there to visit the outpatient clinic, rather than directly inviting them (in writing) to the clinic seemed to lead to a higher response, although this effect could not be statistically discriminated from the difference in response rates between GPs.

Conclusion: The population recruited was not urologically different from the general population. The response depended on age, being highest around the age of 60, and increased with social economic status. It also depended on the GP who recruited the subjects, and/or on the recruitment method.

INTRODUCTION

With increasing age, the prostate often enlarges, usually as a result of benign prostatic hyperplasia (BPH). In response to the increasing resistance to urinary flow, the urinary bladder function changes. The function of the muscle can be assessed by calculating its contractility from urodynamic measurements of pressure and flow rate during voiding. Presently, such pressure measurements are invasive, i.e. a catheter has to be inserted into the blader, an expensive and time-consuming procedure, which is uncomfortable for the patient.

We have developed a non-invasive method of measuring the urinary bladder pressure using an external catheter based on an incontinence condom [1, 2] and we apply this method in a longitudinal study on healthy males [3].

Investigators in most community studies have not considered non-response bias; it is not known whether the study population is truly representative. One preliminary study on potential non-response bias, the Olmsted County Study, suggested that the response might have been affected by concern about urological disease [4] . The age distribution and non-response bias could have a large influence on the measured parameters. We therefore compared our study population with that of another study – the Krimpen study: normal values and determinants of urogenital tract (dys)function in older men [5] . That study is a longitudinal population-based study with 1,688 participants, a response rate of 50% and a non-responder study, in which the representativeness of the participating population was assessed. The authors described that the participants were representative for the total population: they were similar to those not responding on marital status, educational level, smoking and drinking habits, and treatment of chronic diseases, but had a slightly lower perceived general health status and more LUTS (lower urinary tract symptoms). Adjustment for non-response bias resulted in lower prevalences for all definitions of LUTS used. Additionally, to study possible sources of bias, we tested for differences between responders and non-responders in our study, between responders recruited using two different recruitment methods, and factors influencing the response rates. Using both the comparison with the proven representative study, and the tests for factors influencing the response rates, we address the hypothesis that the population of male volunteers that we recruited for a non-invasive longitudinal urodynamic study is unbiased and represents the general population.

MATERIAL AND METHODS

SCHIEDAM STUDY

Subjects for our longitudinal study were mainly recruited in Schiedam, a municipality near Rotterdam with approximately 75,000 inhabitants. General practitioners (GPs) in Schiedam were approached to invite their male patients. Inclusion criteria were signed informed consent from all volunteers, and ability to void in the standing position with a free flow rate of at least 5 ml/s. Men with a history of any heart condition, known neurological conditions, certain known viral conditions such as being HIV-positive, congenital or acquired conditions or surgery of the lower urinary tract (LUT), current LUT or anticoagulating therapy and diseases altering urinary tract function were excluded. Recruitment took place from November 2001 to December 2003. The study aimed at a rectangular age distribution, i.e. recruiting an equal number of patients in eight cohorts of 5 age years between 38 and 77. Two different recruitment methods were used. Using method 1 the GPs invited the selected men by mail, including a patient information form and a description of the study criteria, and asking them to make an appointment at the outpatient clinic of the Erasmus MC.

Using recruitment method 2 the GPs again primarily applied all the inclusion and exclusion criteria but now invited men by mail to visit the GPs' practices for an interview and transabdominal ultrasound examination of the prostate by the investigator. During this visit they were invited to a complete investigation at the Erasmus MC. During the investigations at the outpatient clinic the prostate volume of each subject was assessed by transabdominal ultrasonography using Aloka® SSD-500 or Aloka® SSD-900 Ultrasound Diagnostic Equipment. The prostate volume was calculated by a two-dimensional prolate spheroid approximation. At sufficient sensation of bladder filling, a free uroflowmetry was done to verify if a maximum flow rate (Q_{max}) of at least 5 ml/s could be achieved. If that condition was satisfied at least one non-invasive bladder pressure measurement was attempted as described before [3]. All subjects completed the International Prostate Symptom Score (IPSS).

In this report, we included all subjects invited by 20 GPs (n=9,236), and subdivided these into responders and non-responders. The flowchart (Figure 1) shows the numbers of subjects in each recruitment method. From an official registry a socio-economic continuous rank number (SES), related to all of the almost 4,000 postal areas in The Netherlands, and thus ranging from 1 (high status) to almost 4,000 (low status), was obtained and matched to the subjects by postal code. We stratified the subjects in age groups of 5 years (38-42, 43-47, 48-52, 53-57, 58-62, 63-67, 68-72).

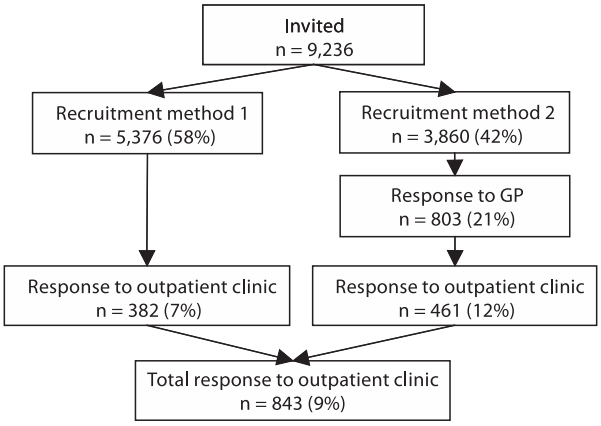

Figure 1. Flowchart showing the numbers of subjects in each recruitment method of the Schiedam study. The subjects were recruited by two different methods. Recruitment method 1: the volunteers were recruited by letter from their GP, asking them to make an appointment with our outpatient clinic at the Erasmus MC. Recruitment method 2: patients of GPs were asked to visit the GP's practice first for an interview and transabdominal ultrasound examination of the prostate. During this visit they were invited for a complete investigation at the outpatient clinic.

KRIMPEN STUDY

Names and addresses of all registered 3,294 men aged 50-75 years were obtained (reference date June 1995) from all general practices of Krimpen aan den IJssel, a commuter suburb near Rotterdam (The Netherlands) with approximately 28,000 inhabitants.

Men who had not undergone radical prostatectomy and had not had prostate or bladder cancer, neurogenic bladder disease or negative advice from their GP, and who were able to complete questionnaires and visit the health center were found eligible. In all cases, the GPs decided whether the patient could enter the study before invitation. The GPs' reasons for excluding any patient were checked by researchers in the electronic medical records. Recruitment took place from August 1995 to January 1998.

Digital rectal examination, transrectal ultrasonography (TRUS), uroflowmetry, post-void residual volume and serum prostate-specific antigen measurements were done at the Urology Outpatient Department.

TRUS was performed with a 7-MHz Brüel & Kjær multiplane sector scanning probe. The planimetric technique of volume measurement was used. This method involves measuring the surface area of transverse sections taken through the prostate at 5-mm intervals. The average

of two intervals multiplied by 5 mm provides the volume for each step and the cumulative volume allows the total prostatic volume (cm^3) to be derived. Uroflowmetry was done using a Dantec® Urodyn 1,000 flowmeter. The men were asked to visit the clinic with a full bladder and were instructed not to void in a toilet before that time.

The post-void residual urine volume (ml) in the bladder was computed by transabdominal ultrasonography, using an Aloka machine with a 3.5-MHz handheld probe using the formula 7/6 x (width) x (height) x (depth). The post-void residual was not computed if a man was unable to void in the uroflowmeter. The initial pre-micturitional bladder volume was calculated by summing the voided volume and the residual volume [6] .

Descriptives were calculated for the variables measured in both studies. As the two populations differ in age range and in exclusion criteria applied, two subpopulations were formed for comparison. In the restricted Schiedam population only patients with the same age range as in the Krimpen study (50 through 75) were included. The restricted Krimpen population was derived by deleting all subjects with a maximum flow rate <5 ml/s, as these were excluded in the Schiedam study. Crude differences between the restricted populations were tested for significance using the unpaired t test. The variables IPSS score, Q_{max}, voided volume and prostate volume were analyzed after logarithmic transformation, because of their positive skewness. Next, these crude differences were corrected for confounding variables, i.e. variables that are observed in both studies (Schiedam and Krimpen), that are known to be differently distributed between the populations and that are also known to have an impact on the four outcome variables considered. The first possibly confounding variable is age. Age is known to have an impact on prostate volume and, due to the design of the present study, its distribution differs between Schiedam (an intentional rectangular distribution) and the population participating in the Krimpen study (a distribution more representative of the general population). The second possibly confounding variable is social economic status. For each outcome variable, the confounding variables age and SES were included in a multiple linear regression model as restricted cubic splines along with population (Schiedam/Krimpen).

The use of restricted cubic splines is a flexible way of efficiently and (almost) optimally adjusting for continuous confounders [7].

Next we analyzed differences in the SES, the age, the recruitment method and the subjects' GPs between responders and non-responders of the Schiedam study. The subjects were stratified in age groups of 5 years, i.e. 37-42, 43-47, etc. We calculated the mean response rates (i.e. the number of responders divided by the number of invited subjects) for those age groups and GPs. We also categorized the SES in four categories and calculated mean response rates for those four categories. Subsequently, we calculated mean SES and recruitment

method for each GP and compared these by analysis of variance. Next we applied multiple logistic regression analysis in order to relate the response simultaneously to these variables. The GP with the lowest response was used as a reference.

Finally, we tested the differences in the distributions of age, SES, IPSS score, Q_{max}, voided volume and prostate volume between the two groups of responders to the outpatient clinic (Erasmus MC): recruited using methods 1 and 2, using unpaired t tests. Apart from age and SES, all variables were log transformed prior to analysis, as the original variables appeared to have positively skewed distributions. Next these variables were tested simultaneously using multiple logistic regression analysis.

RESULTS

In the Schiedam study, 9,236 volunteers were invited by 20 GPs. Figure 1 shows that eventually 843 showed up at the outpatient clinic. In the Krimpen study eventually 1,662 men were included. Summary statistics of the two groups of subjects (Schiedam and Krimpen), and the restricted populations that were made comparable in age range and maximum flow rate are presented in table 1 as mean, median, standard deviation and interquartile range.

A simple unpaired t test (i.e. unadjusted) yielded significant differences with $p<0.0005$ for all variables except age and prostate volume. IPSS, Q_{max} and voided volume were higher in Schiedam than in Krimpen. The SES was also higher in Schiedam, indicating a lower social economic status. After adjusting for the covariables age and SES by using restricted cubic splines with 7 knots, the adjusted mean differences in outcome variables between Schiedam and Krimpen remained virtually the same compared to the crude (unadjusted) mean differences.

Table 1. Descriptives of the covariables age and social economic status and the outcome variables prostate volume, maximum urinary flow rate (Q_{max}), voided volume and International Prostate Symptom Score (IPSS) in both studies (Schiedam, Krimpen).

Variables	Study	n	Mean	Median	SD	IQR
Age	Schiedam	843	55	53	10	48-64
	-restricted	538	60	60	8	53-67
	Krimpen	1,662	61	60	7	55-66
	-restricted	1,469	61	60	6	55-65
SES ranking 1-4,000	Schiedam	840	1,935	2,473	1,285	745-2,889
	-restricted	537	2,133	2,504	1,221	745-2,889
	Krimpen	1,656	1,219	1,003	1,126	216-2,851
	-restricted	1,466	1,213	1,003	1,124	216-2,851
Prostate volume, ml	Schiedam	843	36	31	19	24-41
	-restricted	538	39	34	22	26-47
	Krimpen	1,647	39	35	21	27-44
	-restricted	1,455	39	35	21	28-44
Q_{max}, ml/s	Schiedam	843	18	16	8	11-22
	-restricted	538	16	15	7	11-20
	Krimpen	1,476	11	10	7	6-15
	-restricted	1,292	12	11	7	8-16
Voided volume, ml	Schiedam	843	331	290	186	190-444
	-restricted	538	317	282	169	186-425
	Krimpen	1,474	181	140	144	80-238
	-restricted	1,293	198	160	143	95-253
IPSS	Schiedam	843	6	5	5	2-8
	-restricted	538	6	5	5	1-7
	Krimpen	1,661	5	4	5	1-7
	-restricted	1,471	5	3	5	1-7

Results are also given for subpopulations (restricted). In the restricted Schiedam population, only patients with ages 50 through 75 were included. The restricted Krimpen population was derived by deleting all subjects with a maximum flow rate <5 ml/s.

Table 2 shows the full response rates in the Schiedam study, i.e. the number of subjects presenting at the outpatient clinic (totaling 843), divided by the number invited using both recruitment methods 1 and 2 (n=9,236). Separate mean response rates are shown for the eight age groups, 20 GPs, and four ranges of social economic rank. It appears that the response more or less increased with the age and the SES (a low SES indicates a high social economic status), and was considerably different for different GPs. In addition to that, it can be seen

from Figure 1 that the response to the outpatient clinic appeared higher using recruitment method 2 (461/3,860 = 0.12) than recruitment method 1 (382/5,376 = 0.07). Table 2 also shows that the mean SES score of the patients invited by the different GPs was considerably different, and that there was a strong relation between the recruitment method used and the GP, caused by the fact that most GPs used only one recruitment method. Only GP 15 and 18 used both methods. Both the SES and the recruitment method depended significantly on the GP according to one-way analysis of variance ($p<0.001$). When all these variables were entered simultaneously, the multiple logistic regression showed that the significant explanatory variables were GP, age group and SES. No significant interactions were found, and the recruitment method (1 or 2) was not a significant explanatory variable. The influence of age group on the response was considerable: the odds ratio (OR) of the age group with the highest response (ages 58-62) to that of the age group with the lowest response (ages 38-42) was 2.9. At higher ages the response declined to an OR of 1.7 for the group with ages 73-77 compared to the lowest age group. Similarly, there were large differences between the GPs, the OR varied from 4.7 to 1.2 as compared to the GP with the lowest response (GP 4).

According to the t test (table 3) the IPSS score and voided volume were not significantly different between the two groups recruited differently (p values 0.51 and 0.94 respectively), but all other variables were. Group 1 (the group invited by mail to make an appointment at the outpatient clinic) was on average older than group 2 (invited to visit the GP office first), had a lower social economic status (a higher SES), a lower flow rate, and a lower prostate volume. In the multiple logistic regression analysis, IPSS was again not significant ($p = 0.89$) and age became only marginally significant ($p = 0.07$), given the other highly significant variables ($p < 0.001$): SES, Q_{max}, voided volume and prostate volume. It appeared that voided volume became significant when adjusted for the other variables (especially Q_{max}) in the model. If voided volume increased by 10% (given the other variables in the model) then the odds of belonging to group 2 was multiplied by 0.95 (95% CI: 0.92–0.98). If Q_{max} increased by 10% then the odds of belonging to group 2 was multiplied by 1.10 (95% CI: 1.05–1.14). If prostate volume increased by 10% then the odds of belonging to group 2 was multiplied by 1.06 (95% CI: 1.02–1.10). The effect of the uniform socio-economic ranking (ranging from 1 to 4,000) was significantly modified by age and was given by an OR per 1,000 points higher SES of around 1.3 in the lowest age group to 0.9 in the highest age groups.

Table 2. Mean full response in the Schiedam study in the eight age groups of patients from 20 GPs in four social economic classes. In total, 9,236 patients were invited from which 843 made an appointment, and showed up at the outpatient clinic (see Figure 1). Mean response was 0.09

Age group	Invited, n	Response		
38-42	2,081	0.05		
43-47	1,823	0.05		
48-52	1,575	0.13		
53-57	846	0.11		
58-62	759	0.13		
63-67	787	0.13		
68-72	782	0.11		
73-77	583	0.08		
SES score	**Invited, n**	**Response**		
91-745	2,823	0.12		
790-2,504	1,865	0.10		
2,591-3,474	2,157	0.08		
3,509-3,874	2,374	0.07		
GP	**Invited, n**	**Response**	**SES**	**Recruitment method**
1	469	0.06	3,028	1
2	423	0.06	2,459	1
3	435	0.08	2,940	1
4	418	0.04	2,656	1
5	729	0.08	2,690	1
6	578	0.10	1,730	1
7	645	0.07	2,401	1
8	339	0.06	3,256	1
9	561	0.15	2,157	2
10	442	0.10	2,497	2
11	570	0.11	2,609	2
12	305	0.05	2,564	1
13	428	0.11	1,177	2
14	684	0.06	2,480	1
15	233	0.12	1,531	1.82
16	384	0.13	1,242	2
17	1,147	0.11	868	2
18	208	0.19	2,558	1.66
19	130	0.12	3,124	1
20	105	0.09	2,382	1

The mean SES and mean recruitment method are also shown for each GP. GPs 15 and 18 used both recruitment methods. For them the (two digits after the decimal point of the) displayed number reflect the percentage of patients recruited using method 2.

DISCUSSION

We studied epidemiological aspects of a population of 843 volunteers recruited for a longitudinal non-invasive study of changes in urinary bladder contractility secondary to BPH performed in Schiedam. Our aim was to establish if the population might be biased, or if it may be considered a representation of the general population. To this end we compared a number of variables with a proven representative study, performed in Krimpen. We also studied differences between responders and non-responders, differences between responders recruited using two different methods, and factors influencing the response rates in our population, to assess possible sources of bias.

Global inspection of both (restricted) populations in table 1 seems to show that the SES of the Schiedam population was higher than that of the Krimpen population, which indicates a lower social economic status. Prostate volumes were not significantly different, and although symptom scores were significantly different, the differences were so small they may be called clinically insignificant (the IPSS ranges from 0 to 35). Prostate volumes were measured using different methods in both studies but these methods were compared in a separate study, and were found not to cause significant differences [8].

Maximum flow rate and voided volume both seemed higher in the Schiedam population. This is at least partly due to the different measurement technique applied. While the subjects in the Krimpen study were asked to void in a flow meter if they could, the Schiedam subjects were asked if they had a full bladder, and were encouraged to delay voiding and drink water until this was the case. As a consequence, the Schiedam subjects voided higher volumes. There is a positive relation between flow rate and voided volume: at increasing voided volume, maximum flow rates increase. Therefore, the higher voided volumes in Schiedam may (partly) explain the higher flow rates. It can therefore be concluded that the restricted population from the Schiedam study (i.e. only the subjects with an age range of 50-75) was urologically not different from the population tested in Krimpen, which has been shown to represent the general population [5], although the social economic status was significantly higher in Krimpen.

In the literature, three main types of bias have been distinguished: selection bias, information bias and confounding bias [9]. Confounding, in the context of the ongoing longitudinal study, would mean that the effect (a change in urinary bladder contractility) is caused by other factors than prostatic enlargement. The most likely source of such confounding is aging, especially in view of the knowledge that in a cross-sectional study, bladder contractility in females significantly decreased with age while in males this was not the case (in males it

was probably masked by compensation) [10]. Although this possible source of bias has to be considered when analyzing the outcomes of the longitudinal study, it is not caused by the differences between the study population and the general population, and therefore will not be considered here. In the context of the longitudinal study, information bias would take the form of regression to the mean, i.e. extreme values in the first evaluation will tend to be closer to the center of the distribution in a later measurement [11]. Such regression could affect the longitudinal study, and is one of the reasons for comparing the recruited population with the Krimpen population. Selection bias is the most likely bias in the study. The way in which subjects were recruited influences the composition of the study population, and thus may influence its outcome. Apart from the intentionally rectangular age distribution, which is different from the age distribution in the general population, the study might for instance be biased by self-selection, i.e. perhaps subjects with more-than-average symptoms did more frequently respond. Additionally, subjects with serious symptoms, such as a very low flow rate, were excluded. For this reason we studied factors influencing the response rate of the subjects. We found that the response depended on age, SES and the GP who invited the subjects. When tested separately, also the recruitment method used (i.e. by direct mail from the GP, asking his patient to make an appointment with the outpatient clinic, or by inviting the patients to the GP office first for an interview and trans-abdominal ultrasound examination of the prostate – during this visit they were invited for a complete investigation at the clinic) made a significant difference. However, when all these variables were entered simultaneously in a multiple logistic regression analysis, the recruitment method was not a significant explanatory variable anymore. This was caused by the fact that most GPs only used one of the two recruitment methods, so that there was a strong relation between GP and recruitment method as explanatory variables. The same effect was seen for GP and social economic status. The response was highest at the age of 65 and it increased with social economic status.

The distribution of the IPSS score was about the same in both groups of responders to the outpatient clinic (Erasmus MC): recruited using methods 1 and 2.

All other variables studied were significantly different: voided volume, SES and age were higher in group 1 compared to group 2 (although age was only marginally significant); maximum flow rate (Q_{max}) and prostate volume were lower. However, as judged from the means, the differences in age, voided volume and prostate volume were small, and also the ORs of the logistic regression analyses were limited. It thus appears that although both groups were different, the difference was very limited and may be called clinically irrelevant.

CONCLUSION

In general we conclude that several factors influenced the response rate of subjects we recruited for a non-invasive longitudinal study of changes in bladder contractility secondary to bladder outlet obstruction. Age and social economic status did, the response being highest around the age of 60 years and lower at lower and higher ages, and increasing with social economic status. Recruitment of volunteers in two steps, i.e. asking them first to visit the GP's office, and inviting them there to visit the outpatient clinic, rather than directly inviting them (in writing) to the clinic seemed to lead to a higher response, although this effect could not be statistically discriminated from the difference in response rates between GPs. This latter difference might be ascribed to the relation between subject and his GP, although also a difference of mean social economic status between patient populations of different GPs may have influenced that. In spite of these dependencies, we found that when the recruited population was corrected for intentional differences in age distribution and methodological differences in flow rates, it was not urologically different from the general population.

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Chapter 5

ULTRASONOGRAPHY OF THE PROSTATE VOLUME: THE INFLUENCE OF TRANSABDOMINAL VERSUS TRANSRECTAL APPROACH, DEVICE TYPE AND OPERATOR

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ABSTRACT

Objectives: We conduct a longitudinal non-invasive study of changes in urinary bladder contractility secondary to benign prostatic enlargement. In that study, the prostate volume is estimated by transabdominal ultrasonography. The accuracy of those measurements was verified by comparison of transabdominal to transrectal stepwise planimetric ultrasonography as the gold standard. Also, two different transabdominal devices used were compared, and the influence of different operators was studied.

Materials Methods: Two series of measurements in 100 patients each were done. In the first series, transabdominal and transrectal sonography were pairwise compared in each patient. In the second series, transabdominal measurements were done with two devices (a hospital Aloka1 SSD-1700 and a portable Aloka1 SSD-900). Transrectal scannings were done by three investigators whilst all transabdominal scannings were done by one. Regression graphs, ratio plots and statistical analyses of the data quantified the reproducibility of different methods, observers and device types.

Results: In the transrectal-transabdominal series of prostate volume measurements (in cm^3), the Pearson correlation coefficient was 0.84 (p<0:001), the mean of the means was 51.8 ± 23.0 (mean ± S:D:), and the mean of the differences was 1.0 ± 1.4. In the series with two devices, the Pearson correlation coefficient was 0.73 (p<0.001), the mean of the means was 31.0 ± 10.9, and the mean of the differences was 1.0 ± 1.3.

Conclusion: No statistically significant differences were found between the transabdominal-transrectal ultrasonography, two different transabdominal devices nor between different observers. However, for those using these measurements in everyday clinical practice, it is worth to point out that in our data a transabdominal scan and a transrectal scan in the same patient, on the same day, differed more than 30% in one fourth of the patients and that two transabdominal scans in the same patient (with two different devices, on two different days) differed more than 30% in every fifth patient.

INTRODUCTION

For both clinical and research purposes the prostate volume is an important parameter. It can be measured in several ways using ultrasonography. Comparative studies on the estimation of the prostate volume by transrectal and transabdominal ultrasonography were published earlier [1-3]. Also, the accuracy of transabdominal ultrasound as the standard clinical tool for a rapid, simple and non-invasive screening of the prostate volume has been described [4-6].

Presently, we non-invasively evaluate changes in urinary bladder contractility secondary to benign prostatic hyperplasia. Approximately 1100 volunteers will be studied three times in five years [7]. Among others, the prostate volume is measured non-invasively by transabdominal ultrasonography. Two different methods for recruitment of volunteers are used [8]. In the first of these recruitment methods volunteers are directly invited by their general practitioners (gp) to participate in the study at the hospital. The second method of acquiring volunteers comprises two phases. In the first phase, patients are invited to visit the gp's practice for an anamnesis and a transabdominal ultrasound of the prostate volume before they are invited to the second phase of the study, which includes further measurements in the hospital. As a consequence, two different ultrasound machines are used to assess the prostate volume in this study.

To our knowledge, the impact of using different ultrasound devices and different operators on the prostate volume measured has not been studied before. Therefore, we compared the transabdominal ultrasonography to transrectal step section planimetry as the gold standard [9]. Since the equipment in the gp's practices differed from the one in the hospital, we also tested the agreement between both transabdominal ultrasound devices, and the influence of different operators.

MATERIAL AND METHODS

SERIES OF MEASUREMENTS

In the first series (A) of comparative measurements, 100 patients participating in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) [10] of the department Urology of the Erasmus MC were arbritarily selected. Prior to the transrectal ultrasonography scheduled for the prostate cancer screening an extra transabdominal echographic prostate volumetry was done. This order of the measurements was chosen to exclude any possible ''overestimation'' of the prostate volume by swelling through bleeding

caused by the prostate biopsy procedure in the cancer screening. These two measurements were done in one session.

The second series (B) comprised measurements in 100 consecutive volunteers recruited with the two phase method for our non-invasive longitudinal study. In this studygroup, transabdominal measurements with two different devices were compared. The prostate volume was measured with a portable (Aloka1 SSD-900) device in the gp's practice and with a fixed (Aloka1 SSD-1700) device in the hospital, i.e. in different sessions.

DEVICES AND MEASUREMENTS

Transrectal volumetry of the total prostate gland was done with the Brüel and Kjær Medical Falcon Ultrasone Scanner type 2101 equiped with a 7.5 Mhz MRI transrectal convex probe type 8808. The prostate volume was estimated by 5 mm step section planimetry, using the semiplanimetric ellipsoid formula (¼8(maximum transverse area)⅔ x π x length).

Transabdominal prostate volumetry was done with two different devices: Aloka1 Model SSD-1700 Dyna View, USI-4140 in the hospital and Aloka1 Model SSD-900, USI-146 in the gp's practice both equiped with a 3.5 Mhz electronic convex probe, Type no. UST-979-3.5. Here, the prostate volume was calculated by the internal computer prolate spheroid formula (=0.542 x length x width x height). In both transrectal and transabdominal measurements, the B-mode was used. Each volumetry was done at sufficient bladder sensation.

The transabdominal probe was (transversely) placed just above the symphysis pubis to capture an image of the largest circumference of the prostate on the computer screen, contrasted by the filled bladder. Two marks were put on the upper and lower edges of the image to define an elliptical area for volume estimation.

For practical purposes, transrectal volumetry was done by three different investigators (the second, third and fourth author) whilst all transabdominal measurements were done by the first author. No detailed anamnesis or physical examination were done, and no specific criteria, such as age, were applied. To exclude bias, all results were blinded for all operators.

STATISTICAL ANALYSIS

The reproducibility of the two series of prostate volume measurements was quantified using ratio plots i.e. difference plots according to Bland and Altman [11] on log transformed data. The data of each subject was logarithmically transformed prior to plotting. The calculated mean and standard deviation (S.D.) of the plots were inverse transformed. The S.D. was calculated as half of the difference between the inverse transform of mean +S:D: and the inverse transform

of mean -S.D. Additionally, a regression plot was made, and Pearson's correlation coefficient was calculated.

Prostate volumes in series A and B were pairwise compared using the Wilcoxon Signed Rank Test. Mann-Whitney U-tests were done to compare the prostate volumes measured by the three different observers, and the mean and the differences of the volume readings by the one transabdominal (I) versus the three transrectal observers (A, B, and C). A $p<0.05$ was assumed to be statistically significant.

RESULTS

In series A, 46, 28 and 26 transrectal echographic measurements of the prostate volume were done by three different observers (A, B, and C respectively) of the ERSPC. All repeated transabdominal ultrasound scannings of the prostate volume in both series were done by the first author (observer I).

Table 1 gives the (overall) statistics of the prostate volumes measured in both series A and B. The prostate volumes measured in the ERSPC study group (series A) are statistically significantly larger than those from the longitudinal study (series B), Mann–Whitney U-test, $p < 0.0001$.

Table 1. Overall statistics of the prostate volume measured in the two study groups.

		Range	Mean	Median	S.D.	IQR
Prostate volume (cm^3)						
Series A(n=100)	TRUS (Brüel and Kæjr)	12.6-194.2	57.3	48.4	32.5	15.7
	TAUS (SSD-1700)	23.1-200.1	58.6	51.0	31.0	11.8
Series B (n=100)	TAUS (SSD-900)	10.5-91.5	33.6	30.3	14.3	6.1
	TAUS (SSD-1700)	11.6-117.0	33.0	30.2	15.2	6.5

Series A consists of patients in the ERSPC. Series B consists of volunteers of the longitudinal non-invasive study. TRUS: transrectal ultrasonography; TAUS:transabdominal ultrasonography. SSD-1700 and SSD-900 are two different devices; S.D.:standard deviation; IQR: inter quartile range.

Figures 1 and 3 are plots conform Bland and Altman [11] of the results in the two series respectively. In these figures the ratio of the prostate volume readings in each subject is plotted against the mean of those two values. In Figure 1, the transabdominal observer and the three different transrectal observers are distinguished by three different markers. Additionally, a regression plot (Figure 2) with the line of equality shows the degree of discrepancy between

the transrectal and transabdominal readings. The Pearson's correlation coefficient was 0.84, p<0.001. A similar illustration (Figure 4) is made to show how much discrepancy there was in the prostate volume readings between the two different transabdominal devices, Pearson's correlation coefficient was 0.73, p<0.001. Table 2 illustrates the number of transabdominal readings that were more than 10%, 20% and 30% away from the transrectal readings. For the two different transabdominal devices, Table 3 illustrates the number of the Aloka1 SSD-900 readings that were more than 10%, 20% and 30% away from the Aloka1 SSD-1700 readings.

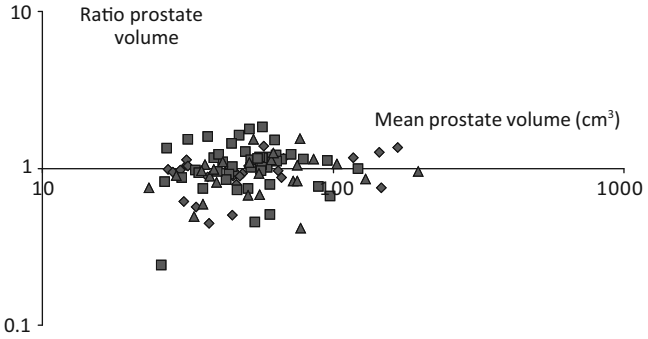

Figure 1. The ratio of the prostate volumes measured transrectally and transabdominally in each volunteer was plotted against the mean of those two volumes for measurement series A. The ratios of the transabdominal observer I and three different observers A, B, and C are distinguished by three different markers (■)(46), (◆) (28) and (▲) (26) respectively. For statistics, Table 2.

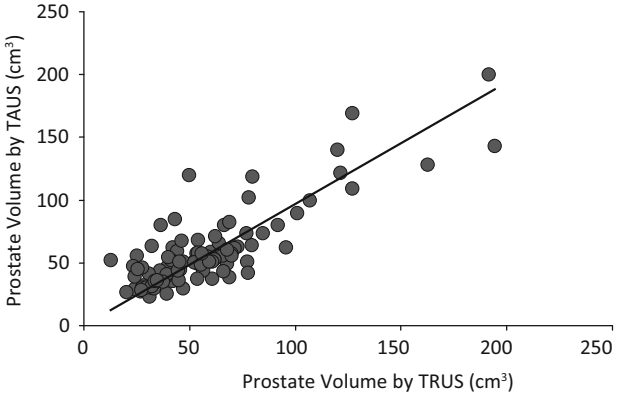

Figure 2. A regression graph showing the prostate volume measured by transrectal ultrasonography (TRUS) and transabdominal ultrasonography (TAUS), with line of equality. Pearson's correlation coeffcient, r=0.84 (p<0.001).

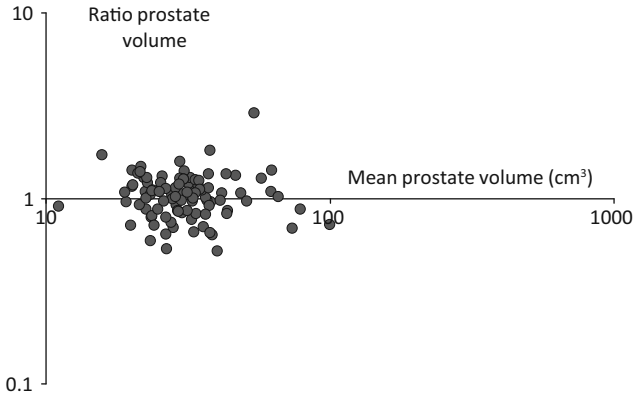

Figure 3. The ratio of the prostate volumes measured with two different transabdominal devices in each volunteer was plotted against the mean of those two volumes for measurements series B. For statistics, Table 3.

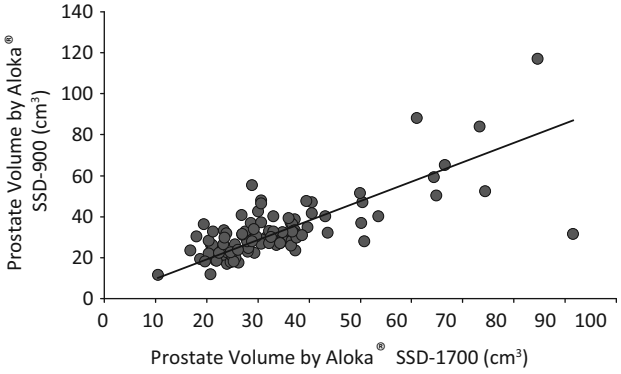

Figure 4. A regression graph showing the discrepancy between the prostate volume readings by two different Transabdominal ultrasounddevices (Aloka® SSD-900 versus Aloka® SSD-1700), with line of equality. Pearson's correlation coeffcient, r=0.73(p<0.001)

Tables 4 and 5 show that the differences of the log transformed data in both series were not systematically different from zero. This indicates that no systematic differences were found. This is as true for the transrectal versus transabdominal method, as well as for the two different transabdominal machines, Wilcoxon Signed Ranks Test in all cases: p<0.0001. The p-values of Mann-Whitney U-tests for the mutual comparison of the observers are given in Table 6.

Table 2. Table illustrating that 70, 40 and 26 of the transabdominal readings differed more than 10%, 20% and 30% from transrectal readings in the same patients, on the same day.

	Deviation from transrectal ultrasonography (TRUS)		
	>10%	>20%	>30%
Numbers of transabdominal readings	70	40	26

Table 3. Table illustrating that 65, 44 and 20 of the transabdominal readings by an Aloka SSD-900 (portable device) differed more than 10%, 20% and 30% from transabdominal readings by an Aloka SSD-1700 (hospital device) in the same patients, on a different day.

	Deviation from readings by Aloka® SSD-1700		
	>10%	>20%	>30%
Numbers of transabdominal readings by Aloka 900	65	44	20

Table 4. Statistics of the inverse log transformed differences (i.e. ratios) and means of two prostate volume readings in each subject in Series A (n=100), which consists of patients in the ERSPC.

	Series	Method & observers	Range	Mean	Median	S.D.	IQR
Ratios	Series A	TRUS (Bruel and Kjær)	0.2-1.8	1.0	1.0	1.4	0.3
		TAUS (SSD-1700)					
		Overall					
		Observer I versus A	0.2-1.8	1.0	1.1	1.4	1.4
		Observer I versus B	0.4-1.4	0.9	0.9	1.3	0.2
		Observer I versus C	0.4-1.5	0.9	0.9	1.4	0.3
Mean (cm^3)	Series A	TRUS (Bruel and Kjær)	23.4-195.05	1.85	1.22	3.02	5.9
		TAUS (SSD-1700)					
		Overall					
		Observer I versus A	25.7-123.05	0.75	2.1	17.7	20.2
		Observer I versus B	26.9-166.0	50.2	45.9	26.6	30.7
		Observer I versus C	23.4-195.05	5.55	4.42	8.03	8.5

The overall and the statistics of the comparative results between the transabdominal observer I and the three transrectal observers A, B, and C are given. TRUS: Transrectal ultrasonography; TAUS: transabdominal ultrasonography. S.D.: standard deviation; IQR: interquartilerange.

Table 5. Statistics of the inverse log transformed differences (i.e. ratios) and means of each pair of two prostate volumes measured in each subject in series B (n=100), which consists of volunteers of the longitudinal non-invasive study

			Range	Mean	Median	S.D.	IQR
Ratios	Series B	TAUS (SSD-900)					
		TAUS (SSD-1700)	0.5-2.9	1.0	1.1	1.3	0.4
Mean (cm^3)	Series B	TAUS (SSD-900)					
		TAUS (SSD-1700)	11.0-100.0	31.0	30.1	10.9	12.9

All transabdominal scannings were done by observer I. TAUS: transabdominal ultrasonography. S.D.: standard deviation; IQR: inter quartile range.

Table 6. p-Values of the Mann-Whitney U-tests to compare the prostate volumes measured by the three different observers, and the mean and the differences between the volume readings by the transabdominal (I) versus the transrectal observers (A, B, and C)

	Prostate volume	Mean of reading by transrectal and transabdominal (I) observers	Difference between reading of transrectal and transabdominal (I) observers
Observer A versus B	0.167	0.338	0.088
Observer A versus C	0.897	0.574	0.063
Observer B versus C	0.315	0.253	0.835

DISCUSSION

This study aimed at analysing the accuracy of the prostate volume measured by different observers, methods and devices. According to Bland and Altman [11], the best way to analyse this accuracy is to examine the reproducibility of differents methods or devices by taking repeated measurements on a series of subjects. We applied this principle to differents methods (transrectal versus transabdominal) and different devices (Aloka® SSD-1700 versus Aloka® SSD-900).

For practical reasons, the transrectal ultrasound measurements were done by three different investigators of the Rotterdam part of the European Randomized Study of Screening for Prostate Cancer (ERSPC) [10]. To exclude possible bias, all volumes measured were blinded for all observers. Measurements in series A (comparison of transrectal and transabdominal ultrasound) were done on the same day, those in series B on different days.

Table 1 shows that the prostate volumes measured in the ERSPC study group are statistically significantly larger than those from the longitudinal study ($p<0.0001$). We believe that, among

other possibilities, a possible reason is that the ERSPC included men with values of PSA≥3 ug/L, whereas the longitudinal study included healthy volunteers [7,8] with unknown (unspecified) PSA levels.

Table 6 shows that no statistically significant differences were found between the three different transrectal observers. Also, no statistically significant differences were found in the mean and the differences of the volume readings by the transabdominal (I) versus the transrectal observers (A, B, and C). It can be seen that there was a slight, but non significant, tendency towards an increased difference between transrectal observers A versus B and A versus C with the transabdominal observer. This implies that observer A tended towards readings that deviated more from the transabdominal observer, than observers B and C.

CONCLUSION

No statistically significant differences were found between the transabdominal and transrectal ultrasonographic prostate volume readings in the same patients. Neither were statistically significant differences found between transabdominal readings in different sessions with two different devices, or in transrectal readings by three different observers. However, for those using these measurements in everyday clinical practice, it is worth to point out that in our data a transabdominal scan and a transrectal scan in the same patient, on the same day, differed more than 30% in one fourth of the patients and that two transabdominal scans in the same patient (with two different devices, on two different days) differed more than 30% in every fifth patient.

ACKNOWLEDGEMENTS

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Chapter 6

CORRELATION OF NON-INVASIVE URODYNAMICS WITH INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS) AND PROSTATEVOLUME

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ABSTRACT

Aim: To study the correlation between non-invasive urodynamic data, the International Prostate Symptom Score (IPSS) and the prostate volume.

Materials and Methods: Data of 667 healthy volunteers participating in a longitudinal study of changes in urinary bladder contractility secondary to BPE were analyzed. The prostate volume was assessed by transabdominal ultrasonography. Uroflowmetry followed to verify if a minimum free flow rate of 4.5 ml/sec could be achieved. While (re)filling the bladder by drinking, the subjects completed the Dutch version of the IPSS. Next, the bladder pressure was non-invasively measured using the condom catheter method. The urethral resistance (URR) was calculated from the maximum condom pressure and the maximum free flow rate.

Results: The IPSS ranged from 0 to 29, (6.1 ± 4.8) (mean ± SD), whereas the prostate volumes ranged from 8 to 140 cm3, (34 ± 18). Twenty eight percent (185/667) of the subjects had a non-invasively quantified high URR and a significantly higher IPSS (7.3 ± 5.2) than those with a low URR (IPSS (5.7 ± 4.6)), Mann-Whitney U-test: $P<0.001$. The IPSS and the URR were significantly correlated, Spearman's rho (ρ) =0.20, $P<0.001$. A significant difference between the prostate volumes, 36 ± 21 cm^3 in the high URR versus 33 ± 17 cm^3 in the low URR group, was not found, P=0.18.

Conclusions: A weak though statistically significant correlation was found between the non-invasively quantified URR and the IPSS. This suggests that an elevated resistance is a necessary, but not a sufficient condition for lower urinary tract symptoms (LUTS). No correlation was found between the URR and the prostate volume.

INTRODUCTION

Different scoring systems are applied worldwide to assess, evaluate, and standardize lower urinary tract symptoms (LUTS). One of these systems, a symptom index for benign prostatic hyperplasia (BPH), developed and validated by a multidisciplinary committee of the American Urological Association (AUA) and adapted by the International Consultation on BPH, is the International Prostate Symptom Score (IPSS) [Barry et al., 1992; Cockett et al., 1994]. It is an internationally highly recommended and frequently used self administered diagnostic tool in the assessment of LUTS due to BPH. Another very important and useful parameter in the clinical evaluation of patients with LUTS is the prostate volume [Roehrborn et al., 1986].

Invasive pressure flow studies in patients with LUTS do generally not show a significant correlation between the IPSS and the grade of bladder outlet obstruction (BOO) [Poulsen et al., 1994; Madersbacher et al., 1996; Rosier et al., 1996; Van Venrooij and Boon, 1996]. On the other hand, a moderate but significant correlation between (some) invasive parameters and the prostate volume has sometimes been reported [Tammela et al., 1999].

Non-invasive urodynamics were recently introduced for non-invasive assessment of subvesical obstruction and urinary bladder contractility [Van Mastrigt and Pel, 1999a,b]. One of these methods is the condom catheter method [Pel et al., 2003], which is used in our non-invasive survey to longitudinally study changes in urinary bladder contractility secondary to BPH [Huang Foen Chung et al., 2002].

In this report, the correlations between the non-invasive urodynamic findings, the IPSS and the prostate volumes were investigated in that study.

MATERIALS AND METHODS

SUBJECTS

The subjects in this longitudinal study of changes in urinary bladder contractility secondary to BPH consisted of volunteers spontaneously responding to publicity, patients invited by general practitioners (GP's), as well as employees from the Erasmus MC invited by email [Huang Foen Chung et al., 2003]. All of these subjects were included on the basis of the same criteria: age 38-77, informed consent, and ability to void in the standing position with a free flow rate of at least 4.5 ml/sec [Pel and van Mastrigt, 2001b]. Exclusion criteria were any heart condition or history of heart failure ever, known neurological condition(s), such as Parkinson's disease, certain known viral conditions, such as being HIV positive, previous surgery and/or congenital

or gained malformation of the lower urinary tract (LUT), and anticoagulating and/or LUTdrug use. In all cases the investigator decided on the basis of anamnesis, the study criteria, and physical examination whether a subject could enter the study.
In 744 subjects at least one free flow rate was attempted. Six hundred ninety six of these had a flow rate _4.5 ml/sec. Drop outs were due to several reasons such as unability to void in the presence of the equipment and/or the investigator (paruresis). Six hundred sixty seven of these 696 subjects successfully completed the measurement session. These were used for this correlation analysis.

INVESTIGATIONS

All measurements took place at the outpatient clinic of the Erasmus MC. First, the prostate volume of each subject was assessed by transabdominal ultrasonography using an Aloka® SSD-500 or Aloka® SSD-900 Ultrasound Diagnostic Equipment. Both machines were equipped with a 3.5 MHz probe. With the probe parallel just above the symphysis pubis of the subject, an image of the largest circumference of the prostate, clearly contrasted by the filled bladder, was captured on the computer screen. The prostate volume was estimated from the diameters of the minor axis and the major axis using an ellipse 3-axis volume formula, the so called prolate spheroid approximation.

Subsequently, at sufficient sensation of bladder filling, a free uroflowmetry was done to verify if a maximum flow rate of at least 4.5 ml/sec could be achieved. If that condition was met at least one non-invasive bladder pressure measurement was attempted using the condom catheter method, as described earlier [Huang FoenChung et al., 2003]. Between the uroflowmetry and the bladder pressure measurement(s), the subjects drank mineral water to refill the bladder. Meanwhile, they completed the IPSS, including the quality of life (QoL) score. TheDutch translation of the IPSS was used.

CONDOM CATHETER METHOD

The bladder pressure was measured using the condom catheter method [Pel and van Mastrigt, 2001a; Huang Foen Chung et al., 2002, 2003]. This method is based on a modified incontinence condom connected to a dome, with three different metal outflow resistances fitted with tubes that can remotely and independently be closed or (re)opened by pneumatic valves. During voiding, the outflow resistance can be stepwise varied by opening and/or closing a combination of the tubes. When all valves were closed and provided that there was an open connection between the condom and the bladder via the urethra, the pressure in the condom represented the isovolumetric bladder pressure.

DATA ANALYSIS

The maxima of the free flow rate (Q_{max}) and of the condom pressure ($p_{cond.max}$) were displayed automatically by a Matlab program. Both parameters were corrected manually if necessary, for instance as in case of an artefact or a spike in the signal. In each session at least two condom pressure measurements were attempted in one subject to evaluate the reproducibility of the condom catheter method [Huang Foen Chung et al., 2003]. The last one of those measurements was used for the purpose of this report.

In an earlier publication on non-invasive urodynamics [Pel et al., 2002] a provisional method was suggested for the definition of urethral obstruction using a diagram of the maximum condom pressure versus the free flow rate.

The borderline between obstructed and non-obstructed patients was defined by: $p_{cond.max} = 5.8 \times Q_{max} - 36.4$. For this reason, in the present study, we calculated the urethral resistance (URR) as $p_{cond.max} \times 5.8 \times Q_{max} - 36.4$. For statistical testing, we classified the URR as ''high'' or ''low.'' Thus, a high flow rate with a low condom pressure, a negative result of the formula, was classified as a low URR. Contrary, a low flow rate with a high condom pressure or positive formula value was classified as a high URR. For comparison with other studies, the IPSS scores were added. An irritative score describing storage symptoms was formed by adding the answers to questions 2, 4, and 7, and an obstructive score describing voiding symptoms was made from the sum of the responses to questions 1, 3, 5, 6. The obstructive and irritative scores were added to the QoL score to give the total IPSS.

STATISTICAL ANALYSIS

The correlation between the non-invasive urodynamic parameters and the IPSS and the prostate volumes was estimated by Spearman's r (rho).To test the significance of the difference between two groups the Mann-Whitney U-test was used. A $P<0.05$ was considered to be statistically significant.

Methods, definitions, units, and nomenclature conform to the standards recommended by the International Continence Society.

RESULTS

So far, the number of suitable subjects included in the longitudinal study with a free flow rate of at least 4.5 ml/sec is 696. All these subjects underwent at least one attempt to a condom pressure measurement. Twenty-nine subjects (29/696=4%) were not able to void through

the condom.Thus eventually, at least one non-invasive bladder pressure measurement was successfully done in 667 subjects, (667/696 =96%).

Based on the provisional formula 28% (185/667) of the subjects had a non-invasively documented high URR. In Figure 1, those are indicated by closed circles. Statistics of the age, the total IPSS, including the QoL score, the obstructive and the irritative IPSS, the prostate volumes, and also the non-invasive urodynamic findings, i.e., the maximum free flow rate (Q_{max}), the maximum condompressure ($p_{cond.max}$), and the calculated URR, are shown inTable I. Values are given for the total population, N=667, the high URR group (N=185), the low URR group (N=482), and the significance of the difference between both URR groups is indicated.

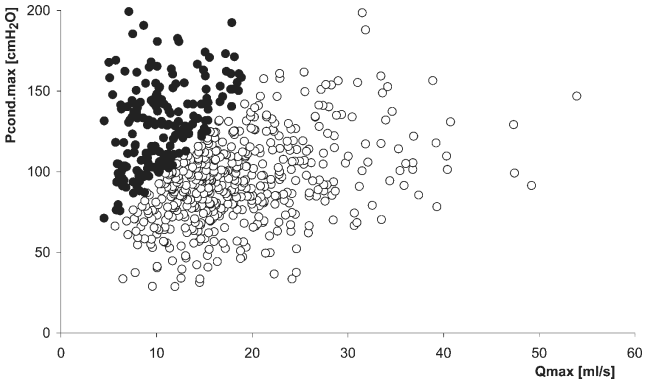

Figure 1. The maximum condom pressure measured was plotted as a function of the separately measured free flow rate. Each symbol represents one volunteer, N=667. The subjects were stratified in a group with a low or a high urethral resistance (URR), based on a provisional formula for non-invasive diagnosis of obstruction, $p_{cond.max}$ - 5.8 x Q_{max} - 36.4. Closed circles represent subjects with a high URR (N=185), a positive outcome of the formula. Open circles reflect subjects with a low URR (N=482), a negative result of the formula.

Subjects with a high URR had a significantly higher total IPSS (7.3 ± 5.2) than those with a low URR (total IPSS (5.7 ± 4.6)), Mann-Whitney U-test: P<0.001, N=667. All the separate scores of the IPSS and the QoL score were also significantly different between both groups, except the scores for frequency (q2) and nocturia (q7). With the exception of the score for nocturia (q7), the separate IPSS scores and the QoL score were significantly correlated with the URR. Therefore, the total obstructive score, ρ=0.21, P<0.001, and the total irritative score, ρ=0.13, P=0.001, as well as the total IPSS, ρ=0.21, P<0.001, were also significantly correlated with theURR.

Table I. Statistics of the Age, the Total International Prostate Symptom Score (IPSS), the Irritative and Obstructive IPSS, the Quality of Life (QoL), the Prostate Volume (PV), and the Non-Invasive Urodynamic Parameters in the Total Population, N=667, the High Urethral Resistance (URR) Group, N=185, and the Low URR Group, N=482-

	Range	Mean	Median	SD	IQR	U-test
Age (year)						
Total population	38-77	56	56	10	14	
Low URR	38-77	55	55	10	14	
High URR	38-77	58	58	10	14	0.001
TotalIPSS						
Total population	0-29	6.1	5.0	4.8	5.0	
Low URR	0-29	5.7	5.0	4.6	3.0	
High URR	0-26	7.3	7.0	5.2	7.0	<0.0001
IRR IPSS						
Total population	0-14	3.4	3.0	2.5	3.0	
Low URR	0-13	3.2	3.0	2.4	3.0	
High URR	0-14	3.9	3.0	2.8	4.0	0.008
OBSTR IPSS						
Total population	0-18	2.7	2.0	3.2	4.0	
Low URR	0-18	2.4	1.0	3.1	3.0	
High URR	0-16	3.4	2.0	3.4	4.0	<0.0001
QoL						
Total population	0-4	1.0	1.0	1.0	2.0	
Low URR	0-4	0.9	1.0	1.0	1.0	
High URR	0-4	1.4	1.0	1.1	2.0	<0.0001
PV (cm^3)						
Total population	8-140	34	30	18	22	
Low URR	8-115	33	30	17	16	
High URR	10-140	37	32	21	24	0.18
Free Q_{max}(ml/sec)						
Total population	4-54	17	15	8	9	
Low URR	6-54	19	17	7	9	
High URR	4-23	11	10	4	5	<0.0001
$p_{cond.max}$ (cm H_2O)						
Total population	29-216	103	100	32	44	
Low URR	29-199	93	91	27	33	
High URR	71-215	130	129	27	40	<0.0001
URR						
Total population	-230-122	-30	-2852	-57		
Low URR	-230 to -1	-53	-46	39	-49	
High URR	0-122	31	25	25	36	<0.0001

IQR, inter quartile range; U-test, Mann-Whitney U-test for the significance of the difference between both URR groups. For other abbreviations see text.

On the other hand, a significant di!erence in the prostate volumes, which were 37 ± 21 cm^3 in the high URR group versus 33 ± 17 cm^3 in the lowURR group was not found, Mann-Whitney U-test: P=0.18, N=667, and prostate volumes and the URR were not significantly correlated, ρ=0.055, P=0.16. The correlation coefficients between the IPSS, the prostate volume, and the URR are given inTable II.

Figures 2 and 3 illustrate the correlation between the IPSS and the non-invasively quantified URR and the prostate volume in the studied population.

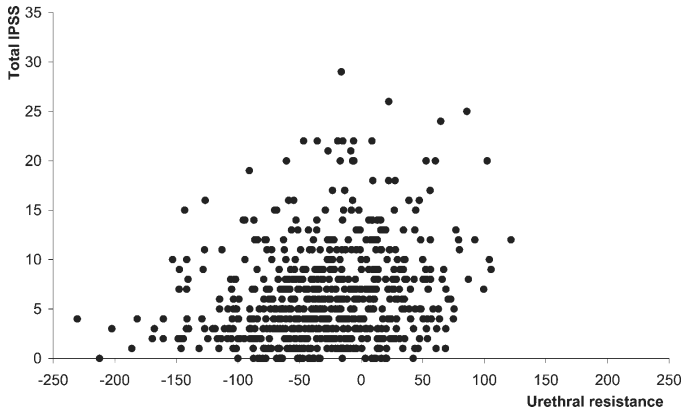

Figure 2. A scatter plot illustrating the correlation between the non-invasively assessed URR and the total International Prostate Symptom Score (IPSS), N=667. Subjects with a high URR (>0) had a significantly higher total IPSS (7.3 ± 5.2) than those with a low URR (total IPSS (5.7 ± 4.6)), Mann–Whitney U-test: P<0.001.

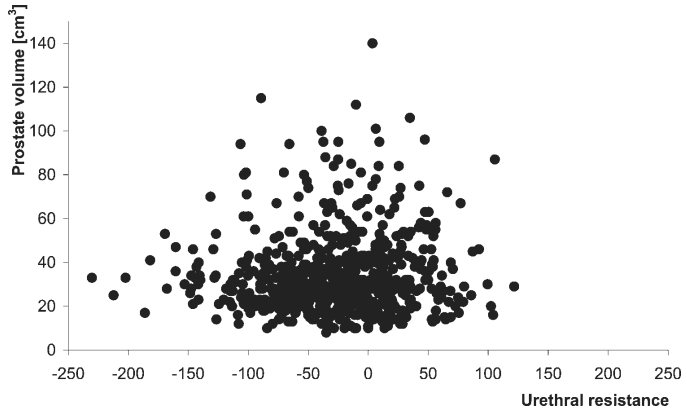

Figure 3. A scatter plot illustrating the correlation between the non-invasively assessed URR and the prostate volume assessed by transabdominal ultrasonography, N =667. No significant correlation was found.

Table 2. Statistics Showing the Association Between the PV, the IPSS, and the QoL With the Non-Invasively Measured URR

	PV	IPSS	QoL	IRR IPSS	OBSTR IPSS
URR					
ρ*	0.055	0.205	0.234	0.134	0.209
P	0.158	<0.0001	<0.0001	0.001	<0.0001

*Spearman correlation test. A P<0.05 is considered to be statistically significant. URR, urethral resistance; PV, prostate volume; QoL, quality of life; IRR IPSS, irritative I PSS; OBSTR IPSS, obstructive IPSS.

DISCUSSION

The non-invasive urodynamic data in this report is drawn from''A longitudinal non-invasive study of changes in urinary bladder contractility secondary to BPH'' which is running at the Erasmus MC. Different recruitment methods were applied, but most of the subjects participating in this study were recruited by GP's. A small number of the subjects consisted of volunteers spontaneously responding to publicity and employees of the Erasmus MC. The recruitment aimed at healthy subjects, but (dormant) LUTS were not excluded.

One inclusion criterion requires a minimum flow rate of 4.5 ml/sec. In an earlier study [Pel and van Mastrigt, 2001], it was shown that when the free flow rate exceeded this value the condom pressure accurately reflected the isovolumetric bladder pressure.

Twenty eight percent of the subjects had a non-invasively quantified high URR.These subjects had a significantly higher total IPSS. The total IPSS and theURR were thus significantly correlated. The correlation and difference, however, were small. Figure 2 illustrates why: at low URR the IPSS is always small. At high URR, the IPSS varies from zero to almost its maximum. This is also reflected in Table I. In the low URR group, the inter quartile range (IQR) is 3, in the high URR group it is 7. It is therefore the variation in IPSS rather than the mean, which correlates with the URR. It thus seems that a high URR is a necessary, but not a sufficient condition for LUTS. Table I also shows that the correlation between the URR and the QoL is slightly higher than that with the IPSS. As this is a clinical study, we aimed at the analysis of the correlation between theURR and the IPSS. Probably for the subjects, however, the QoL is more relevant than the IPSS score.

On the other hand, there was no significant correlation between the prostate volume and the non-invasively calculated URR in the present population. Considering this, it should be kept in mind that this group of subjects is not (yet) suffering from BPH. The prostate volumes are rather small, and may not have reached the level at which symptoms are caused.

A literature search on the correlation between IPSS, prostate volume and invasive pressure flow studies yielded a few publications that (all) reported no association between invasive pressure flow parameters and the IPSS.

In the first study [Madersbacher et al., 1999], a correlation between the obstructive IPSS and the degree of urodynamically proven BOO as defined by a linPURR of ≥2 was not found. In fact, it was concluded that even the separation of the IPSS into irritative (i.e., storage) and obstructive (i.e., voiding) symptoms did not improve its (the IPSS) diagnostic capability.

In the second study [Tammela et al., 1999] on 216 men with LUTS the Abrams-Griffiths nomogram definition of obstruction was used. No significant correlation between $p_{det.Qmax}$ and IPSS was found. As no IPSS stratification was mentioned, we assume the total score was used. Neither was the range of the IPSS reported. A modest but statistically significant correlation was found between $p_{det.Qmax}$ and prostate volume, supporting the hypothesis that prostate size is a contributing factor in symptomatic BPH. The mean volume of the prostate volumes in the patients included in this study was 45 cm^3 (range 17-155), which was (slightly) higher than that in our population, see earlier remark.

In the third study [Eckhardt et al., 2001] on symptoms and QoL versus prostate volume and invasive urodynamic parameters in (even!) 565 selected men with LUTS suggestive of BPH, the prostate volume, and the obstruction grade were not associated with the symptoms index (IPSS).

In summary, invasive pressure flow studies in patients with LUTS do not show a significant correlation between the IPSS and the grade of BOO, even in studies with a large number (N =565) of men with LUTS suggestive of BPH. Our study does show this correlation and is of comparable size (N=667). Even though our study group consisted of volunteers, subjects with LUTS were not excluded. Table I and Figure 2 show that a large part of the subjects had low maximum flow rates, high IPSS scores, and large prostate volumes, which justifies the comparison with populations of LUTS patients.

CONCLUSION

In our population of healthy volunteers, the non-invasive urodynamic data did show a small but statistically significant correlationwith the IPSS confirming that an increased URR is a factor contributing to LUTS. The exact relation between IPSS and URR, as illustrated in Figure 2, suggests that an elevated resistance is a necessary, but not a sufficient condition for LUTS. So far, this has only been demonstrated by non-invasive measurements by one single investigator in one center.

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Chapter 7

COMPARATIVE ANALYSIS OF THE REPRODUCIBILITY AND APPLICABILITY OF THE CONDOM CATHETER METHOD FOR NONINVASIVE URODYNAMICS IN TWO DUTCH CENTERS

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ABSTRACT

Objectives: We compared the applicability and reproducibility of the condom catheter method for noninvasive urodynamics in two Dutch studies.

Materials and Methods: A longitudinal study of changes in bladder contractility secondary to benign prostatic enlargement is taking place at the Erasmus MC in Rotterdam. Volunteers aged 38-77 years will be studied three times in 5 years. The first series of measurements has been completed in 1,020 men. A randomized controlled trial to test the effect of additional water intake on bladder function has been completed at the University of Maastricht. 184 subjects aged 55-77 years with International Prostate Symptom Scores of 8-19 were investigated twice in 6 months. Bladder contractility was measured noninvasively with the condom method. Two consecutive measurements were attempted in each subject. Reproducibility was tested according to Bland and Altman and compared by calculating the normalized standard deviation of the differences by dividing by the difference.

Results: The success rate for single measurements was 95% in both studies. The success rates for double measurements varied from 87 to 90%. The normalized standard deviation of the differences between the double measurements was 0.15 for the longitudinal noninvasive study and randomized controlled trial at baseline, and 0.13 for the randomized controlled trial at 6 months.

Conclusion: Both studies showed good reproducibility of the noninvasive method comparable to invasive urodynamics.

OBJECTIVES

Two large-scale scientific studies using the condom catheter method to measure urinary bladder function noninvasively are being conducted in different centers in the Netherlands. The first, 'A longitudinal non-invasive study of changes in urinary bladder contractility in response to benign prostatic enlargement' (LNS) is taking place at the Erasmus MC in Rotterdam [1]. Volunteers will be investigated three times in 5 years. At the time of writing, the first of the three series of measurements has been completed. These measurements were performed by the first author.

The second study, 'A new approach to the prevention and treatment of prostatic symptoms: drinking water', has recently been completed at the University of Maastricht. In this randomized controlled trial (RCT), volunteers were investigated twice in 6 months to evaluate the effect of additional water intake on the bladder function [2,3] . All measurements in the RCT were performed by the second author. In both studies, measurements of urinary bladder function were carried out (at least) twice in each session on the same day, in order to calculate reproducibility.

Earlier, we published an interim analysis of the reproducibility and applicability of the condom catheter method in measuring isovolumetric bladder pressure in the first 555 volunteers of the LNS [1]. With the completion of both studies, more data are now available for comparing different aspects of the study method.

Presently, we have analyzed and compared the reproducibility of the condom method for noninvasive urodynamics. The stability of the reproducibility was assessed by comparing the results attained by one investigator at different time points, e.g. baseline and 6 months into the RCT. The degree to which the reproducibility depends on the investigator was estimated by comparing the results attained by the two investigators. The success rates gained and the adverse events observed by the two investigators in two completely different study populations are described.

MATERIALS AND METHODS

LONGITUDINAL NONINVASIVE STUDY

This study is taking place at the Erasmus MC in Rotterdam [1]. A population of male volunteers, with a flat age distribution of between 38 and 77 years, was mainly invited by general practitioners (GPs) in Schiedam, a municipality near Rotterdam. Inclusion criteria were: written

informed consent and ability to void standing. Exclusion criteria were: diabetes mellitus and conditions such as heart failure and parkinsonism, previous surgery or medication for the cerebrum, heart, kidney, bladder and/or prostate, and the use of anticoagulants. If a maximum free flow rate below 5.4 ml/s was found at time of the measurements, the volunteer was also excluded [4]. All volunteers will be studied three time in 5 years. From November, 15, 2001 to December, 31, 2003, the first of the three series of measurements was performed in 1,073 volunteers. A flowchart of the study is given in Figure 1 .

RANDOMIZED CONTROLLED TRIAL

In this RCT, the participants were selected from 21 general practices in Maastricht and surroundings. Inclusion criteria were: men aged 55-75 years, written informed consent, ability to void standing and moderate symptom severity, witnessed by an International Prostate Symptom Score (IPSS) of 8-19. Exclusion criteria were: mild (IPSS score 7) or severe (IPSS score 20) symptom severity, diabetes mellitus and conditions such as heart failure and parkinsonism, previous surgery or medication for the cerebrum, heart, kidney, bladder and/or prostate as well as the use of diuretics. Other contraindications for participation were disturbed electrolyte and/or fluid balance, kidney insufficiency, and problematic hypo- or hypertension. Based on questionnaires, 186 male subjects were invited. The subjects were investigated twice in 2003, at baseline and after 6 months, to evaluate the effect of extra water intake on bladder function [2,3]. Figure 2 represents a flowchart of the RCT.

DATA COLLECTION

In both studies, (isovolumetric) bladder pressure was measured noninvasively with the condom catheter method. The patient voided when there was a sensation of full bladder into a measuring unit containing three valves to regulate the outflow resistance. During voiding, the urinary stream was interrupted several times by closing all the valves. With this ‘interrupted flow’ method, the urinary bladder function or contractility was estimated [5]. This procedure has been extensively published previously [1,5,6]. An example of the course of a bladder pressure measurement is given in figure 3. For the purpose of testing the reproducibility of the method, two pressure measurements on the same session (day) were attempted in every subject of both studies. The maximum condom pressure (manually excluding artefacts) recorded at each measurement was used for further analyses.

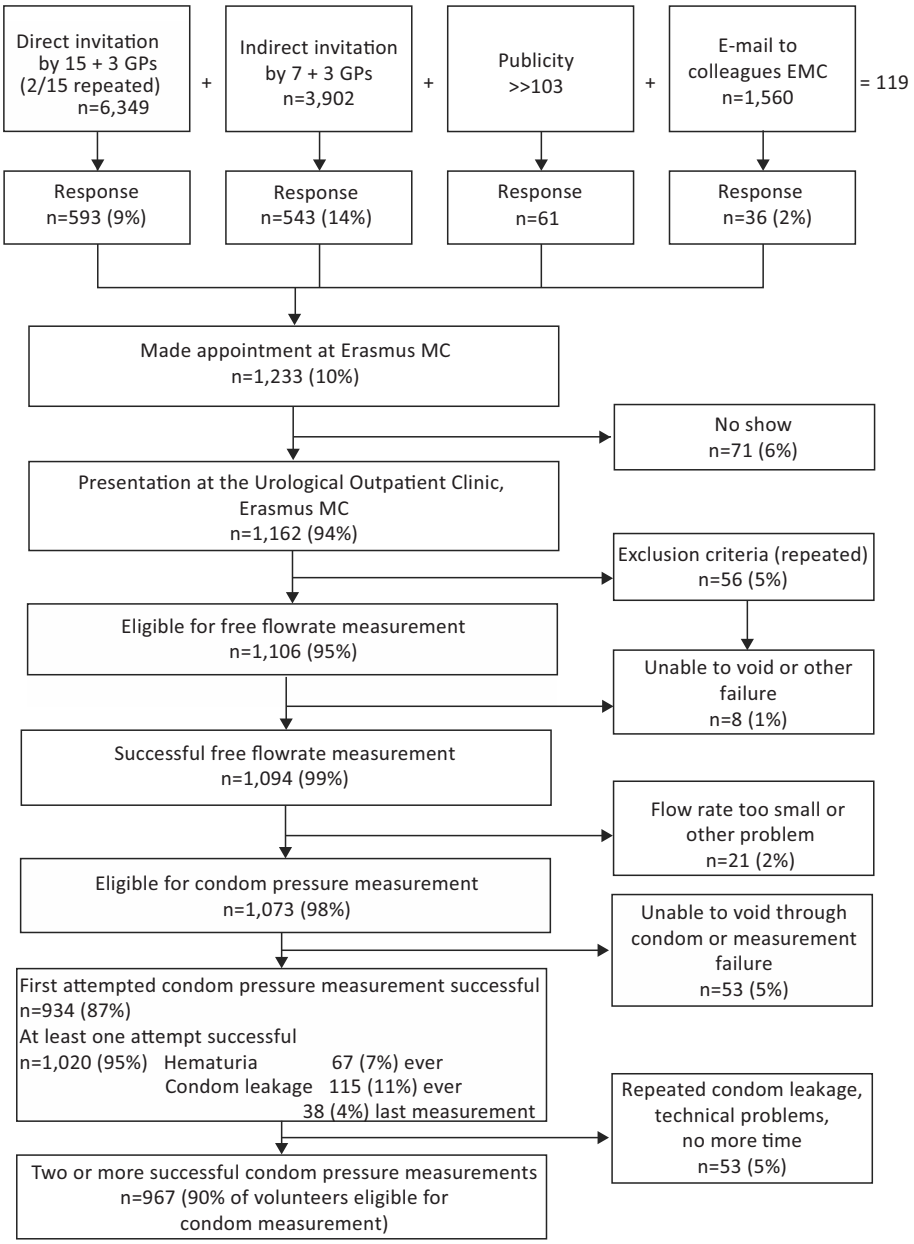
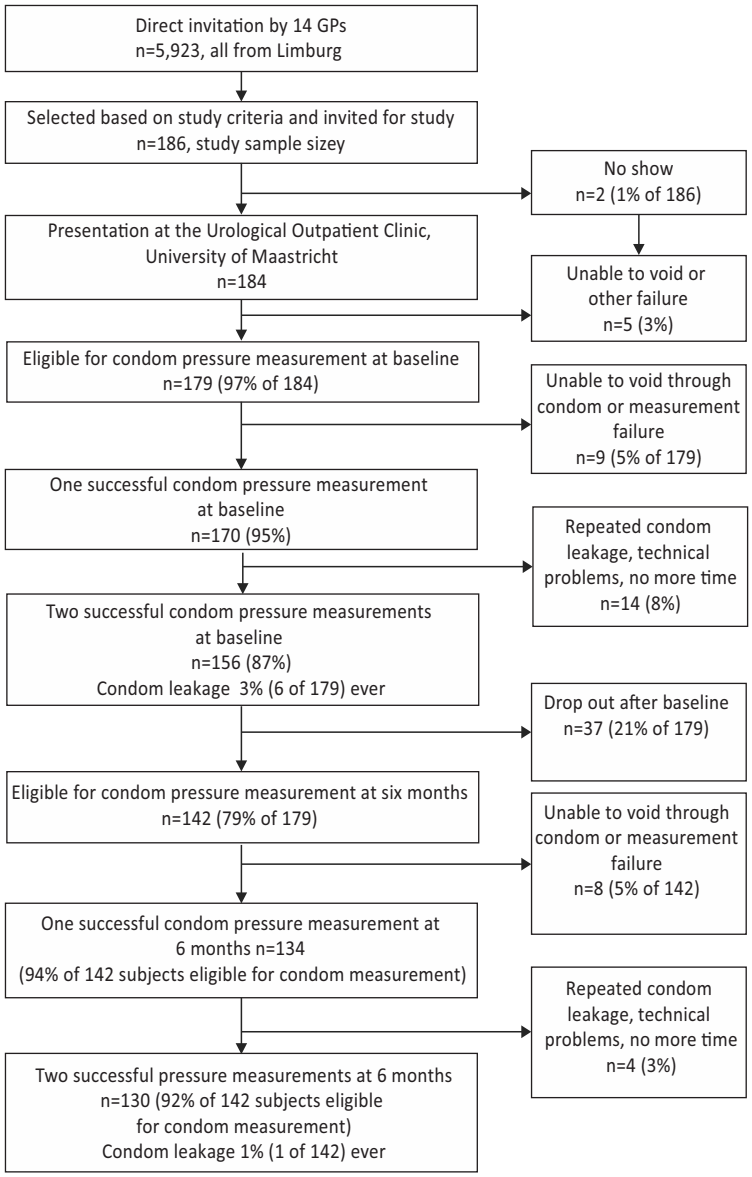


Figure 1. Flowchart describing the recruitment of volunteers and the first series of measurements of the LNS. All 1,020 fully included volunteers will be investigated three times in 5 years to evaluate changes in bladder contractility secondary to benign prostatic enlargement. Success rates for one and for two condom pressure measurements are shown. The ever % is explained in the text



F igure 2. Flowchart of the RCT. Subjects were investigated twice in 2003, at baseline and after 6 months, to evaluate the effect of extra water intake on the bladder function. Success rates for one and for two condom pressure measurements are given. For an explanation of the ever %, see text.

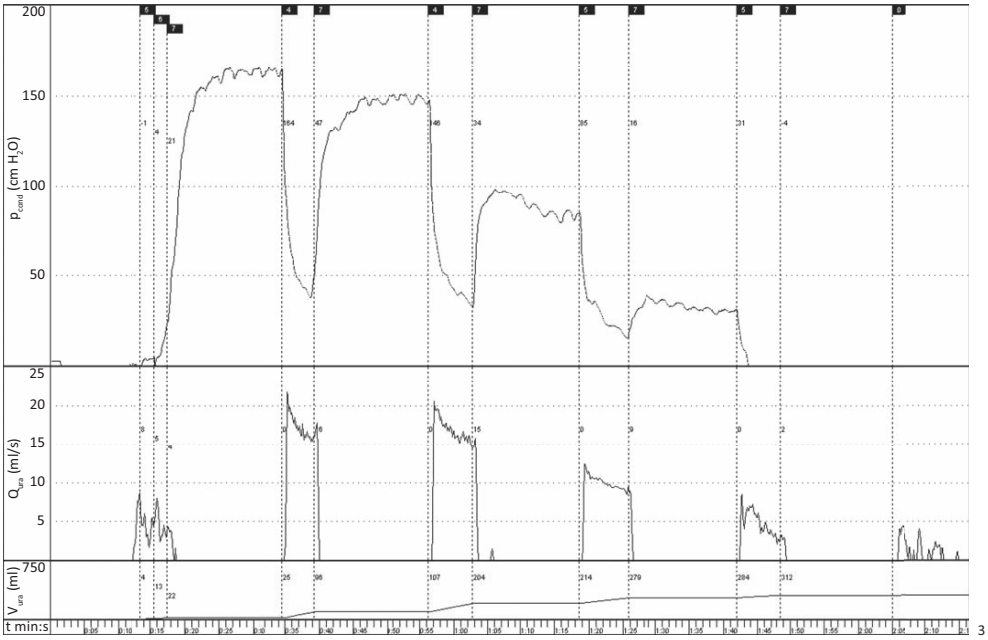


Figure 3. An example of a bladder pressure measurement in the LNS. The upper panel represents the pressure signal, the middle panel displays the interrupted flow rate during measurement, and the lower panel the voided volume. Shortly after voiding started, some valves were closed to build up a preload pressure in the condom. When voiding was interrupted, there was an open connection between the condom and the urinary bladder via the urethra. At that instant, the condom pressure reflected the isovolumetric bladder pressure which is a measure of bladder contractility. By repeating the action of closing and reopening the valves several times, the maximum condom pressure ($p_{cond.max}$) was measured repeatedly.

Although the condom catheter method applied was essentially the same in both studies, the hard- and software for registration and analysis of the data differed between centers. In the longitudinal study, a modified Andromeda Medical Systems® set-up was used. The maximum readings of the condom pressure measured were (automatically) determined by a Matlab® computer program. All readings were graphically presented to the investigator, and manually corrected in case of artefacts. In the RCT, a Multiple Channel Registration System (MKR) developed at the Erasmus University was used. This system required manual analysis of the

data by placing a marker in the recording with a mouse device. The (maximum) pressure value at the marker was indicated on the screen, and copied manually onto an Excel® spreadsheet.

A minimum free flow rate of 5.4 ml/s is a requirement for the condom pressure reading to accurately reflect the bladder pressure [4]. In the LNS, this was one of the study criteria, but in the RCT it was not. However, when analyzing the data from the RCT, no free flow rate values below this limit were found. Before the pressure measurements, the subjects were instructed not to strain during voiding. To maximize the accuracy of the pressure measurement, some preload pressure (in the order of 40-50 cm H_2O) in the condom was first established by closing some valves before closing them all, completely interrupting the flow. If a measurement was performed as described without any leakage of urine, it was considered successful (Figure 3). Pressure measurements with minimal terminal condom leakage, i.e. a small leakage occurring after the highest pressure reading, were considered successful too.

DATA ANALYSES

Data of successful bladder pressure measurements were selected for this comparative analysis of reproducibility from volunteers participating in the longitudinal study and in subjects at baseline ($RCT_{baseline}$) and 6 months (RCTsixth months) from the randomized controlled trial. Although the pressure measurements were performed by two different investigators (first and second author for LNS and RCT, respectively), the traces of all pressure measurements in both studies were analyzed by the first author. Success rates were calculated for at least one and for two successful measurements at the same session (day).

The difference plot method according to Bland and Altman [7] for comparing outcomes of repeated measurements was applied to test the reproducibility. The difference of two measurements in the same subject was plotted as a function of the mean of the two values. The standard deviation of the differences was normalized by dividing by the difference between the 97.5th percentile and the 2.5th percentile of the mean of the two values [8] .

The stability of the reproducibility of the method was assessed by comparing the results of the interim analysis (in the first 555 volunteers) [1] with the present results in 1,020 eligible males in the LNS, and by comparing the results at baseline (RCT baseline) and at 6 months (RCT sixth months) in the RCT. The dependence of the reproducibility on the investigator was assessed by comparing the normalized standard deviation of the differences of the measurements in the LNS to the one of the measurements in the RCT. The difference in normalized standard deviations between the two populations was tested for significance using the bootstrap procedure [9]. From both sets of differences and means of pairs of pressure values, 1,000 realizations were made by random sampling with replacement. For

each realization, the normalized standard deviation was calculated. The two distributions of normalized standard deviations were subtracted, and the 95% CI of the difference was calculated.

The two study populations differed in age, IPSS and prostate volume. To test if these differences influenced the reproducibility, we first tested if they were significant using the Mann-Whitney U test. Additionally, we tested if the reproducibility depended significantly on these variables using the Spearman's correlation test in the LNS as well as in the RCT at baseline. A p value (two-tailed significance) of ! 0.05 was considered statistically significant.

RESULTS

Figures 1 and 2 are flowcharts representing the course of both studies. The percentages given in these figures for hematuria 'ever' and condom leakage 'ever' show how many of the subjects the event occurred in any of the measurements, i.e. not necessarily in all measurements.

Figure 3 illustrates an example of a bladder pressure measurement in the LNS. The pressure signal is drawn in the upper panel; the middle panel shows the interrupted flow rate during the measurement, and the voided volume is displayed in the lower panel. As soon as the measurement was started and after the voiding had begun some valves were closed to achieve a preload pressure of approximately 40 cm H_2O. When subsequently all valves were closed, voiding was interrupted. As a consequence, the condom pressure rose to an equilibrium that reflected the isovolumetric bladder pressure. The maximum condom pressure measured in this example was approximately 165 cm H_2O. The 'numbered flags' represent the position of the valves in a binary code, i.e. 0 means all three valves were open, 7 means all three were closed, etc.

Table 1 gives the overall statistics of the maximum condom pressure readings ($p_{cond.max}$) in the LNS as well as RCT at baseline and 6 months. The success rates for one and for two pressure measurements on the same session (day) are also given.

Figures 4- 6 show the difference plots of both studies according to Bland and Altman. Differences of less than ± 20 cm H_2O in 80, 68 and 70% of the subjects in the LNS, $RCT_{baseline}$ and RCT_{sixth} months were found. As the plots show, there was no obvious relation between the differences and the mean of the pressures, so that standard deviations of the differences could be calculated as shown in table 2 .

Table 1. Overall statistics of the maximum condom pressure readings (pcond.max (1st) and (2nd) in cm H_2O)

Study	Range	Median	Mean	SD	IQR	n1	n2	% success rate (n1/N)/(n2/N)
LNS								
$P_{cond.max}$ (1st)	20-215	101	103	31	82-123	1,020		95% (1,020/1,073)
$P_{cond.max}$ (2nd)	28-228	99	101	32	79-120		967	90% (967/1,073)
RCT								
At baseline								
$P_{cond.max}$ (1st)	33-288	98	107	48	73-133	170		95% (170/179)
$P_{cond.max}$ (2nd)	40-285	101	110	46	78-134		156	87% (156/179)
At 6 months								
$P_{cond.max}$ (1st)	20-314	93	103	46	73-126	134		94% (134/142)
$P_{cond.max}$ (2nd)	41–265	93	104	43	74-128		130	92% (130/142)

N = Number of eligible volunteers or subjects; n = number of volunteers or subjects with one (n1) or two (n2) successful pressure measurements in the same session; SD = standard deviation; IQR = interquartile range.

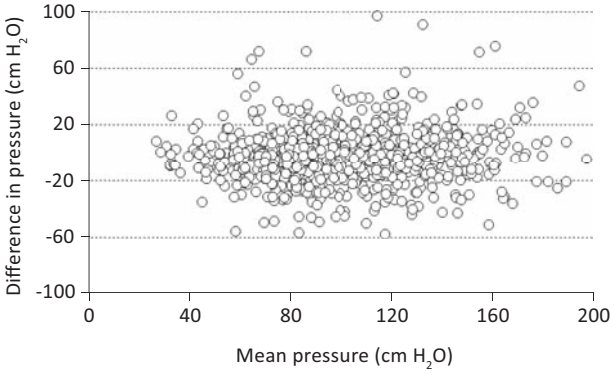


Figure 4. Difference plot according to Bland and Altman representing the reproducibility of the condom catheter method attained in the LNS, consisting of 967 double noninvasive bladder pressure measurements. The difference between each two measurements in each subject was plotted as a function of the mean of those two values. For statistical characteristics of the reproducibility in this series, see table 2.

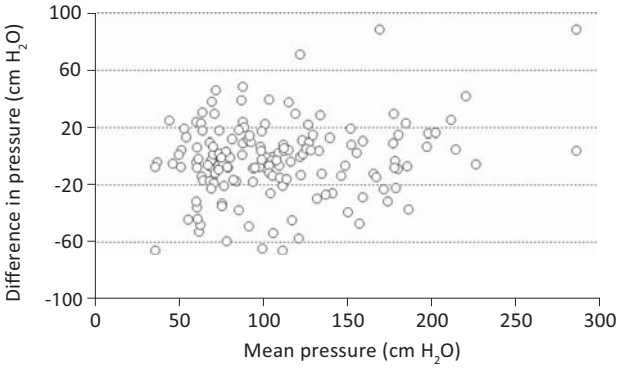


Figure 5. Difference plot according to Bland and Altman illustrating the reproducibility of the condom catheter method attained in the RCT at baseline, consisting of 157 double noninvasive bladder pressure measurements. For statistical characteristics of the reproducibility in this series, see table 2 .

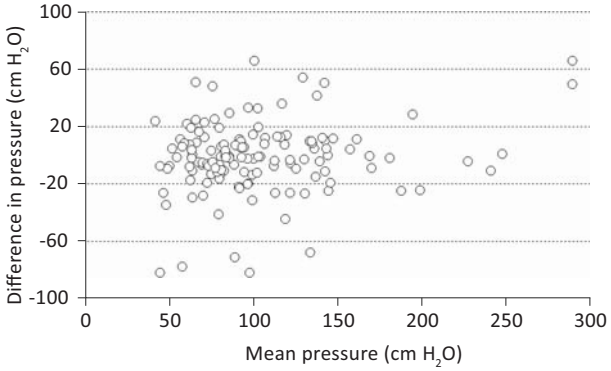


Figure 6. Difference plot according to Bland and Altman illustrating the reproducibility of the condom catheter method attained in the RCT at 6 months, consisting of 130 double noninvasive bladder pressure measurements. For statistical characteristics of the reproducibility, see table 2.

Table 2 also shows the number of double bladder pressure measurements in both studies. In the LNS there were 457 at interim analysis and 967 at the end of the first series of 555 and 1,020 eligible volunteers, respectively [1,8]. In the RCT, the numbers were 156 at baseline and 130 at 6 months of 179 and 142 eligible subjects, respectively (see table 1). The 95% CI of the difference between the normalized standard deviations of the LNS and the RCT at baseline was -0.043 to 0.029, containing 0, so that this difference was not significant.

Table 2. Statistics of the reproducibility of the condom catheter method

Study	n	Range	Mean	SD	2.5th percentile of the mean	97.5th percentile of the mean	SD of the difference/(97.5th-2.5th percentiles)
LNS							
At interim							
Means of each two $P_{cond.max}$	457	29-205	101	31	44	166	
Difference of each two $P_{cond.max}$	457	-58-97	-1	18			0.15
At end of 1st series							
Means of each two $P_{cond.max}$	967	27-217	102	30	47	166	
Difference of each two $P_{cond.max}$	967	-58-97	-2	18			0.15
RCT							
At baseline							
Means of each two $P_{cond.max}$	156	37-287	109	45	50	216	
Difference of each two $P_{cond.max}$	156	-66-88	-3	24			0.15
At six months							
Means of each two Pcond.max	130	46-289	104	43	49	237	
Difference of each two $P_{cond.max}$	130	-82-66	-1	24			0.13

n = Number of subjects with two consecutive bladder pressure measurements; SD = standard deviation. SD of difference/(97.5th-2.5th percentiles) is the normalized standard deviation of the differences, a measure for comparing reproducibilities [6].

Table 3 shows the differences in age, IPSS and prostate volumes between the LNS and the RCT at baseline, and that the reproducibility did not depend on those variables. The adverse events found are summarized in table 4. It must be kept in mind that the percentages given in this table, as the 'ever' % in figures 1 and 2, imply that this is the frequency of occurrence of the event in any of the measurements in one specific subject, but not in all of his measurements.

Table 3. Statistics of age, IPSS and prostate volume in LNS and RCT at baseline and significance of the Mann-Whitney U test

	Age years	IPSS	Prostate volume cm^3
Statistics in LNS/RCT at baseline			
n	963/183	963/183	963/148
Mean	56/64	6/12	35/36
SD	10/5	5/5	19/14
Range	38-77/56-760-26/1-31	8-251/10-100	
Differences in populations			
Mann-Whitney U test	$p < 0.0001$	$p < 0.0001$	$p = 0.08$
Correlation of reproducibility with			
Spearman's correlation in the LNS	-0.002 (n=963)	-0.043 (n=963)	-0.028 (n=963)
Spearman's correlation in the RCT at baseline	-0.123 (n=156)	-0.063 (n=156)	0.020 (n=128)
p value LNS	0.96	0.18	0.38
p value RCT at baseline	0.13	0.44	0.82

Spearman's correlation coefficients showing that in both studies the reproducibility of the condom method was independent of these three variables. $p<0.05$ was considered statistically significant. As a result of some missing data, the numbers of cases in table 3 slightly differ from elsewhere in the tables and text.

Table 4. Adverse events

Study	Hematuria	Pain	Hematoma	Miscellaneous	None
LNS	7% (67/1,020)	9% (95/1,020)	1% (13/1,020)	0.7% (7/1,020)	91% (924/1,020)
RCT					
At baseline	8% (15/179)	4% (6/179)	0%	0.6% (1/179)	81% (145/179)
At 6 months	4% (6/142)	6% (8/142)	0%	0%	89% (127/142)

Hematuria = Terminal self-limiting macroscopic hematuria; pain = short-lasting unpleasant feeling or pain on the glans penis; hematoma = small hematomas on the skin of the penis; miscellaneous = acute urinary re-tention, possible lower urinary tract (bladder) infection, postmicturition syncope; none = no event at all.

DISCUSSION

This study aims at describing the applicability and reproducibility of the condom catheter method. It is based on measurements at two different centers by two different investigators in two different study populations. The flowcharts of both studies illustrate the recruitment and the measurements. We assumed that the reproducibility of the method for measuring the bladder pressure must be independent of age, IPSS, or prostate volume. The results of

Spearman's correlation test shown in table 3 confirm this assumption. Also, the fact that there was no large difference in the reproducibility of the pressure in both studies, although there were significant differences in age, IPSS and prostate volume between both studies, supports it. Therefore, no correction was applied for those differences between the study populations.

In the LNS, 1,020 eligible volunteers underwent an attempt to measure bladder pressure. In the RCT, there were 179 eligible subjects (figures 1 and 2). Differences between the maximum pressure readings in the RCT at baseline and after intervention at 6 months have been published elsewhere [2,3]. Table 1 shows the success rates in both studies for one and for two measurements which were comparable and varied from 87 to 95%. This finding demonstrates the applicability of the method by different investigators in different male populations. Factors causing failure of the measurement could be due to the subject, such as inability to void through the condom or the measuring unit or as a consequence of leakage of urine. Other problems were of a technical nature (computer or network crash) or the subject had no more time. A count of such occurrences is given in the flowcharts.

To compare the reproducibility of the (condom) method between two different centers with different investigators in two different study populations, some kind of normalization was required. This was carried out as no gold standard exists to conclude if a test or method has a good or bad reproducibility.

Earlier, we published a suitable method to compare the reproducibility of different methods for clinical measurements: normalizing standard deviations of differences by dividing by the difference between the 97.5th and 2.5th percentiles of the mean [8]. Normalization was thus performed by dividing by the difference between two extreme values, one being almost the largest value measured, the other almost the smallest, excluding outliers. A smaller number represents a better reproducibility. The results of these calculations for the (double) measurements of both studies are shown in the last column of table 2 .

Based on the results of the difference plots and the normalized standard deviations of differences as shown in table 2 , it can be stated that the condom catheter method had a good overall reproducibility that did not seem to depend on the investigators or the study populations. This reproducibility is comparable to or slightly better than that of invasive urodynamics, as published previously [8].

Despite the noninvasive nature of the condom catheter procedure, some adverse events were encountered (table 4). Those were identical in both studies and occurred during or after the pressure measurement. Mostly, they were very mild and influenced by the sensitivity and/or the vulnerability of the subject undergoing the procedure and were inevitable. More serious events such as acute urine retention had a negligible frequency (0.2%). These events

can be prevented by giving detailed instructions to the subjects such as not to postpone voiding when there is a strong urinary urge or sensation of a full bladder. Antibiotic treatment was not necessary.

Logadottir et al. [10] studied tolerance and acceptance by the patients of invasive urodynamic studies. They found that 50% of the patients experienced some degree of discomfort during the pressure flow study (pQS), 46% of the patients some degree of transient dysuria after pQS and 18.5% voiding problems of varying nature. 2.5% reported fever, and 4.1% had positive culture and symptoms of urinary tract infection (UTI) requiring antibiotic treatment in their study. Such findings were not encountered in our noninvasive study. The 5% of patients with hematuria that they found was comparable with our number.

Porru et al. [11] in the evaluation of morbidity of multichannel pressure-flow studies reported that dysuria of a mild degree was experienced by 33% of the patients, with no significant difference between males and females. This occurrence of dysuria was significantly higher than what we encountered with noninvasive urodynamics. Six patients (5.7%) had macroscopic hematuria of a mild degree. No patient had urinary retention or severe complaints after the investigation and no patient required hospitalization. All of these are comparable to our present noninvasive study. Additionally, they reported postinvestigational UTI and fever in 3.6% of men and 4% of women, a finding which we did not come to.

In 'morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies', Klingler et al. [12] found an overall complication rate, including urinary retention, gross hematuria, urinary tract infection and fever, of 19.0% (12 of 63) for men and 1.8% (1 of 56) for women. The considerably higher rate of complications and morbidity found associated with invasive pressure flow studies compared to the condom method indicates that the insertion of catheters for gaining pressure signals involves higher risks. In these terms, noninvasive urodynamics seems to be a more patient-friendly method.

The statistical figures and findings in these two case studies are promising and may serve as practical guidelines for future application of the (noninvasive) condom method, for example, in (large-scale) clinical and scientific studies, such as noninvasive evaluation of the bladder pressure in patients with LUTS before and after transurethral resection of the prostate (TURP). Comparing the morbidity and reproducibility of the noninvasive condom catheter method with the existing invasive pressure- flow study, we think the former is a more suitable method for large-scale clinical studies. In view of the promising diagnostic accuracy in a pilot study, it might also develop into a suitable method for the diagnosis of prostatic obstruction [13].

CONCLUSION

The condom catheter method was successfully applied in two large-scale scientific studies by different investigators on different study populations in the Netherlands. In both studies, it had a high success rate of 95% for single and 87-90% for double bladder measurements. It was demonstrated by difference plots (Bland and Altman) and the normalized standard deviation of the differences of double measurements that the method had a stable and good reproducibility. In our data, double consecutive pressure measurements by means of the condom method differed by less than ±20 cm H_2O in approximately 80% of the subjects. Despite the noninvasiveness of the method, some mild adverse events were found in both studies with a comparable low frequency.

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Chapter 8

AGE AND VOLUME DEPENDENT NORMAL FREQUENCY VOLUME CHARTS FOR HEALTHY MALES

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ABSTRACT

Purpose: We report age and voided volume stratified normal values for voiding diary parameters, including urine production, in a uniform, nonreferred population of 935 healthy male volunteers.

Materials and Methods: A total of 935 volunteers kept a 3-day voiding diary and also recorded the time of going to bed and getting up. Additionally, prostate volume was measured using transabdominal ultrasound and the maximum free flow rate was measured with a rotating disc flowmeter. From the diaries we calculated median voided volume and the mean number of voids during the day and night. We also calculated mean urine production in ml per hour during the day and night by assuming constant production between voids.

Results: Volunteers voided a median volume of 220 ml 6 times daily and 0.5 times nightly. They produced 83 ml urine per hour during the day and 48 ml per hour during the night. The median maximum flow rate was 16 ml per second and median prostate volume was 31 ml. All diary parameters, free flow rate and prostate volume depended significantly on International Prostate Symptom Score. However, all parameters except urine production during the day depended significantly on age and all except prostate volume depended significantly on voided volume.

Conclusions: Values in a subgroup of 788 volunteers with an International Prostate Symptom Score of 10 or less may be considered normal for male voiding diary parameters. Age and voided volume stratified normal values were also derived.

INTRODUCTION

Frequency-volume charts record voided volumes as well as the time of each micturition during the day and night for at least 24 hours [1].

Reference values for FVC parameters in a healthy male population may help .nd and detect abnormalities in patients with LUTS. Despite the frequent use of FVCs normal FVC values are sparse. van Mastrigt and Eijskoot reported an analysis of voided urine volume measured using a small electronic pocket balance [2]. More recently Parsons et al. presented normative night and day bladder diary measurements in a small group of patients with mixed pathological conditions [3].

At the department of urology outpatient clinic at our institution a noninvasive longitudinal study is being conducted to measure changes in bladder function in response to prostatic enlargement [4-8]. A rectangular, age distributed population of 1,020 healthy male volunteers participates in this study. Participants were studied 3 times in 5 years. We analyzed the FVC of 3 consecutive days, I-PSS, uroflowmetry and prostate size of the first study round done between November 15, 2001 and December 12, 2003 in this population. The main aim of the current analysis was to establish normal values of frequency-volume parameters and their dependence on I-PSS in this group of healthy males. These values are most likely age dependent and, therefore, they were age stratified. A possible dependence on voided volume was also studied. Daytime and nighttime urine production parameters were derived as previously reported [2].

MATERIALS AND METHODS

VOLUNTEERS

A total of 1,020 male volunteers 38 to 77 years old were included in the longitudinal study from November 15, 2001 to December 12, 2003 [5,6,8]. These males were stratified in 8 age groups at 5-year intervals. Eligible and healthy males were studied according to a protocol approved by the medical ethics committee at Erasmus Medical Center, Rotterdam. Most participants were invited by general practitioners in Schiedam, a municipality near Rotterdam. Study inclusion criteria were informed consent and the ability to void in the normal standing position with a minimum free flow rate of 5.4 ml per second. Study exclusion criteria were diabetes mellitus and certain conditions that possibly influence the micturition process, such as a suprapubic catheter, mental and/or sleeping disorders, Parkinsonism, previous surgery or medication

of the cerebral nervous system, heart, kidney, bladder and/or prostate, and anticoagulant use. Dormant and/or untreated LUTS were not an exclusion criterion. Additionally, patients on anticoagulants were excluded from analysis because the noninvasive condom method for measuring bladder pressure used in the longitudinal study resulted in slight hematuria in some patients [5].

DATA COLLECTION

All eligible volunteers were requested to complete an FVC for at least 3 consecutive days, including bedtime and awakening times during normal daily circumstances. A disposable 1 l measuring jug was used. Subsequent examination in the hospital included free uroflowmetry. Q_{max} was assessed with a Dantec® rotating disc flowmeter. Prostate size was measured on transabdominal ultrasound with an Aloka® SSD-1700 device. Earlier we reported that transabdominal and transrectal ultrasonography showed comparable outcomes when estimating prostate size [9]. Additionally, all men completed the I-PSS. Subsequently they underwent 2 noninvasive condom pressure measurements. These results were reported previously [5-8]

FVC ANALYSIS

Only correctly administered FVCs were selected for further analysis. Urine production was calculated by assuming that the bladder was always completely empty after voiding and urine production was constant between voidings. By linear interpolation of bladder volume between voids production was calculated for each of the 24 hours of each day and averaged for the number of days that FVCs were kept [2]. In this way median urine production per hour was calculated during the awake and asleep periods. Several more straightforward parameters were also calculated (table 1).

STATISTICS

All statistical calculations were performed using SPSS®, version 10.1. In the current analysis men were subdivided into 2 groups using an I-PSS of 10 as an arbitrary cutoff value. They were also stratified into 5-year age groups and into 5 groups with different median voided volumes. The median, and 25th and 75th percentiles were used as descriptive statistics. The Mann-Whitney U and Kruskal-Wallis tests were used to test for significant differences between 2 or more groups.

Table 1. Parameters in healthy male volunteers and in groups with I-PSS 10 or less and greater than 10.

	Median (25th-75th percentiles)			
	Healthy	I-PSS 10 or Less	I-PSS Greater Than 10	p Value* (Mann-Whitney U test)
No. pts	935	788	147	
I-PSS	5 (3-8)	4 (2-6)	13 (12-16)	
Age	54 (48-65)	53 (48-64)	59 (50-66)	0.001
Vol (ml)	220 (185-295)	230 (190-300)	200 (158-250)	<0.001
No. voids:				
Day	5.8 (4.8-7.0)	5.7 (4.7-7.0)	6.7 (5.7-8.2)	<0.001
Night	0.5 (0.0-1.0)	0.5 (0.0-1.0)	1.0 (0.5-1.5)	0.001
Urine production (ml/hr):				
Day	83 (60-116)	81 (59-112)	98 (71-128)	0.001
Night	48 (32-73)	47 (31-71)	53 (37-84)	0.010
Q_{max} (ml/sec)	15.6 (16.3-21.6)	6.1 (11.7-22.4)	12.8 (9.6-19.0)	<0.001
Prostate vol (ml)	31 (23-41)	30 (23-40)	34 (25-48)	0.006

* I-PSS 10 or less vs greater than 10.

Table 2. Parameters in 8 age groups.

	Age Group								p Value (nonparametric Kruskal-Wallis test)
	38–42	43–47	48–52	53–57	58–62	63–67	68–72	73–77	
No. participants	103	114	210	107	109	121	113	58	
Median voided vol (ml)	210	225	240	250	225	210	200	200	.006
Mean No. voids:									
Day	5.7	5.5	5.7	6.0	6.0	6.0	6.3	6.2	0.017
Night	0.0	0.3	0.5	0.7	0.7	0.7	1.0	1.0	<0.001
Mean urine production (ml/hr):									
Day	87	78	84	89	87	82	88	74 0	.46
Night	42	41	41	56	53	52	56	48	<0.001
Q_{max} (ml/sec)	20	16	18	15	5	13	13	13	<0.001
Prostate vol (ml)	26	28	29	30	34	36	43	45	<0.001

RESULTS

Of the 1,020 healthy male volunteers 935 (92%) who properly completed an FVC and an I-PSS, and successfully voided in the flowmeter were included in the current analysis. In 788 men the I-PSS was 10 or less, whereas in 147 it was greater than 10. Table 1 shows the 25th percentile, the median and the 75th percentile in the total group of 935 men as well as age, I-PSS, median voided volume, the mean number of daytime and nighttime voids, mean daytime and nighttime urine production, Q_{max} and prostate volume in the 2 subgroups. Table 1 also lists Mann-Whitney U test p values for comparing the 2 subgroups. Of the 935 eligible FVCs 3 days were monitored in 834 cases and 2 nights were monitored in 733, while 37 FVCs included 4 days and 163 included 3 nights. There were a few outliers, including 4 and 3 FVCs showing 5 and 6 days, and 4 and 1 FVCs showing 5 and 6 nights, respectively.

Table 2 lists the number of volunteers and median study parameter values in the 8 age groups. The total of 935 male volunteers were stratified into 5-year age groups, including ages 38 to 42, 43 to 47, 48 to 52, 53 to 57, 58 to 62, 63 to 67, 68 to 72 and 73 to 77 years. As expected, prostate volume increased gradually and statistically significantly with increasing age and Q_{max} decreased accordingly (each $p<0.001$). Median voided volume was significantly different among the age groups (Kruskal-Wallis test $p=0.006$). It seemed to increase from the 38 to 42-year-old age group to the 53 to 57-year-old age group. However, from the 53 to 57-year-old group to the 73 to 77-year-old group median voided volume decreased statistically significantly. The mean number of daytime voids showed marginally statistically significant changes and seemed to increase with age, as did the number of nighttime voids ($p=0.017$ and <0.001, respectively). Mean daytime urine production did not statistically significantly depend on age ($p=0.46$). However, nighttime production changed suddenly between ages 48 to 52 and 53 to 57 years from a median of 41 ml per hour in the lower 3 age groups to 54 ml per hour in the higher 4 groups ($p<0.001$). Table 3 lists median parameter values in the groups, stratified by median voided volume. Prostate volume was not significantly different between the groups ($p=0.70$). However, Q_{max}, the number of voids and urine production were significantly different between the groups during the day and night ($p<0.001$).

Table 3. Parameters by voided volume.

	Median Voided Vol (ml)					p Value (nonparametric Kruskal-Wallis test)
	175 or Less	Greater Than 175–200 or Less	Greater Than 200–250 or Less	Greater Than 250–300 or Less	Greater Than 300	
No. participants	210	197	212	144	172	
Mean age	56	58	55	56	51	<0.001
Mean No. voids:						
Day	6.7	6.0	5.7	5.4	.0	<0.001
Night	0.7	0.5	0.5	0.5	0.3	<0.001
Mean urine production (ml/hr):						
Day	61	74	82	97	114	<0.001
Night	37	44	48	63	63	<0.001
Q_{max} (ml/sec)	12	15	17	16	20	<0.001
Prostate vol (ml)	32	32	30	31	30	0.70

DISCUSSION

Different voiding statistics and parameters were calculated from the FVCs. To calculate urine production we assumed that the bladder was always emptied completely. At this study round we did not control for PVR. At the second study round 2.5 years later PVR was measured in the same group of volunteers and the results were published [10]. After free voiding the median PVR was 18 ml (IQR 37) and it was independent of the amount of fluid intake. Tables 1 to 3 show median urine production during the day and night. Earlier we reported significant physiological variation in urine production throughout the day [2,11]. When averaged over the whole range of ages, which was an almost flat distribution between ages 38 and 77 years, these males voided a median of 220 ml 6 times daily and 0.5 times nightly, and produced 83 ml urine per hour during the day and 48 ml per hour during the night. Median Q_{max} was 16 ml per second and prostate volume was 31 ml.

An I-PSS of 10 was arbitrarily chosen as a cutoff value to divide the study population into 2 subgroups with almost no and mild to moderate LUTS. Each subgroup had a statistically acceptable number of volunteers. Values in the subgroup of 788 volunteers with almost no LUTS (I-PSS 10 or less) may be considered normal. Values beyond the ranges of these percentiles might indicate early LUTS. Comparing findings in the 2 subgroups showed that age, all FVC parameters, Q_{max} and prostate volume were statistically significantly different (table

1). Men with an I-PSS of 10 or less were younger than men with an I-PSS of greater than 10. Obviously with increasing age men had more LUTS, as assessed by FVC and I-PSS. Men with mild to moderate LUTS voided more frequently during day and night than asymptomatic men. They also had a smaller median voided volume and higher urine production during the day and night. The finding of a lower free flow rate in men with mild LUTS underlines the role of altered bladder function or mild bladder outlet obstruction in these men. The statistically significant difference in prostate volume on transabdominal ultrasound between the 2 I-PSS groups again represents a debatable confirmation that increased I-PSS or increasing LUTS somehow correlates with an increase in prostate gland size. Earlier we found a weak but statistically significant correlation between noninvasively estimated UR and I-PSS [12]. No correlation was then found between UR and prostate volume. We suggested that increased resistance is a necessary but not a sufficient condition for LUTS. UR and prostate size may be 2 different and largely independent underlying pathophysiological causes of changed bladder function and/or bladder outlet obstruction in terms of LUTS.

Thus, on cross-sectional analysis all voiding diary parameters, including urine production, depended significantly on age except mean urine production during the day. Median nightly urine production increased suddenly around age 52 years, probably due to cardiac decompensation and the redistribution of venous pooling of body fluid during the night. From that approximate age and thereafter median voided volume decreased from 250 to 200 ml, whereas the number of voids increased during the day and the night. Again, there cannot be much doubt that these related changes have multifactorial causal relations with increasing prostate volume from a median of 26 to 45 ml and increasing UR, as signified by a decreasing Q_{max} rate from a median of 20 to 13 ml per second. If bladder compensation somehow developed in this population, it was obviously insufficient to compensate for the increasing UR. The independence of prostate volume and voided volume does not contradict the earlier found dependence of prostate volume and median voided volume on age. It was caused by the increasing and decreasing pattern of median voided volume (table 2). The decrease in the number of daytime and nighttime voids with increasing median voided volume was obvious at first sight (table 3). How ever, it is remarkable that daytime and nighttime urine production also increased strongly with median voided volume, implying that this volume and the number of voids are not simply inversely related. Although fluid intake was not monitored in this study, the increase in urine production implies that fluid intake must have been higher in volunteers with higher voided volumes. As expected in this group of healthy men, Q_{max} also increased significantly with median voided volume.

CONCLUSIONS

According to 3-day FVCs 935 healthy male volunteers voided a median volume of 220 ml 6 times daily and 0.5 times nightly, and produced 83 ml urine per hour during day and 48 ml per hour during the night. Median Q_{max} was 16 ml per second and prostate volume was 31 ml. Values in the subgroup of 788 volunteers with an I-PSS of 10 or less may be considered normal values in males. All diary parameters, Q_{max} and prostate volume were significantly different in the 147 volunteers with a higher I-PSS. Almost all normal values depended on patient age and voided volume, and separate normal values were derived in groups strati.ed according to these variables.

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Chapter 9

GENERAL DISCUSSION AND CONCLUSION

Benign Prostatic Enlargement (BPE) is very common in elderly men. In more than 68% of men over the age of fifty there is histological proof of BPE. As a consequence they often develop Lower Urinary Tract Symptoms (LUTS). These include symptoms such as a weak voiding stream, daily and nocturnal frequency, sensation of incomplete emptying of the bladder and urinary retention. Two most probable causes for these symptoms are a weakly contracting bladder muscle or an enlarged prostate obstructing the bladder outlet (BOO).

Conventionally, invasive pressure flow studies are recommended for the diagnosis of BOO. Urinary flow rate is combined with the bladder pressure measured during voiding using a catheter inserted via the urethra. This invasive method is time-consuming, expensive and uncomfortable to the patient. The inserted catheter may cause urethral trauma, pain, bleeding and urinary tract infection. Non-invasive pressure flow methods may be more patient friendly and can be large-scale applied in a population of volunteers to study the development of LUTS/BOO.

The development of the condom catheter method for non-invasive measurement of the bladder pressure has been published elswhere. I applied the condom catheter method for non-invasive urodynamics in a group of approximately 1200 male volunteers in a(n ongoing) longitudinal study on changes in bladder contractility in response to BPE. These males were studied in three evaluation rounds in five years. The present thesis only contains results from the first study round.

Due to the increasing resistance to the urinary flow caused by BPE, the pressure generated by the bladder during voiding increases. This (disputed) phase is called compensation of the bladder muscle. A subsequent decompensation phase is undisputed. Here, the urinary bladder is damaged to such a degree that effective bladder emptying is no longer possible, even when the obstruction is relieved. The onset of this phase is poorly defined and no data is available.

The aim of our study was to define the compensation and decompensation phases of the bladder muscle and gain data on the reversibility of this process. Knowledge of the time course of these changes makes it possible to base therapeutic plans and decisions in BPE on the prognosis of changes in bladder contractility. As BPE develops over a long period of time, such a study makes it necessary to regularly evaluate a group of (otherwise) healthy males during forty years: ages 40-80. A more practical implementation was chosen by following a number of age stratified cohort during a shorter period.

Eight cohorts with initial ages of 38-42, 43-47, 48-52, 53-57, 58-62, 63-67, 68-72 and 73-77 have been recruited. Each cohort was followed for five years, so that the age of each cohort of volunteers at the end of the study matched that of the next cohort at the start of the study.

Each cohort was non-invasively studied three times: at recruitment, after 2.5 years, and after 5 years. This thesis is based on results obtained in the first evaluation round only.

In **chapter two** we explored the large scale applicability of the condom catheter method in volunteers to longitudinally study changes in urinary bladder contractility secondary to BPE. The recruitment of subjects went very difficult. Directly inviting patients at the Erasmus MC by letter by their General Practitioner (GP) gave a response of only 9%. A small group of 100 patients who were telephonically interviewed for their reasons for refusal, mostly indicated that the study was too time consuming. A "two phase" procedure, inviting patients first to visit the GP for an echoscopy of the prostate volume had a higher response rate of 12%. Between November 2001 and December 2003, 11,914 males aged 38-77, mentally and physically able to complete a voiding diary and to visit the outpatient clinic were invited, mainly by general practitioners (GPs) in the community of Schiedam, near Rotterdam. Eventually 1233 volunteers made an first appointment at the outpatient clinic of Erasmus MC. Repeated application of the exclusion criteria and exclusion of those who were not able to void in the presence of the investigator resulted in 1094 volunteers who underwent free flowrate measurements. Subsequently excluding those with a free flow rate less than 5 ml/s resulted in 1073 volunteers eligible for condom pressure investigation. In 1020 (95%) of them at least one succesful non-invasive pressure measurement was done in the first study evaluation round. In 967 (90%) volunteers two (or more) condom pressure measurements were done in one session. Some adverse events such as terminal selflimiting hematuria were unexpectedly encountered. It was concluded that the condom catheter method is very suitable for large-scale application and has a high successrate.

In **chapter three** we compared the repeatability of non-invasive and invasive urodynamics. Because no gold standard exists for the repeatability of a test, it is not possible to conclude if a test has good or bad reproducibility. The non-invasive method resulted in an estimate of the isovolumetric bladder pressure; the invasive method yielded several pressures. Most often the detrusor pressure at maximum flow rate is used. This pressure is inherently different from the isovolumetric bladder pressure. For example, not only is the detrusor pressure corrected for changes in abdominal pressure by subtraction of the rectal pressure, but it also is a pressure measured during voiding, which is smaller than an isovolumetric pressure as a result of the ongoing shortening of the detrusor muscle.

Difference plots were made of non-invasive bladder pressure measurements conducted in 457 volunteers in our longitudinal study and of pressure-flow studies in a comparable population of 397 male patients. To compare the repeatability of two different methods for clinical measurement, the standard deviation of differences between repeated measurements

in one individual needs to be normalised. Often a normalisation by dividing by the mean is done, which may lead to erroneous results. We have normalised the standard deviations by dividing by the difference between the 97.5th and 2.5th percentile of the mean of the two observations in each subject. With this we found a normalised repeatability of the non-invasive method of 0.15, that of the various parameters derived from the pressure-flow studies varied from 0.11 to 0.22.

We concluded that the repeatability of the condom catheter method for non-invasive urodynamics in our population of volunteers is comparable to, or slightly better than, that of invasive urodynamics in a number of outpatient populations, both in our and in other centres. The latter repeatability is generally found acceptable [21]. We further concluded that the repeatability of different medical tests, resulting in different physical variables, measured at different scales, may be compared by normalising the standard deviation of the differences between paired observations in one subject by dividing by the difference between the 2.5th and 97.5th percentiles of the mean of those observations.

In **chapter four** we studied epidemiological aspects of a population of 9,236 volunteers invited by 20 GPs, using two different recruitment methods, i.e. by mail only, or during a subsequent visit to the GP's office. Our aim was to establish if the population might be biased, or if it may be considered a representation of the general population. To this end we compared a number of variables with a representative study. We also studied differences between responders and non-responders, differences between responders recruited using two different methods, and factors influencing the response rates in our population, to assess possible sources of bias.

In the recruited population the prostate volumes were not significantly different from the proven representative study, but the international prostate symptom score (I-PSS) was statistically significantly higher, although the difference was so small it may be called clinically irrelevant. Recruitment of volunteers in two steps, i.e. asking them first to visit the GP's office, and then inviting them there to visit the outpatient clinic, rather than directly inviting them (in writing) to the clinic seemed to lead to a higher response, although this effect could not be statistically discriminated from the difference in response rates between GPs. This latter difference might be ascribed to the relation between subject and his GP, although also a difference of mean social economic status between patient populations of different GPs may have had an influence.

In general we concluded that several factors influenced the response rate of subjects recruited for our non-invasive longitudinal study. Age and social economic status did, the response being highest around the age of 60 years and lower at lower and higher ages, and

increasing with social economic status. In spite of these dependencies, when the recruited population was corrected for intentional differences in age distribution and methodological differences in flow rates, it was urologically not different from the general population.

In our longitudinal study, the prostate volume was, both at the GP's office and the outpatient urological clinic, estimated by transabdominal ultrasonography. In **chapter five**, two different transabdominal devices used were compared, and the influence of different operators was studied. As the impact of using different ultrasound devices and different operators on the prostate volume measured has not been studied before, we compared the transabdominal ultrasonography to transrectal step section planimetry as the gold standard. Since the equipment in the gp's practices differed from the one in the hospital, we also tested the agreement between both transabdominal ultrasound devices, and the influence of different operators.

Two series of measurements in 100 patients each were done. In the first series, transabdominal and transrectal sonography were pairwise compared in each patient. In the second series, transabdominal measurements were done with two devices (a hospital Aloka® SSD-1700 and a portable Aloka® SSD-900). Transrectal scannings were done by three investigators whilst all transabdominal scannings were done by one. In the transrectal-transabdominal series of prostate volume measurements, the Pearson correlation coefficient was 0.84 ($p<0.001$), the mean of the means was 52 ± 23 cm^3 (mean±sd), and the mean of the differences was 1 ± 1 cm^3. In the series with two devices, the Pearson correlation coefficient was 0.73 ($p<0.001$), the mean of the means was 31 ± 11 cm^3, and the mean of the differences was 1 ± 1 cm^3. In conclusion, no statistically significant differences were found between the transabdominal- transrectal ultrasonography, two different transabdominal devices nor between different observers. However, for those using these measurements in everyday clinical practice, it is worthwhile to point out that in our data a transabdominal scan and a transrectal scan in the same patient, on the same day,differed more than 30% in one fourth of the patients and that two transabdominal scans in the same patient (with two different devices, on

In **chapter six** we studied correlations of non-invasive urodynamics with the International Prostate Symptom Score (I-PSS) and prostate volume: data of 667 healthy volunteers were analyzed. Urethral resistance (URR) was calculated from the maximum condom pressure and the maximum free flow rate, and quantified as high or low. We found that I-PSS ranged from 0 to 29, (6.1 ± 4.8) (mean±sd), whereas the prostate volumes ranged from 8 to 140 cm^3, (34 ± 18). Twenty eight percent (185/667) of the subjects had a non-invasively quantified high URR and a significantly higher I-PSS (7.3 ± 5.2) than those with a low URR (I-PSS (5.7 ± 4.6)), Mann-

Whitney U-test: P<0.001. The I-PSS and the URR were significantly correlated, Spearman's rho (rho) = 0.20, P<0.001. A significant difference between the prostate volumes, 36 ± 21 cm^3 in the high URR versus 33 ± 17 cm^3 in the low URR group, was not found, P = 0.18. In our population of healthy volunteers, the non-invasive urodynamic data did show a small but statistically significant correlation with the I-PSS. The weak relation suggests that an elevated resistance is a necessary, but not a sufficient or the only condition for LUTS.

In **chapter seven** we were able to compare the applicability and reproducibility of the condom catheter method for noninvasive urodynamics in two large-scale scientific studies conducted in different centers in the Netherlands. For this purpose we used data from the first series of measurements which was completed in 1,020 men aged 38-77 years in the longitudinal study of changes in bladder contractility secondary to BPE. Secondly, we used data from a randomized controlled trial to test the effect of additional water intake on bladder function which was completed at the University of Maastricht. In this study, 184 subjects aged 55–77 years with International Prostate Symptom Scores of 8-19 were investigated twice in 6 months. In both studies, bladder contractility was measured noninvasively with the condom method and two consecutive measurements were attempted in each subject. Reproducibility was tested according to Bland and Altman [20] and compared by calculating the normalized standard deviation of the differences by dividing by the difference (chapter three). The success rate for one measurement in each volunteer was 95% in both studies. The success rates for double measurements varied from 87 to 90%. The normalized standard deviation of the differences between the double measurements was 0.15 for the longitudinal non-invasive study and randomized controlled trial at baseline, and 0.13 for the randomized controlled trial at 6 months.

From this comparative analysis we concluded that the condom catheter method was successfully applied in two large-scale scientific studies by different investigators on different study populations in the Netherlands. In both studies, it had a high success rate of 95% for single and 87–90% for double bladder measurements. It was demonstrated by difference plots [20] and the normalized standard deviation of the differences of double measurements that the method had a stable and good reproducibility. In our data, double consecutive pressure measurements by means of the condom method differed less than 20 cm H_2O in approximately 80% of the subjects. Despite the noninvasiveness of the method some mild adverse events were found in both studies with a comparable low frequency.

The main aim in **chapter eight** was to establish normal values of frequency volume parameters, and their dependence on I-PSS in 935 healthy male volunteers who took part in the longitudinal study. All 935 volunteers kept a 3 day voiding diary and also recorded the time

of going to bed and getting up. From the diaries we calculated the median voided volume, and the mean number of voids during day and night. We also calculated the mean urine production in ml/hr during day and night by assuming constant production between voids. Dependencies on I-PSS, prostate volume and maximum free flowrate Q_{max} were studied too. In conclusion, we found according to 3 day frequency volume charts 935 healthy male volunteers voided a median volume of 220 ml, 6 times a day, and 0.5 times a night and produced 83 ml of urine per hour during the daytime and 48 ml/ hr during the night. They had a median maximum flowrate of 16 ml/s and a prostate volume of 31 ml. The values found in a subgroup of 788 volunteers with I-PSS £10 may be considered normal values for males. All diary parameters, the free flow rate Q_{max}, and the prostate volume were significantly different in the 147 volunteers with a higher I-PSS. Almost all of the normal values depended on the age and the voided volume, and separate normal values could be derived from groups stratified according to these variables.

In this thesis I present the results of the application of the condom catheter method for non-invasive urodynamics in a longitudinal survey exploring changes in bladder contractility secondary to BPE.

In this thesis I present the results of the application of the condom catheter method for non-invasive urodynamics in a longitudinal survey exploring changes in bladder contractility secondary to BPE.

The data presented was collected in the first study round of a longitudinal study consisting of three study rounds, at intervals of 2.5 years. The data therefore does not allow conclusions relating to the general aims of the study; these aims require longitudinal data. However, based on transverse analysis, the data allows a multitude of conclusions to be drawn on two related subjects: The applicability of the condom catheter method for noninvasive urodynamics and the internal consistency of the data in terms of (cor)relations between the measured variables. These conclusions can be summarized as follows:

Epidemiological aspects of a population of 9,236 healthy male volunteers invited by 20 GPs, showed, when corrected for intentional differences in age distribution and methodological differences in flow rates, no urological differences from the general population.

In 1073 volunteers eligible for condom pressure investigation, 1020 (95%) underwent one succesful non-invasive pressure measurement, and in 967 (90%) two (or more) condom pressure measurements were done in one session. Some adverse events such as terminal selflimiting hematuria were unexpectedly encountered. Using a newly developed normalised standard deviation for comparing the repeatability of different clinical methods, we found a normalised repeatability of the non-invasive method of 0.15, that of the various parameters derived from conventional pressure-flow studies varied from 0.11 to 0.22. The reproducibility

of the condom catheter method is therefore comparable to, or slightly better than that of conventional urodynamics.

A comparative analysis of the performance of the condom catheter method applied in two large-scale scientific studies by different investigators on different study populations, showed success rates of 95% for single pressure measurements in both studies. For double measurements, the success rates were 87% in a first study round and 92% in a second study round in the randomised controlled trial and 90% in the longitudinal survey.

The normalized standard deviations of the differences between the double measurements in the two studies were 0.13 and 0.15, revealing a stable and good reproducibility. Mild adverse events with comparable low frequency were found in both studies.

Correlations between the non-invasive urodynamic data and other (non-invasive) urological paramaters such as prostate volumes determined by ultrasound and I-PSS were described too. The non-invasive urodynamic data did show a small but statistically significant correlation with the I-PSS. This suggested that an elevated resistance is a necessary, but not a sufficient condition for LUTS. No significant relation between the prostate volumes and non-invasive urodynamic data was found. Additionally, age and voided volume stratified normal values for frequency volume chart parameters in the healthy males in our population were reported. All diary parameters, the free flow rate Q_{max}, and the prostate volume were significantly different in 147 volunteers with an elevated I-PSS.

This thesis presents an analysis of large-scale application of the condom catheter method and results of the first evaluation round of a longitudinal study on compensation and decompensation of the urinary bladder. At the moment of writing this, completion of the study is expected in january 2010 and results will be published soon afterwards. At the same time, the value and possible benefit of the used non-invasive device in every day urological practice and clinical examination has been made plausible. Performing a health technology assessment is necessary to introduce the method in everyday clinical practice.

Summary

In more than 68% of men over the age of fifty there is histological evidence of Benign Prostatic Enlargement (BPE). As a consequence they often develop Lower Urinary Tract Symptoms (LUTS). Two main causes for these symptoms are a weakly contracting detrusor or an enlarged prostate obstructing the bladder outlet (BOO). Conventionally, invasive pressure flow studies are recommended for the diagnosis of BOO. Non-invasive pressure flow methods may be more patient friendly and can be large-scale applied in a population of volunteers to study the development of LUTS/ BOO. I applied the condom catheter method for non-invasive urodynamics in a group of approximately 1200 male volunteers in a(n ongoing) longitudinal study on changes in bladder contractility in response to BPE. These males were studied in three evaluation rounds in five years. The aim of our study was to define the compensation and decompensation phases of the bladder muscle and gain data on the reversibility of this process. As BPE develops over a period of long time, it is necessary to regularly evaluate a group of (otherwise) healthy males during forty years: ages 40-80. In a more practical approach, we recruited eight cohorts with initial ages of 38-42, 43-47, 48-52, 53-57, 58-62, 63-67, 68-72 and 73-77 and followed these for five years, so that the age of each cohort of volunteers at the end of the study matched that of the next cohort at the start of the study. Each cohort was studied three times: at recruitment, after 2.5 years, and after 5 years.

In **chapter two** the reproducibility of the condom catheter method in the first 659 volunteers in the first evaluation round was analysed using the Bland and Altman method [20]. The difference between two condom pressure measurements in one session was plotted as a function of the mean of those two values. As the difference was independent of the mean, the standard deviation could be used as a measure for the reproducibility of the non-invasive condom method. This standard deviation was 18 cm H_2O. For a lack of a standard to decide whether this reproducibility is good or bad, a method was developed for comparing the reproducibility of different methods for clinical measurement. In **chapter three** we normalised the standard deviation of the differences by dividing it by the difference of the 97.5 and the 2.5 percentile of the mean of those two measurements, resulting in a relative standard deviation of 0.15. This reproducibility was comparable to, or even slightly better than, that of pressure flow parameters derived from a comparable population of patients studied with conventional invasive urodynamic methods.

In **chapter four** we analysed epidemiological aspects of 843 volunteers recruited in the first study round. The aim was to establish if the population might be biased, or if it may be considered a representation of the general population. Several factors influenced the response rate of subjects recruited. Age and social economic status did, the response being highest around the age of 60 years and lower at lower and higher ages, and increasing with social

economic status. Recruitment of volunteers in two steps, i.e. asking them first to visit the GP's office, and inviting them there to visit the outpatient clinic, rather than directly inviting them (in writing) to the clinic seemed to lead to a higher response, although this effect could not be statistically discriminated from the difference in response rates between GPs. This latter effect might be ascribed to the relation between patient and his GP, although also a difference of mean social economic status between patient populations of different GPs may have influenced that. In spite of these dependencies, when the recruited population was corrected for intentional differences in age distribution and methodological differences such as in flow rates, it was not urological different from the general population.

In this longitudinal evaluation of bladder contractility the prostate volumes were measured non-invasively too, by transabdominal ultrasonography. In **chapter five** the accuracy of those measurements was verified by comparison of transabdominal to transrectal stepwise planimetric ultrasonography as the gold standard. We also compared two different transabdominal (a hospital Aloka® SSD-1700 and a portable Aloka® SSD-900) devices, and studied the influence of different operators. No statistically significant differences between the transabdominal- transrectal ultrasonography, two different transabdominal devices nor between different observers were found.

In **chapter six** the correlations of non-invasive urodynamics with the International Prostate Symptom Score (I-PSS) and prostate volume were studied. To this end we used a method to non-invasively estimate the degree of urethral obstruction using a diagram of the maximum condom pressure and the free flow rate. The borderline between obstruction and non-obstruction was defined by: $p_{cond.max}$ minus 5.8 times Q_{max} minus 36.4=0. A positive outcome of the formula was classified as a high urethral resistance (URR) which was found in 20 percent of the subjects. In our population of healthy volunteers, the non-invasive urodynamic data did show a small but statistically significant correlation with the I-PSS. This confirms that an increased URR is a factor contributing to LUTS. The (weak) correlation between I-PSS and URR suggests that an elevated resistance is a necessary, but not a sufficient condition for LUTS. So far, this has only been demonstrated by the non-invasive measurements in this study population. No correlation was found between the URR and prostate volumes.

In **chapter seven** I did a comparative analysis of the reproducibility and applicability of the condom catheter method for noninvasive urodynamics in two Dutch centers. The double pressure measurements with the condom method done in the longitudinal survey (LS) in the outpatient clinic of Erasmus MC in Rotterdam was compared to measurements in a randomized controlled trial (RCT) to test the effect of additional water intake on bladder function at the University of Maastricht. In both studies two consecutive measurements were attempted in

each subject. Reproducibility was tested according to Bland and Altman [20] and compared by calculating the normalized standard deviation of the differences by dividing by the difference. In both studies the success rate single measurement was succesfull in 95% of the attempts. Success rates for double measurements varied from 87 to 90%. The normalized standard deviation of the differences between the double measurements was 0.15 for the longitudinal non- invasive study and randomized controlled trial at baseline, and 0.13 for the randomized controlled trial at 6 months. It was concluded that both studies showed good reproducibility of the non-invasive condom method comparable to invasive urodynamics.

In **chapter eight** age and voided volume stratified normal values for frequency volume charts parameters in the healthy males of our population are reported. A total of 935 volunteers kept a 3 day voiding diary and also recorded the time of going to bed and getting up in adition to the non-invasive measurements. According to the frequency volume charts the volunteers voided a median volume of 220 ml, 6 times a day, and 0.5 times a night and produced 83 ml of urine per hour during the daytime and 48 ml/ hr during the night. The values found in a subgroup of 788 volunteers with I-PSS £10 may be considered normal values for males. All diary parameters, the free flow rate Q_{max}, and the prostate volume were significantly different in the 147 volunteers with a higher I-PSS. Almost all of the normal values depended on the age and the voided volume, and separate normal values were derived from groups stratified according to these variables.

Overall, it is concluded that the non-invasive urodynamic condom catheter method is very suitable for large scale application and that it has a reproducibility comparable to, or even slightly better than invasive urodynamics. Associations between the non-invasive urodynamic data and other (non-invasive) urological parameters were also presented, and a normalised standard deviation was used to compare the repeatability of different clinical methods. Additionally, age and voided volume stratified normal values for frequency volume chart parameters in the healthy males of our population are reported.

Samenvatting

Benigne Prostaat Vergroting oftewel BPE is een vaak voorkomend verouderingsproces bij ouder wordende mannen. In meer dan 68% van de mannen boven de 50 jaar zijn er histologische (weefsel) aanwijzingen voor BPE. Als gevolg daarvan kunnen zich plasklachten (LUTS) ontwikkelen zoals een zwakke straal, vaker beetjes plassen, gevoel van niet uitgeplast zijn tot het achterblijven van urine in de blaas. Hoofdoorzaken van deze klachten kunnen zijn: een zwak contraherende urineblaas of een BPE die de blaashals/ uitgang obstrueert (BOO).

Tot vrij recent bestonden er alleen nog conventionele, veelal patiëntonvriendelijke, invasieve drukflow studies voor het diagnosticeren van BOO. De nieuwe niet-invasieve condoom katheter methode is patiëntvriendelijker en maakt ook toepassing op grote schaal in grote groepen vrijwilligers mogelijk. De condoom methode is toegepast in ruim 1200 mannelijk vrijwilligers in een longitudinaal onderzoek naar veranderingen in de blaascontractiliteit als gevolg van BPE.

Het uiteindelijke doel van dit longitudinaal onderzoek is de bepaling van een 'afkappunt' in het proces van compensatie en decompensatie van de blaascontractiliteit als gevolg van de obstruerende BPE. Inzicht in de (nog) reversibele compensatiefase maakt het mogelijk therapeutische beslissingen daarop te baseren. Om dit langdurige proces van de ontwikkeling van BPE te kunnen koppelen aan de veranderingen in de blaaskracht, werden acht cohorten van 'nagenoeg gezonde' mannelijke vrijwiligers gevolgd. Deze cohorten met leeftijden 38-42, 43-47, 48-52, 53-57, 58-62, 63-67, 68-72 en 73-77 werden driemaal in vijf jaar onderzocht: op tijdstip nul, na 2.5 jaar en na 5 jaar.

In **hoofdstuk twee** wordt de toepasbaarheid en reproduceerbaarheid van de condoom katheter methode besproken. Tusssen november 2001 en eind december 2003 ondergingen 1073 vrijwilligers de eerste evaluatie ronde van het onderzoek met de condoom methode op de poli urologie in het Erasmus MC. Deze mannen voldeden aan de studiecriteria en hadden een urinestroom (urinedebiet) groter dan 5.4 ml/s. In 1020 (95%) vrijwilligers is tenminste één niet-invasieve condoomdrukmeting helemaal goed gelukt. In 967 (95%) vrijwilligers werden (teminste) twee condoomdrukmetingen in één onderzoekssessie helemaal goed uitgevoerd. Enkele kortdurende bijwerkingen werden, geheel onverwachts, gezien. De conclusie is dat de niet-invasieve condoom methode een hoge succesrate heeft en zeer goed toepasbaar is in grootschalig onderzoek.

De reproduceerbaarheid van de condoom methode is bepaald volgens de methode van Bland and Altman [20]. Het verschil tussen de drukwaarden van twee condoomdrukmetingen gedurende dezelfde onderzoekssessie werd uitgezet als functie van het gemiddelde van deze twee meetwaarden. Dit verschil was onafhankelijk van het gemiddelde waardoor de standard deviatie van 18 cm H_2O een maat zou kunnen zijn voor de reproduceerbaarheid. Deze

standard deviatie kan echter niet worden vergeleken met de reproduceerbaarheid van andere klinische (niet)-invasieve methoden. Daarom is in **hoofdstuk drie** een methode ontwikkeld voor de vergelijking van de reproduceerbaarheid van verschillende klinische testmethoden. De standard deviatie van de verschillen werd genormaliseerd door te delen door het verschil van de 97.5 en 2.5 percentielen van het gemiddelde van alle twee meetwaarden. Wij vonden voor de condoommethode een genormaliseerde standard deviatie van 0.15, dat was een vergelijkbare of zelfs iets betere reproduceerbaarheid dan die van invasieve meetmethoden.

In totaal werden 11.914 mannen in de leeftijd van 38-77 door de huisarts uitgenodigd voor deelname aan het onderzoek waarvan uiteindelijk 1233 zich aanmeldden. In **hoofdstuk vier** worden epidemiologische aspecten van 843 vrijwilligers geanalyseerd door deze te vergelijken met een representatieve groep. Wij zagen dat verschillende aspecten en factoren de opkomst percentages beïnvloedden. De respons was het hoogst rond de leeftijd van 60 jaar, daaronder en daarboven lager. De respons nam ook toe met de sociaal economische status. Een twee staps wervingsmethode, waarbij de vrijwilligers eerst de huisarts bezochten en vervolgens voor de poli werden uitgenodigd leidde ook tot een hoger respons. Dit was statistisch niet significant gezien het verschil in opkomst tussen de huisartsen. Na correcties voor de leeftijdsspreidingen en methodologische verschillen, was deze populatie, urologisch gezien, niet verschillend van de algemene.

In dit longitudinaal onderzoek werden prostaat volumes ook niet-invasief gemeten, middels transabdominale echogafie. In **hoofdstuk vijf** werd de nauwkeurigheid van deze metingen getest door vergelijking met de transrectale stapsgewijze planimetrische echografie, als de gouden standaard. Tevens werden twee verschillende ultrasound apparaten (een ziekenhuis Aloka® SSD-1700 en een draagbare Aloka® SSD-900) vergeleken en daarnaast werd de invloed van verschillende gebruikers bestudeerd. Er werden geen statistisch signifcante verschillen gevonden tussen de transabdominaal en transrectale benaderingen, noch tussen de twee verschillende toestellen, noch tussen verschillende gebruikers.

In **hoofdstuk zes** worden correlaties tussen niet invasieve urodynamische data, I-PSS en prostaat volumes beschreven. Middels een (voorlopige) niet-invasieve methode werd de urethrale weerstand (URR) berekend uit de maximale condoomdruk en de maximale vrije urinestroom. In onze populatie van 'nagenoeg gezonde' vrijwilligers had 20% een hoge urethrale weerstand en vertoonde de niet-invasieve urodynamische data een kleine statistisch significante correlatie met de I-PSS. Deze zwakke correlatie tussen URR en I-PSS bevestigt dat een verhoogde urethrale weerstand wel een noodzakelijke maar geen voldoende en zeker niet de enige oorzaak is van plasklachen (LUTS). Geen correlatie werd gevonden tussen URR en prostaat volume.

In **hoofdstuk zeven** wordt een vergelijkende analyse van de reproduceerbaarheid en toepasbaarheid van de condoom methode in twee verschillende Nederlandse studies beschreven. Uitkomsten van dubbele condoommetingen van het longitudinaal onderzoek (LS) in het Erasmus MC werden vergeleken met die van een gerandomiseerd gecontroleerd onderzoek (RCT) in de Universiteit van Maastricht. In de LS werden 1020 vrijwilligers van 38-77 jaar en in de RCT werden 185 vrijwiligers van 55-77 jaar tweemaal binnen zes maanden onderzocht. In beide onderzoeken werd gepoogd om in één sessie twee condoommetingen te doen. De reproduceerbaarheid werd berekend uit de genormaliseerde standard deviatie van de verschillen door deze te delen door het verschil van de 97.5 en 2.5 percentielen van het gemiddelde van de twee meetwaarden. De genormaliseerde standaard deviatie was 0.15 in de LS en 0.13 in de RCT. Het slagingspercentage van één condoomdrukmeting was 95% in beide onderzoeken, en van twee opeenvolgende drukmetingen was dat tussen 87 en 90%.

Inemers werd verzocht een mictiedagboek van (minimaal) drie dagen, inclusief de tijdstippen van in en uit bed gaan, bij te houden. In totaal zijn 935 vrijwilligers ingegaan op dat verzoek. In **hoofdstuk acht** worden naar leeftijd en plasvolume gestratificeerde normale waarden uit deze dagboeken gepresenteerd. Volgens de dagboeken plasten deze mannen een gemiddelde volume van 220 ml, zes keren per dag, 0.5 keer ‘s nachts en produceerden zij 83 ml urine per uur overdag en 48 ml per uur gedurende de nacht. Deze mannen hadden een gemiddelde maximale vrije urinestroom of urinedebiet van 16 ml/s en een prostaat volume van 31 ml. De waarden van een subgroep van 788 vrijwilligers met een I-PSS kleiner de 10 werden beschouwd als normale plaswaarden. Alle parameters uit de mictiedagboeken, de vrije urinestroom en de prostaat volumes waren statistisch significant verschillend in 147 vrijwilligers met een I-PSS groter dan 10.

Dit proefschrift beschrijft de toepassing van de condom catheter methode voor niet invasieve meting van de urineblaasdruk in een grootschalig onderzoek naar veranderingen in de blaascontractiliteit ten gevolge van goedaardige prostaatvergroting bij 1020 vrijwilligers. Het is gebaseerd op data uit de eerste van drie onderzoek ronden. Deze gegevens geven nog geen antwoord op de algemene onderzoeksvraag. Daarvoor zijn longitudinale data van alle drie ronden noodzakelijk. Op basis van de tot nu toe verkregen resultaten kunnen wel de volgende verbanden worden bescrheven en conclusies getrokken. De toegepaste niet invasieve onderzoekmethode heeft een goede toepasbaarheid en een reproduceerbaarheid ruim vergelijkbaar met die van de invasieve drukmeetmethoden. Voor de vergelijking van reproduceerbaarheden van verschillende klinische methoden is een genormaliseerde standard deviatie ontwikkeld. Associaties tussen niet-invasieve urodynamische en andere data

uit het onderzoek en normale waarden voor mictiedagboeken van drie dagen zijn ook in dit proefschrift te vinden.

Dit proefschrift presenteert de bevindingen van de grootschalige toepassing van de condoom catheter methode in, en de resultaten van, de eerste ronde van een longitudinaal onderzoek naar (de)compensatie van de urineblaascontractiliteit. Afronding van alle metingen van het onderzoek wordt in januari 2010 verwacht waarna de resultaten zo spoedig mogelijk zullen worden gepubliceerd.

Tegelijkertijd zijn waarde en nut bewezen van toepassing van de niet invasieve methode voor blaasdrukmeting in de dagelijkse praktijk en het klinisch onderzoek in de urologie. Een “doelmatigheidsonderzoek” lijkt voor de hand te liggen om de methode te implementeren.

Nawoord

Allereerst wil ik u, de lezer, heel hartelijk dankzeggen voor het van kaft tot kaft lezen van mijn proefschrift. Want zoals 'zonder patiënt geen arts' is het ook 'zonder lezer geen proefschrift'. Het heeft, welgeteld vanaf eind 2003, 7 jaar geduurd voordat het erop zit met dit proefschrift. Voor de totstandkoming daarvan ben ik letterlijk en figuurlijk heel veel mensen dank verschuldigd.
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Zonder vrijwilligers geen onderzoek. Ruim 1200 mannelijke vrijwilligers die belangeloos aan het onderzoek deelnamen. Daarvoor de reis naar de poli maakten, minimaal 1.5 liter water dronken, het onderzoek van drie uur ondergingen en minimaal drie maal in mijn nabijheid plasten ! Mannen, jullie waren geweldig, mijn erkentelijkheid is ontzettend.
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Epilogue/ Afterword

First of all, I would like to thank you, the reader, for having read my thesis through to the end. Words only have value if they are read.

Starting at the end of 2003, it has taken me all of seven years to complete this thesis. For their help in completing it I am indebted to many people, some for their practical assistance and others for their moral support.

I would like to begin with my supervisor: By explaining how you made possible this venture into research. It all began with your appointing me as investigator-physician with no prior research experience for a large-scale urological research project; and continued with your patient and tireless guidance and input as principal investigator, teacher, sounding-board ... everything, really. And as I said from the beginning, although the first draft manuscripts came back crisscrossed in red, or even green or blue, I always knew we were on the right track. To say nothing of the opportunities I had to present the material at the podia of three ICS European congresses! Ron, my heartfelt thanks.

Consecutively and at the same time, I had to get acquainted with the Dutch Health Care system. Ruud, you made me gain even more respect for the domaine of Urology and it's specialists than I had, to begin with. Under your supervision I qualified as a medical doctor, a qualification for life. Thank you so much!

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Last, but certainly not least, I wish to thank my two younger sisters and my parents: you have given me so much moral support and love.

Once again, thank you all.
John Huang Foen Chung

Curriculum vitae

John Huang Foen Chung werd geboren op vrijdag 13 maart 1970 te Paramaribo, Suriname. Na zijn studie geneeskunde in 1999 te hebben afgerond aan de Anton de Kom Universiteit van Suriname verhuisde hij in 2001 naar Nederland. Op 01 november van hetzelfde jaar begon hij als promovendus bij de afdeling Urologie, sector Furore van het Erasmus MC te Rotterdam. Tot en met 25 Oktober 2003 stond hij als arts-onderzoeker onder supervisie van Prof. J.L.H.R. Bosch. Daarop behaalde hij zijn vakbekwaamheid als (zelfstandige) arts in Nederland. In de sector Furore heeft hij onder leiding van Prof. Dr. Ir. Ron van Mastrigt zijn onderzoek gedaan dat in dit proefschrift staat beschreven.

John Huang Foen Chung was born on 13 March 1970 in Paramaribo, Suriname. After having completed his medical degree in 1999 at the Anton de Kom University in Suriname, he moved to The Netherlands in 2001, and in November of that year he embarked on a doctoral programme in the Furore section of the Department of Urology at the Erasmus Medical Centre in Rotterdam. Until October 2003 he was investigator-physician under the supervision of Professor J.L.H.R Bosch. He then qualified to practice medicine independently in The Netherlands. Simultaneously he carried out the investigation described in this thesis under the supervision of Professor Ron van Mastrigt.