NON-INVASIVE ASSESSMENT OF URETHRAL RESISTANCE

The work presented in this thesis was done at the department of Urology-Urodynamics, Faculty of Medicine and Health Sciences of the Erasmus University Rotterdam.

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Non-invasive assessment of urethral resistance

Niet-invasieve bepaling van urethrale weerstand

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Wat heb je aan je miljoenen Piet
als je moet piesen en je kan het niet?
-Toon Hermans-

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Van Mastrigt R and Pel JJM (1999) Towards a non-invasive diagnosis of infravesical obstruction. Br J Urol 84: 195-203.

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Pel JJM and van Mastrigt R (2001) A flow rate cut off value as a criterion for accurate measurement of non-invasive bladder pressure. Urology. Submitted.

CONTENTS

1

INTRODUCTION

Adapted from:
Van Mastrigt and Pel JJM (1999) Towards a non-invasive diagnosis of infravesical obstruction. British Journal of Urology International 84: 195-203.

Urine, produced in the kidneys, is temporarily stored in the urinary bladder. Under appropriate circumstances, the bladder muscle (detrusor) contracts and expels the urine through the bladder neck and urethra. The course of voiding mainly depends on the contractility of the detrusor and the urethral resistance. Upon stimulation initiated by the central nerve system, the detrusor shortens which increases the pressure in the bladder. At the same time, the muscle fibres in the bladder neck and in the urethral wall relax which reduces the urethral resistance. When the pressure in the bladder is higher than the pressure in the urethra, urine pushes the urethra open and voiding starts. When the bladder is empty, the detrusor contraction stops, the urethra closes and the kidneys refill the bladder.

In men, the prostate enlarges with increasing age, mostly as a result of benign prostatic hyperplasia (BPH). As the prostate surrounds the urethra, and may thus obstruct it, a poor urinary flow (or flow rate) and frequent voiding are typical symptoms relating to BPH. In general, these symptoms are called Lower Urinary Tract Symptoms (LUTS). At present, 25% of the Dutch men aged 40 and above are known to have these symptoms. In men older than 65 years, this percentage is increased to 33%. In the Netherlands only, the population of interest approximates 1 million. This number will increase as the population is ageing. In some cases, a poor flow rate is caused by a weakly contracting bladder and not by an enlarged prostate. In these patients, the efficacy of a surgical procedure aimed at the relief of an obstruction is doubtful. To test if a low flow rate results from an increased urethral resistance, the pressure in the bladder during voiding needs to be measured. A high bladder pressure combined with a low flow rate indicates that a patient has an obstructed urethra. A low bladder pressure combined with a low flow rate indicates that a patient has a weakly contracting detrusor.

Pressure-flow study

To measure the bladder pressure, a patient needs to undergo a urodynamic test, called a pressure-flow study. During this study, catheters are inserted in the bladder and rectum. When the patient's bladder has been filled, she or he is asked to void into a flow meter while the pressure is measured. The combination of both signals results in a pressure-flow plot. A provisional standard method, known as 'the provisional International Continence Society (ICS) method for definition of obstruction' is based on one point of the pressure-flow plot only, that at which the flow rate is maximal, Q_{max} [Griffiths et al., 1997]. At this point the urethra is maximally open. The pressure generated by the detrusor, p_{det}, is calculated from the difference between the pressure measured in the bladder (intravesical pressure) and the pressure outside the bladder (abdominal pressure). Figure 1.1 represents the ICS-nomogram, which grades the urethral resistance of a patient as non-obstructed, equivocal or obstructed.

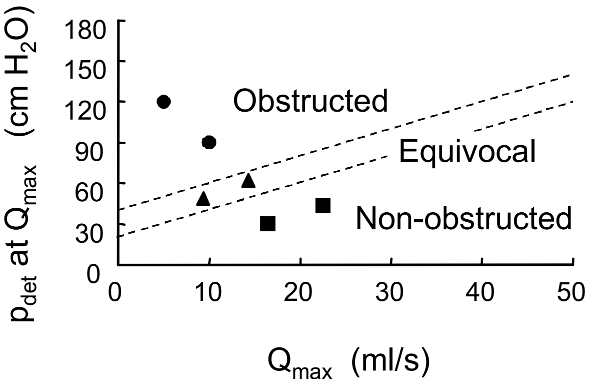


Figure 1.1 *The provisional ICS method for definition of obstruction.*

A pressure flow study is a costly, time-consuming and unpleasant procedure for the patient. As a result, many patients are not urodynamically tested, and surgical treatment is prescribed on the basis of voiding symptoms and a free flow rate measurement only. Therefore, there is a need for cheap, simple and patient friendly methods to diagnose obstruction in patients with LUTS.

A non-invasive approach

Bladder outlet obstruction (BOO) is by definition assessed from a relation between pressure and flow rate; more precisely, by the relation between the pressure drop over the obstruction and the flow rate through it. As the pressure downstream of an obstruction is atmospheric, the pressure decrease over the obstruction equals the pressure upstream of the obstruction relative to atmospheric pressure, i.e. the detrusor pressure. Two methods have been published to measure the isovolumetric detrusor pressure, i.e. the pressure generated by the bladder contracting against a closed bladder outlet, non-invasively [van Mastrigt, 1995; McRae et al.,1995]. The first method proceeds by attaching a pressure transducer to an incontinence condom applied to the penis. Two procedures can be followed. Patients can be asked to void into the closed condom, or they can void through a tube attached to the condom, which is closed at some instant during voiding to measure the pressure; the latter method gives more reproducible results [van Mastrigt, 1995]. The second method is blocking the urinary flow using a small inflatable cuff around the penis. Analogously to blood pressure measurements, it may be possible to estimate the pressure in the penile urethra by slowly inflating or deflating the cuff until flow stops or starts.

It is tempting to try to diagnose BOO from a combination of such an isovolumetric detrusor pressure and a free flow rate measurement. As stated above, an abnormally low flow rate may be the result of an obstruction, or of weakness of the bladder muscle. The last cause can be excluded on the basis of an isovolumetric detrusor pressure measurement. **The aim of this thesis is to develop and test devices to measure the isovolumetric bladder pressure non-invasively and to derive an objective measure for the urethral resistance in males.** The results described in this thesis are based on measurements done in healthy volunteers and in patients with LUTS.

2

NON-INVASIVE MEASUREMENT OF BLADDER PRESSURE USING AN EXTERNAL CATHETER

Adapted from:
Pel JJM and van Mastrigt R (1999) Neurourology & Urodynamics 18: 455-469.

Abstract

Previous studies showed that on the basis of a combination of maximum flow rate and isovolumetric bladder pressure, objectively diagnosing of infravesical obstruction is possible. In this study, we validated a newly developed external catheter to non-invasively measure this pressure, which avoids the risk of damaging or infecting the urethral and bladder wall as in invasive urodynamics. To evaluate the external catheter, we simultaneously recorded the internal bladder pressure signal (measured invasively) and the external pressure signal (measured non-invasively) in forty non-obstructed and obstructed patients. Additionally, we tested if the external pressure depended on bladder volume in five healthy volunteers. The simultaneously measured internal bladder pressure and external pressure showed good agreement in the non-obstructed patients. This agreement was less good in the obstructed group. Nevertheless, the external pressure in these patients was significantly higher than in the non-obstructed patients. The maximum external pressure depended significantly on the bladder volume in all volunteers. We concluded that isovolumetric bladder pressure can be measured non-invasively with the external catheter. In non-obstructed patients this pressure accurately represents the internal bladder pressure. We think that it is possible to discriminate between obstructed patients and patients with a weak detrusor by combining the non-invasively measured isovolumetric bladder pressure with a separately measured maximum flow rate.

Introduction

Low bladder contractility or an obstructed urethra may cause a reduced flow rate. At present, patients suffering from impaired voiding are diagnosed on the basis of the detrusor pressure and associated maximum flow rate measured during a pressure-flow study. To measure the detrusor pressure, the patient needs to be catheterised, which is mostly a painful and time-consuming procedure. However, previous studies showed, that also on the basis of a combination of isovolumetric bladder pressure and maximum flow rate an objective diagnosis of infravesical obstruction is possible [van Mastrigt and Kranse, 1995; Comiter et al., 1996]. The last few years techniques have been proposed to non-invasively measure the isovolumetric bladder pressure [Schäfer et al., 1994; McRae et al., 1995; van Mastrigt, 1995]. Using these techniques the risk of damaging or infecting the urethral and bladder wall is avoided, and a non-invasive urodynamic diagnosis of infravesical obstruction would become possible. One of these methods involves the measurement of bladder pressure using an external catheter connected to a condom, which enforces an isovolumetric condition during voiding. In theory, the external pressure measured in this condition equals the internal bladder pressure, if both pressure transducers are positioned at the same height.

In the present study, we compared this new non-invasive measurement technique with invasive pressure measurements to verify its clinical applicability. Simultaneous measurements of the internal bladder pressure and the external pressure were performed in non-obstructed and obstructed patients. Additionally some fundamental aspects of the external catheter were studied. We measured in five healthy volunteers the relation between the external pressure at different bladder volumes, to investigate if bladder volume should be standardised during these measurements. To secure the external catheter to the penis and to increase the stiffness of the distal urethra and the condom, Parafilm® was taped around a part of the penis and the external catheter. The influence of this elastic tape was analysed using a mechanical model, see appendix.

Materials and methods

We developed an external catheter consisting of the following components: a self-adhesive incontinence condom (POP-ON, Laprolan®), a T-connector (polypropene), two tubes (silicon and PVC), a disposable pressure transducer and a valve, which can be remotely operated, see figure 2.1. The condom was attached to the penis and both were taped with Parafilm® to increase the stiffness. The condom and the silicon tube were connected to opposite sides of the T-connector, so that urine could flow in straight line from the penis through the external catheter into a flow meter. Perpendicular to this direction, the PVC tube and the pressure transducer were connected to the T-connector. The valve was fitted over the silicon tube so that it compressed this tube when it was closed. In this way, all parts in contact with urine could be renewed for each patient.

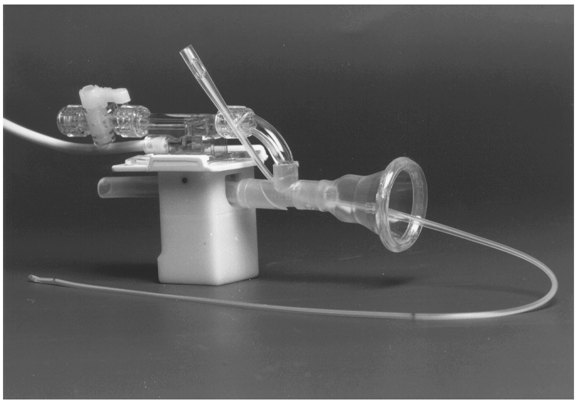


Figure 2.1 *The internal (feeding tube) and external catheter used to simultaneously measure the bladder pressure invasively and non-invasively in a male patient.*

We studied forty patients who first underwent invasive urodynamics. Most of these patients were incontinent or had a reduced flow rate. They were stratified in two groups based on the provisional ICS method for definition of obstruction [Griffiths et al., 1997]: a non-obstructed and an obstructed group. The patients with ICS-classification "equivocal" were added to the group of obstructed patients. URA, a resistance factor to rank different voidings according to the degree of urethral resistance was also calculated [Griffiths et al., 1989]. Additionally, a non-invasive bladder pressure measurement was done. During this test the internal bladder pressure and the external pressure were simultaneously measured. The internal catheter (left in the bladder after the preceding invasive measurements) was guided through a small hole in the T-connector, see figure 2.1. After filling the bladder to capacity via this catheter, it was connected to a pressure transducer to measure the internal bladder pressure. This transducer was installed at the same height as the pressure transducer measuring the external pressure at the end of the external catheter i.e. not at the level of the symphysis pubis. In our study, the pressure transducers measuring the internal bladder pressure and the external pressure were about one metre apart. We visually levelled the transducers. The internal bladder pressure, p_{int}, the external pressure, p_{ext} and the flow rate Q were measured and displayed at a computer screen. Flow rate was measured using a Dantec® rotating disk flow meter. A first-order Butterworth filter with a cut-off frequency of 0.2 Hz. was used to filter all measured signals (Matlab®). Parameters such as maximum signal values were calculated automatically from the filtered signals using a Matlab® program. Borderlines of agreement between the invasive measurement technique and the non-invasive measurement technique were defined using a difference plot [Bland and Altman, 1986]. The mean pressure difference p_{int}-$p_{ext.max}$ in the group of non-obstructed patients was used to calculate these borderlines. Differences between both groups were tested for significance with a Mann-Whitney U-test (SPSS®). The correlation between the pressure difference p_{int}-$p_{ext.max}$ and URA in both groups, was tested with a Spearman correlation test (SPSS®).

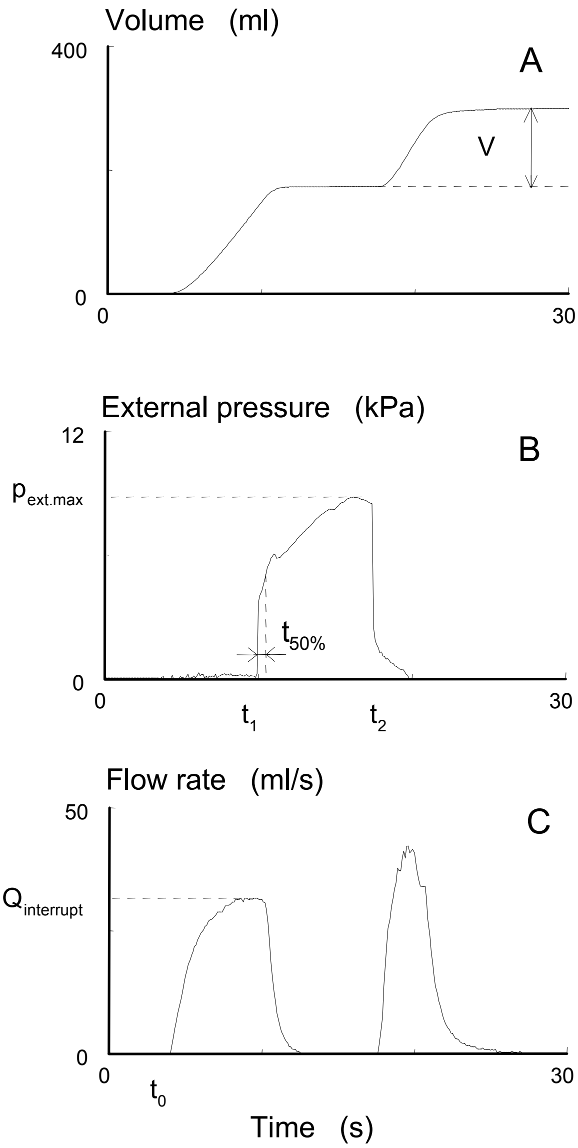


Figure 2.2 *The voided volume (A), the external pressure (B), measured with the external catheter and the flow rate (C) as a function of time during one complete measurement in a healthy volunteer.*

In patients, the external pressure was measured at a certain volume of urine in the bladder. This volume differed in each voiding. We tested the dependence of the maximum external pressure on the bladder volume in five healthy volunteers. These volunteers were asked to void one time each day at different degrees of urgency. In three of these voidings, the external bladder pressure was recorded twice in one voiding. This allowed us to measure the external pressure at small bladder volumes. The bladder volumes and associated pressure readings were fitted with a third order polynomial. The accuracy of the fit was characterised by R^2. This is the relative mean quadratic difference between the measured values and the values predicted by the fitted polynomial. When R^2 equals one, the fitted curve matches all measured points. To investigate the dependence of the external pressure on the bladder volume, we plotted the external pressures and bladder volumes. In each volunteer, we calculated the highest external pressure, called the optimum external pressure and the associate optimum bladder volume. To demonstrate that a the volume dependence exists, the difference between the optimum pressure values and the pressure values at 50% and 200% of the optimum volume were statistically tested for significance using a Wilcoxon signed-rank test (SPSS®). The pressure in the urethra and the condom increased, when the flow rate was interrupted. As a result, the urethra as well as the condom expanded. To limit this expansion and to secure the fit between penis and condom, Parafilm® was taped around a part of the condom and the penis. To test the influence of this elastic tape, one volunteer voided six times with and six times without the elastic tape. The results were analysed using a mechanical model, consisting of a mass, a spring and a damper (see appendix) and statistically tested using a T-test (SPSS®).

Results

Figure 2.2 shows a typical registration of the external pressure measurement in a healthy volunteer. He started voiding in a flow meter at time t_0. At time t_1 the flow was interrupted, $Q_{interrupt}$ by closing the valve. The external pressure in the condom increased until a maximum external pressure, $p_{ext.max}$ was measured. This pressure may be called isovolumetric, because the amount of urine in the bladder, the urethra and the external catheter was constant. The time necessary to reach half the value of the internal bladder pressure in the external catheter is called the 50% rise time, $t_{50\%}$ of the measurement. The valve was opened at time t_2, so that the volunteer could continue voiding without further obstruction. During the measurement of the external pressure, the amount of urine in the bladder and the urethra was ΔV. This volume was read from the recorded volume signal, assuming the bladder was completely empty after voiding. No volunteers or patients experienced pain during the external pressure measurement. A simultaneous recording of the internal bladder pressure and the external pressure was made in forty patients. In eight patients the external catheter was leaking. These measurements only occurred in the beginning of our study and were excluded from further analysis. Four patients closed the sphincter during the pressure measurement and in two patients no internal bladder pressure was recorded, leaving twenty-six successfully measured patients that could be analysed. Based on the preceding invasive investigation, eleven patients were classified as obstructed. In ten patients, the valve was closed a second time during the same voiding, because these patients interrupted voiding at the first valve closure.

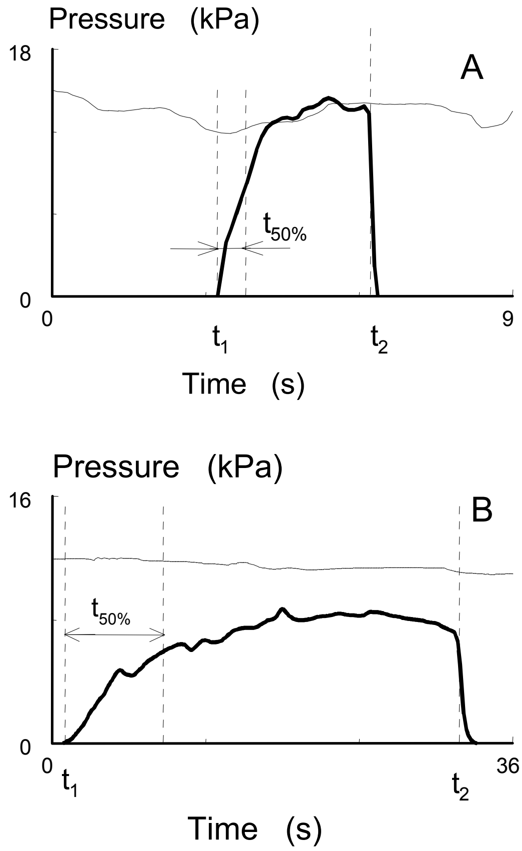


Figure 2.3 *Simultaneous registrations of the internal bladder pressure (thin lines) and the external pressure (thick lines) measured in a non-obstructed patient (A) and an obstructed patient (B). The valve interrupting the flow rate was closed at time t_1 and opened again at time t_2. $t_{50\%}$ is the time necessary for the external pressure to reach 50% of the internal bladder pressure.*

This second pressure measurement was used for further analysis. In six measurements the external pressure values were higher than the internal bladder pressures, see figure 2.3A. We assume that in these cases there was a small difference in the level of the pressure transducers and we did not correct for this difference. Figure 2.3A shows an example of perfect agreement between the internal bladder pressure and the maximum external pressure, measured in a non-obstructed patient. The internal bladder pressure and the external pressure did not agree well in figure 2.3B, measured in an obstructed patient. The pressure difference was about 2.6 kPa. Table 2.1 summarises the measured parameters. The agreement between the internal bladder pressure and the external pressure was better in the group of non-obstructed patients (p_{int}-$p_{ext.max}$ = 0.4 ± 0.9 kPa, mean ± SD) than in the group of obstructed patients (p_{int}-$p_{ext.max}$ = 2.3 ± 2.7 kPa). The internal bladder pressure and the external pressure differed significantly (Mann-Whitney U-test: $p < 0.05$) between both groups. The pressure difference p_{int}-$p_{ext.max}$ correlates significantly with URA (Spearman correlation test: $p < 0.01$). The 50% rise time of the external pressure was not significantly different in the non-obstructed and obstructed patients. Figure 2.4 shows a difference plot. The dotted lines represent the mean difference between the internal bladder pressure and the maximum external pressure ± 2 standard deviations, calculated for the group of non-obstructed patients.

Table 2.1 *Results of the simultaneous registration of the internal bladder pressure and the external pressure in twenty-six patients.*

Patient	p_{int} ($p_{ext.max}$) (kPa)	$p_{ext.max}$ (kPa)	$t_{50\%}$ (s)	URA (kPa)	ICS (-)
1	5.0	5.8	2.6	0.4	0
2	8.1	8.9	0.6	0.4	0
3	7.5	7.4	1.2	0.4	0
4	8.2	8.4	3.3	0.9	0
5	6.3	5.0	10.6	1.0	0
6	11.2	9.7	4.4	1.0	0
7	5.9	6.5	0.6	1.0	0
8	11.0	10.8	0.8	1.0	0
9	6.9	6.2	1.6	1.2	0
10	7.1	6.8	4.8	1.3	0
11	7.0	6.1	1.1	1.4	0
12	8.8	8.0	2.1	1.4	0
13	10.1	8.1	3.9	1.8	0
14	13.6	14.3	1	1.9	0
15	16.0	14.7	2.6	2.1	0
mean	8.8	8.4	2.7	-	-
SD	3.0	2.9	2.6	-	-
16	11.9	10.3	1.7	2.5	1
17	10.3	10.0	1.1	2.6	1
18	10.7	10.1	0.8	2.7	1
19	10.5	10.5	2.1	3.0	1
20	11.0	11.7	1.1	3.8	2
21	12.2	11.1	2.8	4.4	2
22	13.5	9.8	3.3	5.0	2
23	10.7	8.3	4.1	5.2	2
24	11.3	8.7	7.1	5.2	2
25	15.3	9.6	10.1	6.2	2
26	17.6	9.5	25.6	6.2	2
mean	12.3	10.0	5.4	-	-
SD	2.3	1.0	7.3	-	-

Values of the internal bladder pressure p_{int} at the maximum external pressure $p_{ext.max}$ were compared to $p_{ext.max}$. The $t_{50\%}$ is the time necessary to reach half the value of p_{int} ($p_{ext.max}$) in the external catheter. URA is the urethral resistance factor and ICS represents the provisional ICS method for definition of obstruction: 0 = non-obstructed, 1 = equivocal and 2 = obstructed.

Five healthy volunteers were each measured approximately twelve times to test if bladder volume had an influence on the maximum external pressure. Figure 2.5 shows examples of the maximum external pressure as a function of the amount of urine ΔV in the bladder in two volunteers. Table 2.2 summarises the most important findings. In all volunteers an optimum bladder volume ΔV_{opt} at which an optimum pressure $p_{ext.opt}$ was generated was found. In all volunteers the pressures at 50% and 200% of the optimum bladder volume were significantly lower than the pressures at the optimum bladder volume (Wilcoxon signed-rank test: $p < 0.05$). Volunteer B was additionally measured six times with and without Parafilm® around penis and condom to test the influence of this elastic tape. The differences between both measurements were analysed with a mechanical model, see appendix.

Table 2.2 *Results of the simultaneous registration of the internal bladder pressure and the external pressure in twenty-six patients.*

	Volunteers				
Parameter	A (n=13)	B (n=11)	C (n=10)	D (n=13)	E (n=12)
ΔV_{opt} (ml)	350	280	200	170	230
$p_{ext.max}$ (ΔV_{opt}) (kPa)	12.7	12.7	11.9	11.9	14.1
$p_{ext.max}$ (50% of (V_{opt}) (kPa)	11.1	9.7	11.0	10.9	11.3
$p_{ext.max}$ (200% of ΔV_{opt}) (kPa)	9.6	10.4	6.4	8.2	12.1
R^2 (-)	0.73	0.90	0.88	0.81	0.71

ΔV_{opt} is the bladder volume at which an optimum external pressure $p_{ext.max}$ (ΔVopt) was generated. The values $p_{ext.max}$ (50% of ΔV_{opt}) and $p_{ext.max}$ (200% of ΔV_{opt}) are external pressure readings at 50% and 200% of ΔV_{opt}. R^2 is the relative mean quadratic difference between the measured values and the calculated values.

Table 2.3 summarises the most important changes of the mechanical parameters of this model, when applied to the two sets of measurements. The 50% rise time, $t_{50\%}$ was significantly shorter when Parafilm® was applied. The damping of the system also changed significantly. The system was overdamped with elastic tape and underdamped without elastic tape. Lastly, the maximum external pressure and the initial external pressure rise were significantly lower in the set of measurements without elastic tape around the condom. The bladder volumes in both measurements also differed significantly. The volunteer voided about 120 ml more urine without the elastic tape, see figure 2.5B.

Discussion

The external catheter was designed to non-invasively measure the bladder pressure. Before this method can be applied clinically, it should be compared with the existing invasive measurement technique. The difference plot of figure 2.4 demonstrates the agreement between the simultaneously measured internal bladder pressure (measured invasively) and the external pressure (measured non-invasively). Most of the measurements are between the borders of agreement, but four outliers can clearly be detected. These outliers were measured in obstructed patients only. A first possible explanation for these outliers is that there still was a small flow of urine from the bladder to the urethra during the external pressure measurement. The urethra is a visco-elastic tube that distends when pressure increases. Urine keeps flowing as long as the urethra distends. The higher the resistance of the urethra, the higher the pressure difference between the bladder and the external catheter, caused by this flow rate. A second possible explanation is that the interruption of the urinary stream inhibited the bladder contraction or that the bladder neck and the urethra prematurely closed. This phenomenon is sometimes observed during video urodynamics of a stop-test in obstructed patients. In the example shown in figure 2.3A, the external pressure was equal to the internal bladder pressure, so that the urethra must have been open.

Table 2.3 *The effect of Parafilm® on the mechanical properties of the external catheter (mean and standard deviations) determined from six measurements with and six measurements without elastic tape in one healthy volunteer, see also figure 2.5B.*

	mean ± SD		
Parameter	without elastic tape (n=6)	with elastic tape (n=6)	T-test p-value
$p_{ext.max}$ (kPa)	11.5 ± 0.6	12.7 ± 0.6	$p < 0.01$
$\Delta p_{ext}/\Delta t$ (kPa/s)	3.7 ± 0.3	8.6 ± 2.5	$p < 0.01$
z (-)	0.9 ± 0.1	1.5 ± 0.4	$p < 0.01$
$t_{50\%}$ (s)	1.8 ± 0.7	1.1 ± 0.2	$p < 0.05$
ΔV (ml)	393 ± 94	270 ± 85	$p < 0.05$

In the mechanical model (see figure 2.7), h represents the maximum external pressure $p_{ext.max}$, v represents the initial increase of the external pressure $\Delta p_{ext}/\Delta t$ and z is the viscous damping factor. The time necessary to reach half of the total displacement of the mass is the 50% rise time, $t_{50\%}$ and finally ΔV represents the amount of urine in the bladder during the external pressure measurement.

The unusually high internal bladder pressure was caused by the fact, that this pressure was measured at the same level as the external pressure at the end of the external catheter i.e. significantly below the level of the symphysis pubis. In spite of this high pressure, the patient was classified as non-obstructed on the basis of the preceding invasive measurement (which obviously showed a lower voiding pressure). Furthermore, the variation in the internal bladder pressure signal resulted in a higher internal bladder pressure before interruption of the flow rate than during interruption of the flow rate. In the example in figure 2.3B the external pressure reached a plateau below the internal bladder pressure after a 50% rise time of about 8 seconds. This indicates premature closure of the bladder neck, thus producing not one pressure chamber (bladder - urethra and external catheter) but two pressure chambers (bladder chamber apart from urethra and external catheter).

We sometimes noticed a gradual increase of the internal bladder pressure after interruption of the flow rate in non-obstructed patients, as shown in figure 2.3A. Two different physiological explanations are possible for this phenomenon. First of all, the external pressure measurement interferes with normal voiding for a few seconds. In fact, it interrupts shortening of the muscle fibres of the detrusor, changing the shortening contraction temporarily into an isometric contraction. The physiological relation between force (pressure) and shortening velocity (flow rate) of a muscle like the bladder wall, known as the Hill equation [Hill, 1938] has a hyperbolic shape. Therefore the isovolumetric bladder pressure is higher than the bladder pressure at a given flow rate in a non-obstructed voiding. In obstructed voiding, the flow rate is reduced. As the degree of obstruction increases, the bladder pressure shifts towards the isovolumetric pressure. Interruption of an obstructed flow rate does therefore not always result in an increase of the internal bladder pressure, see figure 2.3B. A second explanation of pressure increase seen in non-obstructed patients upon interruption of the flow rate, could be that bladder stimulation changed. Previous research showed that the detrusor of a guinea pig is stimulated sub-maximally during micturition, allowing energy efficient emptying of the bladder [Groen et al., 1994]. If the human bladder is also stimulated sub-maximally during normal voiding, a sudden interruption of the flow rate may cause an increase in stimulation in a last effort to empty the bladder.

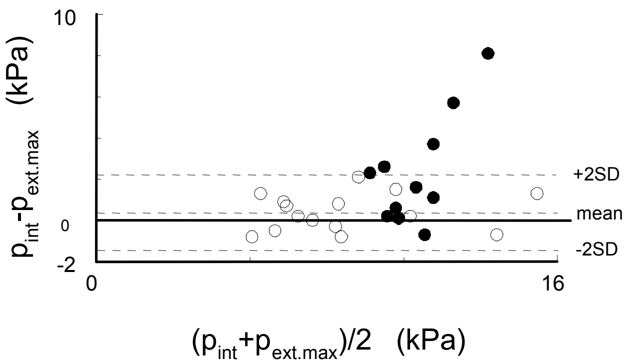
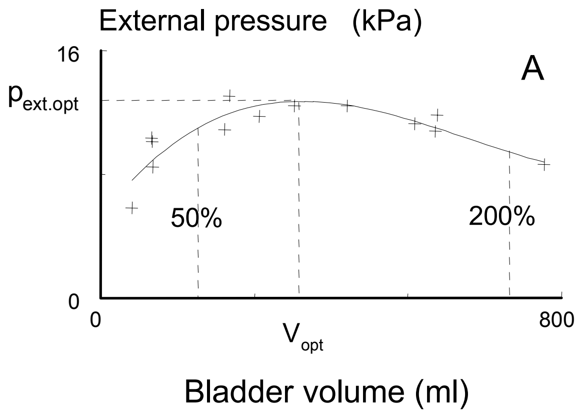


Figure 2.4 *Difference of the simultaneously measured internal bladder pressure (measured invasively) and the external pressure (measured non-invasively) in non-obstructed patients (open circles) and obstructed patients (closed circles). The differences between the internal bladder pressure and the maximum external pressure values are plotted as a function of the mean of both values.*

Table 2.2 shows that in all five volunteers the maximum external pressure depended on the bladder volume. The decrease of the externally measured isovolumetric bladder pressure with the bladder volume above the optimum volume ΔV_{opt} in all volunteers can be understood from geometrical mechanisms [Van Mastrigt et al., 1978]. The length-force relation of bladder wall muscle fibres can be calculated from the external pressure measurement [Van Mastrigt and Griffiths, 1979]. Figure 2.6 shows the total detrusor force as a function of bladder circumferences calculated from the pressure data, measured non-invasively in healthy male volunteers. The nearly linear relation found is consistent with the relation reported for smooth muscle strips of pig bladder [Griffiths et al., 1979] as well as guinea pig bladder [Groen et al., 1994], when maximally stimulated. Hence, the dependence of the maximum external pressure on bladder volume can be explained on the basis of the geometry of the detrusor.



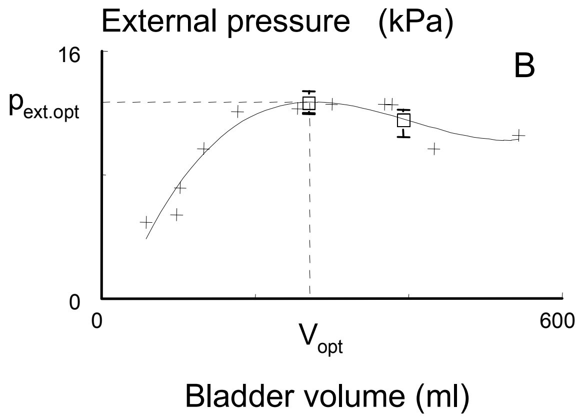


Figure 2.5 *Two examples of maximum external pressure as a function of the amount of urine in the bladder. In panel A, two selected bladder volumes are shown as a function of the optimum bladder volume of the volunteer to investigate dependence of external pressure on bladder volume, see also table 2.2. The two error bars in panel B represent the mean values of the external pressure of the two measurement series with and without the elastic tape measured in this volunteer, see also table 2.3.*

In the past the dependence of the isovolumetric bladder pressure on bladder volume has been studied using different stop-test techniques. Patients were either asked to voluntarily stop voiding or the bladder neck was occluded mechanically by retracting a Foley-balloon catheter during voiding. When patients voluntarily stopped voiding [Susset et al., 1982; Griffiths and van Mastrigt, 1986] isovolumetric bladder pressure was found to be independent of the bladder volume. It was however reported to depend on bladder volume when the bladder neck was mechanically occluded [Constantinou et al., 1984], which is similar to our findings. It has been suggested that premature inhibition of bladder contraction due to stimulation of the bladder neck by the Foley-balloon influenced the isovolumetric bladder pressure reading in the latter case [Sullivan et al., 1995]. From the fact that the length-force relation in figure 2.6 is similar to such relations measured in vitro, it can be concluded that the detrusor contraction was not inhibited during our external pressure measurements. We also concluded, that the bladder in normal voiding works in the ascending part of the force-length curve, which was found to have an ascending and a descending part [Van Mastrigt, 1988]. As the results of the balloon tests are similar to our present results, it is more likely that a voluntary stop leads to inhibition of detrusor contraction and that the detrusor contraction is not inhibited when mechanically occluded.

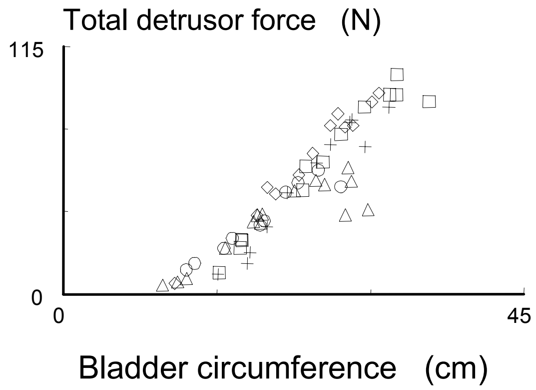


Figure 2.6 *The relation between total detrusor muscle force and bladder circumference calculated from measurements in five healthy volunteers. Figure 2.5 shows data from two of these volunteers.*

A shorter 50% rise time decreases the chance of premature inhibition of bladder contraction during the non-invasive measurement. With the help of the mechanical model, we showed that by taping Parafilm® around the penis and condom the 50% rise time could be decreased. A remarkable finding was the significant difference of maximum external pressure in volunteer B with and without the elastic tape. In general, a long rise time increases the chance of detrusor inhibition, which increases the chance of an incorrect external pressure reading. However, in volunteer B, taping reduced the 50% rise time from 1.8s to 1.1s. Therefore, it is not likely that the difference in rise time explains the differences in pressures (measured with and without tape presented in table 2.3). Rather these differences are basically related to bladder volume dependency, see figure 2.5B. The measurements with the elastic tape were performed at a mean bladder volume closer to the optimum bladder volume ΔV_{opt} than the measurements without the elastic tape.

We learned by performing the external pressure measurements that the valve cannot be opened immediately after the external pressure reaches a maximum value. In some cases a temporary maximum was recorded, although the absolute maximum pressure wasn't reached yet, as illustrated in figure 2.8. There are two possible explanations for this submaximum pressure. Firstly, some of the volunteers experienced a short contraction of the sphincter just after the flow rate was interrupted. It is possible that such a short closure of the urethra reduces the flow of urine for a short moment. Secondly, the increase of pressure in the condom might push the glans of the penis backwards. The free space in the condom first needs to be filled with urine again, before the pressure continues increasing.

Conclusions

We conclude that isovolumetric bladder pressure can be measured non-invasively with the external catheter. This measurement technique is quicker and less painful than the present invasive measurement technique. The accuracy of the approximation of the internal bladder pressure by the maximum external pressure depends uniquely on the degree of obstruction of the patient. In non-obstructed patients the internal bladder pressure and the external pressure are low and correlate well. In obstructed patients both pressures are high but correlate less well. Nevertheless, the less accurate external pressure readings in obstructed patients were significantly higher than the accurate readings in non-obstructed patients. Therefore, we think it will be possible to discriminate between patients with a low flow rate either due to a weak bladder or an obstruction on the basis of the external pressure measurement and a separately measured maximum flow rate. Further investigation is necessary to determine the borderline between both groups of patients. From a practical point of view it must be concluded, that as a consequence of the volume dependence of the external pressure, it may be necessary to repeat the measurement several times to establish a correct reading.

Appendix

During an external pressure measurement, pressure is measured in a closed compartment. This compartment consists of the bladder, the urethra and the external catheter. The bladder is the main pressure generator. The pressure increase measured in the external catheter depends on several physiological and mechanical properties, like the contractile properties of the bladder, the elasticity and damping of the urethra and the external catheter. To better understand these properties, we developed a mechanical model that simulates the rise of the external pressure as a function of time. The model consists of a falling mass supported by a spring and a damper, as shown in figure 2.7.

In the mechanical model a force represents the pressure in the bladder, urethra and external catheter. Between time t_0 and t_1 (see also figure 2.2) the mass m falls downward with velocity v until this fall is interrupted at time t_1. This resembles the free flow of urine through the catheter until this flow is interrupted when the valve is closed. After t_1, the mass exerts force on the spring and the damper. This force represents the pressure in the condom caused by the weight of the urine and the internal bladder pressure. The spring stiffness k and the viscous damping factor z represent the visco-elastic properties of the bladder, the urethra and the condom. The spring and the damper decelerate the mass until at time t_2 the mass is at rest.

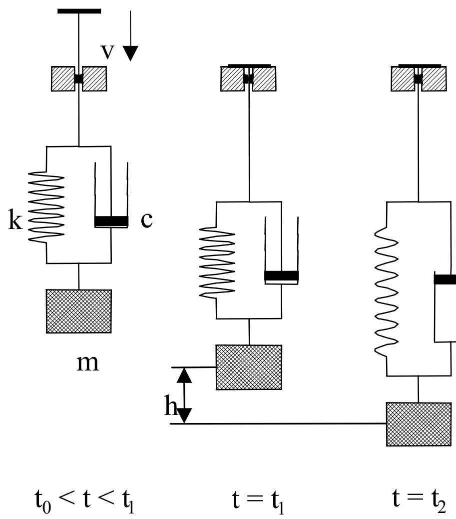


Figure 2.7 *The mechanical model used to analyse the behaviour of the bladder, the urethra and the external catheter during the measurement of external pressure. The model is shown in three phases: during the free fall of the mass ($t_0 < t < t_1$) which represents voiding, during sudden interruption of the fall ($t = t_1$) which represents closure of the valve, and in the equilibrium position of the mass ($t = t_2$) which represents the maximum external pressure reading.*

The numeric values of m, k, c and v can be calculated from an external pressure measurement by fitting the displacement of the mass to the measured external pressure in time (fitting was done in Matlab®) [Meirovitch, 1986]. The initial height h then represents the maximum external pressure $p_{ext.max}$ and the initial velocity v represents the initial increase of the external pressure $\Delta p_{ext}/\Delta t$. The viscous damping factor z of the mechanical model can be calculated. If this value is below one (underdamped), the mass is primarily decelerated by the spring (almost no damping, the mass will oscillate after t_1). If it is above one (overdamped), the damper primarily decelerates the mass and it will slowly creep to its final position. Figure 2.8 shows a detailed example of the measured external pressure signal fitted with the displacement of the mass of the mechanical model.

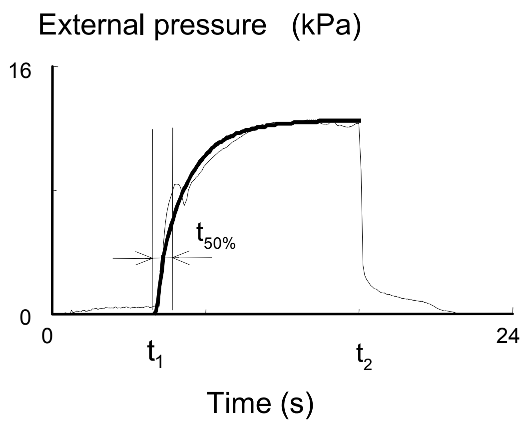


Figure 2.8 *The displacement of the mass of the mechanical model (thick line) shown in figure 2.7 fitted to the shape of the external pressure measured in a volunteer (thin line). The numeric values of m, k, c and v, described by the model, were automatically adapted to minimise the difference between both experimental and fitted curve.*

3

REPEATED NON-INVASIVE BLADDER PRESSURE MEASUREMENTS WITH AN EXTERNAL CATHETER

Adapted from:
Rikken B, Pel JJM and van Mastrigt R (1999) The Journal of Urology 162: 474-479.

Abstract

In previous studies it was shown, that by combining the maximum flow rate and the isovolumetric bladder pressure of a patient, an objective diagnosis of infravesical obstruction is possible. In this study we evaluated a method to non-invasively measure isovolumetric bladder pressures with the aim of developing a method for non-invasively diagnosing obstruction. We used an external catheter consisting of an incontinence condom, a tube and a pressure transducer. Flow rate through the catheter was remotely interrupted to measure the bladder pressure in the condom. Two series of measurements were done in 11 healthy male volunteers. In the first series, we tested if the remainder of the voiding was affected after an interruption of the flow rate. In the second series, we analysed repeated pressure measurements in one voiding to study if the maximum isovolumetric pressures depended on the bladder volume. Flow rate was found to be unaffected after a flow rate interruption for a pressure measurement. Measuring the isovolumetric bladder pressure repeatedly showed that the pressures depended significantly on the bladder volume. On average the volunteers had a maximum isovolumetric pressure of 12.2 kPa at a bladder volume of 251 ml. As no inhibition of voiding was found after a single pressure measurement, repeated non-invasive pressure measurements can be done in one voiding. By measuring repeatedly, the dependence of the isovolumetric bladder pressure on the bladder volume can be taken into account to obtain a reliable estimate of the bladder pressure as a basis for a non-invasive diagnosis of obstruction.

Introduction

At present, a pressure-flow analysis is done invasively. The signals measured in this procedure such as bladder pressure and flow rate are the basis for a urodynamic diagnosis of voiding dysfunction. Although invasive urodynamics is essential, it involves some practical problems. The procedure is time consuming, expensive and sometimes painful for the patient. To avoid these disadvantages, non-invasive bladder pressure measurement techniques have been introduced [Schäfer et al., 1994; van Mastrigt, 1995; McRae et al., 1995]. One of these measurement techniques is a non-invasive bladder pressure measurement with an external condom catheter [van Mastrigt, 1995; Pel and van Mastrigt, 1997]. This article describes pressure measurements with the external catheter in healthy male volunteers. The external catheter consists of a self adhesive incontinence condom, which is attached to the penis, and a soft silicone tube connected to the open side of the condom. During voiding through the external catheter, the tube can be closed by a valve fitted over it. When the valve is closed flow rate is interrupted and a pressure is measured in the condom by a pressure transducer connected to the silicone tube. Theoretically, an isovolumetric condition of the bladder is enforced when the valve is closed. During such a pressure measurement the volume in the bladder is constant.

Previous studies with the external catheter showed that in non-obstructed patients the external pressure and the simultaneously measured intravesical pressure correlated well [Pel and van Mastrigt, 1999a]. Therefore, the non-invasively measured pressure adequately represents the isovolumetric detrusor pressure of a patient. It was shown that by combining this pressure with the maximum flow rate measured separately in a free voiding, an objective diagnosis of infravesical obstruction is possible [van Mastrigt and Kranse, 1995; Comiter et al., 1996; Pel and van Mastrigt, 1998]. In volunteers it was found that more pressure measurements are necessary to obtain a reliable estimate of the bladder pressure [van Mastrigt, 1995]. Other non-invasive studies with the external catheter as well as invasive studies using Foley balloon catheters, showed that single isovolumetric bladder pressures depended on the volume in the bladder [Constantinou et al., 1984; Pel and van Mastrigt, 1999a]. We tested if several bladder pressure readings can be taken in one voiding with the external catheter to obtain a more reliable estimate of the isovolumetric pressure. Therefore, two series of measurements were done. In the first series, we tested if, after interruption of the flow rate for a single pressure reading the remainder of the voiding was (un)affected. In the second series, we tested if the pressures in the repeated measurements with the external catheter depended on the bladder volume.

Materials and methods

In this study the external catheter was used to non-invasively measure bladder pressures in two series of measurements [Rikken et al., 1998]. In the first series eleven healthy male volunteers were asked to void nine times in a rotating disk flow meter (Dantec®) under three different circumstances. Three of those nine voidings were unmanipulated control experiments (free voidings). In the other six a self adhesive incontinence condom (Pop-on, Laprolan®) was attached to the penis. To increase the stiffness of the distal penile urethra and the condom both were taped with 3 strips of Parafilm® (3x15 cm). The open end of the condom was attached to a T-connector (polypropylene). One leg of the connector was connected to a disposable pressure transducer and the other to a soft silicon tube. A mechanical valve that could remotely be closed by the investigator was fitted over this tube. This was done in three out of the six times the volunteer voided through the catheter. In the other 3 times only the application of the condom was tested (uninterrupted voidings through the catheter). The volunteers were asked not to strain during voiding and voided in privacy.

In a separate room the measured flow rate and external pressure signal were displayed on a computer screen during the voiding. The valve was closed and flow rate was interrupted one time before maximum flow rate was reached, during which the external pressure, p_{ext}, was measured. When the maximum external pressure, $p_{ext.max}$, was measured in the condom the valve was reopened and the volunteer continued emptying his bladder. The measured flow rate signals were plotted as a function of the bladder volume [Griffiths and Rollema, 1997]. For each volunteer 3 percentages (70%, 50%, 20%) of the smallest volume voided in the six uninterrupted voidings were calculated (see figure 3.1). At each of those three percentages flow rates were compared between the different types of measurements and volunteers with analysis of variance using a simple factorial design with two independent factors (volunteer and measurement type) in SPSS®.

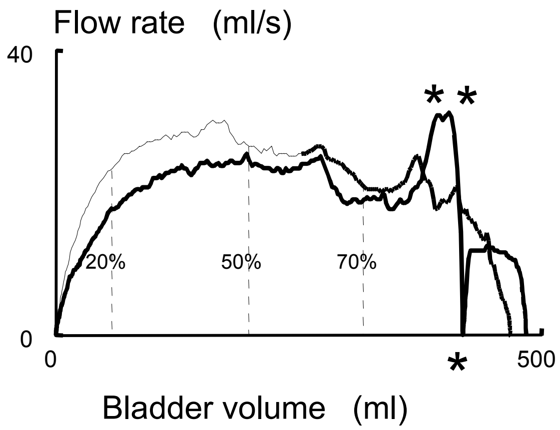


Figure 3.1 *Flow rate as a function of the volume in the bladder. Two of the three different voiding types in one volunteer are superimposed in one figure. Thin line: one of the 6 uninterrupted voidings. Thick line: one of the 3 interrupted voidings. Both voidings must be read from the right (full bladder) to the left (empty bladder). Illustrated are the 3 percentages of the bladder volume at which flow rates were compared. * = mechanical interruption of voiding, ** = overshoot after the interruption (in thick line)*

In the second series of measurements, the valve was closed repeatedly in one voiding. These measurements were done in nine of the eleven volunteers. As in the first series of measurements, the first external pressure reading was taken before the flow rate reached its maximum. In contrast to the first series of measurements the volunteer was not allowed to completely empty his bladder after opening the valve. A few seconds after restart of the flow rate the valve was closed a second time. After the second measurement the same procedure was repeated a few times until the bladder was empty. All measured signals were filtered with a program written in Matlab using a first order Butterworth filter with a cut-off frequency of 0.2 Hz. In each measurement the same program automatically calculated the maximum external pressure and associated bladder volume. Bladder volumes were defined as the difference between maximum voided volume and the volume voided before the pressure measurement. The delay time caused by the distance between pressure transducer and flow-meter was corrected by a lag time of 8 samples (= 0.8s) [Kranse et al., 1995]. An average correction of 20 cmH_2O (~0.2 kPa) was made to allow for the height difference between the symphysis pubis and the pressure transducer.

In nine volunteers we investigated if pressures depended on the bladder volume. Maximum external pressures of all repeated voidings in each volunteer were plotted as a function of the volume in the bladder and fitted with a third order polynomial using least squares regression. The accuracy of the fit was characterised by R^2. This is the relative mean quadratic difference between the measured values and the values predicted by the fitted polynomial. At the best fit R^2 equals 1. A third order polynomial was chosen because this was the lowest order polynomial that seemed visually to fit the data. This was confirmed by satisfactory R^2 values (see table 3.2). The highest value of the third order polynomial was called the optimum external pressure, $p_{ext.opt}$. The bladder volume at $p_{ext.opt}$ was called the optimum bladder volume, V_{opt}. For each volunteer, the value of the fitted polynomial at three percentages (50%, 150%, 200%) of the optimum bladder volume was calculated. Differences between these pressures were statistically analysed using a paired T-test (SPSS). For a general result, external pressure values in each volunteer were normalised by dividing them by the optimum external pressure and bladder volumes were normalised by dividing them by the optimum bladder volume.

Results

In the first series of measurements differences in flow rate with and without application of the condom, and with and without interruption of the voiding were studied in 11 healthy volunteers [age ± SD = 27 ± 8 years.]. Figure 3.1 shows examples of two different voidings in one volunteer. The flow rate was plotted as a function of the bladder volume. Both voiding signals must be read from right (maximum bladder volume) to left (empty bladder). The thick line represents an interrupted voiding. When the valve was closed in this interrupted voiding the flow rate became zero, this point is illustrated with (*). After reopening the valve, the flow rate rose again. An overshoot, indicated with (**), was seen, caused by the expulsion of fluid from the slightly inflated condom. The flow rate signal after the overshoot was analysed. The other voiding, illustrated with the thin line, represents one of the 6 free voidings in this volunteer.

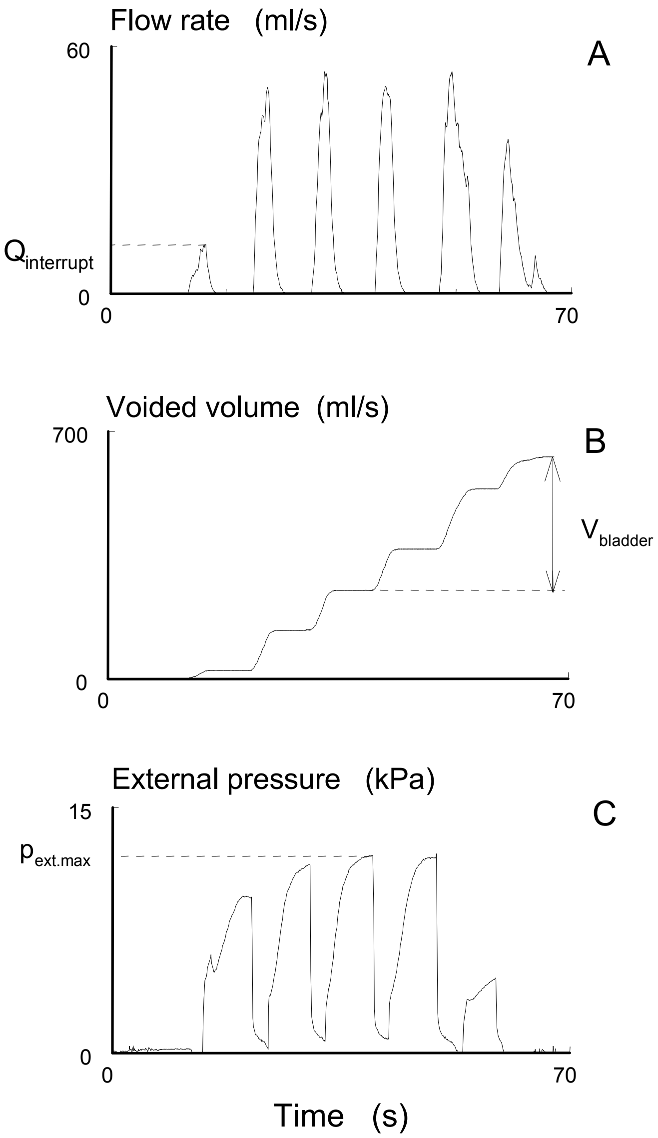


Figure 3.2 *An example of a repeated pressure measurement with the external catheter. The upper panel shows the interrupted flow rate and the middle panel shows the voided volume. Five pressure readings were taken in this voiding as shown in the lower panel.* $p_{ext.max}$ *indicates the maximum pressure in the third pressure measurement. The associated bladder volume is denoted* $V_{bladder}$.

The 3 tested bladder volume percentages at which differences in flow rate were compared are indicated, the volume voided in the smallest uninterrupted voiding was defined as 100%. Table 3.1 shows the results of the analysis of variance. At all 3 percentages of the bladder volume the variance in flow rate associated with the 3 measurement types (without condom, with the condom and with interruption of the flow rate) was not significant compared to the variance within one type of measurement ($p > 0.05$). The variance between volunteers was significant at all 3 tested volume percentages ($p < 0.001$). Repeated pressure measurements in one voiding were done in nine of the eleven volunteers. Two subjects did not participate in this series of measurements for reasons unrelated to the study. In the example shown in figure 3.2 the flow rate was interrupted 5 times for a pressure measurement. The 9 healthy volunteers voided at least 4 times. Two times two volunteers closed the urethral sphincter after closure of the valve. Also two times there was leakage of the condom because it was not correctly applied. The volunteers applied the condoms themselves. These measurements were excluded from further analysis.

Table 3.1 *Statistical results of analysis of variance.*

Variance	Between volunteers		Between measurement types	
% Volume	F-value	p-value	F-value	p-value
70%	20.087	< 0.001	2.222	0.116
50%	28.812	< 0.001	1.119	0.333
20%	28.045	< 0.001	1.146	0.324

At three percentages of the bladder volume differences in flow rate were compared between 3 measurement types (free voiding, voiding through the condom catheter and interrupted voiding) and between 11 volunteers. 100% bladder volume was defined as the smallest voided volume in the six uninterrupted voidings. F-values (between groups variance divided by residual variance) and significance of these values are shown.

In all volunteers maximum external pressures were plotted as a function of the associated bladder volumes. In all volunteers the fitted polynomial showed an optimum external pressure $p_{ext.opt}$, at an associated optimum bladder volume V_{opt}, except in volunteer B. Table 3.2 shows these optimum pressures and volumes of all volunteers. The volume at the optimum pressure was always smaller than the maximum voided volume, except in volunteer B. A Shapiro-Wilk test (SPSS®) showed a normal distribution of the values in table 3.2. Therefore, a paired T-test was used to compare the optimum pressure to the value of the fitted polynomial at 50%, 150% and 200% of V_{opt} (see table 3.2). At these volumes the external pressure was significantly different from the optimum pressure ($p < 0.05$). Values found were (mean ± SD):

p_{opt} - p50% of V_{opt} : -2.4 ± 1.1 kPa (p = <0.001)

p_{opt} - p150% of V_{opt} :-1.1 ± 0.43 kPa (p = 0.001).

p_{opt} - p200% of V_{opt} :-3.1 ± 1.6 kPa (p = 0.006).

Discussion

Non-invasively measuring bladder pressures repeatedly with the external catheter may lead to a faster, easier, less painful and less expensive diagnosis of voiding dysfunction. In the present study some aspects of this method were investigated in 11 healthy male volunteers. In a first series of measurements the completion of voiding after the interruption of the flow rate was studied. Practically, this remainder of the voiding is the bladder volume range in which more external pressure measurements can be taken if the voiding is not inhibited by the interruption of the flow rate or by the application of the condom.

Table 3.2 *Results of repeated pressure measurements in one voiding in nine healthy volunteers.*

	Volunteers								
	A	B	C	D	E	F	G	H	I
n (-)	32	24	24	20	15	22	20	21	19
Q_{max} ± SD (ml/s)	32 ± 3.3	20 ± 1.3	28 ± 2.4	12 ± 0.9	36 ± 5.1	29 ± 3.6	31 ± 4.8	33 ± 4.4	21 ± 4.9
V_{max} (ml)	719	290	680	342	725	213	514	603	463
V_{opt} (ml)	323	290	262	147	278	174	266	320	199
p_{ext} (kPa)	12.2	11.7	12.2	9.0	14.7	16.2	9.8	12.2	11.9
p_{ext} (50% of V_{opt}) (kPa)	9.7	10.3	10.0	7.7	11.7	11.7	8.1	9.2	10.4
p_{ext} (150% of V_{opt}) (kPa)	10.9	-	11.0	8.4	13.0	9.4	10.8	-	11.1
p_{ext} (200% of V_{opt}) (kPa)	9.3	-	9.5	7.7	10.0	-	-	9.6	10.4
R^2 (-)	0.94	0.64	0.84	0.68	0.92	0.9	0.87	0.95	0.83

Q_{max} is the average maximum flow rate ± standard deviation and V_{max} is the maximum volume voided, n is the number of pressure measurements, V_{opt} is the optimum bladder volume at which an optimum pressure $p_{ext.opt}$ was generated. The values p_{ext} (50% /150% /200% of V_{opt}) represent the value of the fitted third order polynomial at 50%, 150% and 200% of V_{opt}. R^2 is the relative mean quadratic difference between the measured values and the calculated values.(*) Data on these volunteers is missing because 150 or 200% of V_{opt} was larger than V_{max}.

With the exception of two different voidings in two volunteers we found that bladder contraction was not inhibited due to a single interruption of the flow rate. In these exceptional cases voiding did not continue after reopening the valve. This lasted for a period of 5-7 seconds. Closing the valve too soon after the initiation of the voiding probably caused this apparent inhibition of voiding. In these cases the valve was closed one time at a flow rate of approximately 5 ml/s, while the maximum flow rate in all free voidings with and without condom in these two volunteers was above 20 ml/s. Probably, the initiation of voiding is vulnerable to external interference. As the volunteers restarted voiding after a few seconds, we think that the inhibition was not due to detrusor contraction inhibition but due to a sphincter contraction. On the basis of this experience, we decided that it would be best to precede the external catheter measurements in a volunteer with a free voiding so that the maximum flow rate is known. In later measurements this was done in all volunteers and none of them showed signs of inhibition of voiding due to too early interruption of the flow rate. An EMG registration of the pelvic-floor muscles was not done in this study, but could in future studies be used to monitor possible sphincter contractions. Closing the valve at higher flow rate values or choosing the wrong size condom could cause other problems. When the investigator waits until the flow rate reaches high values, the volunteer has already voided a significant volume of urine so that less measurements can be taken. The investigator therefore must choose between interrupting the flow rate at an early moment with the risk of inhibition of voiding or interrupting the flow rate at maximum flow rate with the risk that only a few pressure measurements can be taken. In our measurements we interrupted the stream at a flow rate of at least half of the maximum flow rate. As for condoms, the volunteers could choose between 4 sizes (large, intermediate, medium and small). They were advised to start with a medium size and after the measurement asked about possible pain and fitting. When a particular size was not adequate, the volunteer was asked to use another condom size for subsequent measurements. A condom which is too large, accommodates too much urine during the interrupted period. This results in a slow increase of pressure and a large overshoot (as seen in figure 3.1) when the accumulated urine is expelled after reopening the valve. As the flow rate during this "overshoot" does not reflect bladder properties, but rather the condom elasticity, it is different from the free flow rate. Condom and penis were taped in with Parafilm® to increase stiffness. The 50% rise time (time to reach half of the maximum external pressure) significantly improved as a result of this tape [Pel and van Mastrigt, 1999a]. Care was taken not to apply the tape too tightly, as this might cause obstruction. This was verified by comparing free flow rates and instrumented flow rates (table 3.1) which were not significantly different.

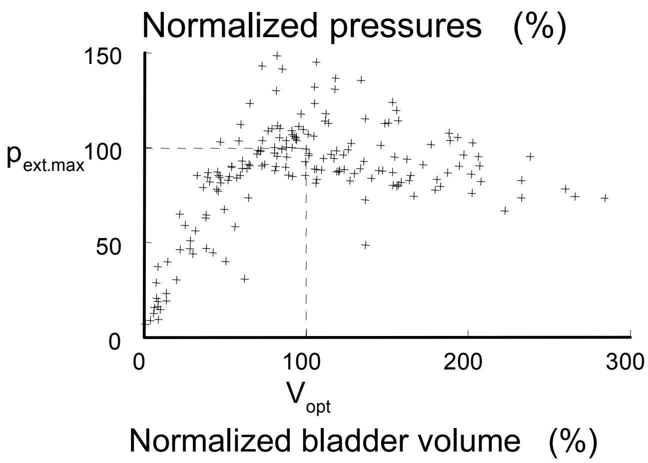


Figure 3.3 *Normalised maximum pressures of all nine volunteers plotted as a function of the normalised bladder volumes. At small bladder volumes the external pressure decreases steeply. At high bladder volumes, the external pressures are also lower but not as dramatically as those at the smaller volumes.*

Our first series of measurements explored the possibilities and limitations of single pressure measurements based on single interruptions of the flow rate in one voiding. As no inhibition of the flow rate was found after a single interruption of the stream, we concluded that at least one more and probably many more pressure measurement(s) can be taken in one voiding. In the second series of measurements we studied repeated measurements in one voiding. As stated in the introduction it was found in previous studies that the pressures measured with the external catheter depended on the bladder volume. In one of these studies the valve was closed and the stream was interrupted one time [Pel and van Mastrigt, 1999a]. Also in invasive studies intravesical isovolumetric bladder pressures were found volume sensitive [Constantinou et al., 1984; Craggs and Rushton, 1996]. Such a volume dependence of isovolumetric pressures not only necessitates several measurements in one volunteer to derive a reliable estimate of the bladder pressure, it is also a possibly clinically relevant physiological mechanism. Therefore, we investigated if this volume dependence can be measured by repeatedly interrupting voiding using the external catheter. Maximum values of the pressures were plotted as a function of the volume in the bladder. We found that in all volunteers the measured pressures depended significantly on the bladder volume. The optimum pressure was found at a bladder volume situated between 147 ml and 323 ml (on average 52 % of the maximum bladder volume). Figure 3.3 shows that the external pressures at volumes below the optimum bladder volume are much lower than the external pressures above the optimum bladder volume. It should be noted that at the very small volumes (less than 10% of the maximum bladder volume) the pressures are not reliable as the urethral sphincter may already have been closed at the moment of reopening the valve. This might have been the case in the last measurement in figure 3.2. In these cases the external catheter may have measured urethral pressures instead of bladder pressures.

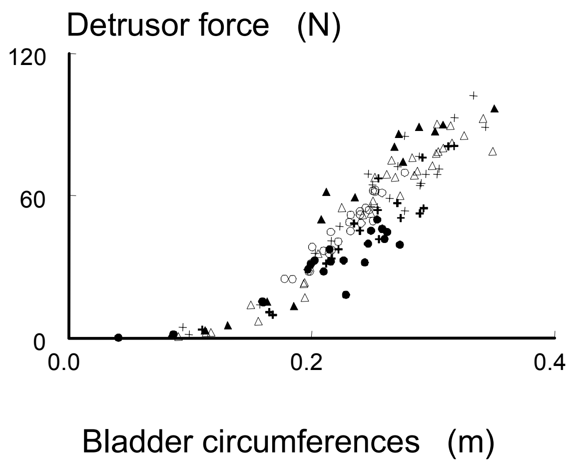


Figure 3.4 *Total detrusor force as a function of the bladder circumference, calculated from the maximum external pressure and the bladder volumes measured, in all nine male volunteers.*

The normalised isovolumetric pressure-volume relationship shown in figure 3.3 depends on the force-length characteristic of the detrusor smooth muscle. This force-length relation can be calculated from the external pressure and bladder volume van Mastrigt, 1979]. In figure 3.4 the total detrusor force is plotted as a function of the bladder circumference. An almost linear relation was found. In earlier studies in pig bladder smooth muscle it was found that the detrusor muscle generates a maximum force at an optimum muscle length and decreases at higher lengths [van Mastrigt, 1988]. Traditionally this length dependence of muscle force generation has been ascribed to a variation in overlap of actin and myosin filaments [Huxley, 1957]. At small muscle lengths the large overlap of the actin and myosin filaments causes reduced forces, and at larger lengths the reduced overlap causes a similar reduction. In the data shown in figure 3.4 the overlap theory might explain the reduced detrusor muscle force at small circumferences. An alternative explanation is that during normal voiding the detrusor smooth muscle is not always fully neurologically activated. Evidence for an incomplete activation of the detrusor muscle during normal voiding has been presented earlier [Groen et al., 1994a]. Figure 3.4 does not show a reduction in force generation at larger muscle lengths as found in vitro. One explanation is simply that in normal voiding the detrusor muscle does operate at lengths below the optimum muscle length [Groen et al., 1994b]. Circumstantial evidence for this hypothesis can be found in in vitro studies. In contrast to the behaviour of striated muscle, the passive force exerted by smooth muscle kept at the optimum length for force generation is so high that the muscle deteriorates rapidly [Anderson et al., 1968]. This makes it unlikely that in vivo the muscle operates in this length range. In any case, it is obvious that the decrease of the pressure volume relation at bladder volumes above the optimum (in figure 3.3) must simply be explained by the geometry of the bladder as at the highest circumferences (in figure 3.4) the detrusor force still increases [van Mastrigt and Griffiths, 1979].

The volume dependence found in the repeatedly measured external pressures supports our earlier conclusion that more than one interruption of the flow rate does not cause inhibition of the voiding. Even in a third pressure measurement (as illustrated in figure 3.2) sometimes a higher pressure was found than in the first measurement. In three volunteers flow rate was additionally interrupted once at the end of the voiding to see if the prolongation of the voiding by interrupting repeatedly resulted in detrusor fatigue. The repeatedly measured external pressures were not smaller when they were compared with pressures measured onetime at the end of the voiding. In these three volunteers the bladder pressure dependence on bladder volume had already been measured in an earlier study, where flow rate was only interrupted once at approximately the maximum flow rate [Pel and van Mastrigt, 1999a]. In these volunteers we found the same volume dependence as with repeated measurements. A similar volume dependence has also been measured invasively [Craggs et al., 1998]. We therefore conclude that repeated interruptions can be done in one voiding to measure a reliable bladder pressure, and that the prolonged voiding inherent to this procedure does not cause muscle fatigue.

Conclusions

In our study in healthy non-obstructed male volunteers we found that non-invasively measuring the bladder pressure by interrupting voiding with an external catheter does not affect the flow rate in the remainder of the voiding. Therefore, the detrusor contraction does not seem inhibited due to such an external bladder pressure measurement. We conclude that reliable repeated pressure readings can be taken in one voiding using this method. The isovolumetric pressures measured in this way depend on the bladder volume. At small bladder volumes the pressures may not always be reliable but at larger bladder volumes a clearly defined optimum in the pressure-volume relationship was found. We thus further conclude that the bladder volume dependence must be taken into account, to obtain a reliable estimate of the isovolumetric bladder pressure. By doing repeated measurements in one voiding this can be accomplished while avoiding long measurement sessions. A combination of the, thus measured, isovolumetric bladder pressure with an independently measured maximum flow rate could in future form a non-invasive tool for objectively diagnosing infravesical obstruction due to Benign Prostatic Hyperplasia (BPH). The data of the healthy male volunteers in the present study can be of help in establishing discrimination lines between non-obstructed and obstructed patients.

4

DEVELOPMENT OF A STRATEGY TO NON-INVASIVELY CLASSIFY BLADDER OUTLET OBSTRUCTION IN MALE PATIENTS WITH LUTS

Adapted from:
Pel JJM, Bosch JLHR, Blom JHM, Lycklama à Nijeholt AAB and van Mastrigt R (2001)
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Abstract

To diagnose bladder outlet obstruction in male patients with LUTS, it is necessary to measure the bladder pressure via a transurethral (or suprapubic) catheter. This procedure induces some risk of urinary tract infection and urethral trauma and is sometimes painful to the patient. We developed an external condom catheter to non-invasively measure the bladder pressure and developed a strategy to classify BOO on the basis of this measurement. 75 patients with a wide range of urological diagnoses underwent a PFS followed by a non-invasive study. We tested 5 different strategies to classify the patients using the provisional ICS method for definition of obstruction as a gold standard. Leakage of the external catheter occurred in 40% (8) of the first 20 tested patients. In the remaining 55 patients, only 9% (5) of the measurements failed because of leakage. 56 of the 75 patients were successfully tested non-invasively. According to the ICS-nomogram, the PFS showed that 22 of these patients were non-obstructed, 12 patients were equivocal and 22 patients were obstructed. 10 of these 56 patients strained, and we found that the relatively high abdominal pressures in these patients were not reflected in the externally measured bladder pressure. Of the remaining 46 patients, 12 of 13 non-obstructed patients and 30 of 33 combined equivocal and obstructed patients could be correctly classified. We developed a simple, non-invasive classification strategy to identify bladder outlet obstruction in those male patients who did not strain during voiding.

Introduction

Over the years, the predictive role of urodynamic pressure-flow studies in assessing the outcome of elective prostatectomy has been recognised [Neal et al., 1989; Abrams, 1989] and nowadays urodynamic grading of obstruction is an important tool for a differential diagnosis of impaired voiding [Abrams et al., 1997]. During a pressure-flow study, bladder pressure and flow rate are measured simultaneously. A high bladder pressure combined with a low flow rate indicates that a patient has an obstruction somewhere in the outflow tract. A low bladder pressure combined with a low flow rate indicates that a patient has a weakly contractile bladder, possibly combined with an obstruction. To measure the bladder pressure, a patient needs to be catheterised. This procedure induces some risk of urinary tract infection and urethral trauma [Porru et al., 1999] and is sometimes painful for the patient. The last few years techniques have been proposed to non-invasively measure the intravesical pressure to avoid the risk of catheterisation. For a detailed discussion and a complete overview of these non-invasive techniques, we refer to [van Mastrigt and Pel, 1999] and for recently developed methods to [Griffiths et al., 1999; Pel and van Mastrigt, 2001, Sullivan and Yalla, 2000]. One of these techniques involves the measurement of the isovolumetric bladder pressure using an external condom catheter and was extensively discussed [Gommer et al., 1999; Schäfer, 1999; Pel and van Mastrigt, 1999a, b]. It was shown that the accuracy of this non-invasive method depends on the degree of obstruction of the patients.

By international consensus, a method has been established to classify patients on the basis of invasive pressure-flow measurements: the provisional ICS method for definition of obstruction [Griffiths et al., 1997]. In this method, the bladder outlet resistance is quantified using the maximum flow rate and the detrusor pressure at maximum flow rate. Patients are classified in three groups: obstructed, equivocal and non-obstructed. In the present study, we tried to develop a similar classification strategy to identify bladder outlet obstruction from a combination of flow rate and bladder pressure measured non-invasively using the external condom catheter. A pilot study on this topic was published earlier [Pel and van Mastrigt, 1998].

Materials and methods

The study was done in 75 patients with Lower Urinary Tract Symptoms (LUTS). As the aim of the study was to identify BOO using the non-invasive technique, we tested in a population of both non-obstructed and obstructed patients by including all patients scheduled for a standard PFS in three hospitals (St. Franciscus Hospital Rotterdam, Leiden University Medical Centre and University Hospital Rotterdam). The patients had a wide variety of symptoms but most had a reduced flow rate or were incontinent. We did not include healthy volunteers in the present study. Patients with dysfunctional voiding patterns or neurogenic bladder symptoms were excluded. In addition to the standard invasive PFS the patients underwent an non-invasive test. The non-invasive tests were done by the same investigator in all hospitals.

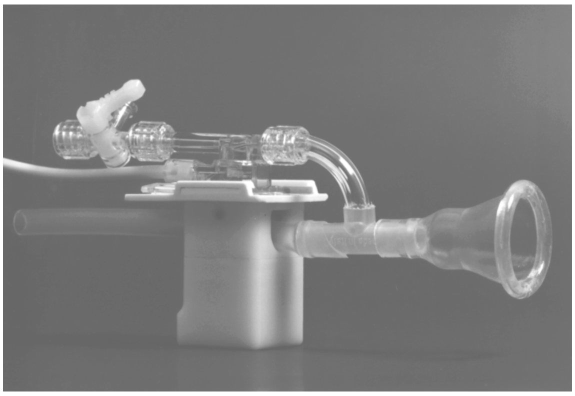

Figure 4.1 *The external condom catheter made to non-invasively measure the bladder pressure in a male patient. All components except the valve are disposable and were renewed for every patient. The valve is fitted over a tube and not in contact with urine (figure reproduced with permission).*

Invasive and non-invasive test
The measurement procedure started with a standard invasive PFS. To diagnose the patient, the difference between the intravesical and the abdominal pressure, the detrusor pressure, was plotted as a function of the flow rate in a pressure-flow plot. The point of maximum flow rate, Q_{max}, and associated detrusor pressure, $p_{det.Qmax}$ was plotted in the ICS-nomogram so that the patient could be classified as non-obstructed, equivocal or obstructed. After the invasive test, a single lumen 5 Fr. catheter was left in the bladder. For the non-invasive technique itself, no catheters need to be inserted into bladder and/or urethra, but the present study required the bladder to be refilled after the invasive test. Furthermore, the invasive catheter was used in a subgroup of the patients to compare invasively and non-invasively measured pressures. To keep the population uniform, we left the invasive catheter in the bladder. To differentiate between both measurements, we used the terms invasive and non-invasive despite the fact that in the present study the invasive catheter remained in the bladder during the non-invasive test. Also the rectal catheter, which was installed for the invasive study, was left in place. The external catheter was fitted over the internal catheter and adjusted to the penis. Parafilm was used to secure the fit. The external catheter consisted of an incontinence condom, connected to a tube to guide the urine into a flow meter and a pressure transducer to measure the pressure in the condom. A remotely controlled mechanical valve was fitted over the tube to interrupt the flow rate, see figure 4.1. After filling the bladder, the patient was asked to start voiding through the external catheter. During voiding the flow rate was repeatedly interrupted. The investigator monitored the flow rate signal on a computer screen and interrupted the voiding when a stable value was reached. After reaching a stable pressure reading, the

valve was reopened and flow recommenced. If a new stable flow rate was reached and the bladder was not too empty, another interruption was done. Thus the total number of interruptions depended on the flow rate and voided volume and was different in each patient. A previous study showed that after an interruption of the flow rate the remainder of the voiding was unaffected, thus allowing repeated interruption of the flow rate for reliable measurements of isovolumetric bladder pressure [Craggs et al., 1998; Rikken et al., 1999]. The flow rate value just prior to the interruption was called the interrupt flow rate, $Q_{interrupt}$. During each interruption the external catheter filled with urine and the transducer measured the resulting pressure, which was called the external pressure, p_{ext}.

Non-invasive classification

The external pressure, p_{ext}, the abdominal pressure, p_{abd}, and the flow rate, Q, were recorded and displayed on a computer screen. All pressure transducers were installed at the same height as the pressure transducer of the external catheter, i.e. about 20 cmH_2O below the symphysis pubis. We did not correct the pressure values for this difference in height between the transducers and the symphysis pubis. From the measured flow rate and external pressure signals recorded in one voiding in each patient, we selected the highest external pressure and the preceding interrupt flow rate value for further analysis. During each flow rate interruption, the condom slightly inflated. Upon opening of the valve, this sometimes led to a flow rate overshoot, see for example figure 4.2, middle panel. In the cases that no reliable interrupt flow rate value could be selected due to this effect, the first interrupt flow rate value of the test was used in combination with an external bladder pressure value not necessarily measured during that interruption. We classified the patients in 5 different ways:

I) only using the maximum flow rate, Q_{max}, measured during the invasive test (for future application a free flow rate should be used);

II) using a combination of the interrupt flow rate, $Q_{interrupt}$, and the maximum external pressure, $p_{ext.max}$, measured during the non-invasive test;

III) using a combination of $Q_{interrupt}$ and the difference between the maximum external pressure and the abdominal pressure, $p_{ext.max}$-p_{abd};

IV) using a combination of Q_{max}, and the maximum external pressure, $p_{ext.max}$ (both values measured in separate voidings);

V) using a combination of Q_{max} and the difference between the maximum external pressure and the abdominal pressure, $p_{ext.max}$-p_{abd};

Logistic regression was used to calculate separation lines between non-obstructed and equivocal and between equivocal and obstructed patients. Differences between groups were tested for significance using the Mann-Whitney U-test (SPSS, version 9, SPSS Inc.).

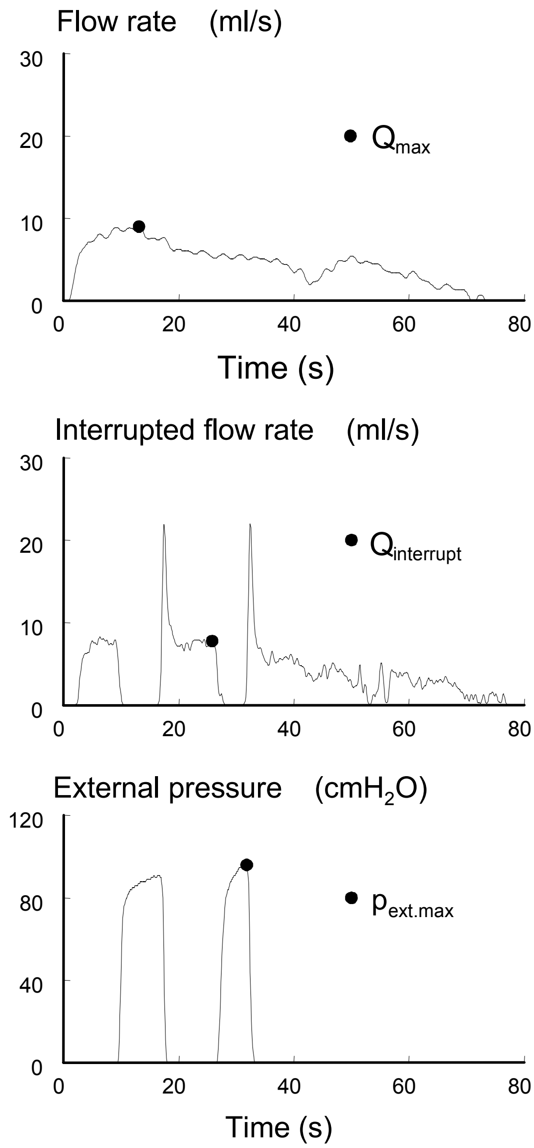

Figure 4.2 *An example of a non-invasive test in a non-obstructed patient. The upper panel shows the flow rate measured during the standard PFS. The middel panel shows the repeatedly interrupted flow rate and the lowest panel the non-invasively measured external pressure in the same patient. The maximum flow rate Q_{max} and the interrupt flow rate $Q_{interrupt}$ were combined with the maximum external pressure $p_{ext.max}$ in the tested non-invasive classification strategies to identify patients with bladder outlet obstruction.*

The patients tested had a wide variety of symptoms and thus flow rates. A number of the patients could correctly be classified on the basis of maximum flow rate alone.

Furthermore, some patients were not able to void without straining, despite our encouragement not to do so. As the abdominal pressure may have a compressing effect on the urethra, effectively increasing its resistance, this could result in a lower external bladder pressure. We re-tested the five strategies in the patients who could not be identified on the basis of maximum flow rate alone and who did not strain during the invasive test. Again logistic regression was used to calculate separation lines to identify non-obstructed from equivocal and equivocal from obstructed patients. We also calculated separation lines between (1) the obstructed and a combined group of non-obstructed and equivocal group and (2) the non-obstructed and a combined group of equivocal and obstructed patients. The reproducibility of these lines was statistically estimated using the Jackknife method [Diaconis and Efron, 1983]. This method proceeds by randomly removing a number of observations from the original data set and recalculating the statistics of interest for each of the thus created data sets.

Table 4.1 *Parameters measured with the standard invasive pressure-flow test and with the non-invasive test in patients stratified in non-obstructed, equivocal and obstructed according to the ICS-nomogram. The number of patients correctly classified using the 5 strategies described in the text is given.*

	Obstructed	Equivocal	Non-obstructed	% correct
Parameters	INVASIVE TEST (mean SD)			
Q_{max} (ml/s)	6 ± 3	8 ± 2	17 ± 13	-
$p_{det.Qmax}$ (cmH_2O)	73 ± 16	48 ± 5	27 ± 11	-
	NON-INVASIVE TEST (mean SD)			
$Q_{interrupt}$ (ml/s)	5 ± 3	9 ± 3	11 ± 9	-
$p_{ext.max}$ (cmH_2O)	108 ± 26	105 ± 20	86 ± 31	-
Strategy	NON-INVASIVE CLASSIFICATION			
I: Q_{max}	15 / 22	6 / 12	14 / 22	63%
II: $Q_{interrupt} / p_{ext.max}$	16 / 22	7 / 12	15 / 22	68%
III: $Q_{interrupt} / (p_{ext.max}-p_{abd})$	11 / 18	4 / 9	16 / 19	67%
IV: $Q_{max} / p_{ext.max}$	14 / 22	9 / 12	18 / 22	73%
V: $Q_{max} / (p_{ext.max}-p_{abd})$	13 / 18	5 / 9	15 / 19	72%

Results

Invasive and Non-invasive test

75 patients underwent standard invasive urodynamic testing. These patients were classified as non-obstructed, equivocal or obstructed according to the provisional ICS method for definition of obstruction. Additionally, all 75 underwent a non-invasive study. In the beginning, we faced some difficulties in correctly applying the condom to the penis of the patient. Leaking of the external catheter occurred in 40% (8) of the first 20 patients. In the 55 patients who were subsequently studied, only 9% (5) of the measurements failed because of leakage. There was thus a definite learning curve for preventing leakage. From the 62 patients that did not leak, 1 patient was not able to void, 2 patients felt uncomfortable during the measurement and in 3 measurements data storage of the non-

invasive signals failed leaving 56 successfully measured patients. The overall success rate, including the first few measurements in which we were totally inexperienced was thus 75%. On the basis of our present experience we expect a future success-rate of 85% (from the 55 patients 1 was not able to void, 2 felt uncomfortable and 5 leaked).

According to the ICS-nomogram, the standard invasive study showed that 22 of the 56 successfully measured patients were non-obstructed (age 62 ± 12; mean ± SD), 12 were equivocal (age 51 ± 16; mean ± SD) and 22 patients were obstructed (age 62 ± 12; mean ± SD). Table 4.1 summarises the results of the invasive and non-invasive tests and the classifications applied to the 56 patients. Figure 4.2 shows an example of the flow rate signal measured in one of the patients during the invasive test (upper panel). In the middle and lowest panel of the same figure, the flow rate and the external pressure signal measured during the non-invasive test in the same patient are shown. This patient was classified as non-obstructed on the basis of the invasive study. The middle panel shows the interrupted flow rate, $Q_{interrupt}$, just before the second interruption of the flow rate to measure the associated, maximum external bladder pressure, $p_{ext.max}$ (lowest panel). In 4 patients the recording of the abdominal pressure failed and in 6 patients the rectal catheter was accidentally removed before the non-invasive test. In the preceding invasive tests, abdominal pressure was successfully recorded in all patients. 10 patients (9 non-obstructed and 1 obstructed) strained during the invasive test.

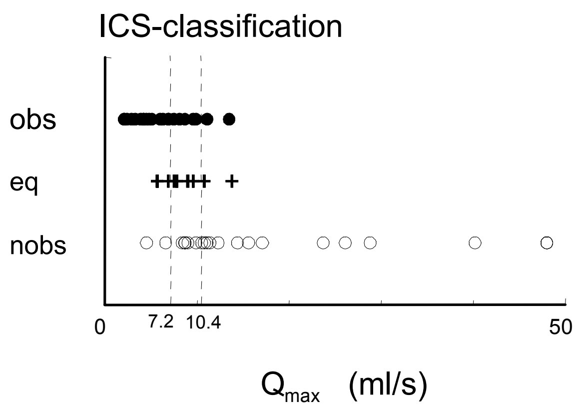

Figure 4.3 *Classification of non-obstructed (nobs, open circles), equivocal (eq, plusses) and obstructed (obs, closed circles) patients on the basis of maximum flow rate alone. The classification lines were calculated using logistic regression.*

Non-invasive classification

In the first strategy, we tested a classification on the basis of Q_{max} alone, see figure 4.3. The open circles are the non-obstructed (nobs), the plusses the equivocal (eq) and the closed circles the obstructed patients. The classification lines calculated using logistic regression correctly identified 62% of the 56 patients, see table 4.2. In the second strategy, we plotted for each patient $p_{ext.max}$ versus $Q_{interrupt}$, see figure 4.4, upper panel. Logistic regression was used to calculate separation lines between non-obstructed and equivocal and equivocal and obstructed patients. On the basis of the two classification lines thus calculated, we found that 68% of the patients could be correctly classified. The equivocal zone was delineated by crossing lines.

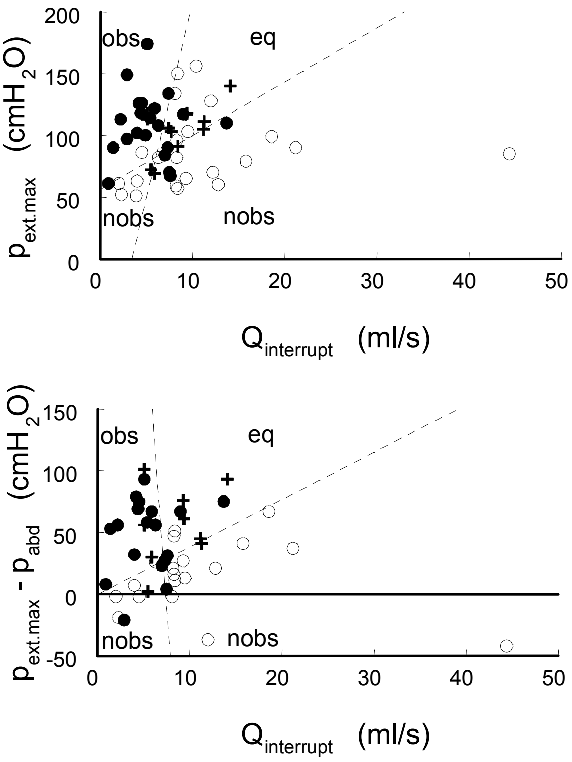

Figure 4.4 *The upper panel shows the maximum external pressure plotted as a function of the interrupt flow rate (strategy II). In the lower panel, the abdominal pressure was subtracted from the maximum external pressure and plotted as function of the interrupt flow rate (strategy III). In both panels, classification lines were calculated to separate obstructed from equivocal patients and equivocal from non-obstructed patients using logistic regression, see also table 4.1.*

In the third strategy, we subtracted from the maximum external bladder pressure the corresponding abdominal pressure. In figure 4.4, lower panel, we plotted $Q_{interrupt}$ versus $p_{ext.max}$-p_{abd}. We found that 10 patients strained during the invasive test of which 9 were non-obstructed and 1 obstructed according to the invasive test. In these patients $p_{ext.max}$-p_{abd} was negative (sometimes down to -40 cmH_2O). In the fourth strategy, we combined Q_{max} and $p_{ext.max}$, see figure 4.5, upper panel. On this basis, 73% of the patients could correctly be classified and the equivocal zone was not defined by crossing lines. In the fifth strategy, we again subtracted from the maximum external bladder pressure the corresponding abdominal pressure but now plotted Q_{max} versus $p_{ext.max}$-p_{abd}, see figure 4.5, lower panel.

Including the abdominal pressure in the third and fifth strategy did not improve the accuracy of the test compared to the associated second and fourth strategy. 63% of the patients could correctly be classified by maximum flow rate alone, a relatively large group.

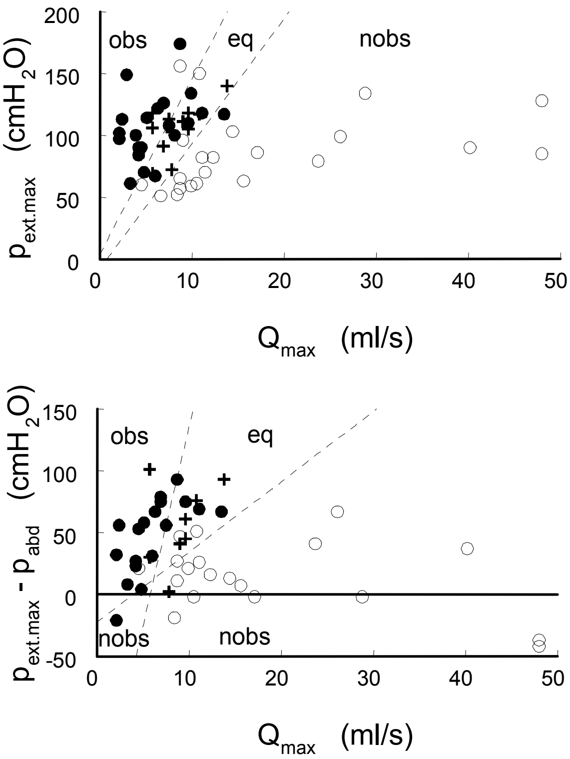

Figure 4.5 *The upper panel shows the maximum external pressure plotted versus the maximum flow rate (strategy IV). In the lower panel, the abdominal pressure was subtracted from the maximum external pressure and plotted versus the maximum flow rate (strategy V). The classification lines were calculated using logistic regression to separate obstructed from equivocal patients and equivocal from non-obstructed patients, see also table 4.1.*

However, a 100% correct identification on the basis of maximum flow rate alone (thus no overlap between groups) was only possible in 30% of the patients in this population: all patients with Q_{max} < 4.5 ml/s were obstructed (8 cases) and all patients with Q_{max} > 13.8 ml/s were non-obstructed (9 cases). To identify BOO in the remaining 70% of patients, measurement of bladder pressure is necessary. We re-calculated the 5 strategies in the patients who did not strain and who could not be classified with 100% certainty on the basis of maximum flow rate alone, thus all patients with 4.5 ml/s ≤ Q_{max} ≤ 13.8 ml/s. Table 4.2 summarises the invasive and non-invasive test results of this subgroup of 36 patients. As expected, the overall success-rate in strategy I dropped from 63% to 38%. Surprisingly, it did not improve in strategy II, III, IV and V. Figure 4.6 shows the classification lines calculated in strategy II (crossing lines, upper panel) and strategy IV (lower panel). Finally, we calculated a separation line between (1) the obstructed group versus the combined equivocal and non-obstructed group and (2) a combined obstructed and equivocal group versus the non-obstructed group. Since previously no improvement was found when the abdominal pressure was included, we only re-calculated classification strategy II and IV.

The standard deviation of the separation lines was calculated using the Jackknife method. This method proceeds by randomly removing a number of observations from the original data set. We chose to create 12 subgroups of 33 patients by removing 12 times randomly 3 observations from the 36 patients. Using logistic regression we recalculated for these 12 truncated data sets the overall success-rates. The mean and standard deviations of these values are summarised in table 4.2. In figure 4.7, upper panel, we plotted the 12 classification lines using combination (1) in strategy II. Using this strategy, the obstructed patients were identified best (77%). In figure 4.7, lower panel, we again plotted the 12 classification lines, now using combination (2) in strategy IV. In this way, the best overall identification was found (90 ± 3%).

Table 4.2 *Parameters measured with the standard invasive pressure-flow test and with the non-invasive test in a subgroup of patients, who had a maximum flow rate between 4.5 ml/s and 13.8 ml/s, stratified in non-obstructed, equivocal and obstructed according to the ICS-nomogram. The number of patients correctly classified using the five strategies described in the text is given.*

		Obstructed	Equivocal	Non-obstructed		% correct
Parameters		INVASIVE TEST (mean ± SD)				
Q_{max} (ml/s)		8 ± 3	8 ± 2	9 ± 2		-
$p_{det.Qmax}$ (cmH_2O)		76 ± 17	48 ± 5	28 ± 9		-
		NON-INVASIVE TEST (mean ± SD)				
$Q_{interrupt}$ (ml/s)		6 ± 3	8 ± 3	8 ± 3		-
$p_{ext.max}$ (cmH_2O)		113 ± 27	105 ± 20	68 ± 14		-
Strategy		NON-INVASIVE CLASSIFICATION				
I: Q_{max}		8 /14	0 / 12	6 / 10		38%
II: $Q_{interrupt}$ / $p_{ext.max}$		10 / 14	8 / 12	8 / 10		72%
III: $Q_{interrupt}$ / ($p_{ext.max}$–p_{abd})		8 / 12	5 / 9	7 / 8		69%
IV: Q_{max} / $p_{ext.max}$		8 / 14	8 / 12	9 / 10		69%
V: Q_{max} / ($p_{ext.max}$–p_{abd})		8 / 12	5 / 9	6 / 8		66%
		COMBINED GROUPS (mean ± SD)				
Strategy	obs+eq	nobs	%	obs	eq+nobs	%
II: $Q_{interrupt}$ / $p_{ext.max}$	22 / 26	9 / 10	86 ± 2%	11 / 14	17 / 22	77 ± 3%
IV: Q_{max} / $p_{ext.max}$	23 / 26	9 / 10	90 ± 3%	10 / 14	15 / 22	67± 4%

Discussion

Urodynamic pressure-flow analysis is a standard invasive procedure to investigate dysfunction of the lower urinary tract. Previous studies showed, that for diagnosing one of the most frequent voiding disorders, BOO, the maximum flow rate and the isovolumetric bladder pressure can also be used [van Mastrigt and Kranse, 1995; Comiter et al., 1996]. In the present study, we developed a classification strategy to assess bladder outlet obstruction in male patients on the basis of a non-invasively measured isovolumetric bladder pressure combined with a flow rate measurement. We started the study with 75 patients to test whether non-invasive identification of BOO in male patients was feasible. After gaining experience with the non-invasive measurements, we tested 5 classification strategies in 56 patients.

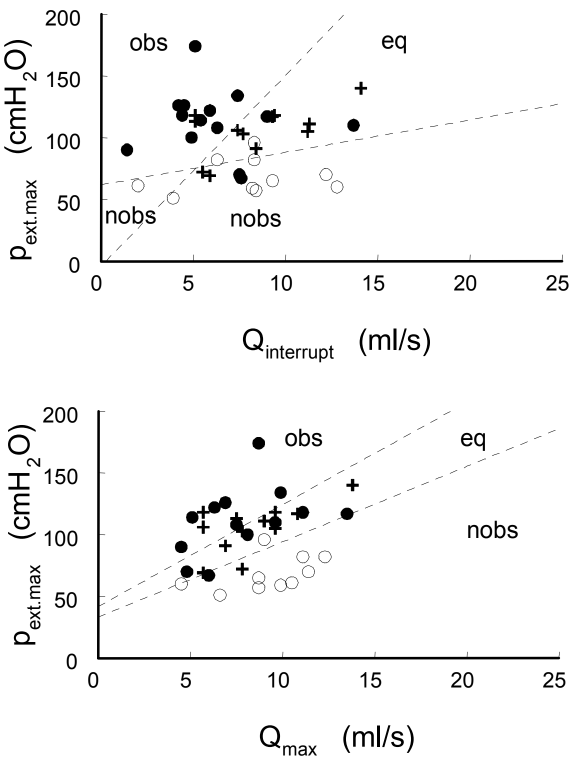

Figure 4.6 *The upper panel shows the external pressure plotted as a function of the interrupt flow rate (strategy II) measured in the subgroup of patients who did not strain and with maximum flow rates between 4.5 ml/s and 13.8 ml/s. In the lower panel, the maximum external pressure is plotted versus the maximum flow rate (strategy IV) in the same subgroup of patients. Again, classification lines were calculated using logistic regression to separate obstructed from equivocal patients and equivocal from non-obstructed patients, see table 4.2.*

The patient population selected for the non-invasive test had a wide variety of urological symptoms ranging from BOO to incontinence. Due to this variety, a relatively wide range of maximum flow rates was found. 63% of the patients could be classified as obstructed, equivocal or non-obstructed by the maximum flow rate alone (strategy I). Despite our encouragement not to strain during voiding, 10 patients still did. 9 of these were classified as non-obstructed on the basis of the invasive test and most were diagnosed as incontinent. In these patients the straining led to a negative difference between the non-invasively measured bladder pressure and the abdominal pressure (strategy III and V).

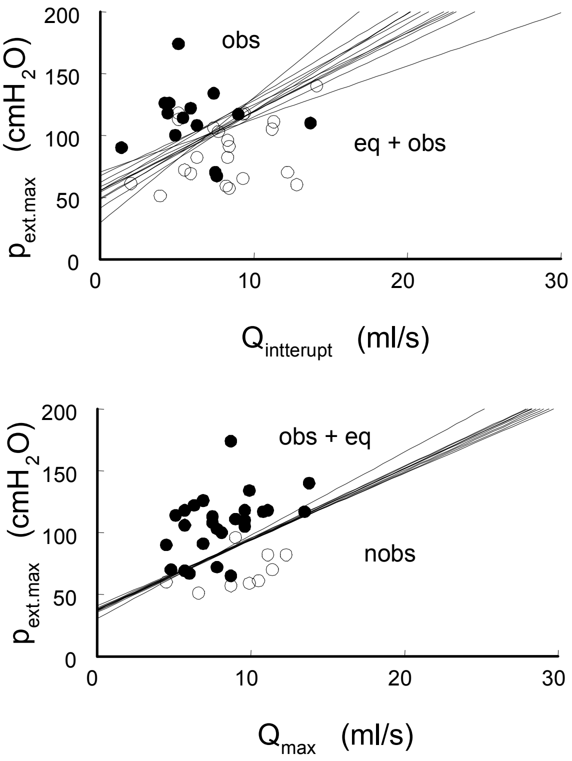

Figure 4.7 *12 different subgroups of patients were formed according to the Jackknife method and in each subgroup a classification line was calculated using logistic regression. The upper panel shows all 12 lines separating the combined non-obstructed and equivocal group best from the obstructed group using strategy II (overall success-rate: 77% ± 3%; mean ± SD). The lower panel shows all 12 lines separating the non-obstructed group best from the combined equivocal and obstructed group using strategy IV (overall success-rate: 90% ± 3%; mean ± SD), see table 4.2.*

The relatively high abdominal pressures were obviously not reflected in the pressure measured in the condom. In previous studies, authors reported that abdominal straining in men with lower urinary tract symptoms does not appear to have any effect on the maximum flow rate [Jensen et al., 1983; Reynard et al., 1995], whereas others found that straining did increase the maximum flow rate in cases of anterior urethral stricture or stress incontinence [Hasegawa et al., 1983]. At first sight, straining increases the abdominal pressure and therefore the pressure in the bladder (intravesical pressure), and not the pressure at the meatus. Hence, it increases the pressure difference over the urethra. However, the abdominal pressure may also have a compressing effect on the urethra, effectively increasing its resistance. Therefore, the effect of straining on voiding may differ between patients and especially, may depend on the location of the obstruction. We found that straining in our patients mainly had a compressing effect on the urethra, which resulted in bad coupling between bladder and condom. We therefore conclude that the non-invasive test should be done in non-straining patients only.

As mentioned, the tested population comprised patients with a variety in maximum flow rates. All patients voiding with maximum flow rate lower than 4.5 ml/s in this population were obstructed and all those voiding with maximum flow rate higher than 13.8 ml/s were non-obstructed. We also applied the 5 classification strategies in the subgroup of patients who did not strain and who could not be identified on the basis of flow rate alone. The results of the invasive and non-invasive tests in this subgroup are summarised in table 4.2. The percentage correctly classified patients on the basis of Q_{max} alone (strategy I) dropped from 63 to 38%. This illustrates the necessity of combining flow rate and bladder pressure for identification of BOO. The best classification was found using strategy II (72%). This relatively low overall success-rates found is caused by the poor classification of the equivocal patients (see strategy II to V). In most strategies, the equivocal zones were delineated by crossing lines indicating that this zone cannot be uniquely defined on the basis of non-invasively measured parameters. A comparative study [Pel and van Mastrigt, 1999a] showed that the accuracy of the non-invasive bladder pressure measurement depended uniquely on the degree of obstruction of the patient. $P_{ext.max}$ values measured in the group of non-obstructed patients equalled the simultaneously invasively measured pressure values but those in the group of obstructed patients were too low. However, these pressures were still significantly higher than the pressures measured in the non-obstructed patients. That study was performed in a subgroup of the patients of the present study and the present group was still of comparable age range and had similar symptoms and voiding mechanics. Again, the $p_{ext.max}$ values measured in the equivocal as well as in the obstructed group were significantly higher than those in the non-obstructed group (Mann-Whitney U-test: $p < 0.05$), but no significant difference was found between the pressures measured in the equivocal group and the obstructed group. We therefore combined the equivocal patients with (1) the non-obstructed patients and (2) the obstructed patients, see table 4.2. We re-tested strategy II and IV only, since addition of the abdominal pressure did not seem to improve the earlier classifications. The best identification of obstructed patients (11 of 14) was found using combination (2) in strategy II. The best overall success-rates were found using combination (1) in strategy II and IV (86% and 90% respectively). This non-invasive classification of BOO in non-straining patients with maximum flow rates between 4.5 ml/s and 13.8 ml/s in two classification areas was better than classification on the basis of Q_{max} alone.

In strategy II, the interrupt flow rate value is combined with the externally measured bladder pressure. The investigator interrupted the flow rate at the moment it had stabilised. This value is not necessarily the same as the maximum flow rate value. The accuracy of this strategy thus depended on the investigator and it may therefore be expected that this strategy is less reproducible than strategy IV. The best overall success-rate was found using strategy IV. Figure 4.8 illustrates a proposal for a two steps classification strategy of the 46 patients who did not strain during the test. The equivocal patients were combined with the obstructed patients (closed circles). In this two step approach, a first classification is done on the basis of maximum flow rate alone: 7 obstructed patients voided with Q_{max} < 4.5 ml/s and 3 non-obstructed patients voided with Q_{max} > 13.8 ml/s. In the remaining 36 patients the maximum flow rate is considered together with the measured bladder pressure. 32 of the 36 patients with 4.5 ml/s ≤ Q_{max} ≤ 13.8 ml/s are correctly assigned to a non-obstructed area and a combined equivocal and obstructed area. As the ICS report [Abrams et al., 1988] stated that the equivocal group might include unrepresentative micturitions in either obstructed or non-obstructed patients, or underactive detrusor function with or without obstruction, the combined equivocal and obstructed area may prevent false negative identification of the tested patients.

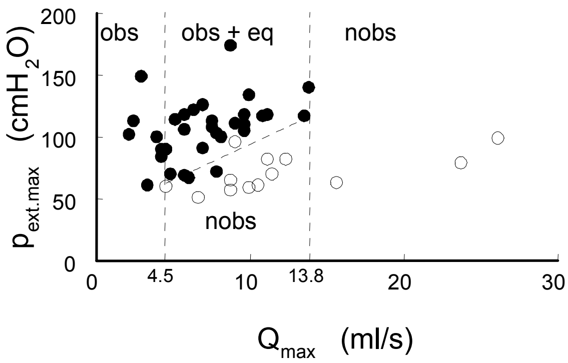

Figure 4.8 *The maximum external pressure was plotted versus the maximum flow rate in 46 patients who did not strain. 12 of 13 non-obstructed patients and 30 of 33 combined equivocal and obstructed patients are correctly classified using a two step approach: patients with a Q_{max} < 4.5 ml/s or Q_{max} > 13.8 ml/s are diagnosed on the basis of the flow rate measurement alone. The remaining patients are classified using a combination of maximum flow rate and a separately measured external bladder pressure.*

The present study required the bladder to be refilled shortly after the invasive test, but for future application, no catheters need to be inserted into bladder and/or urethra. Firstly a flow rate measurement and depending on the maximum flow rate secondly a non-invasive measurement of the bladder pressure must be done. In between these measurements, the bladder needs to fill naturally. Future patients with suspected (prostatic) obstruction or underactive detrusor might be classified non-invasively using the classification areas presented. For a general application, these areas should be recalculated in a large group of patients at different institutes.

Conclusions

We succeeded in developing a technique to correctly measure the bladder pressure with an external catheter. Leakage of the external condom catheter occurred in 40% (8) of the first 20 studied patients and only in 9% (5) of the remaining 55 patients. It was shown that straining must be avoided during the non-invasive test. A combination of a maximum flow rate and a separately measured maximum external bladder pressure best classified our male population. 12 of 13 non-obstructed patients and 30 of 33 combined equivocal and obstructed patients could be identified. This strategy depends on the patient population studied, and should be re-tested in a larger patient population at different institutes. We conclude that a non-invasive identification of bladder outlet obstruction based on an isovolumetric bladder pressure measured with an external catheter and a separately measured maximum flow rate is feasible in the male patient population.

5

A FLOW RATE CUT OFF VALUE AS A CRITERION FOR ACCURATE MEASUREMENT OF NON-INVASIVE BLADDER PRESSURE

Adapted from:
Pel JJM and van Mastrigt R (2001) Submitted to Urology.

Abstract

We developed an external condom catheter to non-invasively measure the bladder pressure during an interruption of voiding. In a previous study, it was concluded that the accuracy of this pressure measurement depended on the urethral resistance of the patient. The aim of the present study was to develop a non-invasive criterion to predict the accuracy of the non-invasive pressure measurement. In a previous study, we simultaneously measured the bladder pressure (invasively) and the condom pressure (non-invasively). To this end, an external condom catheter was fitted over a transurethral catheter. The flow rate was repeatedly interrupted to measure the bladder pressure non-invasively. We reanalysed these measurements and calculated the mean difference between the bladder pressure and the condom pressure. The cumulative percentage of patients that fell within 1 standard deviation of this mean pressure difference was plotted as a function of the flow rate value at interruption. The mean pressure difference in the combined group of non-obstructed and equivocal patients was 9 ± 13 cmH_2O; mean ± SD. In 80% of the tested patients, the condom pressure accurately reflected the bladder pressure. In this group the flow rate before interruption exceeded 5.4 ml/s. To successfully measure the bladder pressure non-invasively, the patient must have a flow rate exceeding 5.4 ml/s, the flow rate must be interrupted near the maximum flow rate, the flow rate must be continuous and the patient must avoid straining while voiding.

Introduction

At present, an invasive pressure flow study is necessary to diagnose bladder outlet obstruction (BOO) in patients with lower urinary tract symptoms (LUTS). The invasiveness of the test limits clinical application, especially in patients with symptoms of benign prostatic hyperplasia (BPH). We developed an external condom catheter to non-invasively measure the bladder pressure, avoiding the risk of damaging or infecting the urethral wall [van Mastrigt and Pel, 1999]. This catheter consists of an incontinence condom connected to an outflow tube and pressure transducer. A pneumatic valve is fitted over the outflow tube to remotely interrupt the flow rate. A patient starts voiding through condom and tube into a flow meter. During voiding, the flow rate is repeatedly interrupted by closing the valve, resulting in a pressure increase in the condom to a maximum value. In theory, this maximum condom pressure is equal to the bladder pressure when the bladder neck is open.

In a previous study it was shown that the accuracy of the non-invasive pressure measurement depended on the urethral resistance of the patient [Pel and van Mastrigt, 1999a]. The aim of the present study was to develop a criterion that predicts the accuracy of a non-invasive pressure measurement on the basis of the flow rate of the patient. In a pilot study it was shown that interruption of the flow rate induces the risk of premature detrusor inhibition or sphincter contraction [Pel and van Mastrigt, 1999c]. The time necessary to reach the maximum pressure in the condom depends on the flow rate. When the flow rate at the moment of interruption is high, the condom quickly fills with urine. A too low flow rate at the moment of interruption prolongs the pressure measurement in the condom, which could thus result in an unreliable pressure reading. We reanalysed a group of patients in whom we simultaneously measured the pressure in the condom with the external catheter and the bladder pressure with an invasive catheter.

Materials and methods

Data, measured in a group of 56 patients during an invasive and non-invasive urodynamic test from an earlier study [Pel et al., 2001] was re-analysed. The patients were stratified in a group of non-obstructed and a group of equivocal and obstructed patients according to the provisional ICS method for definition of obstruction [Griffiths et al., 1997]. During the non-invasive test, the bladder pressure was measured using an incontinence condom (Rochester®) guided over the invasive catheter and attached to the penis with laboratory film. A tube was connected to the outflow opening of the condom to guide the urine into a flow meter (Dantec®). A pneumatic valve was fitted over this tube, to interrupt the flow rate. A pressure transducer, installed at the level of the external catheter, recorded the pressure in the condom when the flow rate was interrupted. After filling the bladder through the invasive catheter, this catheter was connected to a pressure transducer to measure the internal bladder pressure, p_{int}, simultaneously with the external pressure in the condom, p_{ext}. The flow rate just prior to the interruption was called the interrupt flow rate,

$Q_{interrupt}$. The patients were encouraged not to strain during both the invasive and non-invasive test.

From the flow rate and pressure signals measured in one voiding in each patient, we selected the highest condom pressure value, the corresponding internal pressure and the preceding interrupt flow rate value for further analysis. During each flow rate interruption, the condom slightly inflated. Upon opening of the valve, this sometimes led to a flow rate overshoot, see for example figure 5.1, upper panel. When no reliable interrupt flow rate value could be selected due to this effect, the first interrupt flow rate of the test was used in combination with a condom pressure value not necessarily measured during that interruption.

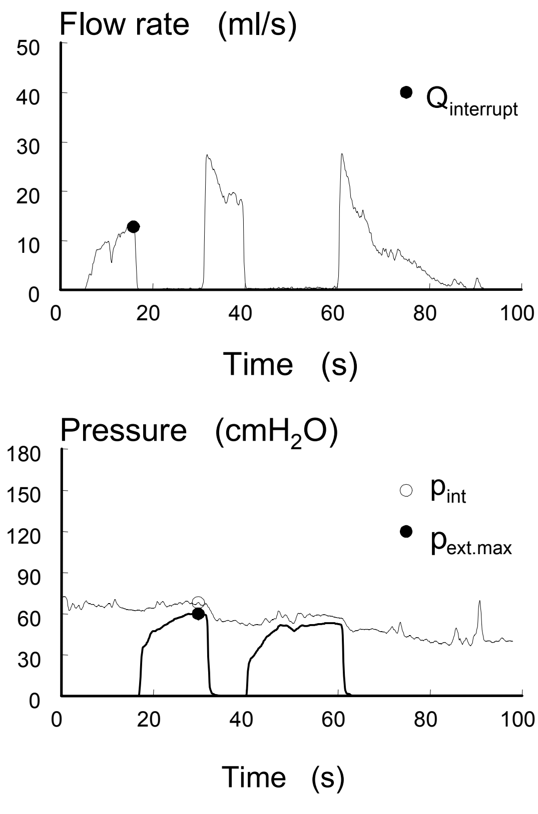

Figure 5.1 *The flow rate (upper panel) and the simultaneously measured bladder pressure (thin line; transurethral catheter) and condom pressure (thick line; external catheter) in a non-obstructed patient. The maximum condom pressure and bladder pressure are low and correlate well. The interrupt flow rate is about 13 ml/s.*

To calculate a minimum flow rate value at which a non-invasive pressure measurement is reliable, we plotted the difference between the invasively and non-invasively measured pressure as a function of the interrupt flow rate. The mean ± 1 standard deviation (SD) of the pressure difference in the combined group of equivocal and non-obstructed patients was selected as reliability interval. The flow rate cut off value was calculated on the basis of the percentage of correctly measured patients that fall inside this interval.

Results

Despite the encouragement not to strain during voiding, 10 of the 56 patients tested did strain during both tests. In 3 patients, the simultaneous internal bladder pressure measurement failed, leaving 43 patients for further analysis. According to the ICS-nomogram, the standard invasive study showed that 13 patients were non-obstructed, 10 were equivocal and 20 patients were obstructed.

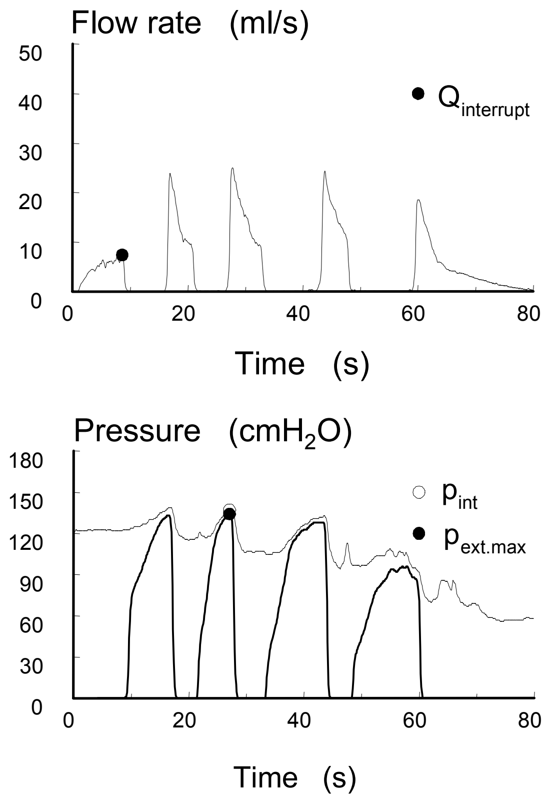

Figure 5.2 *The flow rate (upper panel) and the simultaneously measured bladder pressure (thin line; transurethral catheter) and condom pressure (thick line; external catheter) in an obstructed patient. The maximum condom pressure and bladder pressure are high and correlate well. The interrupt flow rate is about 8 ml/s.*

Figure 5.1 is an example of a typical measurement using the external condom catheter. The upper panel is the flow rate and the lower panel the simultaneously measured bladder pressure and condom pressure. The flow rate at the moment of interruption was about 13 ml/s. During the first interruption the highest pressure in the condom (~63 cmH_2O) was measured. This pressure value corresponded well with the simultaneously measured bladder pressure (~70 cmH_2O). This patient was classified as non-obstructed.

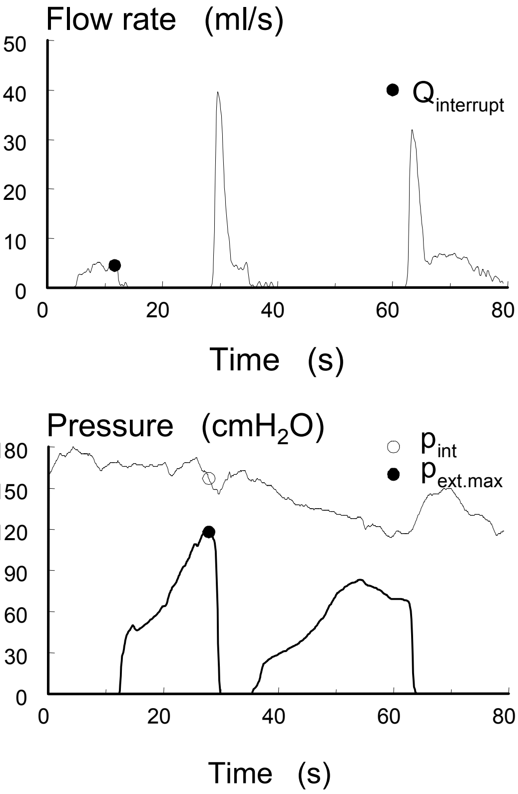

Figure 5.3 *The flow rate (upper panel) and the simultaneously measured bladder pressure (thin line; transurethral catheter) and condom pressure (thick line; external catheter) in an obstructed patient. The maximum condom pressure and bladder pressure are high and don't correlate well. The interrupt flow rate is about 4 ml/s.*

Figure 5.2 is an example measured in an obstructed patient. The flow rate was first interrupted at about 7 ml/s. The highest pressure in the condom, measured during the second interruption, again corresponded well with the bladder pressure (both values ~135 cmH_2O) and both were much higher than those measured in the non-obstructed patient in figure 5.1. Figure 5.3 shows less agreement between the condom pressure (~120 cmH_2O) and the bladder pressure (~160 cmH_2O). This example was also measured in an obstructed patient, but the $Q_{interrupt}$ of this patient of about 4 ml/s was lower than that measured in figure 5.2. Upon interruption of the flow rate, the pressure in the condom increased slowly. At reopening of the valve, the pressure difference between bladder and condom was about 40 cmH_2O. During the second interruption, both pressures even decreased.

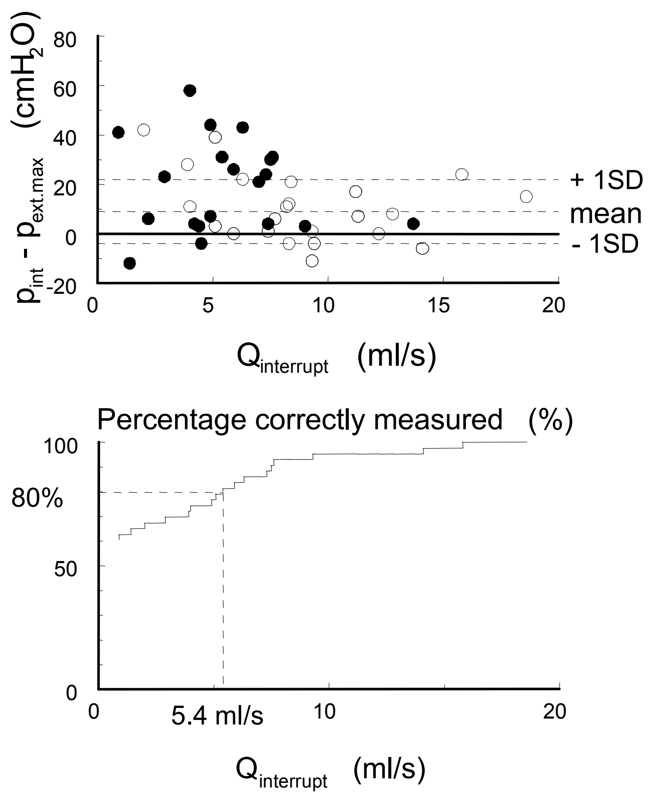

Figure 5.4 *The difference between the bladder pressure and the condom pressure measured in non-obstructed and equivocal patients (open circles) and obstructed patients (closed circles) as a function of the interrupt flow rate (upper panel). In the lower panel, the successive improvement in accuracy of the condom pressure measurement is plotted against the increasing flow rate.*

To derive a criterion for the accuracy of the non-invasive measurement method, we plotted for the combined non-obstructed and equivocal patients (open circles) as well as the obstructed patients (closed circles) p_{int}-$p_{ext.max}$ as a function of $Q_{interrupt}$, see figure 5.4, upper panel. The mean pressure difference in the combined group of non-obstructed and equivocal patients was 9 ± 13 cmH_2O; mean ± SD and that in the group of obstructed patients was 19 ± 19 cmH_2O. The former interval of ± 1 SD was also plotted in this figure. In the lower panel, the cumulative percentage of patients that fell within 1 standard deviation of this mean was plotted as a function of $Q_{interrupt}$. Thus, seen from right to left, every time a symbol fell outside the range of 1 SD, the percentage correctly measured patients decreased. This figure thus shows the successive improvement in accuracy of the non-invasive bladder pressure measurement when the flow rate through the external catheter increases. When the interrupt flow rate was higher than 5.4 ml/s, the condom pressure accurately reflected the bladder pressure in the combined non-obstructed and equivocal patients and the obstructed patients.

Discussion

The external catheter was developed to non-invasively measure the bladder pressure during a mechanical interruption of voiding. During this interruption, the condom fills with urine until equilibrium exists between the pressure in the condom and the bladder pressure. In figure 5.1 (non-obstructed patient) and figure 5.2 (obstructed patient), the maximum condom pressure and the associated bladder pressure correlate well. Compared to the non-obstructed patient, the pressures measured in the obstructed patient are high and the flow rate is low because of the higher urethral resistance. In theory, upon interruption of the flow rate, the shortening velocity of the bladder wall reduces to zero. The bladder contraction becomes isometric. The relation between the bladder pressure and shortening velocity of the bladder wall is described by a hyperbolic curve, known as the Hill equation [Hill, 1938]. Thus when the shortening velocity of the bladder wall decreases, the bladder pressure should increase. In figure 5.1, a slight increase in bladder pressure upon flow rate interruption can be seen. The pressures are relatively small, which indicates that this patient voids with a weakly contracting bladder. In figure 5.2, the predicted increase in bladder pressure was clearly measured upon repeated interruption of the flow rate.

When the flow rate is low, the time necessary to pressurise the condom becomes longer, see figure 5.3. This sometimes leads to detrusor inhibition or premature sphincter contraction. Although the condom pressure reached quite a high value in figure 5.3, there still was a pressure difference of 40 cmH_2O between the bladder pressure and the condom pressure when the valve was reopened, resulting in an unreliable non-invasive pressure reading. It was the aim of this study to define a flow rate cut off value for this unreliability. We calculated that when the interrupt flow rate exceeded 5.4 ml/s the pressure in the condom accurately reflected the bladder pressure. This result did not depend on whether or not a patient is obstructed or non-obstructed. For a successful non-invasive pressure measurement, therefore, first the free flow rate of the patient should be measured. If the maximum flow rate exceeds 5.4 ml/s, the flow is continuous and the patient voids without straining, a non-invasive measurement of the bladder pressure can be done. During such a measurement, the flow rate is best interrupted near its maximum value, when the detrusor is most probably fully activated.

To overcome the problem of sphincter contraction and detrusor inhibition, we developed a variable outflow resistance catheter [Pel and van Mastrigt, 2001]. Using this catheter, the isovolumetric bladder pressure is estimated without complete interruption of the flow rate. The accuracy of this technique also depends on pressure transmission from the bladder to the condom by the urine voided. Therefore, the flow rate cut off value of 5.4 ml/s also applies to this variable outflow resistance catheter.

Conclusions

The bladder pressure can be measured non-invasively during interruption of the flow rate using an external condom catheter. As the interruption of flow sometimes causes a premature sphincter closure or bladder inhibition, the measured pressure is sometimes unreliable. In the present study we calculated a flow rate cut-off value. When the interrupted flow rate exceeded 5.4 ml/s, the condom pressure accurately reflected the bladder pressure in the tested population.

6

DEVELOPMENT OF A LOW COST FLOW METER TO GRADE THE MAXIMUM FLOW RATE

Adapted from:
Pel JJM and van Mastrigt R (2001). Accepted for publication in Neurourology & Urodynamics.

Abstract

We developed an inexpensive flow meter to grade the maximum flow rate of individuals at locations other than the clinical setting. This flow meter consists of a funnel connected to a collecting tube with a number of exit ports. Urine, directed into this tube, flows through one or more ports and is collected in a measuring cup to measure the voided volume. The number of ports emitting the liquid is a measure for the flow rate. We made four experimental models to test and compare some of the physical properties. One of these models was selected as a prototype and was tested in 5 healthy volunteers. All volunteers voided repeatedly in a standard rotating disc flow meter and in this prototype to test its accuracy. The response time of the experimental models depended on the outlet resistance of the exit ports and the volume of the collecting tube. In two models, this time was comparable to that of currently used volume based electronic flow meters (~2s). In healthy volunteers, the maximum flow rates graded with the selected prototype and that measured with the rotating disc flow meter showed good agreement (difference = 0.4 ± 2.6 ml/s; mean ± SD). The low cost flow meter may be used to repeatedly grade the maximum flow rate at private and familiar locations (for example at home), which may increase the accuracy of evaluating the urinary stream in patients with LUTS.

Introduction

Flow rate measurements are the most frequently used diagnostic tool to evaluate the urinary stream in patients with lower urinary tract symptoms (LUTS). These measurements are commonly used to characterise the flow rate by its maximum value, the shape of the curve and the amount of voided urine [van de Beek et al., 1997]. Flow rate measurements are simple, non-invasive and patient-friendly and a wide diversity of flow meters exists [Ryall and Marshall, 1983]. Due to the costs involved, most of these are only used in the clinic. As a result, the evaluation of the urinary stream is usually based on one flow rate measurement in a patient. It was shown in previous studies that to obtain reliable maximum flow rate values more than one flow rate measurement needs to be done [Sonke et al., 1999; Gurevitch et al., 1999]. Others reported that different voiding positions result in variations in flow rate measurements [Yamanishi et al., 1999], which emphasises the fragility of evaluating the urinary stream on the basis of one or a few recordings. These findings underline that the introduction of a simple and cheap flow meter could lower the threshold for uroflowmetry and could enhance its accuracy by enabling repetitive measurements.

About 50 years ago, a non-electronic device to quantify the flow rate was proposed, consisting of a cylinder, mounted above a larger cylinder divided into 5 compartments [Drake and Camden, 1954]. Holes were made in the cylinder to guide the urine into the different compartments. A normal flow rate was defined by the presence of urine in all the chambers. Recently, a similar, low cost and easy access device to self-test urinary flow rates was introduced [Currie, 1998]. It consists of a plastic cup with an exit port and an indication line to quantify if the maximum flow rate exceeds 12 ml/s or not. For a flow rate measurement with a low cost device, we developed a flow meter with a large number of well-defined exit ports, to actually grade the maximum flow rate in a large number of classes. A mathematical model was developed to calculate the physical properties of this device. The model simulates the flow rate through the new flow meter and is described in the appendix. We verified the predictions of this design tool, by constructing four experimental models. From these models, we selected one as a prototype for a test in 5 healthy volunteers. All voided privately and repeatedly in a Dantec® rotating disc flow meter and in the prototype to test its accuracy in practice.

Materials and methods

The flow meter consists of a funnel connected to a collecting tube, see figure 6.1 for a schematic drawing. The collecting tube contains an exit port at the underside and a number of exit ports in the sidewall, all with a certain outlet resistance. Urine directed into the funnel is collected in the collecting tube and exits through one or more ports: the higher the flow rate voided into the funnel, the more exit ports emit the urine. During voiding the number of Ports Emitting the Liquid (PEL) will increase to a maximum value. Under a number of conditions (to be discussed further on), this maximum number of ports, PEL_{max}, is a measure for the maximum flow rate. The models used in the present study contained 1 exit port at the underside and 7 exit ports in the sidewall and were placed in a measuring cup to measure the voided volume. PEL_{max} was visually established during all tests.

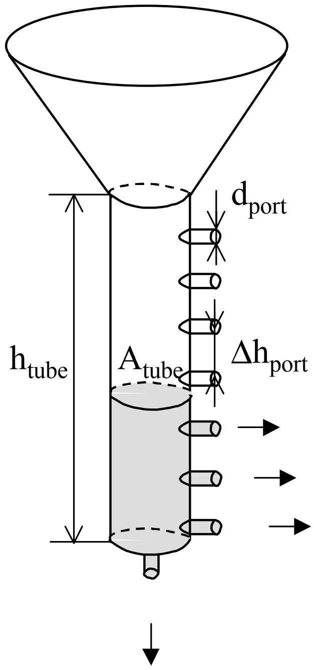

Figure 6.1 *A schematic drawing of the funnel, the collecting tube and the exit ports of the low cost flow meter, see also table 6.1.*

Experimental tests

The accuracy of grading the maximum flow rate by the low cost flow meter depends on the flow rate uncertainty interval associated with each exit port (see also the appendix) and the delay time caused by filling the collecting tube with urine, the response time. To experimentally verify the influence of the outlet resistance of the exit ports and the volume of the collecting tube, we constructed four different experimental models, see table 6.1 for the physical properties applied.

Table 6.1 *Overview of the physical properties of four experimental models of the low cost flow meter, see also the schematic drawing in figure 6.1.*

	h_{tube} (mm)	A_{tube} (mm^2)	d_{port} (mm)	Δh_{port} (mm)
model 1	120	500	2.16	14
model 2	120	500	2.80	14
model 3	120	125	2.16	14
model 4	120	125	2.80	14

with, h_{tube}, the height and A_{tube}, the area of the collecting tube, d_{port}, the inner diameter of each exit port and Δh_{port}, the distance between two exit ports.

To measure the response time, we applied stepwise flow rate changes to the four models using a flow generator. The outflow from each model was led into a calibrated [Kranse and Van Mastrigt, 1995] Dantec® rotating disc flow meter (21K02 Uroflow transducer). From the output signal of this electronic flow meter, the response time of each experimental model, $t_{95\%}$, defined as the time needed to reach 95% of the flow rate value applied, was calculated using a Matlab® program.

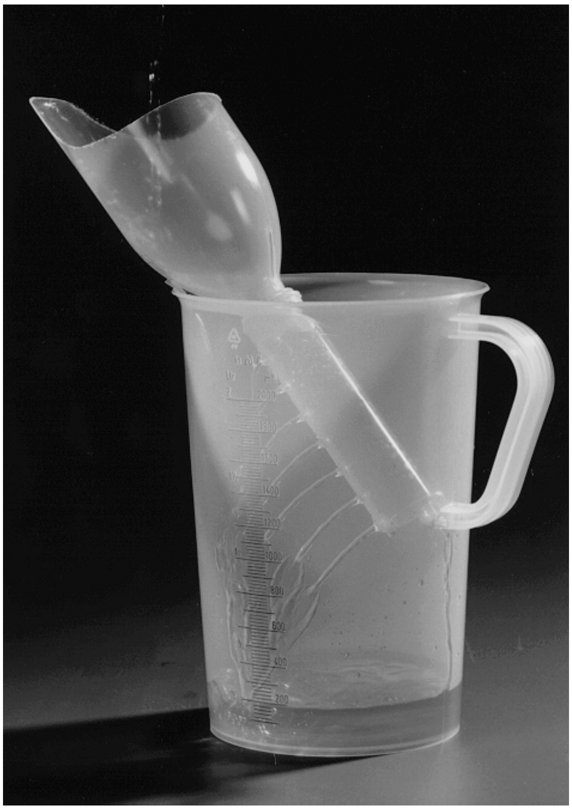

Figure 6.2 *A self-made prototype of the low cost flow meter with the dimensions of experimental model 2 (see table 6.1) to grade the maximum flow rate. The funnel and collecting tube are placed in a measuring cup to measure the voided volume.*

To calibrate each experimental model, we applied different constant flow rates again using the flow generator. By observing the PEL at each flow rate, borderlines of the flow rate uncertainty interval associated with each exit port were established. We calculated the flow rate value in the middle of the uncertainty interval of each exit port, see also the appendix. In this way, we constructed a calibration plot, showing for each PEL_{max} a corresponding Q_{tube}, i.e. we graded the maximum flow rate, Q_{max}, on the basis of PEL_{max}.

Test in volunteers

We constructed a prototype of the low cost flow meter with the dimensions of experimental model 2, see figure 6.2. We tested this prototype in 5 healthy male volunteers. All repeatedly voided in the rotating disc flow meter and in the prototype to test its accuracy. For analysis, the flow rate signal of the rotating disc flow meter, Q_{rota}, was plotted on a PC-screen. The maximum flow rate, $Q_{rota.max}$, was verified. Q_{tube} was determined from PEL_{max} using the calibration plot. Previous study showed that the flow rate of an individual depends on the voided volume [von Garrelts, 1957]. To compare the flow rates through both devices, we therefore pair-wise selected voidings with comparable voided volumes and plotted both values using a difference plot [Bland and Altman, 1986].

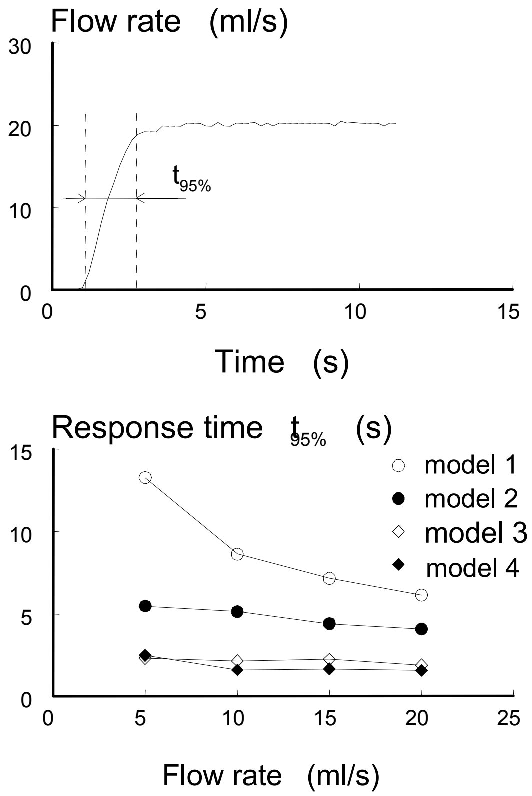

Figure 6.3 *The flow rate signal of a rotating disc flow meter (Dantec®) downstream from prototype 4 of the new flow meter, was plotted as a function of the time. The response time is the time needed to reach 95% of the applied flow rate value, $t_{95\%}$. In the lower panel, the response times measured in all four experimental models are plotted as a function of the flow rate applied to measure the step response.*

Results

Experimental tests

Liquid directed at the funnel is collected in the collecting tube and flows through the sidewall exit ports. We applied steady flow rates to the collecting tube to test the response time. This is the time needed to fill the collecting tube until an equilibrium is established between inflow (of the steady stream) and outflow. When the response time is long, rapid variations in flow rate will be 'accumulated' by the collecting tube i.e. these rapid variations are filtered out. When the response time is short, rapid flow rate changes for example due to coughing or abdominal straining may be detected by a short expulsion of liquid through one of the exit ports. Figure 6.3, upper panel, shows the step response measured in experimental model 4. The flow rate signal of a rotating disc flow meter (Dantec®) downstream from this model, was plotted as a function of time. In the lower panel, the response times measured in all four models are plotted as a function of the steady flow rates applied to measure the step response. The fastest response time was found in models 3 and 4 (~2s). Figure 6.4 shows a calibration plot of experimental model 2. The diamonds indicate the middle of each interval. The measurement range of this prototype was limited to 30 ml/s. At flow rates higher than 30 ml/s, all seven ports were active. The mean uncertainty interval for each port of prototypes 2 and 4, having the same low outlet resistance, was on average 5 ml/s (measurement range from 0 to 30 ml/s) and for prototypes 1 and 3, having a high outlet resistance, on average 3 ml/s (measurement range from 0 to 20 ml/s).

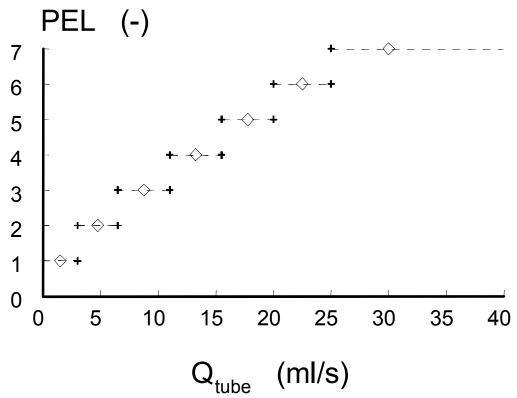

Figure 6.4 *The number of Ports Emitting the Liquid (PEL) is plotted as a function of the flow rate through the collecting tube of experimental model 2, Q_{tube}. Using a flow rate generator, constant flow rates were applied to this model to measure the borderlines of the uncertainty intervals (plusses) associated with each exit port. The diamonds represent the middle of each uncertainty interval.*

Test in volunteers

All volunteers privately voided a number of times in the rotating disc flow meter and in the prototype of experimental model 2 (response time ~4s and a measurement range from 0 to 30 ml/s). None of the male volunteers (age 40 ± 13 years; mean ± SD) found it difficult to simultaneously void and observe PEL_{max}. From this value, we selected the corresponding Q_{tube} value using the calibration plot shown in figure 6.4. Table 6.2 summarises the main results. The maximum flow rate values displayed for each volunteer were measured at different voided volumes, so that they cannot directly be compared. Therefore, we pair-wise selected measurements at approximately the same voided volume in each volunteer. Figure 6.5 shows a difference plot combining the measurements done with the standard and the new flow meter. The borderlines of agreement between both measurement devices ($Q_{rota.max}$–Q_{tube} = 0.4 ± 2.6 ml/s; mean ± SD) were calculated. The mean value did not significantly differ from zero (Wilcoxon signed rank test; p = 0.275), indicating that the prototype was not biased.

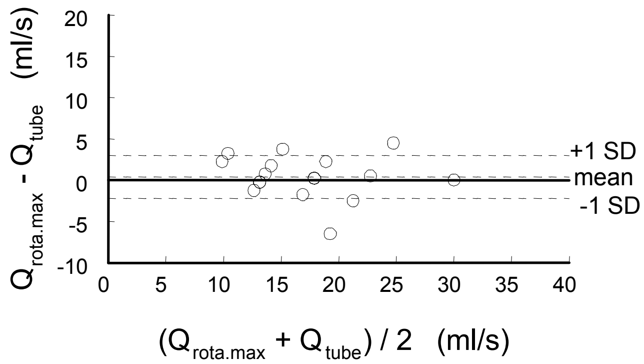

Figure 6.5 *The difference between the maximum flow rate measured with a Dantec® rotating disc flow meter, $Q_{rota.max}$, and graded with the prototype of the low cost flow meter, Q_{tube}, as a function of the mean of both values. Each symbol represents two values measured at approximately the same voided volume in the same volunteer.*

Discussion

Flow rate measurements are frequently used to evaluate the urinary stream in patients. Mostly this evaluation is based on one measurement made in the clinic. We developed a low cost flow meter to determine the maximum flow rate and the voided volume at any location. This flow meter is reusable (different individuals can use one device) and because of its low price (estimated end-selling price: $25) a urologist or a private practitioner may instruct a patient to do repeated flow rate measurements at home. The response time found for the experimental models 3 and 4 used in the present study was ~2s, see figure 6.3. This time is inferior to that of the rotating disc flow meter (~0.1s), but comparable to the response time of the clinically most often used type of electronic flow meter that weighs the collected urine. The low cost flow meter thus seems adequate to repeatedly grade the flow rate, which may increase the reliability of the measurements and thus the accuracy of the clinical evaluation of the urinary stream. Note that this flow meter is not designed with the intention to completely replace the function of currently used flow meters in the clinic, but to present an alternative low cost device. Application outside the clinic might lower the threshold for uroflowmetry and enhance its accuracy.

A mathematical model (described in the appendix) was used as a design tool to predict the flow rate uncertainty intervals and step response for flow meters with different dimensions. We constructed four experimental models to verify this mathematical model. We found that the flow rate uncertainty intervals can easily be adjusted by adapting the total number of the exit ports, their outflow resistance values or the distance between the exit ports. In this way, flow meters may be designed for specific purposes, for example to monitor flow rate changes in response to drug therapy (an alpha-blocker) or after surgical intervention (a TURP).

Table 6.2 *Results of repeatedly voiding in the low cost flow meter (experimental model 2) and in the rotating disc flow meter by 5 healthy male volunteers to test the accuracy.*

	mean ± SD					
	Low cost flow meter			Rotating disc flow meter		
Volunteer	n (-)	Q_{tube} (ml/s)	V (ml)	n (-)	$Q_{rota.max}$ (ml/s)	V (ml)
1	6	17 ± 3	247 ± 55	10	17 ± 2	204 ±68
2	8	11 ± 3	242 ± 102	8	12 ± 1	271 ±81
3	6	24 ± 3	487 ± 152	13	27 ± 3	440 ± 94
4	2	20 ± 3	250 ± 1	2	20 ± 1	248 ± 4
5	2	20 ± 3	240 ± 7	2	19 ± 6	255 ± 127

with n the number of voidings, Q_{tube} the maximum flow rate graded with the low cost flow meter (see also figure 6.2), $Q_{rota.max}$ the maximum flow rate measured with the rotating disc flow meter (in separate voidings) and V the voided volume.

We tested a prototype based on experimental model 2 in healthy volunteers. The accuracy of this model was estimated to be between 2 and 3 ml/s, see figure 6.4. From the measurements done in healthy volunteers, we calculated a standard deviation of 2.6 ml/s for the difference between measurements made with the new flow meter and a standard rotating disc flow meter, see figure 6.5. This confirms the estimated accuracy, despite the fact that two separate voidings were compared in each volunteer. None of the volunteers had difficulties with visually counting the maximum number of exit ports through which urine was flowing. However, for patients with some frailty or cognitive impairment, this could be automated by for example fixing indication paper to the exit ports or by adding a simple electronic circuit connected to the collecting tube.

For an application in patients with LUTS, it would be better to use experimental model 3 in stead of model 2 used in the healthy volunteers. Experimental model 3 had a response time of ~2s, a measurement range of 0 to 20 ml/s and an estimated accuracy between 1.2 and 2 ml/s. This model could thus grade the maximum flow rate more accurate at lower flow rates than model 2. When a patient repeatedly grades the flow rate using the new flow meter, measures the associated voided volumes and notes the voiding frequencies, as in a voiding diary [Griffiths et al., 1997], a urologist may be able to more accurately evaluate the patient's voiding function before recommending treatment [Schacterle et al., 1996; Blanker et al., 2000].

Conclusions

The low cost flow meter presented in this study can be used by different individuals to grade the maximum flow rate. These measurements can repeatedly be done at locations other than the urologic clinic, for example at home. Its response time is comparable to that of a conventional flow meter that weighs the collected urine used in the clinic. In combination with associated voided volumes and voiding frequencies, it may increase the accuracy of evaluating the urinary stream in patients with LUTS.

Appendix

Figure 6.1 shows a schematic drawing of the low cost flow meter. During voiding, urine flows from the collecting tube through a number of exit ports (3 ports in figure 6.1). The velocity of urine, with density ρ_{urine}, through one of the ports can be calculated from the Bernoulli equation [Griffiths, 1980a]:

$$\left.\begin{array}{l} \frac{1}{2}\cdot\rho_{urine}\cdot v_{port}^2 = \Delta p_{urine} \\ v = \frac{Q_{port}}{A_{port}} \end{array}\right\} \Leftrightarrow \tag{1}$$

$$R_{port}\cdot Q_{port}^2 = \Delta p_{port} \quad \text{and } R_{port} = \frac{\rho_{urine}}{2\cdot A_{port}^2}\left(=\frac{8\cdot\rho_{urine}}{\pi^2\cdot d_{port}^4}\right)$$

with $\Delta\rho_{urine}$ the pressure drop over the exit port and R_{port} the outflow resistance to urinary flow, Q_{port}, through the exit port. When we assume, that the urine pressure in the collecting tube is only static ($\sim\rho gh$) and neglect its dynamic component ($\sim\rho v^2$), the flow rate through this exit port can be calculated as follows:

$$R_{port}\cdot Q_{port}^2 = \rho_{urine}\cdot g\cdot\left(h_{urine} - h_{port}\right) \Leftrightarrow$$

$$Q_{port} = \left(\frac{\rho_{urine}\cdot g}{R_{port}}\cdot\left(h_{urine} - h_{port}\right)\right)^{\frac{1}{2}} \tag{2}$$

with g the gravitational acceleration and h_{urine}-h_{port} the height of urine in the collecting tube relative to the height of the exit port ($h_{urine} \geq h_{port}$). Flow rate measurements in pipes are often based on acceleration of a fluid stream through some form of nozzle, placed inside the pipes (restriction flow meters). As a result, vena contracta appear at the exit of these nozzles. In order to calculate the flow rate through such a pipe, it is necessary to include a discharge coefficient in the Bernoulli equation to calculate the actual mass flow through the vena contracta. We did not place such type of nozzle in the collecting tube or the exit ports and inclusion of a discharge coefficient in equation 1 was therefore not necessary. However, vena contracta also appear when flow separation occurs at sharp inlet corners of exit ports (generally these are considered minor losses).

To study the magnitude of this effect, we calculated on the basis of our experimental model and data the pressure loss at the inlet, using the energy equation for steady, incompressible pipe flow [Fox and McDonald, 1985]. We estimated that 10% pressure loss occurred at the inlet of the exit ports due to flow entrance. We then tested if this pressure loss changed the quadratic relation between the height of the liquid in the collecting tube (pressure) and the flow rate (velocity). Figure 6.6, upper panel, shows a measurement of the height of urine in the collecting tube of experimental model 4 as a function of the flow rate through one of its exit ports. This data indeed shows a quadratic relation. Equation 2 was therefore fitted to this data using a least square criterion. For the outflow property $(\rho_{urine} \cdot g)/R_{port}$ of the exit port a value of 3.80 $ml^2/(cm \cdot s^2)$ was calculated. Using equation 1, this gives d_{port} = 2.4 mm for the diameter of this port. In reality this port had an inner diameter of 2.8 mm, see table 6.1.

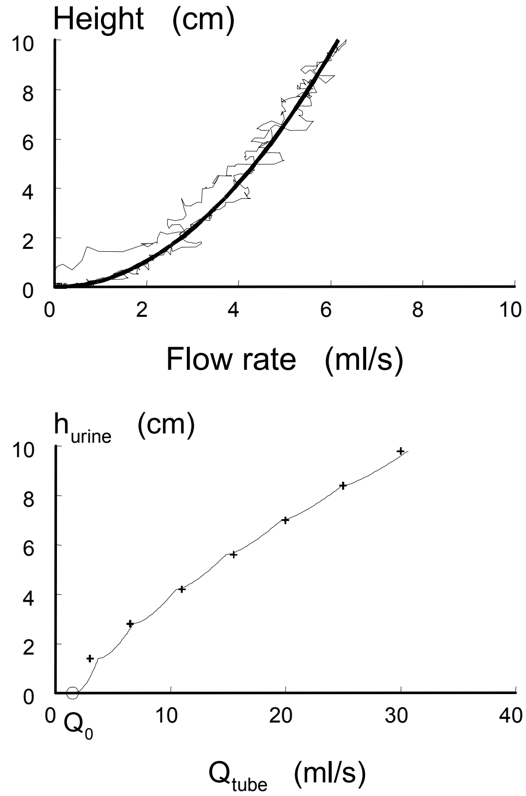

Figure 6.6 *Upper panel: The height of the urine in the collecting tube was plotted as a function of the flow rate through one exit port of experimental model 4. The quadratic curve (thick line) was fitted to the data to calculate the outlet property $\rho_{urine} \cdot g/R_{port}$ of this exit port. Lower panel: A mathematical model of the flow meter was fitted to the calibration curve measured in experimental model 4, see figure 6.4. Two parameters were varied in the fitting procedure: the outflow property $\rho_{urine} \cdot g/R_{port}$ and the off-set flow rate Q_0. The measured (upper panel) and calculated (lower panel) outflow properties showed good agreement.*

This small disagreement between model and experiment is of the same magnitude as the energy loss due to small vena contracta at the entrance of the exit ports (turbulence). Another factor contributing to this small difference might be internal friction of the fluid (viscosity). Despite the assumptions we made to simplify the theoretical model, we think that its accuracy is adequate to use it as part of a design tool. When during voiding the maximum flow rate Q_{max} is reached:

$$Q_{max} = Q_{tube} = Q_0 + \sum_{PEL=1}^{PEL_{max}} Q_{port\,PEL} \tag{3}$$

with Q_0 the flow rate through the exit port at the underside of the collecting tube, see also figure 6.1.

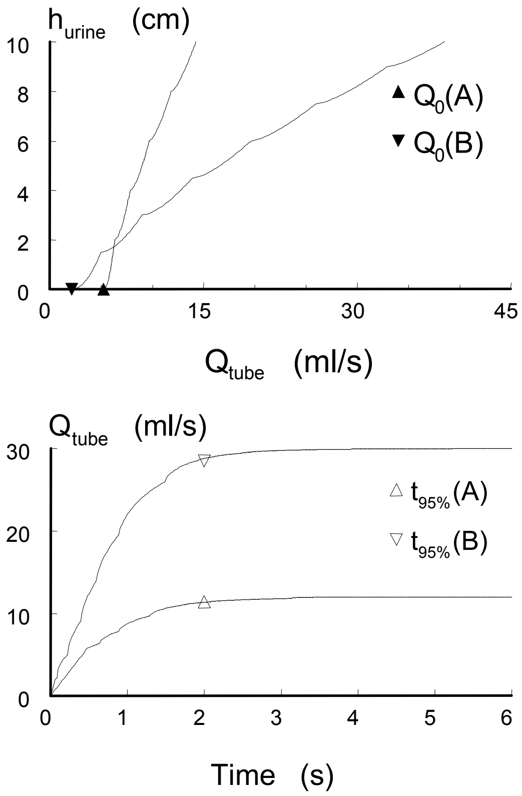

Figure 6.7 *As an example of designing special purpose flow meters, we used the mathematical model described in the appendix to design two special flow meters. Flow meter A measures flow rates between 5-15 ml/s in steps of 2 ml/s and flow meter B measures flow rates between 0-42 ml/s in steps of 6 ml/s. We plotted the theoretical calibration curves (upper panel) and the response time curves (lower panel) for both flow meters.*

It should be noted that also Q_0 depends on the height of urine in the collecting tube. When the diameter of this exit port is in the same order as the diameter of the sidewall exit ports, Q_0 should be incorporated as one of the exit ports in the sidewall. However, in the experimental models tested, the diameter of the port at the underside was small compared to the diameter of the ports in the sidewall. We therefore considered Q_0 as a constant in this mathematical model. $Q_{portPEL}$ is the flow rate through exit port number PEL. Assuming that all exit ports have the same outflow resistance, we find by combining equations 2 and 3:

$$Q_{tube} = Q_0 + \sum_{PEL=1}^{PEL_{max}} \left(\frac{\rho_{urine} \cdot g}{R_{port}} \cdot \left(h_{urine} - h_{port_{PEL}} \right) \right)^{\frac{1}{2}} \qquad (4)$$

Again using a least squares criterion, we fitted equation 4 to the calibration curve measured in experimental model 4, see figure 6.4 and figure 6.6, lower panel. Note that the y-axes are different in both figures. Two parameters were adapted in the fitting process; we found $(\rho_{urine} \cdot g)/R_{port} = 3.33\ ml^2/(cm \cdot s^2)$ and $Q_0 = 1.5$ ml/s. The former value reflects the mean of this property for the seven exit ports used in experimental model 4. Notice that this value is comparable to the value calculated for one exit port from figure 6.6, upper panel. Using these results, we simulated a step response of experimental models 2 and 4. We calculated a $t_{95\%}$ of 4.9s and 1.3s respectively (at a pre-set flow rate of 18 ml/s), values comparable to those presented in figure 6.3.

The mathematical model can be used to design special versions of the flow meter for special purposes. For instance: a flow rate range between 5-15 ml/s in steps of 2 ml/s may be required for a study in patients with BOO (model A) or a flow rate range between 0 – 42 ml/s in steps of 6 ml/s for a study in patients before and after TURP (model B). Using those values, and the desired flow rate intervals, we constructed the calibration curve. Equation 4 was fitted through these points with $(\rho_{urine} \cdot g)/R_{port}$ and Q_0 as the unknown fit parameters, see figure 6.7, upper panel. Using equation 1, we calculated from these fit parameters that for model A the exit ports in the side wall must have an inner diameter $d_{port} = 1.5$ mm and the exit port at the underside $d_{port} = 3.9$ mm. The response time $t_{95\%}$ of this flow meter is 2 s, when $A_{tube} = 60\ mm^2$ (at a constant inflow of 12 ml/s). For model B the exit ports in the side-wall must have an inner diameter $d_{port} = 2.6$ mm and the one at the under side $d_{port} = 2.5$ mm. When $A_{tube} = 250\ mm^2$ the response time of this flow meter also becomes 2 s (at a constant inflow of 30 ml/s), see figure 6.7, lower panel. The two examples illustrate how special versions for specific purposes may be designed using the mathematical model. Note in these designs, the exit ports are regularly spaced and the properties of the ports are all equal. These properties may however be varied for specific design reasons.

7

THE VARIABLE OUTFLOW RESISTANCE CATHETER: A NEW METHOD TO MEASURE THE BLADDER PRESSURE NON-INVASIVELY

Adapted from:
Pel JJM and van Mastrigt R (2001) The Journal of Urology 166: 647-652.

Abstract

In a previous study, an external condom catheter was used to non-invasively measure the bladder pressure during interruption of the flow rate. The pressure rise in the condom sometimes caused a sphincter contraction, which made the bladder pressure measurement unreliable in those cases. We therefore developed a new variable outflow resistance catheter to non-invasively measure the bladder pressure without interruption of the flow rate. The new catheter consists of an incontinence condom connected to a set of different outflow tubes and a pressure transducer. A remotely controlled pneumatic valve was used to interrupt the flow through one of the tubes. We measured in nine healthy male volunteers the isovolumetric pressure, the maximum flow rate and the pressure and flow rates at different outflow resistances. We derived a mathematical equation to estimate the isovolumetric pressure from the pressure and the flow rate values measured at different outflow resistances. The difference between the estimated isovolumetric pressures and the truly measured values was 0 ± 6 cmH_2O (mean ± SD). The new variable outflow resistance catheter can be used to non-invasively measure the isovolumetric bladder pressure without interruption of the flow rate. It has been shown before, that a combination of this pressure and a separately measured maximum flow rate may be used to non-invasively diagnose bladder outlet obstruction.

Introduction

Recently, several urodynamic research groups have developed techniques to non-invasively measure the bladder pressure. For a detailed discussion and a complete overview of these non-invasive techniques, we refer to [van Mastrigt and Pel, 1999] and for recently developed methods to [Griffiths et al., 1999; Pel and van Mastrigt, 1999d] not in this overview. One of these techniques is an external condom catheter to non-invasively measure the bladder pressure [Gommer et al., 1999; Pel and van Mastrigt, 1999a]. Using this type of catheter, the flow rate is repeatedly interrupted during voiding to measure the isovolumetric bladder pressure in a special condom. The accuracy of this method was extensively discussed [Schafer, 1999; Pel and van Mastrigt, 1999b]. It was shown that it depends on the degree of obstruction of the patients [Pel and van Mastrigt, 1999a,b], meaning that in non-obstructed patients the approximation of the bladder pressure in the condom is good and in obstructed patients it was less good. It was suggested that in obstructed patients the bladder neck and the urethra might prematurely close upon interruption of the urinary stream. Radiographic images, made in a few patients during interruption of the flow rate, showed that the urethra and bladder neck remained open [Gommer et al., 1999]. This condition allows good transmission of bladder pressure to the condom. These few observations, however, do not imply that in all patients studied the urethra and bladder neck remain open. Also, in obstructed patients, a low flow rate prolongs the rise time of the pressure in the catheter during the interruption of voiding. This might result in bladder inhibition and thus an unreliable pressure reading in the condom.

To improve this measurement method, we developed a new type of condom catheter: a variable outflow resistance catheter (Dutch patent: 1011576). The advantage of this new technique is that the isovolumetric pressure in the condom is not measured during interruption of the flow rate, but estimated from different pressures in the condom at different outflow resistance values. As the flow rate is not interrupted, it is certain that the sphincter is open during the pressure measurement, which reduces the risk of bladder inhibition. In the present study, we applied this new technique in nine healthy volunteers. We first measured the isovolumetric pressure in each volunteer using the old technique, in which we interrupted the flow rate through the external catheter. Next, we measured pressure and flow rate values at different outflow resistance values using the new variable outflow resistance catheter without interruption of the flow rate. We developed a method to estimate the isovolumetric pressure from the data measured with this new catheter. The accuracy of the new technique was determined by comparing the estimated value with the directly measured isovolumetric pressure using the old technique.

Materials and methods

In a first series of measurements, we measured in 9 healthy volunteers the maximum free flow rate, Q_{max}, and the isovolumetric pressure, p_{iso}, by repeatedly interrupting the flow rate using the old technique [Rikken et al., 1999]. After developing and testing this measurement technique in healthy volunteers and patients for a period of about one year, we developed the new variable outflow resistance catheter. All volunteers were asked to volunteer for a second series of measurements using this new catheter since none of them had experienced changes in flow rate or voided volumes in the intermediate time.

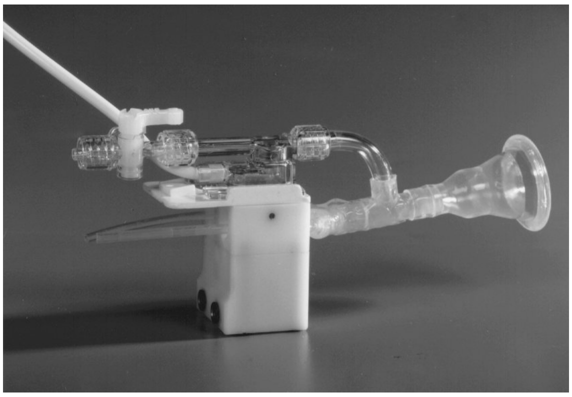

Figure 7.1 *The variable outflow resistance catheter used to non-invasively measure the bladder pressure in a healthy volunteer.*

In the second series, all volunteers voided three times through the new variable outflow resistance catheter, see figure 7.1. Again, we asked all volunteers to void at normal urge sensation in order to repeat the measurements at comparable volumes in each volunteer. To this end, an incontinence condom (POP-ON, Rochester Medical Corporation®, Stuartville, MN, USA) was attached to the penis. To secure the condom to the penis and to increase its stiffness, Parafilm® (type 'M', American National Can, Chicago, II, USA) was taped around a part of the condom and penis. We connected two parallel tubes with different diameters to the outflow opening of the incontinence condom, to guide the urine into a flow meter. A pneumatic valve was fitted over each tube to interrupt the flow rate, Q_{cond}, through it. A pressure transducer recorded the pressure in the condom, p_{cond}, and was installed at the level of the catheter, i.e. on average 20 cm below the symphysis pubis. All volunteers voided three times through the variable outflow resistance catheter, but in each voiding a different combination of tubes was used. In total, three different outflow tubes with resistances of approximately 1.6, 0.66 and 0.24 $(cmH_2O)/(ml^2/s^2)$ were used. In each voiding, each volunteer voided through each of the two tubes and through both simultaneously. Thus pressure and flow rate signals were measured at a total of six different outflow resistances in three voidings in each volunteer. The outflow resistances were selected in such a way that the flow rate in each volunteer was reduced in a number of equally sized steps. At the onset of voiding, all volunteers voided through both tubes, thus through the lowest outflow resistance. When the pressure in the condom had stabilised (visually checked on a computer screen), the outflow resistance was increased. This procedure was repeated until the highest outflow resistance was applied. When the pressure in the condom had stabilised in this situation, the lowest outflow resistance was again applied, so that all volunteers were able to complete voiding. In each volunteer, the investigator tried to apply the different outflow resistances at the same moment in time during voiding, to compare the measured signals from three different voidings at more or less equal voided volumes. The volunteers were asked not to strain during the measurement and voided in privacy.

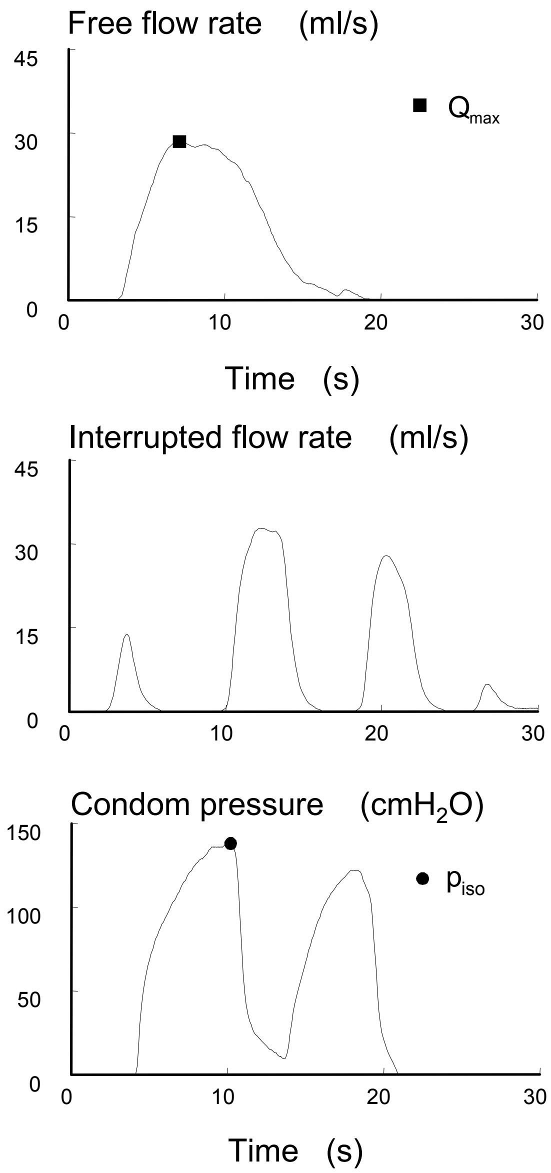

Figure 7.2 *The maximum flow rate, Q_{max}, measured in a free voiding (upper panel) and the isovolumetric pressure, p_{iso}, (lowest panel) measured during interruption of the flow rate (middle panel) in a separate voiding in volunteer D, see also table 7.1.*

Flow rate and pressure signals were displayed at a sample rate of 10 Hz on a computer screen. A first-order Butterworth filter with a cut-off frequency of 0.2 Hz was used to filter all measured signals. The delay caused by the distance between the pressure transducer and the flow meter was corrected by applying a lag time of 8 samples [Kranse et al., 1995]. For data selection and analysis, specially written programs were used (Matlab, version 5, The Math Works Inc., Natrick, MA, USA). For each volunteer, the measurements were combined in a condom pressure - flow plot. We assumed that the condom pressure increased monotonously with increasing outflow resistance. Therefore, the pressure and flow rate values were sorted in an increasing order using a computer algorithm [Kranse and van Mastrigt, 1991]. The pressure values were grouped into bands with a width of 5 cmH_2O. The flow rate values describing the upper part of the condom pressure - flow rate plot were automatically calculated in each pressure band. In the appendix we show how this curve can theoretically be understood and derived. To the selected data points, we fitted a second order polynomial:

$$p_{cond} = p_{iso} + b \cdot Q_{cond} + c \cdot Q_{cond}^2 \qquad (1)$$

In this formula p_{cond} = condom pressure [cmH_2O], Q_{cond} = flow rate through the condom [ml/s], p_{iso} = the isovolumetric pressure measured separately with the external catheter [cmH_2O], b = slope [$cmH_2O/(ml/s)$], c = curvature [$cmH_2O/(ml^2/s^2)$]. To derive a mean curve, the condom pressure values of each volunteer were normalised by dividing them by the volunteers isovolumetric pressure, p_{iso}, and the flow rate values were normalised by dividing them by the intercept on the flow rate axis calculated from equation 1 in each volunteer. Equation 1 was again used to fit the normalised data of each volunteer. From the resulting parameters, the mean normalised slope $\bar{b}$ and the mean normalised curvature $\bar{c}$ were calculated to form a normalised equation:

$$p_{cond} = p_{intercept} + \bar{b} \cdot \left(\frac{p_{intercept}}{Q_{intercept}} \right) \cdot Q_{cond} + \bar{c} \cdot \left(\frac{p_{intercept}}{Q_{intercept}^2} \right) \cdot Q_{cond}^2 \qquad (2)$$

In this formula, the values $p_{intercept}$ and $Q_{intercept}$ are the only two unknown parameters, i.e. the intercepts of the fitted curve on the pressure- and flow rate axis.

To test the normalised equation 2, it was used to estimate the isovolumetric pressure from the data measured with the variable outflow resistance catheter only, i.e. without taking the separately measured isovolumetric pressure value into account. The reproducibility of the estimated values was tested using the Jackknife method [Diaconis and Efron, 1983]. This method proceeds by randomly removing observations from the original data set and recalculating the value of interest for each of the thus created data sets. Analysis of variance was used to statistically analyse these results (SPSS, version 8, SPSS Inc.). Finally, differences between the separately measured maximum flow rates and the intercepts on the flow rate axis were statistically tested using a Wilcoxon signed-rank test (SPSS).

Table 7.1 *Results of fitting a second order polynomial (equation 1) through the isovolumetric pressure measured with the external catheter and the data measured with the variable outflow resistance catheter in 9 healthy volunteers.*

	Volunteers								
Parameters	A	B	C	D	E	F	G	H	I
p_{iso} (cmH_2O)	137	129	127	144	135	142	135	126	91
Q_{max} (ml/s)	32.2	20.0	24.0	29.0	28.6	32.9	32.1	26.3	12.9
b (cmH_2O/(ml/s))	-2.58	-0.86	-2.36	-2.95	-2.56	-1.41	-1.73	-0.28	-3.18
c ($cmH_2O/(ml^2/s^2)$)	-0.06	-0.21	-0.06	-0.05	-0.06	-0.10	-0.07	-0.15	-0.12
$Q_{intercept}$ (ml/s)	31.2	23.0	30.0	31.7	30.5	31.3	33.3	28.2	17.1

p_{iso} is the isovolumetric pressure measured with the external catheter, Q_{max} is the separately measured maximum free flow rate, b is the slope and c is the curvature of the second order polynomial, $Q_{intercept}$ is the intercept of the polynomial on the flow rate axis.

Results

None of the 9 volunteers suffered any discomfort and no leakage occurred during any of the voidings. Figure 7.2 shows the maximum flow rate, Q_{max}, measured in a free voiding (upper panel) and the isovolumetric pressure, p_{iso}, measured using the old technique (external catheter) in volunteer D (lower two panels). In this volunteer, the flow rate was interrupted twice (middle panel), and during each interruption the pressure rise in the condom was measured (lowest panel). The highest pressure in the condom was assumed to best represent the isovolumetric pressure, p_{iso}, of the volunteer. Figure 7.3 shows a typical measurement using the new technique (variable outflow resistance catheter), again in volunteer D. At the onset of voiding (upper panel), the volunteer voided through both tubes, thus through the lowest outflow resistance. When the pressure in the condom had stabilised (middle panel), the outflow resistance was increased by closing the tube with the smallest diameter. When the pressure in the condom had stabilised again, the outflow resistance was increased once more so that the volunteer voided through the tube with the smallest diameter (lowest panel). When the pressure in the condom had stabilised once more, both valves were re-opened, so that the volunteer completed voiding through both tubes. Upon opening of valves, we often detected an overshoot in the flow rate signal. This was caused by expulsion of some urine from the slightly inflated condom. As this overshoot did not reflect bladder properties, we only analysed flow rate and pressure values between the first stabilised condom pressure reading and the maximum stabilised condom pressure. The selected signal part is indicated with dotted lines in figure 7.3, upper two panels.

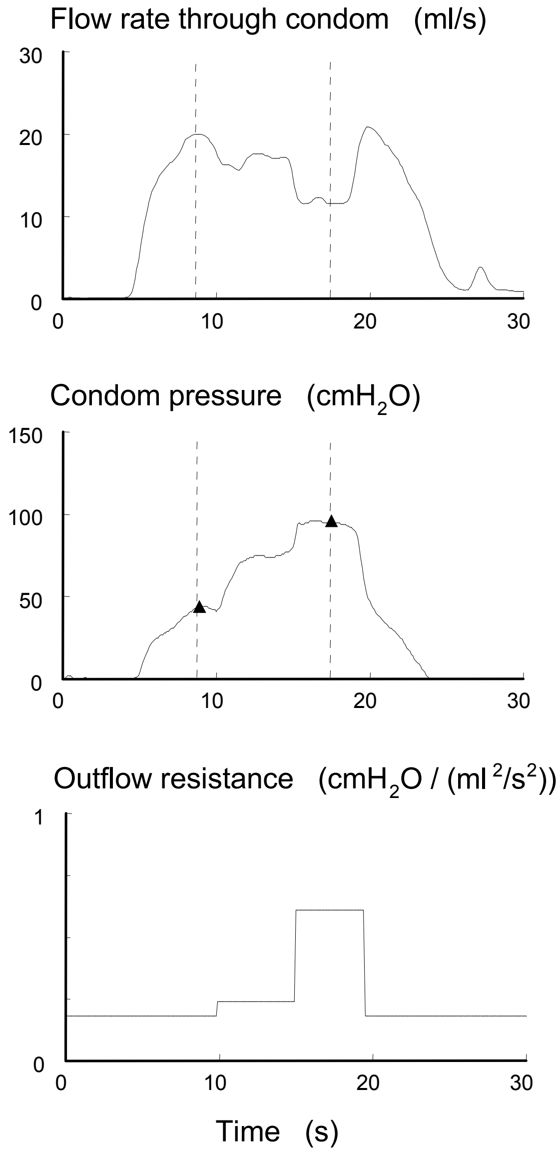

Figure 7.3 *The flow rate (upper panel) and the condom pressure (middle panel) measured at different outflow resistances (lowest panel) with the variable outflow resistance catheter in healthy volunteer D (figure 7.1 shows the free voiding and the measurement with the external catheter in this volunteer). The data between the dotted lines was selected for further analysis.*

The selected data of the three measurements in volunteer E is combined in figure 7.4, upper panel. Superimposed are the resistance relations of the three applied outflow resistances (dotted lines). When the outflow resistance was increased, Q_{cond} and p_{cond} switched from one resistance relation to the next, see also figure 7.3, first two panels, so that the flow rate through the condom decreased and the pressure in it increased. Due to this pressure increase, the elastic extension of condom and urethra increased, leading to gradual stabilisation towards higher pressure and flow rate values on the outflow tube resistance relation. Therefore the high pressure part of the condom pressure - flow rate curve was selected for further analysis using a computer algorithm. The lower panel of figure 7.4 combines p_{iso}, measured using the old technique (closed circle) and the selected highest combinations of p_{cond} and Q_{cond}, measured using the new technique (open circles). Equation 1 was fitted to the data. The flow rate axis intercept, $Q_{intercept}$, is an estimate of the maximum free flow rate in this volunteer (open square). Figure 7.5 shows the combined data and fitted curves of all nine volunteers. The fitted parameter values are given in table 7.1.

The normalised data of each volunteer was fitted again using equation 1. From this data set, the mean normalised slope $\bar{b} = -0.44$ and mean normalised curvature $\bar{c} = -0.56$ were calculated to form a simplified polynomial (equation 2). This curve was fitted to the data measured with the new technique in each volunteer, without taking the "true value" of the isovolumetric pressure, p_{iso}, into account. In figure 7.6, this procedure is shown for volunteer C and the results are summarised in table 7.2. The mean pressure difference p_{iso}–$p_{intercept}$ = 0 ± 6 cmH_2O (mean ± SD). We tested the reproducibility of this estimation using the Jackknife method. 9 times, we removed the data from one of the volunteers from the original data-set, recalculated $\bar{b}$ and $\bar{c}$ and estimated p_{iso} of the volunteer that was removed from the group. In this way we found a mean pressure difference p_{iso}–$p_{intercept}$ = 0 ± 7 cmH_2O (mean ± SD). Analysis of variance revealed that the differences between the "estimated and true" isovolumetric pressure values did not significantly depend on the used $\bar{b}$ and $\bar{c}$ parameters (calculated with the Jackknife method) but that these differences were significantly different between the volunteers.

Table 7.2 *Results of estimating the isovolumetric pressure using a mean polynomial in 9 healthy volunteers.*

	Volunteers								
Parameters	A	B	C	D	E	F	G	H	I
$p_{intercept}$ (cm H_2O)	132	141	124	137	130	147	135	131	88
p_{iso}–$p_{intercept}$ (cm H_2O)	5	-12	3	7	5	-5	0	-5	3
$Q_{intercept}$ (ml/s)	30.5	23.5	29.3	30.5	30.1	31.8	33.4	30.6	16.7
Q_{max}–$Q_{intercept}$ (ml/s)	1.7	-3.5	-5.3	-1.5	-1.5	1.1	-1.3	-4.3	-3.8

$p_{intercept}$ is the estimated value of the isovolumetric pressure, p_{iso} is the "true" isovolumetric pressure, $Q_{intercept}$ is the estimated value of the maximum flow rate and Q_{max} is the "true" maximum flow rate.

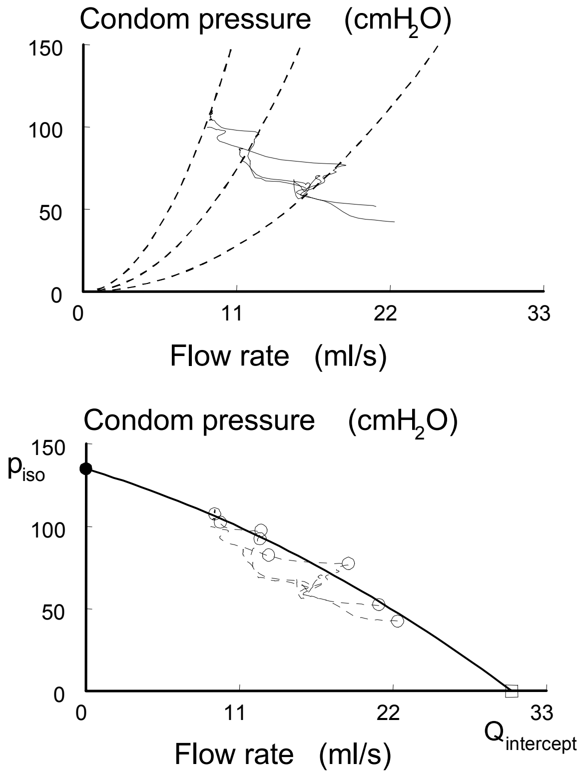

Figure 7.4 *The upper panel shows the condom pressure as a function of the flow rate measured in three voidings in volunteer E. In this data set the highest condom pressure and flow rate values were automatically selected (lower panel, open circles). A second order polynomial was fitted to these points and the separately measured isovolumetric pressure.*

Discussion

A diagnosis of bladder outlet obstruction may be based on the maximum flow rate combined with a separately measured isovolumetric bladder pressure [van Mastrigt and Kranse, 1995]. This pressure can be measured non-invasively with an external condom catheter during interruption of the flow rate. As this condition might cause bladder inhibition or even a sphincter contraction, the isovolumetric pressure might sometimes be unreliable. As an alternative, we developed a variable outflow resistance catheter to non-invasively measure the bladder pressure. The advantage of this new measurement technique is that the flow rate is not completely interrupted, so that it is certain that the sphincter is open during the pressure measurement and that the risk of bladder inhibition is reduced. Furthermore, the pressure rise in the condom is lower than that during an isovolumetric pressure measurement, which reduces the risk of leakage. We tested the variable outflow resistance catheter in a group of healthy volunteers. We found that in each volunteer the isovolumetric pressure could be estimated with an accuracy of 12 cmH_2O (2 SD) without interruption of the flow rate. Analysis of variance showed that the estimated value did not depend on the parameters used for the extrapolation curve, but that is was significantly different between the volunteers. In this study, each volunteer voided three times because we used a small number of different outflow resistances. By increasing the number of outflow resistances, we think that a reliable estimation of this pressure can be made from only one voiding.

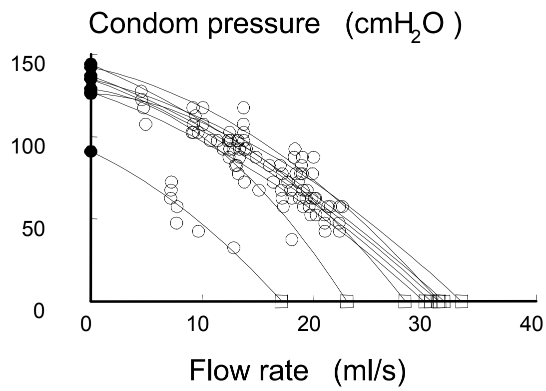

Figure 7.5 *Overview of the condom pressures as a function of the flow rates measured in all healthy volunteers (open circles) using the variable outflow resistance catheter. The closed circles are the separately measured isovolumetric pressures. The open squares are the maximum flow rates estimated from the curve fitted to the condom pressure and flow rate values of each volunteer.*

The procedure applied also yields an estimate for the maximum free flow rate ($Q_{intercept}$). When this value was compared to the "true" maximum flow rate (Q_{max}) measured in these volunteers, the difference Q_{max}–$Q_{intercept}$ = -2.0 ± 2.4 ml/s (mean ± SD). Although this difference in flow rates was not significant (Wilcoxon signed rank test; $p = 0.051$), it indicates that $Q_{intercept}$ overestimates Q_{max}. This caused by the fact that when the pressure builds up in the condom during the non-invasive test the urethra extends which decreases its resistance. In the appendix it is shown, that as a result Q_{max} is overestimated.

The accuracy of this new non-invasive technique (as well as the old technique) depends on the pressure transmission from the bladder, via the urethra, to the condom by the urine voided from the bladder into the condom. Therefore, the accuracy mainly depends on the flow rate. A previous study done in patients using the old technique showed good accuracy of this technique when the maximum flow rate was at least 5.6 ml/s [Pel and van Mastrigt, 1999c]. In addition, for a reliable pressure reading in the condom, the urinary stream has to be continuous, not interrupted and abdominal straining should be avoided. For application in patients with lower urinary tract symptoms it may therefore be necessary to first measure a free flow rate to qualify the patient's urinary stream before a non-invasive bladder pressure measurement is attempted.

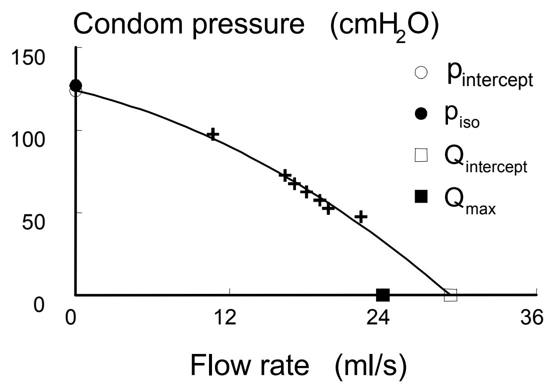

Figure 7.6 *Estimation of the isovolumetric pressure by fitting the mean normalised curve, equation 2 with a mean normalised slope* $\bar{b}$ *= –0.44 and mean normalised curvature* $\bar{c}$ *= –0.56 to the data measured with the variable outflow resistance catheter in healthy volunteer C.* $p_{intercept}$ *is the isovolumetric pressure estimated from the curve.* p_{iso} *is the "true" isovolumetric pressure, measured separately.* $Q_{intercept}$ *is the maximum flow rate estimated from the curve and* Q_{max} *is the "true" maximum flow rate, measured separately.*

Conclusions

We developed a variable outflow resistance catheter to non-invasively estimate the isovolumetric bladder pressure. The difference between the estimated pressures and the truly measured pressures was 0 ± 6 cmH_2O (mean ± SD). We have shown earlier that combining a non-invasively measured bladder pressure with a separately measured maximum flow rate may be used to non-invasively diagnose bladder outlet obstruction.

Appendix

We developed a variable outflow resistance catheter to non-invasively estimate the isovolumetric bladder pressure. When this new non-invasive technique is compared to standard invasive urodynamics, the main difference is that the pressure signal is measured at the distal end of the urethra (condom) and not at the proximal end of it (bladder). Furthermore, during the non-invasive test the pressure in the urethra increases upon increasing the outflow resistance, causing elastic extension of the urethra and thus reducing its resistance. In this appendix, we show how the curve fitted through the non-invasively measured data can theoretically be understood and derived. The upper panel of figure 7.7 shows a theoretical urodynamic pressure – flow plot. The starting point of the curve is at the origin. When the bladder is filled, the detrusor pressure slightly increases due to the limited bladder compliance. Upon the initiation of voiding, the detrusor pressure (difference between the intravesical and abdominal pressure) increases to an opening pressure, p_{open}, to unfold the urethra. During voiding, the urethra opens further to a most relaxed state accommodating a maximum flow rate, Q_{max}. The pressure in the bladder at Q_{max} is the isovolumetric pressure, p_{iso}, minus the pressure drop in the bladder due to shortening of the muscle fibres according to the hyperbolic shaped Bladder Output Relation [Griffiths, 1980b], BOR, analogous to the Hill equation [Hill, 1938] for contracting muscle. When the flow through the bladder neck is interrupted, for example with a Foley balloon, the pressure in the bladder increases to p_{iso}. The shape of the BOR depends among others on the degree of activation of the bladder muscle. When this increases or decreases, the BOR shifts up- or downward accordingly. After attaining its maximum, the flow rate decreases through a maximally relaxed urethra. At the closing pressure, p_{clo}, the urethra closes. The line fitted to the lowest part of the pressure flow plot is called the Passive Urethral Resistance Relation [Schäfer, 1990], PURR, and represents the pressure drop over the urethra (a distensible tube) at different flow rates.

During the non-invasive test, urine not only flows through the urethra, but also through one of the outflow resistances of the catheter. When the outflow resistance during voiding is increased, the shortening velocity of the muscle fibres is reduced. Assuming that the degree of activation of the bladder does not change upon increasing the outflow resistance, the BOR will remain unchanged. However, upon increasing the outflow resistance, the increasing urethral pressure will further extend the urethral wall [Lecamwasam et al., 1996] and thus reduce the PURR to PURR', see figure 7.7, middle panel. When the flow rate through the urethra is interrupted, it remains open and the pressure drop over it reduces to zero. Therefore, in contrast to the PURR, the PURR' intersects with the axes at the origin. The pressure, measured at the distal end of the urethra in the condom, is the difference between the pressure in the bladder given by the output relation BOR and the pressure drop over the urethra given by PURR'. The condom pressure (Δp in the middle panel) is plotted in the lower panel as a function of the flow rate during voiding.

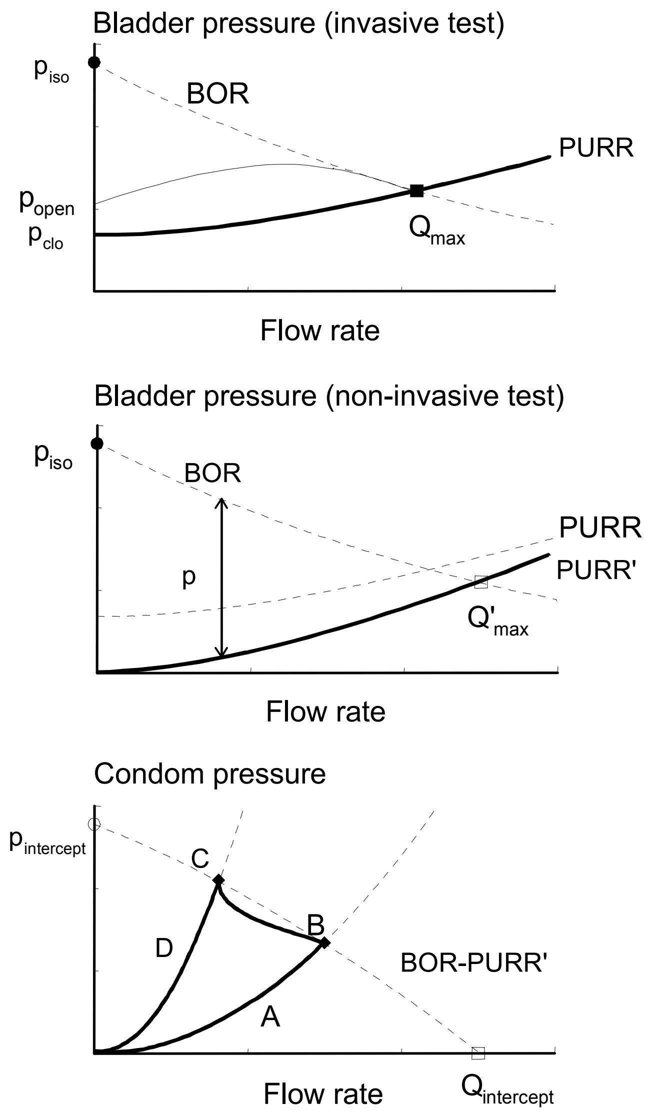

Figure 7.7 *Upper panel: a theoretical pressure flow plot, describing a standard invasive pressure – flow study. The detrusor pressure is plotted as a function of the flow rate. Middle panel: the passive urethral resistance relation (PURR) reduces to PURR' upon elastic extension of the urethra when the outflow resistance is increased. Voiding takes place of the intersection of PURR' and the bladder output relation (BOR). Lower panel: an example of a theoretical condom pressure - flow plot, as derived from the non-invasive study. The shape of the fitted curve can be explained on the basis of the BOR curve and PURR', see middle panel.*

To better illustrate the voiding pattern during the non-invasive test, only two outflow resistances (instead of three as used in this study) are drawn to simplify the discussion. The starting point is at the origin. The pressure in the bladder has to increase to the opening pressure before urine flows through the urethra and the lowest outflow resistance curve (A) of the catheter until a stabilised pressure is reached (B). The resistance curve (A) that is followed results from the addition of PURR' and the lowest outflow resistance. When the outflow resistance is increased, the flow rate through the condom decreases and pressure in it increases. A second stabilised pressure is reached (C) along the addition of PURR' and the highest outflow resistance curve. When voiding ends, it proceeds via this resistance curve (D) until the closure pressure of the urethra is reached. The shape of the curve fitted through the high condom pressure - flow rate curve can thus be explained on the basis of the BOR (hyperbolic shape) and PURR' (monotonous increasing curve). Upon increasing the outflow resistance, the increasing urethral pressure will extend the urethral wall and reduce the PURR to PURR', see figure 7.7, middle panel. As a result, the BOR and the PURR' intersect not at Q_{max} but at a higher value Q'_{max}, see figure 7.7, middle panel. This explains that the intercept value $Q_{intercept}$ of the curve fitted through the non-invasively measured data points overestimates Q_{max}.

8

PRELIMINARY RESULTS OF NON-INVASIVE EVALUATION OF PATIENTS WITH LUTS BEFORE AND AFTER TURP

Abstract

To diagnose BOO in patents with LUTS, measuring the bladder pressure via a transurethral (or suprapubic) catheter is necessary. In a previous study, we developed a non-invasive classification strategy to identify patients with BOO. The aim of this (preliminary) study was to evaluate this strategy in patients who underwent a TURP. We measured in two separate voidings the free flow rate and the bladder pressure using a condom type catheter in patients. Both measurements were done one day before TURP and repeated approximately six weeks after the operation. For each patient, we plotted the isovolumetric bladder pressure against the maximum flow rate before and after the operation. After the operation the maximum flow rate was significantly increased and the isovolumetric bladder pressure only slightly. The previously described non-invasive classification strategy applied to this data set confirmed the urodynamic improvement after the operation in a majority of the patients. A reliable bladder pressure was measured in patients who could void uninterruptedly and who did not strain during voiding. The results show that the developed non-invasive urodynamic test may be used to identify BOO in patients with LUTS and to evaluate the effect of the treatment.

Introduction

In men the prostate enlarges with increasing age, most often as a result of benign prostatic hyperplasia (BPH). It may thus obstruct the passage of urine from the bladder causing a decreased flow rate, urinary frequency or even urinary infection. The flow rate may also be reduced as a result of a weakly contracting bladder. To test if the urethra is obstructed, a patient needs to undergo a pressure-flow study. In this test, the bladder pressure is measured with an invasive catheter inserted via the urethra. This is a costly, time-consuming and unpleasant procedure for the patient. As a result, many patients are not urodynamically tested, and surgical treatment is prescribed on the basis of voiding symptoms and a free flow rate measurement only. This treatment may fail if the symptoms are caused by low contractility of the bladder and not by bladder outlet obstruction.

The last few years techniques have been proposed to non-invasively measure the intravesical pressure to avoid the risk of catheterisation [van Mastrigt and Pel, 1999]. One of these measurement techniques is based on a condom type catheter [Pel and van Mastrigt, 1999a; Pel and van Mastrigt, 2001]. In a previous study, a non-invasive classification strategy was developed on the basis of this new technique [Pel et al., 2001]. In that study, the provisional ICS method for definition of obstruction was used as a 'gold standard'. It was shown that patients, who did not strain during voiding, could be successfully classified as obstructed or non-obstructed on the basis of a combination of maximum flow rate and separately non-invasively measured bladder pressure. In the present study, we evaluated this strategy in patients who underwent a Trans Urethral Resection of the Prostate (TURP). To this end, we measured the maximum flow rate and the maximum bladder pressure non-invasively one day before and approximately six weeks after the operation using the condom type catheter.

Material and methods

The study was done in 17 patients, aged 66 ± 11 years (mean ± SD), who underwent a TURP. Informed consent of each patient was obtained. The day before the TURP, patients were asked to drink about half a litre of water to produce two separate voidings. We first measured the free flow rate to evaluate the urinary stream using a rotating disc flow meter (Dantec®). The signal of the flow meter was plotted on a PC-screen to verify the automatically selected maximum flow rate value, Q_{max}, and the voided volume. Patients who severely strained during this test were not included in the study. In the second measurement, an incontinence condom (POP-ON, Rochester Medical Corporation®, Stuartville, MN, USA) was attached to the penis. To secure the condom to the penis and to increase its stiffness, laboratory film was taped around a part of the condom and penis. In the beginning of this study, we used the external condom catheter to interrupt the flow rate in one step [Pel and van Mastrigt, 1999a]. Later, we used a variable outflow resistance catheter [Pel and van Mastrigt, 2001] to step-wise increase the outflow resistance during voiding. This catheter consisted of three parallel tubes with different diameters connected to the outflow opening of the incontinence condom, to guide the urine into a flow meter. A pneumatic valve was fitted over each tube to interrupt the flow rate through it, see figure 8.1.

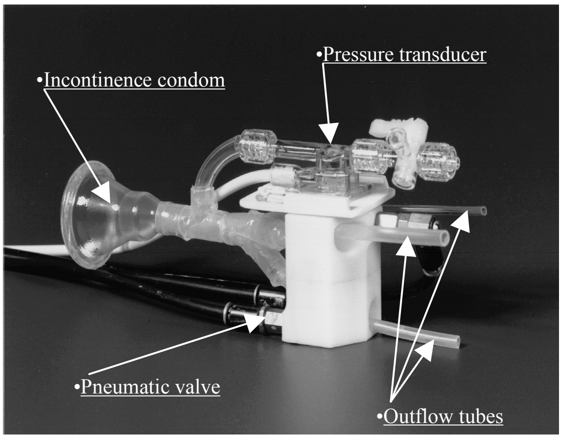

Figure 8.1 *The variable resistance catheter consisted of an incontinence condom connected to three tubes with different diameters. A triple pneumatic valve was fitted over the tubes to interrupt the flow rate through it. During voiding, the outlet resistance of the catheter was step-wise increased by successively closing the tubes.*

In this way, eight different outflow resistance values could be applied. These values were selected such that the flow rate could be decreased in a number of equal steps. In both types of catheters a pressure transducer was installed at the level of the catheter, i.e. on average 20 cm below the symphysis pubis, to record the pressure in the condom, p_{cond}. All patients voided in privacy. Both the free flow rate and the interrupted flow rate measurements were repeated six weeks after surgery. With the exception of 3 patients, invasive urodynamics was not done. The flow rate and condom pressure signals were displayed at a sample rate of 10 Hz on a computer screen. A first-order Butterworth filter with a cut-off frequency of 0.2 Hz was used to filter all measured signals. The delay caused by the distance between the pressure transducer and the flow meter was corrected by applying a lag time of 8 samples [Kranse et al., 1995]. For data selection and analysis, specially written Matlab® programs were used. For each volunteer both signals were combined in a condom pressure - flow rate plot. The pressure and flow rate values were sorted in an increasing order using a computer algorithm [Kranse and van Mastrigt, 1991].

$$p_{cond} = p_{iso} - 0.44 \cdot \left(\frac{p_{iso}}{Q_{intercept}} \right) \cdot Q_{cond} - 0.56 \cdot \left(\frac{p_{iso}}{Q^2_{intercept}} \right) \cdot Q^2_{cond} \quad (1)$$

The pressure values were grouped into bands with a width of 5 cmH_2O. The highest flow rate values were calculated in each band.

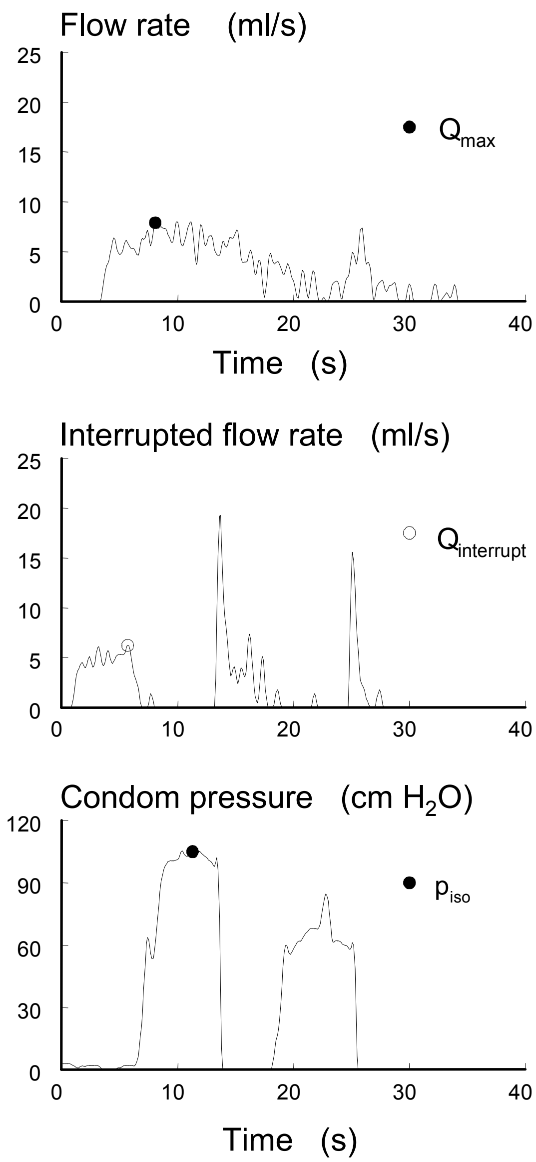

Figure 8.2 *The free flow rate signal, measured with a rotating disc flow meter, was plotted on a PC screen to verify the maximum value, Q_{max} (upper panel). The interrupt flow rate (middle panel) and the condom pressure (lowest panel) were measured in the same patient using the external condom catheter. The flow rate was interrupted twice and the highest isovolumetric pressure, p_{iso}, was measured during the first interruption of the flow rate.*

Then, the flow rate values were grouped into bands with a width derived from the flow rate at the moment of interruption, $Q_{interrupt}$, divided by the number of outflow resistances applied, i.e. 2 in case of the external condom catheter (zero resistance and infinite resistance).The highest pressure values were calculated in each flow rate band.The isovolumetric bladder pressure was calculated by fitting a normalised second order polynomial with slope –0.44 and curvature –0.56, derived in a previous study [Pel and van Mastrigt, 2001], to this data (equation 1). P_{cond} is the condom pressure, Q_{cond}, the flow rate through the condom, and p_{iso} and $Q_{intercept}$ are the unknown parameters, i.e. the intercept of the fitted curve on the pressure axis, which is the isovolumetric pressure, and on the flow rate axis. For a non-invasive evaluation of the urodynamic changes after the TURP, we plotted for each patient the maximum condom pressure, p_{iso}, versus the maximum free flow rate, Q_{max} [Pel et al., 2001]. Note that this type of classification is different from the ICS-nomogram, which is based on the detrusor pressure at maximum flow rate and the maximum flow rate. A paired T-test was used to test for differences in measurements before and after the operation.

Results

None of the 17 patients felt uncomfortable during the measurements. Before the operation, 1 pressure measurement failed due to leakage. After the operation, one free flow rate failed and 6 patients were excluded from the study (2 were incontinent, 2 still had painful wounds, 1 practised self-catheterisation and 1 patient ended the study for private reasons). Thus in 9 patients the effect of the treatment could be studied on the basis of non-invasively measured flow rate and bladder pressure. Figure 8.2, upper panel shows an example of the free flow rate of a patient before surgery. In 11 patients, the maximum pressure was measured by completely interrupting the stream of the urine using the external condom catheter, as in figure 8.2, middle and lowest panel. In this example, the flow rate was interrupted twice, the highest condom pressure, p_{iso}, was measured during the first interruption. In 5 patients, this pressure was measured by step-wise increasing the outflow resistance using the variable outflow resistance catheter. Figure 8.3 shows an example of the flow rate and the condom pressure curves measured with this procedure. In the lowest panel, the automatically selected signal parts from which p_{iso} was calculated are shown. Figure 8.4 shows for all patients the maximum pressure in the condom, p_{iso}, versus the maximum free flow rate, Q_{max}.

Table 8.1 *Results of non-invasive urodynamics in 17 patients before and after TURP*

	mean ± SD	
	Before TURP	After TURP
Q_{max} (ml/s)	7.8 ± 2.7	20.5 ± 6.8
# of patients	(n = 17)	(n = 16)
p_{iso} (cmH_2O)	84 ± 23	105 ± 30
# of patients	(n = 16)	(n = 10)

with Q_{max} the maximum flow rate and p_{iso}, the isovolumetric bladder pressure.

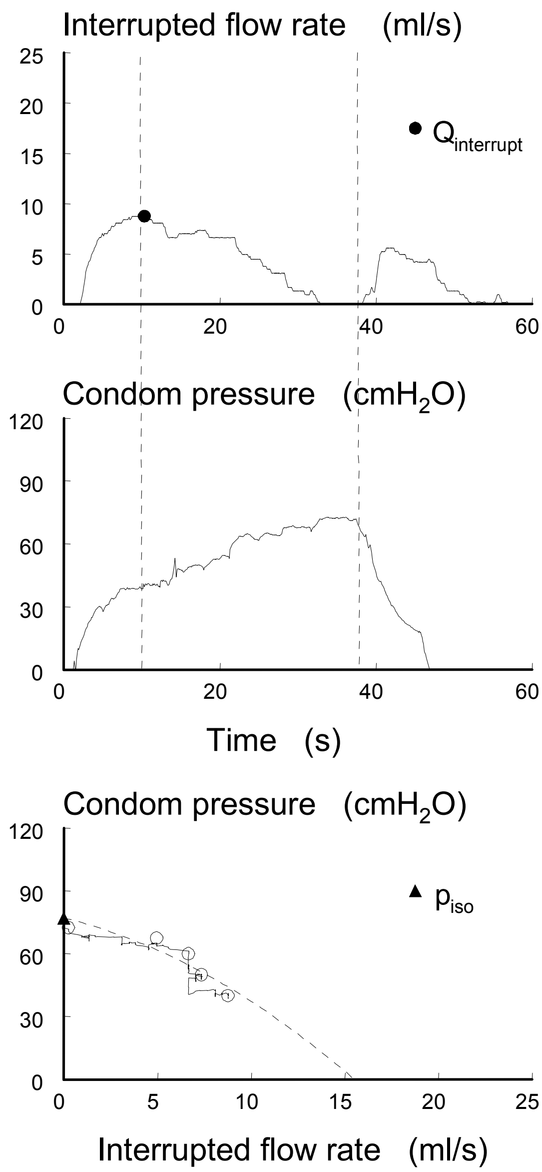

Figure 8.3 *The interrupted flow rate (upper panel) and the condom pressure (middle panel) measured in a patient using the modified variable outflow resistance catheter shown in figure 8.1. Between the dotted lines, the outflow resistance of the catheter was step-wise increased until the flow rate was completely interrupted. Data between the dotted lines was selected and plotted in lowest panel. Equation 1 was fitted to the data points (open circles) to calculate,* p_{iso} *(closed triangle).*

In 9 patients, a thin line connects the measurements before and after TURP. In 1 patient, the flow rate and the condom pressure remained the same after the operation (1), implying that this patient voided with a weakly contracting bladder. In 1 patient, both the flow rate and the condom pressure increased enormously after the operation (2). This patient voided intermittently before the operation, which led to an unreliable pressure reading in the condom. After the operation, the flow rate of the patient was improved and a higher condom pressure was measured. In the remaining 7 patients, the maximum flow rate increased on average 160% ($p < 0.05$) and the condom pressure 20% (not significant: $p = 0.086$) after TURP, see table 8.1.

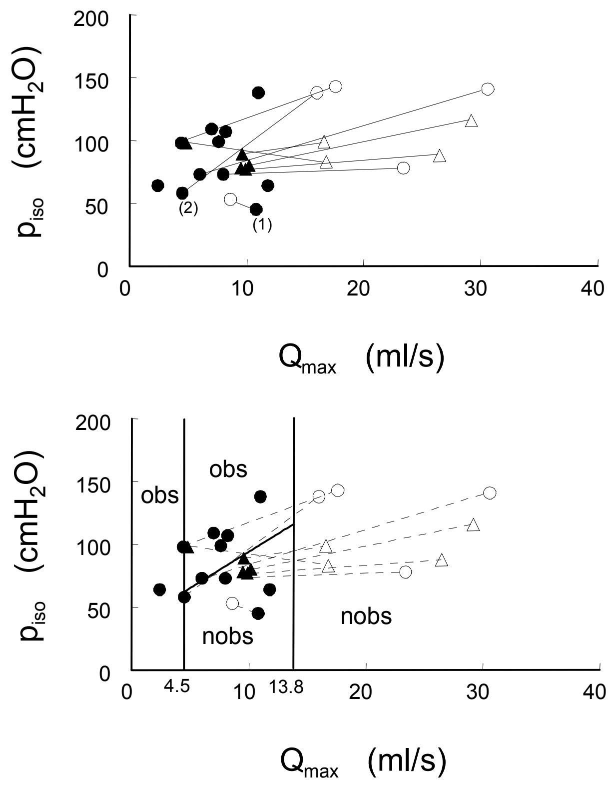

Figure 8.4 *The maximum condom pressure, piso, was plotted against the maximum flow rate, Qmax, in patients before (closed symbols) and after (open symbols) a TURP. The data points plotted as circles were measured using the external condom catheter, the triangles were measured using the modified variable outflow resistance catheter. In the upper panel, the lines connect the measurements done in the same patient. In the lower panel, the data set was plotted in the classification areas that were derived in a previous study.*

In figure 8.4, lower panel, the previously derived non-invasive classification areas were plotted into the condom pressure – flow rate plot. 9 of the 16 successfully measured pre-operative evaluations fell in the obstructed areas (obs) and 8 of the 9 post-operative evaluations fell in the non-obstructed areas (nobs).

Discussion

We studied patients who were selected for a TURP before and after the operation using a condom type catheter. The accuracy of this technique depends on the coupling between the bladder, the urethra and the condom [Pel and van Mastrigt, 1999c]. As the urine voided from the bladder into the condom realises this coupling, the accuracy mainly depends on the flow rate. In a previous study, it was shown that a reliable pressure measurement with the condom is possible when the maximum (free) flow rate of a patient is at least 5.4 ml/s. In addition, for a reliable pressure reading in the condom, the urinary stream has to be 'continuous' not 'staccato' and abdominal straining should be avoided [Pel et al., 2001]. The upper panel of figure 8.4 shows that the surgical relief of the obstruction was successful in 8 patients. The maximum flow rate increased dramatically. The maximum pressure in the condom did not change significantly. On average, the pressure values were slightly higher after TURP. We think that this increase does not reflect a change in bladder properties, but results from a better coupling between bladder and condom due to the increased flow rate.

In 13 of the 16 patients, the decision to operate was not based on a urodynamic evaluation of the degree of outflow obstruction. Invasive urodynamic tests were not done in these patients and the non-invasive test was done on the first day of hospitalisation, prior to surgery. The result of the test was unknown to the surgeon. Figure 8.4, lower panel, shows that 9 patients preoperatively fell in the obstructed area and 7 patients in the non-obstructed area. Nevertheless, 4 of the patients that fell in the non-obstructed area, all near the obstructed area borderline, showed improvement after the operation. The question thus arises on what basis a patient should be defined as non-obstructed. One possibility is to test whether or not the urethral resistance significantly changes after a TURP [Schäfer, 1995]. The classification lines of the provisional ICS method for definition of obstruction are not based on such a test, but are based on a compromise between a number of different classification strategies. As our non-invasive classification is derived from the ICS-nomogram, our preliminary finding suggests that some patients (invasively) diagnosed as non-obstructed on the basis of the ICS-nomogram might still benefit from surgical relief of the prostate, in the sense of having a higher flow rate afterwards. This does not necessarily imply that the operation was necessary in these patients though. Furthermore, we did not define a non-invasive equivalent of the equivocal zone in the ICS-nomogram in which patients fall who cannot be correctly classified as non-obstructed or obstructed. The non-invasive classification areas that we derived were calculated between the group of non-obstructed patients and the combined group of equivocal and obstructed patients. In this way, the transition from the non-obstructed to the obstructed area is not gradual as in the

ICS-nomogram. On the basis of the non-invasive evaluation, we were able to identify at least one patient in whom the operation did not lower the urethral resistance.

A majority of the patients in the present study were not able to void without straining, voided a very small volume or had an indwelling catheter. Most of these patients had suffered symptoms for years before they consulted a general practitioner or a urologist. During this long period, many of them had adapted their voiding patterns, and these adaptations were not in favour of the non-invasive pressure measurement. Although, the preliminary results show that a non-invasive urodynamic test might be a simple measurement tool to identify BOO it is recommended that a free flow rate is done prior to deciding if the non-invasive test can be applied to a patient. If the measured maximum flow rate exceeds 5.4 ml/s, the flow is continuous and the patient voids without straining, a non-invasive measurement of the bladder pressure can be done.

Conclusions

By far not all TURP patients are urodynamically tested. In a previous study, a classification strategy based on flow rate and non-invasively measured bladder pressure was developed. In the present study, we evaluated this strategy in patients before and after a TURP. The preliminary results show that a non-invasive urodynamic test might be a simple measurement tool for pre-operative testing. For a successful application of this tool, first the free flow rate needs to be evaluated. Based on this pre-selection, a non-invasive measurement of bladder pressure could be done to identify BOO and to evaluate the effect of the treatment.

9

General discussion

The invasiveness of a pressure-flow study (PFS) to diagnose bladder outlet obstruction (BOO) limits both scientific and clinical application. The aim of this thesis was to develop and test measurement devices to measure the bladder pressure non-invasively. For worldwide acceptance of this methodology, it is necessary that research continues and that more urodynamic centres become involved in testing and evaluating non-invasive measurement techniques. In this chapter, some of the latest improvements and newly initiated research projects will be discussed with the aim to further study the physical and physiological properties of the lower urinary tract.

Non-invasive assessment of voiding parameters

It has often been proposed to diagnose obstruction on the basis of free flow rate measurements alone but this is fundamentally impossible. However, flow rate measurements can be used to pre-select patients for further testing [van Mastrigt and Pel, 1999]. This limits the number of invasive studies necessary in a given population of patients. At present, flow rate measurements are done using expensive electronic devices. Due to the cost of these, most devices are only used in the clinic, which often results in only one flow rate measurement for evaluation of the urinary stream. The reproducibility of such measurement is poor especially since the measurement is done at locations that are not private and familiar. To stimulate repeated flow rate measurements outside the clinic for a correct evaluation of the urinary stream, a low cost flow meter was developed, see figure 6.2. It consists of a funnel connected to a collecting tube with a number of exit ports. Urine, directed into this tube, flows through one or more ports and is collected in a measuring cup to measure the voided volume. The maximum number of ports emitting the liquid is a measure for the maximum flow rate. It was shown that the response time of this device is comparable to that of a conventional flow meter used in the clinic. Therefore, this device may be suitable to be used by a patient at home to repeatedly test voidings.

In the first part of the thesis, the testing and developing of the external condom catheter to non-invasively measure the isovolumetric bladder pressure has been described. As mentioned in the introduction, this catheter was one of two non-invasive measurement techniques that have been published. The other non-invasive technique, based on the measurement of bladder pressure using an inflatable cuff around the penis, has been further explored by dr. C.J. Griffiths and colleagues of the department of Medical Physics and Urology, Freeman Hospital, Newcastle upon Tyne, United Kingdom. They too reported promising results [Griffiths et al., 2000]. The simultaneous pursuit of two methods in two centres has greatly stimulated the development of both methods. The condom type catheter, see figure 4.1, consists of an incontinence condom connected to a tube that can be closed by a valve. The condom is adjusted to the penis and taped with laboratory tape to increase its stiffness. When a volunteer or patient voids in the condom, the flow rate through the condom and tube is interrupted by closing the valve. During this interruption, the condom fills with urine and a pressure transducer measures the pressure rise until a maximum pressure in the condom is reached. In theory, this maximum condom pressure equals the bladder pressure when the bladder neck is open. The application of this catheter in a group of healthy volunteers showed that the isovolumetric pressure in the condom depended on the bladder volume, meaning that at a certain bladder volume the condom pressure is the highest. It was further shown that after a single flow rate interruption the remainder of the voiding was unaffected and that the bladder volume dependence of the condom pressure could reliably be modelled on the basis of repeatedly interrupted voiding. To validate the condom pressure, it was compared to the simultaneously measured bladder pressure in a group of patients, see figure 3.1. It was sometimes observed that sphincter contraction or even detrusor inhibition influenced the pressure reading. The time necessary to reach the maximum pressure in the condom depends on the flow rate. When the flow rate at the moment of interruption is high, the condom quickly fills with urine. A too low flow rate at the moment of interruption prolongs the pressure measurement, which might result in an unreliable pressure reading. Thus, using the external condom catheter, the bladder pressure can be repeatedly measured in one voiding to measure the highest pressure but in some cases it remains doubtful if the sphincter is open during the pressure measurement.

With the development of the variable outflow resistance catheter, see figure 7.1, the chance of sphincter contraction and detrusor inhibition was reduced. Instead of interrupting the flow rate in one step, the outflow resistance was step-wise increased until the flow rate was (almost) interrupted. This catheter, consisting of two outflow tubes to apply 3 different outflow resistance values, was again tested in a group of healthy volunteers. Using 3 different catheters, nine different outflow resistance values were applied in three voidings. From these measurements, a mathematical equation was derived to estimate the isovolumetric bladder pressure from the condom pressure and flow rate measured at these nine different outflow resistances. The estimated isovolumetric bladder pressure (measured without interrupting the flow rate) corresponded well with the truly measured isovolumetric bladder pressure in each volunteer. To test this catheter in patients, the number of outflow tubes was increased to 3, see figure 8.1. Using 3 tubes, 7 different outflow resistance values could be applied in just one voiding. In a majority of these measurements done in patients, the condom pressure and flow rate values were successfully recorded, but is was not possible to assess the pressure repeatedly to test bladder volume dependence. Thus applying the variable resistance catheter, the chance of sphincter contraction or detrusor inhibition is lowered but in most cases it is unclear if the pressure measured is the highest.

In the last two months of the PhD project, a new approach to measure the condom pressure was tested with the aim to measure the bladder volume dependence in one voiding and to simultaneously check for sphincter contraction or detrusor inhibition. In an analogy with the application of pre-stressed iron bars in many mechanical constructions, it was tested if preloading the urethra would enhance the pressure measurement. The upper panel in figure 9.1 shows the flow rate of a healthy volunteer. When the flow of urine started, the outflow resistance was step-wise increased to slightly fill the condom and the urethra. In the third panel, it can be seen that as a result of the small outflow resistance, the pressure in the condom increased.

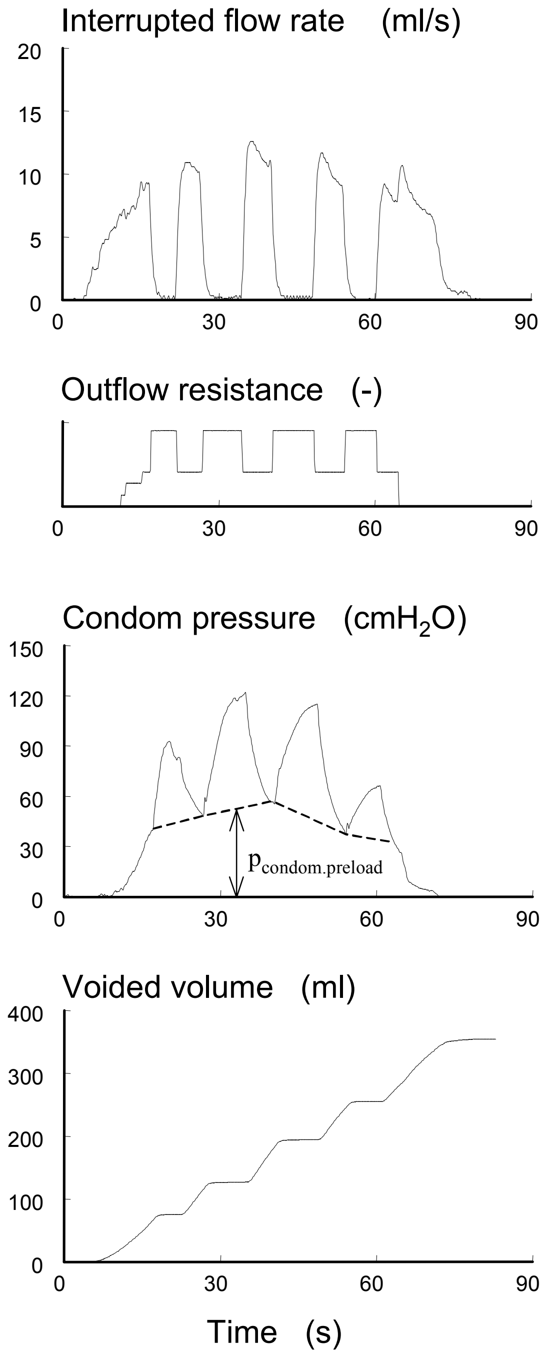

Figure 9.1 *An example of a new approach to measure the condom pressure using the variable outflow resistance catheter. The outflow resistance is slightly increased to apply a preload,* $p_{condom.preload}$*. Then the flow rate is repeatedly interrupted to test the bladder volume dependence.*

Then the flow rate was interrupted completely four times at different bladder volumes (see the third and fourth panel) to measure the isovolumetric pressure in the condom. Following each measurement, the outflow resistance value was reduced to the preload, see the second panel. In this way, the pressure in the condom did not decrease to atmospheric pressure (as in the repeated measurements shown in figure 3.2) but decreased to approximately the same preload value in the condom, $p_{condom.preload}$. In the example it can be seen, that $p_{condom.preload}$ slightly increased and decreased during the isovolumetric pressure measurement in the condom. If a sphincter contraction or detrusor inhibition would occur during the interruption of the flow rate, $p_{condom.preload}$ would strongly decrease. Measuring the pressure this way thus enables the investigator to repeatedly interrupt the flow rate to test for bladder volume dependence and to simultaneously evaluate if the sphincter remains open during each pressure measurement.

Non-invasive classification

At present, the diagnosis of BOO is based on a combination of the maximum flow rate and the corresponding invasively measured detrusor pressure as presented in the ICS-nomogram, see figure 1.1. To derive an objective measure for the urethral resistance on the basis of flow rate and non-invasively measured bladder pressure, 5 different classification strategies were tested in a group of patients with LUTS. First, the patients underwent an invasive pressure-flow study. On the basis of the ICS-nomogram, the patients were diagnosed as non-obstructed, equivocal or obstructed. Then these patients were tested non-invasively. It was shown that the accuracy of the pressure reading in the condom correlated significantly with the urethral resistance of the patient, meaning that in non-obstructed patients the bladder and condom pressure were low and correlated well. In obstructed patients, both pressure values were high and correlated less well. Furthermore, the relatively high abdominal pressures in patients who strained during voiding were not reflected in the condom pressure thus corrupting the measurements in these patients. A simple classification strategy was found in those who did not strain during voiding. Non-obstructed patients were successfully separated from a combined group of equivocal and obstructed patients on the basis of a combination of maximum flow rate and non-invasively measured isovolumetric bladder pressure. However, to successfully classify a patient with LUTS, it is recommended that a free flow rate is done first to evaluate the urinary stream. The maximum flow rate of the patient should exceed 5.4 ml/s to reliably measure the bladder pressure non-invasively, his urinary stream should be continuous and during the non-invasive test he should not strain.

Industrial collaboration

This PhD project was funded by the Technology Foundation, STW. During the project, the research progress was reported on a regular basis to a user committee assigned by the

STW. The members of this committee were both urologists and representatives of companies producing urodynamic equipment. Among other things, the co-operation with the user committee facilitated the improvement of the incontinence condoms used for the pressure measurements. Rochester Medical Corporation® produced especially made condoms suitable for the non-invasive pressure measurement. This new type of pressure condom might increase the general applicability of the variable outflow resistance catheter at urologic clinics.

In co-operation with the STW, two patent applications were submitted on the newly developed non-invasive measurement techniques. In the first application, the non-invasive measurement of the bladder pressure using the variable outflow resistance catheter was described. A patent was obtained, but could not be sold to a commercial partner within one year. Presently, a number of companies are interested in producing this catheter. In the second application, the disposable flow meter to grade the maximum flow rate during voiding was described. This application failed because a similar device was described in 1954 [Drake and Camden, 1954], but fortunately the development of this product continues. Fortunately, because for research groups at the university, collaboration with industrial partners has become more and more of a necessity. During the last years, the budget for new research of universities, foundations and government has been cut back to an alarmingly low level.

The STW stimulates the collaboration between research groups and industry. It financed for example the costly patent applications with the aim to lower the threshold for (new) companies to market and produce the newly developed measurement devices. To uphold a patent for some years is very costly. The role of the STW in financing and guiding research projects to this respect is clearly intermediary. It was therefore frustrating to us, that the patent application on the variable resistance catheter was not sold within the year that the STW upheld the patent. It must be remarked that the research field of urodynamics within urology is relatively small and that worldwide only a few companies produce urodynamic equipment. These companies want to be sure that newly developed products will be bought by first line users of urodynamic equipment, the urologists. However, urologists will only start using a new product when its reliability is warranted. Thus, when it comes to the marketing and selling a new product an impasse may develop. At some point in time, research results may force a breakthrough in the development of a new product. However, when this point is reached after the period of upholding a patent, it becomes difficult for a research group to claim financial compensation for knowledge development.

The university plays a leading role in knowledge protection and in negotiations in selling knowledge to industrial partners. At present, the head of a department or a project leader fulfils that role. However, at the borderline between knowledge development and marketing some tension may develop as a result of conflicting interests. Therefore a clear need exists for an intermediary, that enables research from 'bench to bedside'. For our project this role was fulfilled by the STW.

Scientific and clinical application

As stated earlier, the invasiveness of a PFS to diagnose BOO limits both scientific and clinical application. The use of non-invasive urodynamic measurement devices might extend the general applicability of urodynamics, for instance to population based research. Recently, a grant was awarded to the sector urodynamics of the department of urology, Erasmus University Rotterdam, to longitudinally study the changes in bladder pressure in response to obstruction of the lower urinary tract caused by prostatic enlargement using the variable outflow resistance catheter (Kidney foundation). Furthermore, in a study conducted by the department of General Practice of the University of Maastricht to relate bladder pressure to daily intake of fluid this catheter is also incorporated. Thus for scientific research, this device seems a promising tool.

However, some practical disadvantages may limit its clinical application. The non-invasive diagnosis is based on a combination of a maximum flow rate and a maximum condom pressure. These values are measured in separate voidings. In patients, both measurements take less than five minutes time, but the natural filling of the bladder in between measurements could last several hours, which restricts patient management at a urology clinic. Also, the location of the obstruction, at the prostatic region or further downstream the outflow tract cannot be established. In all fairness it must be remarked that such a localisation cannot be done using the traditional, invasive PFS either. The only clinical test that does allow localisation is the measurement of a urethral pressure profile (UPP). In this notoriously unreliable test, a catheter is slowly retracted from the bladder through the urethra. A pressure rise somewhere along the outflow tract locates the obstruction. However, during this test the patient is not voiding and it therefore remains unclear if the thus located obstruction causes a poor flow rate. Since PFS and UPP are routinely measured in patients, some of the clinical research done in this field should be aimed at studying the relation between the passively measured UPP and the actively measured PFS. To this end, the development of a new non-invasive measurement technique could replace both clinical tests.

Suggestions for future research

A measurement method that could measure urethral obstruction and its location in one voiding might be the measurement of noise produced in the urethra during voiding. Urine passing through the urethra, and especially through the narrowed section in the prostate, produces noise that can be recorded at the body surface. In the third year of the PhD project, a pilot study on this noise method was done. An example is presented in figure 9.2. Urinary flow rate (upper panel) was measured using a rotating disk flow meter. Simultaneously, urethral noise was recorded using a dynamic microphone pressed against the perineum (middle panel). The microphone was suspended in a specially designed housing to optimise the transfer of the urethral noise to the microphone diaphragm.

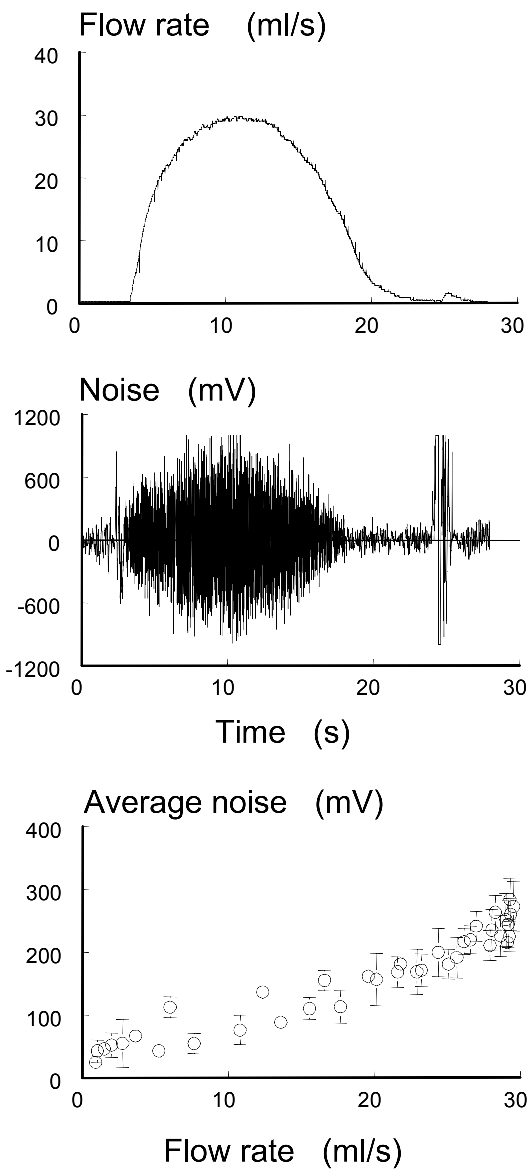

Figure 9.2 *Simultaneous measurement of flow rate (upper panel) and urethral noise (middle panel) using a microphone. The average noise was plotted against the flow rate (lowest panel) to illustrate the dependency.*

The lowest panel shows that, on average, noise increased with flow rate, illustrating that a relation between both signals exists. It has been suggested that the recorded noise may be caused by turbulence in the narrowing of the urethra through the enlarged prostate [Bradley et al., 1977; van Koeveringe and van Mastrigt, 1991]. However, after initial testing this method in a small group of volunteers, it was concluded that a biophysical model of the urethra is necessary as a theoretical basis to relate the recorded noise to the degree and type of obstruction. So far, none of the few physical models of the bladder and the urethra incorporate properties of the urethral musculature, geometry and type of obstruction [Griffiths, 1980a; Teriö, 1991]. Its development may be used to study the relation between muscle and geometry properties and (obstructed) flow rate and, for example, to explain UPP measurements. In mechanical engineering, an analysis method to calculate the strength and safety of complicated geometrical constructions, the Finite Element Method (FEM) has been developed [Fagen, 1993]. Over the years, this method has been refined and nowadays it can be used to for example simulate flow rate through rigid conduits. At the department of biomedical mechanical engineering of the University of Twente development and testing of a new finite element was initiated to simulate the contractile properties of striated muscle fibres. In this way, the applicability of the FEM was extended to biological systems. The FEM is one of the few analysis methods available in which muscle fibres properties can be combined with the complex geometry of the urethra. For future research in urodynamics, it would be worthwhile to apply the FEM in urology by developing a finite element that simulates smooth muscle properties of the urethral wall. Simulated flow turbulence patterns through a urethral model might relate to the degree of deformation of the urethral muscle elements and the type of obstruction applied (compressive vs. constrictive). These results could provide a theoretical basis for explaining noise recordings in healthy volunteers and patients with LUTS, which may lead to the development of a new non-invasive diagnostic tool to identify obstruction in one voiding on the basis of urethral noise.

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SUMMARY

In most ageing males, the prostate enlarges which may obstruct the urethra that it surrounds. As a result, the flow rate may be reduced, voiding becomes more frequent and the chance of residual urine in the bladder after voiding increases. A weakly contracting detrusor also reduces the flow rate. To differentiate between both causes of impaired voiding, the bladder pressure needs to be measured. The International Continence Society (ICS) provided a provisional method for diagnosing obstruction on the basis of bladder pressure measured via catheters in the bladder and rectum. The invasiveness of these measurements limits the applicability of this test, both for clinical decision making and scientific research. The aim of the present thesis was to develop a method for non-invasive assessment of urethral resistance to diagnose bladder outlet obstruction in males. To this end, measurement devices were developed and tested in healthy volunteers. Subsequently, these devices were tested in patients to study the clinical applicability.

The project started with the external condom catheter. This catheter consists of an incontinence condom connected to a tube, a valve and a pressure transducer. The condom is adjusted to the penis and taped with laboratory film to increase its stiffness. When a volunteer or patient voids in the condom, the flow rate through it is interrupted by closing the tube with the valve. During this interruption, the condom fills with urine and the pressure transducer measures the pressure rise until a maximum pressure in the condom is reached. In theory, this maximum condom pressure equals the bladder pressure when the bladder neck is open. The external catheter was first tested in healthy volunteers [chapter 2]. All of these were able to apply the condom and the laboratory film correctly and were able to 'continue' voiding during flow rate interruption. However, the condom pressure values measured were poorly reproducible. We found that the condom pressure depended on the volume of the bladder at the moment of flow rate interruption. Thus to reliably assess the bladder pressure, repeated interruptions in one voiding are necessary to correct for the volume dependence. Two series of measurements were done to study whether or not repeated interruptions of the flow rate were feasible [chapter 3]. In the first series, it was shown that after a single flow rate interruption the remainder of the voiding was unaffected. In the second series, the bladder volume dependence of the condom pressure was established by repeatedly interrupting voiding enabling a non-invasive diagnosis of bladder outlet obstruction.

To validate the non-invasively measured bladder pressure, it was compared to the simultaneously measured 'true' bladder pressure in non-obstructed and obstructed patients [chapter 2]. The 'true' pressure was measured using a small catheter guided into the bladder via the condom. It was shown, that the accuracy of the pressure reading in the

condom correlated significantly with the urethral resistance, meaning that in non-obstructed patients the bladder and condom pressure were low and correlated well. In obstructed patients, both pressure values were high and correlated less well. Subsequently, a strategy to classify bladder outlet obstruction on the basis of parameters measured non-invasively using the external condom catheter was developed in a group of patients [chapter 4]. First, the patients underwent an invasive pressure-flow study. On the basis of the provisional ICS method to diagnose obstruction, the patients were diagnosed as non-obstructed, equivocal or obstructed. Five classification strategies were tested for a similar diagnosis on the basis of non-invasively measured bladder pressure and flow rate. It was shown, that the relatively high abdominal pressures in patients who strained during voiding were not reflected in the condom pressure thus corrupting the measurements in these patients. In those who did not strain, a simple classification strategy to separate non-obstructed form obstructed patients was found on the basis of a combination of maximum condom pressure and a separately measured maximum flow rate.

The time necessary to reach the maximum pressure in the condom depends on the flow rate. When the flow rate at the moment of interruption is high, the condom quickly fills with urine. A too low flow rate at the moment of interruption prolongs the pressure measurement in the condom, which could result in an unreliable pressure reading. We concluded that the accuracy of the condom pressure depends on the urethral resistance [chapter 2]. As this criterion is based on invasively measured parameters, a flow rate cut-off value was calculated to non-invasively specify this accuracy [chapter 5]. If the flow rate exceeded 5.4 ml/s, the condom pressure reflected the bladder pressure well in the tested patients. For a successful non-invasive pressure measurement, the flow rate must further be continuous and the patient should avoid straining while voiding.

At present, the flow rate measurements necessary for both the traditional invasive and the newly developed non-invasive diagnosis methods are done using expensive electronic devices. Due to the cost of these, most devices are only used in the clinic, which often results in only one flow rate measurement for evaluation of the urinary stream. The reproducibility of such a measurement is poor. To stimulate repeated flow rate measurements preferably outside the clinic, a low cost flow meter was developed that grades the maximum flow rate [chapter 6]. It consists of a funnel connected to a collecting tube with a number of exit ports. Urine, directed into this tube, flows through one or more ports and is collected in a measuring cup to measure the voided volume. The maximum number of ports emitting the liquid is a measure for the maximum flow rate. It was shown that the response time of this device is comparable to that of a conventional flow meter. The low cost flow meter could be used to test the urinary stream before a non-invasive pressure measurement is done. It is expected that in the near future, this device will become commercially available.

To reduce the risk of premature sphincter closure or detrusor inhibition during interruption of the flow rate, a variable outflow resistance catheter was developed to measure the bladder pressure without interrupting the flow rate [chapter 7]. For this device a patent was obtained. It consists of an incontinence condom connected to a set of outflow tubes and a pressure transducer. Remotely controlled pneumatic valves are used to interrupt the flow of urine through each tube. We measured in nine healthy male volunteers the isovolumetric pressure, the maximum flow rate and the pressure and flow rates at different outflow resistances. A mathematical equation was deduced to estimate the condom pressure during flow interruption from the pressure and flow rate values measured at different outflow resistance values. It was shown in a group of healthy male volunteers, that the estimated pressure values using this 'new' catheter correlated well with the truly measured values using the 'old' external condom catheter.

The non-invasive classification strategy was validated by applying both the external condom catheter and the variable outflow resistance catheter in patients before and after a transurethral resection of the prostate [chapter 8]. Most of these patients were not urodynamically tested before they underwent surgery. After the operation, the maximum flow rate of most patients increased dramatically. The maximum pressure in the condom slightly increased (not significantly), which may result from a better coupling between bladder and condom due to the increased flow rate. The preliminary results show that a non-invasive urodynamic test might be a simple measurement tool for pre-operative testing. For a successful application of this tool, first the free flow rate needs to be evaluated. Based on this pre-selection, a non-invasive measurement of bladder pressure could be done to identify bladder outlet obstruction (BOO) and to evaluate the effect of the treatment.

The invasiveness of a pressure-flow study (PFS) to diagnose BOO limits both scientific and clinical application. The aim of this thesis was to develop and test measurement devices to measure the bladder pressure non-invasively. To successfully non-invasively classify a patient, it is recommended that a free flow rate is done to evaluate the urinary stream. The maximum flow rate of the patient should exceed 5.4 ml/s to be able to reliably measure the bladder pressure non-invasively, his urinary stream should be continuous and during the non-invasive test he should not strain. For worldwide acceptance of this methodology, it is necessary that research continues and that more urodynamic centres become involved in testing and evaluating non-invasive measurement techniques. The use of non-invasive urodynamic measurement devices might extend the general applicability of urodynamics, for instance to population based research. For future research, it may be worthwhile to develop and test a new measurement method that could measure urethral obstruction and its location in one voiding on the basis of noise produced in the urethra during voiding [chapter 9].

SAMENVATTING

Urine, geproduceerd in de nieren, wordt tijdelijk opgeslagen in de blaas. Op gepaste momenten kan de blaas, die in feite een holle spier is, samenknijpen waardoor de druk erin toeneemt. Het moment van plassen wordt bepaald door het samenspel tussen het vermogen van de blaasspier (detrusor) en de weerstand van de plasbuis (urethra). Als de detrusor door het zenuwstelsel wordt geprikkeld, verkorten de spiervezels in de detrusor zich en neemt de druk in de blaas toe. Gelijktijdig ontspannen zich de spiervezels in de blaashals en in de wand van de urethra. Als de blaasdruk groter is dan de urethrale druk, stuwt de urine de urethra open en begint het plassen. Op het moment dat de blaas leeg is, stopt het samenknijpen van de blaas, de urethra vouwt zich dicht en de blaas wordt voor een volgende plas gevuld door de nieren.

Bij mannen op leeftijd kan prostaatvergroting leiden tot een zwakker wordende urinestroom tijdens het plassen. De meestal goedaardige prostaatvergroting, benigne prostaat hyperplasie (BPH) genoemd, vormt een belemmering voor de urinestroom door de urethra, ook wel obstructie genoemd. Het is van groot belang dat de urethrale obstructie urodynamisch wordt vastgesteld, omdat een zwakke straal ook het gevolg kan zijn van een zwakke blaas en een prostaatoperatie daarvoor geen oplossing vormt. Gedurende een urodynamisch onderzoek wordt o.a. de blaasdruk middels katheters, die via de urethra in de blaas worden gebracht, gemeten. Aangezien dit onderzoek kostbaar, tijdrovend, niet zonder infectiegevaar en onaangenaam is voor de patiënt, wordt het slechts in een deel van de patiënten met plasklachten uitgevoerd. Het doel van het onderzoek beschreven in dit proefschrift is het ontwikkelen van een meetmethode om op een goedkope, eenvoudige en vooral patiëntvriendelijke wijze de urethrale weerstand in mannen te meten.

Het onderzoek startte met een externe condoomkatheter. Deze katheter bestaat uit een incontinentie condoom bevestigd aan een slang, een klep en een drukmeter. Het condoom wordt vastgemaakt aan de penis en het geheel wordt verstevigd met laboratorium tape. Als een vrijwilliger of patiënt in het condoom plast, kan de urinestroom erdoorheen worden onderbroken door de slang dicht te knijpen met de klep. Op dat moment vult het condoom zich met urine waardoor de druk toeneemt. De druk in het condoom, geregistreerd m.b.v. de drukmeter, neemt toe tot een maximum waarde. In theorie is de maximum druk waarde in het condoom gelijk aan de druk in de blaas als de blaashals en de urethra open zijn. De externe condoomkatheter is eerst getest bij gezonde vrijwilligers [hoofdstuk 2]. Ze konden allen het condoom correct aanbrengen en gedurende de onderbreking van de urinestroom 'doorplassen'. Desondanks werd er bij elke vrijwilliger verschillende drukwaarden in 1 plas gemeten. Er werd gevonden dat de druk in het condoom afhangt van het blaasvolume. Om de hoogste blaasdruk te kunnen meten is het noodzakelijk meerdere onderbrekingen van de urinestroom in één plas te doen. In meetseries gedaan bij vrijwilligers werd getest of dit mogelijk was [hoofdstuk 3]. Uit de eerste meetserie bleek dat het onderbreken van de urinestroom het vervolg ervan niet beïnvloedde. Uit de tweede meetserie bleek dat de hoogste druk betrouwbaar gemeten kon worden door de urinestroom herhaaldelijk te onderbreken.

Bij een groep patiënten werd de druk in het condoom vergeleken met de druk in de blaas [hoofstuk 2]. De blaasdruk werd gemeten m.b.v. een klein slangetje dat door het condoom heen in de blaas werd geschoven. Het bleek, dat de beide drukken goed overeenkwamen in patiënten met een lage urethrale weerstand (niet geobstrueerd). In patiënten met een hoge urethrale weerstand (geobstrueerd) bleek de druk in de blaas hoger te zijn dan de druk in het condoom. Echter de drukken gemeten in de patiënten met een verhoogde urethrale weerstand waren significant hoger dan die gemeten in patiënten met een lage urethrale weerstand. Aansluitend, werd een classificatiestrategie ontwikkeld om de niet-geobstrueerde van de geobstrueerde patiënten te onderscheiden op basis van de niet-invasief gemeten data [hoofdstuk 4]. De patiënten ondergingen voor de niet-invasive test eerst een standaard invasieve test. Op basis van de uitkomst van deze test werden de patiënten geclassificeerd als niet-geobstrueerd, onbepaald of geobstrueerd. Vijf strategieën werden getest om patiënten te classificeren op basis van urinestroom en de condoomdruk. Uit de meetresultaten kwam naar voren, dat de vaak hoge drukken in de blaas veroorzaakt door persen tijdens het plassen niet goed werden teruggevonden in de condoomdruk. Dus de drukken gemeten in patiënten die persten tijdens het plassen waren onbetrouwbaar. Bij hen die niet persten tijdens het plassen werd een eenvoudige classificatiemethode ontwikkeld op basis van een combinatie van de maximale urinestroom en de maximale condoomdruk.

De tijd die nodig is om de hoogste druk in het condoom te bereiken hangt af van de urinestroom. Als de urinestroom op het moment van onderbreken groot is, wordt het condoom snel gevuld. Als de urinestroom laag is op het moment van onderbreken duurt de drukopbouw in het condoom lang, waardoor de kans op het sluiten van de blaashals (sfincter contractie) of het stoppen van het samenknijpen van de detrusor (detrusor inhibitie) toeneemt. In die gevallen wordt een onbetrouwbare blaasdruk in het condoom gemeten omdat er dan geen open verbinding meer is tussen blaas en condoom. Op basis van de patiëntmetingen werd er een urinestroom ondergrens berekend om de betrouwbaarheid van een niet-invasieve meting te kunnen voorspellen [hoofdstuk 5]. Als de maximum waarde van de urinestroom boven de 5.4 ml/s ligt, dan komt de druk in de blaas goed overeen met de druk in het condoom. Verder moet voor een succesvolle drukmeting de urine straal continu zijn en, zoals al genoemd, moet de patiënt niet persen tijdens het plassen.

Op dit moment wordt voor het meten van urinestroom gebruik gemaakt van dure elektronische apparaten. Vanwege de hoge kosten, worden deze apparaten alleen in het ziekenhuis toegepast, waardoor vaak maar één plas van een patiënt wordt gemeten. De reproduceerbaarheid van één meting is erg slecht, ook doordat de meting niet plaatsvindt op een voor de patiënt vertrouwde locatie. Om te stimuleren dat patiënten vaker en het liefst buiten het ziekenhuis urinestroommetingen kunnen doen, werd een goedkope flowmeter ontwikkeld [hoofdstuk 6]. Deze flowmeter bestaat uit een trechter en een stijgbuisje met daarin een aantal uitstroomopeningen. De urine geplast in de trechter verlaat via één of meerdere uitstroomopeningen het stijgbuisje. Het maximale aantal openingen waar urine doorheen stroomt is een maat voor de maximum urinestroomwaarde. Het bleek dat de responsietijd van het apparaat vergelijkbaar is met dat van een in het ziekenhuis veel toegepast apparaat. De goedkope flowmeter zou heel goed gebruikt kunnen worden om de urinestroom van een patiënt te testen voordat een niet-invasieve drukmeting kan worden gedaan.

Om de kans op sfinctercontractie en detrusorinhibitie te verkleinen werd een nieuw type katheter ontwikkeld om de druk in het condoom te meten zonder de urinestroom volledig te onderbreken [hoofdstuk 7]. Deze variabele uitstroomweerstandkatheter bestaat uit een incontinentiecondoom verbonden met een set slangen en een drukmeter. Op afstand bedienbare kleppen worden gebruikt om de flow door elk slangetje te kunnen onderbreken. Deze katheter werd getest bij een groep vrijwilligers. In drie plassen moest ieder vrijwilliger door drie verschillende katheters plassen. Op die manier werd urinestroom en condoomdruk bij negen verschillende uitstroomweerstanden gemeten. Op basis van de verkregen resultaten werd een wiskundige vergelijking afgeleid om te kunnen schatten hoe hoog de druk in het condoom zou zijn geweest bij volledige onderbreking van de urinestroom. Het bleek dat de geschatte drukwaarde goed overeenkwam met de echte waarde die tevens bij elke vrijwilliger apart was gemeten met de externe condoomkatheter.

De niet-invasieve classificatiestrategie werd gevalideerd bij een groep patiënten voor en na het ondergaan van een prostaatoperatie [hoofdstuk 8]. In het begin van het onderzoek werd de condoomdruk in deze groep patiënten gemeten met de externe condoomkatheter en later met de variabele uitstroomweerstandkatheter. De meeste patiënten ondergingen voor de operatie geen invasief onderzoek. Na de operatie was de urinestroom van de meeste patiënten aanzienlijk verbeterd. De condoomdruk nam iets toe, wat waarschijnlijk verklaard kan worden uit het feit dat de koppeling tussen de blaas en het condoom na operatie was verbeterd. De voorlopige resultaten duiden erop dat niet-invasief testen van patiënten voor de operatie mogelijk is. Voor het succesvol toepassen van deze methode is het aan te bevelen eerst de urinestroom van de patiënt te evalueren. Op basis van deze voorselectie is het vervolgens mogelijk om patiënten met een verhoogde urethrale weerstand te identificeren en om het effect van de behandeling te testen.

Het invasieve karakter van een urodynamisch onderzoek bemoeilijkt het doen van wetenschappelijk en klinisch onderzoek in patiënten met plasklachten. In dit proefschrift staat o.a. de ontwikkeling van een meetmethode om de blaasdruk niet-invasief te meten. Met de ontwikkelde variabele uitstroomweerstandkatheter is een goede blaasdrukmeting inderdaad mogelijk als aan een aantal voorwaarden wordt voldaan. Indien de maximum urinestroom van een patiënt hoger is dan 5.4 ml/s, de urinestraal onafgebroken is en persen kan worden vermeden, dan kan vervolgens op basis van de niet-invasief gemeten blaasdruk de urethrale weerstand van de patiënt worden geclassificeerd. Het gebruik van deze niet-invasive meetmethode maakt het mogelijk dat een deel van de patiëntpopulatie geen invasief urodynamisch onderzoek meer hoeft te ondergaan. Tevens maakt de toepassing van de variabele uitstroomweerstandkatheter het doen van bevolkingsonderzoek mogelijk. Recentelijk heeft de sector urodynamica van de afdeling urologie, Erasmus Universiteit Rotterdam, subsidie van de Nierstichting ontvangen om de verandering van de blaasdruk als gevolg van prostaatvergroting in een grote groep mannen te meten m.b.v. deze katheter. Verder vervolgonderzoek op het gebied van de niet-invasieve urodynamica zou zich kunnen richten op het testen van een techniek om de plaats en grootte van urethrale obstructie vast te stellen met behulp van 'geruis in de plasbuis' tijdens het plassen [hoofdstuk 9].

DANKWOORD

Het is waar: plassen is fascinerend. En helemaal als plassen wordt gecombineerd met een incontinentiecondoom. Vier jaar lang heb ik het voorrecht gehad de wetenschappelijke impact van deze niet-alledaagse combinatie te onderzoeken. Mede dankzij de hartelijke ondersteuning van collega's, vrijwilligers, patiënten, familie en kennissen, kon dit onderzoek tot een bevredigend einde worden gebracht.

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Johan Pel
Rotterdam, 20 juni 2001

CURRICULUM VITAE

Johan Pel werd geboren op 4 maart 1972 te Apeldoorn. Hij volgde het middelbaar onderwijs aan het Christelijk Lyceum te Apeldoorn en behaalde in 1990 zijn vwo-diploma. In hetzelfde jaar ging hij werktuigbouwkunde studeren aan de Universiteit Twente. Hij ontving het ingenieursdiploma in 1996 na het afronden van een afstudeeropdracht bij de vakgroep biomedische werktuigbouwkunde onder leiding van prof.dr.ir. H.J. Grootenboer en prof. dr. P.A. Huijing. In maart 1997 werd hij onderzoeker in opleiding bij de sector urodynamica van de afdeling urologie, Erasmus Universiteit Rotterdam. Onder leiding van dr.ir. R. van Mastrigt onderzocht hij meetmethoden om niet-invasief de urethrale weerstand van mannen te meten. De resultaten van dit onderzoek staan beschreven in dit proefschrift.

AANTEKENINGEN