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Marinus Kranse
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Promotor(en): Prof. dr. F.H. Schröder

Overige leden: Prof. dr. J.L.H.R. Bosch
Prof. dr. ir. J.D.F. Habbema
Prof. dr. T.A. Boon

Copromotor(en): Dr. ir. R. van Mastrigt

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Contents.

List of abbreviations.	5
Introduction.	9
0.1 The pressure flow measurement.	10
0.2 Video urodynamics.	11
0.3 Lagtime correction.	11
0.4 The estimation of bladder outlet resistance.	11
0.5 The estimation of bladder contractility.	14
0.6 The diagnosis of bladder outlet obstruction.	15
0.7 The papers.	16
Linearization of a urinary flow transducer.	19
Estimation of the lag time between detrusor pressure and flow rate signals.	27
Computer assisted pressure-flow analysis.	43
3.1 Introduction.	43
3.2 Urodynamic pressure-flow studies.	45
3.3 The urethral resistance relation.	46
3.4 Models for the urethral resistance relation.	49
3.5 Which model fits the urethral resistance relation best ?	50
3.6 Urethral resistance factors and classifications.	52
3.7 Some clinical applications of urethral resistance factors.	54
3.8 A detrusor contractility parameter.	56
3.9 Optimum method for pressure-flow analysis.	58
3.10 Conclusions.	59
Pre selection of patients for pressure-flow analysis based on the maximum flow-rate.	63
Relative bladder outlet obstruction.	83
Bladder outlet resistance.	101
The weak correlation between bladder outlet obstruction and the probability to void to completion.	111
Causes for variability in repeated pressure flow measurements.	121
Summary of the papers	131
9.1 Linearization of the Dantec Urodyn 1000 urinary flow transducer.	131
9.2 Estimation of the lag time between detrusor pressure- and flow rate- signals.	131
9.3 Computer assisted pressure-flow analysis .	131

9.4 Pre selection of patients for pressure flow analysis based on the maximum flow rate.	132
9.5 Relative bladder outlet obstruction.	132
9.6 Bladder outlet resistance.	133
9.7 The weak correlation between bladder outlet obstruction and the probability to void to completion.	135
9.8 Causes for variability in repeated pressure flow measurements.	136
General Summary and Conclusion.	139
Samenvatting	141
Dankwoord	149
Curriculum vitae	151

List of abbreviations.

AUC : Area under the (receiver operating characteristic or ROC) curve.

BCI : bladder contractility index.

Measure for bladder contractility, see e.g. page 14, 112.

BOOI : bladder outlet obstruction index.

Measure for bladder outlet resistance, see e.g. page 112.

ICS : international continence society.

LPURR : linearized passive urethral resistance relation.

Measure for bladder outlet resistance, see e.g. pages 15, 116.

OBI : obstruction index.

Measure for bladder outlet resistance, see e.g. page 54.

ROC : receiver operating characteristic.

Summarizes test characteristics, the area under the ROC curve estimates the percentage of correctly classified measurements in a two alternative forced choice experiment, see e.g. page 133.

PURR : passive urethral resistance relation.

Measures bladder outlet resistance, see e.g. page 49.

URA : urethral resistance factor

Measures bladder outlet resistance, see e.g. page 51.

W_{\max} , $W_{Q\max}$, W_{20} , W_{80} : Watts factors

Measures for bladder contractility, see e.g. page 15.

Quite generally in science, when predictions based on our present knowledge succeed, we are pleased but have not learned much. It is only when our best predictions fail that we acquire new fundamental knowledge. But all such subtleties are lost on those who do not comprehend the distinction between deduction and inference, and try to suppress all mention of human information on the grounds that it is “subjective”. Well, human information is all we have and we had better recognize that fact

E.T. Jaynes.

(10th Workshop on Maximum Entropy and Applied Bayesian Statistics, University of Wyoming, Laramie, July 30-Aug 3, 1990)

Introduction.

This thesis is about urination.

Urine is produced by the kidneys and is transported via the ureters (tubes) to the bladder, where it gradually accumulates. The bladder is a urine storage reservoir for most of the time. The degree of fullness of the bladder is sensed by the nervous system and typically at a socially convenient moment, as the bladder is sensed as being “full”, the urine is expelled. The bladder contracts and at the same time the muscles that normally keep the bladder outlet closed (the sphincters) relax, allowing the passage of urine from the bladder via the urethra (another tube) into the outside world. In this thesis we will only discuss this voiding phase of the bladder and not the preceding filling phase. In doing so we will simplify the above described system of tubes, valves and reservoirs by an imaginary dichotomy, the bladder - bladder outlet system¹. The simplification implies that a lot of different anatomical structures are pooled. This is especially true for the bladder outlet (roughly consisting of the bladder neck, the internal/external sphincter, the prostate (in males), the urethra and the meatus (the end of the urethra)). The bladder and the bladder outlet both have clearly defined functions during urination. The bladder contracts in order to expel the urine it contains and the bladder outlet conducts it into the outside world. The contractile properties of the bladder and the flow-rate conducting properties of the bladder outlet are called bladder contractility and bladder outlet resistance. They can be quantified on the basis of physical signals that are measured during voiding, in a so called pressure-flow measurement. The sub discipline of urology that studies, amongst others, this issue and that typically conducts pressure-flow measurements is called urodynamics. Two papers (chapter 1 and 2) that have been included in this thesis discuss specific technical aspects of this pressure-flow measurement. The other papers basically deal with different aspects of the quantification of bladder outlet resistance and bladder contractility on the basis of information obtained by pressure-flow measurements. In order to facilitate a better understanding of these papers we, hereunder, give a brief description of a pressure-flow measurement. In fact we describe the local procedures for pressure-flow measurements (between

institutions small variations in the procedures do occur). We also briefly introduce some of the methods proposed for the quantification of bladder outlet resistance and bladder contractility that feature in our work. A particularly important application of a pressure-flow measurement in males that is often addressed in the included papers and that therefore warrants a short introduction is the diagnosis of bladder outlet obstruction.

0.1 The pressure-flow measurement.

Before urination (micturition, voiding) can take place the bladder must contain fluid. In the measurement situation this often is a saline solution which is slowly infused transurethrally (i.e. via the urethra) through one passage of a double lumen catheter (one catheter with two internal tubes) into the bladder. Typically the bladder is emptied before filling starts so that the empty bladder at the start of filling may serve as a reference point for subsequent bladder volume calculations. If the patient indicates a desire to void the filling process is stopped. The filled volume is known. If the urine production by the kidneys is assumed negligible in comparison to the filled volume the bladder volume may be assumed equal to the filled volume. Then micturition starts. During the process of filling and voiding the pressure in the bladder is measured through the other water filled passage of the double lumen transurethral catheter by means of a disposable pressure transducer. The rectal pressure, which approximates the pressure in the abdominal cavity, is also measured by means of a water filled line. Voiding is done with both catheters in place, in either a sitting or standing position into a flow-meter that records the flow-rate. If females void in a standing position (which is sometimes necessary in video urodynamics (discussed hereunder) the urinary flow is conducted to the flow-meter by means of a hand held receptacle. If males void in a standing position the height of the flow-meter is adjusted accordingly. Therefore, in females, measurements done in sitting and standing position have to be processed differently, taking into account the extra delay caused by a hand held receptacle, if used. This is not necessary for processing measurements done in males. If the bladder is incompletely emptied the post void residual volume may be approximated by subtracting the voided volume from the filled volume (again neglecting the urine production by the kidneys). The pressure measured in the bladder (called intravesical pressure) is affected by the pressure in the abdominal cavity (which is approximated by the rectal pressure). In urodynamic

dataprocessing the “detrusor pressure” is calculated by subtracting the rectal pressure from the intravesical pressure. When the relationship between the flow-rate and associated pressures is studied, the detrusor pressure is used (and not the pressure that is measured in the bladder i.e. the intravesical pressure). The rationale for doing so is that the pressure in the abdominal cavity affects both the pressure in the bladder and the pressure in the flow-rate controlling zone of the bladder outlet to an approximately equal extent. All signals (i.e. the rectal- and intravesical- pressures and the flow-rate) are sampled at a 10 Hz sampling rate and stored on computer disk for further processing.

0.2 Video urodynamics.

Sometimes during filling and/or voiding the function of the lower urinary tract is monitored by means of continuous x-ray visualization. The images may be recorded on videotape (or on a computer storage medium in digital format) for retrospective study. In video urodynamics the saline solution is replaced by a fluid that shows up on the x ray images. Video urodynamics is e.g. used to study incontinence in females. In this type of measurements females sometimes void in a standing position using a hand held receptacle.

0.3 Lagtime correction.

The flow-rate and the detrusor pressure are measured at different locations, the pressures are measured in the patient, the flow-rate in an external flow-meter at a distance that depends on the type of measurement. Due to the finite velocity of the stream exiting the meatus the flow-rate measured at a certain point in time is therefore related to a pressure that was recorded at an earlier point in time. Since a joint (simultaneous) study of the detrusor pressure and the flow-rates is the key idea in the analysis of a pressure-flow measurement the application of an appropriate lag time correction is of theoretical importance. Historically heuristic values (somewhere between 0.5 and 1 s) have been used for this purpose.

0.4 The estimation of bladder outlet resistance.

From the detrusor pressure, the instantaneous bladder volume and the flow-rate the bladder outlet resistance and the bladder contractility can, in principle, be estimated at any moment during voiding. For this purpose, several methods that vary in level of

sophistication, have been described. All these methods are based on the same physical signals. However, the way in which these signals are logically related to estimates of bladder contractility and bladder outlet resistance, varies considerably. On the one hand methods exist in which the information in a pressure-flow measurement is processed using formulae or algorithms that are proposed by experts in the field. Why the formulae are like they are is left unspecified (we have to trust the experts). At the other extreme methods exist in which the information in pressure-flow measurements is transformed to measures for bladder outlet resistance or bladder contractility by means of formulae or algorithms that have a clear (and published) physical rationale. Bladder contractility and bladder outlet resistance typically vary during voiding. Therefore, to enable e.g. treatment efficacy studies, they are calculated at predefined (special) moments during voiding. One such moment, that is most often used, is the moment of maximum flow-rate. The flow-rate at this moment and its associated detrusor pressure will be denoted symbolically by Q_{\max} and $p_{\det.Q_{\max}}$ from now on. Other “special” moments are the moment of maximum power generated per unit of bladder surface area and the moments when 80 and 20% of the (totally) voided volume has been expelled. The latter three moments feature only in the quantification of bladder contractility.

In this thesis a number of methods for the quantification of bladder outlet resistance are used. Two of these methods (BOOI² and URA³) are based on different transformations of the Q_{\max} , $p_{\det.Q_{\max}}$ datapair. The reason for this choice is that Q_{\max} typically occurs for the least flow-rate impeding (i.e. the most relaxed) state of the bladder outlet. This state is of clinical importance as it sets a lower bound to bladder outlet resistance. In a patient the bladder outlet resistance can never be lower than the bladder outlet resistance of the fully relaxed bladder outlet. The Q_{\max} , $p_{\det.Q_{\max}}$ data pair is reduced to one number by means of a formula that is based on expert opinion in the case of BOOI and on the statistical comparison of two groups of patients in the case of URA. Unfortunately the precise details of the latter procedure have never been published to such a degree of detail that a replication by an independent researcher is possible. A third method for the quantification of bladder outlet resistance that we will discuss is basically an extension of the above outlined idea. Instead of using just one data pair for the quantification of bladder outlet resistance (Q_{\max} , $p_{\det.Q_{\max}}$), as in BOOI and URA, more measured data pairs that are

observed for the most relaxed state of the bladder outlet (besides Q_{max} , $p_{det.Qmax}$) are taken into account. These additional data pairs constitute the bottom of a “pressure-flow plot” which is obtained by plotting the measured detrusor pressure as a function

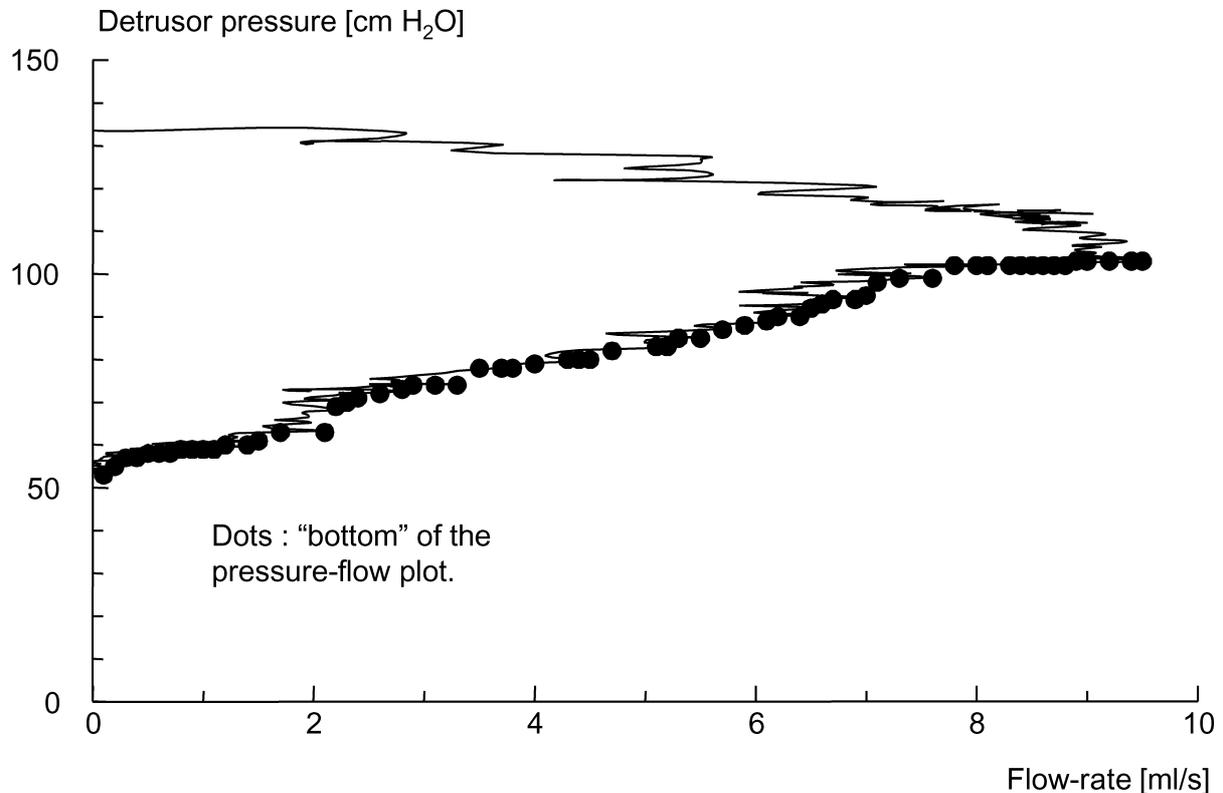


Figure 1. A pressure-flow plot in which the dots depict the “bottom” of the data.

of the flow-rate during voiding (Figure 1 gives an example).

To clarify the rationale for using the “bottom” of this plot as a starting point for the quantification of bladder outlet resistance the bladder may be assumed a flow source, an imaginary device that generates a constant flow whatever the resistance of the outlet that is connected to it. It is now clear that if (at the same flow-rate) the bladder outlet resistance increases the pressure that must be generated by the flow source must increase in order to keep the flow-rate constant. If this argument is reversed it follows that the lowest detrusor pressure that is observed at a particular flow-rate contains information about the least flow-rate impeding state (i.e. lowest resistance) of the bladder outlet at that flow-rate. The set of these “lowest pressures” for all measured flow-rates (i.e. the “bottom” or lowest monotonically increasing part of a pressure-flow plot) therefore contains the total amount of information that is available in a pressure-flow measurement about the least flow-rate impeding state of

the bladder outlet. As this bottom of a pressure-flow plot contains a number of elements that typically varies from measurement to measurement it cannot directly be used for the quantification of bladder outlet resistance. E.g. patient ranking with respect to bladder outlet resistance and the evaluation of treatment efficacy are complicated by this fact. Therefore a procedure (a model, an algorithm, a formula) is needed to reduce the variable number of points in the bottom of a pressure-flow plot to one number, an index for bladder outlet resistance. Schäfer⁴ proposed to model the bladder outlet as a rigid nozzle (a rigid hole in the bladder wall) that opens and starts to conduct urine once the detrusor pressure exceeds a certain threshold (the opening pressure). It can be shown that the relationship between the pressure drop over this nozzle can be expressed as the sum of a quadratic function of the flow-rate and an opening threshold pressure. This model (named PURR or passive urethral resistance relation) can be fitted to the bottom of a pressure-flow plot. In this way two parameters are obtained that characterize this bottom, the estimated opening threshold pressure and a parameter that estimates the linear dependency of the detrusor pressure on the flow-rate squared. Having two parameters still compromises patient ranking, and for this reason Schäfer proposed to use only the assessed opening pressure. In later years people noted that the rigid nozzle is perhaps too much of a simplification of the bladder outlet and proposed more realistic models (the model of the collapsible distensible tube that was described by Griffiths¹ and applied by Spångberg⁵ and Teriö⁶). This model is without a doubt more realistic, which is reflected by the fact that it fits real measurements much better than does PURR. But the “collapsible distensible tube model” contains three parameters, even more complicating the issue of how to reduce these parameters to one measure for bladder outlet resistance. What, e.g. if after an intervention one parameter increases and the other two decrease?

0.5 The estimation of bladder contractility.

For the quantification of bladder contractility we have used two methods in this thesis, one based on expert opinion (the bladder contractility index : BCI²) and one based on an extrapolation of the physical properties of a contracting muscle strip to a hollow spherical muscle (a model for the contracting bladder)^{7,8}. BCI is defined by $p_{\text{det.Qmax}} + 5 Q_{\text{max}}$. This formula is another example of a formula that has no published underpinning (it is simply posed by an expert). The precise details of the second

method are beyond the scope of this introduction. It is important to note that the measures for bladder contractility obtained by the second procedure are related to the mechanical power generated per unit surface area of the contracting bladder wall. They are called Watts factors. In order to compare bladder contractility between patients and measurements, the maximum observed bladder contractility during one voiding (w_{\max}), the bladder contractility at the maximum flow-rate ($w_{Q_{\max}}$) and the bladder contractility calculated at 80 and 20% of the voided volume (w_{20} and w_{80} respectively) are used.

0.6 The diagnosis of bladder outlet obstruction.

Bladder outlet obstruction is a disease that may be diagnosed on the basis of the information in a pressure-flow measurement. A number of different methods have been proposed for this purpose. E.g. in the provisional ICS nomogram⁹ for the definition of bladder outlet obstruction in males the Q_{\max} , $p_{\det.Q_{\max}}$ data pair is plotted in a graph in which three zones are distinguished and labeled obstructed, equivocal and unobstructed. The LPURR¹⁰ method uses the Q_{\max} , $p_{\det.Q_{\max}}$ data pair in a similar way but discerns more categories (the obstruction category is slightly different from that in the ICS nomogram). Bladder outlet obstruction may also be diagnosed on the basis of URA, a measurement is obstructed if $URA \geq 29$ ¹¹. Note that in the later case bladder outlet obstruction is clearly defined as a special high state of bladder outlet resistance since URA is intended to measure bladder outlet resistance. But also BOOI (another measure for bladder outlet resistance) and the demarcation line of the obstruction category in the ICS nomogram are related. The demarcation line is given by $p_{\det} = 40 + 2 Q_{\max}$ and $BOOI = 40 - 2 Q_{\max}$. Thus for the demarcation line in the ICS nomogram BOOI is constant (40 [cm H₂O]), the demarcation line corresponds to a constant level of bladder outlet resistance.

What is striking thus far is the throng of competing methods (especially for the quantification of bladder outlet resistance and the definition of bladder outlet obstruction). It is at least remarkable that so many methods coexist in the competitive scientific environment. A possible explanation is that the difference between the methods is not too important (i.e. the methods that survive perform not too bad for the purposes for which they have been designed). On the other hand an explanation may be that no proper procedure exists to compare the methods in a scientific way.

The development of such a scientific method is difficult. Moreover, if the methods based on expert opinion do not function too badly it is not stimulated either (why bother if it works well?). Still a standardization of methods for the quantification of bladder outlet resistance, bladder contractility and the definition for bladder outlet obstruction seems to be called for. A coherent view may serve to weed out redundant or false methods. But it may also serve to link the three concepts together. They, after all, are logically related. This may be appreciated by observing that a bladder outlet that is obstructed for a certain bladder may not be obstructed for a stronger bladder and an unobstructed bladder outlet for a certain bladder may be obstructed for a less contractile bladder.

0.7 The papers.

The research reported in the papers included in this thesis was conducted over a twelve year period. The papers have, with one exception, been included in chronological order. Therefore more recent papers may contradict earlier ones on some issues. This reflects our own learning curve. Despite the fact that the 7th paper was accepted later than the 8th it precedes it in this thesis as it is a direct logical extension of the contents of the 5th and 6th paper.

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Linearization of a urinary flow-transducer.

Ries Kranse and Ron van Mastrigt.

published in : Med. Biol Eng Comput. 33: 835-7, 1995.

Abstract. In urodynamics, a subdiscipline of urology, the urinary flow-rate is measured to quantify properties of the lower urinary tract.

A frequently used flow-transducer in urodynamics (Dantec Urodyn 1000) has a non linear transfer function. In the commercially available urodynamic measurement systems this non linearity is corrected. As a result of the cost of such a complete system, and the limited possibilities in a research environment, many users may simply want to hook up transducers to a PC to form a custom designed measurement system. This article describes a simple method to test and correct for the non-linearity of the flow-rate-transducer in such a system.

Introduction.

Urodynamics is a subdiscipline of urology concerned with the function of the lower urinary tract on the basis of information in physical signals such as the urinary flow-rate, pressures measured in the bladder and the rectum (or abdominal cavity) as well as voltage variations reflecting pelvic floor muscle activity (EMG)¹. This work focuses on the measurement of the urinary flow-rate.

In urodynamics at least two different types of flow-meters are in use. The first type simply measures the weight of the voided volume as a function of time. Differentiation of this signal provides an assessment of the urinary flow-rate^{2,3,4}. The essential part of the second type of flow-meter is a rotating disk. This disk is kept at a constant angular velocity by means of a feedback control system. Urine that hits the disk is accelerated to the circumferential speed of the disk. The extra energy necessary for this acceleration is proportional to the mass of the urine that "flows through" the device per unit of time. The rotating disk technique has important advantages over the other type of flow-meter^{5,6,7}.

As rotating disk flow-transducers have a non-linear transfer function, the output signal should be linearized. In commercial urodynamic measurement systems such a linearization is built in by the manufacturer. These complete measurement systems are very expensive and not very attractive to research institutions (real time output signals are usually not available and the possibilities for signal processing are limited). We

have therefore decided to develop a urodynamic measurement system using a personal computer, an analog to digital converter and a flow-transducer. This work describes a simple linearization procedure for this type of flow-transducer. The method has been tested on 6 flow-transducers.

Materials and methods.

Six rotating disk flow-rate transducers⁸ were studied. The output of the transducers was electrically amplified and fed to a 12 bit AD-converter board (PCL818) in a standard personal computer. The amplifier output was sampled at a rate of 10 [Hz]. The same amplifier and AD-board were used in all measurements. The input range of the AD-converter was 0-10 [V].

The quiescent output of each flow-transducer was determined by sampling it for approximately 1 minute (no flow-rate applied). Apart from an offset that was digitally subtracted from each sample in subsequent measurements, this yielded an impression of the transducer-output variability which places a limitation on the smallest flow-rate that can be measured with the device.

Each transducer was tested 10 times by pouring in a precise volume of water with a varying flow-rate. Care was taken never to exceed the measurable flow-rate range. Subsequently the zero level was measured again. From each sample the offset value was subtracted. The total number of samples in each artificial voiding was counted and the sum and squared sum of the samples were calculated.

Two hypothetical relationships between transducer output and flow-rate were tested : linear and parabolic (2nd order polynomial).

For each flow-transducer the following systems of equations (linear in the parameters a , b_1 , b_2 and c) were solved by means of a linear least squares method.

$$VOL_i = \sum_{j=1}^{N_i} (a + b_1 x_{ij}) \quad (1)$$

$$VOL_i = \sum_{j=1}^{N_i} (a + b_2 x_{ij} + c (x_{ij})^2) \quad (2)$$

where N_i is the number of samples in the i -th voiding (i runs from 1 to 11, i.e. including the zero measurement), a , b_1 , b_2 and c are model parameters, VOL_i is the volume poured into the flow-meter in the i -th measurement and x_{ij} is the j -th sample of the i -th measurement (the unscaled output of the AD converter).

Systems (1) and (2) were solved by means of the SPSS linear regression procedure. This procedure lists the least squares solutions of the parameters as well as their standard errors (based on the assumption of independent zero mean, constant variance noise).

Following the calculation of a, b_1, b_2 and c , 5 verification measurements were performed (i.e. 4 volumes of 400 [ml] with varying flow-patterns and 1 volume of 30 [ml] in drops, with an average flow-rate of 1 [ml/s], were poured into the transducer). We compared these volumes with the volumes calculated using the determined parameters for each individual flow-meter. An additional 5 verification measurements were performed where volumes were calculated using the averaged parameters a_{av} , b_{2av} and c_{av} (for the quadratic model only) for all six flow-transducers. The absolute values of the differences between the measured and applied volumes were ranked and compared by means of a Mann-Whitney U-test.

Statistical analysis was carried out using the SPSS statistical package.

Results.

Figure 1 shows the output of one of the transducers when 400 [ml] of water was poured in, note the wide range of flow-rate values that thus contributed to the linearization process.

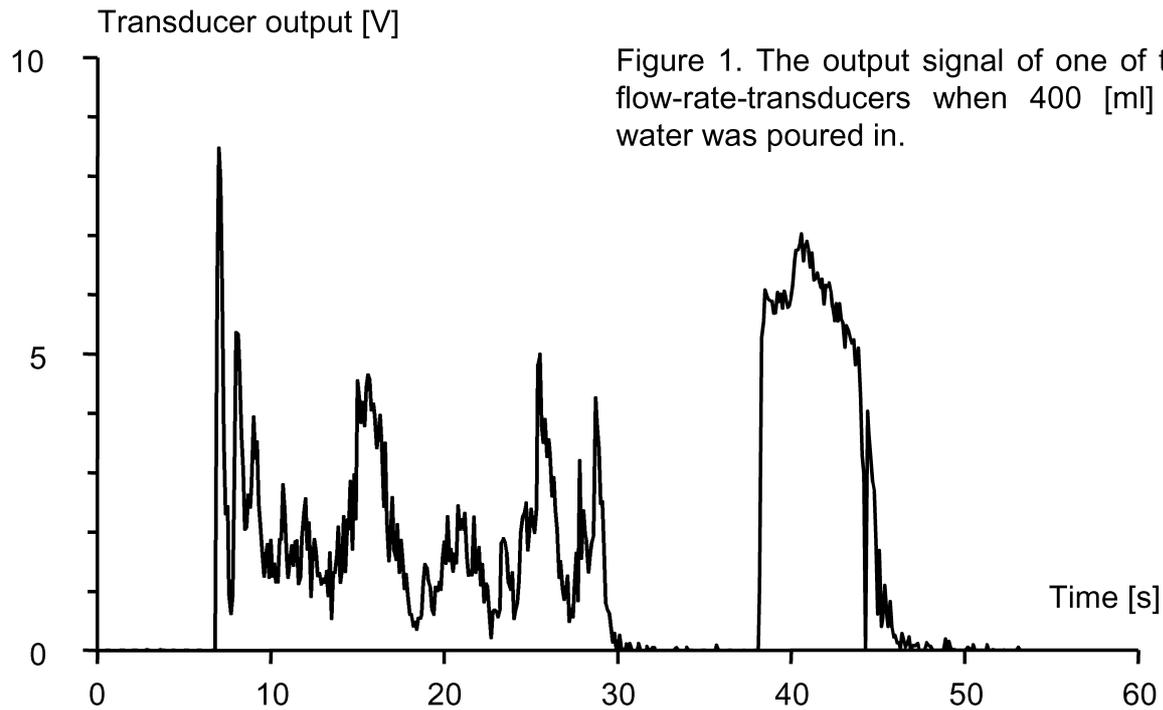


Figure 1. The output signal of one of the flow-rate-transducers when 400 [ml] of water was poured in.

Table 1 lists the transducers' offsets and the standard deviations. Two measurements were performed for each transducer (at intervals of 1 week). It can be seen that the individual transducers have quite different offsets but comparable standard deviations.

Flow-transducer serial number	Offset [V]	Standard deviation [mV]	Number of samples
989	0.32	12	641
	0.33	10	1814
3835	0.44	12	676
	0.44	12	623
3839	0.37	39	558
	0.36	15	1071
3841	0.36	10	633
	0.37	12	1237
5299	0.41	15	736
	0.41	15	1041
5304	0.47	17	604
	0.50	17	1557

Table 1. Measurements of transducer -offset and -standard deviation (measurements separated in time by 1 week).

Estimates and standard errors for b_1 , b_2 and c in eqns. 1 and 2 are summarized in Table 2. The a parameters were zero (as the offset value was subtracted from each sample). From Table 2 the average b_2 and c parameters were derived ($b_{av2} = 395 \times 10^{-2} [\text{ml s}^{-1} \text{V}^{-1}]$, $c_{av} = 138 \times 10^{-3} [\text{ml s}^{-1} \text{V}^{-2}]$).

Flow- transducer serial number	b_1 (mean \pm stderr) $*10^{-2} [(\text{ml/s})/\text{V}]$	b_2 (mean \pm stderr) $*10^{-2} [(\text{ml/s})/\text{V}]$	c (mean \pm stderr) $*10^{-3} [(\text{ml/s})/\text{V}^2]$
989	430 \pm 4	392 \pm 2	117 \pm 5
3835	446 \pm 4	410 \pm 4	133 \pm 12
3839	471 \pm 4	377 \pm 4	141 \pm 10
3841	451 \pm 4	411 \pm 2	112 \pm 5
5299	438 \pm 8	393 \pm 4	180 \pm 19
5304	430 \pm 4	385 \pm 4	143 \pm 17

Table 2. Parameter estimates (plus accuracy-estimates) for the 6 different flow-transducers tested (see formulae 1 and 2).

Table 3 lists descriptive statistics of the absolute values of the differences between applied volumes and measured volumes when individual optimal parameter values were used for the linear and the quadratic transfer function and when average parameters were used.

It follows from these results that the use of a linear model leads to unacceptable inaccuracies for the transducer.

Figure 2 shows the optimal quadratic and linear calibration graphs for a particular transducer (989). The straight line and the parabola yield nearly identical results for flow-rates ≤ 20 [ml/s]. This is confirmed by the results of the 30 [ml] measurements (drops) given in Table 3. For higher flow-rates the quadratic term is essential to obtain accurate results (a reference measurement with 400 [ml] and relatively high and constant flow-rates yielded a volume of 406 [ml] when the quadratic characteristic was used and a volume of 214 [ml] when the linear characteristic was used).

Relative errors in the voided volumes were 6 /30 (20%) for the 30 [ml] volumes and

Type of calibration curve used	Volume difference for 30 [ml] measurements (N=6) in drops, (mean \pm sd)	Volume difference for 400 [ml] volumes (N=24), continuous flow, (mean \pm sd)	Volume difference pooled measurements (N=30), (mean \pm sd)
Individual parameters (linear model)	4.8 \pm 3.6	127.2 \pm 41.1	102.7 \pm 61.8
Individual parameters (quadratic model)	6.0 \pm 3.4	4.9 \pm 3.5	5.1 \pm 3.4
Averaged parameters (quadratic model)	7.7 \pm 3.6	9.7 \pm 7.4	9.3 \pm 6.8

Table 3. Mean and standard deviation of the differences between applied volumes and measured volumes when individual parameter values were used for the linear and the quadratic model and when averaged parameter values were used (for the quadratic model) for "the drop type measurements", the "normal, continuous flow rates" and both types of measurements pooled.

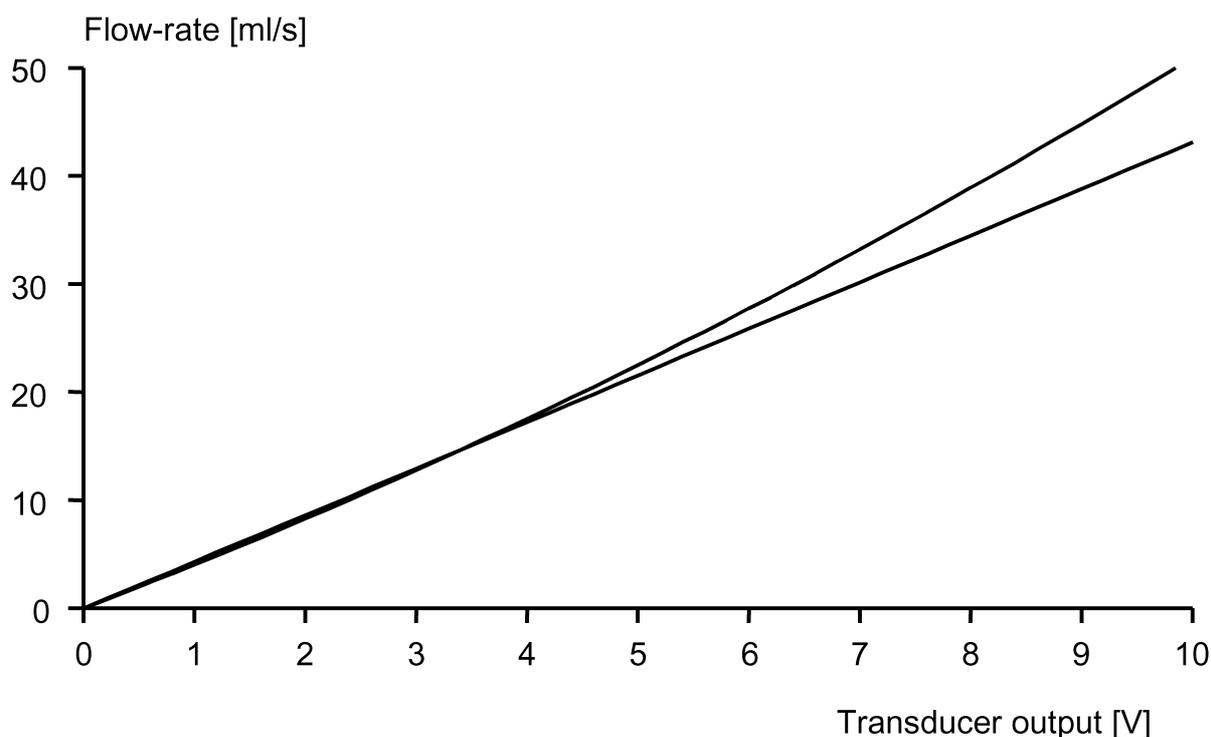


Figure 2. Linear and quadratic calibration curves for transducer 989.

4.9/400 (1%) for the 400 [ml] volumes when the quadratic model was used with optimal (i.e. flow-meter specific) parameters. These figures were 7.7/30 (26%) and 9.7/400 (2%) respectively when average parameters were used. When optimal parameters were used instead of average parameters the difference between the calculated volumes and the actual volumes was significantly smaller for the 400 [ml] ("continuous flow") measurements ($p = 0.027$ Mann Whitney U-test). No such statistically significant difference was found for the 30 [ml] measurements.

Discussion.

Accurate flow-meter linearization (of non linear flow-rate-transducers) is possible using the method described in this work without the use of calibrated flow sources. Prerequisites for this method are a standard personal computer, an AD-converter board and a measuring cylinder. It is based on a non linear transfer function (i.e. the relation between transducer output and flow-rate is a parabola). This non-linearity is important as it almost certainly assures that the eqns. (1) and (2) are linearly independent (the flow patterns are different in every measurement). A test for the theoretical possibility of linear dependence can easily be incorporated into the method.

When 6 flow-meters of the same type (Dantec 1000) were linearized using the described method, we found that the offset values differed considerably between different devices but remained stable over time. As all transducers were connected to the same amplifier this difference must be ascribed to differences between the transducers. In practice an individual offset correction needs to be used for each transducer. The offset variability (12 [mV] on average or approximately 0.05 [ml/s]) implies that roughly speaking flow-rate values below 0.1 [ml/s] cannot be detected. As a consequence measurements at low flow-rates with this transducer are inaccurate (left hand column, Table 3, on average 20% error in volume). Such very low flow-rates occur frequently in urodynamics, e.g. in adult males with obstruction problems and in children. Usually the measured flow-rate is integrated to derive the voided volume which is compared to the volume infused into the bladder to verify if the bladder was emptied completely. The difference is used as an estimate of the amount of post void residual urine which is a very important parameter in urodynamics. It is used in the calculation of bladder contractility parameters⁹ for example. The data show that, in the case of low flow-rates, voided volumes should be assessed by means of a measuring cylinder and

not be derived from the flow-rate measurements.

The accuracy of the rotating disk flow-meters in the case of "normal" flow-rates was in accordance with manufacturer's specifications which we find acceptable for urodynamics. Although the voided volume calculated by the average parameter values was significantly less accurate (in statistical terms) than the voided volume calculated with the "optimal" parameters we feel that the advantage of using equal parameters for different transducers outweighs the (on average) small error thus introduced.

Conclusions.

In summary we can state that the Dantec 1000 rotating disk flow-transducer can be linearized using the described method in such a way that flow-rates can be measured accurately. It must be noted however that the measurement accuracy of this type of flow-meter for small flow-rates is limited.

Acknowledgement.

Electronic equipment to control and amplify the flow-rate-transducers was designed and built by Henk van de Giessen, Hans de Haan and Hans van Rhijn, Central Instrumentation Department, Erasmus University Rotterdam.

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Estimation of the lag time between detrusor pressure and flow-rate signals.

Ries Kranse, Ron van Mastrigt and Ruud Bosch.

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Abstract. In a urodynamic measurement setup there is a considerable spatial separation between the uroflow-meter and the location where the detrusor pressure is measured. Therefore, a "time shift" (or lag time correction) has to be applied to one of these signals in order to align related samples in studies where pressure and flow-rate are considered simultaneously (e.g. assessment of bladder contractility or bladder outlet resistance).

Currently, a heuristic value for this time shift of 0.8 [s] is applied. In this article, we present a method to estimate the lag time directly from the measurements.

Using this method we have found, amongst others, that the mean lag time in our clinic is 0.6 [s] for males, 0.4 [s] for females voiding in sitting position and 1.1 [s] for females voiding in standing position using a special receptacle in video urodynamics. Furthermore, we found that sphincter/urethral activity during voiding (which causes a drop in flow-rate and an accompanying increase in detrusor pressure) is associated (on average) with shorter lag times than straining (when a positive pressure rise accompanies an increase in flow-rate).

Additionally strong evidence is provided that lag time correction is not a major source of error in urodynamics.

Introduction.

In urodynamics, physical signals are measured in order to derive objective measures of the function of the lower urinary tract. These signals are, amongst others, the urinary flow-rate and the detrusor pressure defined as the difference between the pressure measured in the bladder (the intravesical pressure) and the rectal pressure, which is considered equivalent to the abdominal pressure. In a urodynamic setup, the detrusor pressure is thought to originate from the bladder, whereas the flow-rate is measured by a flow-meter that is separated by a distance of 15-60 [cm] (dependent on the specific type of measurement) from the external meatus of the patient. Therefore, there is a delay time between the measured flow-rate-signal and the measured detrusor pressure signal.

A simultaneous study of detrusor pressure and flow-rate-signals allows estimation of bladder outlet resistance^{1,2,3,4} and bladder contractility^{1,5}, two properties that aid the

physician in the differential diagnosis of voiding dysfunction and the choice of an adequate treatment modality⁶. In such a study, related samples in pressure and flow-rate-signals have to be aligned by applying a time shift. Values of approximately 1 [s]⁷ have been suggested. For our setup a time shift of 0.8 [s] has been in use. Possible values up to 5 [s] have been reported⁸.

So far no systematic procedure has been published that allows determination of the lag time in a specific measurement setup. In a pilot study⁹ we presented a first attempt to estimate the lag time directly from the detrusor pressure and flow-rate-signals. The method used, however, can be criticized. In this article we present a superior method which enables the estimation of the average time shift that has to be applied to align detrusor pressure and flow-rate-signals in a specific measurement setup. It was applied to 260 measurements conducted in both males and females. The latter voided in two different positions. The different lag times involved were studied and the consequences for modelling of the urinary tract are discussed.

Materials and methods.

260 urodynamic measurements in 56 male and 74 female patients (30 female patients underwent video urodynamics, 44 underwent a standard urodynamic investigation) were studied (2 consecutive measurements for each patient). For all patients the filled volume, flow-rate, abdominal (p_{abd}) and intravesical pressures (p_{ves}) and a low pass filtered (5 [Hz]) rectified pelvic floor EMG were measured. All signals were sampled at a 10 [Hz] sampling rate (after 5 [Hz] analog low pass anti aliasing filtering) and stored in a personal computer. The detrusor pressure was calculated as $p_{ves}-p_{abd}$. Men voided in sitting or standing position. The position of the funnel of the flow-meter was adjusted in such a way that the distance to the meatus for both situations was comparable. Women voided in standing (video urodynamics, 60 measurements) or sitting position (standard urodynamics, 88 measurements). In standing position a special hand held funnel was used to guide the urine to the flow-meter (length of the device approximately 50 [cm]). The flow-rate signal was measured by means of a Dantec rotating disk flow-meter (Urodyn 1000), pressure signals were measured by means of disposable pressure transducers connected to water filled catheters.

The voiding phase of the detrusor pressure and flow-rate-signals was selected for processing. To these signal parts a mathematical procedure was applied that is basically comparable to the calculation of the cross correlation function as was done in a previous study⁹. In the present procedure an additional pre-processing step (called pre-whitening) was applied to the signals. The details of the method are explained in appendix A, Figure 1 gives a graphical overview. A cross correlation function is derived by first calculating the correlation coefficient between two signals. Then one of the signals is shifted by one sample and the correlation coefficient is calculated again. This procedure is repeated for all possible time shifts. The correlation coefficients calculated in this way are presented as a function of the time shift applied. Usually time shifts are applied in two directions; in our specific application negative time shifts correspond to physical impossibilities or non causal events i.e. variations in flow-rate can never be measured before the associated pressure variations. Loosely speaking, a correlation coefficient measures the degree of likeliness with respect to mutual variations between two signals. Therefore, the calculated cross correlation function can be expected to attain an extreme value for the time shift that causes a "best match" between common signal variations. This time shift equals the lag time caused by the distance that separates flow-meter and pressure transducer. Common signal variations can be positively or negatively correlated and thus positive and negative peaks can occur in the cross correlation function. An interpretation of the polarity of the extreme in urodynamics is deferred to the discussion section of this article. The position (i.e. the lag time), the statistical level of significance or p-value (see Appendix A) and the polarity of the extreme of the first 100 time-shifts in positive and negative direction were determined from the calculated cross correlation functions of all measurements.

In order to obtain an average lag time estimation, the absolute values of the correlation functions for all male patients, all female patients who underwent standard urodynamics and all female patients who underwent video urodynamics were summed. In the summed functions information on the type of extreme (positive or negative) is lost and therefore the absolute values of the negative and positive parts of the sample cross correlation functions were also summed separately.

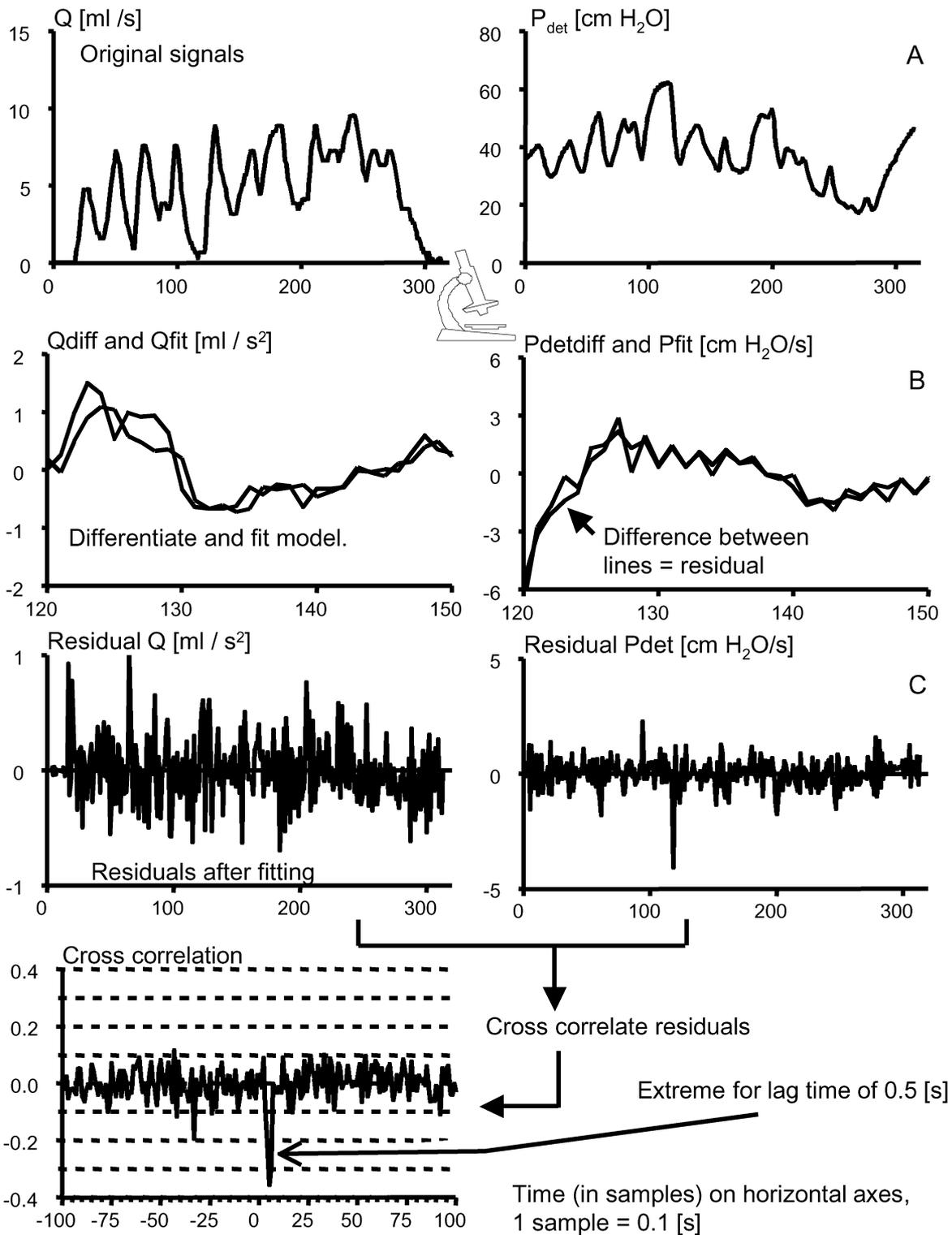


Figure 1. Overview of the signal processing involved in the estimation of the lag time between detrusor pressure and flow-rate signals. The lag time between these signals is caused by the distance that separates the locations where these signals are measured in a urodynamic setup. Row A shows the original signals, row B shows small episodes of the differentiated original signals in conjunction with the response of the fitted autoregressive models. In row C the residuals that result from the subtraction of the fitted models from the differentiated original signals are depicted. The sample cross correlation function is obtained by "cross correlating" these two residuals.

As a first attempt towards quantifying the clinical significance of applying a correct time shift, values for the detrusor pressure at maximum flow-rate ($p_{\text{det.Qmax}}$), the detrusor opening pressure (p_{op})¹⁰ (a flow-threshold of 1 [ml/s] was used) and the detrusor closure pressure (p_{cl} , defined in analogy to the detrusor opening pressure) were determined with- and without applying the appropriate time shift (i.e. 0.6 [s] for males, 0.4 [s] for females in standard urodynamics and 1.1 [s] for females in video urodynamics). For each parameter studied, the absolute value of the difference (between values derived from lag time corrected and uncorrected data) was calculated for each measurement. In this way separate estimates of the error caused by omission of lag time correction were obtained for the first and second measurement in each patient. Secondly for each parameter studied the absolute value of the difference between the parameters obtained in the two consecutive measurements in each patient was calculated (the inter measurement variation) in two ways (with and without lag time correction applied). The intra and inter measurement parameter-variations thus obtained were compared by means of the Mann Whitney U-test.

Results.

Figure 2 shows an example of a measurement with a negative extreme in the cross correlation function. The cross correlation function shows an estimated lag time of 0.4 [s]. Application of this time shift to a small section of the measured signals is shown in Figure 3. Figures 4 and 5 show similar graphs of a measurement with a very significant positive extreme in the cross correlation function.

In 47 of the 112 measurements in male patients, a significant extreme (either positive or negative, $p \leq 0.001$) was found in the cross correlation function. In 37 cases this peak was located in the causal part of the sample cross correlation function, i.e. in the part that can be explained on a physical basis (see materials and methods section). Seven measurements were found with a peak with $p < 0.000001$, the associated lag times were respectively 4, 6, 6, 8, 8, 10 and 12 samples.

In the measurements in female patients, 59 significant extremes were found 18 of which occurred for negative lags (non causal). 14 measurements had a peak with $p < 0.000001$, the associated lag times were respectively -79, -21, 2, 4, 4, 5, 5, 7, 9, 9, 9, 11, 15 and 22 samples.

Figure 6 shows the cumulative cross correlation function for the male patients together with the separate cumulative cross correlation functions for positive and negative excursions only. The lag time for the overall extremes was 0.6 [s]. Figure 7 gives the same graphs for female patients who underwent standard urodynamics and Figure 8 gives the results obtained for female patients who underwent video urodynamics. The overall lags for these two measurement types in women were 0.4 [s] and 1.1 [s] respectively.

Table 1 compares the errors in $p_{\text{det.Qmax},p_{\text{op}}}$ and p_{cl} when lag time correction was omitted with the differences between two successive measurements in the same patient. The former variation was significantly smaller than the latter one (in Table 1, of all possible comparisons, only the least significant p-values are listed). The influence of the receptacle used in video urodynamics can be observed from the higher inter measurement parameter variability in this group.

Discussion.

In the current study, the lag time between the detrusor pressure and flow-rate signals in a urodynamic measurement setup was estimated by means of a statistical procedure based on the cross correlation function. Related variations in detrusor pressure and flow-rate-signals are shifted in time as a consequence of the distance that separates the flow-meter from the location of pressure measurement. When common signal variations occur the lag time causes a statistically significant peak in the calculated cross correlation function.

We found only 106 (47 for males + 59 for females) significant ($p \leq 0.001$) extremes in 260 measurements studied, implying that for the majority of measurements (154 = 260 - 106) no lag time estimation was possible. This can be explained in two ways. The most probable explanation in our view is that in these measurements related variations in the detrusor pressure and flow-rate signals were absent. An alternative explanation is that the lag time varied drastically during these measurements so that none of the "fluctuating lag times" present gave rise to a significant peak in the cross correlation function. Such a variation might possibly result from variations in the position of the point of impact of the urinary stream on the flow-meter funnel.

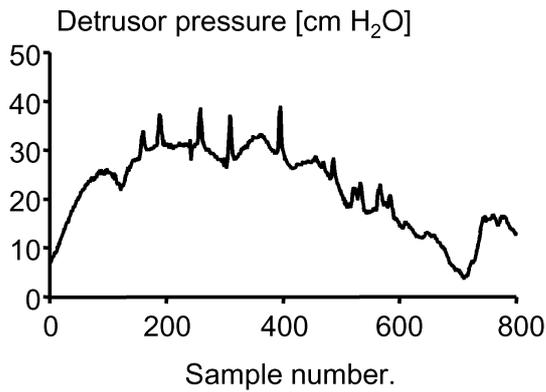
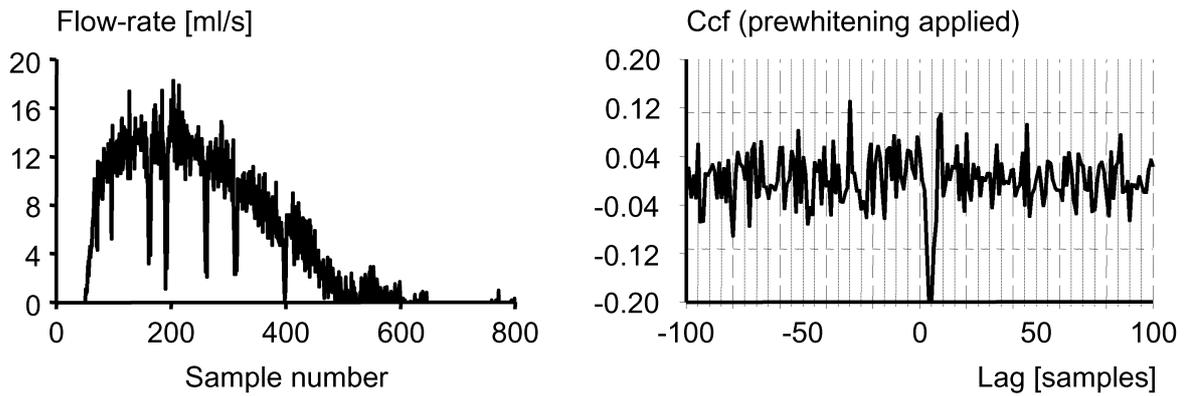


Figure 2. Flow-rate signal, detrusor pressure signal and cross correlation function of a measurement with a negative extreme. Such a negative extreme implies that variations in flow rate and detrusor pressure signals have opposite polarities. These variations are probably related to urethral or sphincter activity.

Time on horizontal axes in samples, 1 sample = 0.1 [s].

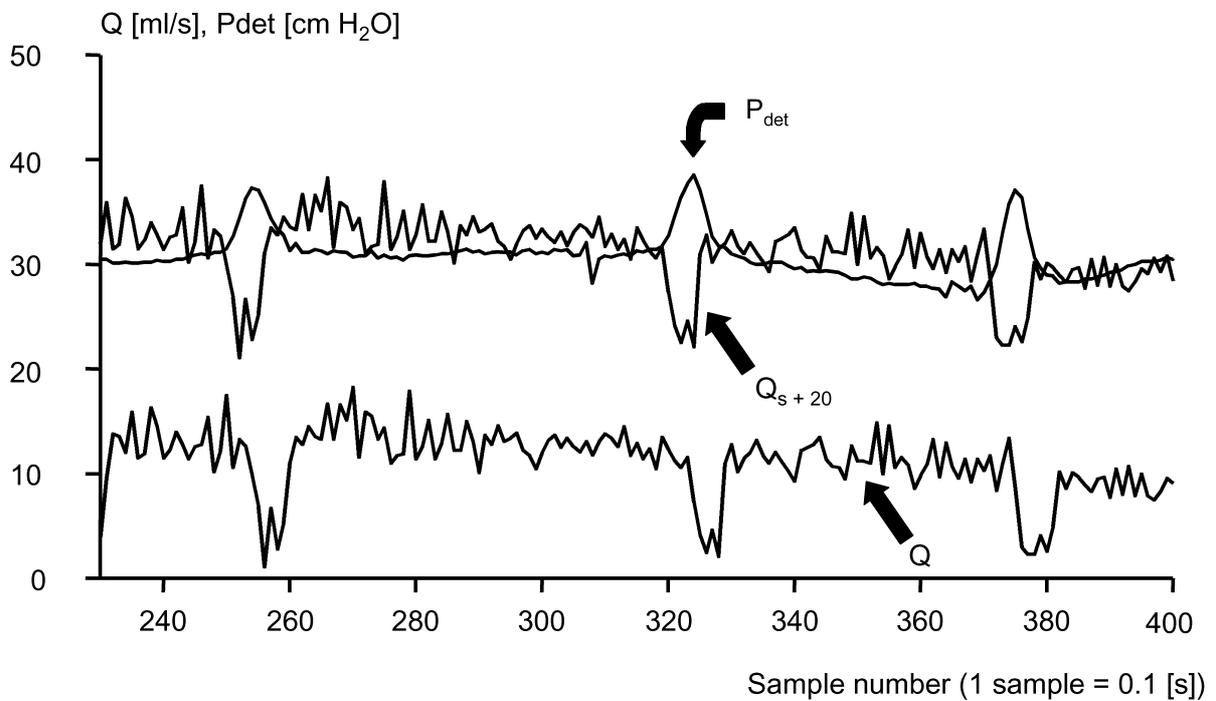


Figure 3. Application of the lag time estimated from the cross correlation function in Figure 2 (of 0.4 [s]) to a small section of it. The lag time corrected flow rate was shifted upwards to facilitate the comparison with associated pressure variations.

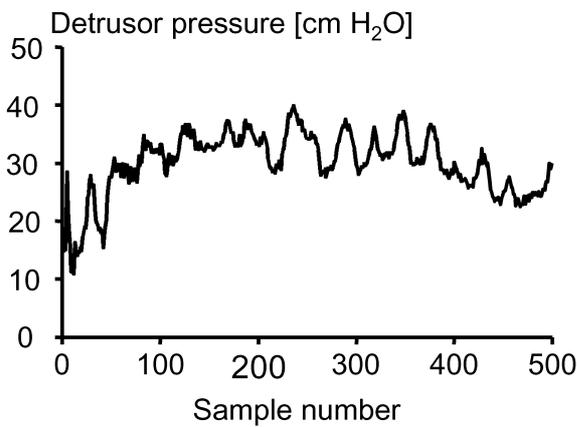
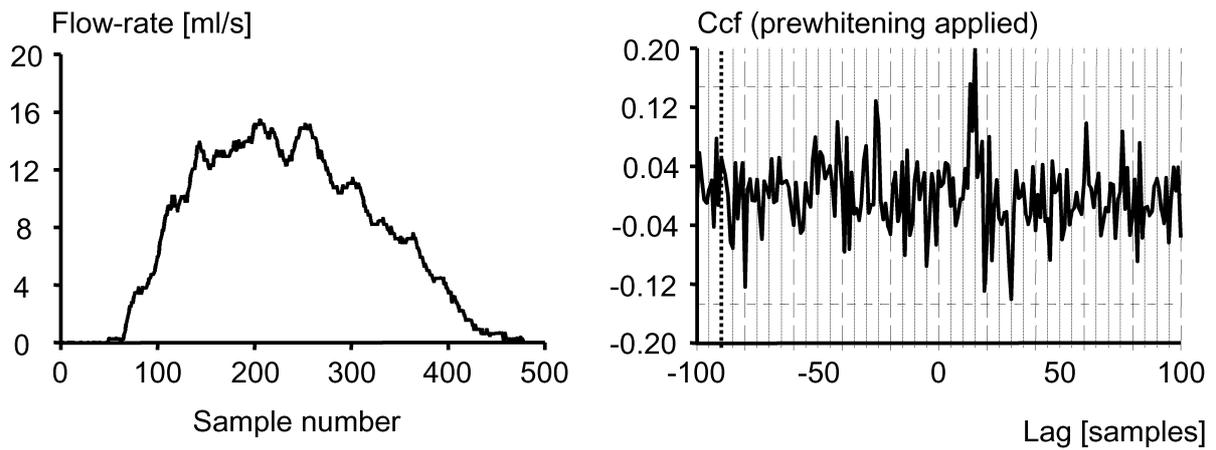


Figure 4. An example of a measurement with positively correlated signal variations (note the positive peak in the cross correlation function). The shown signal variations are very likely related to straining.

Time on horizontal axes in samples, 1 sample = 0.1 [s].

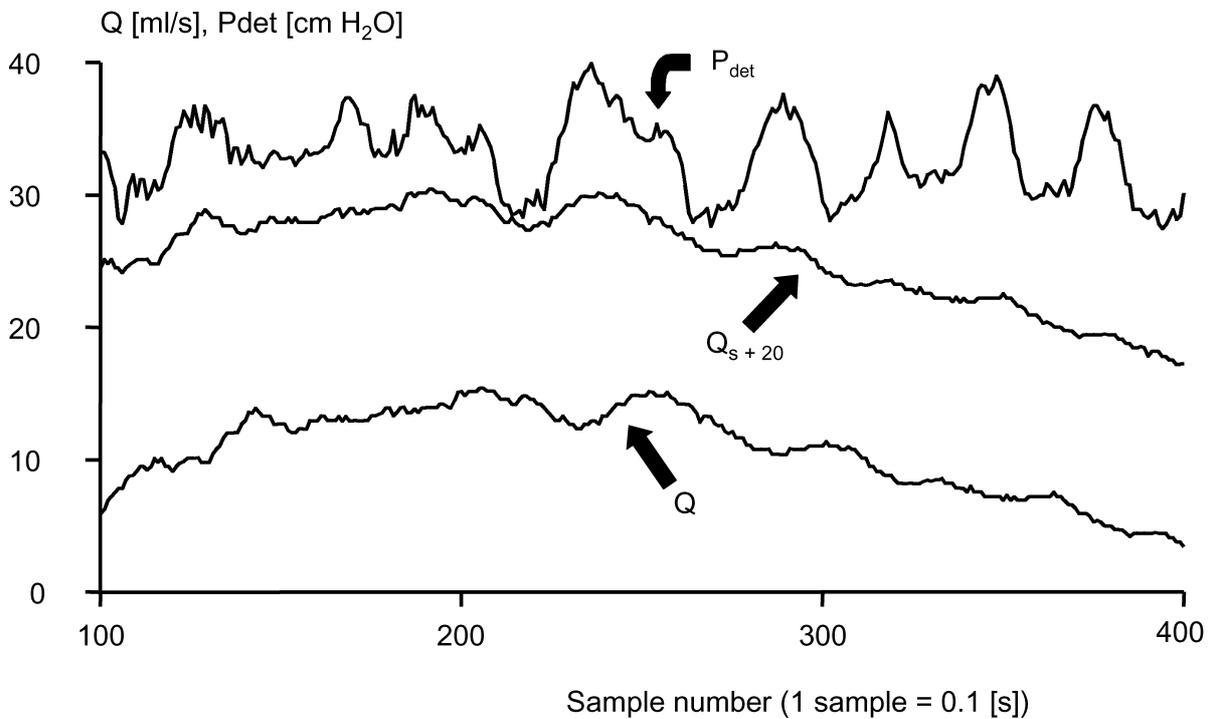


Figure 5. Application of the estimated lag time (of 1.5 [s]) to a small section of Figure 4. As in Figure 3 the lag time corrected flow was shifted upwards.

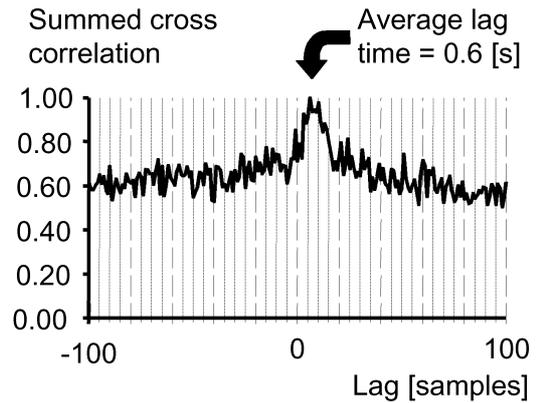
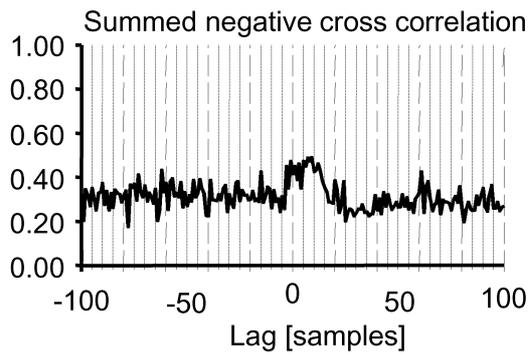
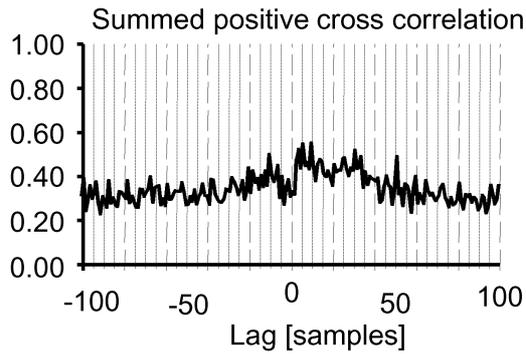


Figure 6. Male patients. Summed cross correlation and separately summed positive and negative cross correlation functions for males. The extreme in the summed cross correlation function represents an average lag time in male patients of 0.6 [s].

Time on horizontal axes in samples, 1 sample = 0.1 [s].

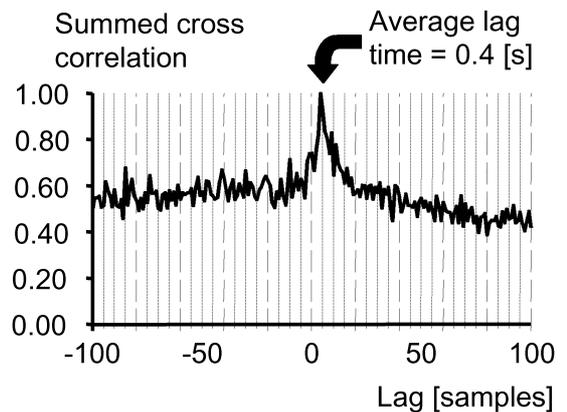
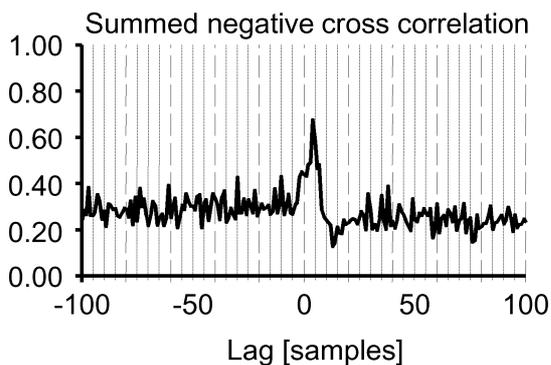
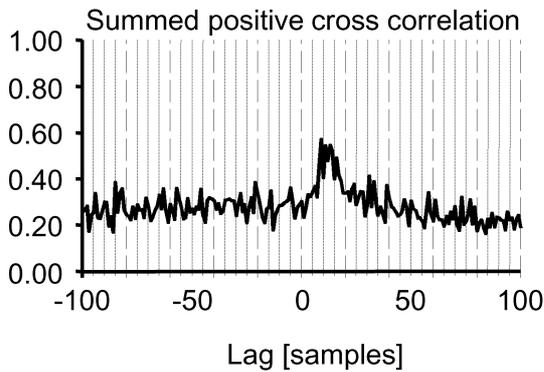


Figure 7. Female patients (standard urodynamics).

Summed cross correlation and separately summed positive and negative cross correlation functions for females that underwent standard urodynamics (average lag time = 0.4 [s]).

Time on horizontal axes in samples, 1 sample = 0.1 [s].

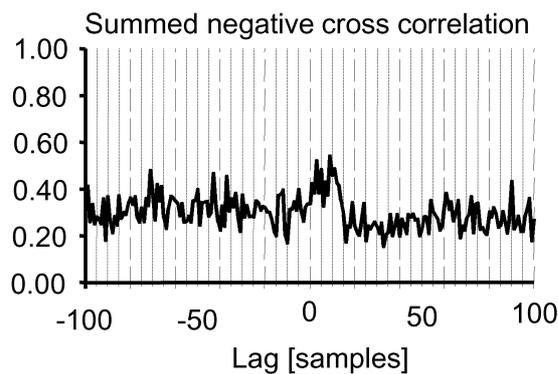
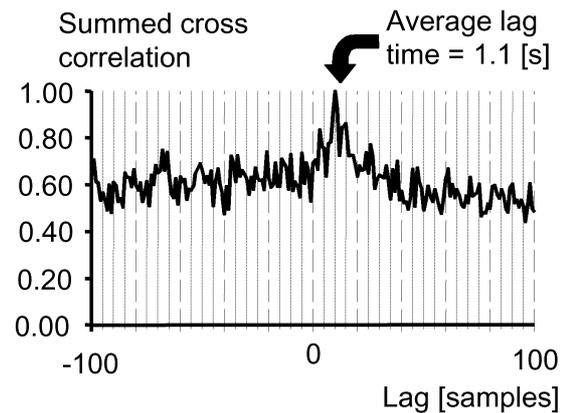
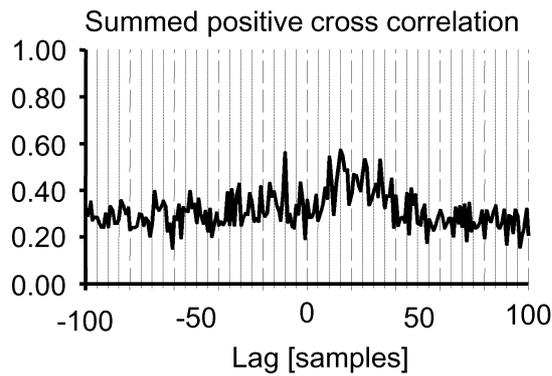


Figure 8.
Female patients (video urodynamics).

Summed cross correlation and separately summed positive and negative cross correlation functions for females that underwent video urodynamics (average lag time = 1.1 [s]).

Time on horizontal axes in samples, 1 sample = 0.1 [s].

Patients	Parameter studied	Error caused by omission of lag time correction [cm H ₂ O]		Difference in parameter studied between successive measurements in one patient [cm H ₂ O]	
		Measurement 1	Measurement 2	No time shift applied	Time shift applied
Males, 0.6 [s]	$p_{det.Qmax}$	1.6 **	2.1 **	9.1	8.7
	p_{op}	2.0 **	2.1 **	13.0	13.2
	p_{cl}	3.7 **	3.6 **	19.0	19.8
Females, standard urodynamics lag time 0.4 [s]	$p_{det.Qmax}$	1.2 **	1.0 **	6.2	6.4
	p_{op}	2.3 **	1.5 **	9.5	9.1
	p_{cl}	2.4 **	2.2 **	11.5	9.2
Females, video urodynamics, lag time 1.1 [s]	$p_{det.Qmax}$	3.6 (p = 0.02)	2.0 (p = 0.007)	7.9	6.8
	p_{op}	4.6 (p = 0.003)	3.7 (p = 0.006)	9.2	9.0
	p_{cl}	6.0 (p = 0.007)	3.0 (p = 0.002)	15.3	12.0

Table 1. The error in detrusor pressure at maximum flow rate $p_{det.Qmax}$, the opening pressure (p_{op}) and the closure pressure (p_{cl}) when lag time correction was omitted compared to the difference between two successive measurements in the same patient (of all possible comparisons the least significant p-values are listed)

** p < 0.0001.

Twenty-eight (10 for males and 18 for females) significant peaks occurred for negative delays (i.e. non causal events, see materials and methods section) which correspond to physical impossibilities. These numbers can be explained on the basis of the p-value used in the definition of a significant extreme ($p \leq 0.001$). We searched for significant extremes in 260 cross correlation functions. The search was limited to 201 points (i.e. no lag, 100 non causal lag times and 100 causal lag times) so that $201 * 260 = 52260$ cross correlation entries were inspected. Therefore, $0.001 * 52260 = 52$ spurious extremes could be expected. Half of these should occur in the causal part of the cross correlation function which compares favourably with 28 occurrences found. The previous argument also leads to the conclusion that only $106 - 2 * 26 = 54$ of the extremes detected from the total of 260 measurements processed (roughly 20%) correspond to common signal variations that are shifted in time. Interpretation of a cross correlation function of an individual measurement is further complicated by the fact that in some rare cases (2 measurements, both in females, out of 260) common signal variations were present that cannot be causally related but that did give rise to a very significant extreme in the calculated cross correlation function ($p \leq 0.000001$). This does not disqualify the method used; visual inspection of the measurements showed common artifacts in both signals.

In conclusion, we can state that because of the difficulties with the interpretation of extremes (i.e. is an extreme spurious or not?) the practical applicability of the method used in individual measurements, is limited.

Summation of the absolute values of the sample cross correlation functions in the whole group of patients tested, however, yielded a clear impression of the average lag time for the specific measurement setup in males, females who underwent standard urodynamics and females who underwent video urodynamics. Figure 6 shows that the summed cross correlation function for males has an extreme for a lag time of 0.6 [s] and it is obvious that most of the extremes in this summed cross correlation can be related to negatively correlated variations in detrusor pressure and flow-rate-signals (as can be observed by studying the separately summed positive and negative cross correlation functions). Negative correlations can be associated with urethral or sphincter activity (a decrease in flow-rate accompanied by an increase in detrusor pressure, see the

example in Fig 2). Comparison of the graphs in Figure 7 shows that the extreme for females who underwent standard urodynamics occurred for a delay of 0.4 [s]. In these measurements positive as well as negative correlations were found. As the peak in the separately summed positive correlations is positioned to the right (at 0.9 [s]) of the peak in the separately summed negative correlations (at 0.4 [s]), we conclude that positive correlations (very likely related to straining where an increase in detrusor pressure is accompanied by an increase in flow-rate) are related to longer lag times. In addition lag times caused by positively correlated events (straining) seem to vary over a wider range of values than lag times caused by negatively correlated events. This latter observation can be explained by the fact that the degree of straining can be varied whereas urethral or sphincter activity has a more or less on-off character. The extreme of the cumulative cross correlation function for video urodynamic measurements (females who voided in a standing position using a hand-held funnel) occurred for a lag time of 1.1 [s]. Again positive and negative lags were found and again it seems that positive correlations are "slower" than negative ones (it seems from Figure 6 that this is probably also true for males). The fact that negative correlations occur at smaller lag times than positive ones in all patient groups can be explained by the observation that urethral/sphincter contraction during a bladder contraction usually occurs in that part of micturition where the fluid velocity is relatively high. In contrast straining usually occurs when voiding is troublesome (and probably at low fluid velocities).

Inspection of Figures 6,7 and 8 leads to the conclusion that in our measurement setup lag times are (approximately) limited to the interval of 0.2-2 [s].

Comparison of Figure 7 and 8 shows that voiding through the hand held funnel (as used for video urodynamics) leads to an extra signal delay of 0.7 [s] and to extra noise.

The fact that the error in $p_{det.Qmax}$, p_{op} and p_{cl} caused by omission of lag time correction was significantly smaller than the difference between two successive measurements in one patient (Table 1) indicates that the clinical relevance of optimal lag time correction is probably limited. Although the parameters mentioned are not the only urodynamic parameters that might depend on lag time we think it is very unlikely that other parameters or functions (e.g. bladder contractility as a function of bladder volume) are more sensitive to optimal lag time correction.

In conclusion, it can be stated that the method presented in this study is very suitable to assess the average lag time between detrusor pressure and flow-rate-signals in a specific urodynamic measurement setup. Estimation of these average lag time values enables the application of optimal time shifts in the calculation of bladder contractility and bladder outlet resistance parameters in males and females (in standard and video urodynamics). Based on our results we suggest to use lag time corrections of 0.4 [s] (for sitting voiding) and 1.1 [s] (for standing voiding using a hand held receptacle) when studying measurements in females and of 0.6 [s] when studying measurements in males (if a comparable setup is used).

Application of the method further showed that pressure and flow-rate variations associated with urethral or sphincter activity have smaller lag times than signal variations associated with straining and that the range of lag times associated with signal variations caused by straining is wider than that for signal variations caused by urethral or sphincter activity.

When no lag time correction was applied the error in the detrusor pressure at maximum flow-rate amounted to 3.6 [cm H₂O] in the worst case (females voiding in a standing position through a hand held funnel). When compared to the observation that the average difference between two consecutive measurements in the same group amounted to 6.8 [cm H₂O] this strongly suggests that lag time correction is not a major source of error in urodynamics.

Appendix A.

The theory used in this appendix is discussed in much greater detail in "The analysis of time series" by C.Chatfield¹¹ and in "Spectral analysis and its applications" by Jenkins and Watts¹².

The lag time estimation procedure applied to the detrusor pressure- and flow-rate-signals comprised the following steps (see Figure 1) : first the detrusor pressure and flow-rate-signals were detrended by differentiation (in this way slow trends were removed from the signals). Next a statistical model was fitted to the data (an auto regressive model). The result of this process of differentiation and model fitting is depicted in row B of Figure 1. The residuals (which equal the difference between the fitted models and differentiated signals) can be described as white noise (see row C of Figure 1). They, however, still contain common time shifted variations provided these were present in the original signals. Cross correlation of the residuals gave a function that attained an extreme value for the correct time-shift. Mathematically the calculation of the cross correlation function can be formulated as follows :

$$r_{xy}(k) = \frac{c_{xy}(k)}{\sqrt{(\text{stddev}(x) \text{stddev}(y))}} \quad (1)$$

where $k = -(N-1)..N-1$, $r_{xy}(k)$ is the cross correlation for time shift k , $c_{xy}(k)$ is the cross covariance for time shift k and $\text{stddev}(x) * \text{stddev}(y)$ denotes the product of the standard deviations of the time series x and y .

$C_{xy}(k)$ is defined by (2) and (3).

$$c_{xy}(k) = \sum_{t=1}^{t=N-k} (x_t - x_m)(y_{t+k} - y_m) / N \quad (2)$$

for $k = 0,1 .. N - 1$, and

$$c_{xy}(k) = \sum_{t=1-k}^N (x_t - x_m)(y_{t+k} - y_m) / N \quad (3)$$

for $k = -1, -2, \dots, -(N - 1)$.

In formulae 2 and 3 x_t and y_t denote the individual samples of time series x and y , N the total number of samples in the series and x_m and y_m are the averages of the time series x and y .

Extremes in this sample cross-correlation function can be interpreted in a statistical context if the two signals x and y are white noise processes. For two such uncorrelated white noise signals the expected value of the sample cross correlation function varies around a mean of zero with a standard deviation of $1 / \sqrt{N}$ (N is the number of samples used in the calculation). Two adjacent terms of this sample cross correlation function are practically uncorrelated for large values of N . Assuming that entries in the sample cross correlation function are distributed according to a normal distribution (which is reasonable for large values of N because they basically equal the sum of a large number of identically distributed random variables, see formulae 1,2 and 3), a test for non zero cross correlation can be used.

Computer simulation experiments indicated that lag times between two time-shifted series could be detected even when the amplitude of noise signals equalled 2.5 times the amplitude of the shifted signals.

All signal processing was done by means of the Matlab[™] system identification package. The Matlab source code of the procedure outlined above can be obtained from the authors.

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Computer assisted pressure-flow analysis.

Ron van Mastrigt and Ries Kranse.

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3.1 Introduction.

To an increasing extent computers are penetrating modern society. In clinical urologic practice and research a number of fundamentally different tasks can be identified in which computers can, do, will or might play a role to a varying degree and with different impact¹. Apart from administrative applications, in which computers already are prominent, the most critical and promising field for computer use in urology is in the analysis of urodynamic data². The many signals such as pressures, flow-rates, volumes and electromyograms that are measured in urodynamics carry information that is essential for a correct diagnostic work up of the lower urinary tract. Abstracting this information from the signals is a laborious and not always straightforward task. Because all modern urodynamic equipment uses a computer for the measurement and display of urodynamic signals it is inevitable that this machine will also be used for the analysis of the data, and eventually for a computer-suggested diagnosis. For this reason a real discussion of advantages and disadvantages of the use of computers for urodynamic analysis seems irrelevant, but a few remarks can be made. Apart from the obvious efficiency, computer based analysis ensures objectivity, in the sense that human observer bias and incidental errors are excluded. This might even be a precondition for clinical trials that involve statistical data processing. A possible disadvantage that is mentioned frequently is that automatic data analysis may introduce errors by misinterpretation of artefacts and measurement errors. This can be illustrated using many of the existing computerized urodynamic measurement systems that automatically display a maximum flow-rate. Very often the displayed value is simply the mathematical maximum of the flow-rate signal in the observation interval. Kicking the flow-meter during the measurement gives an artefactually high reading. To prevent this type of errors, automatic data analysis necessitates embedded data quality control. A simple solution for the above maximum flow-rate artefact was implemented as early as in 1980 in the computer program CLIM³ : The measured

flow-rate signal is displayed together with a cross-hair to indicate the calculated maximum. This could be accepted or corrected by the user. Better solutions to this simple problem include filtering, or verifying the duration of the maximum, illustrating that correct automatic interpretation of data corrupted by artefacts is what users of urodynamic equipment may (eventually) expect. This article discusses automatic interpretation of urodynamic pressure-flow studies.

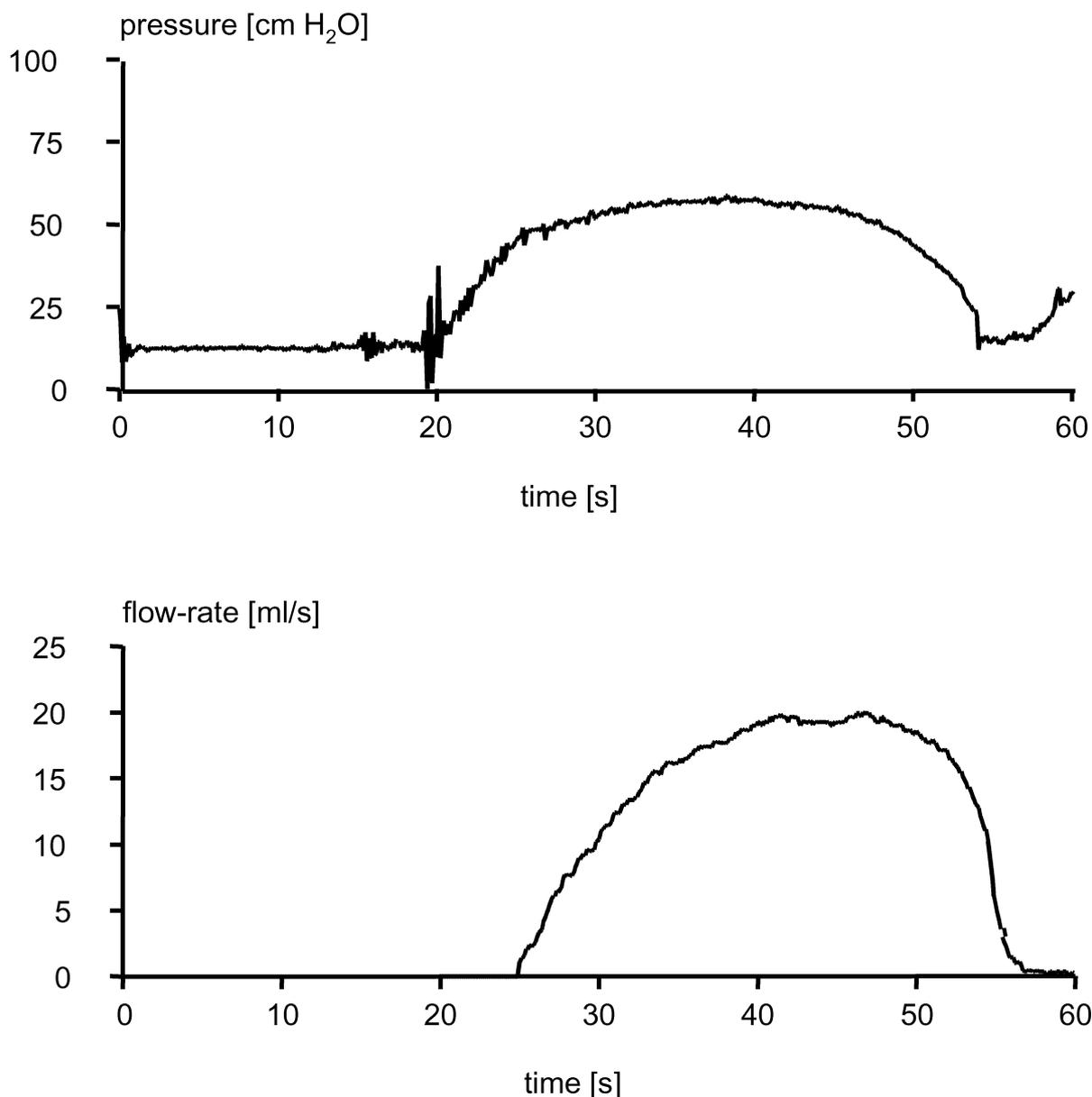


Figure 1. Detrusor pressure and flow-rate measured during voiding cystometry in a male patient. Data sampled at a rate of 10/second using a PC.

3.2 Urodynamic pressure-flow studies.

The properties and format of urodynamic pressure flow studies have been described in another contribution to this issue⁴. Briefly summarized, detrusor pressure, the difference between the pressure measured in the bladder and the abdominal pressure measured in the rectum, and instantaneous flow-rate are measured simultaneously during voiding. Figure 1 shows an exceptionally beautiful example of such a measurement. The measured signals reflect properties of both the detrusor and the urethra : In modeling terms the interaction of the contractility of the detrusor and the resistance of the urethra results in the instantaneous pressure and flow-rate values⁵. Therefore, these values carry information relating to both the detrusor contractility and the urethral resistance. Unfortunately the information is somehow concealed. Neither the pressure, nor the flow-rate signal is uniquely related to resistance or contractility. It is the purpose of pressure-flow analysis to uncover the diagnostically relevant concealed information. This information takes the form of single or multiple parameter values that represent the desired properties. We now discuss urethral resistance parameters and contractility parameters.

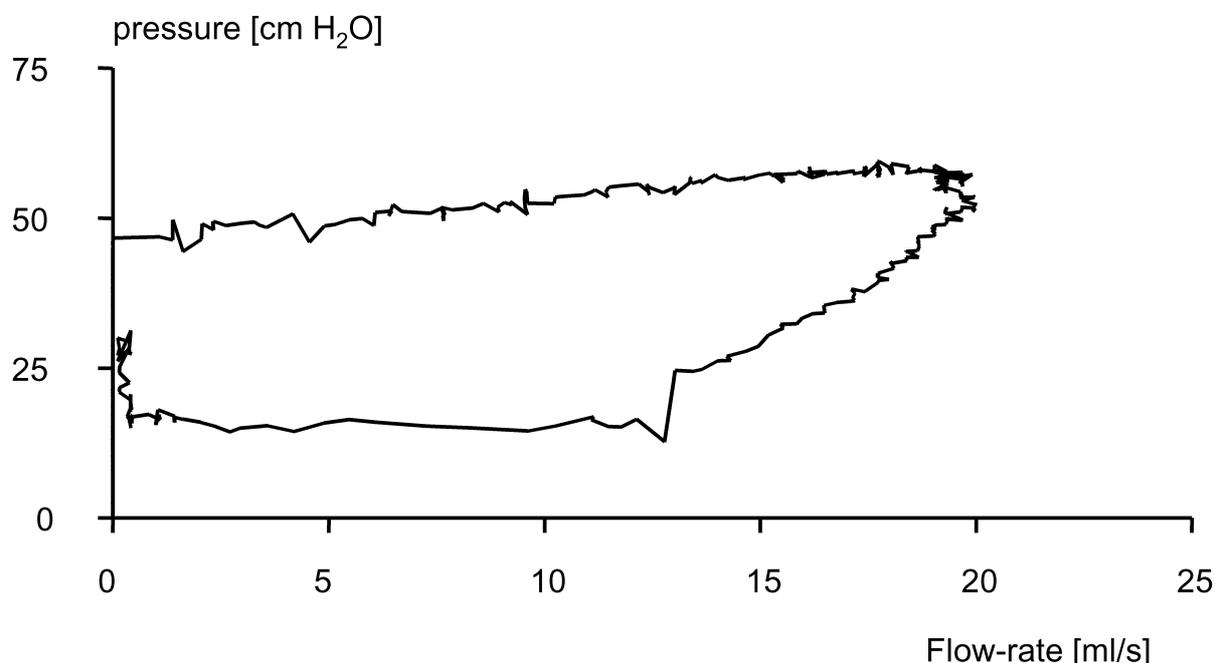


Figure 2. The detrusor pressure displayed in Figure 1 plotted as a function of the flow-rate. To compensate for the distance between the (rotating disk) flowmeter and the (external) pressure transducer the pressure-signal was delayed by 8 samples or 0.8 seconds.

3.3 The urethral resistance relation.

Pressure-flow data are not plotted as a function of time, as shown in Figure 1, but as an x-y plot. Figure 2 shows such a presentation of the data in Figure 1. It is obvious from this plot that the state of relaxation of the urethra and bladder neck varied during the voiding : at each flow-rate value high and low pressure values were measured. The high pressure values represent a relatively unrelaxed state of the urethra, the low pressure values a more relaxed state. Therefore, the low pressure values of the pressure-flow plot (the part of the "loop" closest to the flow-rate axis) represent the urethral resistance of the patient in the most relaxed state and are called the urethral resistance relation. This part of the pressure-flow plot can be selected automatically from the measured data using a simple computer program⁶, and the 40 circles in Figure 3 are the data resulting from application of such a program to the information presented in Figure 2. To prevent artefacts from biasing this selection process prior filtering of the pressure-flow data is necessary⁷. The selected data points, the circles in Figure 3, are a measure for the urethral resistance of the patient during the pressure-flow study. The direct use of this data is impractical. Not only is this a considerable set of numbers (on average 31 pressure values and 31 flow-rate values when data are sampled at a rate of 10/second) but it is very difficult to compare these sets between patients before and after treatment. Models are used to reduce this number of data points to a few parameters. Such a model is a mathematical description of the relation between the flow-rate and the pressure-values.

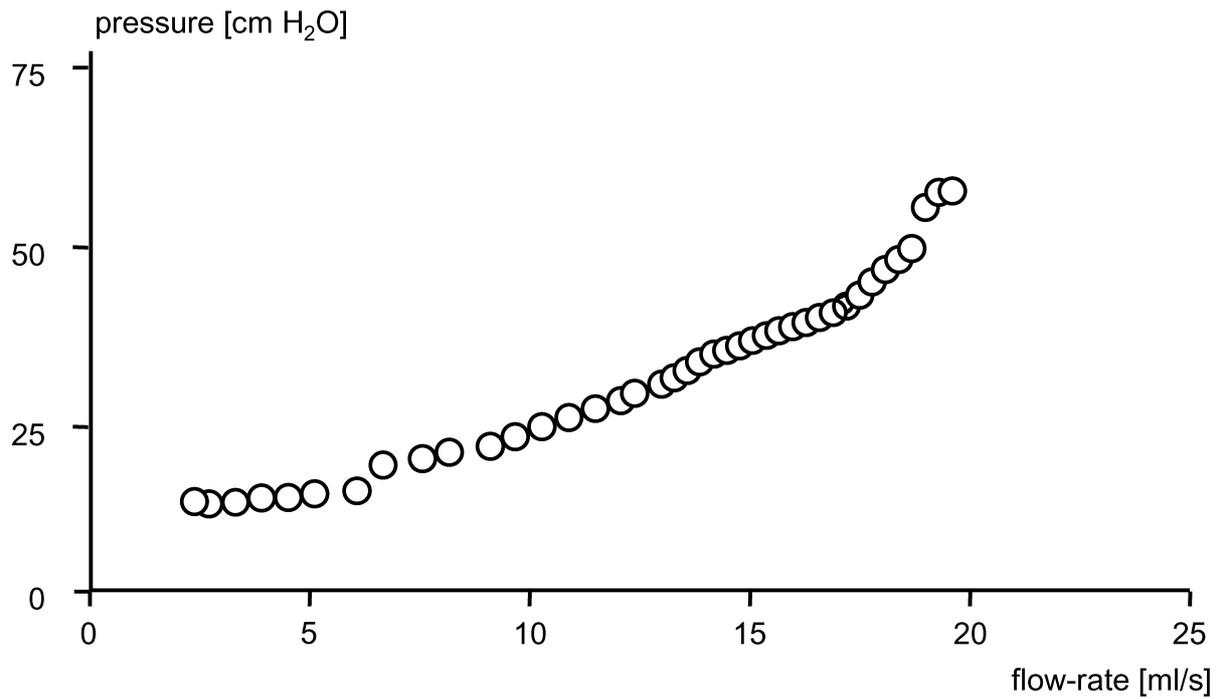


Figure 3. The part of the pressure-flow data in Fig. 2 closest to the flow-rate axis, as automatically selected using a computer program. The 40 pressure and flow-rate values (circles) represent the urethral resistance of the patient during this voiding.

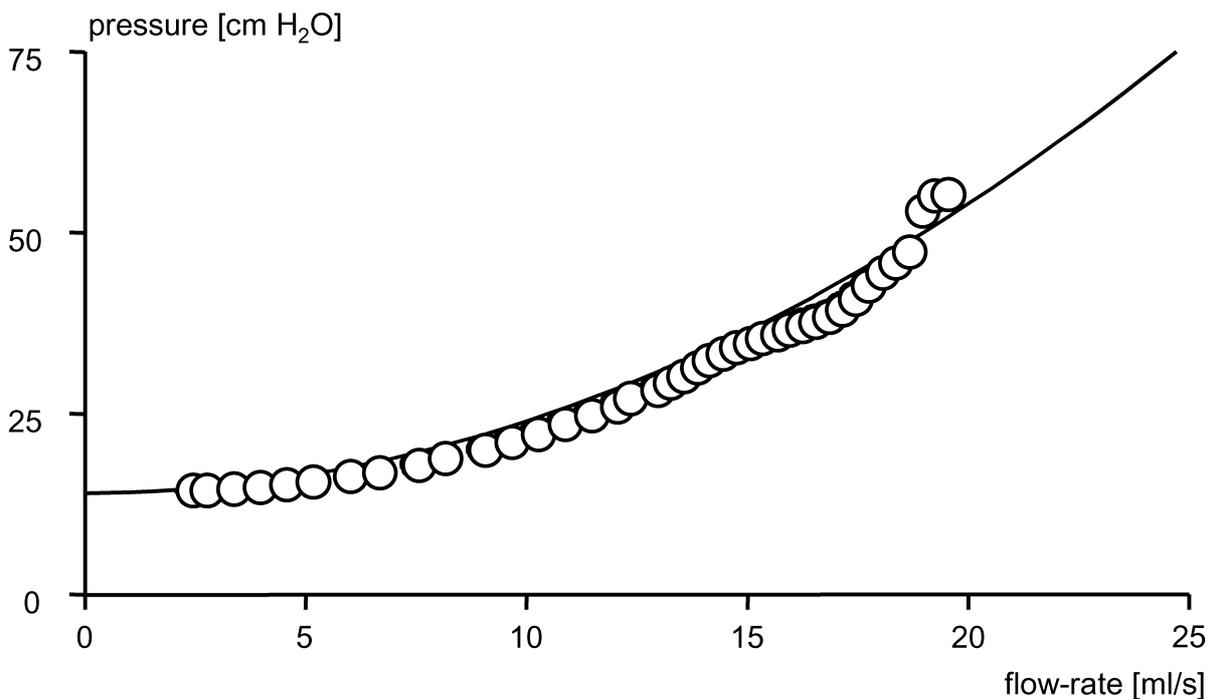


Figure 4. A parabola with a theoretical opening pressure of 14 [cm H₂O] and a steepness of 0.10 [cm H₂O/(ml/s)²] matches the data points of Fig.3 perfectly.

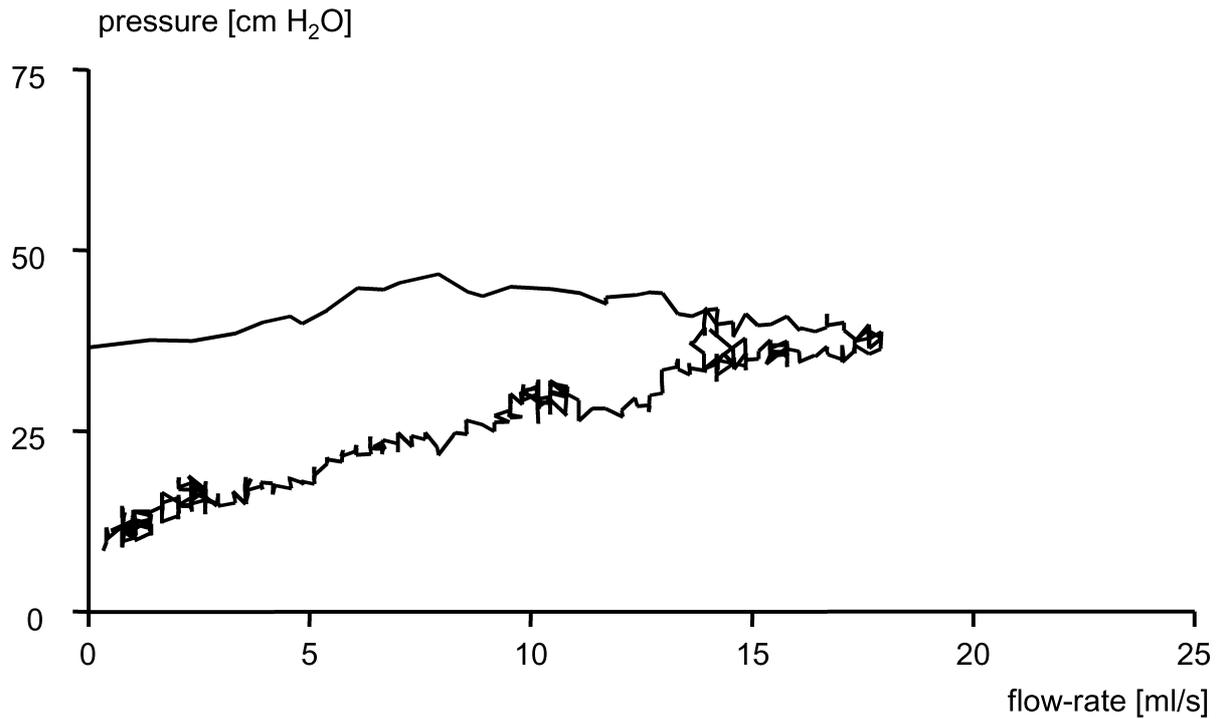


Figure 5. A pressure-flow plot that does not show a quadratic relation between pressure and flow-rate.

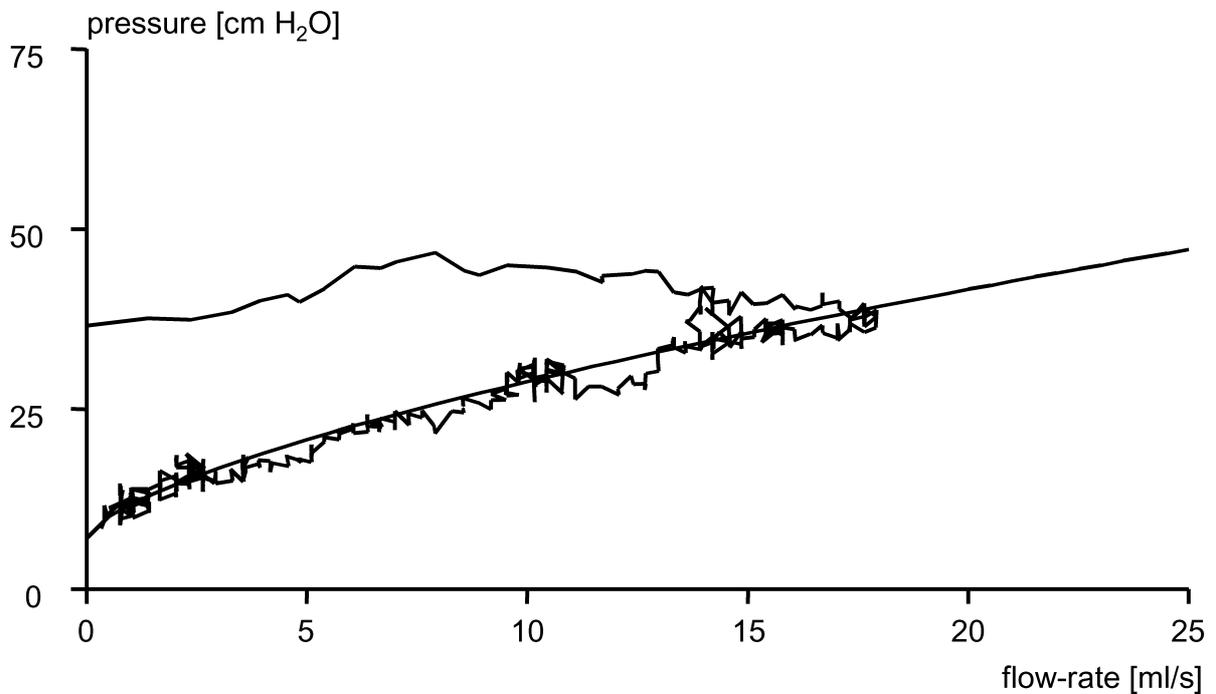


Figure 6. Using the exponential model the pressure-flow data of Fig. 5 can be characterized by a theoretical opening pressure of 7 [cm H₂O], a steepness of 4.7 [cm H₂O/(ml/s)^{0.66}] and a shape factor of 0.66. The bold line shows how this model fits the low pressure values of the data.

3.4 Models for the urethral resistance relation.

At present four models are in use for analysis of pressure-flow data, (1) "quadratic", (2) "linear", (3) "exponential" and (4) "polynomial".

The quadratic model describes fluid flow through a rigid nozzle and has been in use for quite a while (PURR⁸). It describes the relation between pressure and flow-rate in the urethra in terms of a parabola defined by two parameters : its steepness, and its intersection with the pressure-axis. The terminology for the latter parameter is very confusing, we will call it the theoretical opening pressure. With the quadratic model, which perfectly matches the pressure-flow data shown in Figures 1,2 and 3, this data can be represented adequately by a theoretical opening pressure of 14 [cm H₂O] and a steepness of 0.10 [cm H₂O/(ml/s)²]. Figure 4 shows how well a parabola with these parameters fits the data points of Figure 3. Unfortunately most pressure-flow plots do not have a quadratic appearance. In a study of 21 elderly men without voiding problems only 9% of the 76 measured pressure flow plots was quadratic⁹ and in 28 men with BPH 15% of the 175 measured curves was quadratic¹⁰. The reason for this aberration is that even in BPH the urethra does not behave like a rigid nozzle, but instead, like a distensible tube.

The exponential model¹¹ allows for this distension. It was applied practically to pressure-flow data by assuming that there are a limited number of ways in which the cross-sectional area of the urethra may depend on the pressure in the urethra. This results in a pressure-flow relationship with three parameters, a theoretical opening pressure, a steepness, and a shape factor that can have five different values (0.66 - 1 - 1.33 - 1.6 - 2)¹². When the shape factor is 2 the model equals the quadratic model, when it is one it equals a straight line, or the linear model. Figure 5 shows an example of pressure-flow data that does not match the quadratic model. When the exponential model is used, the computer tries all five shapes, and chooses the one that fits the data best. Figure 5 is best fitted with a shape factor of 0.66 as is shown in Figure 6. Although the exponential model adequately fits most pressure flow plots it has some unfavourable statistical properties : Its parameters are not independent, i.e. one and the same pressure-flow measurement can be characterized by different sets of parameters¹³. This has (negative) consequences for the reproducibility of

these parameters.

The polynomial model consists of a number of orthogonal terms, which means that they are statistically independent. Changes in one term or parameter do not influence another term or parameter, which contribute to optimum reproducibility of the parameters. In practice this model has been applied with three terms, (1) a constant (like the theoretical opening pressure), (2) a linear (straight line) and (3) a quadratic (parabola) term.

The linear model, a straight line, can be considered a special (and very simple) case of either the exponential model, or the polynomial model.

3.5 Which model fits the urethral resistance relation best?

The four models were applied to pressure-flow data measured in 297 unselected, consecutive male patients of mixed pathology. Detrusor pressure (difference between intravesical and rectal pressure, both measured with external transducer) and flow-rate (measured with a rotating disk flow-meter) were stored on computer disk at a rate of 10 samples per second. In 38 measurements one of the models was not successfully fitted. Visual inspection of these measurements showed that in 5 cases a (flow-meter) calibration signal was accidentally included in the measurement. The calibration signal was deleted and the measurement reanalysed. In the other 33 measurements (11%) various artefacts in the pressure recordings (mostly negative pressures) were found. These measurements were omitted. Table 1 shows the average and standard error of the mean of the sum of squares of the remaining 264 pressure-flow measurements for the four models. This sum of squares is a measure for the difference between the model and the data, i.e. it characterizes how well the model describes the data. It was significantly different for all models (Wilcoxon matched pairs signed rank test, $p < 0.0001$). For a comparison : The sum of squares of Figure 4 was 185 [cm H₂O²] and that of Figure 6 was 38 [cm H₂O²].

From Table 1 it seems clear that the polynomial model fits the pressure-flow data best; however, two reservations should be made. The number of parameters in the four models is not equal, both the quadratic and the linear model have two parameters, and the other two have three. Models with more parameters generally fit better. Strictly speaking, it can only be concluded that the linear model fits the tested data better than the quadratic model, and the polynomial model fits it better than the exponential model.

The other reservation concerns the patient population. The models were applied to pressure flow plots of 264 consecutive male patients of mixed pathology. Using the

model	number of parameters	sum of squares [cm H ₂ O ²]
quadratic	2	458 ± 47
linear	2	367 ± 33
exponential	3	267 ± 23
polynomial	3	213 ± 13

Table 1. Mean and standard error of the mean of the sum-of-squares for four models applied to pressure-flow measurements in 264 consecutive male patients of mixed pathology. The sum-of-squares measures how well the model fits the (low pressure values of the) pressure-flow data.

urethral resistance parameter URA (discussed later in this article) it was found that 94 (36%) of this population had obstruction. According to the Abrams-Griffiths nomogram method¹⁴ 26% had obstruction and the majority (60%) was equivocal. It may be expected that a different mix of patients favours different models. For instance in a population of 100% patients with strictures the quadratic model fits better than the linear model. Taking into account, however, that both the quadratic and the linear models can be considered special cases of the polynomial model, and that this model, which has favourable statistical properties fits better than the exponential model, the polynomial model should be preferred.

3.6 Urethral resistance factors and classifications.

Using one of the described models, pressure-flow measurements can be represented adequately by a limited set of parameters. For instance, as indicated in the legend, the pressure-flow plot data shown in Figure 6 can, using the exponential model, be characterized with a theoretical opening pressure of 7 [cm H₂O], a steepness of 4.7 [cm H₂O/(ml/s)^{0.66}] and a shape factor of 0.66. The sum-of-squares (fit error) then amounts to 38 [cm H₂O²]. Alternatively the plot can be represented using the orthogonal polynomial model with an average height of 26.6 [cm H₂O], an average slope of 1.61 [cm H₂O/(ml/s)] and an average curvature of -0.0319 [cm H₂O/(ml/s)²], which yields a lower sum-of-squares of 29 [cm H₂O²] i.e. a better fit. For diagnosis and evaluation of treatment such a set of parameters is not easy to handle. When the patient data in Figure 6 are compared to those in Figure 3 there is no problem, because in Figure 3 all parameter values are higher (results of polynomial model fitted to Figure 3 : average height 29.5 [cm H₂O], average slope 1.90 [cm H₂O/(ml/s)] and average curvature 0.145 [cm H₂O/(ml/s)²], which yields a sum-of-squares of 86 [cm H₂O²]) and therefore the patient of Figure 3 undoubtedly has a higher urethral resistance than the patient in Figure 6. In many cases however when patients or measurements are compared before and after treatment, some parameters are increased and others decreased. This makes it difficult to use such a set of parameters as a diagnostic criterium. Two solutions have been proposed to solve this problem : (1) classification of the parameters or (2) combination into one urethral resistance factor.

Classification of the parameters implies that for each of the parameters borderlines are chosen so that the parameter falls into a limited number of classes. Minimally the number of classes is two, classifying measurements as obstructed or not obstructed. A larger number of classes allows grading of the severity of obstruction. Some examples of such classification systems for pressure-flow analysis are the Abrams-Griffiths nomogram¹⁴, LPURR¹⁵, Chess¹⁶ and Spångbergs method¹⁷. The Abrams-Griffiths nomogram applies 3 classes to one parameter and is not based on a pressure-flow model but on one data point of the pressure-flow plot, the point of maximum flow-rate and associated pressure. LPURR uses 7 classes for the same single data point of the pressure-flow plot. Chess applies 16 classes to the two

parameters of the quadratic model and Spångbergs method uses 15 classes for the three parameters of the exponential model. Generally it can be observed that the smaller the number of classes in a classification method, the more insensitive the method is for detecting differences between patients or measurements. As an illustration of this principle it was shown that the statistically significant decrease in urethral resistance in a group of patients treated with an alpha blocker was obscured if the data were classified using nine or fewer equidistant classes for one parameter¹³. If all parameters behave similarly, this critical number of classes should be raised to the power of the number of parameters.

An alternative to classification of parameters is a combination of parameters into one urethral resistance factor. The classic urethral resistance factor p/Q^2 ,¹⁸ is based on a simplified version of the quadratic model which misfits almost all pressure-flow measurements and therefore is unreliable¹⁹. Two different approaches have been published to combine the sets of parameters that result from using the four described models into one urethral resistance parameter.

In the first approach the quadratic model was fitted to pressure flow data of a mixed group of patients²⁰. An experimental statistical relation was established between the two parameters of the model, (1) theoretical opening pressure and (2) steepness. By inserting this relation into the model we derived an equation with only one parameter. This one parameter has been called URA, and it can be calculated from any point along the pressure-flow curve. In all clinical applications the point of maximum flow-rate and associated detrusor pressure is used.

In a second approach the parameters from the exponential model and the parameters from the polynomial model were reduced to one urethral resistance parameter by using a statistical method called Fishers linear discriminant. In this method pressure-flow measurements are represented by a dot in an n-dimensional space (n is the number of parameters of the model) and the dots are projected on a line through the origin. The line is rotated until it best separates a group of obstructed and unobstructed patients. The distance along the line then is the new combined single obstruction parameter. In contrast to the original use of the

exponential model with five different shape factor values^{9,10} a continuous version of this model was used, where the shape factor could have any value. This resulted in very unreliable parameters, because one and the same pressure flow plot could be fitted with several curves with completely different sets of parameters. The orthogonal polynomial model did not suffer from this problem because the parameters of this model are designed to be statistically independent. With the polynomial model it was found that the curvature parameter was very unreliable, and was not reproducible, even within patients²¹. For this reason only the average height and average slope of the polynomial model were combined in the single urethral resistance factor OBI²². This implies in practice that the linear model was used in this approach.

3.7 Some clinical applications of urethral resistance factors.

A few examples of clinical application of the urethral resistance factors URA and OBI are discussed. With some exceptions parameter values were calculated immediately following each urodynamic measurement, using a special computer program. This program (CLIM^{23,24,3,25}) enables connection of a personal computer to urodynamic equipment and storage, retrieval and analysis of urodynamic data.

In a small pilot study of ten patients²⁶ the diameter of the prostatic urethra was measured from transrectal ultrasound recordings at the apex, the midurethra and the bladder neck. Measurements were taken at maximum flow-rate. Spearman's rank correlations between the three diameters and URA were -0.70 (p=0.013), -0.48 (p=0.079) and -0.71 (p=0.011). Rank correlations with OBI were : -0.62 (p=0.027), -0.60 (p=0.032) and -0.60 (p=0.032). These data show that the urethral resistance as quantified by the parameters URA and OBI is determined to a large degree by the urethral diameter during voiding. URA and OBI were also determined in a series of 29 patients before and after TURP^{27,28}. The patients were selected using conventional clinical criteria. It was found that the population consisted of two groups, (1) a group of obstructed patients with high URA before the operation and a significantly decreased URA value afterwards (N=19), (2) and a smaller but significant group (N=10, approximately 35%) of unobstructed patients with low URA values both before and after the operation.

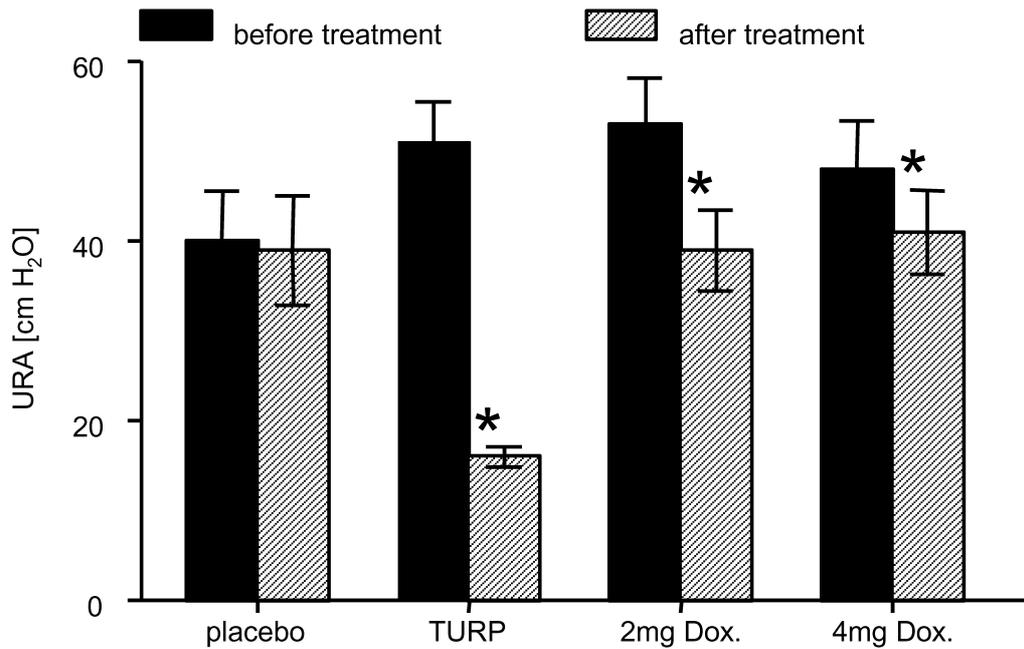


Figure 7. Mean and standard error of the mean of the single urethral resistance factor URA, determined from pressure-flow studies in groups of 14, 19, 16 and 15 patients before and during/after treatment with placebo, TURP, and 2 and 4 mg of the alpha blocker Doxazosine. * Indicates a significant (Wilcoxon signed rank test $p=0.05$) reduction in URA as a result of the treatment.

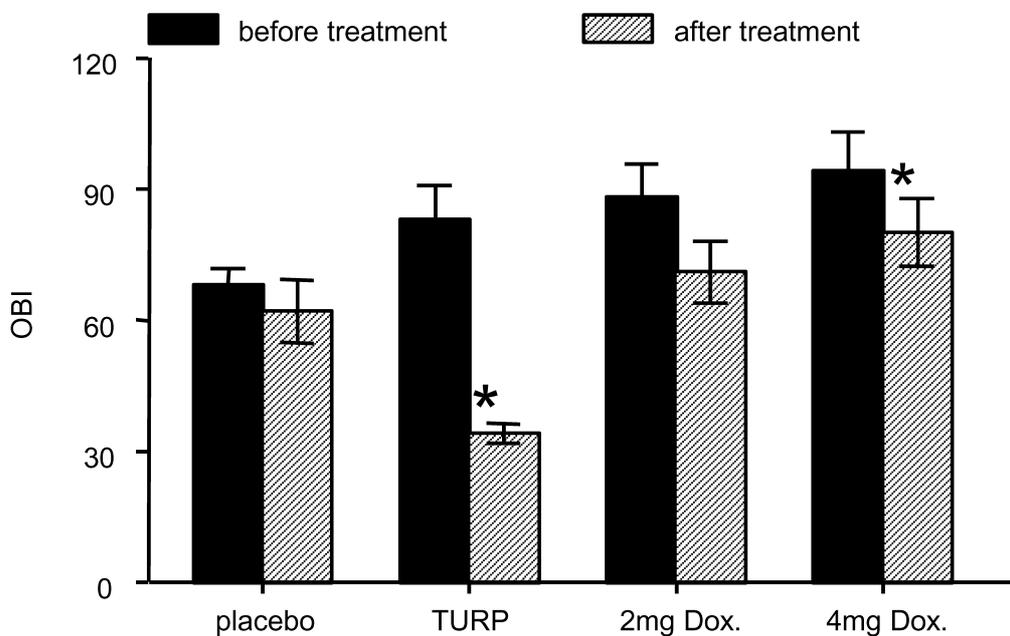


Figure 8. Mean and standard error of the mean of the single urethral resistance factor OBI, determined from pressure-flow studies in groups of 14, 19, 16 and 15 patients before and during/after treatment with placebo, TURP, and 2 and 4 mg of the alpha blocker Doxazosine. * Indicates a significant (Wilcoxon signed rank test $p=0.05$) reduction in OBI.

The fact that the outcome of surgery in terms of subjective symptomatology was less favourable in these patients provides strong arguments for including preoperative testing in terms of the described parameters before prostatic surgery²⁷. Figure 7 shows the change in URA in response to TURP in obstructed patients compared to the changes in URA in response to two dosages of the alpha blocker Doxazosine²⁹ and placebo in similar groups of patients. The figure shows that although the effect of the drug is dramatically smaller than that of the operation, there is nevertheless a significant reduction in the parameter URA in both the patient group treated with 2 and in the one treated with 4 [mg]. Figure 8 shows similar data for the urethral resistance parameter OBI in the same groups. Apart from the group treated with TURP, this parameter shows a significant change only in the 4 [mg] group.

3.8 A detrusor contractility parameter.

As discussed previously, voiding results from the interaction of detrusor contractility and urethral resistance. Although both voiding factors seem equally important, there is considerable less controversy around the subject of contractility. A measure of detrusor contractility can be derived from pressure-flow studies. This measure is based on the Hill equation for contracting (striated) muscle³⁰, which is in first approximation also valid for smooth muscle³¹. Basically the Hill equation is a trade off relation : a muscle has a limited power available for contraction, which can be used for maximum force generation or for shortening at maximum velocity, or for a compromise, a limited force generation combined with shortening at a limited velocity. In a hollow muscular organ like the bladder, force generation in the wall results in pressure development, and shortening is related to urine flow out of the bladder. In only a very small number of patients (12% in a test population of 2073 measurements taken from a mixed group of patients) can the complete Hill equation be estimated reliably from pressure-flow data³². In all pressure-flow data, however, the pressure and flow-rate signal can be combined into a function that represents for each moment in time during the emptying of the bladder the approximated power generated by the bladder muscle per unit of surface area³³. Figure 9 shows this approximated power plotted as a function of the instantaneous bladder volume, calculated from the pressure-flow study shown in Figure 1.

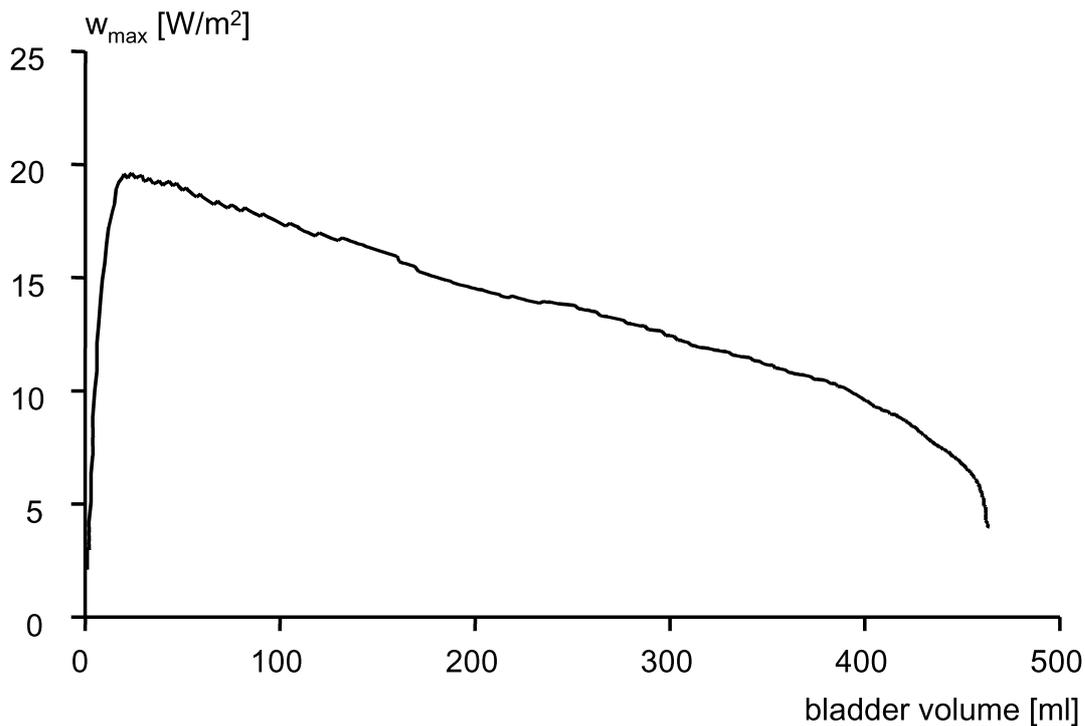


Figure.9. The approximated power per unit of surface area generated by the bladder wall plotted as a function of the instantaneous bladder volume. This function was calculated from the pressure-flow study shown in Figure 1.

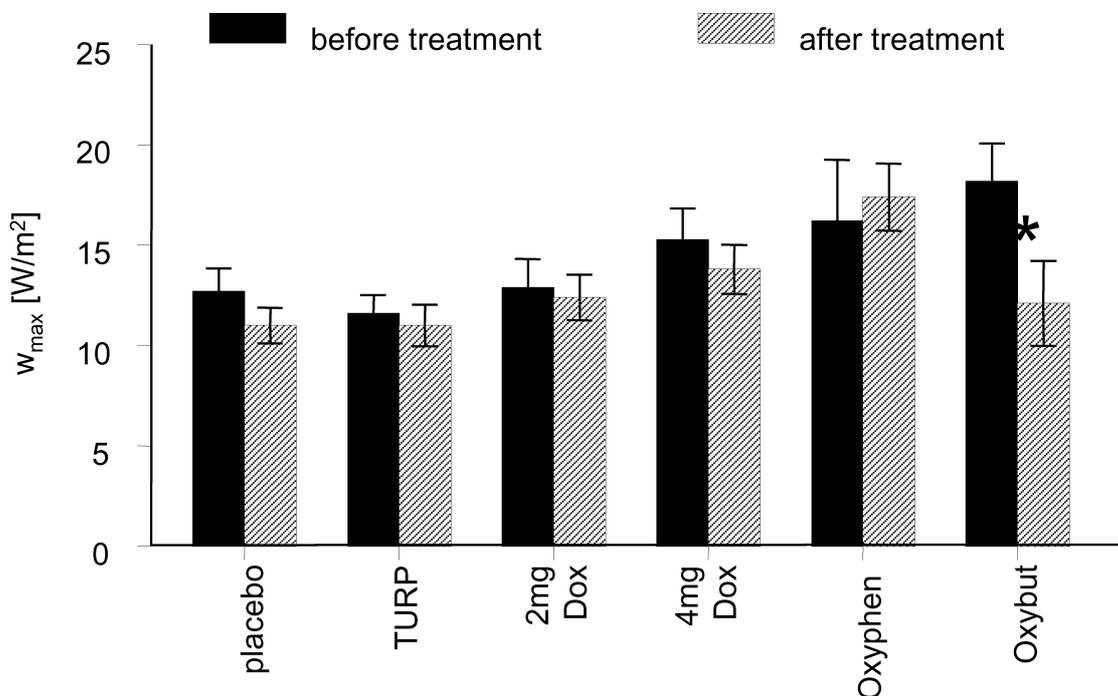


Fig.10 The mean and standard error of the mean of the detrusor contractility parameter w_{max} for the same groups of patients for which the urethral resistance was displayed in Figs.7 and 8. Additionally data are shown for two groups of 6 children that were treated for reflux related the bladder hyperactivity with oxyphenonium bromide and oxybutynin hydrochloride. Only in the latter case the parameter changed statistically significantly (Wilcoxon matched pairs signed rank test $p=0.05$).

The maximum of this function (i.e. 19.6 in Figure 9) forms the contractility parameter w_{\max} that can thus be derived from any pressure flow study. Figure 10 shows values for this contractility parameter for the same groups of patients shown in Figures 7 and 8 but also for two groups of six children treated with oxyphenonium bromide and oxybutynin hydrochloride³⁴. These children were treated for reflux related to bladder hyperactivity. The treatment with oxybutynin was successful in that a significant reduction in the reflux grade was found, the treatment with oxyphenonium was not. The figure shows that this finding was correlated with a significant reduction in the bladder contractility as quantified by w_{\max} when applying oxybutynin. All other treatments, including TURP had no significant effect on this contractility parameter, illustrating that it is not biased by even dramatic changes in urethral resistance.

3.9 Optimum method for pressure-flow analysis.

Apart from specifying a provisional method for definition of obstruction, which has been discussed elsewhere in this issue⁴, the International Continence Society has committed itself to comparing all published methods for pressure-flow analysis with the aim of reaching a consensus on their use³⁵. To this end the analysis methods will be applied to four databases of pressure-flow studies.

Database 1 consists of pressure-flow studies in untreated men with symptoms and signs of BPH, and is used to determine which existing or new methods adequately describe the actual pressure-flow plots of BPH patients. As a first approximation to this aim in this article all published models have been fitted to pressure-flow plots of 297 unselected male patients of mixed pathology. It was found that the orthogonal polynomial model fits these measurements best.

Database 2 consists of studies repeated after a time interval with no intervention, to determine the reproducibility of the methods. It follows from the measurements in patients treated with placebo in Figures 7 and 8 that the urethral resistance factors URA and OBI do not change significantly over a period of four weeks.

Additionally, in a study on 130 male patients the difference between a first pressure-flow study and a second that followed immediately was determined for the parameters of the orthogonal polynomial model. It was found that the median

relative difference was 12% for the average height of the measurements and 36% for the average slope. The average curvature was not reproducible and was therefore excluded from the urethral resistance factor OBI as discussed previously.

Database 3 of the International Continence Society test consists of pressure-flow studies before and after TURP to determine in which groups of patients TURP significantly reduces urethral resistance, and hence which patients are indeed obstructed. Figures 7 and 8 show results for the urethral resistance factors URA and OBI when applied to 19 obstructed TURP patients. The nineteen patients were those for whom URA decreased significantly from a group of 29 patients who underwent TURP on conventional clinical criteria²⁷. In this group of patients the percentage of correctly classified measurements was compared for URA, OBI and the classification based method LPURR¹⁵. It was found that although there were slight differences in performance, OBI being the best method followed by URA and finally LPURR, the performance were in first approximation comparable, 90% of measurements was correctly classified by all three methods^{36,19}.

Finally database 4 consists of pressure-flow studies before and after alternative therapeutic intervention that causes a small change in urethral resistance, and is used to test the sensitivity of the various methods to small changes in urethral resistance. Application of an alpha blocker is a favourable possibility for such an intervention. Again Figures 7 and 8 show that the urethral resistance factors URA and OBI demonstrate significant changes in groups of patients on application of Doxazosine. The LPURR nomogram failed to demonstrate a significant change in urethral resistance on application of indoramin and prazosin³⁷. This is understandable in view of the reduced sensitivity of methods using a limited number of classes for classifying urethral resistance as was discussed previously.

3.10 Conclusions.

A pressure-flow study is the only reliable method to measure or diagnose the degree of infravesical obstruction. Many methods have been proposed to analyse the resulting pressure-flow plot. These methods differ in aim, models used, dataprocessing technique applied and resulting resolution. Two aims can be

distinguished : (1) diagnosing obstruction and (2) measurement of urethral resistance (e.g. to evaluate the efficacy of treatment). Methods that aim to measure urethral resistance simply can be extended with decision rules for diagnosing obstruction, whereas methods that aim to diagnose obstruction can often not be used for measuring urethral resistance, so that the former may be called more universal. From the limited material presented in this study it seems that the orthogonal polynomial model provides the best description of patient data. In practice only the first two terms of this model can be determined reliably, implying that on average a simple straight line is the most adequate description of pressure-flow data. The independent parameters that define this straight line orthogonally (average height and average slope) directly can be used as urethral resistance parameters, but for simple diagnosis and sensitive testing of the efficacy of treatment it is advantageous to combine these parameters in one urethral resistance factor. Some successful clinical applications of such a combined parameter (OBI) and an earlier single resistance factor (URA) have been discussed. Clinically both perform comparably, but because URA is based on a less adequate model (quadratic) it frequently "misfits" the pressure-flow data. Both of the parameters were calculated from the pressure flow data using a computer (For URA this is not necessary, for OBI it is). Apart from being efficient and enabling the use of more advanced data analysis methods, the application of a computer in analysing urodynamic data ensures objectivity : all data are processed uniformly according to predefined rules and no human observer errors and biases are introduced. Such objectivity is required in statistical processing of data for such tasks as testing the effect of pharmacological treatment. Of course adequate methods should be implemented to avoid errors and bias caused by artefacts in the measurements. Methods for analyzing pressure flow data that do not involve computers (although all new urodynamic equipment available includes a computer) usually are based on a classification system with a limited number of classes. Such methods have a sensitivity too low for testing the efficacy of some treatment modalities.

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Pre selection of patients for pressure-flow analysis based on the maximum flow-rate.

Ries Kranse and Ron van Mastrigt.

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Objective. To study the effects of the application of flow-rate prescreening to select men for invasive pressure-flow studies, notably the reduction of invasive pressure-flow measurements that can be achieved and the proportion of men in whom, on the basis of the application of a prescreening, an invasive measurement is unjustly not indicated (false negatives). In addition the variables on which these effects depend are studied.

Materials and methods. Two hundred and sixty-two pressure-flow measurements in 131 patients (2 measurements / patient) and 89 free flow measurements that preceded the invasive measurements in some patients were studied. A mathematical model was developed based on the outcomes of the invasive measurements. By means of the model the effects of several flow-rate prescreening scenarios were estimated. A comparison of the model predicted- and actually observed effects of flow-rate pre screening was made for those measurements that were preceded by a free flow-rate measurement.

Results. The application of a free flow-rate prescreening may result in a reduction of the number of invasive measurements of 20-30% at a 5% false negative rate. The reduction that may be achieved at an assumed constant false negative rate depends on the distribution of the maximum flow-rate in the population and on the definition of bladder outlet obstruction used. When the measurement selection procedure was applied to the free flow-rate measurements that were available in 89 patients a 21% reduction in invasive measurement indications was found (25% expected). Four patients (4.5%) would have been unjustly excluded from invasive procedures (maximally 5% expected), 3 of these four patients were borderline obstructed.

Conclusion. Considering the bother and risk to the patient and the cost of invasive measurements we think that a 20-30% gain in efficiency at a 5% risk of unjustly declaring a patient unobstructed makes a flow-rate pre screening procedure cost effective in the diagnosis of bladder outlet obstruction.

Introduction.

In the voiding phase the lower urinary tract may be modeled as two subsystems¹: The bladder that contracts and forces the urine out and the bladder outlet that conducts it into the outside world. In this model the primary power source is the contracting bladder. The power generated by the bladder is partly dissipated in the bladder outlet. The remaining power is in the external urinary stream that exits the meatus.

The Q_{max} , $p_{det.Qmax}$ pair.

The simultaneous measurement of the urinary flow-rate and detrusor pressure during voiding is considered the state of the art method to monitor the function of the bladder (the bladder contractility) and the bladder outlet resistance during voiding. More specifically one pair of values of the two measured signals is used, the maximum flow-rate (Q_{max}) and the simultaneously measured detrusor pressure $p_{det.Qmax}$. The product of these two values equals the external mechanical power generated at the maximum flow-rate. The data pair Q_{max} , $p_{det.Qmax}$ features in the provisional ICS nomogram for the diagnosis of bladder outlet obstruction². In this nomogram three classes of Q_{max} , $p_{det.Qmax}$ pairs are distinguished: those from clearly obstructed and unobstructed measurements and an intermediate or equivocal class. The same Q_{max} , $p_{det.Qmax}$ pair is also used in the LPURR nomogram³. This nomogram distinguishes more than three classes for obstruction, and, in addition, classifies contractility (as very weak, weak, normal and strong).

Why the Q_{max} , $p_{det.Qmax}$ pair ?

Two mathematical models exist that describe the two subsystems that conceptually form the lower urinary tract. The one relating to the bladder originates from the mathematical model for the contraction of striated muscle⁴. This so called Hill equation, describes the relation between the shortening velocity and the force generated by contracting muscle. It represents the mathematical formulation of the trade off balance that limits the performance of contracting muscles to either contracting forcefully at relatively small shortening velocities or contracting less forcefully at relatively higher shortening velocities. Assuming a spherical bladder geometry the Hill equation can be transformed into the bladder output relation, BOR⁵, that relates pressure to flow-rate for a bladder studied in isolation. Like the Hill equation this is a hyperbolic function. For the bladder outlet a linear relation between the detrusor pressure and the flow-rate may be assumed⁶. During voiding, the properties of the bladder and the bladder outlet change. Thus during voiding many bladder output relations and many bladder outlet resistance relations occur. The measured flow-rate and pressure values during voiding represent the intersection of a specific bladder output relation and a specific bladder outlet resistance relation at one instant. Within a reasonable approximation the Q_{max} , $p_{det.Qmax}$ pair typically occurs for the most relaxed state of the bladder outlet and the most contractile state of the

bladder. The assessment of both these states is of clinical relevance and their combination is used as the basis for a differential diagnosis. It is noteworthy that some slight differences in opinion exist on whether it is reasonable to use the external power as a measure for bladder contractility. These relate to the fact that the external power is zero for a zero flow-rate and for a high flow-rate at zero pressure, and that, in the calculation of the external power the instantaneous bladder volume is not taken into account. These two drawbacks are corrected for in the Watts factor concept^{5,7}.

Purpose of the study.

The Q_{\max} , $p_{\det.Q_{\max}}$ pair can only be determined by means of an invasive pressure-flow study. Such a measurement is time consuming, bothersome to the patient and is not without risk (infection). A prescreening of patients on the basis of a simple determination of Q_{\max} , which requires a non invasive flow study only, has been suggested to reduce the number of invasive urodynamic investigations⁸. In the proposed procedure men with a high Q_{\max} (≥ 12 [ml/s] in the cited study) are considered to be unobstructed and men with a very low Q_{\max} (< 4.8 [ml/s]) are considered to be obstructed. The remaining men (approximately 50%) are candidates for invasive pressure-flow studies. It is plausible that if more information is added to the maximum flow-rate the diagnosis of bladder outlet obstruction can be made without invasive urodynamics with more certainty. A recent study showed that the AUA symptom index and the ultrasound assessed prostate volume may be used to this end⁹. In this paper we focus on one source of information (Q_{\max}) that can be obtained by a non invasive procedure. It can be measured easily and repeatedly (possibly by means of ambulatory uroflowmetry) at relatively low costs.

In designing a prescreening algorithm a trade off has to be made between the reduction in invasive measurements and the number of false negative findings as a consequence of this policy. A false negative finding here refers to the case that invasive urodynamics was unjustly not advised on the basis of the Q_{\max} prescreening. This can occur if a patient is unobstructed but has a very low Q_{\max} value (caused by a very poor contractile bladder) or when a patient is obstructed but has a very high Q_{\max} value (caused by a very strong bladder). From a computational point of view the number of false negative findings can be determined if the joint statistical distribution of Q_{\max} and $p_{\det.Q_{\max}}$ were known. Given the frequent use of the Q_{\max} , $p_{\det.Q_{\max}}$ pair it is remarkable that no attempts have been made to study its statistical distribution. The

nomograms for obstruction mentioned above (the provisional ICS nomogram and the LPURR nomogram), are based partly on what is to be considered normal or abnormal in the eyes of a group of experts and partly on the effect of a trans urethral resection of the prostate (TURP) on bladder outlet resistance and bladder contractility. We have studied the distribution of Q_{\max} , $p_{\det.Q_{\max}}$ in measurements in an unselected male outpatient clinic population. Published data from the ICS BPH study¹⁰ were used to test if our findings can be generalized.

The derived Q_{\max} , $p_{\det.Q_{\max}}$ distribution was used to study if and to what extent the efficacy of a Q_{\max} pre screening depends on the properties of the Q_{\max} , $p_{\det.Q_{\max}}$ distribution in the population to which it is applied and on the definition of obstruction used. A possible prescreening scenario was tested on the free flow-rates that preceded most, but not all, of the invasive pressure-flow measurements from which the Q_{\max} , $p_{\det.Q_{\max}}$ distribution was derived.

Materials and methods.

We have studied an unselected series of 262 simultaneous measurements of the flow-rate and the detrusor pressure during voiding in males (2 consecutive measurements in each patient). In 89 (68%) of 131 patients a “free flow” measurement that preceded the invasive pressure-flow studies was available. All measurements were done in the out patient clinic of the University Hospital Rotterdam, the Netherlands. The availability of two measurements in each patient enabled us to test if adaptation of the patient to the procedure occurred.

The rectal pressure and the intravesical pressure were measured with disposable pressure transducers connected to water filled catheters. The flow-rate was measured by means of a Dantec ® 1000 rotating disk flow-transducer connected to a specially designed amplifier with built in low pass anti aliasing filter (cut of frequency 5 [Hz]). The men voided in standing or sitting position, the height of the funnel of the flow-meter was adjusted accordingly. All signals were sampled at a 10 [Hz] sampling frequency and stored on computer disk. The detrusor pressure was obtained by calculating the difference between the pressure measured in the bladder (intravesical pressure) and the rectal pressure. It was delayed 0.6 [s] with respect to the flow-rate

signal to account for the spatial separation of the flow-meter and the pressure transducers¹¹.

When prescreening patients on the basis of a maximum flow-rate the percentage of false negative findings depends on the joint statistical distribution of Q_{\max} , $p_{\det.Q_{\max}}$ (denoted by $\text{prob}(Q_{\max}, p_{\det.Q_{\max}})$) and the definition of obstruction used. The distribution gives the probability that a specific Q_{\max} , $p_{\det.Q_{\max}}$ pair is observed in the population. To estimate it two ingredients are needed : the distribution of the detrusor pressure as a function of the flow-rate and the distribution of the flow-rate. In the appendix the details of all derivations are given.

To study the extent to which our findings can be generalized we have compared the positive predictive value of $Q_{\max} < 10$ [ml/s] and $Q_{\max} < 15$ [ml/s] with respect to obstruction in the population studied with the positive predictive values (PPV) cited in a report on the ICS-BPH study¹⁰.

Finally, we calculated the number of patients that would not have been selected for invasive measurements despite the fact that they were obstructed if an “upper flow-

Parameter estimate	Average	95% credible interval	p-value
a [log (ml/s)]	-0.20	-0.34 - -0.07	0.003
b [log (cm H ₂ O)]	1.89	1.76 – 2.02	<0.001
c	-0.039	-0.058 - -0.021	<0.001

Table 1. Parameter estimates of fitting model 1 i.e. : $\text{Prob}(\log(p_{\det.Q_{\max}|Q_{\max}})|Q_{\max}) \sim N(a * \log(Q_{\max}) + b + c * n_{\text{seq}}, \sigma)$ to the data. See the discussion section for an explanation.

rate threshold only” pre selection algorithm was applied to the free flow-rates.

Results.

Figures 1 and 2 and Table 1 contain the information that is needed to calculate the joint distribution of Q_{\max} , $p_{\det.Q_{\max}}$, i.e. the distribution of the detrusor pressure (log transformed) as a function of the flow-rate (log transformed) and the distribution of the flow-rate (log transformed). The probability of being obstructed as a function of Q_{\max} given the former distribution is depicted in Figure 3.

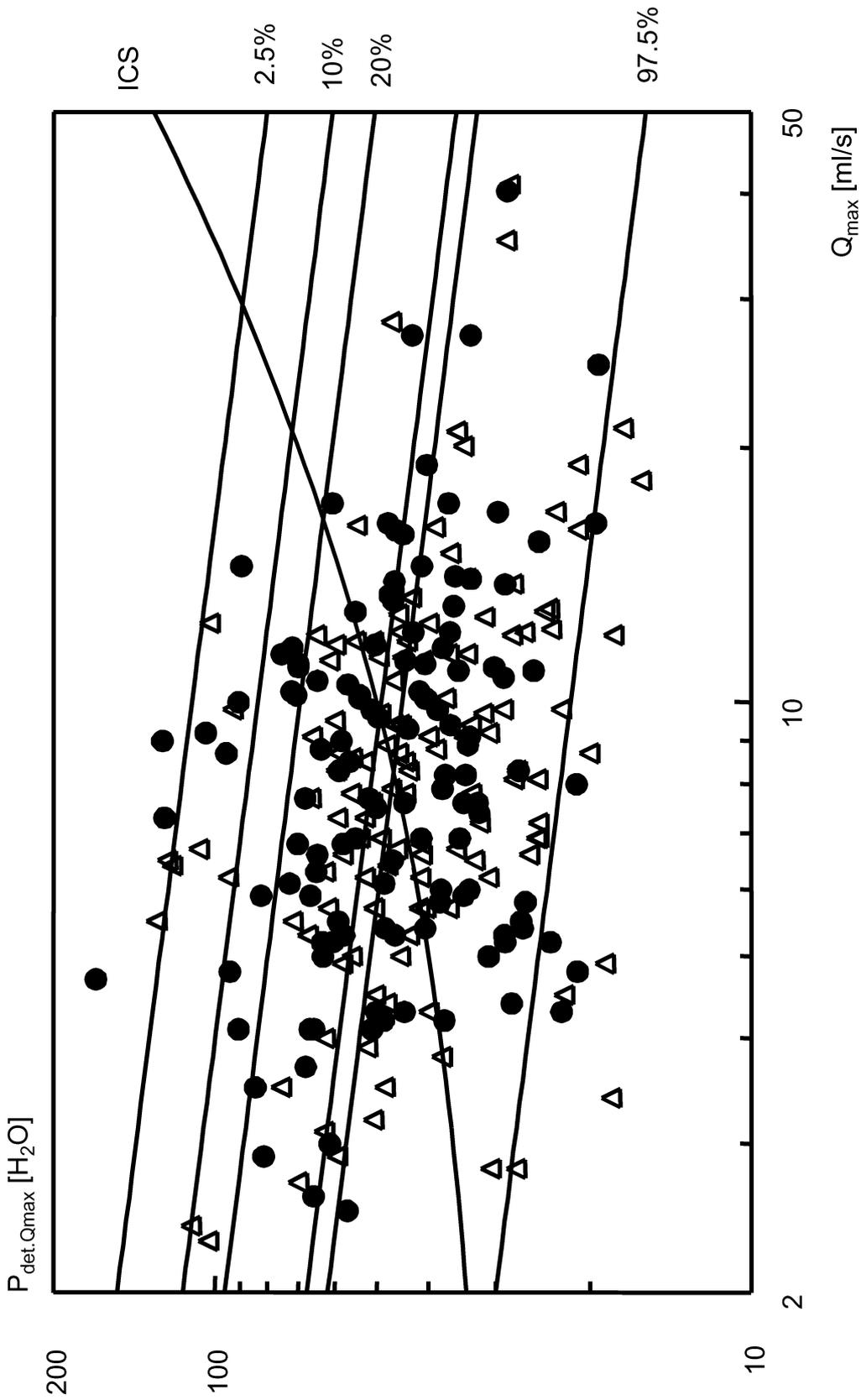


Figure 1. A scatterplot of the measured Q_{\max} $P_{\text{det.}Q_{\max}}$ pairs on a double logarithmic scale. Closed circles depict the first measurements done in a patient; open triangles the second. The percentile lines are obtained from fitting model 1 to the data (see materials and methods section). The curved line represents the ICS threshold for the definition of bladder outlet obstruction.

The joint probability distribution of Q_{max} , $p_{det.Qmax}$ was used to calculate the probability that a measurement was obstructed on the basis of the maximum flow-rate for two different definitions of obstruction (the ICS definition of obstruction and LPURR \geq category 2).

The number of false negative findings and the reduction of measurements achieved by flow-rate pre screening depended on the flow-rate distribution and the definition of obstruction used (see Table 2). A 20-30% reduction in the number of measurements was possible at a 5% false negative rate. The application of a high flow-rate threshold (i.e. an invasive measurement is indicated if $Q_{max} < \text{threshold}$) appeared to be more affective than the application of both a low and a high flow-rate threshold (i.e. an invasive measurement is indicated if Q_{max} is between a low and a high flow-rate threshold).

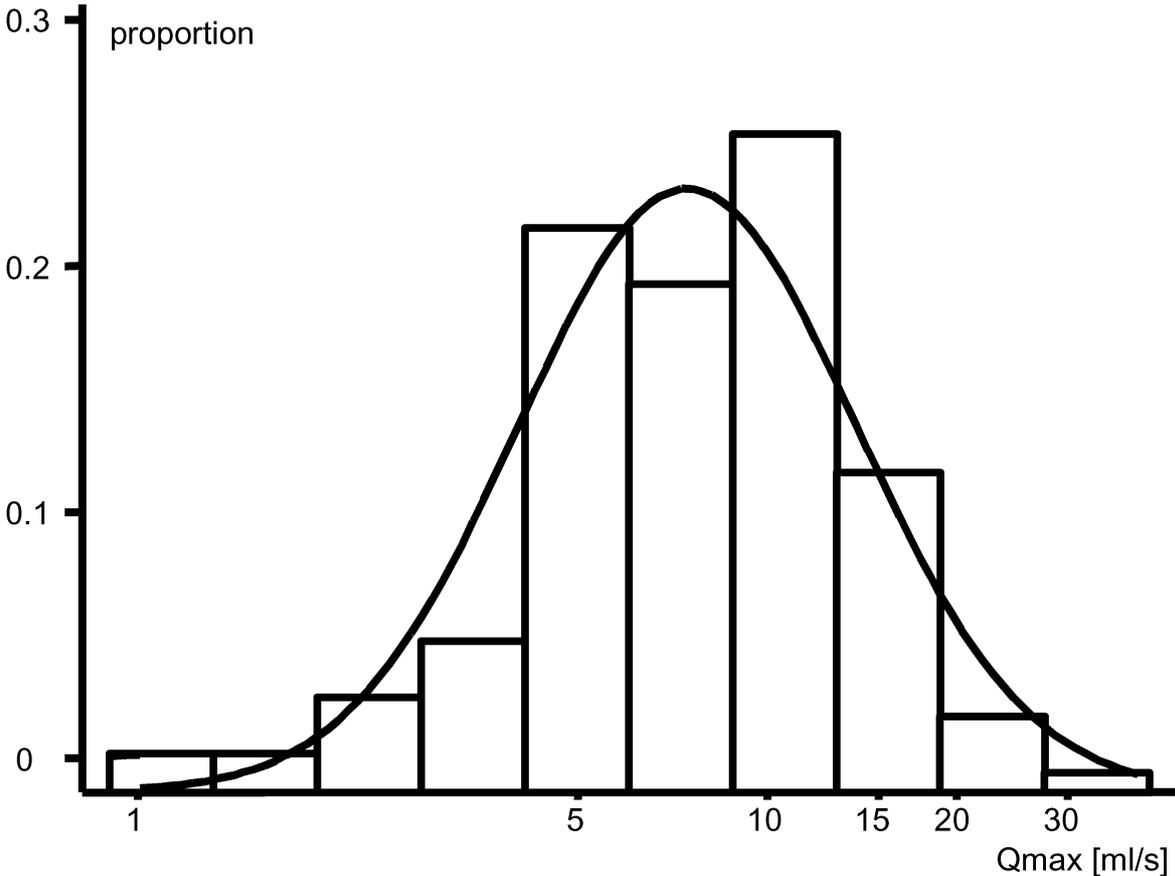
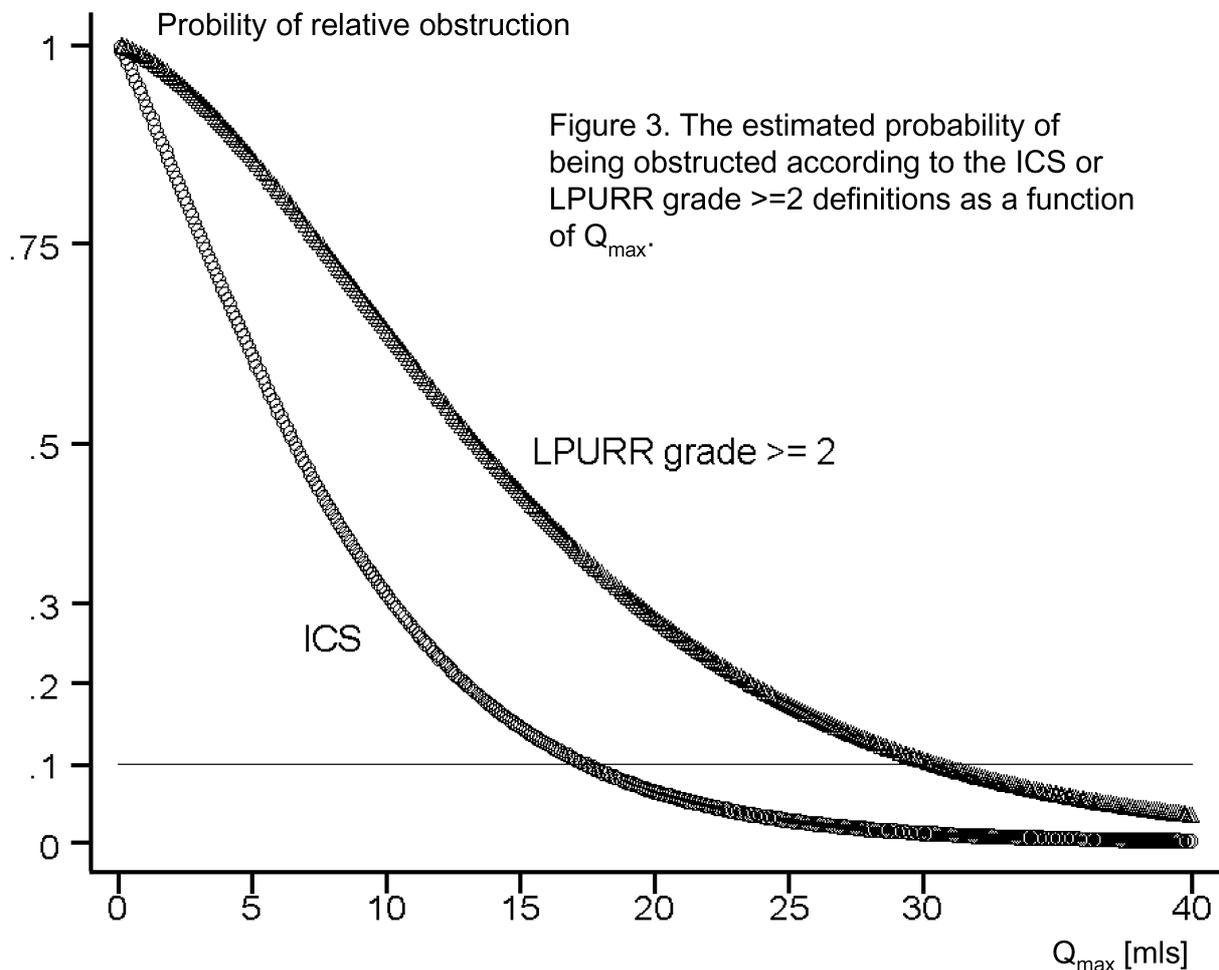


Figure 2. The distribution of Q_{max} in the population studied on a logarithmic scale and a superimposed log normal distribution. The distribution describes the spread in the data accurately except for the very low flow ranges.

Table 2. The reduction in invasive measurements attained by applying flow-rate pre selection criteria as a function of the maximum flow-rate distribution in the population to which it is applied and the definition of obstruction used. The reductions in percentage of invasive measurements needed are given for two pre screening scenarios. 1) A “low and high Q_{max} cut off level” scenario in which measurements with a Q_{max} value lower than the high cut off level or lower than the low cut off level are candidates for invasive urodynamics. 2) A “high Q_{max} only cut off level” scenario in which measurements with Q_{max} higher than the high cut off are excluded from invasive urodynamics. The cut off levels are calculated in such a way that a maximum of 5 % of patients are unjustly excluded from invasive urodynamics. See results and discussion section for a detailed description of how to interpret this table.



mean Q_{\max} [ml/s]	range [ml/s]	definition used	2.5% low cut off [ml/s]	% reduction	2.5% high cut off [ml/s]	% reduction	5% high cut off [ml/s]	% reduction
7.4	2.2 – 25	ICS obs	1.8	1.1	14.6	13.8	12.6	19.7
		Lpur >= 2	2	1.8	17.7	8.1	15.2	12.4
	1.7 – 32	ICS obs	2.3	0.9	17.3	18.9	15.1	25.4
		Lpur >= 2	2.6	1.5	21.4	11.1	18.5	16.1
10	2.8 – 19.6	ICS obs	1	1.3	9.8	7.4	8.3	11.9
		Lpur >= 2	1.1	1.9	11.3	4.7	9.5	8.1
	3.0 – 33.8	ICS obs	1.3	1.0	15	17.2	12.7	23.5
		Lpur >= 2	1.5	1.6	19	10.4	16.0	15.1
4	2.3 – 43.2	ICS obs	1.7	0.9	17.4	22.9	14.9	29.6
		Lpur >= 2	1.9	1.3	22.3	14.1	19.0	19.5
	3.8 – 26.5	ICS obs	0.8	1.6	10.6	9.5	8.8	14.4
		Lpur >= 2	0.8	1.6	12.9	5.8	10.6	9.5
4	1.2 – 13.5	ICS obs	2.4	1.2	13.9	10.3	12.2	15.8
		Lpur >= 2	2.6	1.8	16	6.1	14.0	10.1
	0.9 – 17.2	ICS obs	3.1	0.9	17	14.3	15.0	20.7
		Lpur >= 2	3.4	1.5	20	8.2	17.6	12.8
4	1.5 – 10.6	ICS obs	1.4	1.8	8.7	5.8	7.6	9.7
		Lpur >= 2	1.4	1.8	9.6	3.8	8.3	7.0

In the latter scenario lower reductions in invasive measurement indications were achieved at the same false negative rate (Table 2).

A detailed discussion of the derivation of the results is given in Appendix A.

In 89 of the 131 (68%) patients a free flow-rate was recorded before the invasive measurements. In 19 patients (i.e. 21%, 25.4% expected, see Table 2), Q_{\max} exceeded 15.1 [ml/s] (the 1-sided upper flow-rate pre screening threshold using the ICS definition for obstruction, see Table 2). In 4 of these men at least 1 of the 2 invasive measurements indicated an obstruction according to the ICS definition (i.e. 4.5%, 5% expected maximally). In only 1 of these 4 men both invasive measurements that followed the free flow-rate indicated an obstruction. Men in whom a free flow-rate measurement preceded the invasive measurement had a slightly, but not statistically significantly, lower bladder outlet resistance (measured by BOOI) than men in whom no free flow-rate was measured.

Discussion.

It has been put forward that the number of invasive urodynamic measurements can be greatly reduced if a flow-rate prescreening is applied⁸. In the proposed scenario only those men with a maximum flow-rate which is between two thresholds are candidates for invasive procedures. The remaining men (roughly 50% in the cited reference) are declared unobstructed if $Q_{\max} \geq$ the upper threshold applied and obstructed if $Q_{\max} \leq$ the lower threshold applied. In the present study we explore the effect of the variation in the statistical distributions of the relevant parameters (Q_{\max} and $p_{\det.Q_{\max}}$) on such a prescreening procedure. In addition obstruction may be defined differently (ICS nomogram, LinPURR, URA, etc). We have also studied the impact of that factor in the light of our present analysis. The reported 50% reduction in invasive procedures needed seems to be too optimistic, a 20 to 30% reduction however is feasible.

We have described the probability distribution of $p_{\det.Q_{\max}}$ at a given Q_{\max} value by a simple linear regression model. It does not seem unreasonable to assume that this distribution is approximately invariant between different populations of patients. Although a recent paper on the ICS-BPH study¹⁰ does not provide enough information to enable a thorough comparison with our findings, an approximate comparison is

however possible. In Table 3 we partly reproduce Table 2 of that study¹⁰. It gives the positive predictive value of Q_{max} for bladder outlet obstruction (BOO) for two different flow-rate thresholds. We have assumed that obstruction is defined as $LPURR \geq 2$.

Q_{max} [ml/s]	< 10	< 15
PPV	70% [252/359]	67% [446/661]

Table 3. Positive predictive value of Q_{max} for bladder outlet obstruction (see ¹⁰). PPV : positive predictive value (those sick with a positive test means that Q_{max} is lower than the threshold parameter estimates of fitting model 1 i.e either 10 or 15 [ml/s]).

In our study the positive predictive values for $Q_{max} < 10$ [ml/s] and < 15 [ml/s] (using LPURR category 2 or higher to define obstruction) equaled 70% and 64%, both values are thus in good agreement with the ICS data. Furthermore, in the ICS BPH study a significant negative correlation between Q_{max} and the grade of obstruction (which is related to $p_{det.Qmax}$) was reported. This is in line with the negative correlation between Q_{max} and $p_{det.Qmax}$ found in the present study. This qualitative aspect of a negative correlation between Q_{max} and $p_{det.Qmax}$ is perhaps more interesting than the quantitative way in which the statistical model describes the distribution of the observations. It can be understood if one considers the fact that the product of Q_{max} and $p_{det.Qmax}$ equals the external mechanical power. At increasing flow-rates the pressure must tend to zero because the bladder contractility is finite. Both Q_{max} and $p_{det.Qmax}$ take on positive values only. A positive correlation between the two would imply that higher Q_{max} values on average go with higher expected $p_{det.Qmax}$ values, which implies that the expected external power would continuously increase. Therefore over the whole range of possible flow-rate values, the correlation between Q_{max} and $P_{det.Qmax}$ for every population must be negative, simply because the external power must remain finite for large flow-rates. This power depends on the Hill equation in which the force (related to the detrusor pressure after a suitable correction for the spherical geometry of the bladder) decreases monotonically with the shortening velocity (related to the flow-rate).

In Table 2 (see Appendix) it is assumed that $\text{prob}(p_{det.Qmax}|Q_{max})$ is constant. Nine different Q_{max} distributions were studied (three different mean values each with three spreads). For each population the effects in terms of the reduction of the number of

invasive measurements needed at fixed percentages of false negative findings is calculated (two sided 5% and one sided 5%).

It is important to note that we have reduced the ICS nomogram (and the LPURR) nomogram to a dichotomy distinguishing only between obstructed and non obstructed patients. In doing so we have taken the ICS equivocal range as unobstructed. From Table 2 we see that at the same level of false negative findings the reduction in invasive measurements is less if the LPURR definition for obstruction is used. If a part of the equivocal range of the ICS nomogram would be obstructed (instead of unobstructed as is assumed in the calculations) a similar decrease in the reduction of invasive measurements will result.

Invasive urodynamics is currently the gold standard to define bladder outlet obstruction. Therefore it is practically unavoidable that, if a non invasive procedure is used as a pre screening device, false negative diagnoses will result unless the prescreening method is perfect. There is evidence that prolonged bladder outlet obstruction affects the detrusor muscle¹²⁻¹⁴. These effect may be irreversible. The clinical importance of false negatives (which implies missing an obstructed case if a high flow-rate threshold is used) is however unclear especially in the case of border line obstruction. Longitudinal studies in which repeated estimates of both bladder contractility and the bladder outlet resistance are made over time are needed to answer this question. Depending on the outcomes of such studies a 5% false negative rate may be too high or too low. A careful weighting of the positive and negative consequences of flow-rate pre screening is needed. This weighting is facilitated if a quantitative estimate of its effects and the dependence of it on certain variables (the topic of this paper) is available.

Typically the maximum flow-rate will vary between measurements in the same individual but this is true for the diagnosis of bladder outlet obstruction as determined by means of invasive urodynamics as well. Apparently there exists some variability in bladder contractility and bladder outlet resistance between voids. The extent of the variability in the maximum flow-rate can be assessed by doing repeated measurements (possibly by means of ambulatory uroflowmetry). Although this variability may have consequences for the conclusions drawn for an individual patient we do not expect that it has consequences for the conclusions drawn from this study in

which a group of patients and measurements has been studied. It is reasonable to assume that in this cross sectional study this source of variation averages out.

If a maximum flow-rate pre selection algorithm using a flow-rate threshold of 15.1 ml/s was applied to the free flow-rate measurements available in 68% of the patients, 4.5% were unjustly classified as unobstructed. On the other hand the number of invasive measurements could have been reduced by 21%. These results are in very good agreement with the theory that was developed.

Conclusions.

In the population studied a 21% reduction in the number of invasive pressure-flow studies can be achieved by pre screening on the basis of maximum flow-rates. This efficacy depends on the distribution of the maximum flow-rate of the population studied and on the definition of obstruction used. A one sided test (excluding only patients with a high Q_{max} from a pressure-flow study) was usually more efficient than a two sided test (excluding also patients with a very low Q_{max}).

Given the effects that the variables studied in this paper have on the efficacy of a flow-rate pre screening procedure and considering the unavoidable negative aspects (false negatives) it seems sensible that guidelines for its use are set up, preferably by the ICS. General practitioners may use a flow-rate pre screening algorithm to decide which patients to refer to a urologist. The material presented in this paper may be the basis for such guidelines.

Appendix A.

A1 Materials and methods (detailed information).

The joint statistical distribution of Q_{\max} , $p_{\det.Q_{\max}}$ (denoted by $\text{prob}(Q_{\max}, p_{\det.Q_{\max}})$) is the product of the distribution of Q_{\max} and the distribution of $p_{\det.Q_{\max}}$ at a certain value of Q_{\max} (denoted by : $\text{prob}(p_{\det.Q_{\max}}|Q_{\max})$). Given that

$$\text{Prob}(Q_{\max}, p_{\det.Q_{\max}}) = \text{prob}(Q_{\max}) \text{prob}(p_{\det.Q_{\max}}|Q_{\max}),$$

the percentage of men that are obstructed according to the provisional ICS definition was calculated as follows :

$$\text{Prob}(Q_{\max}, p_{\det.Q_{\max}} \geq \text{threshold}_{\text{ICS}}) = \text{prob}(Q_{\max}) \text{prob}(p_{\det.Q_{\max}} \geq \text{threshold}_{\text{ICS}}|Q_{\max}).$$

$\text{Threshold}_{\text{ICS}}$ refers to the threshold pressure used to define obstruction in the provisional ICS nomogram (i.e. $40 + 2 * Q_{\max}$). We refer to $\text{prob}(Q_{\max}, p_{\det.Q_{\max}} \geq \text{threshold}_{\text{ICS}})$ by $\text{prob}(Q_{\max}, \text{obstructed})$ in the following paragraphs.

The number of false negative findings was calculated as the sum (integral) of the probability that a measurement is unobstructed ($1 - \text{prob}(Q_{\max}, \text{obstructed})$) below the lower flow-rate threshold and the probability that a measurement is obstructed above the upper flow-rate threshold applied in the Q_{\max} pre selection algorithm.

The distribution of Q_{\max} was approximated by a log normal distribution, i.e. the distribution of the logarithm of the flow-rate was assumed to be Gaussian. We have estimated the distribution by fitting a log normal model to the data (we used the first measurement done in every male for this purpose). A correction for a (relatively unimportant) deviation of this flow-rate distribution from log normality for $Q_{\max} < 2$ [ml/s] was applied (see results section).

A plot of the log transformed maximum flow-rate and the associated detrusor pressure was made using different symbols to denote the first and second measurement in the same patient. We assumed the following model for the log transformed value of

$p_{\det.Q_{\max}}$:

$$\text{Prob}(\log(p_{\det.Q_{\max}}|Q_{\max})|Q_{\max}) \sim N(a * \log(Q_{\max}) + b + c * n_{\text{seq}}, \sigma) \quad (1)$$

Here the “~” symbol is used to denote “is distributed as”. The N stands for the normal or Gaussian distribution, which has two parameters, a mean and a standard deviation. A description of the mathematical structure of the mean is given as the first argument, σ denotes the standard deviation. A, b and c are parameters. The covariate n_{seq} (the sequence number) was coded as 0 or 1, 0 for the first of the two sequential measurements in the same individual, 1 for the second. The “a” parameter measures the linear dependency of $\log(p_{det.Q_{max}})$ on $\log(Q_{max})$, The b parameter represents the expected pressure in the absence of flow-rate and the “c” parameter measures the effect of doing a second measurement in the same patient. It represents a contrast, positive c values indicate that the second measurement is on average associated with higher $p_{det.Q_{max}}$ values, negative c values indicate that the second measurement is on average associated with lower $p_{det.Q_{max}}$ values.

The values of the parameters a, b, c and σ of the model were determined by fitting the model to the observed log transformed $p_{det.Q_{max}}$ values. The residuals (difference of model and data) were checked for normality by means of the Shapiro Wilks test.

From the fitted model the probability that a measurement with a certain Q_{max} value was obstructed according to the ICS nomogram was calculated as follows : First the log transformed ICS nomogram threshold (i.e. $\log_{10}(40 + 2 * Q_{max})$) was subtracted from the expected value (i.e. $a * \log_{10}(Q_{max}) + b$, using only the first of the two sequential measurements for this purpose, so $c = 0$). The ratio of this difference and the standard deviation σ was calculated to obtain a z-score. This z-score is related to the probability that, assuming a Gaussian distribution, a particular observation, or a more extreme one, occurs. For example if the z-score = + 1.96 (the familiar $p = 5\%$ 2-sided threshold of statistical significance) 2.5% of the observations are estimated to have a more extreme value than the one observed.

According to this procedure the probability of being obstructed at a certain Q_{max} denoted by $\text{prob}(Q_{max}, \text{obstructed})$ was calculated from 0 to 40 [ml/s] with an increment of 0.1 [ml/s]. Analogously the probability that a measurement is classified as being obstructed according to the LPURR nomogram (grade ≥ 2) at a given Q_{max} was calculated.

A2 Sensitivity analysis.

The reduction in invasive measurements and the percentage of false negative findings depends on the statistical distributions of Q_{\max} and $p_{\det.Q_{\max}}$ in the population, on the flow-rate thresholds applied and on the definition of bladder outlet obstruction that is used. The extent to which this balance depends on several assumptions has been studied. The reductions achieved in nine different hypothetical flow-rate distributions for two definitions of bladder outlet obstruction at 2 different levels of acceptable false negative findings were calculated.

The nine flow-rate distributions consisted of three log normal distributions with different mean flow-rates (6 [ml/s], 7.4 [ml/s] and 10 [ml/s]) combined with three different standard deviations. The definitions of obstruction studied were the ICS definition (i.e. $p_{\det.Q_{\max}} \geq 40 + 2 * Q_{\max}$) and LPURR ≥ 2 , i.e. $p_{\det.Q_{\max}} \geq 30 + 1/0.84 Q_{\max}$). A two sided 5% level (i.e. a lower threshold at 2.5% and an upper threshold at 97.5%) and a one sided upper 5% level (i.e. only an upper flow-rate threshold at 95%) were used to define acceptable proportions of false negative findings.

A3 Results (detailed description).

The conditional probability distribution of $p_{\det.Q_{\max}}$ on Q_{\max} , i.e. $\text{prob}(p_{\det.Q_{\max}}|Q_{\max})$ obtained by fitting model (1) to the measured Q_{\max} , $p_{\det.Q_{\max}}$ pairs is given by $\text{Prob}(\log(p_{\det.Q_{\max}}|Q_{\max})|Q_{\max}) \sim N(-0.20 * \log(Q_{\max}) + 1.89 - 0.039 n_{\text{seq}}, 0.18)$. Table 1 lists the 95% credible intervals of these parameter estimates. The linear correlation coefficient was -0.28 ($p < 0.001$). The standard deviation of the residual (σ in equation 1) was 0.18 at the [log cm H₂O] scale (which translates e.g. to a 95% credible interval of 34.5-175 [cm H₂O] at an expected value of 78 [cm H₂O] at $Q_{\max}=0$ [ml/s], see Figure 4), the variance thus equaled 0.03 (0.18*0.18) at the same scale squared.

Figure 4 shows a histogram of the residuals. The outcome of the Shapiro Wilks test was that the Null Hypothesis of “normality” of the distribution was not rejected ($p = 0.18$).

Due to the double log transformation applied to the data it is not easy to interpret the fitted model on the basis of the parameter estimates only. Figure 1 is a plot on a double logarithmic scale that can be read in a familiar way. It displays the measured data and some details of the fitted model, notably the expected value, the 95% credible intervals, and the 1-sided 10 and 20% percentiles. The percentile lines are

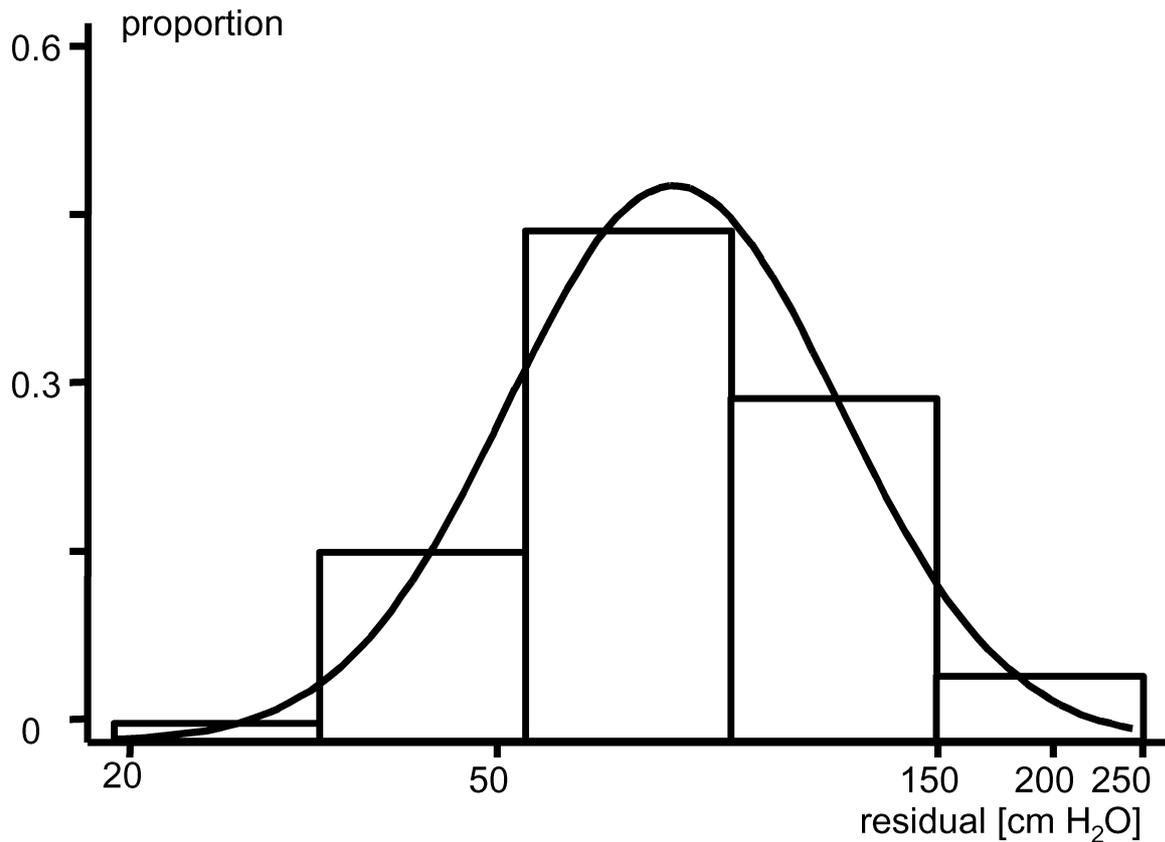


Figure 4 A plot of the residuals of fitting model 1 to the data, calculated at $Q_{\max} = 0$ [ml/s]. Due to the double logarithmic transformation applied to the data, the residual expressed at the non transformed flow rate and pressure scales will vary as a function of the Q_{\max} value chosen. The purpose of the plot is to show that the data can be described quite well by means of a Gaussian distribution.

derived from the fitted probability model $\text{prob}(p_{\text{det},Q_{\max}}|Q_{\max})$. If a certain Q_{\max} , $P_{\text{det},Q_{\max}}$ pair is e.g. on the 20% percentile line it is estimated that 20% of all men with an identical Q_{\max} value have pressures equal or higher than the value indicated by the line. The curved line represents the line used in the ICS nomogram to differentiate between obstructed and equivocal measurements. The curvature is caused by the double log transformation applied to the axes.

The distribution of the Q_{\max} values of the first measurement made in each patient and a projected log normal distribution is given in Figure 2. It is clear that the low flow-rates deviate significantly from log normality (Shapiro Wilks 2-sided p-value = 0.52 for $Q_{\max} \geq 2$ [ml/s], and 0.01 for all values). In the present study 3% (4 out of 131) of the Q_{\max} values were lower than 2 [ml/s].

The probability that a measurement with a given maximum flow-rate is obstructed according to model 1 (using the ICS definition of obstruction and the LPURR \geq

category 2 definitions) can be read from Figure 3. It represents $\text{prob}(\text{obstructed}|Q_{\text{max}})$. The probability of being obstructed according to the ICS provisional nomogram decreases much more rapidly with increasing Q_{max} values than the probability of being obstructed according to the LPURR system (\geq grade 2).

Table 2 gives an overview of the effects of applying a flow-rate based pre selection algorithm to reduce the number of invasive pressure-flow studies. It should be read as follows (taking the first line as an example). If a population is studied with a log normal flow-rate distribution with a mean of 7.4 [ml/s] and a 95% flow-rate range from 2.2 [ml/s] – 25 [ml/s] and using the provisional ICS definition for obstruction the number of invasive procedures can be reduced by 13.8% if no pressure-flow studies are done for $Q_{\text{max}} > 14.6$ [ml/s]. If this rule is applied less than 2.5% of the measurements are classified unobstructed on the basis of Q_{max} whereas in reality (using the ICS nomogram as a gold standard) they are obstructed. This same kind of logic in reading the Table can be applied for the lower threshold, however an estimated 3% must be added to the values listed in Table 2 due to the poor fit of the log normal distribution to the Q_{max} values measured in the low flow range (i.e. < 2 [ml/s]).

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Relative bladder outlet obstruction.

Ries Kranse and Ron van Mastrigt.

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Purpose. Currently bladder outlet obstruction in males is defined by the provisional ICS nomogram which is partly based on expert opinion and partly on measurements before and after transurethral prostate resection. Recently there has been some interest in the development of a similar nomogram for females.

Materials and methods. We studied the possibility to define bladder outlet obstruction on the basis of one of the signs that it causes, namely post void residual urine.

Results. The probability of a relative residual exceeding 20% of the bladder capacity can be modeled (both in males and females) using one parameter, the ratio of the obstruction parameter URA and the bladder contractility parameter w_{20} . URA/w_{20} represents relative bladder outlet resistance, i.e. bladder outlet resistance normalized for bladder contractility. Above a threshold of $URA/w_{20} = 6.8$ for females and 8.2 for males a relative residual exceeding 20% is found in 90% of the measurements. These thresholds may be used to define relative obstruction. The provisional ICS nomogram for obstruction in males was transformed into an identical nomogram for females by equating the probabilities of residuals in each gender. The latter differs from that for men in that the lines demarcating the zones are horizontal or flow rate independent, but the intercepts are approximately the same (i.e. 20 and 40 [cm H₂O]).

Conclusions. We suggest that, instead of defining obstruction as an absolute level of bladder outlet resistance, it is better to define it relatively, i.e. as a level of bladder outlet resistance that depends on the contractility of the bladder.

Introduction.

The lower urinary tract can be modeled as two subsystems, the bladder and the bladder outlet¹. In the voiding phase the bladder contracts and the bladder outlet relaxes. Ideally voiding is done to completion. Post void residual urine is associated with increased morbidity due to infections. In association with other symptoms it is considered an indication for therapeutic intervention. The probability of incomplete voiding increases with increasing bladder outlet resistance and decreasing bladder contractility. Furthermore a previous study has shown that it depends on the bladder capacity².

The detrusor pressure and flow rate during voiding are related to the contractile state of the bladder and the degree of resistance to bladder outlet flow. To assess bladder contractility and bladder outlet resistance during voiding the convoluted contributions

of both the bladder and the bladder outlet to these signals must be disentangled. Several procedures have been proposed to accomplish it. Typically these procedures try to quantify properties of bladder contractility and bladder outlet resistance by means of one number, an index. An index for bladder contractility is the Watts factor^{3,4} which approximately represents the power per unit of bladder wall area. In the past the ratio of the detrusor pressure and the flow rate or the square of the flow rate⁵ have been proposed to quantify bladder outlet resistance. Both these indices ignore, amongst others, the fact that a minimum pressure is needed to open the urethra. For this reason we have used the more recently proposed indices for bladder outlet resistance in males URA⁶ and BOOI⁷ (the former Abrahams Griffiths number).

Bladder outlet obstruction is a special high state of bladder outlet resistance. It is defined in the provisional ICS nomogram for males⁸. The nomogram reflects expert opinions and information from intervention studies (pre and post trans urethral resection of the prostate (TURP) measurements).

In this paper we introduce a new concept, “relative bladder outlet resistance” or “relative underpowering of the detrusor”, which establishes a relationship between bladder outlet resistance (as expressed by URA or BOOI), bladder contractility (as expressed by the Watts-factors) and the probability of a post void residual. The two names for the concept may be interchanged, we have arbitrarily chosen to use the former. Using the concept we were able to define bladder outlet obstruction in males in terms of a probability of a post void residual. This objectively verifiable criterion for the definition of obstruction may have an attractive advantage over the currently used provisional ICS nomogram for the definition of bladder outlet obstruction in males since the latter is for a large part based on expert opinion. Moreover if one accepts the ICS nomogram as a de facto standard, the concept of relative bladder outlet resistance enables a transformation of the ICS nomogram for males into a nomogram for bladder outlet obstruction in females, a topic that has recently drawn considerable attention⁹.

Materials and methods.

We studied 614 and 503 pressure-flow measurements in 614 females and 503 males with various symptoms were studied. The measurements were selected from 12.112 urodynamic measurements stored at three locations in the University Hospital Rotterdam. From this database we selected measurements in adult males and females made at one location only (the video cystometry room) by one and the same investigator. For most patients more than one study was available, the first complete filling/voiding cycle was selected. Artifacts, incomplete studies and invalid analysis results were excluded by selecting only measurements with residual urine, filled volume, voided volume, maximum flow rate, detrusor pressure at maximum flow rate, the urethral resistance parameter URA, and the contractility parameters w_{max} , w_{Qmax} , w_{20} and w_{80} greater than zero. For all measurements filling took place at a medium filling rate (80 [ml/min]), trans-urethrally, using a 5F catheter with a room temperature saline solution until the patients indicated the desire to void. The rectal and intravesical pressures were measured by means of a disposable pressure transducer connected to a water filled catheter. The flow rate was measured by means of a Dantec rotating disk flow meter. All signals were sampled at a 10 [Hz] sampling rate and stored on computer disk. An appropriate low pass filter with a cut off frequency of 0.5 [Hz] was applied to the signals in order to minimize the influence of artifacts and noise on the measurement outcomes. For measurements in males the measured detrusor pressure was delayed 0.6 [s] with respect to the measured flow rate signal to account for the spatial separation of the transducers¹⁰. For females voiding in a sitting position this delay was 0.4 [s], for females voiding in a standing position 1.1 [s].

The maximum urinary flow rate and the associated detrusor pressure value were automatically selected from the low pass filtered signals. The voided volume was calculated by integrating the urinary flow rate. The post void residual volume was calculated as the difference between the filled volume and the calculated voided volume, i.e. urine production during filling was neglected. This does not affect our conclusions since the procedure is conservative, the actual residual is equal or greater than the calculated residual. A significant absolute residual was defined as a residual exceeding 100 [ml], a significant relative residual was defined as a residual exceeding 20% of the filled volume. For all measurements the Watts factor at the

maximum flow rate ($w_{Q_{max}}$) and the Watts factors at 80 and 20% (w_{20} and w_{80}) of the voided volume and the urethral resistance parameters URA and BOOI were calculated.

Statistical analysis.

Several multivariate logistic regression analyses¹¹ were carried out to find those variables that best predicted the absence or presence of a post void residual. The first set of analyses used a significant absolute residual in males and females as the dependent variable (absent or present) and the filled volume, one of the obstruction parameters and one of the contractility parameters as independent parameters. The second set of analyses used a significant relative residual as dependent variable and an obstruction parameter and a contractility parameter as predictors (independent variables). To compare the performance of Q_{max} and $p_{det.Q_{max}}$ in the context of these models a separate logistic regression was carried out using these parameters as predictors. In the logistic regression analyses only measurements with a filled volume exceeding 200 [ml] were included.

The area under the receiver operating curve (ROC) was used to compare the quality of the models¹². It represents the fraction of pairs, each consisting of one patient with residual and one without, in which the patient with the highest probability of a residual according to the logistic regression is truly the one with the residual.

A final logistic regression model predicting a significant relative residual as a function of the ratio of URA and w_{20} (URA/w_{20}) was fitted to the data.

Using the logistic model with a significant relative residual as outcome and Q_{max} , $p_{det.Q_{max}}$ as predictors the two lines in the provisional ICS nomogram demarcating the obstructed, equivocal and unobstructed zones in males were expressed in terms of probabilities of a residual. A logistic model on the basis of Q_{max} , $p_{det.Q_{max}}$ for females, combined with the probabilities derived for males was used to construct similar lines for females. The mathematical details of this procedure are given in appendix A.

Results.

Table 1 gives the descriptive statistics of the parameters measured in this study. Considering the non Gaussian (not normal) distributions of most of these we have chosen to report inter quartile ranges and median values rather than mean values and standard deviations.

Table 2 shows an overview of the number of measurements with a filled volume exceeding 200 [ml] that were used for the logistic regression analyses. The table shows that the percentages of measurements with an absolute or relative residual are roughly comparable (within gender). Between genders a post void residual is more common in males than in females in the population studied.

Tables 3 and 4 give a selection of the results of the logistic regression analyses. The odds ratios in these tables give the relative increase of the odds of a residual resulting from a 1 unit change in one of the predictors, keeping the other predictors constant.

Parameter	Measurements in females (N = 614)		Measurement in males (N = 503)		Unit
	Median	Inter quartile range (25% percentile – 75% percentile)	Median	Inter quartile range (25% percentile – 75% percentile)	
filled volume	440	165	387	217	ml
absolute residual	80	138	134	205	ml
Q_{\max}	13.2	9.7	7	5	ml/s
$p_{\det.Q_{\max}}$	28	18	54	35	cm H ₂ O
URA	14	11	30	23	cm H ₂ O
BOOI	0.95	32	37	42	cm H ₂ O
$W_{Q_{\max}}$	5.5	3.4	7.5	4.4	W/m ²
W_{20}	5.4	4.1	6.2	4.3	W/m ²
W_{80}	4.7	3.1	7.2	4.4	W/m ²

Table 1. Descriptive parameters of the measurements made in males and females.

	females	males
Total	614	503
With a filled volume exceeding 200 [ml]	546	435
With a post void residual ≥ 100 [ml] and a filled volume ≥ 200 [ml]	251 (46%)	292 (67%)
With a relative post void residual $\geq 20\%$ and a filled volume ≥ 200 [ml].	237 (43%)	268 (62%)

Table 2. Overview of the number of measurements in subjects with a filled volume ≥ 200 [ml] that were used in the logistic regression analyses.

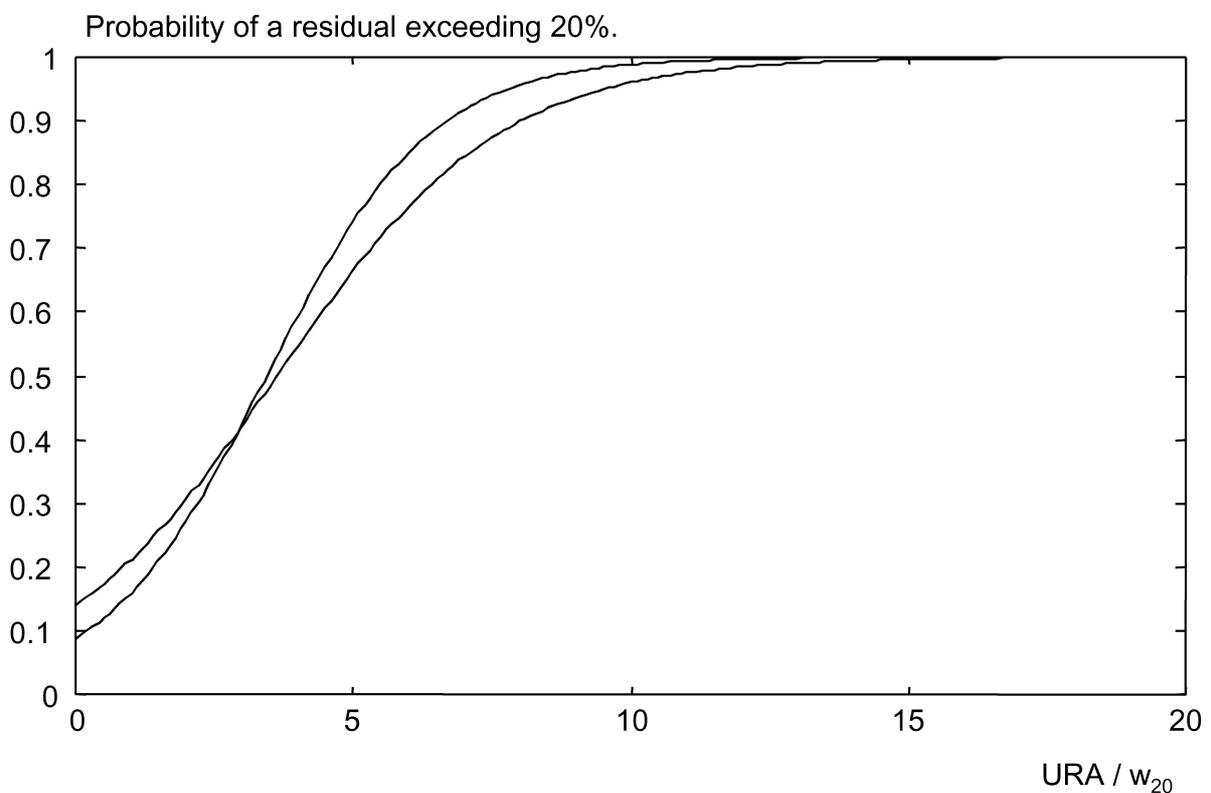


Figure 1 The probability of a relative residual exceeding 20% as a function of the ratio of URA and w_{20} (URA/w_{20}) for males and females.

Predicted	Predictor	Odds ratio (2-sided pvalue),	Predictor	Odds ratio (2-sided pvalue)	Predictor	Odds ratio (2-sided p value)	Area under the ROC curve
Absolute Residual	filled volume	1.0042 *	Q_{max}	0.85 *	$p_{det, Q_{max}}$	1.0099 (0.06)	0.78
	filled volume	1.0038 *	W_{20}	0.64 *	URA	1.13 *	0.84
	filled volume	1.0030 *	W_{80}	0.69 *	URA	1.14 *	0.78
	filled volume	1.0030 *	$W_{Q_{max}}$	0.70 *	URA	1.14 *	0.78
	filled volume	1.0041 *	W_{20}	0.63 *	BOOI	1.05 *	0.85
Relative Residual	filled volume	0.9996 (0.63)	W_{20}	0.63 *	URA	1.15 *	0.84
			W_{20}	0.63 *	URA	1.15 *	0.84
					URA/ W_{20}	1.96 *	0.84

Table 3. A selection of the results of fitting the logistic regression models to the data for measurements in females.

* = $p < 0.05$ (2-sided).

Predicted	Predictor	Odds ratio (2-sided pvalue)	Predictor	Odds ratio (2-sided pvalue)	Predictor	Odds ratio (2-sided p value)	Area under the ROC curve
Absolute Residual	filled volume	1.003 *	Q_{\max}	0.81 *	$p_{\det, Q_{\max}}$	1.007 (0.09)	0.76
	filled volume	1.002 (0.004)	w_{20}	0.73 *	URA	1.070 *	0.78
	filled volume	1.002 (0.02)	w_{80}	0.76 *	URA	1.080 *	0.76
	filled volume	1.002 (0.016)	$w_{Q_{\max}}$	0.79 *	URA	1.072 *	0.76
	filled volume	1.003 (0.002)	w_{20}	0.63 *	BOOI	1.050 *	0.80
Relative Residual	filled volume	0.999 (0.53)	w_{20}	0.74 *	URA	1.074 *	0.79
			w_{20}	0.74 *	URA	1.075 *	0.79
					URA/ w_{20}	1.644 *	0.80

Table 4. A selection of the results of fitting the logistic regression models to the data for measurements in males.
= $p < 0.05$ (2-sided).

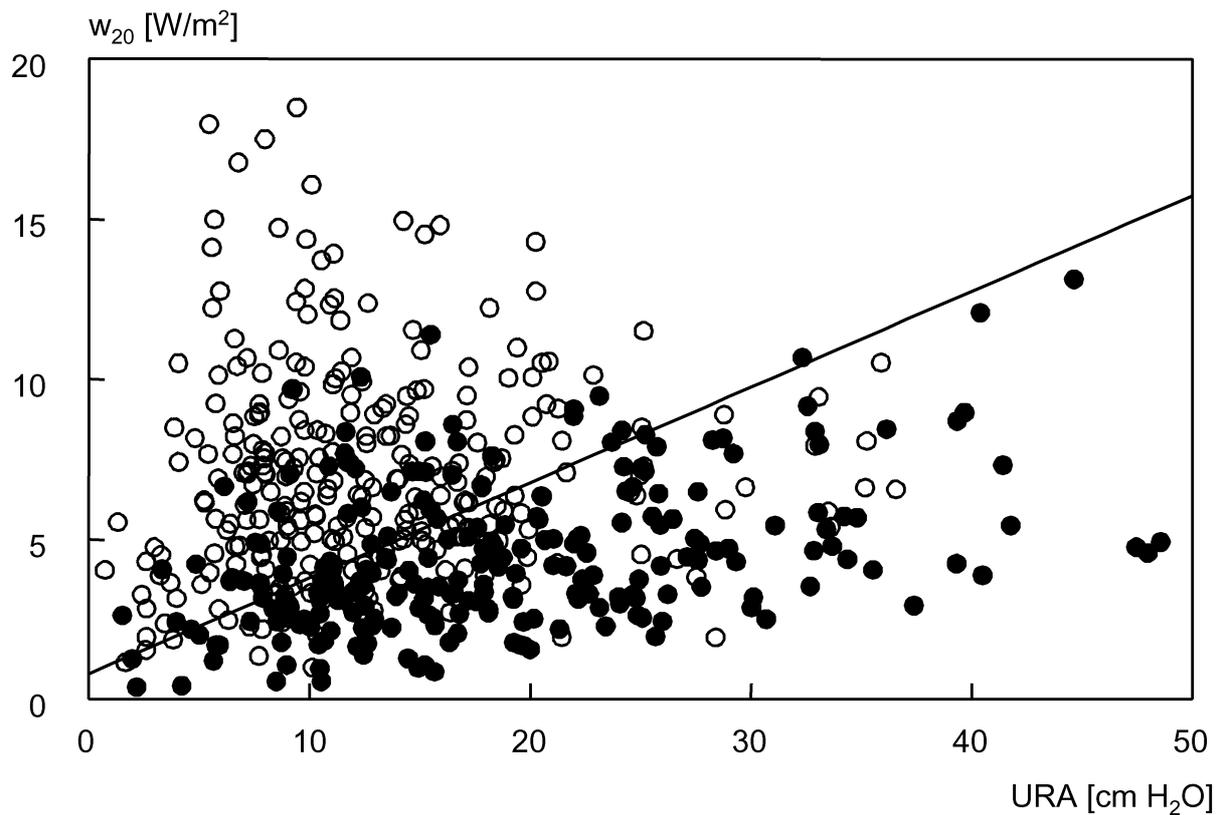


Figure 2. A scatterplot of URA and w_{20} values for measurements in females, open dots denote the absence of a significant relative residual, closed dots its presence. The straight line in the graph best classifies the measurements according to the logistic regression model. Figure 3 gives identical information for measurements in males.

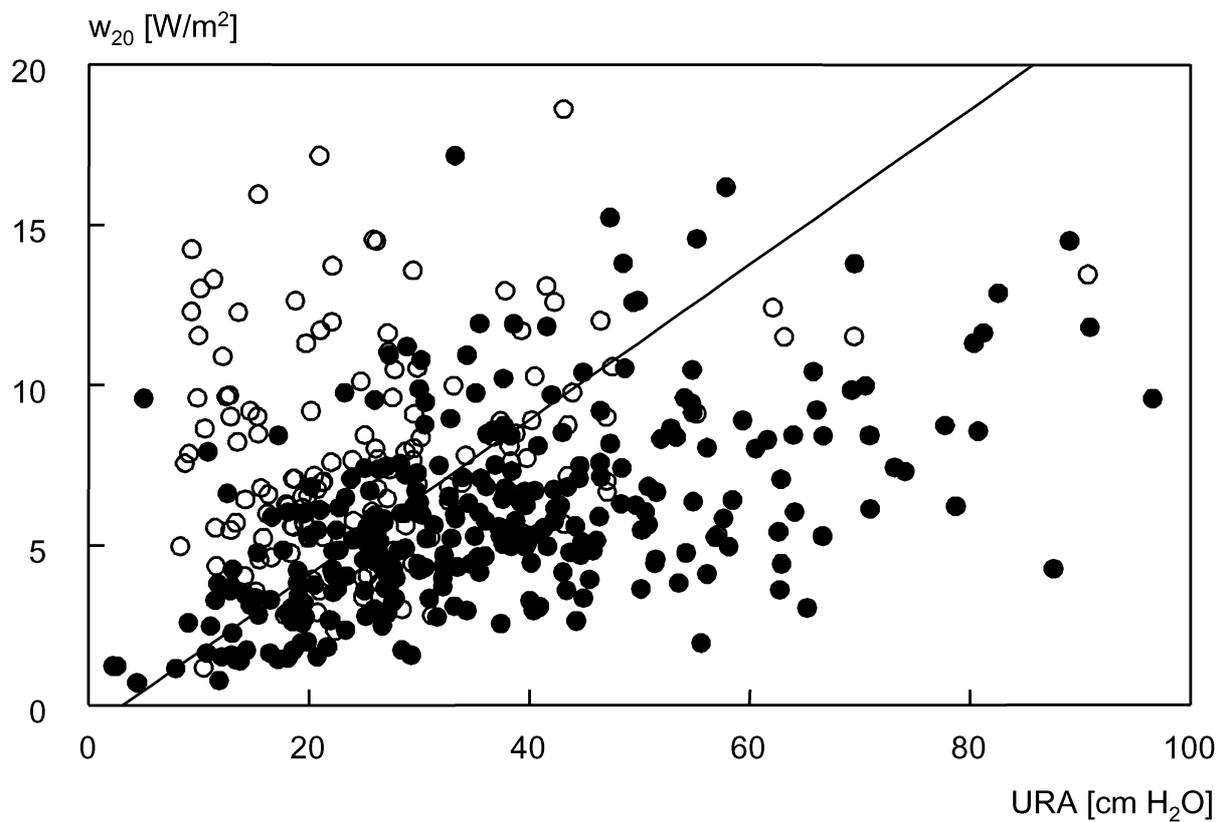


Figure 3. A scatterplot of URA and w_{20} values for measurements in males, open dots denote the absence of a significant relative residual, closed dots its presence. The straight line in the graph best classifies the measurements according to the logistic regression model.

Another way of viewing the results of these tables that more directly relates to clinical practice is to calculate the increase in a predictor that is needed to double (or halve in the case of a ratio < 1) the odds ratio. E.g. in Table 3 the odds ratio for URA equals 1.15 for the prediction of a relative residual in women. This implies that URA has to increase an estimated $2/0.15 = 13.3$ [cm H₂O] in order to double the odds of a residual (when w_{20} is unchanged).

Figure 1 illustrates the probability of a relative residual exceeding 20% as a function of the ratio of URA and w_{20} (URA/ w_{20}) for males and females. When the ratio URA/ w_{20} exceeds 6.8 90% of all females are expected to have a relative residual exceeding 20%. This 1-sided 90% threshold equals 8.2 for measurements in males.

Figure 2 shows a scatterplot of URA and w_{20} values for measurements in females, open dots denote the absence of a significant relative residual, closed dots its presence. The straight line in the graph best classifies the measurements according to the logistic regression model. It represents a probability of 0.5 for a significant post void residual in this population and was calculated by setting the linear equation in the exponent of the logistic regression formula equal to zero¹¹. Figure 3 shows identical information for measurements in males.

The best separation of obstructed and equivocal measurements in females, obtained from a transformation of the ICS nomogram for males (details in Appendix A), is given by a horizontal line through $p_{\text{det.Qmax}} = 40.7$ [cm H₂O]. The line separating non obstructed from equivocal patients is also horizontal, through $p_{\text{det.Qmax}} = 21.2$ [cm H₂O]. Of course for practical purposes these values can be read as 40 and 20 [cm H₂O].

Discussion.

Bladder outlet obstruction is currently de facto defined without an objectively verifiable quantitative justification (in terms of the prevalence of the signs that are commonly associated with it such as a post void residual or a low maximum flow rate). Furthermore it is only and provisionally defined for measurements in males. Although bladder outlet obstruction in females is much less prevalent, a clear need for its definition exists⁹.

We have studied whether it is possible to model the probability of a residual volume after voiding in terms of parameters for bladder outlet resistance, bladder contractility and bladder capacity. For bladder outlet resistance we used the parameters URA and BOOI. For bladder contractility we used Watts factors instead of the sometimes used product of the detrusor pressure and the flow rate, since these factors account for the average amount of energy that is left in the urinary stream after exiting the meatus. All measurements were done with a double lumen transurethral catheter, a fact that very likely affected the measurement of the bladder outlet resistance¹³. This was however the case for all measurements we did and it is the case for the majority of urodynamic measurements in the rest of the world. We therefore expect that the conclusions derived from this paper are applicable to other populations as long as the measurement procedure is comparable and as long as the populations studied are not too different.

From Tables 3 and 4 it can be appreciated that an absolute residual exceeding 100 [ml] can only be predicted accurately when the bladder capacity is taken into account (the filled volume was a significant predictor for a significant residual in all models for measurements in males and females). A more compact model is therefore possible if a relative residual instead of an absolute residual is used as the dependent parameter. In none of the logistic regression models using a relative residual as the output parameter the filled volume was a significant predictor. Therefore it could be omitted from the model. Only patients with a filled volume exceeding 200 [ml] were analyzed in this study. In patients with a smaller capacity the influence of the bladder volume on predicting a residual became larger. Obviously smaller bladders are emptied disproportionately more easily.

The bladder contractility parameter w_{20} , the power per unit bladder surface area at 80% of the voided volume, best predicted a post void residual in all models studied. This finding is not surprising as it is intuitively appealing that the probability of a residual is associated with bladder contractility at the end of voiding. The qualitative observation that contractility at the end of voiding is important was already made in 1979¹⁴. A possible confounding factor is that Watts factors are (amongst others) derived from the shortening velocity of the bladder wall which is calculated from the

instantaneous bladder volume and the flow rate. Since the residual is part of the instantaneous volume it affects the calculated shortening velocity and therefore the Watts factors. This is true for all Watts factors but it is especially true for w_{20} because the relative contribution of the residual to the instantaneous bladder volume increases as the bladder is emptied. In the extreme case (when all residual related information is contained in w_{20}) the residual would be perfectly predicted by w_{20} and the bladder outlet resistance parameter in the model would have no predictive value at all (i.e. the odds ratio would equal 1). Since the odds ratio for URA is higher for w_{20} than for w_{80} or $w_{Q_{max}}$ (see Tables 3 and 4), and certainly significantly higher than 1, we can rule out this explanation.

A final reduction in model complexity was accomplished by taking into account that the classification lines depicted in Figures 2 and 3 run roughly through the origin. This is an indication that the ratio of URA and w_{20} may have equal predictive properties as URA and w_{20} separately. This indication was quantitatively confirmed by means of a logistic regression analysis with the ratio URA/w_{20} as a single parameter. The results of these analyses are given in the last rows of Tables 3 and 4.

The pattern that emerges from the data analysis strongly suggests that in males and females similar mechanisms lead to the condition of a post void residual. Its odds increase with increasing URA values and decrease with increasing w_{20} values. This observation quantitatively underlines what is intuitively obvious, that a high bladder outlet resistance does not necessarily lead to incomplete voiding (or to a low maximum flow rate), rather the combination of bladder outlet resistance and bladder contractility in a particular patient leads to that condition. Therefore the concept of (absolute) bladder outlet obstruction as defined by the ICS may clinically be sub-optimal. Even slightly increased (equivocal) bladder outlet resistance may lead to incomplete voiding in men with a less than average contractile bladder and may therefore be an indication for therapeutic intervention, while a considerable absolute obstruction may cause no problems in men with a strong bladder.

From Tables 3 and 4 it is furthermore clear that the Q_{max} $p_{det.Q_{max}}$ pair less accurately predicts a post void residual than a combination of bladder outlet resistance and contractility parameters (URA, BOOI and the Watts Factors). When Q_{max} , $p_{det.Q_{max}}$ was used to transform the provisional ICS nomogram for males into a nomogram for

females (details in Appendix A), it was found that the lines that demarcate the zones (obstructed, equivalence, non obstructed) are horizontal for practical purposes, i.e. independent of the Q_{\max} value. Given the poor quality of the Q_{\max} , $p_{\det.Q_{\max}}$ model to account for the observed data and the rather personal choice that we have made to carry out the transformation (the probability of a residual) we do not claim that this is THE nomogram for bladder outlet obstruction in females. We however think that our analysis has the important message that the contribution of the detrusor pressure to the definition of obstruction is much less important in females than in males. This finding is in line with the nomogram proposed in a recent paper on this subject⁹. The lines in that proposal are either horizontal or have a slope of 1 [cm H₂O/(ml/s)].

The ratio of bladder outlet resistance and bladder contractility measures what may be termed the relative bladder outlet resistance, bladder outlet resistance normalized for bladder contractility. If the relative bladder outlet resistance is so high that nearly all voidings (e.g. 90% as adopted in this paper) are incomplete a measurement may be labeled relatively obstructed. Alternatively the concept may be termed “relative detrusor underpowering”, meaning that, given a certain bladder outlet resistance, the detrusor is, very likely, not powerful enough to void to completion. The latter phrasing is e.g. more appropriate in the explanation of a post void residual in frail elderly women which is almost always explained by an impaired detrusor contraction. We have arbitrarily opted to use the term “relative bladder outlet obstruction” rather than “relative detrusor underpowering” but from the above example it is clear that being “relatively obstructed” does not imply being “obstructed”.

The merits of the concept of relative bladder outlet obstruction become clear when one considers its use as an indication for a TURP. Suppose that prior to a TURP both URA and w_{20} are measured, and suppose that URA can be reduced to 20 [cm H₂O] in all patients, then the concept of relative bladder contractility enables us to predict prior to the intervention which men are likely to void to completion post operatively. The predictive value of pre operative contractility with respect to post operative subjective symptomatology is supported by data of a previous clinical study in which pre and post TURP invasive urodynamic measurements were compared¹⁵. Of course no guarantee can be given to an individual man scheduled to

undergo a TURP on the basis of a probabilistic model but the odds of success of the intervention can be predicted adequately.

Conclusion.

The level of urethral resistance at which a significant residual occurs, increases strongly with the bladder contractility. We therefore suggest that instead of defining obstruction as an absolute level of bladder outlet resistance, it is better to define it relatively, i.e. as a level of bladder outlet resistance that depends on the contractility of the bladder.

In contrast to the current definition of obstruction, which is partly based on expert opinion, a definition of obstruction in terms of relative resistance can be based on the absence or presence of a post void residual. Thus a correlation with dysfunctional voiding is in fact "built into" this concept which gives it an advantage over currently used urodynamic parameters that often show a poor correlation with signs or symptoms. Furthermore, because it is derived from a measurable quantity, the concept of relative bladder outlet resistance greatly facilitates scientific discussion, and it appears to be generally applicable (i.e. it is not gender specific). The conversion of the ICS nomogram for bladder outlet obstruction in males into one for females illustrates this point.

Appendix.

The line demarcating the obstructed from the equivocal zone in the provisional ICS nomogram for the definition of bladder outlet obstruction in males ($p_{\text{det.Qmax}}=40 + 2 * Q_{\text{max}}$) was transformed into a line demarcating the same zones in a nomogram for females as follows :

The probability of a significant relative residual according to the logistic model is given by :

$$p(\text{residual}) = 1 / (1 + \exp -(c + a_{\text{male}} * Q_{\text{max}} + b_{\text{male}} * p_{\text{det.Qmax}})).$$

Here c reflects the prevalence of a significant residual in the population under study.

Filling in the parameter values that were found by fitting the model to the data for males and the line that demarcates the zones ($p_{\text{det.Qmax}}=40 + 2 * Q_{\text{max}}$) yields :

$$p(\text{residual})_{\text{males}} = 1/(1 + \exp (-1.875 + 0.1936 * Q_{\text{max}} - 0.00869 * (40 + 2 * Q_{\text{max}}))$$

The logistic model for females was :

$$p(\text{residual})_{\text{females}} = 1/(1 + \exp (-1.86 + 0.1680 * Q_{\text{max}} - 0.0089 * (a + b * Q_{\text{max}})))$$

In this equation a and b denote the parameters of the line demarcating the obstructed zone in a nomogram for females.

Solving for equal probabilities for $Q_{\text{max}} = 0$ [ml/s] and $Q_{\text{max}} = 15$ [ml/s], yields a linear system of 2 equations with 2 unknowns that can be solved :

$$a = 40.7 \text{ [cm H}_2\text{O]}.$$

$$b = -0.9 \text{ [cm H}_2\text{O}/(\text{m/s})]$$

A negative value for b has serious implications for the interpretation of the line as a demarcation line for the definition of absolute obstruction in females. Indeed, on the basis of such a line we can find two measurements with the same $p_{\text{det.}Q_{\text{max}}}$, one with a low Q_{max} that is unobstructed and one with a higher Q_{max} that is obstructed, a clearly absurd result from a physical point of view. Unfortunately the system of equations has no solutions for a positive b value, which leads us to conclude that the closest line that agrees with the system of equations and that does not lead to classifications that are physically absurd is a horizontal line with a cut off value of 40.7 [cm H₂O]. Following an identical procedure, the line demarcating the border of the equivocal zone and the unobstructed zone was found. This leads to a horizontal threshold of 21.2 [cm H₂O]. Of course for practical purposes these values can be set to 40 and 20 [cm H₂O].

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Bladder outlet resistance.

Ries Kranse and Ron van Mastrigt.

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Purpose. To develop a method to objectively compare methods for the quantification of bladder outlet resistance.

Materials and methods. 131 unselected voiding cystometries from 131 male patients were studied. Several models proposed for bladder outlet resistance were fitted to the lowest monotonically increasing part (bottom) of the pressure-flow plots. In conjunction with a parameter for bladder contractility, the parameters of the models were used as predictors for a post void residual exceeding 20% of the filled volume.

Results. The pressure drop over the relaxed bladder outlet is best described by a linear function of the flow-rate. The flow-rate independent and the flow-rate dependent part of that function are both statistically significant predictors for a residual. They can however be combined into one index that is as efficient as the two numbers separately in predicting a residual. This index is the average pressure of the bottom of the pressure-flow plot.

Conclusions. This paper describes how different models for the quantification of bladder outlet resistance can be compared objectively on the basis of their ability to predict a significant post void residual. Using this criterion in an unselected group of measurements the average pressure of the bottom of the pressure-flow plot performed best as an index for the quantification of bladder outlet resistance. It combines (or weights) two components (the flow-rate dependent and the flow-rate independent) without loss of power in predicting a post void residual.

Introduction.

Conceptually, the lower urinary tract consists of two subsystems : the bladder and the bladder outlet¹. During voiding, the bladder contracts and forces urine through the bladder outlet. The properties of the bladder relevant to this process are commonly referred to by the term contractility, those of the bladder outlet by bladder outlet resistance.

Malfunction of one or both of these subsystems may lead to clinical symptoms such as a low maximum urinary flow-rate or a post void residual. In a urodynamic pressure-flow study the pressure and flow-rate during voiding are recorded. As these two signals depend on both bladder contractility and bladder outlet resistance they cannot directly be used for diagnostic purposes. Therefore procedures have been developed to transform the signals into clinically relevant measures for bladder

contractility and bladder outlet resistance. In this paper we focus on the quantification of bladder outlet resistance.

The bladder outlet may be viewed as a collapsible distensible tube that is normally closed¹. A minimum pressure is needed to open it. An extra pressure head is needed on top of this opening pressure to drive a flow-rate through it. Therefore, bladder outlet resistance should, from a physical perspective, be quantified by at least two parameters : One for quantifying the opening pressure, and at least one more to quantify the relation between the extra pressure head and the flow-rate. The precise form of the flow-rate dependence has been the subject of several studies^{2,3}.

In the literature an increased minimum opening pressure has been associated with compressing the bladder outlet. A higher than normal pressure increase with increasing flow-rate is ascribed to a constricted bladder outlet^{2,4}.

The fact that bladder outlet resistance should be quantified by at least two parameters complicates patient ranking with respect to bladder outlet resistance or treatment efficacy evaluation. Such ranking requires a weighting of the parameters and the question arises how to value the different aspects.

In this paper we address the following issues related to the quantification of bladder outlet resistance :

- 1) What is an appropriate model for the relationship between the detrusor pressure and the flow-rate of the relaxed bladder outlet ;
- 2) Can bladder outlet resistance be quantified by one index which enables (amongst others) the ranking of patients?
- 3) If this can be done, what is the best index?

We show that it is possible to answer these questions if one is willing to accept the premise that the best (i.e. most relevant) parameter for bladder contractility and the best parameter for bladder outlet resistance predict a post void residual most accurately.

Materials and methods.

We have studied 131 simultaneous measurements of the detrusor pressure and the flow-rate in a group of 131 unselected male patients. All men were investigated at the outpatient clinic of the University Hospital Rotterdam, The Netherlands. All measurements started with filling an empty bladder. The residual urinary volume after micturition was calculated as the difference between the filled volume and the voided volume. A significant absolute residual was defined as a residual exceeding 200 [ml]. A significant relative residual was defined as a residual exceeding 20% of the filled volume. Intravesical and rectal pressures were measured with fluid filled lines, and the flow-rate was measured with a Dantec ® rotating disk transducer. The resulting signals were sampled at a 10 [Hz] sampling rate and stored on computer disk. The detrusor pressure was calculated as the difference of the intravesical and rectal pressure. The bladder contractility parameters w_{20} , w_{80} , w_{max} and w_{Qmax} were calculated. These parameters estimate the power at 80 and 20% of the voided volume, the power at the maximum flow-rate and the maximum power generated per unit area of bladder wall surface^{5,6}.

The detrusor pressure was plotted as a function of the flow-rate and the lowest monotonically increasing part of this plot, which we will call the bottom of the pressure-flow plot, was calculated. This bottom reflects the most relaxed state of the bladder outlet in a certain voiding³, and represents the least flow-rate impeding (i.e. least obstructive) state of the bladder outlet. It was obtained by sorting the set of flow-rate and detrusor pressure data pairs on increasing flow-rate. From this sorted set the sample pair with the lowest pressure and a flow-rate higher than the flow-rate of the previously selected sample pair was selected. This step was repeated until the selection of the sample pair with the lowest pressure at the maximum flow-rate completed the algorithm.

The passive urethral resistance relation (PURR⁷), a simple linear model and an orthogonal polynomial model⁸ were fitted to the calculated bottoms of the pressure-flow curves. PURR models the pressure over the relaxed bladder outlet in terms of an opening pressure and a quadratic flow-rate dependent part ($p = p_{muoPURR} + c_{PURR} Q^2$). The quadratic model is a rough abstraction of the underlying physical structure since the bladder outlet is modeled as a rigid nozzle. In

the simple linear model ($p = p_{\text{muoLIN}} + c_{\text{LIN}} Q$) the relationship with the flow-rate is linear. The orthogonal polynomial model is given by $p = a_{\text{ORT}} + b_{\text{ORT}}(Q - \beta) + c_{\text{ORT}}(Q - \gamma_1)(Q - \gamma_2)$. Here β , γ_1 and γ_2 are constants determined from the data in such a way that the orthogonality criterion is fulfilled (see discussion section). This model is capable of fitting data that obeys the quadratic model as well as data that obeys the linear model.

The linear correlation coefficients between c_{PURR} and c_{ORT} and c_{PURR} and b_{ORT} as well as their squared values (the percentage of variation in one variable explained by the other) were calculated.

In addition, for all measurements two proposed indices for bladder outlet resistance URA^9 and BOOI^{10} were calculated.

A set of multivariate logistic regression analyses¹¹ was carried out using the parameters of each of the models for bladder outlet resistance in combination with one of the contractility parameters to try to predict the presence of a post void residual exceeding 20% of the filled volume. The precise procedure has been described elsewhere¹². The outcome of a logistic regression analysis is an odds ratio that measures the increase of the relative odds of the outcome (in this case a residual) as a function of a unit change of one of the predictors in the model (assuming that all other predictors remain unchanged).

The area under the ROC curve was used as an indicator for the degree to which the models account for the variation observed in the data. It estimates the percentage of correctly classified measurements in a two alternative forced choice experiment¹³.

All p-values listed in the paper are 2-sided. Descriptive statistics are given in terms of the median value (or 50% percentile i.e. 50% of the measurements have a value lower than or equal to this value) and inter quartile range (25 and 75% percentiles).

Results.

In 65 of 131 patients the residual volume did not exceed 20% of the filled volume. The median value and the 25 and 75% percentiles for some variables measured in the 131 patients and relevant to this study were URA : 25 (19-35) [cm H₂O]; w_{20} : 6.9 (5.1-9.9) [W/m²]; w_{80} : 7.2 (5.3-9.2) [W/m²]; w_{max} : 9.3 (7.2-13.1) [W/m²]; w_{Qmax} : 8.0 (6.3-11.0) [W/m²] and the filled volume : 394 (273-505) [ml].

Figure 1 illustrates the procedure used to analyze the data. It shows a pressure-flow plot the bottom of which was selected by means of the algorithm described in the materials and methods section. To this bottom a 2nd degree orthogonal polynomial and the passive urethral resistance relation PURR were fitted. In this example the parameter associated with the quadratic flow-rate term of PURR was 0.55 [cm H₂O/(ml/s)²] and the average quadratic trend measured by the orthogonal polynomial was -0.18 [cm H₂O/(ml/s)²].

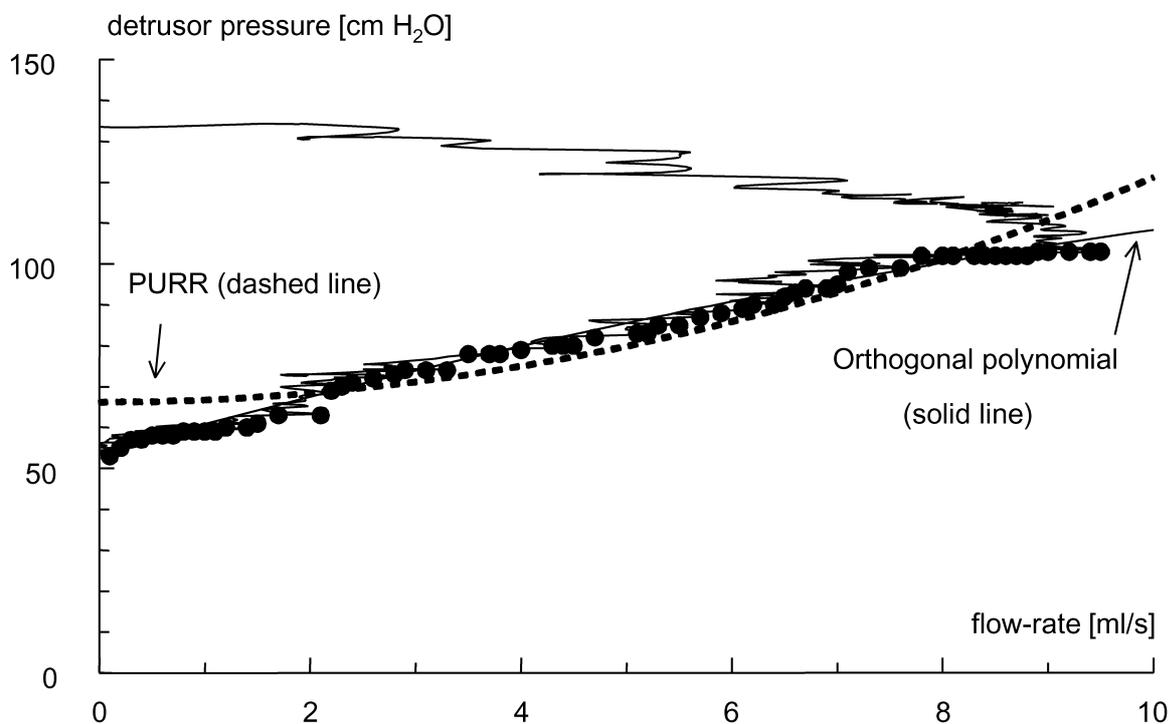


Figure 1. The thin line traces the detrusor pressure as a function of the flow-rate during voiding in a male patient. The filled circles represent the “bottom” of the pressure-flow plot as selected by the algorithm explained in the materials and methods section. To this lowest part a second degree orthogonal polynomial (of which only the last, slightly downward curving section is clearly visible in the plot) and the passive urethral resistance relation PURR (dashed) were fitted.

In the multivariate logistic regression analyses the w_{20} parameter had the strongest predictive value of all the contractility parameters tested in all models. This is in line with the results obtained in a previous study¹².

Table 1 lists the odds ratios (and the 2-sided p-values) of the predictors in the models studied and the percentages of cases in a two alternative forced choice experiment in which a relative residual was correctly predicted (i.e. the areas under the ROC curves).

The linear correlation coefficient between c_{PURR} and c_{ORT} equaled -0.20 ($p = 0.02$) implying that 4% of the variation in c_{PURR} is explained by variation of c_{ORT} . The linear correlation coefficient between c_{PURR} and b_{ORT} was 0.92, 85% of variation in c_{PURR} can therefore be explained by variation in b_{ORT} .

Discussion.

The parameters that quantify the properties of the bladder outlet are typically obtained by fitting some mathematical model^{7,14,3} to the lowest increasing part (or bottom) of a plot of the detrusor pressure as a function of the flow-rate. All models include a minimum opening pressure, but express the dependency of the detrusor pressure on the flow-rate differently. In real measurements a variety of curvatures of the bottom is observed.

We propose to use the presence of a significant residual urine controlled for bladder contractility as an objective and verifiable judge to compare the proposed models (and indices) for bladder outlet resistance by means of a multivariate logistic regression analysis. This statistical tool is applicable as its underlying assumptions are met by the data. Other methods (multinomial logistic regression with more than 2 categories of residual urine and possibly even linear regression) imply more assumptions about the data and are therefore less reliable/robust. The threshold used to define a significant relative residual (20% of the filled volume) does not seem critical, 5 and 10% have been tested as alternatives leading to comparable results (data not given). Theoretically, other criteria than the presence of residual urine. e.g. the maximum flow-rate (using some threshold flow-rate), could have been used in an identical way. It is however not certain that that approach would have been unbiased

Predicted	Model	Model parameter	Odds ratio (p-value ; * = < 0.01)	Area under the ROC curve
Relative residual exceeding 20 % of the filled volume.	W ₂₀ + BOOI	W ₂₀	0.52 *	0.89
		BOOI	1.07 *	
	W ₂₀ + URA	W ₂₀	0.60 *	0.88
		URA	1.11 *	
	W ₂₀ + 2 nd degree orthogonal polynomial	W ₂₀	0.39 *	0.91
		a _{ORT}	1.14 *	
		b _{ORT}	1.03 (0.67)	
		c _{ORT}	1.01 (0.97)	
	W ₂₀ + 1 st degree orthogonal polynomial	W ₂₀	0.39 *	0.91
		a _{ORT}	1.14 *	
		b _{ORT}	1.03 (0.66)	
	W ₂₀ + average pressure only (i.e. 0 th degree orthogonal polynomial)	W ₂₀	0.38 *	0.91
		a _{ORT}	1.14 *	
	W ₂₀ + PURR	W ₂₀	0.44 *	0.91
		P _{muoPURR}	1.13 *	
C _{PURR}		3.77 (0.10)		
W ₂₀ + simple linear model	W ₂₀	0.44 *	0.91	
	P _{muoLIN}	1.12 *		
	C _{LIN}	1.40 *		

Table 1. The odds ratios, p-values and the power of the different models to predict a residual exceeding 20% of the filled volume. Higher areas under the curve are associated with better models.

as the maximum flow-rate is used in some, but not all, of the models for bladder outlet resistance (BOOI, URA) and thus would favor these models.

All models studied for bladder outlet resistance in conjunction with the contractility parameter w_{20} apparently predict residual urine quite good as can be appreciated from the areas under the curve given in Table 1 (for comparison, the area under the curve of PSA and free PSA to predict prostate cancer in sextant biopsies equals 0.74^{15}).

It can be concluded from this study that the average curvature of the bottom of the pressure-flow plot does not have any predictive power with respect to the probability of a residual in the material studied (the areas under the curve for the 1st and 2nd degree orthogonal polynomials are equal). Therefore a 1st degree orthogonal polynomial (and thus a linear relationship) is a better choice than a 2nd degree one as the same predictive power is achieved with less parameters.

Both the opening pressure (p_{muoLIN}) and the slope (c_{LIN}) of the simple linear model are statistically significant predictors for the presence of a post void residual. Only the average pressure (a_{ORT}) of the orthogonal polynomial model has statistically significant predictive value for residual urine. However both models for the bladder outlet result in the same relation between the detrusor pressure and the flow-rate (as only one straight line can be fitted to the same set of data points using a least squares criterion) and are equally powerful in predicting a residual (see the area under the curve in Table 1). Therefore the average pressure may be considered a summary measure that adequately combines the information related to “voiding to completion” in the estimated opening pressure and the slope of a simple linear model.

As the average pressure is roughly halfway the urethral opening pressure and the detrusor pressure at Q_{max} , it may be considered a compromise between two proposed methods to quantify bladder outlet resistance, the minimum opening pressure as estimated from e.g. PURR or URA and the Q_{max} , $p_{\text{det.qmax}}$ pair used in the provisional ICS nomogram for bladder outlet resistance in males.

A comparison of the flow-rate dependency parameter of the PURR model with the average quadratic trend of the polynomial model shows a strong disagreement (despite the fact that the correlation is significant only 4% of the variation in C_{PURR} is explained by C_{ORT}). As a good agreement between the two parameters is expected if the bottom of the pressure-flow plot is truly a quadratic function of the flow-rate it must be concluded that the quadratic PURR model does not, on average, describe the bottom adequately. PURR in combination with w_{20} , however, is capable to predict a post void residual quite accurately. This paradoxical observation may be explained by the strong correlation of the PURR quadratic flow-rate dependency factor with the slope of the bottom of the pressure-flow plot ($R = 0.92$). The estimated opening pressures by both models are comparable (data not shown). So, roughly said, the curvature estimated by PURR and the average slope of the simple linear model differ only in scaling which makes it no surprise that despite the poor fit to the data the parameters of PURR (in combination with w_{20}) are quite capable to predict a post void residual.

The two other indices for bladder outlet resistance tested (URA and BOOI) perform equally well in predicting a residual (when controlled for bladder contractility).

Summary.

Quantitatively all tested models for bladder outlet resistance performed quite well. The parameters of the models (and the indices) for bladder outlet resistance were all capable to predict a post void residual to an acceptable degree when combined with bladder contractility. Conceptually however large differences surfaced, e.g. the parameters of a simple linear model fitted to the bottom of the pressure-flow plot adequately characterize the bladder outlet resistance. Adding higher order flow-rate terms to the model (such as the quadratic term) seems useless.

The minimum opening pressure and the slope of the simple linear model estimate the flow-rate independent and the flow-rate dependent aspect of bladder outlet resistance. Both aspects can be weighted into an index for bladder outlet resistance by either calculating the average pressure of the bottom of the pressure-flow plot, or, what roughly amounts to the same thing, adding the slope times half the maximum flow-rate to the minimum bladder outlet opening pressure. In this weighting process

the information with respect to the two different aspects of bladder outlet resistance is lost. We may therefore say that by doing so we lose information about the type of resistance but gain the possibility to rank and compare patients.

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The weak correlation between bladder outlet obstruction and the probability to void to completion.

Ries Kranse and Ron van Mastrigt.

submitted.

Objective. To investigate the weak correlation between bladder outlet obstruction (BOO) as diagnosed using the provisional ICS nomogram for the definition of bladder outlet obstruction in males and residual urine.

Materials and methods. The relationship between voiding to completion and several indices for bladder outlet resistance and bladder contractility was studied in 131 pressure-flow studies in male patients by means of a multivariate logistic regression analysis.

Results. The ICS nomogram and the related obstruction index BOOI predict residual urine weakly (areas under the ROC curve 0.63 and 0.64 respectively). BOOI measures primarily bladder outlet resistance. If the nomogram or BOOI is augmented with bladder contractility information residual urine can be predicted significantly better (e.g. area under the ROC curve 0.89 for the combination of BOOI and BCI).

Discussion. The weak correlation between bladder outlet obstruction and post void residual urine is related to the fact that emptying the bladder to completion depends on bladder contractility as well as on bladder outlet resistance. It is possible to estimate the probability to void to completion quite accurately on the basis of bladder outlet resistance and bladder contractility. We named this probability “relative bladder outlet resistance”. A high probability of a post void residual may be assumed to indicate “relative bladder outlet obstruction”. By its very nature the correlation between “relative bladder outlet obstruction” and a residual is good

Introduction.

Signs and symptoms of dysfunction of the lower urinary tract (Lower Urinary Tract Symptoms or LUTS) correlate weakly with urodynamically defined BOO (Bladder Outlet Obstruction)¹. We have studied this issue focusing on one sign, post void residual urine.

The lower urinary tract conceptually consists of two subsystems, the bladder and the bladder outlet ².

During voiding the bladder contracts. Bladder contractility can be quantified by means of the Watts factors^{3,4,5} which estimate the power generated by a unit surface area of the bladder wall. Recently it has been proposed to quantify bladder contractility by means of the bladder contractility index BCI⁶.

The flow-rate impeding properties of the bladder outlet are referred to by bladder outlet resistance⁷. Bladder outlet resistance can e.g. be quantified by means of the bladder outlet obstruction index (BOOI)⁶, the average pressure of the bottom of the pressure-flow plot (o_1)⁸ or the bladder outlet resistance factor URA⁹.

BOOI and BCI are derived from the maximum flow-rate and its associated detrusor pressure (Q_{max} and $p_{det.Qmax}$). $BOOI = p_{det.Qmax} - 2 Q_{max}$, $BCI = p_{det.Qmax} + 5 Q_{max}$.

The ICS has proposed a provisional nomogram for the definition of bladder outlet obstruction in males¹⁰. Based on Q_{max} , $p_{det.Qmax}$, this nomogram distinguishes three categories of patients, i.e. obstructed, equivocal and unobstructed. BOOI and the ICS nomogram are related. Obstructed patients have $BOOI > 40$ [cm H₂O], equivocals 20 [cm H₂O] $< BOOI \leq 40$ [cm H₂O] and unobstructed patients $BOOI \leq 20$ [cm [H₂O]].

Materials and methods.

We have studied 131 consecutive urodynamic measurements in males. The measurements were standard urodynamic filling and voiding studies, the details of the measurement procedure have been described elsewhere^{8,11,12}.

The detrusor pressure and flow-rate signals were filtered by means of a 1 Hz low pass filter to remove noise¹². Q_{max} and $p_{det.Qmax}$ were automatically selected from these low pass filtered signals. The Watts factors W_{max} , W_{Qmax} , W_{20} and W_{80} and BCI were calculated as parameters for bladder contractility. The bottom of the pressure-flow plots were estimated by means of a computer algorithm. This part of the pressure-flow plots contains information about the least flow-rate impeding state of the bladder outlet⁸. The bladder outlet resistance parameters BOOI, BCI and URA and the average pressure of the bottom of the pressure-flow plots o_1 were calculated⁸.

The voided volume was calculated by integrating the flow-rate. As before filling the bladder was emptied the residual was calculated as the difference of the filled volume and the voided volume. A significant relative residual was defined as: post void residual volume / filled volume ≥ 0.2 . Natural urine production during filling was not accounted for.

A series of logistic regression analyses with a significant relative post void residual as outcome (present or absent) and one contractility parameter (w_{20} , w_{80} , $w_{Q_{max}}$, w_{max} , BCI) and/or one bladder outlet resistance parameter (o_1 , BOOI, URA, ICS nomogram classifications), as predictors were carried out¹³. In addition logistic regression analyses that used the ratios of o_1 and w_{20} (denoted by o_1w_{20}), BOOI and w_{20} (denoted by $BOOIw_{20}$) and URA and w_{20} (denoted by $URAw_{20}$) and the Q_{max} , $p_{det.Q_{max}}$ datapair were carried out. The ICS nomogram classification was implemented by means of two binary indicator variables. One indicator for the obstructed category, and one for the equivocal category. An unobstructed measurement is coded with both indicators equal to zero.

The results of these analyses are given as odds ratios representing the relative increase in odds of the relative residual when one of the predictors changes 1 unit keeping the other unchanged. For each regression model the area under the ROC curve (AUC) was calculated as a measure of the quality of the model. The AUC corresponds to the percentage of correctly classified measurements in a two alternative forced choice experiment¹⁴

Credible intervals of the AUC's were calculated by means of the bootstrap procedure¹³. These AUC's and their credible intervals cannot be used for model comparison (since they are calculated from the same dataset, i.e. not independent). For this reason the model comparison was based on the AUC's and credible intervals of two roughly equally sized random subsets of the data (which are independent).

All p-values in this paper are two sided.

Results.

The outcomes of the univariate logistic regression analyses are given in Table 1 (i.e. just one of the predictors listed in the Materials and Methods section is used to

Model parameter	Odds ratio	Area under the Roc curve (95% credible interval)
ICS nomogram	2.35, 3.09*	0.63 (0.53-0.73)
URA	1.07*	0.69 (0.59-0.79)
BOOI	1.02*	0.64 (0.54 – 0.75)
O ₁	1.0	0.51 (0.40 – 0.62)
W ₂₀	0.65*	0.81 (0.73 – 0.89)
W ₈₀	0.85*	0.64 (0.53 – 0.74)
BCI	0.96*	0.77 (0.68 – 0.86)
URA/w20	2.41*	0.89 (0.83 – 0.95)
BOOI/w20	1.62*	0.83 (0.75 – 0.90)
O ₁ /w20	3.02*	0.88 (0.82 – 0.95)

Table 1. Outcome of the univariate logistic regression analyses that were used to study the relationship between incomplete voiding and a bladder contractility parameter, a bladder outlet resistance parameter, or a relative bladder outlet resistance index (defined as a ratio of a bladder outlet resistance parameter and a bladder contractility parameter). For the ICS nomogram two odds ratios are given, the first for the obstructed category indicator, the second for the equivocal category indicator. (* p < 0.05 2-sided).

predict residual urine). Table 2 lists the results for bi-variate models that typically contain both a bladder contractility and a bladder outlet resistance parameter.

Model		Odds ratios		Area under the ROC curve (95% credible interval)
1 st model parameter	2 nd model parameter	1 st model parameter	2 nd model parameter	
URA	W ₂₀	1.11*	0.60*	0.88 (0.82 – 0.94)
URA	W ₈₀	1.13*	0.66*	0.82 (0.74 – 0.89)
URA	BCI	1.08*	0.96*	0.83 (0.76 – 0.91)
BOOI	W ₂₀	1.07*	0.52*	0.89 (0.83 – 0.95)
BOOI	W ₈₀	1.07*	0.58*	0.81 (0.73 – 0.89)
BOOI	BCI	1.04*	0.95*	0.84 (0.77 – 0.91)
ICS nomogram	BCI	6.44, 2.82	0.95	0.82 (0.74 – 0.90)
O ₁	W ₂₀	1.14*	0.38*	0.91 (0.85 – 0.97)
O ₁	W ₈₀	1.06*	0.66*	0.73 (0.63 – 0.83)
O ₁	BCI	1.08*	0.93*	0.83 (0.76 – 0.90)
P _{det.Qmax}	Q _{max}	0.99	0.70*	0.84 (0.77 – 0.91)

Table 2. Outcome of the bi variate logistic regression analyses that were used to study the relationship between incomplete voiding and both a bladder contractility parameter and a bladder outlet resistance parameter. For the ICS nomogram two odds ratios are given, the first for the obstructed category indicator, the second for the equivocal category indicator. (* p < 0.05 2-sided).

The area under the ROC curve for the ICS nomogram equaled 0.66 with a standard error of 0.068 for the first subgroup of measurements (N = 59). The area under the ROC curve for the “best” model in Table 2 (the model that includes both o_1 and w_{20}) was 0.95 with a standard error of 0.03 for the second subgroup of measurements. As these estimates represent independent samples we can compare the difference by means of the t-test (2 sided p-value of the difference is <0.001). A similar comparison between the areas under the ROC curve (AUC) in the subgroups for the model that contained BOOI and BCI (or Q_{max} , $p_{det.Qmax}$) and the w_{20} , o_1 model yielded no significant difference (0.95 and 0.87, $p = 0.15$). The AUC’s for w_{Qmax} and w_{max} were lower (in the univariate and bi variate analyses), than the AUC’s for w_{20} (results not listed in the tables).

Discussion.

Univariately, bladder outlet resistance and bladder contractility parameters predict residual urine weakly (e.g. the area under the ROC curve (AUC) for BOOI is only 0.64, Table 1). Throwing a fair coin instead of using BOOI to predict a residual would have yielded an expected AUC of 0.5. Bladder outlet obstruction as defined by the ICS nomogram (row 3 Table 1) also correlates weakly with residual urine. Additionally the odds ratios for the ICS nomogram categories show an atypical pattern, the odds ratio for the equivocal category is higher than for the obstructed category. This suggests that the equivocal range of the ICS nomogram corresponds to a higher probability of incomplete voiding than the obstructed category.

Bladder outlet resistance parameters combined with bladder contractility parameters predict residual urine much better (Table 2, due to the rather time consuming bootstrap procedure formal statistical significance was only tested for o_1 - w_{20} model versus the ICS nomogram, see results section). In this Table the odds ratios for bladder outlet resistance parameters are ≥ 1 and the odds ratios for bladder contractility parameters are < 1 . Thus at the same level of bladder contractility increased levels of bladder outlet resistance go with an increased probability of a residual volume (odds ratio > 1). The probability of a residual decreases if at the same level of bladder outlet resistance the bladder contractility increases (odds ratio < 1). These properties may be expected for parameters aimed to measure bladder outlet resistance and bladder contractility. If the ICS nomogram is augmented with

contractility parameters the increase in the AUC is only slightly less than that of BOOI augmented with the same contractility parameter (Table 2 rows 6 and 7). The odds ratios for the equivocal and obstructed category are, contrary to the univariate analysis, in line with expectation.

Therefore it may be concluded that the weak correlation between obstruction (as defined by the ICS) and incomplete voiding is to a large extent explained by the fact that the nomogram measures bladder outlet resistance. Whether voiding is to completion depends on bladder contractility as well. The limited resolution of the nomogram in distinguishing levels of resistance when compared to BOOI apparently contributes only slightly to the weak correlation (since the AUC for the combination BCI, BOOI is only slightly higher than the AUC for the combination BCI, ICS nomogram, Table 2, rows 6 and 7).

Since other definitions used for bladder outlet obstruction than the ICS nomogram method are either based on the parameters studied in this work (e.g. $URA \geq 29$ [cm H₂O]¹⁵) or closely linked to the methods studied (the LPURR¹⁶ nomogram may be considered a refined ICS nomogram) it is unlikely that bladder outlet obstruction defined by these methods correlates much better with incomplete voiding.

On the other hand, a bladder outlet obstruction parameter and a bladder contractility parameter derived from a pressure-flow measurement suffice to quite accurately predict the probability to void to completion. This probability may either be labeled relative bladder outlet resistance or relative bladder power (we prefer the former). A special high probability of incomplete voiding e.g. $\geq 90\%$ may be coined relative bladder outlet obstruction. Alternatively the ratio of e.g. URA and w_{20} (and not the probability derived from it by means of a logistic regression analysis model) may be used directly for the same purpose as it also predicts residual urine quite well (see AUC of models given in last three rows of Table 1).

As an aside we note that BOOI and BCI are derived from the same information carriers, Q_{max} and $p_{det.Qmax}$ by simple linear transformations. One may therefore just as well use Q_{max} and $p_{det.Qmax}$ directly in the logistic regression analysis. The area

under the curve for the model that uses Q_{\max} and $p_{\det.Q_{\max}}$ equals that of the model that uses BOOI and BCI in Table 2 (both are 0.84).

The impression may rise that the use of Watts factors as an independent predictor for voiding to completion in the logistic regression analyses may be criticized because in the calculation of Watts factors the instantaneous bladder volume is used. We note that despite the fact that the residual urine is a part of this instantaneous bladder volume this does not imply that a built in correlation exists between the Watts factors and a residual volume. This can be appreciated by observing that the instantaneous bladder volume was calculated as the filled volume (assuming an empty bladder at the start of filling) minus the voided volume up to the moment of interest (i.e. the integrated flow-rate until that moment). The residual volume was not used in this calculation. w_{20} and w_{80} refer to percentages of the voided volume, not to percentages of the total bladder volume, so this too introduces no coupling. These logical arguments are corroborated by experimental findings. First, we note that almost identical results were obtained for BCI and Watts factors. In the calculation of BCI no use is made of the residual volume. Secondly we note that if the assumed built in correlation between Watts factors and residual volume were an issue the predictive value of bladder outlet resistance parameters for a residual volume would decrease if the relative contribution of a residual with respect to the instantaneous bladder volume would increase. The opposite is observed, the odds ratio for URA is higher for w_{20} than for w_{80} . In the calculation of w_{20} the residual volume, however, constitutes a larger percentage of the instantaneous bladder volume than in the calculation of w_{80} (please note that w_{20} is defined as the value of the Watts factor when 80% of the total voided volume is actually voided and w_{80} is defined as the value of the Watts factor when 20% of the voided volume is actually voided).

In the logistic regression analyses the outcome variable is a relative residual exceeding 20%. This “20% choice” is not critical. Reprocessing the data, using a 10% threshold, yielded only minimal changes of the values listed in Tables 1 and 2. The overall conclusions were not affected. Furthermore one may argue that in an invasive measurement, with catheters in place, the probability of incomplete voiding is probably higher than in a free flow measurement (so probability of incomplete voiding as calculated in this paper overestimates the true probability). On the other

hand one can argue that this effect is on average counteracted by the fact that urine production of the kidneys during the investigation was not accounted for. If it were possible to account accurately for both factors it is likely that the results of the regression analyses would improve. However the accurate estimation of both factors requires a considerable amount of extra work. The procedure described in this paper is based on standard invasive urodynamic measurements and can be verified easily at other institutions. It is unlikely that both factors affect the present outcomes qualitatively.

Conclusion.

The weak correlation between voiding to completion and bladder outlet obstruction (defined by means of the ICS nomogram) may be explained for a very large extent by the fact that the nomogram measures bladder outlet resistance. Voiding to completion depends on bladder contractility as well. The relation between bladder outlet resistance, bladder contractility and the probability to void to completion can be studied quantitatively by means of a statistical model (logistic model). The predicted probability is, if both bladder outlet resistance and bladder contractility are accounted for, in good agreement with the actually observed absence or presence of post void residual urine. We propose to name this probability “relative bladder outlet resistance”. Measurements in which the estimated probability of a residual is high (e.g. $\geq 90\%$) may be labelled “relatively obstructed”.

In this work the assumption was used that the best methods for the quantification of bladder outlet resistance and bladder contractility predict a post void residual best. This assumption may serve a broader purpose than the explanation of the weak correlation between incomplete voiding and bladder outlet obstruction. It leads to the concepts of relative bladder outlet resistance and relative bladder outlet obstruction and may provide a scientific (i.e. expert opinion independent) basis for the comparison of different methods for the quantification of bladder outlet resistance, bladder contractility and definitions for bladder outlet obstruction.

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Causes for variability in repeated pressure-flow measurements.

Ries Kranse and Ron van Mastrigt.

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Objectives. The maximum flow-rate Q_{max} and the associated detrusor pressure $p_{det.Qmax}$ vary considerably between measurements. Due to the central role of Q_{max} , $p_{det.Qmax}$ in the diagnosis of bladder outlet obstruction this is reason for concern. In this paper we study the causes for this variation.

Methods. Spectral analysis was carried out on two consecutive urodynamic measurements in 131 patients. Parameters for bladder outlet resistance and bladder contraction strength were determined and difference plots were made to study systematic variations. A logistic regression analysis was used to study if differences represent true changes of the function of the lower urinary tract.

Results. Signal components in the detrusor pressure and the flow-rate signal with frequencies ≥ 1 [Hz] may be considered noise. Filtering out these frequencies changes estimates of Q_{max} and $p_{det.Qmax}$, but not the between measurement difference in them. Bladder contractility and bladder outlet resistance were systematically lower in the second measurement. Both their systematic and non systematic between measurement variation were statistically significant predictors for a post void residual.

Conclusions. The non systematic between measurement variability in Q_{max} and $p_{det.Qmax}$ apparently reflects true variability in the physiological state of the bladder outlet. It therefore does not discredit the pressure-flow study as the preferred method in the diagnosis of bladder outlet obstruction. Rather, the pressure-flow study is the only currently available method to study and quantify the apparent within patient variability in bladder outlet resistance and bladder contractility.

Introduction.

The lower urinary tract consists of two subsystems, the bladder and the bladder outlet. Several methods have been proposed to objectively quantify bladder outlet resistance and bladder contractility from the flow-rate and the detrusor pressure measured during voiding. Some use the maximum flow-rate and its associated detrusor pressure, denoted by Q_{max} , $p_{det.Qmax}$. From this data pair it can be assessed if a patient is obstructed or not, e.g. by means of the provisional ICS nomogram¹ or the LPURR nomogram². Alternative procedures transform the data pair into one number (e.g. URA³ or BOOI⁴) and compare these indices with a more or less established threshold value for bladder outlet obstruction (30 [cm [H₂O] for URA and 40 [cm H₂O] for BOOI).

A large between measurement, within individual variation in the Q_{max} , $p_{det.Qmax}$ data pair

has been reported⁵. This variation has been ascribed to variations in bladder outlet resistance. However, at least two alternative explanations or causes for the variability are possible. Firstly the bladder contraction strength may vary between measurements and secondly an external factor, totally or partially unrelated to true variations in bladder outlet resistance or the bladder contraction strength (noise, artefacts), may cause it. Any combination of the three factors may be a valid explanation too.

We have studied the intermeasurement variations in pressure-flow studies from a broader perspective treating variations in the Q_{\max} , $p_{\det.Q_{\max}}$ as a special case.

Materials and methods.

131 consecutive pairs of urodynamic measurements (in a roughly 1 hour session) in 131 unselected male patients were evaluated. The patients voided in either sitting or standing position during standard urodynamics using water filled lines and a rotating disc flow-meter. The height of the flow-meter funnel was adjusted accordingly.

The measured signals were sampled at 10 [Hz] and stored on computer disk. A delay of 0.6 [s] was applied to the detrusor pressure signal to compensate for the average time it took urine to travel the distance separating the transducers⁶. The number of patients who were classified obstructed, equivocal and unobstructed according to the ICS nomogram¹ in the two measurements and the number of patients who changed categories between the measurements were counted.

Spectral analysis⁷ was carried out to determine the average power spectrum of the detrusor pressure and flow-rate signals. Additionally an average coherency spectrum was determined that estimates the average squared linear correlation between the power in identical frequency bands in both signals. These spectra represent the relative importance of fast and slow signal variations in a pressure-flow study. If e.g. fast transitions in the detrusor pressure and flow-rate spectra are relatively underrepresented and on average uncorrelated (revealed by the coherency spectrum) they may be considered noise, because the clinically relevant information in a pressure-flow study is in the joint variations.

Additionally the detrusor pressure and flow-rate signals were low pass filtered by means

of 2-nd order Butterworth filters with cut off frequencies of 2, 1 and 0.25 [Hz].

From each of these filtered signals the urodynamic parameters Q_{\max} , $p_{\det.Q_{\max}}$ were automatically calculated.

For all measurements the Watts factors w_{\max} , $w_{Q_{\max}}$, w_{20} , w_{80} ^{8,9} BOOI (i.e. the former Abrams-Griffiths number⁴), URA and the average pressure of the bottom of the pressure-flow plot (denoted by σ_1 ¹⁰, see Figure 1) were calculated from the 1 [Hz] low pass filtered signals. The Watts factors measure bladder contractility by estimating the power per unit bladder surface area at different moments during voiding. w_{\max} represents an estimate of the maximum contractility, $w_{Q_{\max}}$ an estimate at the maximum flow-rate, w_{20} and w_{80} denote estimates of the power at respectively 80 and 20% of the voided volume. URA and BOOI are indices for bladder outlet resistance. Summary statistics and difference plots were made for all parameters. In a difference plot, the change in a parameter between 2 measurements (between measurement difference) is plotted as a function of the average of the parameter. Such plots are used to study (amongst others) the between measurement variation of a parameter¹¹. We refer to such a difference (if present) by systematic difference in this paper.

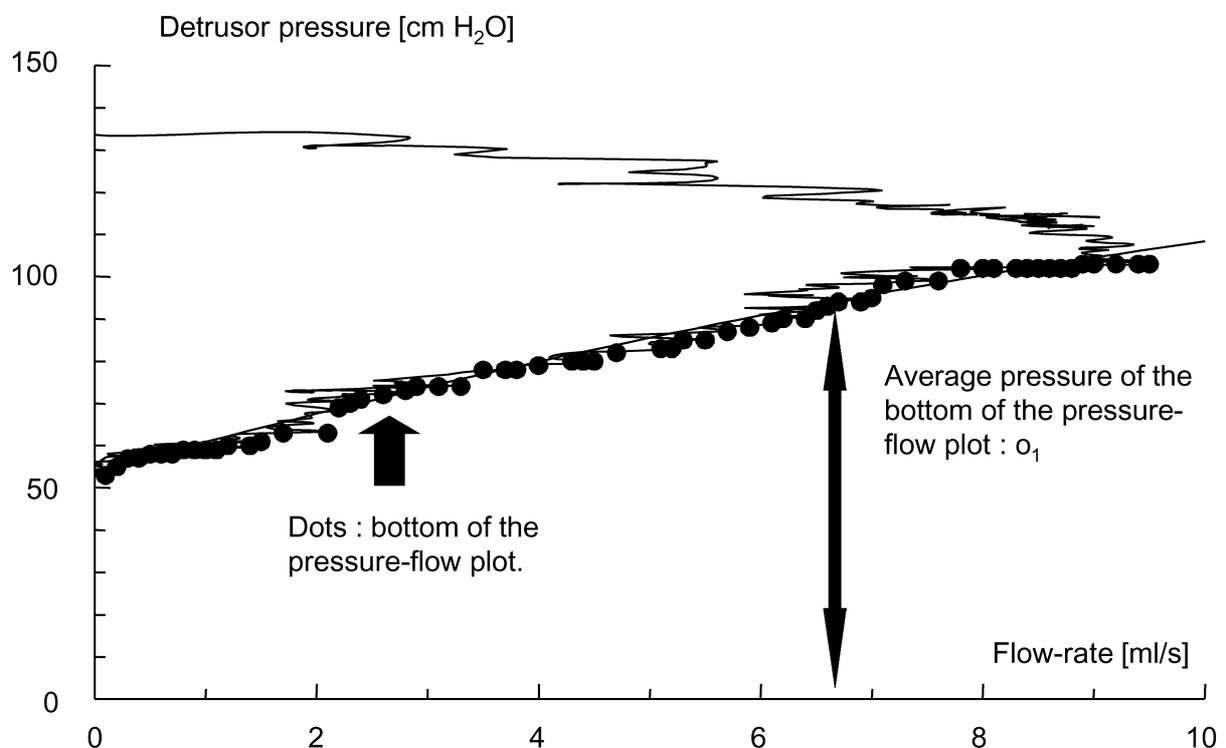


Figure 1. A pressure-flow plot in which the dots depict the automatically detected “bottom” of the data and the parameter σ_1 is the solid line (the average pressure of the bottom).

A repeated measures logistic regression analysis¹² (measurements in one patient were considered a cluster) with a significant relative residual (present / absent) as output parameter and w_{20} , and o_1 of the initial measurement, the differences in w_{20} and o_1 between the first and the second measurement and an indicator for measurement (0 for the first measurement and 1 for the second) as predictors was carried out. The analysis was restricted to measurements in which the bladder capacity exceeded 200 [ml]. For bladder capacities < 200 [ml] the influence of the bladder volume becomes disproportionately greater as smaller bladders are emptied more easily¹³. A significant post void residual was defined as (residual volume) / (filled volume + residual previous voiding) ≥ 0.2 . O_1 and w_{20} were chosen as predictors because this combination of bladder outlet resistance and bladder contractility parameters predicted a residual best¹⁰. The outcome of the regression analysis is given in terms of odds ratios which estimate the relative change in odds of a post void residual if a predictor changes 1 unit.

In this paper 2-sided p-values are given.

Results.

According to the first measurement 49 of the 131 patients (37%) were unobstructed, 39 (30%) equivocal and 43 (33%) obstructed. In the second measurement these figures were 52 (40%), 47 (36%) and 32 (24%) respectively. Five patients changed from equivocal in the 1st measurement to obstructed in the 2nd, one from unobstructed to obstructed. Seventeen patients changed from obstructed in the 1st measurement to equivocal in the 2nd, none changed from obstructed in the 1st to unobstructed in the 2nd.

Table 1 lists the summary statistics of a selection of the parameters studied. The last column of this table gives the outcomes of a difference plot analysis for these parameters. In 104 measurements (79%) the difference in Q_{max} was < 2 [ml/s] between the 2 measurements, in 117 (89 %) $p_{det.Q_{max}}$ differed < 15 [cm H₂O].

Table 2 lists the effects of low pass filtering on the difference between Q_{max} and $p_{det.Q_{max}}$ values in consecutive measurements..

Parameter	1 st measurement median (25% - 75%)	2 nd measurement median (25% - 75%)	1 st measurement > 2 nd measurement (N)	Difference plot analysis	
				Mean	Se of difference between 1 st and 2 nd measurement p-value
Q _{max} [ml/s]	9.0 (5.9 – 12.1)	8.9 (6.7 – 12.4)	59	-0.25	0.25 0.31 ns
p _{det,Qmax} [cm H ₂ O]	45.7 (35.7 – 63.6)	45.0 (31.7 – 55.3)	98	4.4	1.1 < 0.01
BOOI [cm H ₂ O]	27.0 (14.7 – 48.0)	25.6 (10.7 – 39.4)	93	4.9	1.2 < 0.01
o ₁ [cm H ₂ O]	34.6 (24.4 – 47.2)	31.4 (21.2 – 40.5)	98	4.5	0.7 < 0.01
w ₂₀ [W/m ²]	6.9 (5.1 – 9.9)	5.9 (4.6 – 8.0)	91	1.3	0.23 < 0.01
postvoid residual [ml]	65 (13 – 202)	139 (66 – 266)	22	-58	8 < 0.01

Table 1. Summary statistics of a selection of the parameters studied. The last column gives the outcomes of the difference plot analysis (N = 131).

filter applied	Difference	Mean	Standard error (2 sided p-value)	25 % centile	75% centile
0.25 [Hz]	$Q_{\max 1} - Q_{\max 2}$	-0.27	0.24 (0.27)	-1.5	1.4
1 [Hz]	$Q_{\max 1} - Q_{\max 2}$	-0.23	0.25 (0.36)	-1.6	1.5
2 [Hz]	$Q_{\max 1} - Q_{\max 2}$	-0.23	0.27 (0.39)	-1.6	1.8
0.25 [Hz]	$P_{\det.Q_{\max 1}} - P_{\det.Q_{\max 2}}$	4.65	1.0 (<0.001)	-1.3	10.9
1 [Hz]	$P_{\det.Q_{\max 1}} - P_{\det.Q_{\max 2}}$	4.38	2.2 (<0.001)	0.1	11.5
2 [Hz]	$P_{\det.Q_{\max 1}} - P_{\det.Q_{\max 2}}$	4.57	1.1 (<0.001)	-0.7	10.8

Table 2. The effect of applying 3 different low pass filters on the intermeasurement differences in Q_{\max} (listed in [ml/s]) and $p_{\det.Q_{\max}}$ (listed in [cm H₂O]).

parameter	Odds ratio	95 % confidence interval
w [W/m ²]	0.32	0.22 – 0.48
w _{20dif} [W/m ²]	0.42	0.29 - 0.58
$o_{1\text{meas}1}$ [cm H ₂ O]	1.18	1.11 – 1.27
$o_{1\text{dif}}$ [cm H ₂ O]	1.16	1.07 – 1.25
measurement indicator (i.e. 1 st or 2 nd measurement in each patient).	2.73	1.31 – 5.69

Table 3. The outcomes of the repeated measures logistic regression analysis. All odds ratios have a p-value < 0.001 except for the measurement indicator (p = 0.007).

The signal power of the measurements showed that the bulk of the signal power was found in frequencies < 1 [Hz]. The average coherency spectrum decreased with increasing frequency, it equalled 1% for 0.3 [Hz] and < 0.6% for 1 [Hz].

Table 3 gives the results of the repeated measures logistic regression analysis for the 226 measurements with a bladder capacity exceeding 200 [ml]. All odds ratios are statistically significantly different from 1 at the 2 sided 5 % level.

Discussion.

In several publications a considerable within patient-, between measurement-variation has been reported in an important urodynamic summary measure, the Q_{\max} , $p_{\det.Q_{\max}}$ pair. In the material at hand 11% of the $p_{\det.Q_{\max}}$ values and 21% of the Q_{\max} values measured

differed more than 15 [cm H₂O] and 2 [ml/s] respectively. Like Sonke et al.⁵ we found that in 35% of patients the ICS obstruction category changed between measurements. In line with the authors of previous papers^{5,14} we agree that this variation is of importance in view of the prominent role of this summary measure in urodynamic clinical decision making (amongst others in the provisional ICS nomogram¹ for the quantification of bladder outlet obstruction and in the LPURR nomogram²).

A simple explanation for the observed intermeasurement variation in the Q_{\max} , $p_{\det.Q_{\max}}$ pair (and therefore in BOOI, that is derived from it⁴) may be that urodynamic measurements are affected by noise. Visual application of the power spectra and coherency spectrum criteria outlined in the materials and methods section shows that signal components with a frequency ≥ 1 [Hz] may be considered (“high” frequency) noise¹⁵. If a low pass filter is applied to the signals the estimates of Q_{\max} and $p_{\det.Q_{\max}}$ change systematically (results not shown). As a part of the frequency contents of the original signal is removed by low pass filtering this finding is not too surprising. This means that the parameter estimates Q_{\max} and $p_{\det.Q_{\max}}$ derived from one measurement are indeed affected by noise. The effects of applying identical low pass filters with different cut off frequencies to repeated measurements of the flow-rate and detrusor pressure are shown in Table 2. The differences in the Q_{\max} , $p_{\det.Q_{\max}}$ values were not significantly affected by the cut off frequency of the applied filter.

We therefore conclude that the between measurement variation in urodynamic parameters is not grossly related to the presence of high frequency noise in the signals.

Three other possible explanations for the observed between measurement variation in Q_{\max} , $p_{\det.Q_{\max}}$ remain :

- 1) the bladder contractility and bladder outlet resistance vary systematically between two consecutive measurements in the same patient (i.e. the average between measurement difference in bladder contractility and/or bladder outlet resistance is different from 0).
- 2) the bladder contractility and bladder outlet resistance vary non systematically. (average between measurement difference is 0).
- 3) artefacts (variations in the measured signals unrelated to bladder contractility and bladder outlet resistance) other than noise in the measured flow-rate and detrusor

pressure signals account for the observed between measurement variations in Q_{\max} , $p_{\det.Q_{\max}}$.

The difference plot analyses of w_{20} , BOOI and o_1 (the average pressure of the bottom of the pressure-flow plot) indicate that all three values were systematically higher in the first measurement than in the second (Table 1). Bladders were on average more contractile and bladder outlets were on average less relaxed in the first measurement, a fact that has been observed before. The between measurement spread in the parameters was considerable, even after 1 [Hz] low pass filtering (see standard deviations).

The difference plots reveal changes in bladder contractility and bladder outlet resistance. However, they do not reveal the effects of these changes. The multivariate logistic regression analysis overcomes this shortcoming.

In order to find out if the systematic variations in bladder contractility and bladder outlet resistance affected the symptoms we used a measurement indicator variable in the logistic regression analysis. Its odds ratio equalled 2.7 ($p = 0.007$, 95 % confidence interval 1.3-5.7, see Table 3) indicating that the joint systematic decrease in bladder contractility and bladder outlet resistance led to an average 2.7 times higher odds of a post void residual in the second measurement. Apparently the systematic decrease in bladder contractility did not compensate the decrease in bladder outlet resistance.

The remaining non systematic variations in both bladder contractility ($w_{20\text{dif}}$) and bladder outlet resistance ($o_{1\text{dif}}$) were strong predictors for the presence of a post void residual as well (see Table 3, 2nd and 4th row). This observation is incompatible with the assumption that artefacts in the measured signals are the primary cause for the observed variation as in that case a relation with a post void residual is highly unlikely.

Conclusion.

In pressure-flow studies, Q_{\max} and $p_{\det.Q_{\max}}$ vary considerably between measurements. However, instead of dismissing the pressure-flow study as the gold standard in urodynamics because of this observation, we think that our data (as well as the data presented by Sonke et al⁵) suggest exactly the opposite.

As the variations in Q_{\max} and $p_{\det.Q_{\max}}$ partly explain variations in residual urine they represent true variations in bladder contractility and bladder outlet resistance. In order to

derive a reliable diagnosis from a pressure-flow study, therefore, at least 2 measurements should be done, so that an estimate of the stability of the diagnosis in that patient may be gained.

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Summary of the papers.

9.1 Linearization of the Dantec Urodyn 1000 urinary flow-transducer.

In our measurement setup we used a specific type of flow-transducer (a rotating disk type¹). It has a non linear transfer function. This means that changes in the flow-rate are not proportionally related to changes in the output of the transducer (a voltage). Relatively expensive calibrated flow-sources are in use for the calibration of these devices. In this paper we describe an alternative procedure that does not use these flow-sources but requires only that known volumes are poured into the flow-meter at varying flow-rates.

9.2 Estimation of the lag time between detrusor pressure- and flow-rate- signals.

A method is described to assess the lag time from the measurements of the flow-rate and the detrusor pressure in a pressure-flow study. The average time shift needed to properly “align” the flow-rate and the detrusor pressure signals was estimated for measurements in males (0.6 [s]), measurements in females voiding in a sitting position (0.4 [s]) and females voiding in a standing position using a hand held receptacle in video urodynamics (1.1 [s]). Evidence is presented that a precise lag time correction is very likely not important in urodynamic data processing (a heuristic value of 0.8 [s] is quite appropriate).

9.3 Computer assisted pressure-flow analysis .

This paper is included as it discusses extensively the idea of the quantification of bladder outlet resistance on the basis of the bottom of the pressure-flow plot. The rationale for this idea is outlined in the introduction of this thesis. The paper describes a statistical method that may be used to reduce a multiparameter representation of the bottom of a pressure-flow plot to an index for bladder outlet resistance. Such a multiparameter representation is obtained if e.g. the physical model for a collapsible distensible tube is fitted to the bottom of the pressure-flow plot (in that case a 3 parameter representation is obtained). The draw back of this method (Fisher’s linear discriminant method²) is that it requires two groups of measurements that are labeled obstructed and non obstructed by an expert. This “labeling” was done years before the use of this particular application of Fishers linear discriminant methode was even

considered, thus a direct influence of the expert can be ruled out. However, the mere fact that an expert is needed in the data reduction process is sufficient to consider the method as being scientifically suboptimal. Applications of the quantification of bladder outlet resistance (e.g. in intervention studies) are given. The impression may be gained from this paper that the choice for a particular method for the quantification is a very critical one. In the light of our more recent research I, presently, do not support this view.

9.4 Pre selection of patients for pressure-flow analysis based on the maximum flow-rate.

At present bladder outlet obstruction in males can only be diagnosed on the basis of an invasive pressure-flow measurement (e.g. by means of the provisional ICS nomogram). In this paper we show that roughly 20-25% of these diagnoses can be made on the basis of a non invasive free flow-rate measurement only, with an acceptable risk of making the wrong diagnosis (less than 5%). Given the associated risks and bother to the patient of an invasive pressure-flow measurement and the relatively simple and cheap measurement of the maximum flow-rate this is a very attractive possibility to achieve a considerable reduction in cost together with an improved patient friendliness.

9.5 Relative bladder outlet obstruction.

In this paper we introduce the concept of relative bladder outlet obstruction. We found that the probability of more than 20% residual urine after voiding can be modeled as a function of the bladder outlet resistance and the bladder contractility. The statistical procedure used is called logistic regression analysis³, the output of which is typically presented in terms of odds ratios. In the context of our research the odds ratio of e.g. a parameter for bladder contractility may be interpreted as the relative increase in odds of a relative residual exceeding 20% with respect to a reference odds as a consequence of a 1 unit increase in the parameter for bladder contractility. The reference odds equals the odds of a post void residual for an average bladder contractility and an average bladder outlet resistance. The odds ratio of a post void residual was <1 for bladder contractility parameters and >1 for bladder outlet resistance parameters. This is a reassuring observation, the parameters perform in line with the intended purpose. A higher estimated bladder

contractility corresponds with a lower probability of a post void residual and a higher estimated bladder outlet resistance with a higher probability. Based on the logistic regression model we have proposed to define a measurement as being relatively obstructed if the probability of a relative post void residual exceeding 20% on the basis of the model exceeds a certain threshold (e.g. 90%). Please note that under these conditions relative bladder outlet obstruction may be diagnosed even if a relative post void residual exceeding 20% does not actually occur in that measurement.

A similar relationship between a relative post void residual and Q_{\max} , $p_{\det.Q_{\max}}$ could be derived. This model fitted the observations (i.e. the presence or absence of a 20% relative residual in a measurement) less well than the model that uses measures for bladder contractility and bladder outlet resistance as determinants for a residual. Despite this slightly lesser fit the model enabled a transformation of the ICS nomogram for the definition for bladder outlet obstruction in males into a nomogram for the definition of bladder outlet obstruction in females. This derived nomogram showed a remarkable correspondence with a nomogram proposed independently for the same purpose by an expert urodynamicist⁴ (apparently without a scientific basis).

9.6 Bladder outlet resistance.

Quantification of bladder outlet resistance may be done in many ways. Besides using expert opinion as a judge no method existed to compare these different methods. Even if an impartial expert judge could be found comparison of the methods is complicated as the methods sometimes quantify bladder outlet resistance by different numbers of parameters (e.g. 3 in the case of the collapsible tube model and two for PURR). These multiparameter characterizations of bladder outlet resistance can be reduced to one number by means of Fishers linear discriminant method, but this, again, requires expert opinion.

We propose to solve this problem by means of the logistic regression analysis outlined in section 9.5 and the assumption that the best model for the quantification of bladder outlet resistance predicts a post void residual best. Of course the same method for the quantification of bladder contractility should be used for all methods for bladder outlet resistance quantification that are being compared. We have used the area under the receiver operating characteristic (ROC) curve to compare the different logistic regression models⁵. This area under the ROC curve is a concept that

originates from an application in radar technology where the performance of radar operators may be compared in a two alternative forced choice experiment. In such an experiment (for radar operators) series of pairs of bleeps on a radar screen, one being the reflection of a flock of birds, the other being the reflection of an incoming hostile plane have to be identified. Bleeps associated with flocks of birds have a different appearance on the radar screen than bleeps associated with reflections of a plane but there is a considerable overlap. An operator can apply different thresholds to allocate a bleep to birds or to a plane. With each threshold applied a different sensitivity and specificity results. A plot can be made in which the sensitivity is plotted as a function of the complement of the specificity (i.e. $1 - \text{specificity}$) using the applied threshold as a parameter. Such a plot is called a receiver operating characteristic curve. It can be shown that the area under this curve estimates the percentage of correctly classified bleeps. This method can be mapped one to one to the comparison of different models for the quantification of bladder outlet resistance. In this mapping the outcome of the logistic regression model (a probability of a relative residual exceeding 20%) corresponds to the bleep on the radar screen. A plane and a flock of birds correspond to the presence or absence of a relative residual exceeding 20% respectively and the model represents a radar operator. The area under the ROC curve in this case estimates the percentage of correctly classified measurements that have a relative residual exceeding 20% or not. It is reasonable to assume that the best model for the quantification of bladder outlet resistance best predicts which of the two members of such a pair is the one with a relative residual exceeding 20%.

The method outlined above for the comparison of methods for the quantification of bladder outlet resistance can also be used to reduce multi parameter models for bladder outlet resistance to one index. The extension of the idea to this particular problem is straight forward if we make one further assumption. I.e. we restrict ourselves to procedures in which such a multi parameter representation is reduced to an index by summing the individual parameters multiplied by some weighting factors. If a multiparameter representation is entered into the logistic regression method outlined above the percentage of correctly classified residuals is a function of the weighting factors of its elements. For some set of weighting factors the percentage of correctly predicted residuals reaches a maximum. The thus obtained weighted sum of the elements of the multiparameter representation for bladder outlet resistance

may be used as an index for bladder outlet resistance. Using this method we showed that the average pressure of the bottom of the pressure-flow plot is an adequate predictor for a post void residual, additional parameters that specify e.g. the average dependence of the detrusor pressure of the bottom of the pressure-flow plot on the flow-rate (or its quadratic dependency) do not provide extra information in this respect.

9.7 The weak correlation between bladder outlet obstruction and the probability to void to completion.

By, again, using bladder outlet contractility and bladder outlet resistance as predictors for a relative post void residual exceeding 20% we showed that the categories used in the ICS nomogram for the diagnosis of bladder outlet obstruction in males measure categorical degrees of absolute bladder outlet resistance. These categories are, without a correction for bladder contractility, very poor predictors for a residual. We thus observe a very strong discrepancy between a classic symptom of bladder outlet obstruction (a residual)⁶ and its urodynamic definition. Maybe this observation explains why according to the literature⁶, 20% of the men who are diagnosed with urodynamic bladder outlet obstruction (on the basis of the ICS nomogram) do not benefit from surgical intervention. In the urodynamic definition of bladder outlet obstruction bladder outlet resistance is predominantly driving the diagnosis (and thus indirectly a possible intervention), so that bladder contractility is insufficiently incorporated in the diagnostic and therapeutic decision making process. Based on these considerations we propose to redefine bladder outlet obstruction, which is presently defined absolute as relative. In this way urodynamically defined bladder outlet obstruction will better correlate with a classic symptom of the disease. We can simply illustrate that, from a logical point of view, obstruction is a relative concept. A certain bladder outlet that is obstructed for some bladder may be unobstructed for a stronger one and on the other hand an unobstructed bladder outlet for some bladder may be obstructed for a less contractile one.

For planning a therapeutic intervention we propose to use the pre intervention assessed bladder contractility and a reasonable estimate of the post operative bladder outlet resistance (such estimates for post intervention bladder outlet resistance are available in the literature) to assess the probability of a post void residual (by means of the logistic regression model). If this probability is high the

success rate of the intervention is expected to be low as the classic sign of the disease is not effectively treated.

A careful interpretation of the Table given at the end of this paper shows that the different methods for the quantification of bladder outlet resistance proposed by experts perform comparably as measured by our “objective criterion” (i.e. the area under the receiver operating characteristic curves do not differ too much between the logistic regression models). In predicting a post void residual it is apparently not that important which method for the quantification of bladder outlet resistance is chosen as long as bladder contractility is controlled for.

9.8 Causes for variability in repeated pressure-flow measurements.

This paper studies 131 pairs of two successive pressure-flow measurements in 131 consecutive patients. It has been reported that pressure-flow measurements vary within patients⁷. As a consequence parameters derived from pressure-flow measurements such as Q_{max} , $p_{det.Qmax}$ vary between measurements and of course the diagnosis of bladder outlet obstruction may vary accordingly (e.g. if the zone demarcating lines in the ICS nomogram are crossed). In this paper we show that the variation between measurements is related to true variations in bladder contractility and bladder outlet resistance. It is shown that this variation is partly caused by the fact that the two measurements per patient were done consecutively. Apparently patients get used to the measurement procedure and typically the bladder outlet resistance is lower in the second measurement than in the first one. The bladder contractility is lower in the second measurement too. This may be caused by the fact that the bladder gets exhausted if it has to contract two times within a short period of time. Another explanation is that the bladder contraction simply adjusts to the lower bladder outlet resistance. After correction for this systematic between measurement variation, the remaining non systematic variation proved to be a statistically significant predictor for the observed variation in the occurrence of a relative post void residual exceeding 20%. Thus the remaining variations observed in bladder contractility and bladder outlet resistance correspond to true variations in the functioning of the bladder-bladder outlet system.

It was furthermore found that the between measurement variation in Q_{max} and $p_{det.Qmax}$ was not related to high frequency components (frequencies ≥ 1 [Hz]) since

filtering out these signals did not decrease the average between measurement difference. Such a decrease would be expected if high frequency noise would be a major factor explaining the observed between measurement variation. In summary, not noise but actual systematic and non systematic changes in bladder contractility and bladder outlet resistance are the dominant explanations for the observed between measurement variation in e.g. Q_{\max} and $p_{\det.Q_{\max}}$ in the same individual. The variation in functioning in itself may be of clinical relevance as it may explain variability in symptoms. The only way to estimate the variability is to carry out at least two pressure-flow measurements in an individual.

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General Summary and Conclusion.

At present the function of the bladder-bladder outlet system during voiding can only be studied on the basis of a joint measurement of the detrusor pressure and the flow-rate. This is widely agreed upon as is illustrated by the use of both signals in most of the methods proposed in the literature for the quantification of bladder outlet resistance, bladder contractility and in all methods for the diagnosis of bladder outlet obstruction. The multitude of different models that co-exist (in a highly competitive scientific environment) illustrates that this consensus does not exist with respect to the question which of the methods is best for its intended purpose. This lack of standardization does not facilitate the communication between researchers nor does it facilitate the uniform and clear presentation of the outcomes of e.g. clinical trials. Thus far, despite its apparent importance standardization could not be carried out as no scientific method existed to this end.

It is our belief that the study of the relationship between bladder contractility, bladder outlet resistance and the probability of a relative post void residual, as presented in this thesis, may serve this purpose. The central idea is that the best method for the quantification of bladder outlet resistance and the best method for the quantification of bladder contractility predict a residual best. Using this idea we showed that no major differences in performance exist between many of the proposed methods for the quantification of bladder outlet resistance and bladder contractility. This, however, is not true for the diagnosis of bladder outlet obstruction. We presented a simple logical argument together with supportive experimental evidence that bladder outlet obstruction is a relative concept and not, as it is according to its present definition, a special high degree of absolute bladder outlet resistance. This erroneous definition explains the poor correlation of bladder outlet obstruction with symptoms, as symptoms do not depend on bladder outlet resistance only, they depend on bladder contractility as well.

Two related applications of the same idea are :

- the derivation of indices for bladder outlet resistance from multiparameter models
- the study of the cause of between measurement within patient variation in pressure-flow studies.

The material presented in this thesis provides new insights into urodynamic data processing. These ideas are not only of theoretical interest. As outlined above a coherent view of the relationship between bladder outlet resistance, bladder contractility and bladder outlet obstruction may be the basis for a standardization of procedures in urodynamic dataprocessing. Such a standardization facilitates communication, and may thus improve therapeutic and diagnostic decision making. This serves the interest of the patient and that is what it is all about.

A final personal note.

It took me 12 years to complete this PhD research. The fact that bladder outlet resistance was defined nearly proved to be a final insurmountable stumbling block. You cannot argue about a definition (which is correct per definition).

But in hindsight my doubts appear to have been unjustified and the presence of the “defined” ICS nomogram for bladder outlet obstruction in males proved to be fertile ground. This is not surprising since it is only when our best predictions fail (the use of the ICS nomogram to define bladder outlet obstruction) that we acquire new fundamental knowledge.

Statistische urodynamica.

In de wetenschap zijn we in het algemeen blij als voorspellingen gebaseerd op onze huidige kennis van de stand van zaken ook daadwerkelijk uitkomen. We hebben dan echter niet veel geleerd. We leren pas wat nieuws als onze beste voorspellingen niet uitkomen. Maar dit is allemaal niet besteed aan hen die het verschil niet begrijpen tussen deductie en inductie (plausibel redeneren), en proberen elke verwijzing naar menselijke inbreng te onderdrukken omdat dit subjectiviteit zou impliceren. Welnu, als er gewerkt moet worden met onvolledige informatie is menselijke inbreng onvermijdelijk en daar kunnen we maar beter aan wennen.

Vrij naar : E.T. Jaynes.

(10th Workshop on Maximum Entropy and Applied Bayesian Statistics, University of Wyoming, Laramie, July 30-Aug 3, 1990)

Samenvatting.

Dit proefschrift gaat over plassen.

Bij het plassen spelen veel verschillende anatomische structuren een rol. Om de discussie te versimpelen reduceren we al die structuren in de hierna volgende bespreking tot een dichotomie, het "blaas-blaasuitgangs-systeem". Beide deelsystemen hebben tijdens het plassen een duidelijk verschillende functie. De blaas moet samentrekken om de erin opgeslagen urine naar buiten te persen en de blaasuitgang moet gedurende dat samentrekken de urine zo gemakkelijk mogelijk naar buiten geleiden. De eigenschappen van de blaas, voor zover ze betrekking hebben op het samentrekken, worden in het vervolg aangeduid met blaascontractiliteit. De eigenschappen van de blaasuitgang, voor zover ze betrekking hebben op de urine geleidende eigenschappen daarvan, met blaasuitgangsweerstand. Men kan door middel van een gelijktijdige meting van de urinestroom en de druk in de blaas het functioneren

van het “blaas-blaasuitgangs-systeem” bestuderen. De druk in de blaas wordt door middel van een door de plasbuis ingebrachte katheter gemeten. Het inbrengen van deze katheter kan leiden tot infecties. Zo’n gelijktijdige meting van de druk en urinestroom zullen we hierna aanduiden met “druk-flow meting”. De meting gebeurt gewoonlijk op de afdeling urologie (of gynaecologie) van een ziekenhuis. Het deelgebied van de urologie dat, onder andere, het functioneren van het “blaas-blaasuitgangs-systeem” bestudeert wordt urodynamica genoemd.

Het is belangrijk om te beseffen dat zowel de druk als de flow die tijdens een “druk-flow meting” worden geregistreerd bepaald worden door zowel de blaascontractiliteit als de blaasuitgangsweerstand. In deze tijd van geautomatiseerde gegevensverwerking spreekt het voor zich dat zowel de druk als de flow beschikbaar zijn in digitale vorm. Er kunnen dus door middel van computerprogramma’s eenvoudig ingewikkelde berekeningen op beide signalen worden uitgevoerd.

Samenvatting van de in dit artikel opgenomen artikelen.

Twee van de in dit proefschrift opgenomen artikelen gaan over de technische aspecten van een “druk-flow meting”. Het eerste artikel beschrijft een nieuwe methode voor het ijken van een speciaal type flow-meter, het tweede behandelt een technische complicatie van een “druk-flow meting” die wordt veroorzaakt door het feit dat de druk en de flow niet op dezelfde plaats worden geregistreerd. De druk wordt via katheters in het lichaam gemeten. De flowmeter staat buiten het lichaam. Dit betekent dat op hetzelfde moment in de computer opgeslagen waarden van beide signalen niet bij elkaar horen. Immers de op een bepaald moment geregistreerde flow is gerelateerd aan een eerder in het lichaam gemeten druk omdat de urinestroom een eindige snelheid heeft. De gemiddelde tijd die een denkbeeldige druppel urine in de urinestroom nodig heeft om de afstand van de blaas tot de flow meter af te leggen kan worden geschat. Deze geschatte gemiddelde tijdsduur kan bij computer berekeningen die gebruik maken van zowel de druk als de flow als eerste orde benadering voor de werkelijk optredende verplaatsingstijd van de urinestroom worden gebruikt. Uit de studie blijkt overigens dat deze correctie geen grote invloed heeft op de uitkomsten van een aantal in de

urodynamische dataverwerking gebruikte analysemethoden die uitgaan van de druk en de flow.

Doordat de druk en de urinestroom bepaald worden door zowel de blaascontractiliteit als de blaasuitgangsweerstand, is het onmogelijk om de blaascontractiliteit of de blaasuitgangsweerstand éénduidig terug te rekenen uit de druk en de flow. Het is echter wel mogelijk om op basis van druk en flow klinisch relevante schattingen van beide grootheden te maken. Het derde in dit proefschrift opgenomen artikel beschrijft een aantal van die methoden en een aantal klinische toepassingen ervan. Sommige van die methoden maken gebruik van de kennis van een expert op het gebied van de urodynamica. Dit is in de wetenschap, die streeft naar objectiviteit, natuurlijk een heikel punt.

In het vierde artikel wordt ingegaan op “blaasuitgangsobstructie” (de “oude mannen kwaal”). Deze ziekte kan urodynamisch worden gediagnosticeerd op grond van de maximale flow en de erbij optredende druk in de blaas. De diagnose wordt gesteld door deze gegevens in een zogenaamd nomogram op te tekenen. In zo’n nomogram zijn 2 (of meerdere) zones te onderscheiden. In het veel gebruikte nomogram voor het diagnosticeren van blaasuitgangsobstructie in mannen van het ICS zijn drie zones onderscheiden, “geobstrueerd”, “onduidelijk” en “niet geobstrueerd”. Uit het feit dat obstructie op deze manier gedefinieerd is volgt dat een invasieve “druk-flow meting” nodig is voor het stellen van de diagnose. Een invasieve meting is immers vooralsnog de enige manier om de voor de diagnose benodigde informatie te verkrijgen. Zo’n meting is duur, vervelend voor de patiënt en niet zonder risico (infecties). In het vierde artikel wordt aannemelijk gemaakt dat op grond van een niet-invasieve meting van de urinestroom ongeveer 20 tot 25% van de patiënten met redelijke betrouwbaarheid als “niet geobstrueerd” gediagnosticeerd kan worden. De toepassing van zo’n niet-invasieve preselectie methode zou een aardige kostenbesparing kunnen opleveren. Een aan een eventuele invasieve meting voorafgaande niet-invasieve preselectie methode verhoogt bovendien de patiëntvriendelijkheid van de procedure als geheel, de patiënt wordt immers niet onnodig belast.

In het vijfde tot en met het achtste artikel wordt zeer uitgebreid ingegaan op de onderlinge samenhang die bestaat tussen blaasuitgangsweerstand, blaascontractiliteit en de kans op het al dan niet goed leegplassen van de blaas. Dat dit verband er kwalitatief moet zijn is makkelijk in te zien, gemiddeld gezien zal de kans op het niet volledig leegplassen van de blaas (een urinesidu) toenemen als de blaascontractiliteit afneemt en/of als de blaasuitgangsweerstand toeneemt. In de artikelen wordt voor dit verband een wiskundige formulering bepaald. Er wordt aangetoond dat deze formulering onder andere gebruikt kan worden om verschillende in de literatuur voor het meten van blaasuitgangsweerstand beschreven methoden wetenschappelijk met elkaar te vergelijken. Met wetenschappelijk wordt hier onder meer bedoeld dat voor het vergelijken geen kennis van een expert op het gebied van de urodynamica nodig is. Verder is de relatie die bestaat tussen de kans op een residu en twee van zijn determinanten gebruikt om het ICS nomogram voor de diagnose van blaasuitgangsobstructie bij mannen om te zetten naar een nomogram voor hetzelfde doel bij vrouwen. Belangrijker is echter de toepassing van de genoemde relatie op de bestudering van de slechte correlatie tussen urodynamisch gediagnosticeerde obstructie en symptomen en op de bestudering van de oorzaken van de variatie in de uitkomsten van twee kort achter elkaar in dezelfde patiënt uitgevoerde “druk-flow metingen”. De slechte correlatie tussen symptomen en urodynamisch gediagnosticeerde blaasuitgangsobstructie wordt zeer waarschijnlijk veroorzaakt door het feit dat de huidige methoden die voor de diagnosestelling gebruikt worden gebaseerd zijn op het meten van absolute blaasuitgangsweerstand. Maar obstructie is een relatief begrip waarin ook blaascontractiliteit een rol zou moeten spelen, we komen hier verderop nog op terug. In het laatste in dit proefschrift opgenomen artikel wordt, wederom op basis van de relatie tussen de kans op een residu en blaascontractiliteit en blaasuitgangsweerstand, aangetoond dat de variatie tussen twee kort op elkaar volgende “druk-flow metingen” voornamelijk berust op werkelijke variaties in blaascontractiliteit en blaasuitgangsweerstand en niet, zoals wel eens is geopperd, door artefacten in de gemeten signalen. Deze observatie heeft mogelijk klinische implicaties omdat variaties in blaascontractiliteit en blaasuitgangsweerstand mede verklarend

zouden kunnen zijn voor het klachtenpatroon van een patiënt. Om de variatie in kaart te kunnen brengen, moeten er minstens twee “druk-flow metingen” per patiënt gedaan worden. Dat wordt op dit moment lang niet in elke kliniek routinematig gedaan.

Conclusie.

Op dit moment is het doen van een “druk-flow meting” de enige methode om de werking van het “blaas-blaasuitgangs-systeem” te onderzoeken. Dit wordt vrij algemeen geaccepteerd zoals kan worden opgemaakt uit het gebruik van zowel druk- als flow-waarden in de vele methoden die voor bovengenoemde doeleinden in de literatuur zijn beschreven. Het is echter opvallend dat, in de hoogst competitieve wetenschappelijke wereld, zoveel verschillende methoden voor hetzelfde doel al gedurende zeer lange tijd naast elkaar worden gebruikt. Dit geldt voor het kwantificeren van blaasuitgangsweerstand en blaascontractiliteit en ook voor het diagnosticeren van blaasuitgangsobstructie. Dit gebrek aan standaardisatie is bepaald slecht voor de ideeënuitswisseling tussen onderzoekers. Het kan bovendien een bijzonder complicerende factor zijn in de vergelijking van de uitkomsten van bijvoorbeeld klinische studies, en daarom ook de wetenschappelijke vooruitgang belemmeren.

Standaardisatie van methoden voor het kwantificeren van blaasuitgangsweerstand, blaascontractiliteit en de diagnose van blaasuitgangsobstructie werd tot op dit moment gedaan door de standaarden te definiëren in plaats van ze te motiveren op grond van wetenschappelijk te toetsen criteria.

Het in dit proefschrift beschreven verband tussen blaascontractiliteit, blaasuitgangsweerstand en de kans op een residu biedt de mogelijkheid methoden die in gebruik zijn bij de gezamenlijke verwerking van druk- en flow- signalen op een wetenschappelijk gemotiveerde manier te standaardiseren. Uit het materiaal dat is opgenomen in dit proefschrift blijkt dat, bij een eventuele standaardisatie van methoden voor het kwantificeren van blaasuitgangsweerstand en blaascontractiliteit, de keuze tussen de verschillende in de literatuur beschreven methoden geen al te kritische keuze is. De methoden presteren vergelijkbaar op basis van het in dit proefschrift voorgestelde

wetenschappelijke criterium. Dit geldt echter niet voor de manieren die zijn voorgesteld voor de diagnose van blaasuitgangsobstructie. Eigenlijk kan hier geen enkele methode de toets der kritiek doorstaan. De logische argumenten en de empirische onderbouwing van die argumenten weergegeven in de artikelen opgenomen in dit proefschrift maken het aannemelijk dat blaasuitgangsobstructie een relatief concept is. Een voor een bepaalde blaas geobstrueerde blaasuitgang is mogelijk niet geobstrueerd voor een sterkere blaas en een voor een bepaalde blaas niet-geobstrueerde blaasuitgang kan geobstrueerd zijn voor een minder contractiele blaas. De nu kennelijk geldende opvatting dat blaasuitgangsobstructie overeenkomt met een verhoogde blaasuitgangsweerstand is maar de helft van het verhaal. Zolang de huidige definitie voor de diagnose van blaasuitgangsobstructie in dit opzicht niet wordt aangepast zal er een slechte correlatie blijven bestaan tussen urodynamisch gediagnosticeerde blaasuitgangsobstructie en symptomen. Simpelweg omdat blaascontractiliteit, in de diagnose, niet of onvoldoende is meegewogen.

Het materiaal dat is opgenomen in dit proefschrift verschaft nieuwe inzichten in het verwerken van “druk-flow metingen”. Deze ideeën zijn niet alleen van theoretisch belang. Zoals hierboven is uitgelegd is een samenhangende visie op het onderlinge verband tussen blaasuitgangsweerstand, blaascontractiliteit en het al dan niet leegplassen van de blaas de mogelijke basis voor een standaardisatie van methoden. Doordat die standaardisatie de communicatie tussen onderzoekers bevordert en de kwaliteit van diagnostische en therapeutische keuzes zal verbeteren zal de zorg voor de patiënt verbeteren. En daar gaat het uiteindelijk om.

Tot slot een persoonlijke noot :

Het heeft me 12 jaar gekost om dit proefschrift af te ronden. Het feit dat blaasuitgangsobstructie in feite al door experts gedefinieerd was is bijna de spreekwoordelijke druppel geweest die mijn emmer deed overlopen. Over een definitie valt immers, per definitie, niet te discussiëren.

Terugkijkend zijn mijn bedenkingen onterecht geweest. Met name het bestaan van het ICS nomogram bleek vruchtbare grond. En eigenlijk is dat ook helemaal niet zo

verbazend want juist als de voorspellingen op basis van ons beste model niet uitkomen (de slechte correlatie tussen symptomen en blaasuitgangsobstructie gedefinieerd volgens het ICS nomogram) staan we op het punt om wat nieuws te leren.

Tot slot.

Het is onmogelijk iedereen te bedanken die me op een of andere manier geholpen heeft bij het tot stand komen van dit proefschrift. In het algemeen dus collega's, vrienden : bedankt.

Natuurlijk wil ik toch wat mensen en 1 instituut in het bijzonder in een volkomen willekeurige volgorde noemen.

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Louis Decae en Huib Kranse.

Lenet.

Lieve Sam en Olaf, natuurlijk is dit boekje eigenlijk voor jullie (al was het maar om om te lachen). Ik hoop niet dat jullie in jullie leven ooit een uroloog nodig zullen hebben. Doe in ieder geval een gelzadel op je racefiets en fiets nooit zonder fietsbroek. Een kratje bier op een avond is ook iets dat ik, vanuit urodynamisch oogpunt bezien, van harte afraad. Mocht er toch een uroloog op jullie pad komen, voor een PSA prikje of zo (ik noem maar wat) kom dan in ieder geval even met papa praten. Je kunt overigens ook mama over deze onderwerpen consulteren, die weet (en heeft) er inmiddels meer dan genoeg van.

Curriculum vitae Ries Kranse.

Marinus (roepnaam Ries) Kranse werd op 3 januari 1960 in Rotterdam geboren. Hij behaalde in 1978 zijn Atheneum B diploma en studeerde vervolgens 1 jaar elektrotechniek aan de TH Delft. Daarna heeft hij elektrotechniek gestudeerd aan de HTS Rotterdam (diploma in 1983). Van 1983 tot en met 1986 was hij werkzaam bij de Centrale Research Werkplaats (meer precies de afdeling Automatische Signaal Verwerking (ASV)) van de Erasmus Universiteit Rotterdam, de eerste 18 maanden in het kader van de vervangende dienstplicht. Daarna volgde een 1 jarige arbeidsperiode als systeem analist/programmeur bij het Integraal Kankercentrum Rotterdam (IKR) na 1 jaar gevolgd door een terugkeer op het "CRW/ASV nest". Toen de CRW werd gesplitst in 1989 in een ziekenhuis- en een faculteits- deel deed de mogelijkheid zich voor om AIO te worden bij de afdeling Urologie (werkgroep Urodynamica) o.l.v. Dr. Ir. Ron van Mastrigt. Gedurende deze AIO periode (1989 – 1993) heeft hij een aantal colleges in Delft gevolgd op de afdeling technische natuurkunde en afgerond met een examen (systemen en signalen, parameterschatten, numerieke analyse, statistiek voor fysici). Gedurende de AIO periode werden de fundamenten gelegd voor het nu voor u liggende proefschrift. Van 1994-1999 volgde een periode van onderzoek bij de prostaatcancer screening-studie geleid door Prof. Dr. F.H. Schröder op de afdeling Urologie aan het Academisch Ziekenhuis in Rotterdam. Deze studie is in feite een haalbaarheidsonderzoek waarin in internationaal verband wordt bekeken of een 20% ziektespecifieke mortaliteitsreductie bereikt kan worden door een vroegtijdige detectie en behandeling van prostaatcancer. Vanaf 1999 is hij werkzaam als statisticus/programmeur bij het Integraal Kankercentrum Rotterdam.

Hij is in 1990 getrouwd met Lenet Vissers, zij hebben twee kinderen, Sam en Olaf.

