Urethral Pressure Reflectometry

A method for simultaneous measurements of pressure and cross-sectional area in the female urethra

Niels Klarskov

The present review is based on the following publications, referred to in the text by Roman numerals


PREFACE

This study was carried out during my appointment at the Department of Obstetrics and Gynecology at Glostrup Hospital (now merged and moved to Herlev Hospital), University of Copenhagen.

I wish to express my greatest gratitude towards my mentor and supervisor Professor, MD. DM.Sc. Gunnar Lose. Gunnar was the ideas man and introduced me to the project. He has always been extremely enthusiastic and inspiring and has thought me about science, clinical work and about life. Steen Brabrand Rasmussen is the inventor of the reflectometry technique used in this thesis and should be thanked for introducing reflectometry to me and for the fruitful and inspiring work during the development of Urethral Pressure Reflectometry. I am grateful towards the continence and project nurses Mette Hulbæk Andersen and Bert Sejer Larsen who have been of invaluable support during the examinations. My deepest thanks goes to my friends and colleges in the urogynaecological team Pia Sander, Søren Brostrøm and Lone Mouritsen who have thought me urogynaecology and helped me include patients. Gordon Hosker should be appreciated for his linguistic advice for the thesis. Oticon is thanked for making the equipment available for me and for financial support during initiation of the study and a special thank to the engineers Jan Stavngaard, Peter Foged, Bjarne Larsen, Jacob Riiser, and Adam Dyrbø who have built the UPR equipment and helped me with the analyses. I thank Pfizer Ltd. for financial support during initiation of the project and for the sponsoring of paper VI. The daily work would not have been the same if it was not for my office-mates Mette Hornum Bing, Eva Dreisler, Astrid Ammendrup, Marie-Louise Saaby and Marie Bønnelycke who have contributed with fantastic sarcasm, humour and laughs as well as helped organising my life. My always supporting parents should have the warmest thanks. Last but not least should my beloved wife Louise and my lovely kids Anna Freja and Carl Emil be thanked for making everyday life fabulous.

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SUMMARY

A novel technique for simultaneous measurements of pressure and cross-sectional area (CA) in the female urethra, denoted Urethral Pressure Reflectometry (UPR), was devised. A very thin and highly flexible polyurethane-bag was placed in the urethra. A pump applied increasing and decreasing pressures to the polyurethane-bag and thereby opened and closed the urethra. Sound waves were continually sent into the polyurethane-bag and the cross-sectional area (CA) of the bag (urethra) could be measured from the reflections with Acoustic Reflectometry. The CA of the bag was measured for each mm of the bag and 10 times per second. The examinations were performed with the women supine relaxing, supine squeezing, and standing relaxing. The examination provided measures of the opening pressure (the pressure exactly needed to open the urethra), the closing pressure (the pressure where the urethra closes again after dilation), the opening elastance (the resistance against dilation), the closing elastance (urethra's ability to close again after dilation) and the hysteresis (the energy which dissipates when urethra is dilated). The examination was reliable both in vitro and in vivo. All the UPR parameters except the hysteresis were decreased in stress urinary incontinence (SUI) women compared to continent women. Thus the parameters seem to be relevant regarding SUI. UPR examination was performed before and after urethral bulking and from these examinations a mechanism of action of the bulking procedure was proposed. A randomised, double-blinded placebo-controlled cross-over study demonstrated that UPR is valuable in developing and monitoring pharmacological treatments for SUI. Cases demonstrated that UPR has potential to sub-classify SUI in accordance to the pathophysiology and establish pathological conditions i.e. a stricture.

INTRODUCTION

Urethral pressure

The lower urinary tract comprises a complicated unit with two opposing functions; voiding (expulsion) and continence (filling). The urethra acts as an open conduit during expulsion whilst it acts as a closed, non-compliant sphincter during the filling phase. Insufficient sphincter function might lead to stress urinary incontinence (SUI). Understanding of the continence function is fundamental for understanding the genesis of SUI. Unfortunately, this function is still only rudimentarily understood [1,2]. Basically, a patient becomes incontinent if the bladder pressure exceeds the urethral pressure. This simple assumption has led to widespread use of different techniques and methods for pressure measurements in the urethra and bladder. The pressure in the urethra has been quantified using different techniques; all requiring insertion of a catheter into the urethra during measurement. Pressures in the urethra have been measured as being lower in SUI compared to continent women and this is independent of the technique used [1]. However, because of considerable overlap in the values between these two groups, conventional pressure measurements have low diagnostic power [1,3-16]. No clear association exists between the severity of SUI and the urethral pressure [17-19] and the methods used so far cannot subdivide patients into different pathophysiological groups [20]. Consequently, conventional urethral pressure measurements have low clinical and scientific value. The problems with the conventional techniques for urethral pressure measurement are manifold. Firstly, there are inherent conceptual issues. The simple equation with a bladder pressure higher than the urethral pressure leading to incontinence is only true when urethral pressure is defined as: “the fluid pressure needed to just open a closed (collapsed) urethra” [21,22]. However, conventional methods all require the introduction of a probe into the urethra and hence opening of the lumen. A catheter based pressure recording will primarily measure the external urethral compression as opposed to its inner softness and mechanical properties [23]. It also remains unclear to which extent static measurements elucidate the dynamic events in case of stress incontinence. The insertion of a catheter per se will influence the measured pressure since it depends on the cross-sectional area (CA) of the catheter [24-28]. The catheter will change the natural shape of the lumen and straighten the urethra which may influence the recorded pressure and give rise to artefacts because of interaction between the catheter and the urethral wall and catheter movement [22,29]. Secondly, conventional techniques are subject to significant test-retest variation [16,20]. Thirdly, lack of standardisation of the measurement techniques make it very difficult to compare results between centres [20].

Pressure/Cross-sectional area relation

In order to enhance the clinical and scientific value of urethral pressure measurements, new techniques for simultaneous measurements of related values of pressure and CA at a given site in the urethra were introduced in the 80’s [24-27,30,31]. From the simultaneous measurements of pressure and CA, a stress-strain relation for the urethral wall could be established. Characteristic material properties such as the elastance and the hysteresis were calculated from the stress-strain relation in addition to an opening pressure for the urethra. Regnier et al. [26] described a catheter which could increase in diameter. The catheter consisted of several 5 French (F) vinyl tubes glued together in such a way that the catheter progressively increased in CA to 6 different CA’s from 5 F to 30 F. This catheter could estimate the elastance of the urethra (the results were given as compliance, which is the inverse of elastance). From the examinations with this catheter Susset et al. [27] suggested that incontinent patients could be subdivided into a group with urethral hyperlaxity (low elastance) and a group with urethral rigidity (high elastance). Colstrup et al. [32,33] designed a probe which could measure the pressure and CA simultaneously. The probe consisted of a tube with 4 ring electrodes; which were surrounded by a balloon filled with a saline solution. The CA was measured between the two middle ring electrodes by the field gradient principle. The pressure in the balloon and thus the CA could be controlled by changing the level of a saline filled container connected to the balloon. The measurements enabled the elastance of the urethra to be calculated (denoted: “stiffness” by Colstrup), and the non-instrumented opening pressure could be assessed by extrapolation. With this probe the closure mechanism was investigated in healthy females [24,34-36]. Lose et al. made dynamic measurements possible by adding two micro transducers to the catheter, one inside the balloon and one in the part of the catheter placed inside the bladder [37]. Fast pressure increases could be performed with a syringe and the pressure could be measured at CA in the range from 13 mm² to 79 mm². The pressure at CA=13 mm² was called P_min. A subdivision of SUI women into two groups was suggested based on measurements with this probe [38]. One large group had low P_min and low elastance which corre-
responds to the condition Susset et al. called urethral hyperlaxity. A second group had a low P_min and a high elastance which corresponds to the condition Susset et al. called urethral rigidity [27]. Thus the two groups cannot be separated by the P_min alone.

Measurements of related values of pressure and CA provide parameters which give a meaningful description of urethral closure mechanism and therefore the parameters have the potential to subdivide SUI based on pathophysiology. However, the field gradient principle has some obvious drawbacks: The catheter used is relatively thick (~10 mm²) and stiff, and therefore insertion opened and distorted the urethra. Only CA’s larger than 13 mm² can be measured which is outside the CA of the lumen during micturition [39,40]. Measurements could only be carried out at one site along the urethra at a time (i.e. 2 mm slices corresponding to the distance between the detecting electrodes) which made repetitive investigations unreliable. A robust catheter for clinical workup was never launched. Therefore developing a novel technique for simultaneous measurements of pressure and CA is desirable.

**Acoustic Reflectometry**

Acoustic reflectometry is a technique which can measure the CA of a cavity without a catheter inside the cavity. A technique based on acoustic reflectometry can potentially eliminate the artefacts and drawbacks of the previous techniques which all require a catheter in the urethral lumen during the examination.

**Basic principle of acoustic reflectometry**

A sound pulse is generated outside the cavity, the sound wave passes into the cavity where echoes arise. The echoes are reflected, recorded, and analysed by a computer. When the size of the entrance of the cavity is known, the CA of the cavity can be calculated from the magnitude of the reflections. The CA of the entire cavity can be determined when the time between the reflections and the speed of sound is known.

**The history of acoustic reflectometry**

The technique was developed for analysis of the stratification of the earth’s crust and used in the sixties in the search for oil [41]. An explosion was performed with dynamite and an oil strike could be detected from the reflections. In 1971 Sondhi and Gopinath [42] described how acoustic reflectometry theoretically could be used for determination of the vocal tract shape. Jackson et al [43] used this technique in 1977 for measurements in excised lungs from dogs, with a spark as the sound source. Fredberg et al. [44] were in 1980 the first to use acoustic reflectometry in humans; they measured the upper airway and tracheal geometry with a loudspeaker as the sound source. In 1989 acoustic rhinometry was introduced by Hilberg [45]. This technique uses a digital signal processor to generate a modulated signal where the impulse and response had to be separated.

**Aims of the present study**

The aims of the present study were to:

- Develop a catheter-free method for simultaneous measurement of pressure and CA in the female urethra based on acoustic reflectometry.
- Test the reliability of the method in vitro and in vivo.
- Explore the clinical utility of different parameters for patients with stress urinary incontinence.

**URETHRAL PRESSURE REFLECTOMETRY; EQUIPMENT AND PARAMETERS**

**Equipment**

Hitherto, reflectometry had been used to measure dimensions of cavities which were naturally open. As the urethra is closed in the continence phase, the methodology had to be modified. A catheter which consisted of a 45 cm long polyvinyl chloride (PVC) tube (inner/outer diameter of 3.7/5.3 mm ± 0.3 mm) with a 6 cm long, very thin (wall thickness 0.025 mm, diameter 5 mm), highly flexible polyurethane bag glued on the tip was constructed (figure 1 and 2). The purpose of the catheter was to create a closed space. The closed space has two functions: A) To be able to create a pressure above the urethral pressure inside the polyurethane bag and thereby open the urethra. B) To enclose the reflectometry energy and thereby avoid dissemination of energy in order to optimise the result of the CA measurements within the urethra. An air pressure pump and a transducer were connected to the system which made it possible to apply and measure different pressures in the polyurethane bag simultaneously with measurement of the CA. The CA was measured with equipment as described by Djupesland [46]. This technique uses a digital signal processor to generate wideband sound (100 Hz-16 KHz) which is sent from a transmitter into the cavity and the reflections from the cavity are recorded by a microphone and relayed to a computer where the reflections are converted to profiles of the cavity. The modified equipment and methodology for measurements in the female urethra is called Urethral Pressure Reflectometry (UPR), and is schematically drawn in figure 1.

**Figure 1**

Schematic diagram of the equipment. The digital signal processor (DSP) and the pump are incorporated in the computer. The probe contains a microphone and a loudspeaker. The catheter is made by a plastic tube (red) and a thin distensible plastic bag (green). The plastic bag is placed in the urethra.
The equipment measured approximately 20 CA-profiles (figure 3) per second, which was sufficient to determine more than 99% of the pressure changes during a cough [47]. In this study measurements were not performed during fast pressure changes, thus there was no requirement for a very high number of measurements per second. Instead the CA-profiles were paired in order to reduce noise and increase the accuracy of the examination. In this study the equipment therefore measured approximately 10 CA-profiles per second.

The CA-profile is based on a CA measurement for every 1 mm of the length of the bag, thus the high pressure zone can be identified and measured without movement artefacts. The UPR examination is essentially a “catheter-free technique”, as identified and measured without movement artefacts. The elastance of the length of the bag, thus the high pressure zone can be measured approximately 15 mm. Two vertical dotted lines cut off the very first and the very last artefactual parts of the traces, leaving the middle of the traces (second part) where the CA is measured accurately. Five parameters can be obtained from the Pressure/CA-graph. The opening and closing pressures can be defined in two different ways: I) the interception between the vertical line which marks the closed urethra (dotted line which separates part 1 and 2 in figure 4) and the slope of the 2nd part of the opening and closing curves respectively. These pressures are denoted the opening and closing pressure in this review. II) The interception between the y-axis (CA=0) and the slope of the 2nd part of the opening and closing curve respectively is denoted Op/mm and Cl/mm in this review. The Op/mm and Cl/mm are a little lower than the corresponding opening and closing pressure. This difference between the parameters is due to energy loss through the polyurethane bag at low pressures. The elastance (cmH2O/mm²) can be measured both for the opening trace (opening elastance) and the closing trace (closing elastance) and is defined as the slope (Elastance=ΔPressure/ΔCA) of the second part of the increasing curve and the decreasing curve respectively. The hysteresis of the urethra is defined as the difference between the area under the increasing curve and decreasing curve from 0-10 mm² and is given as a percentage of the area under the increasing curve (area increasing curve-area decreasing curve * 100/area increasing Curve)

Opening pressure: The opening pressure is measured as the air pressure needed to force the urethra open, which is in agreement with the physical definition of pressure [21] and very close to the International Continence Society’ definition of the urethral pressure ("the fluid pressure needed to just open a closed (collapsed) urethra" [21,22]). The urethra will open and the woman will leak if the bladder pressure exceeds the opening pressure, therefore the opening pressure is a meaningful parameter for investigating incontinence. Previously, it has not been possible to measure the opening pressure, instead it has been estimated by extrapolation [24,25]. The opening pressure can be measured with the patient resting, during provocative manoeuvres and during squeeze supine and erect. Measurement during rest may express the permanent closure force.
while squeezing may evaluate the voluntary sphincter function.

Closing pressure: The closing pressure expresses the pressure at which the urethra closes after dilation. The greater the difference between the opening and closing pressure, the more the patient will leak when the bladder pressure exceeds the opening pressure.

Elastance: The elastance ($\Delta P/\Delta V$) is defined as the resistance of an object to deformation by an external force [48] and is the inverse of compliance. In the urethra the elastance is measured as the relation between the pressure and CA, which has been shown to be linear [24, 25, 28].

The opening elastance expresses the resistance against dilation of the urethra. The lower the opening elastance is, the more the urethra will open when the bladder pressure exceeds the opening pressure. Thus a strong urethral sphincter has a high opening elastance.

The closing elastance expresses the urethra’s ability to close against a pressure after dilation.

Hysteresis: The hysteresis expresses the energy which dissipates from the structure when it is stretched. Each type of fibre in the body has its own well-defined hysteresis [49] and the hysteresis may reveal different fibre compositions in the urethra in different groups of women. A high value of hysteresis could be an indication of fibrosis/scarification of the urethra.

The CA in the third part on the Pressure/CA graph (figure 4) is not the same at different examinations, therefore to make

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**Figure 4.** The figure shows an UPR measurement from the high pressure zone of a healthy female volunteer relaxing and supine. The upper curve is produced while inflating the plastic-bag. The lower curve is produced while deflating the plastic-bag. The curves are divided in 3 parts by 2 dotted vertical lines. The first and last parts of the curves are artefactual and disregarded. The opening pressure and closing pressure (cmH$_2$O) are defined as the pressure where the slope of the second part of the curve intercepts the first vertical dotted line on the upper and lower curves respectively. $O_p$ and $O_c$ are the pressures where the slope of the second part of the upper and lower curve intercept the y-axis respectively. The elastances (cmH$_2$O/mm$^2$) are the slopes of the second part of both the upper (opening elastance) and lower (closing elastance) curves. The hysteresis is the area between the upper curve and the lower curve from 0-10 mm$^2$ (red area) measured as a percentage of the area under the upper curve.

**Figure 5.** The curves show simultaneous measurements of pressure and minimum CA from 3 consecutive UPR examinations with a woman relaxing in the supine position. The x-axis shows the time (from 12.27 to 12.35 pm). The upper trace shows the minimum CA from the CA-profile (the minimum CA is marked with a circle on figure 3). The lower trace shows the pressure inside the bag. Ten pairs of corresponding minimum CAs and pressures are measured each second. These pairs can be plotted against each other giving a pressure/CA plot as is shown in figure 4.
comparisons between different examinations reliable, the hysteresis was only measured for CAs from 0 to 10 mm².

MATERIAL AND METHOD

In vitro method

The accuracy and reproducibility of the CA measurements were tested in models with known CA’s from 4-16 mm² (l). Three models had quadratic cross-section (2×2, 3×3 and 4×4 mm²), one model had a rectangular cross-section (1×4 mm²) and two had round cross-sections (4 mm² and 9 mm²). Two of the models had two identical constrictions in each. In the first model the constriction reduced the CA to 50% (from 16 mm² to 8 mm²) (figure 6), and in the second the CA was reduced to 25% (from 16 mm² to 4 mm²).

Ten measurements were made in each of the eight models at pressures from 10-200 cmH₂O at standard conditions (37 °C and 35-40 dB SPL background noise). In addition, measurements were made in the model with a CA of 3×3 mm² at 20 °C and with 67 dB SPL background noise.

Clinical material

The patients were referred to the department of gynaecology and obstetrics at Glostrup Hospital because of urinary incontinence, while the healthy volunteers were found by advertising in local newspapers. In all, 143 women have been included in the six studies (I-VI). Sixty-eight had pure urodynamic stress incontinence, 13 had detrusor overactivity incontinence, 17 had both urodynamic stress incontinence and detrusor overactivity incontinence, seven had other diagnoses and 38 were healthy volunteers.

In vivo method

The women had a detailed history obtained, and filled in the International Consultation on Incontinence Questionnaire on Urinary Incontinence (Short Form). Urine dipstick, pelvic examination, uroflowmetry, post voiding residual urine, UPR measurement and a urethral pressure profile (UPP) were performed. In addition the patients had a sitting cystometry and a pressure-flow study performed.

Uroflowmetry and post voiding residual urine measurements

All the women had a standard free-flow uroflowmetry (Medtronic Urodyen 1000), alone in a restroom, with a comfortably full bladder. If the voided volume was less than 150 ml or the curve was pathological, the examination was repeated up to 3 times. Immediately after the spontaneous voiding the residual urine was measured (Diagnostic Ultrasound Corporation Bladderscan BVI 2500).

Cystometry and pressure flow study

Two lubricated Charrier (Ch) 5 catheters were inserted into the bladder, one for filling and one for measurement of intravesical pressure. A filling rate of 50 ml/min was used. Rectal pressure was measured with a water-filled 8 Ch catheter. The patient was asked to cough at each 50 ml infused. The patients were assessed sitting and, if leakage was not demonstrated, the cystometry was repeated with the patient in the standing position. The catheters were left in situ for pressure-flow studies. Dantec Duet Multi-P equipment (Medtronic Functional Diagnostics, DK-2740 Skovlunde, Denmark) was used for the measurements.

Urethral pressure reflectometry

The bladder was emptied with a Ch 8 catheter and the women were examined with an empty bladder (except the patients included in the placebo controlled cross-over study (VI) who also were included in the long time reproducibility examination (III). They had 150 ml 9 % NaCl at 37ºC instilled). The polyurethane-bag was placed in the urethra using a Ch 5 baby-feeding tube as a guide wire. The PVC tube was anchored to the urethral meatus using duroderm™ plaster. The pressure was increased until the plastic bag was completely open and then decreased to 0 cmH₂O to ensure that the plastic bag was placed correctly.

Supine and relaxing: All the parameters shown in figure 4 were measured. In addition the pressure at an opening of 5.1 mm² (Op₁ reopening) was calculated (Op₁ reopening = 5.1 mm² X opening elas-tance + Op₀ opening), in order to make comparisons with UPP carried out with a Ch 8 catheter (CA of Ch 8 = 5.1 mm²).

Supine and squeezing: A specially urodynamically-trained nurse instructed the patients to squeeze and watched if they did it correctly (inward lift of the perineum) [50]. The Op₀ reopening pressure and opening elas-tance were obtained from the measurements.

In some of the studies (II,III,IV) measurements were made with the women standing with a relaxed pelvic floor in the same manner as while lying and relaxing. All the parameters from figure 4 were measured in this position.

Only the measurements from the high pressure zone were systematically evaluated. The high pressure zone was defined as the minimum CA at a given pressure.

Urethral pressure profilometry

The UPP was carried out before the UPR except in study VI and the long-term reproducibility in study III where the UPP was carried out after the UPR examination. The perfusion technique was used as described by Brown and Wickham [51] with a Dantec Duet Multi-P equipment (Medtronic Functional Diagnostics, DK-2740 Skovlunde, Denmark). An Ch 8 single-lumen catheter with two side-holes, 5 cm from the tip, was used for recording the urethral pressure in a lateral orientation. A withdrawal speed of 2 mm/s and a perfusion rate of 2 ml/minute were used. With this setting, the maximum measurable rate of pressure increase measured with blocked side-holes was 60 cmH₂O/second. Two successive profiles were obtained in the supine position with the patient relaxed. In II,III,VI an additional UPP was carried out during a squeeze. The maximum urethral pressure (MUP) and the maximum urethral closure
pressure (MUCP) were determined from the UPP measurements [21].

Statistics
A two-tailed p<0.05 was regarded significant. For parametric variables the paired and the unpaired t-test were used to test for significance. The independent non-parametric variables were tested with the Mann-Whitney test while the paired data were tested with Wilcoxon signed-rank sum test. For categorical data the Chi-squared test was used. Spearman’s rank correlation coefficient test was used to test for correlation. The data in the cross-over study (VI) were analysed using an ANCOVA model (SAS version 8.2 software).

The coefficient of variation was calculated as the standard deviation divided by the mean and expressed as a percentage. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [52].

The studies were approved by the regional scientific ethical committee and the women signed an informed consent.

Comments on the clinical method
UPR examination. In the clinical studies only the high pressure zone was evaluated because the in vitro study showed that CA measured behind a constriction was unreliable. The bladder pressure was not measured as this would negate the catheter-free principle and a suprapubic catheter was considered to be too invasive. Rectal and vaginal pressures were also not measured, but might be included in future studies.

UPP examination. The perfusion technique was used for the UPP measurements as this is the gold standard for pressure measurements in the urethra [21]. UPP is regarded unreliable in the erect position [53,54] and erect UPPs were not done.

Order of examinations. The sequence between the UPR and UPP examinations was not randomized as a fixed examination program was preferred. An order effect might therefore exist in the comparison between the UPR and UPP measurements. However, an order effect has not been reported for resting urethral pressure measurements previously [55,56].

Irrational the examinations should have been double blinded; however, neither the investigator nor the women were blinded to examination as this was found practically impossible.

RELIABILITY
General considerations
The reliability of a parameter depends on its accuracy and reproducibility. The accuracy expresses how close the parameter is to the true value and is ideally established by comparing the parameter to the true value. In cases where the true value is not known, the parameter can be compared to an equivalent parameter measured with another method. In this way the accuracy between the two techniques can be established, but an agreement between the two parameters does not necessarily mean that they measure the true value. This comparison does not point out which technique is closest to the true value. The reproducibility is the agreement between repeated examinations with one method. The examinations can be repeated immediately after each other, or there can be shorter or longer time between the examinations. The reproducibility is influenced by methodological as well as biological factors. The methodological factors can be investigated in in-vitro studies while clinical studies are both influenced by methodological and biological factors.

The reproducibility can be expressed as the variability or the coefficient of variation (CV). The variability is measured as two SD between the examinations. When the result of an examination is known, a second examination will with 95% probability be the same as the first examination plus/minus the variability. The CV is calculated as the mean of the observations divided by one SD between the observations and expressed as a percentage. Thus a second examination will with 95% probability be between plus/minus two CV. A difference between two examinations is called the bias [60].

The following example demonstrates the interpretation of accuracy and reproducibility figures from the literature of urethral pressure measurements. Sand et al. [57] found that an MUCP less than 20 cmH\textsubscript{2}O was an indicator for failed retropubic urethropexy. This cut-off level has been used for counseling patients and for deciding on treatment. However, it is well-established that the measured pressure is proportional to the CA of the catheter [24-28] and the measured pressure depends

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<td>Short- and long-term reproducibility; the short-term were results from consecutive measurements in 143 women, and the long-term from 17 patients, with results for the mean of two sessions, at each session using the mean of two consecutive measurements. The bias is the difference between the first and second measurement.</td>
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*p=0.001; all other biases not significant. SD: standard deviation. CV: coefficient of variation.
on the technique. A difference of up to 24.5 cmH₂O between two techniques have been demonstrated by Wang et al [58]. Thus a cut-off value of 20 cmH₂O with one technique may correspond to a cut-off value of 44.5 cmH₂O with another. The cut-off value suggested by Sand et al [57] is therefore only valid with the same calibre catheter and technique (microtip transducer, patient sitting). Lack of reproducibility of the technique increases the number of false positive and false negative results. Studies have shown very high variability of the MUCP measurements [16]. In one study 2 standard deviations (SD) was 33 cmH₂O [59], thus, a patient with a MUCP of 50 cmH₂O will with 95% probability have a MUCP between 17 and 83 cmH₂O in a second measurement. The second examination could therefore categorise the patient as having a "low pressure urethra" or a normal to high pressure in the urethra. This example shows that a cut-off value can only be useful if the test has well-established accuracy and good reproducibility.

**Accuracy of Urethral Pressure Reflectometry**

In vitro: In the in vitro study, the CA measurement of the UPR was tested in models with conditions comparable to the high pressure zone and the bladder neck of the female urethra. At the area comparable to the high pressure zone, the accuracy was acceptable because the maximum error was 1.2 mm² at pressures from 30-200 cmH₂O. The area comparable to the bladder neck was not measured acceptably when the area comparable to the high pressure zone was nearly closed. The pressure transducer was found very accurate when comparing against a water column (error < ± 1 cmH₂O between 10-150 cmH₂O).

In vivo: In the in vivo studies, the true urethral pressure at different CAs is not known, thus, the accuracy has to be established against another technique. The gold standard for pressure measurements in the urethra is UPP performed with a water-perfused catheter [21]. With this technique the maximum urethral pressure (MUP) can be measured at the CA of the catheter used for the examination. A Ch. 8 catheter (CA of 5.1 mm²) was used for the UPP examination, thus the MUP measured with UPP corresponds to the UPR pressure measured at an opening of 5.1 mm² (Op₅.₁mm²). This comparison was made in 143 women and showed that the two techniques measure the same pressure (UPR: mean Op₅.₁mm²: 51.7 cmH₂O vs. UPP: mean MUP: 52.9 cmH₂O) (III). However, there was a considerable difference between the individual measurements expressed as a SD of 9 cmH₂O between the two parameters. This means that if the MUP or Op₅.₁mm² is 50 cmH₂O with the one technique it is with 95% probability going to be between 32 and 68 cmH₂O with the other. Whether this difference relates to poor reproducibility of the UPP or UPR technique or both of them cannot be established by this comparison, but the reproducibility of the individual parameters can be compared. There are no gold standards for measuring elastance, closing pressure and hysteresis. Therefore, the accuracy of these parameters could not be established and the reliability of these parameters are solely evaluated from the reproducibility of the parameters.

**Reproducibility of Urethral Pressure Reflectometry**

In vitro.

In the in vitro study the short-term reproducibility (difference between 10 successive CA-profiles made within 1 s) was excellent as the CV did not exceed 1.3 % under any circumstances. The background noise, temperature, shape of the cross section, calibration procedure and the catheters had minimal influence on the measurements. A tendency was noted that the higher the pressure in the polyurethane bag, the more the area was underestimated. The phenomena might be due to an increase of density of the air which increases linearly with the pressure. The density of the air affects the sound propagation and thus the measurements (I).

In vivo.

In the clinical study the short-term reproducibility of the UPR and UPP parameters were calculated from two consecutive measurements in 143 women in the supine position (table I). The long-term reproducibility of UPR and UPP were analysed for 17 women, who had two examinations separated by 14-34 days (table I). The value of the short and long term reproducibility of the UPP measurement was comparable with previous studies [16].

In the erect position, the short-term reproducibility for the UPR parameters was calculated for 80 women. There was a significant bias between the first and second opening and closing pressure but no bias between the second and third measurement. Reproducibility was therefore calculated between the second and third measurement (table II).

Both the short- and long-term reproducibility of the UPR (Op₅.₁mm²) was significantly better than the short- and long-term reproducibility of the UPP (MUP) in terms of variability (Short-term variability (2SD): 9.5 cmH₂O vs. 13.8 cmH₂O,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurements, means</th>
<th>2SD</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure, cmH₂O</td>
<td>71.3 74.2 0.00001 74.2 8.8 5.9 2nd vs 3rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening elastance, cmH₂O/mm²</td>
<td>1.9 1.9 0.43 1.9 0.9 22.4 2nd vs 3rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closing pressure, cmH₂O</td>
<td>61.4 62.7 0.02 63.3 10.4 8.2 2nd vs 3rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>opening elastance, cmH₂O/mm²</td>
<td>1.8 2.0 0.01 1.9 0.9 24.4 2nd vs 3rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysteresis, %</td>
<td>12.3 13.9 0.14 13.4 13.4 49.1 2nd vs 3rd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reproducibility of all the opening pressures (supine, erect and during squeeze) was good, whilst the reproducibility of the elastance was moderate. In future studies the reproducibility of the elastance might be improved by increasing the numbers of measuring points on the slope. The consequence of measuring CA in pressure steps of 5 cmH₂O was that in extreme cases, e.g. with elastances below 1 cmH₂O/mm², the elastance measurement might be based on only 2 points while with elastance of 3 cmH₂O/mm² there might be 9 points on the slope. A syringe pump which can continually increase the pressure while measuring the CA might improve the reproducibility of the elastance because there will be more measuring points. A syringe can for example increase the pressure from 0 to 120 cmH₂O in 120 seconds which will give 320 points on the curve with an elastance of 1 cmH₂O/mm² (16 mm² × 1 cmH₂O/mm² × 1 seconds/cmH₂O × 20 points/second) and 960 points with an elastance of 3 cmH₂O/mm². Future studies must clarify whether the syringe pump can improve reproducibility of the elastance without jeopardising the good reproducibility of the opening pressure. The reproducibility of the hysteresis was poor and, with the current equipment, it cannot be used for diagnosis of individual patients it can only be used for comparison of larger groups. The reproducibility of the hysteresis depends on the reproducibility of the opening and closing pressures and the opening and closing elastances. A syringe might therefore also improve the reproducibility of the hysteresis.

**Table III. Urethral Pressure Reflectometry and Urethral Pressure Profile parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volunteers n=30</th>
<th>SUI n=30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine relaxed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (cmH₂O)</td>
<td>72 (33)</td>
<td>40 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Closing pressure (cmH₂O)</td>
<td>57 (28)</td>
<td>32 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opening elastance (cmH₂O/mm²)</td>
<td>2.1 (1.0)</td>
<td>1.5 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Closing elastance (cmH₂O/mm²)</td>
<td>2.1 (1.0)</td>
<td>1.4 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hysteresis (%)</td>
<td>18 (10)</td>
<td>19 (9)</td>
<td>0.5</td>
</tr>
<tr>
<td>UPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUP (cmH₂O)</td>
<td>80 (38)</td>
<td>47 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MUCP (cmH₂O)</td>
<td>72 (36)</td>
<td>39 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Supine squeeze</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (cmH₂O)</td>
<td>89 (40)</td>
<td>52 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opening elastance (cmH₂O/mm²)</td>
<td>2.5 (1.4)</td>
<td>2.0 (1.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>UPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUP (cmH₂O)</td>
<td>87 (38)</td>
<td>57 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MUCP (cmH₂O)</td>
<td>79 (35)</td>
<td>50 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Erect relaxed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (cmH₂O)</td>
<td>103 (43)</td>
<td>66 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Closing pressure (cmH₂O)</td>
<td>87 (38)</td>
<td>57 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opening elastance (cmH₂O/mm²)</td>
<td>2.3 (0.8)</td>
<td>1.8 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Closing elastance (cmH₂O/mm²)</td>
<td>2.4 (1.0)</td>
<td>1.8 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hysteresis (%)</td>
<td>13 (12)</td>
<td>12 (7)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Mean values are provided with 2 standard deviations (2 SD) in brackets.  
UPR: Urethral Pressure Reflectometry.  UPP: Urethral Pressure Profile  
MUP: Maximum Urethral Pressure.  MUCP: Maximum Urethral Closure Pressure

**CLINICAL RELEVANCE**

*Continent versus incontinent women*

Thirty women with pure stress urinary incontinence were measured with both UPR and UPP in the supine position while resting, and during squeezing. In the erect position only UPR was performed. The measurements were compared to 30 healthy women; the results are shown in table III. All parameters except the hysteresis were significantly decreased in the SUI women compared to the healthy women. Thus, all the parameters (except hysteresis) seem to be directly or indirectly related to SUI and might therefore be useful for exploring the pathophysiology of SUI. The overlap of MUCP between continent and incontinent women was large, which is in agreement with the literature. In a review a weighted mean MUCP for continent women was estimated to 54+/-50 cmH₂O (2SD) and to 39+/-48 cmH₂O for incontinent women [1]. Although the mean pressure in SUI women is decreased, the overlap makes it useless for diagnosis. The opening pressure was better to discriminate between continent and SUI women compared to MUP and MUCP (IV). Discrimination on its own is of limited importance. More important is pathophysiology information and the ability to subdivide SUI in groups based on pathophysiology.

The pressure increase, when changing from supine to erect position, was significantly higher in healthy women compared to SUI women (31 vs. 25 cmH₂O, p=0.01). Similar results have previously been reported [25]. This difference may reflect decreased muscle activity or a decreased passive “transmission” of the abdominal pressure in the SUI women. In future studies it will be interesting to compare the changes in the
bladder or abdominal pressure from supine to erect position together with the changes in the opening pressure. At UPR the squeezing opening pressure increased in all subjects compared to the opening pressure during relaxation, while MUP and MUCP increased during squeezing in 47 subjects but decreased by up to 22 cmH₂O in 13 women (10 continent and 3 SUI women) (IV). A pressure drop during squeeze has been described in healthy and SUI women when using a microtip transducer catheter (61, 62), however, a lower pressure during squeeze is not likely to be a physiological phenomenon in healthy women. It is rather an artifact due to displacement of the measuring point in relation to the high pressure zone or lack of reproducibility with UPP. Thus, UPR seems to be a more reliable method for evaluating squeeze function compared to UPP.

Changes after intervention
A test to evaluate a treatment must be sensitive to changes after the treatment and show a difference between success and failure.

Bulking Procedure
The mechanism of action of a bulking procedure is unknown although they have been used for more than a decade (63). The UPR was used to investigate the possible action of this treatment. Fifteen women with predominant SUI were measured with UPR before and after a bulking procedure with Aquamid® or Bulkamid®. The squeezing opening pressure showed a statistically significant increase (p=0.01) from 39 cmH₂O before the bulking procedure to 45 cmH₂O after. The other parameters were unchanged after the procedure. The patients were divided into a group with subjective effect of the treatment (n=10) and a group without effect (n=5). The mean squeezing opening pressure increased significantly (p<0.01) more in the group with effect (11 cmH₂O) compared to the group without effect (2 cmH₂O). Thus the voluntarily closure force was reinforced after the operation in the patients with effect. This increased strength of the periurethral muscles may be explained by increasing the central filler volume (IV). A sphincter cannot consist of muscle fibre alone as this will require the innermost fibre to contract to zero length which is impossible; thus the sphincter needs some central filler volume to compress the lumen (2). An increased central filler volume will increase the sarcomere length and hence the muscle power (48). With this mechanism of action some assumptions can be made; the material should be deposited at the luminal side of the sphincter and the patient needs to be able to activate the striated peri-urethral muscles to gain effect of the increased strength of the sphincter (V).

Pharmacological testing
The usefulness of UPR and UPP in a pharmacological study was tested in a randomized, double-blind, placebo controlled cross-over study (VI). Seventeen women with predominant SUI received 4 mg oral dose esreboxetine (highly selective norepinephrine reuptake inhibitor) or matching placebo for 7 to 9 days with a washout period of 7 to 30 days before crossing over treatments. UPR and UPP were performed at the beginning and end of each treatment period (VI). The OPmax increased 13.7 cmH₂O during active treatment compared to placebo (p<0.0001) while the MUCP and MUP increased 8.4 cmH₂O (p=0.06) and 9.9 cmH₂O (p=0.04) respectively. The opening elastance increased 0.3 cmH₂O/m² (p=0.02). The patients had 8.3 fewer incontinence episodes per week in the active period compared to the placebo period (14.2 vs. 5.9 incontinence episodes p<0.001). Thus, esreboxetine reinforces the continence mechanism which results in symptom relief. Based on the variability found in the study, a sample size calculation was made for a cross-over study to have a power of 80% with an α of 0.05 to detect a difference of 10 cmH₂O. Seven women are required when using the opening pressure as endpoint, whilst a study needs 23 or 26 women when MUCP or MUP is used as endpoint (VI). Hence UPR measures the changes in the continence mechanism more sensitively compared to UPP and may provide a more efficient study design, and might therefore be preferred for exploring pharmacological induced pressure changes in the female urethra.

Accessibility
For the examination to be implemented into daily clinical practice the resources needed for the examination must be reasonable and the discomfort and risk for the patient must be within acceptable ranges. A supine UPR and UPP lasted about 15 min. each while the entire UPR examination including both supine and erect examinations lasted 30 to 45 min. The women found the UPR examination less uncomfortable compared to the UPP examination and to a normal vaginal examination (III). The only type of complication noticed after the examination was cystitis. In study IV the women were screened for bacteriuria at the following visit about one week after each UPR and UPP examination with a urine dipstick. A culture was performed when the dipstick was positive for either leucocytes or nitrates. The 17 women had four UPR and UPP examinations each and only one woman was diagnosed with asymptomatic bacteriuria based on a positive culture. Thus this complication was uncommon and bacteriuria was in the same range as seen with conventional invasive urodynamics (64). Thus the examination was swift and safe with limited discomfort. The catheter used for the examination was disposable. The catheters were handmade, packed, and sterilised. It took about 20-30 minutes to make each catheter. The equipment was engineered by Oticon but it is not commercially available.

Case stories
Case-story one and two: Low pressure urethra with “hyperlaxity” and “rigidity”
Figure 7 shows a curve from 2 patients with a “low pressure urethra”. Patient one was 73 years old with SUI. She never had vaginal or incontinence surgery. The MUP was 30 cmH₂O and the MUCP was 16 cmH₂O. With UPR all parameters were very low (table 4). Patient two was an 86 years old woman with mixed incontinence and continuous leakage of urine. During the last 3 years she had suffered from chronic cystitis and had previously had a Burch colposuspension. All the UPP and UPR parameters were similar to patient one except the opening elastance which was very high (table 4). Patient one represents a typical patient with genuine SUI with low parameters and an uncomplicated medical history. Patient two has a medical history and a UPR examination which fits the description of “urethral rigidity”. The condition is characterised by a low opening pressure and a high opening elastance (27, 38).
Patient one was cured by a mid-urethral sling. Patient two was referred to a bulking procedure, before the injection the surgeon had to dilate the urethra in order to introduce the cystoscope. She had a follow-up visit one week after, where she reported some effect of the treatment. The opening pressure was increased while the opening elastance was decreased. The other UPR parameters were unchanged (table 4). The condition “low pressure urethra” probably covers different pathophysiological conditions; one with urethral hyperlaxity with low elastance and one with a rigid urethra with a high elastance. UPP cannot distinguish between the pathophysiological conditions which might explain why the “low pressure urethra” has not given an unambiguous response in intervention studies [16].

Case story three: Urethral stricture

Figure 8 shows an UPR examination from a 47 years old patient, who suffered from slow stream and urethral pain. She had 4 previous excisions of urethral carunculae at her local hospital; pathology showed no malignancy. The free-flow uroflowmetry showed a box-like flow curve with a maximum flow rate of 7 ml/s and a voided volume of 402 ml suggesting a stricture. The residual volume was zero. The UPR measurement showed two compressions (figure 8 B), one consistent with the high pressure zone two cm into the urethra, and one consistent with a stricture one cm from the urethral meatus. Under general anaesthesia a stricture was demonstrated with an ureteroscopy and Sachse urethrotomy was performed. After the operation the patient performed clean intermittent catheterization one time every fourteen days. Seven months after the operation she was no longer suffering from slow stream or urethral pain. The case story shows that UPR is capable of demonstrating a stricture. Obstructions in the female urethra are uncommon, thus the need for a diagnostic procedure for examining obstructions is limited. In the male urethra, by contrast, obstructions are the most common cause of lower urinary tract symptoms. Thus UPR may be very useful in localising and describing the obstructed area in the male urethra.

CONCLUSIONS

The accuracy of the cross-sectional area (CA) measurements in the in vitro models was good in front of and within a constriction. The error was less than 1.2 mm$^2$ at the site of a constriction imitating the high pressure zone in the female urethra. Measurements behind a narrow constriction are not realistic. This means that a constriction behind the high-pressure zone (e.g. bladder neck) cannot be measured exactly when the high pressure zone is closed or nearly closed. The repeatability of the measurements was excellent and the examination is very robust to fluctuations in the environment.

The in vivo studies show that it is feasible to measure pressure and cross-sectional area simultaneously with Urethral Pressure Reflectometry (UPR) in the female urethra. The UPR measures the urethral pressure with the same accuracy as a gold standard (Urethral Pressure Profile), but with better reproducibility. It produces physiologically sound parameters which add to the conventional armamentarium in the assessment of female urinary incontinence. The parameters are affected in women with stress urinary incontinence compared to normal volunteers, and the parameters are sensitive to both medical and surgical interventions.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient 1 Before treatment</th>
<th>Patient 2 Before treatment</th>
<th>Patient 2 After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (cmH$_2$O)</td>
<td>23</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Closing pressure (cmH$_2$O)</td>
<td>20</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Opening elastance (cmH$_2$O/mm$^2$)</td>
<td>1.0</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Closing elastance (cmH$_2$O/mm$^2$)</td>
<td>1.0</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Hysteresis (%)</td>
<td>12</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>UPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUP (cmH$_2$O)</td>
<td>30</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>MUCP (cmH$_2$O)</td>
<td>16</td>
<td>21</td>
<td>-</td>
</tr>
</tbody>
</table>

surgical intervention. UPR may separate different conditions such as urethral hyperlaxity, urethral rigidity and urethral strictures.

**REFERENCES**


**FUTURE ASPECTS**

A) Stress incontinence happens during dynamic events, thus UPR examination during events such as coughing and straining would be preferable for studying the pathophysiology of SUI.

B) The urethra and the bladder are a functional unit and therefore UPR measurements during cystometry might provide important physiological and pathophysiological information on the interaction between bladder and urethra.

C) Potentially, the UPR technique might be useful in the study of other biological tubes such as the male urethra, the anal canal and the oesophagus.

D) All aspects of the technique and examination needs to be standardised.

**REFERENCES**


