Urethral Instability: current pathophysiological concept

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Summary

The role of urethral pressure variations during filling cystometry is seldom assessed as a potential cause of voiding dysfunction and/or storage disorders. In this article, we review current research in the field of urethral pressure variations and discuss the way of determining urethral pressure variations, the value for clinical practice and hypothesize the origin of urethral pressure variations. The observation and recognition of urethral pressure variations (urethral instability) could be valuable in the diagnosis and evaluation of therapy in functional lower urinary tract disorders.


**Introduction**

The role of urodynamics in diagnosis as well as evaluation of treatment for storage disorders is scrutinized by many involved in this area. Correlations between traditional urodynamic outcome parameters and outcome of different treatment modalities remain poor. This is even true for the well-accepted and defined observation of rise in detrusor pressure during filling cystometry (i.e. detrusor overactivity). Filling cystometry is performed to register the impact of natural bladder filling on behaviour of the lower urinary tract. In this process both bladder and urethral behaviour are involved. So far only bladder behaviour during filling cystometry has been studied extensively. However, urethral function may be even more important in influencing bladder function than vice versa, if one takes the concept of the guarding reflex into account. The urethral external sphincter appears to serve as the ‘on-off’ switch for voiding, relaxation of the external urethral sphincter (releasing the guarding reflex) initiates micturition, whereas contraction suppresses bladder contractility [1]. Consequently it makes sense to measure and register detrusor and urethral function during filling and voiding, in an as much as possible physiological setting. It is known and accepted that for optimal bladder function as a storage organ a stable, non-fluctuating detrusor pressure is of eminent importance. Logically, this should also hold true for the urethra. In this respect, urethral instability (URI) remains a controversial item and the debate on the importance and clinical relevance of observed urethral pressure variations during filling cystometry is still on. These urethral pressure variations are considered as physiological or artificial, or even irrelevant and therefore ignored by most authors [2]. The definition and the term detrusor overactivity (DO) have been changed several times over the past years by the sub-committee on terminology of the International Continence Society (ICS). However, despite an increased interest in the relevance of urethral pressure for urgency [3], till now, the ICS has not succeeded in defining the term “urethral instability” although it has attempted in the past [4]. Urethral pressure measurement is still first and foremost a research tool [5].

We herewith review the literature on the observation of URI, terminology for urethral pressure changes, association with clinical symptoms, relevance in daily practice, and hypothesize its origin.
Survey on terminology and observations of urethral pressure fluctuations

‘The unstable urethra’
Although urethral pressure variations during filling cystometry are not frequently routinely dealt with in clinical practice, the observation of urethral pressure variations during filling cystometry is studied intensively by several authors. In 1981, the ICS committee on standardisation of terminology defined URI as a condition in which there is an involuntary fall in urethral pressure during filling, resulting in urinary leakage, in the absence of detrusor activity [6]. In 1988 however, the ICS did not redefine URI and stated that further investigations would be necessary to formulate a proper definition [7]. In 2002, a revision on terminology of lower urinary tract function was published by the standardisation sub-committee of the ICS [4]. Again, the sub-committee did not define the term “unstable urethra” by arguing that the clinical significance of decreases in urethral pressure during filling cystometry is unclear and does not correlate with symptoms. According to the ICS, it is better to give a full description if symptoms are seen in association with a decrease in urethral pressure during cystometry.

Most of the literature dealing with the phenomenon of URI was published decades ago. Study of the literature makes it evident that different definitions for the entity of URI are used by various authors. Furthermore, the clinical implication of urethral pressure variations during filling cystometry for explaining lower urinary tract symptoms is not consistent.

Clinical implications of the ‘Unstable urethra’
Various descriptions are used for urethral pressure variations during filling cystometry. In order to correlate urodynamic findings with clinical significant findings, McGuire reported on 11 patients with incontinence and large post void residual volumes [8]. Complete urethral relaxation, associated with perineal floor electrical silence and an observed decrease in urethral closing pressure was found in this group of patients. McGuire suggested that in this group of patients, urethral behaviour is compatible with that seen in reflex micturition, in spite of the lack of bladder contraction. Turner Warwick did notice voiding without any detectable detrusor pressure rise in a few females, apparently by reflex relaxation of their urethral sphincter mechanisms. Conceptually, disturbance of this reflex may result in inappropriate relaxation and “urethral instability” may be an occasional cause of incontinence in females [9].

Pressure based definitions of URI.
Most authors consider momentary urethral pressure variations, exceeding an amplitude of 15 cm water, as an abnormal finding [10-17]. Others defined an unstable urethra as an urethral pressure decrease of at least 20 cm water unrelated to a detrusor contraction, an increase of intra-abdominal pressure, or pulsations of the vascular bed [18,19]. Plevnic and Janez used a lower cut-off value and defined pressure variations of > 10 cm water as URI [20]. Wise et al. advocated the definition of URI as a spontaneous fall in maximum urethral pressure of one-third or more, in the absence of detrusor activity, over a 2-minute period [21].
Pathological urethral pressure variations should be distinguished from physiological urethral pressure variations according to Vereecken. One should focus on the following criteria: amplitude, duration, sphincteric EMG, repetition throughout the filling phase and loss of urine. A pronounced amplitude of at least one-third of the maximum urethral closure pressure (usually >25 cm water), a short duration (1-5 sec), a simultaneous inhibition of EMG activity in urethral and/or anal sphincter, and the occurrence of the phenomena starting at the beginning of bladder filling indicates pathological urethral pressure variations. [22].

McLennan et al. defined URI by recording resting urethral pressure for 2-minutes after 50 ml bladder filling and, later on, during filling cystometry. Urethral pressure variations were calculated as the ratio of MUP (difference between highest and lowest maximal urethral pressure), divided by the highest MUP. URI was defined if a ratio >33% was documented during the 2-minute resting period. Using this definition, URI occurred in 12.6% whereas if in the same group the definition of pressure changes of > 15cm water was used, the prevalence increased to 31% [23]. Four patterns of urethral pressure variations during a 2-minute resting cystometry (with 50 ml bladder filling) as well as during filling cystometry were observed by McLennan et al. They observed; a) resting pressure variations without detrusor activity; b) resting URI as well as DO during filling; c) no resting URI but detrusor contraction preceded by a fall in urethral pressure (so called type II DO); d) resting URI and type II DO. Because it is well-known than with the exception of patients with detrusor-sphincter dyssynergia, the urethra always relaxes prior to a detrusor contraction, urethral abnormality (eg URI) may be the primary disorder in patients with complaints of OAB. It was stated that differentiation between subtypes of URI may be important for directing therapy.

Clinical significance of urethral pressure variations

The observation of urethral pressure changes during filling cystometry may indicate functional or morphological changes in or around the urethra. Vereecken and Das showed URI in 14.4% of 173 patients with a history of incontinence [13]. In 52% of these patients, no concomitant DO was present. Urethral pressure variations over 35 cm water provoked urgency. Weil et al. found URI associated with DO in 27% of 427 patients [14]. Most investigators suggest a link between URI and DO. A close association between URI and DO was also reported by Clarke. In patients with URI, DO was present in 64%. In 608 patients, a prevalence of URI of 6.4% was found. URI appeared to cause urgency/frequency and seemed to be a negative prognostic factor that increased the risk of urinary incontinence [16]. In contrast to the believed association of URI and pathology, Kulseng-Hansen found urethral pressure variations of more than 20 cm water in more than 50% of normal females [19]. Hence, other than in previous definitions, he considered urethral pressure variations of more than 10, 15 or 20 cm water not as pathologic anymore. The urethral pressure variation (MUP) was calculated as the difference between the highest (MUPH) and the lowest (MUPL) maximum urethral pressure observed during one minute of urodynamic recording. In his study however, the maximum urethral pressure in patients during filling cystometry was significantly lower than in the control group of normal females [19]. This suggests differences in studied groups. Venema and Kramer studied 71 female patients with complaints of urge, stress or mixed incontinence. URI was seen in 66%. DO was reported to occur in 24% of all patients [10].
Symptoms related to urethral instability
The ICS does not define urethral pressure changes during filling cystometry since the significance of the fluctuations and the term ‘unstable urethra’ lack clarity. It is difficult to fully interpret the variations in urethral pressure during filling cystometry, but they should not be ignored. Although studies are few, often there is a focus on the role of urethral pressure variations or URI in sensory storage symptoms [24]. It is getting more and more clear that sensations, e.g. urgency, noticed by the patient during filling cystometry, without changes in the traditional urodynamic parameters, are important in understanding symptoms. URI might explain symptoms related to sensory symptoms. URI, defined as pressure changes >15 cm water and occurring in the absence of any bladder event, was reported to be a common condition in enuretic male and female patients. Combined URI and DO was seen in 35%, isolated URI in 45%, and isolated DO in 10% of these patients [12]. URI is a common condition in enuretic patients. In this respect, URI might play a causal role in enuresis, as isolated DO is present in only the minority of these patients. Furthermore, a significant drop in urethral pressure can trigger detrusor contraction [12]. In 427 female patients with lower urinary tract symptoms, urethral pressure variations of >15 cm water that were not related to an increase in intra-abdominal pressure or to vascular pulsations, were found in 16.4%. URI was related to frequency, nocturia, urgency, and a history of urethral syndrome (2 or more symptoms like dysuria, frequency or urgency). However, DO was stronger associated with urge urinary incontinence, nocturia and urgency than URI [14]. According to Vereecken pressure variations, exceeding 35 cm water may provoke urgency [13]. On the contrary, Wise et al. reported no difference between patients with or without URI in terms of prevalence or severity of urgency/frequency, nocturia or urge incontinence. Combined URI and DO was significantly more common in women presenting with stress incontinence [21]. Venema and Kramer already stated that URI is an expression of sensory urge [10]. URI may also be an important element in dysfunctional voiding. URI may cause the urge sensation during filling and the staccato voiding phase in patients with dysfunctional voiding [25].
Discussion

Filling cystometry is most often used as a representative of natural bladder filling. Data recorded by filling cystometry give an impression of the storage phase of the micturion cycle. Throughout the day, the bladder is filled with urine and emptied during voiding. Unfortunately, the co-operation between bladder and urethra may be affected and lead to storage disorders. For this reason, both bladder and urethral pressure recording should be done during filling cystometry when evaluating storage disorders.

Various descriptions have been used in the past to define the entity of urethral pressure changes during filling cystometry. There is still debate on whether certain urethral pressure variations should be regarded as physiological or pathophysiological (i.e. URI). The prevalence of URI in literature varies, due to the use of different definitions, together with inappropriate urethral pressure recordings. To rule out artefacts, like movement or incorrect position of the urethral pressure sensor, the use of more than one urethral pressure sensor is advocated. Only in this way, correct urethral pressure recordings are achieved and results can be compared.

Urethral pressure is defined as the fluid pressure needed to just open a closed (collapsed) urethra [26]. Due to lack of general agreement on the relevance of urethral pressure measurements, the use of urethral pressure measurement in routinely performed filling cystometry is limited [5]. The significance for clinical practice of urethral pressure variations, often defined as URI, is still not fully understood and thus often neglected. Moreover urethral pressure variations during filling cystometry are considered as an artefact and therefore of no relevance for explaining patients symptoms by some investigators [2]. Slow wave, rhythmic urethral pressure variations have been shown in healthy volunteers and may be an aspect of normal urethral physiology that could contribute to continence and urinary tract infection prevention, and need to be considered as pathophysiological [27]. McLennan et al. published on the significance of urethral pressure measurements during filling cystometry. When accepting certain urethral pressure variations as pathological (URI), differentiation in URI subtypes might be important for directing therapy. It has to be stated that in this study, as well as in many other studies, only 1 urethral pressure sensor was used together with one sensor measuring detrusor pressure [23]. To rule out artefacts, like movement of the pressure sensor during urodynamic testing, the use of more than one urethral sensor is to be preferred. Only in this way, more accurate recordings are achieved.

The prevalence of urethral pressure variations and the clinical significance is matter of discussion. Review from the literature shows different prevalence's in different studies with different definitions for ‘urethral instability’. One might wonder if all authors are discussing the same topic. Furthermore, what is the explanation for the reported urethral pressure variations and how should these pressure variations be interpreted?

Schaefer et al. noticed urethral pressure changes to be important for the sensation of urgency. The sensation of urgency was better synchronized with decline in urethral pressure than with subsequent detrusor activity. Current concepts of OAB, DO and urge urinary incontinence, originate from traditional cystometry, without measuring urethral pressure variations, and need to be reconsidered [3].
It is postulated that urethral pressure variations can be found in females with and without lower urinary tract complaints. A prevalence of 7-14% is found in females without voiding complaints [24]. The prevalence of URI in patients with lower urinary tract symptoms is considerably higher (up to 84%) and depends on patient selection, the technique used to measure urethral pressure changes, and interpretation of these pressure variations. URI is demonstrated significantly more often in patients compared to healthy volunteers and therefore is an important topic in describing storage symptoms. Urethral pressure variations are seen in patients with urge urinary incontinence (both with and without DO) more often than in patients with complaints of stress incontinence. URI is more related to symptoms of an OAB and is relevant to understand bladder storage dysfunction.

Morphological changes in the urethra are considered to be related to the occurrence of urethral pressure variations during filling cystometry. In fact, a significant shorter functional urethral length was present in women with unstable urethra behaviour [23]. Chaliha et al. demonstrated a significant decrease in functional urethral length in women with DO. It was suggested that urethral function was affected by the presence of DO. She suggested that for a correct assessment of urethral function, DO has to be treated first [28]. Earlier reports also found morphological changes of the urethra in patients with DO compared to those with normal urodynamic testings. A smaller total urethral diameter and circumference as a result of loss of smooth muscle thickness was found. This could result in a decrease in urethral resistance, enabling urine to enter the bladder neck, initiating detrusor contraction. It however remains unclear whether urethral function differences are the result of DO rather than its cause [29]. By observing both bladder and urethral pressure we often observe that the changes in urethral pressure are (just) prior to the changes in bladder pressure: the concept that urethral function is more leading bladder function than the other way around, is supported by the concept of the guarding reflex [1].

In therapy evaluation like in SNM, it was evident that the delay in FSF was correlated with the success of the treatment [30]. In our data on SNM therapy, abolition of URI was noticed in successful patients after SNM [31]. URI is most likely a better parameter to predict the outcome of SNM than DO. In this study, URI was defined when pressure changes of more than 15 cm water in all 3 urethral pressure sensors were observed with the mid urethral sensor positioned at the maximum urethral pressure. Furthermore, in patients successfully treated with SNM because of refractory complaints of an OAB, we demonstrated an instant recurrence of both DO and URI after a bilateral pudendal blockage with lignocaine whereas these observations were absent before the pudendal blockage [32]. This observation draws attention on the importance of the pudendal nerve in understanding the origin of both URI and DO. In our opinion, FSF is often derived from observed urethral pressure changes. In accordance with the criteria of Vereecken [22] we find a pathological early FSF in the majority of patients with URI. A drop in urethral pressure is often present at the FSF. Therefore, we believe that the importance of URI as a cause of sensory urgency and therefore as a ‘sensory’ marker is underestimated in literature.

The origin of URI is still not fully understood. Kenton et al. observed no increase in urethral pres-
sure during filling cystometry and suggested that urethral pressure changes do not reflect the integrity of the striated urethral sphincter. Urethral pressure measurements, performed intraluminally, reflect to all anatomical components surrounding the lumen of the urethra. It is possible that these measurements are not sensitive enough to detect changes in the striated rhabdosphincter [33]. In contrast, others observed that urethral pressure changes were found to be caused by activity of the urethral sphincter or pelvic floor muscles. Urethral muscle contractions are of the fast type whereas pelvic floor activity can be either slow or fast, resulting in slow or fast urethral pressure fluctuations [34].

The neurophysiologic explanation of URI is unclear. URI may be caused by diminished sympathetic influence or by increased parasympathetic activity. More in general, urethral pressure variations are considered as a pudendal nerve reflex mechanism, and as an expression of abnormal reflex activity in sympathetic and/or parasympathetical nerves.

We experienced that SNM therapy is capable in abolishing URI [31]. By stimulation of sacral nerves at the level of the sacral foramen, both afferents and efferents are activated. Only A-α fibers are stimulated, the threshold for stimulation of C-fibers and A-δ fibers is too high. It is generally accepted that the modulating effect of SNM is generated by stimulation of the afferent nerves. Somatic and sensory fibers from the pudendal nerve and tibial nerve converge at S3. Stimulation of the afferent pudendal nerve branches of the dorsal penile and clitoral nerve leads to inhibition of detrusor activity. This is also seen by stimulation of the afferent pelvic nerve fibers from bladder, urethra and anorectal region [35]. These afferent pudendal and pelvic fibers enter the spinal cord via the dorsal rami. It seems that these nerves are responsible for the afferent signal transmission of SNM. A hypothesis for the inhibition of detrusor activity generated by stimulation of the afferent sacral nerves is a diminished parasympathetic motoric response. If URI is due to increased parasympathetic activity and SNM results in decreased parasympathetic activity, then this does explain our observations of decreased URI in successful treated SNM patients.
Conclusions

The presence of urethral pressure variations during filling cystometry is well documented by various investigators. Unfortunately, this did not lead to a better understanding of the phenomenon so far. Different definitions for different types of pressure variations patterns have been reported. For a good and reliable recording of urethral pressure changes, the use of more than one urethral pressure sensor is advocated.

Urethral pressure variations particularly cause sensory urge complaints. Reflexes like the guarding reflex illustrate the “leading” role of urethral function. Morphological changes within the urethra together with sympatic activity might explain urethral pressure fluctuations.

Too often, investigations failed to illustrate treatment results (e.g. medical treatment) by only observing bladder function and/or DO. Given the growing acceptance of the relevance of sensory parameters, the often disappointing outcomes of bladder-function-only related studies, we recommend recording of urethral pressure variations, with more than one pressure sensor, in the diagnosis and evaluation of treatment modalities in patients with complaints of an OAB. In the future, urethral pressure variations should be recorded with a reliable and standarized method.
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